GermanStemCellNetwork



14th GSCN Conference

Speakers & Abstracts

9 – 11 September 2026
Max Delbrück Center
Berlin

www.gscn.org





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14th GSCN Conference

9 – 11 September 2026

Max Delbrück Center

Berlin

Organizer:

German Stem Cell Network (GSCN)

c/o Charité Universitätsmedizin

Luisenstr. 65, 10117 Berlin

GermanStemCellNetwork

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Dear colleagues and friends, partners and participants,



The German Stem Cell Network (GSCN) is delighted to welcome you to the 14th GSCN Conference taking place from 9 – 11 September 2026 in the capital of Germany, Berlin at the Max Delbrück Center, MDC.C.

This year's GSCN Conference focuses on the latest frontiers of stem cell and organoid biology, embryonic and tissue-derived stem cells, bioengineering, and developmental biology.

We are once again excited to unite top experts from academia, industry, and the clinic from across the country and worldwide to discuss the latest news in stem cell research. From year to year, more and more people are drawn to the key stem cell event in Germany. Attendees can look forward to meeting exceptional international keynote speakers, selected presentations from submitted abstracts, and a distinguished Presidential Symposium featuring our GSCN awardees for the GSCN 2026 Hilde Mangold Award, the GSCN 2026 Young Investigator Award, and the GSCN 2026 Publication of the Year Award.

A comprehensive industry exhibition and dedicated sessions will provide insights into the latest developments in R&D and translational stem cell research. Expect to encounter exciting new scientific discoveries and engage in lively discussions during breaks at the two poster sessions and at our legendary GSCN Networking Event with dinner and party. Don´t miss this unique opportunity to be part of our growing and vibrant stem cell community, enjoy networking, engage in discussions, and connect with fellow scientists and future collaborators!

At this point, I would like to extend my sincere thanks to everyone who made this conference possible: the GSCN office, the local organizers and program committee, the speakers, the Max Delbrück Center staff who made this happen, and of course, all of you — whose presence and contributions will make this event a vibrant space for knowledge, inspiration, and connection.

I wish all of us stimulating discussions, meaningful encounters, and fresh ideas to carry back to our labs, clinics, and communities. Thank you very much — and let's have a successful conference!



Heiko Lickert
GSCN President

For the program committee

Sina Bartfeld (Berlin), *Daniel Besser* (Berlin), *Aydan Bulut-Karslioglu* (Berlin), *Sebastian Diecke* (Berlin), *Mina Gouti* (Berlin), *Simon Haas* (Berlin), *Heiko Lickert* (Munich), *Alexander Meissner* (Berlin), *Maike Sander* (Berlin), *Ludovic Vallier* (Berlin), *Claudia Waskow* (Jena)

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Conference Information

Venue

Max Delbrück Communications Center (MDC.C)
Robert-Rössle-Straße 10
13125 Berlin

Date

Wednesday, 9 September – Friday, 11 September

Lunch

You can have also lunch at the MDC Mensa, MDC Café, or Café Max (Thursday and Friday) on campus, all of which offer a variety of dishes. Please note that lunch is at your own expense. All three locations accept both card and cash payments. Their locations are indicated on the campus map on page 7.

Registration

Regular fee	€ 620,-
Regular member fee	€ 400,-
Student fee	€ 310,-
Student member fee	€ 200,-

The registration fee includes admission to all scientific sessions, additional scientific events, poster and commercial exhibition, the get-together on 9 September and the networking evening on 10 September, lunch and coffee breaks, free internet access, conference bag including badge and access to the GSCN web app.

Internet

Internet access via Wireless LAN is free of charge.

Poster Exhibition

Posters will be displayed during the conference in two sessions. Authors are asked to be present at their poster during the poster session. Even numbers will be presented on Wednesday, 9 September from 16:30 – 17:30 h and odd numbers will be presented 17:30 – 18:30 h. On Thursday, 10 September even numbers will be presented from 17:00 – 18:00 h and odd numbers from 18:00 – 19:00 h.
You will find the number of your poster in this abstract volume. Please prepare the size DIN A 0 portrait for the poster. Otherwise, there are no specifications. Posters in poster session I should be mounted on Wednesday 12:00 – 16:00 h and removed at latest on Thursday, 12:00 h. Poster in poster session II should be mounted on Thursday 12:00 – 16:30 h and removed latest on Friday at 14:00 h.

Poster Sessions

Session I: Wednesday, 9 September, 16:30 – 18:30 h

Basic, translational, applied hematopoiesis	(P001 – P011)
Computational stem cell biology	(P012 – P016)
Stem cells in disease modeling & drug development	(P017 – P059)
Stem cells in regenerative therapies	(P060 – P087)

Note: P064 – P087 will be displayed in the MDC.C Foyer - Mezzanine

This poster session is supported by Biomerieux.

Session II: Thursday, 10 September, 17:15 – 19:15 h

Pluripotency, differentiation & PSC-derived models	(P088 – P135)
Stem cells in aging & disease (cancer stem cells)	(P136 – P142)
Tissue-derived stem cells & organoids	(P143 – P172)

Note: P150 – P171 will be displayed in the MDC.C Foyer - Mezzanine

The poster session II is supported by Eppendorf.

GSCN Awards 2026

Travel awards

The following participants have been selected for the GSCN travel awards.
Anita Florkowska (Warsaw, PL)
Ronja Friede (Heilbad Heiligenstadt)
Hamideh Karimi (Istanbul, TR)
Martina Mankarious (Aachen)
Dawn Shuiping Lin (Heidelberg)
Vera Nischalke (Aachen)
Yiwen Zhang (Heidelberg)

Poster awards

There will be two poster awards for each poster session. Members of the poster jury have a red dot on their badge – please present them your poster with due attention. The awardees will receive € 500 each. Authors are asked to be present at the poster award ceremony on Friday, 11 September 2026 at 15:30 – 15:50 h in Axon1/2.

ACTIVE BIOSCIENCE PROTEINS · CELLS · ANTIBODIES PeptiGrowth
The poster awards are supported by Active Bioscience and PeptiGrowth.

Scientific awards

A top-class commission supported GSCN in choosing this year´s awardees. The three awardees will give a presentation in the Presidential Symposium on Thursday, 10 September 2026 at 14:30 – 17:00 h.
GSCN 2026 Young Investigator Award: ***Jesse Veenvliet***, Max Planck Institute of Mol. Cell. Biol. and Genetics, Dresden
GSCN 2026 Hilde Mangold Award: ***Maike Sander***, Max Delbrück Center, Berlin (Pres.: Friday 14:45 - 15:30 h)
GSCN 2026 PoY: ***Annika Zink***, ***Alessandro Prigione*** et.al., Heinrich-Heine-University, Düsseldorf

Elsa-Symposium

Genome editing: biomedical, ethical, and regulatory challenges

Increasingly precise genome-editing technologies make direct in vivo treatment a promising option for genetic diseases. Preclinical and clinical studies highlight the importance of targeting affected tissues to improve efficacy while minimizing off-target effects, particularly in the germ line. This distinction between somatic gene therapy and germ-line interventions is firmly established in current regulations. At this year's conference, we will deepen the discussion of in vivo genome editing. On Wednesday evening, keynote speaker Stepan Jerabek of Columbia University Irving Medical Center will present his research on base editing in human embryos in vitro, exploring editing efficiency, developmental competence, and chromosomal integrity. Thursday morning's ELSA Symposium will broaden the discussion to examine on-target efficacy and unintended effects across a wider range of genome-editing applications. Promising liver-targeted in vivo base-editing approaches may reduce the perceived medical need for germ-line interventions, as somatic treatments could also be offered to affected individuals in future generations. At the same time, advances in precise editing of human embryos raise new questions about interventions at the earliest stages of development. For disorders affecting multiple tissues or acting early in development, fetal or embryonic intervention could theoretically offer advantages over tissue-specific treatment later in life. However, at these developmental stages, modification of germ cells may be difficult – or, in the case of embryo editing, impossible – to avoid. As technical advances may reduce some of the previously recognized risks of embryo genome editing, the fundamental question becomes increasingly relevant: could heritable genome editing ever be medically, ethically, and societally acceptable?

Social Events

Get-together

On Wednesday, 9 September, 19:15 – 21:00 h, all participants and exhibitors are invited to the get-together with dinner buffet in the Mensa on the Campus Buch, which is a 2-minute walk from the conference center. The Mensa can be found on the map below.





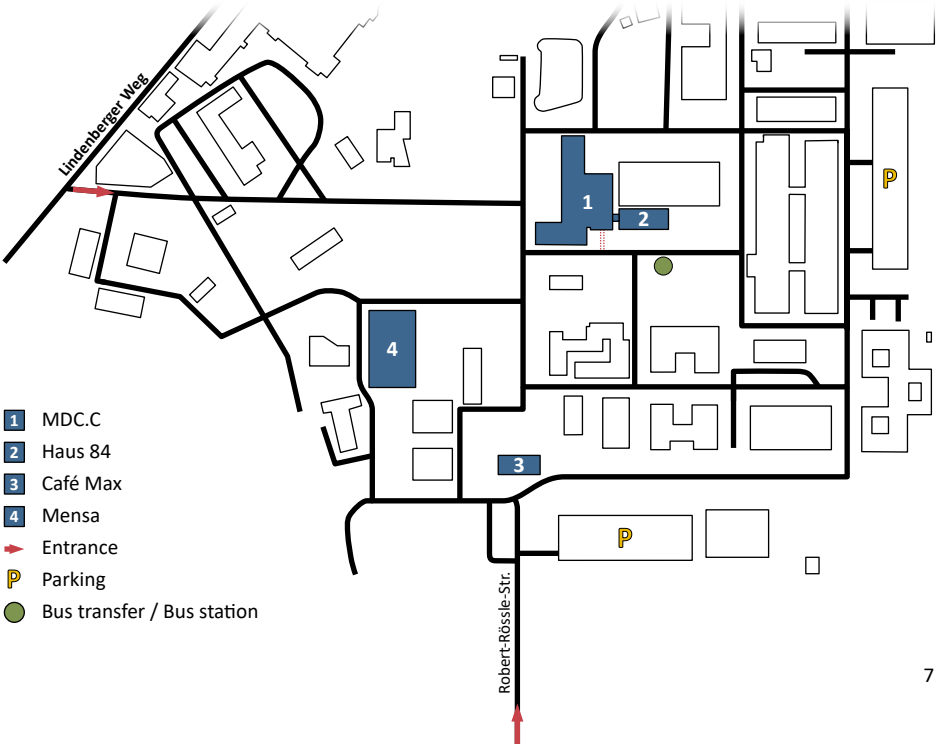
Networking Event

The GSCN Networking Event with dinner buffet and DJ is open for all participants and exhibitors and will take place on Thursday, 10 September, 19:30 – 01:00 h at the Café am Neuen See. From 19:15 h, there will be a bus transfer from the conference center to Café am Neuen See. The departure point for the buses, starting at 18:45 h, at the MDC.C can be found on the map below.

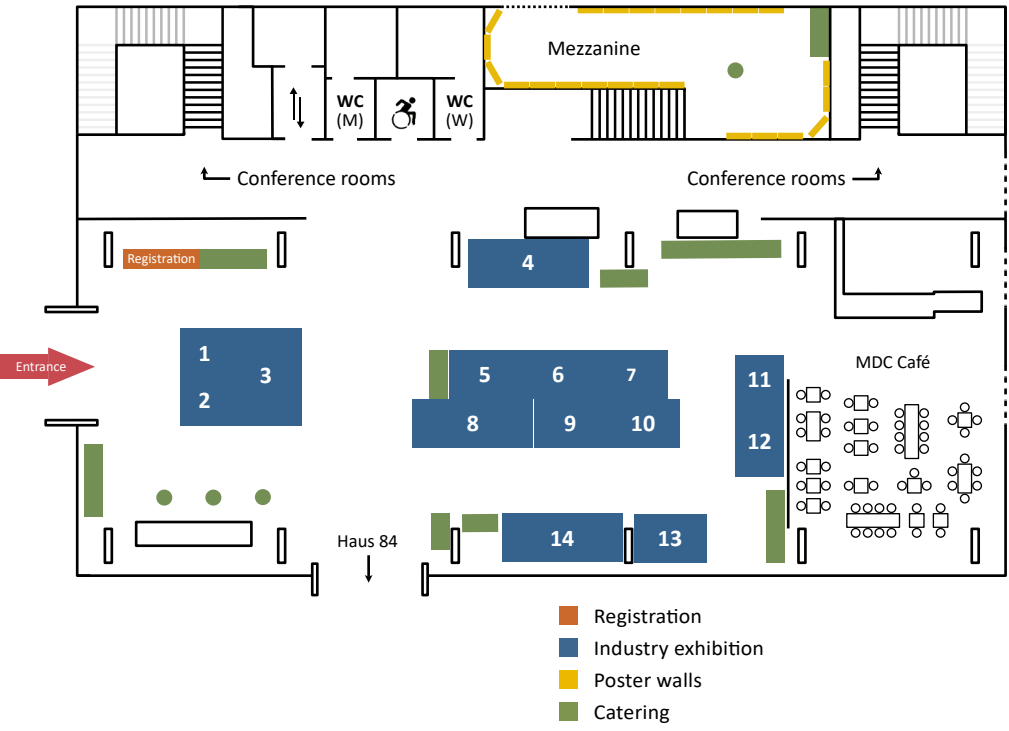
Café am Neuen See
Lichtensteinallee 2
10787 Berlin



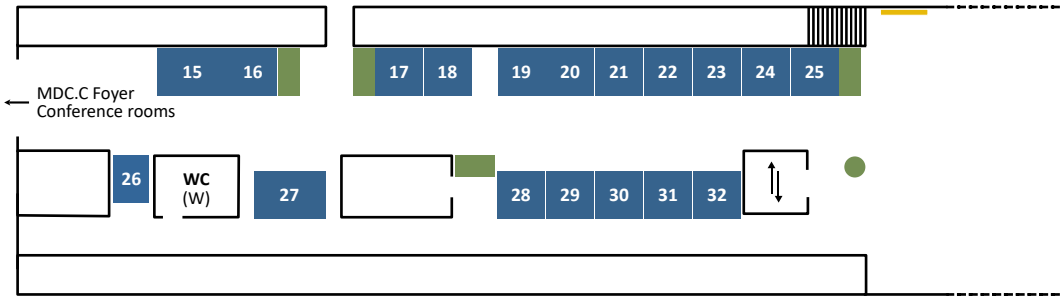
Site plan Campus Berlin-Buch



MDC.C Foyer



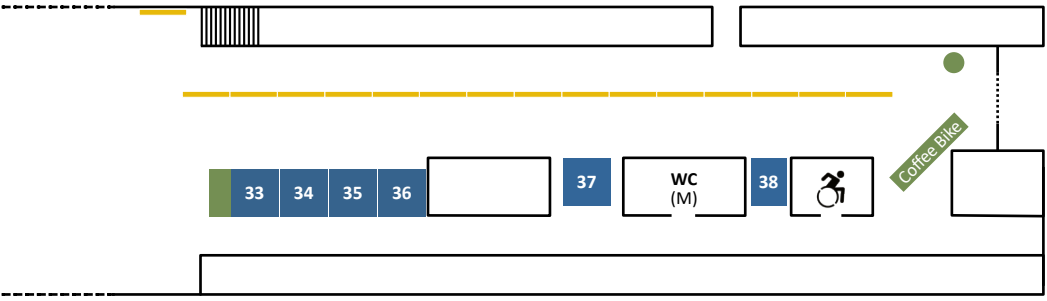
Haus 84



List of exhibitors

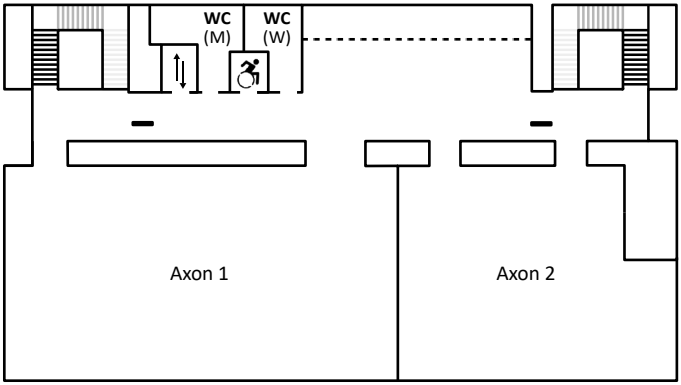
Nr.	Company
1	Waters Biosciences (Formerly BD Biosciences)
2	PromoCell GmbH
3	STEMCELL Technologies
4	ACROBiosystems
5	Evotec SE
6	Miltenyi Biotec B.V. & Co. KG
7	Biomerieux
8	Sartorius
9	Molecular Devices GmbH
10	Corning Life Sciences
11	CYTENA
12	Thermo Fisher Scientific
13	Countstar
14	Active Bioscience / PeptiGrowth
15	Eppendorf
16	Axion BioSystems
17	Fujifilm Biosciences
18	Green Elephant Biotech
19	ibidi GmbH

Nr.	Company
20	IDT Germany GmbH
21	I&L Biosystems
22	MedChemExpress
23	Nationales Netzwerkbüro GCT Germany
24	Nippon Genetics Europe GmbH
25	iotaSciences
26	TCS Group
27	R&D Systems™ by bio-techne
28	PL BioScience GmbH
29	Proteintech Germany GmbH
30	Scinus
31	Sekisui
32	Biomol GmbH
33	Valicare GmbH
34	Novogene Europe
35	Xceltis GmbH
36	Vazyme Biotech
37	Cyagen Biosciences B.V.
38	Cenibra

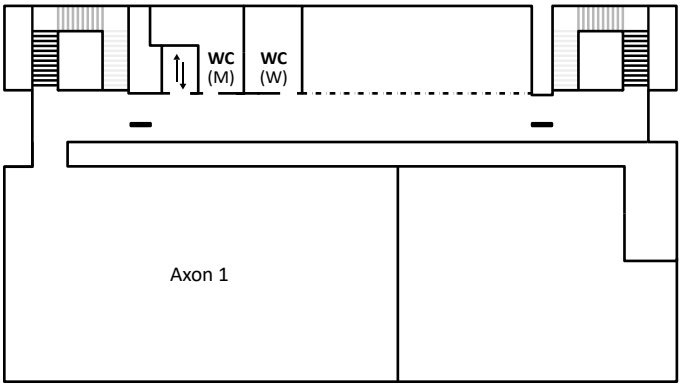


MDC.C Floor plans

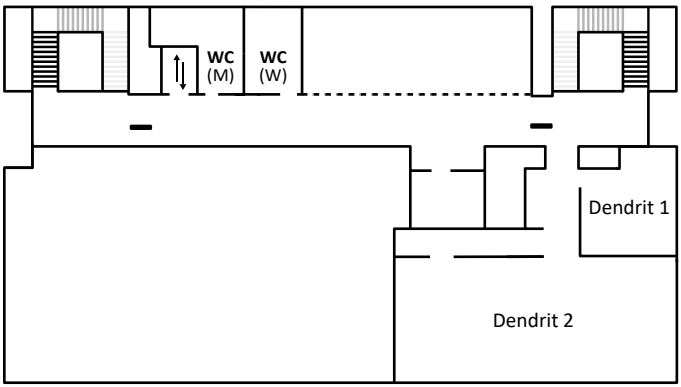
1st Floor



2nd Floor



3rd Floor



Public outreach event (in German)

Wie verändert Stammzellforschung die Medizin von morgen?

Ein Abend mit führenden Forschenden über Chancen, Grenzen und Perspektiven moderner Zellforschung.

Zeit und Ort

Freitag, 11. September 2026
18:30 – 20:30 Uhr
Max Delbrück Center - Berlin Institute for Medical Systems Biology (MDC-BIMSB)
Hannoversche Straße 28, 10115 Berlin

Programm

18:30 Uhr: Begrüßung
Kurzfilme der Forschenden
Podiumsdiskussion
20:00 Uhr: Stellen Sie Ihre Fragen!

Neue Hoffnung für die Medizin – verständlich erklärt

Stammzellen gehören zu den faszinierendsten Zellen unseres Körpers. Sie ermöglichen Wachstum, Regeneration und Heilung – und eröffnen zugleich neue Wege in der Medizin.
Doch was ist heute bereits möglich? Welche Therapien befinden sich in der Entwicklung? Wo liegen Chancen, Risiken und Grenzen der Stammzellforschung?
Unsere Expertinnen und Experten geben verständliche Einblicke in ihre aktuelle Forschung und diskutieren mit Ihnen über die Medizin von morgen.

Darüber sprechen wir

– Wie könnten Zelltherapien Menschen mit Diabetes helfen?
– Welche Hoffnung gibt es für Menschen mit Muskelerkrankungen?
– Was sind Organoide – und warum gelten sie als Schlüsseltechnologie der modernen Medizin?

Auf dem Podium

Prof. Dr. Heiko Lickert, Helmholtz München, Diabetes und Stammzellforschung
Prof. Dr. Sina Bartfeld, Technische Universität Berlin, Organoide und Krankheitsmodelle
Prof. Dr. Maike Sander, Max Delbrück Center, Diabetes und Stammzellforschung
Prof. Dr. Georg Duda, Berlin Institute of Health (BIH) & Charité, Biomechanik und regenerative Medizin
Prof. Dr. Simone Spuler, Max Delbrück Center & Charité, Muskelerkrankungen und Zelltherapien

Moderation: *Dr. Stefanie Seltmann*, Wissenschaftsjournalistin

Im Anschluss laden wir Sie herzlich ein, bei Getränken mit unseren Wissenschaftlerinnen und Wissenschaftlern bis 20:30 Uhr ins Gespräch zu kommen und Ihre Fragen zu stellen.

Program overview – Wednesday

	Max Delbrück Center			
09:00 – 19:00	Registration			
	Axon 1	Axon 2	Dendrit 2	MDC.C: Foyer - Mezzanine & Haus 84
11:00 – 11:30	**Opening**			
11:30 – 12:15	**Keynote lecture I** *Andreas Trumpp*			
12:15 – 13:00	**Keynote lecture II** *James M. Wells*			
13:00 – 14:30	Lunch break / Industry exhibition			
14:30 – 16:00	**Concurrent scientific working group session I**			
	Pluripotency, differentiation & PSC - derived models I	Basic, translational & applied hematopoiesis	Computational stem cell biology & systems biology	
16:00 – 16:30	Break time / Industry exhibition			
16:30 – 17:30				**Poster session I** even numbers
17:30 – 18:30				**Poster session I** uneven numbers
18:30 – 19:15	**Keynote lecture III** (on ELSA topics) *Stepan Jerabek*			
19:15 – 21:00	Informal **GSCN get-together** with dinner buffet at the MDC Mensa			

Program overview – Thursday

	Max Delbrück Center				
08:00 – 18:00	Registration				
	Axon 1	Axon 2	Dendrit 1	Dendrit 2	MDC.C: Foyer - Mezzanine & Haus 84
09:00 – 10:30	**Concurrent scientific working group session II**				
	Stem cells in regenerative therapies	Stem cells in aging & disease	Elsa Symposium	Stem cells in disease modeling & drug development I	
10:30 – 11:30	Break time / Industry exhibition				
10:45 – 11:30		**GSCN Members Meeting**			
11:30 – 13:00	**Industry session: "Technologies from GSCN industry partners"**				
	STEMCELL Technologies ACRO Biosystems Active Bioscience/ PeptiGrowth	Biomerieux Evotec SE Eppendorf Miltenyi Biotec B.V. & Co. KG Sartorius		Countstar R&D bio-techne Molecular Devices GmbH Thermo Fisher Scientific Corning Life Science	
13:00 – 14:30	Lunch break / Industry exhibition				
14:30 – 15:15	**Presidential Invite I** *Janet Rossant*		**Presidential Symposium**		
15:15 – 15:45	**Young Investigator Award** *Jesse Veenvliet*				
15:45 – 16:30	**Keynote lecture V** *Jason Spence*				
16:30 – 17:00	**Publication of the Year Award** *Annika Zink*				
17:00 – 17:30	Break time / Industry exhibition				
17:00 – 18:00					**Poster session II** even numbers
18:00 – 19:00					**Poster session II** uneven numbers
20:00 – 01:00	**GSCN networking event** for all participants with dinner buffet & DJ at Café am Neuen See, Berlin				

Program overview – Friday

	Max Delbrück Center		
08:00 – 16:00	Registration		
	Axon 1	Axon 2	Dendrit 2
09:00 – 10:30	**Concurrent scientific working group session III**		
	Stem cells in disease modeling & drug development II	Tissue-derived stem cells & organoids	Pluripotency, differentiation & PSC-derived models II
10:30 – 11:00	Break time / Industry exhibition		
11:00 – 12:30	**Concurrent strategic working group session**		
	Clinical trials & regulatory affairs	Technologies in stem cell research	Career development
12:30 – 14:00	Lunch break / Industry exhibition		
14:00 – 14:45	**Keynote lecture IV** *Takanori Takebe*		
14:45 – 15:30	**Hild Mangold Award** *Maike Sander*		
15:30 – 15:50	**Award Ceremony** *Daniel Besser*		
15:50 – 16:00	**Closing remarks by the GSCN president** *Sina Bartfeld*		
	END OF CONFERENCE		

Program – Wednesday, 9 September 2026

11:00 – 11:30
Axon 1/2

Opening
GSCN Conference 2026

11:00 – 11:10
Welcome to Max Delbrück Center, Berlin
Holger Gerhardt, Deputy Director Max Delbrück Center, Berlin

11:10 – 11:20
Welcome address from the Berlin Institute of Health at Charité (BIH)
Christopher Baum, Chair of the BIH Board of Directors

11:20 – 11:30
Opening of GSCN Conference 2026
Heiko Lickert, President GSCN

11:30 – 12:15
Axon 1/2

Keynote lecture I
K1 – From stem cells in leukemia to neurons in pancreatic cancer
Andreas Trumpp, German Cancer Research Center, Heidelberg
Chair: *Claudia Waskow*

12:15 – 13:00
Axon 1/2

Keynote lecture II
K2 – Endoderm organogenesis from human pluripotent stem cells: some assembly required
James M. Wells, Cincinnati Children's Hospital Medical Center, USA
Chair: *Mina Gouti*

13:00 – 14:30 Lunch break / Industry exhibition supported by Countstar

14:30 – 16:00 **Concurrent scientific working group session I**

14:30 – 16:00
Axon 1

Pluripotency, differentiation & PSC-derived models I supported by ACROBiosystems
Chairs: *Micha Drukker* & *Ralf Jauch*

14:30 – 15:00
T01 – Super-SOX-mediated generation of pluripotent stem cells with enhanced developmental potential
Hans Schöler, Max Planck Institute, Münster

15:00 – 15:15
T02 – Mosaic gastruloids reveal a temporal restriction for developmental cell competition
Joshua Frenster, University of Freiburg

15:15 – 15:30 T03 – HERVHLin coordinates LIN28A/let-7 activity to preserve genome stability during early human development
Zsuzsanna Izsvak, Max Delbrück Center, Berlin

15:30 – 15:45 T04 – HERVH-derived boundary elements shape 3D genome architecture in eFORM human pluripotent stem cells
Saba Mottaghinia, Max Delbrück Center, Berlin

15:45 – 16:00 T05 – A multi-individual iPSC resource from five non-human primate species for comparative biology and in vitro developmental studies
Vera Zywitza, Leibniz Institute for Zoo and Wildlife Research (IZW), Berlin

14:30 – 16:00 **Basic, translational & applied hematopoiesis**
Axon 2 Chairs: *Simon Haas* & *Mick Milsom*

14:30 – 15:00 T06 – Metabolic regulation of aged hematopoietic stem and multipotent progenitor cells
Nina Cabezas-Wallscheid, ETH Zürich, Switzerland

15:00 – 15:15 T07 – The development of simultaneous single-cell tRNA and mRNA profiling reveals dynamic tRNA programs in human hematopoiesis
Marius Külp, Goethe University, Frankfurt

15:15 – 15:30 T08 – Identification of a deeply dormant CD150neg hematopoietic stem cell population
Dawn Shuiping Lin, German Cancer Research Center (DLFZ), Heidelberg

15:30 – 15:45 T09 – Multiscale biological interactions define clinical trajectories in acute myeloid leukemia
Jan Barinka, Berlin Institute of Health (BIH) at Charité/Max Delbrück Center, Berlin

15:45 – 16:00 T10 – Molecular characterization and functional interrogation of dormant cancer stem cells in JAK2V617F-driven myeloproliferative neoplasms
Elif Saf, German Cancer Research Center (DKFZ), Heidelberg

14:30 – 16:00 **Computational stem cell biology & systems biology**
Dendrit 2 Chairs: *Ingmar Glauche* & *Carsten Marr*

14:30 – 15:00 T11 – Combining pooled single cell screens and deep learning to identify phenotypes driven by oncogenes
Nils Blüthgen, Humboldt University of Berlin

15:00 – 15:15	T12 – Slow genes are soft genes: lineage memory and perturbation sensitivity share a common origin *Ida Büschel*, Helmholtz Munich
15:15 – 15:30	T13 – Emergent cell-type order in epithelia: a hallmark of stem cell fate characteristics in homeostasis? *Philip Greulich*, University of Southampton, UK
15:30 – 15:45	T14 – Epigenetic fidelity of hiPSC-derived T cell progenitors: Accurate remodeling and aberrant DNA methylation imprints *Marcel Finke*, Berlin Institute of Health (BIH) at Charité
15:45 – 16:00	T15 – SON maintains innate immune homeostasis in HSCs via splicing and retroelement control *Mariela Cortez Lopez*, Helmholtz Munich
16:00 – 16:30	Break time / Industry exhibition supported by R&D Systems™ by bio-techne
16:30 – 18:30 Haus 84 MDC.C: Foyer - Mezzanine	**Poster session I – Poster number P001 – P087 (with beverages)** Basic, translational, applied hematopoiesis (P001 – P011) Computational stem cell biology (P012 – P016) Stem cells in disease modeling & drug development (P017 – P059) Stem cells in regenerative therapies (P060 – P087) supported by Biomerieux **Even numbers: 16:30 – 17:30** **Odd numbers: 17:30 – 18:30** Note: posters P064 - P087 will be displayed in the MDC.C Foyer - Mezzanine
18:30 – 19:15 Axon 1	**Keynote lecture III (on ELSA topics)** K3 – Highly efficient base editing at PCSK9 and normal development in human embryos *Stepan Jerabek*, Columbia University, New York, USA Chair: *Tobias Cantz*
19:15 – 21:00 MDC Mensa	**GSCN Get-together for all participants** Dinner buffet

Program – Thursday, 10 September 2026

09:00 – 10:30 **Concurrent scientific working group session II** supported by Thermo Fisher Scientific

09:00 – 10:30 **Stem cells in regenerative therapies**
Axon 1 Chairs: *Ludovic Vallier* & *Wolfgang Wagner*

09:00 – 09:30 T16 – Human pluripotent stem cell therapies to the heart and beyond: current status and challenges
Robert Zweigerdt, Hannover Medical School (MHH)

09:30 – 09:45 T17 – Decoding neurovascular dysfunction in ADHD: Patient-specific iPSC-derived blood-brain barrier (BBB) models uncover hidden metabolic drivers beyond PARK2 genetics
Antje Appelt-Menzel, University Hospital Würzburg

09:45 – 10:00 T18 – "Heps in a Bag", an engineered hepatic patch against acute liver failure
Fabian Bachinger, Berlin Institute of Health (BIH) at Charité

10:00 – 10:15 T19 – Off-the-shelf immune-shielded iPSC-derived CAR γδ T cells as novel cell therapy to treat hepatocellular carcinoma
Stephanie Sontag, Evotec

10:15 – 10:30 T20 – Engineering basal cells to modulate epithelial-macrophage interactions in COPD
Lili Rusznyak, Helmholtz Munich

09:00 – 10:30 **Stem cells in aging & disease**
Axon 2 Chairs: *Michael Rieger* & *Andreas Trumpp*

09:00 – 09:30 T21 – Attenuation of stem cell aging to target aging-associated diseases
Hartmut Geiger, University Ulm

09:30 – 09:45 T22 – A human brain organoid model of ageing identifies chromatin-mediated control of transposable elements during neural ageing
Elisa Gabassi, University of Innsbruck, Austria

09:45 – 10:00 T23 – Extreme heterogeneity in hematologic aging is predominantly driven by stochastic variation, not by environmental nor genetic variation
Yiwen Zhang, German Cancer Research Center (DKFZ), Heidelberg

10:00 – 10:15 T24 – Ontogenetically distinct bone marrow macrophages regulate HSC integrity and megakaryocyte-biased expansion
Nina Henning, Leibniz Institute on Aging (FLI), Jena

10:15 – 10:30 T25 – Clonal trajectories of adult B-ALL in medullary sites and brain infiltration at single-cell resolution
Hui Ming Tew, University Hospital Frankfurt

09:00 – 10:30 **Stem cells in disease modeling & drug development I**
Dendrit 2 Chairs: *Oliver Brüstle* & *Bert Klebl*

09:00 – 09:30 T26 – Starting matters: quality and reproducibility in PSC-based research
Bert Klebl, LDC Dortmund, *Michael Peitz*, University of Bonn,
Harald Stachelscheid, Berlin Institute of Health (BIH)

09:30 – 09:45 T27 – Microglia modulate neurodevelopmental responses to micro- and nanoplastic exposure in human brain organoids
Nelli Blank-Stein, University of Bonn

09:45 – 10:00 T28 – Dissecting the pathogenesis of Canavan disease using neuroglial organoids
Shreenidhi Vitchanthangal Prathivathibayankaram, University of Bonn

10:00 – 10:15 T29 – Patient-specific iPSC-derived sensory neurons as a gateway to individualized neuropathic pain modeling and treatment
Anika Neureiter, RWTH Aachen

10:15 – 10:30 T30 – In vitro/in silico reciprocal modeling of human neuronal networks reveals presynaptic vesicle dynamics underlying epileptiform activity
Jianbin Wen, University of Bonn

09:00 – 10:30 **ELSA symposium**
Dendrit 1 Panel: *Stepan Jerabek*, Moderation: *Tobias Cantz*

10:30–11:30 Break time / Industry exhibition supported by Evotec SE

10:45 – 11:30 **General Member Meeting**
Axon 2 Executive Board & Managing Director
Heiko Lickert, Claudia Waskow, Sina Bartfeld, Michael Cross, Andreas Trumpp, Daniel Besser

11:30 – 13:00 **Industry session: "Technologies from GSCN industry partners"**

11:30 – 13:00 **Main Supporter**
Axon 1 Chairs: *Michael Cross*
11:35 – 12:05 C01 – Streamlining advanced in vitro models: Principles and tools for stem cell-derived NAMS
Katharina Debowski, STEMCELL Technologies Germany GmbH

12:05 – 12:25 C02 – Enabling the future of cell therapy: From discovery to the clinic
Beau le Roy, ACROBiosystems

12:25 – 12:45 C03 – Next-generation synthetic peptide growth factors/cytokines for regenerative medicine and cell therapy
Kazuki Shigematsu, PeptiGrowth Inc.

11:30 – 13:00 **Supporter II**
Axon 2 Chair: *Mareike Albert*

11:35 – 11:50 C04 – Closing the analytical gap in cell therapy manufacturing: Automated at-line flow cytometry for QC from research to GMP release
Félix A. Montero-Julian, Biomerieux, Accellix

11:50 – 12:05 C05 – Integrating patient data and hiPSC microglia to model Alzheimer's disease for drug discovery
Henrik Renner, Evotec SE

12:05 – 12:20 C06 – 3D bioreactor stem cell culture: Consistent from R&D to commercial manufacturing
Philipp Nold, Eppendorf SE

12:20 – 12:35 C07 – Characterizing human PSC-derived cerebral organoids across imaging, cytometry, and sequencing
Hannah Johannsen, Miltenyi Biotec B.V. & Co. KG

12:35 – 12:50 C08 – Unlocking the future of gene-modified cell therapy with non-viral lipid-based transfection
Nadia Mazzaro, Sartorius

11:30 – 13:00 **Supporter III**
Dendrit 2 Chairs: *Laura Steenpaß*

11:35 – 11:50 C09 – Watching stem cells live: Continuous live-cell imaging in iPSC and organoid research
Ceren Güneş, Countstar

11:50 – 12:05 C10 – Interrogating inflammatory signaling in human iPSC-derived pancreatic ductal organoids with a fully defined animal component-free matrix
Joel Cresser-Brown, bio-techne

12:05 – 12:20 C11 – Advancing human relevant models: From AI-driven automated culture to high-content imaging and machine learning analysis - an end-to-end solution for iPSC and organoid workflows
Robert Storm, Molecular Devices Germany GmbH

12:20 – 12:35 C12 – Building more relevant and reliable human iPSC-derived neuronal models with the new neurobasal PhysioPlus medium
David Kuniger, Thermo Fisher

12:35 – 12:50 C13 – Innovative approaches and tools for investigating stem cell-based tissue culture
Francesca Aglialoro, Corning Life Sciences

13:00 – 14:30 Lunch break / Industry exhibition supported by Corning Life Sciences

14:30 – 17:00 **Presidential Symposium**
Axon 1/2 Chairs: *Sina Bartfeld* & *Heiko Lickert*

14:30 – 15:15 **Presidential Invite**
PS1 – Stem cells, embryos and embryo models: from science to ethical concerns
Janet Rossant, The Hospital for Sick Children, Toronto, Canada

15:15 – 15:45 **GSCN 2026 Young Investigator Award**
PS2 – Building towards understanding: from embryo models to principles of development (& back)
Jesse Veenvliet, Max Planck Institute of Molecular Cell Biology and Genetics, Dresden

15:45 – 16:30 K5 – Human intestinal organoids (HIOs) to study human intestine development, differentiation and disease
Jason Spence, University of Michigan, Ann Arbor, USA

16:30 – 17:00 **GSCN Publication of the Year 2025 – 2026 Award**
PS4 – Pluripotent stem-cell-based screening uncovers sildenafil as a mitochondrial disease therapy
Annika Zink, Heinrich-Heine-University, Düsseldorf

17:00 – 17:30 Break time / Industry exhibition supported by Molecular Devices GmbH

17:00 – 19:00 **Poster session II – Poster number P088 – P171 (with beverages)** supported by Eppendorf
Haus 84
MDC.C: Foyer - Mezzanine
Pluripotency, differentiation & PSC-derived models (P088 – P135)
Stem cells in aging & disease (cancer stem cells) (P136 – P141)
Tissue-derived stem cells & organoids (P142 – P171)
Even numbers: 17:00 – 18:00
Odd numbers: 18:00 – 19:00
Note: posters P150 - P171 will be displayed in the MDC.C Foyer - Mezzanine

20:00 – 01:00 **GSCN networking event for all participants** supported by STEMCELL Technologies
Bus transfer starting at 18:45, the entrance fee is collected onsite
Event location: **Café am Neuen See**, Berlin

Program – Friday, 11 September 2026

09:00 – 10:30 **Concurrent scientific working group session III**

09:00 – 10:30 **Stem cells in disease modeling & drug development**
Axon 1
Chairs: *Michael Peitz* & *Harald Stachelscheid*

09:00 – 09:15 T31 – Cooperative GNAS-KRAS signaling shapes intraductal papillary mucinous neoplasm phenotype and grade
Meike Hohwieler, University of Ulm

09:15 – 09:30 T32 – Unveiling the genetic landscape of UV-induced cellular responses: A CRISPR whole genome screening approach
Rafaela Ntzani, Leibniz Research Institute for Environmental Medicine (IUF), Düsseldorf

09:30 – 09:45 T33 – ELAPOR2 controls pancreatic endocrine differentiation through cell cycle regulation
Osvaldo Rodrigues Pereira, Helmholtz Munich

09:45 – 10:00 T34 – Human iPSC models for safer drug discovery through predictive teratogenicity assessment
Bastian Zimmer, Evotec SE

10:00 – 10:15 T35 – Fabry iPSC-derived dorsal root ganglia (DRG) model
Ferdinand Teichert, University of Leiden, Netherlands

09:00 – 10:30 **Tissue-derived stem cells & organoids II**
Axon 2 Chairs: *Mina Gouti* & *Robert Zweigerdt*

09:00 – 09:30 T36 – Intersectional genetics for precise manipulation and tracing of lung and skeletal muscle stem cells
Thomas Braun, Max Planck Institute Bad Nauheim

09:30 – 09:45 T37 – Characterization of naïve human neuroepithelial stem progenitor cells with unlimited self-renewal and broad neurogenic potential
Angeliki Spathopoulou, Leopold Franzens University Innsbruck, Austria

09:45 – 10:00 T38 – Lymphatic vasculature reprograms liver epithelium in assembloids and patients
Milad Rezvani, Charité University Medicine Berlin

10:00 – 10:15 T39 – Liver regeneration is programmed in the epigenetic landscape of cholangiocytes during fetal development
Irene Talon, Max Planck Institute for Moelcular Genetics, Berlin

10:15 – 10:30 T40 – Liver regeneration during chronic liver disease: SOX4 and KLF6 play a role in liver cell plasticity
Marta Cagna, Berlin Institute of Health at Chaité

09:00 – 10:30 **Pluripotency, differentiation & PSC-derived models II**
Dendrit 2 Chairs: *Sebastian Diecke* & *Stefan Liebau*

09:00 – 09:15 T41 – PluripotencyScreen - A new epigenetic framework to quantify cell fate decisions of pluripotent stem cells
Vera Nischalke, RWTH Aachen

09:15 – 09:30 T42 – Modeling primate atherosclerosis using iPSC-derived macrophages
Eva Briem, LMU Munich

09:30 – 09:45 T43 – CTCF insulates gene expression to safeguard migratory myogenic progenitor cells
Sören Hüttner, McGill University, Montréal, Canada

09:45 – 10:00 T44 – Bioengineered muscle tubuloids: a human stem-cell-based model of neuromuscular development and innervation
Anita Florkowska, Polish Academy of Sciences, Warsaw, Poland

10:00 – 10:15 T45 – Multi-omics profiling reveals MAGEL2-driven defects in human corticogenesis shared across Prader-Willi and Schaaf-Yang syndromes
Baran Enes Güler, University of Heidelberg

10:30 – 11:00 Break time / Industry exhibition supported by Sartorius

11:00 – 12:30 **Concurrent strategic working group session**

11:00 – 12:30 Axon 1 **Clinical trials & regulatory affairs**
Chairs: *Nina Graffmann* & *Zoltan Ivics*

11:00 – 11:30 S1 – Driving multimodal AI in precision medicine
Ulrike Weirauch, Fraunhofer Institute for Cell Therapy and Immunology (IZI), Leipzig

11:30 – 12:00 S2 – Translating regulatory expectations into context-specific genome-editing safety assessment
Sandra Ammann, University Hospital Freiburg

12:00 – 12:30 S3 – Off-target effects in CRISPR-Cas genome editing for human therapeutics: Progress and challenges
Giandomenico Turchiano, AstraZeneca, Cambridge, UK

11:00 – 12:30 Axon 2 **Technologies in stem cell research**
Chairs: *Sebastian Knöbel* & *Ole Pleß*

11:00 – 11:30 S4 – Polymeric gene delivery agents, an emerging class of RNA nanocarriers
Aidan Izuagbe, University of Würzburg

11:30 – 12:00 S5 – Engineering mutation-specific and mutation-agnostic gene therapy approaches and their delivery
Jefferey Truong, Helmholtz Munich

12:00 – 12:30 S6 – "Translational tool making" to develop and improve vector-based research tools
Leszek Lisowski, Children's Medical Research Institute, Sydney, Australia

11:00 – 12:30	**Career development**
Dendrit 2	Chairs: *Pascal Röderer* & *Insa Schröder*
	Panel discussion: Scientific mobility in a changing world
	with *Hartmut Geiger*, *Kimberly Hartl* and *Sedona Murphy*
12:30 – 14:00	Lunch break time / Industry exhibition supported by Miltenyi Biotec B.V. & Co. KG
14:00 – 14:45	**Keynote lecture IV**
Axon 1/2	K4 – Designing complex miniature organs in a dish from pluripotent stem cells
	Takanori Takebe, Cincinnati Children's Hospital Medical Center, USA
	Chair: *Aydan Bulut-Karslıoğlu*
14:45 – 15:30	**GSCN 2026 Hilde Mangold Award**
Axon 1/2	PS3 – Studying diabetes with engineered stem cell islet organoids
	Maike Sander, Max Delbrück Center, Berlin
	Chair: *Heiko Lickert*
15:30 – 15:50	**Award ceremony**
Axon 1/2	*Daniel Besser*
	Poster awards supported by Active Bioscience/PeptiGrowth
	Travel awards
15:50 – 16:00	**Closing remarks by the GSCN president**
Axon 1/2	*Sina Bartfeld*
	End of GSCN Conference 2026

Speaker abstracts

14th GSCN Conference
German Stem Cell Network

9 – 11 September 2026

Max Delbrück Center
Berlin

Keynote lectures: K1 - K5

K1 From stem cells in leukemia to neurons in pancreatic cancer
Andreas Trumpp

K2 Endoderm organogenesis from human pluripotent stem cells: some assembly required
James Wells

K3 Highly efficient base editing at PCSK9 and normal development in human embryos
Stepan Jerabek

K4 Engineering human organoids towards next generation regenerative therapeutics
Takanori Takebe

K5 Using organoids to interrogate human development and cellular heterogeneity
Jason Spence

Abstract No. K1

From stem cells in leukemia to neurons in pancreatic cancer

Andreas Trumpp[1,2]

[1] Division of Stem Cells and Cancer, German Cancer Research Center (DKFZ), Heidelberg
[2] Heidelberg Institute for Stem Cell Technology and Experimental Medicine (HI-STEM gGmbH)

In my presentation, I will cover two recent research directions: the heterogeneity and role of leukemic stem cells (LSCs) in therapy resistance and a cancer neuroscience study investigating the role of individual peripheral neurons in pancreatic cancer (PDAC).

The BCL-2 inhibitor Venetoclax (VEN) in combination with 5-AZA is transforming Acute Myeloid Leukemia (AML) therapy (1), yet clinically relevant biomarkers predicting treatment response are lacking. We identified LSCs as primary targets of 5-AZA/VEN whose elimination determines therapy outcome (2). LSCs from refractory patients displayed perturbed apoptotic dependencies. We therefore developed and validated the flow cytometry-based "MAC-Score," linking the ratio of protein expression of BCL-2, BCL-xL, and MCL-1 in LSCs. MAC-Scoring predicts initial response with a positive predictive value >97%, is associated with increased event-free survival, and outperforms genetic predictors of poor VEN response, including TP53 mutations and complex karyotypes (2). Thus, combinatorial levels of BCL-2-family members in AML-LSCs are a key determinant of therapeutic response.

Although mutations influence the MAC-Score of LSCs, additional factors such as differentiation plasticity can mediate secondary VEN resistance and relapse. We recently identified four distinct AML-LSC types. Quiescent hematopoietic stem cell-like LSCs (HSC-LSCs) exhibit low apoptotic priming, contributing to chemotherapy resistance. Conversely, lineage-primed LSCs maintain stemness while exploiting differentiation programs that alter BCL-2 family expression. During BCL-2 inhibition, LSCs can shift from BCL-2-dependent Lymphoid-Myeloid-Primed-Progenitor LSCs (LMPP-LSCs) toward Megakaryocytic-Erythrocytic-Progenitor LSCs (MEP-LSCs). The latter are primed toward MEP-lineage output and show increased BCL-xL expression, leading to VEN escape. In rare, aggressive cases, patients possess LSCs outside the classical stem-progenitor state, resembling lineage-committed Monocytic/Dendritic precursors (MoDe-LSCs).

Together, AML encompasses heterogeneous LSC types beyond the canonical HSPC-myeloid state. Their lineage priming can adapt plastically under therapeutic pressure, thereby mediating resistance.e also presented a new mathematical model, SCIFER, for inferring stem cell dynamics in normal haemopoiesis and CH (3). We have now applied SCIFER to MDS as it evolves to AML.

Finally, if time permits, we will present a new mouse model that enables study of clonal competition with the sequential introduction of subclonal mutations in blood cells. This should also enable more detailed perturbation studies of clonal competition.

(1) Andreas Trumpp and Simon Haas (2022). Cancer stem cells: The adventurous journey from hematopoietic to leukemic stem cells. Cell. Apr 14; 185(8), 1266-1270

(2) Alexander Waclawiczek*, Aino-Maija Leppä*, Simon Renders* et al. and Andreas Trumpp (2023). Combinatorial BCL-2 family expression in Acute Myeloid Leukemia Stem Cells predicts clinical response to Azacitidine/Venetoclax. Cancer Discovery, June: 13:1408-1427

Abstract No. K2

Endoderm organogenesis from human pluripotent stem cells: some assembly required

Jonathan Brassard[1, 2], *Patrizia Tornabene*[1, 2], *Daniel Kechele*[1, 2], *Lizza Roman*[1, 2], *Michael Helmrath*[1,3], *Aaron Zorn*[1, 2], and *James Wells*[1, 4,*]

[1] Center for Stem Cell and Organoid Medicine, Cincinnati Children's Hospital Medical Center, USA
[2] Division of Developmental Biology, Cincinnati Children's Hospital Medical Center, USA
[3] Division of Pediatric Surgery, Cincinnati Children's Hospital Medical Center, USA
[4] Divisions of Dev. Biology and Endocrinology, Cincinnati Children's Hospital Medical Center, USA

*Presenting author

Successful efforts to direct the differentiation of human embryonic and induced pluripotent stem cells (PSCs) into specific organ cell types in vitro have been guided by studies of embryonic organ development. Based on this, we can now direct the differentiation of human PSCs into gastrointestinal (GI) organoids including esophageal, gastric fundus, gastric antrum, small intestinal and colonic organoids. GI organoids contain complex epithelial structures and diverse cell types that are unique to their representative organ; esophageal organoids develop a stratified squamous epithelium, gastric organoids have a glandular epithelium that secrete digestive enzymes, and acid, and intestinal organoids secrete mucins and hormones and absorb nutrients. However, the first generation of GI organoids were lacking important cell types and functions that limited their utility. As such, we developed a modular approach to incorporate neurons, mesenchyme, vascular cells and immune cells into a variety of different organoids and are now able to engineer additional complexity at will. For example, we have engineered gastrointestinal organoids to have functionally innervated smooth muscle and functional immune cells. This modular approach was used to developed pancreatic organoids that form endocrine islets and a branching ductal network that end in functional acini. PSC-derived organoids are now routinely used to uncover the molecular basis of congenital malformations; to identify new pathologies in patients with diseases including inflammatory bowel diseases, diabetes, and pancreatitis; and to develop and test new therapeutics.

Abstract No. K3

Highly efficient base editing at PCSK9 and normal development in human embryos

Stepan Jerabek[1,2,], Chanju Jung[3], Michelle Kappy[1], Zhao Qiaojin[1], Julie Sung[1], Ning Wang[1], Euihyun Kim[1], Jimin Kim[1], Marcos Iuri Roos Kulmann[4,5], Madeleine Bliss King[6,7], Mitchell John McAndrew[7], Meng Li[1], Sakshi Bhatele[1], Melissa Isado[1], Hong-Su Jang[8,9], Michal Dolezal[2], Michal Dolezal[2], Robert Prosser[1], Shuangyi Xu[1], Gue-Ho Hwang[3], Iva Pichova[2], Jia Xu[10], Diego Martin[10,11], Jae-Sung Woo[9], Sangsu Bae[3], Nathan Treff[10,11,12], Audrone Lapinaite[7],* and *Dieter Egli[1]*

[1] Columbia University, New York, USA; [2] Institute of Organic Chemistry and Biochemistry, Prague, Czech Republic; [3] Seoul National University, Republic of Korea; [4] Institute of Molecular Genetics &[5] Charles University, Prague, Czech Republic; [6] Arizona State University, Tempe, USA; [7] University of California Irvine, USA; [8] Korea University, Seoul, Republic of Korea; [9] Institute for Basic Science, Daejeon, Republic of Korea; [10] Genomic Prediction Inc., North Brunswick, USA; [11] Rutgers University, New Jersey, USA

*Presenting author

Genome-editing technologies enable the induction of defined and targeted genetic lesions, representing valuable tools for investigating DNA repair pathways. This study aims to evaluate the DNA repair outcomes of mismatches and DNA nicks introduced using CRISPR-Cas9 base editors at two targets, PCSK9 and HBG, in human preimplantation embryos.

More than 200 single blastomeres were collected from cleavage-stage human embryos injected with CRISPR-Cas9 ribonucleoprotein (RNP), ABE mRNA, or ABE RNP with HBG and/or PCSK9 sgRNAs. The most efficient editor used, ABE8e-V106W, enabled the modification of all PCSK9 target alleles after its delivery as an RNP into MII oocytes during intracytoplasmic sperm injection, thus consistently reaching 100% editing efficiency. No insertions or deletions were detected by Sanger sequencing at two targeted sites in the analyzed blastomeres. Long-range PCR analysis in over 150 single-cell and multi-cell samples from ABE-treated embryos did not show any on-target large deletions. However, analysis of single-nucleotide polymorphism array data revealed that on-target ABE editing can lead to rare segmental chromosomal changes with a frequency below 2%. Breakage analysis in Cas9-injected embryos with HBG sgRNA and comparison with in silico-predicted off-target sites led to the identification of 11 ABE off-targets. In addition to chromosomal and editing analyses, an abnormal early developmental arrest was observed after ABE mRNA injection into human zygotes. The arrest was caused by sgRNA-independent catalytic activity of the editor. In contrast, human embryos base-edited with ABE RNP at the one-cell stage developed efficiently into high-grade blastocysts, allowing the derivation of nine edited human embryonic stem cell lines, six with an intended homozygous base change in PCSK9.

In summary, base editing demonstrates both high efficiency and precision in preimplantation human embryos; it can cause chromosomal changes, albeit with low frequency, and RNP-mediated editing at fertilization is compatible with normal development to the blastocyst stage.

Turocy, J., Jerabek, S. et al. Asymmetric attrition and secondary chromosome destabilization after double-strand breaks in human embryonic development. Nat Commun 17, 7140 (2026)

Jerabek, S. et al. Efficient base editing and development in human embryos without chromosomal alterations. bioRxiv 2026.05.30.728989 (2026). doi:10.64898/2026.05.30.728989

Abstract No. K4

Engineering human organoids towards next generation regenerative therapeutics

Takanori Takebe[1,2]

[1] Div. Gastroenterol., Hepatol. & Nutrition; & Director Commercial Innovation CuSTOM, Cincinnati Children's Hospital Medical Center, USA
[2] Premium Institute for Human Metaverse Medicine (WPI-PRIMe), University of Osaka & Institute of Science Tokyo, Japan

Pluripotent stem cell and organoid research is entering a new phase. Rather than simply repairing damaged tissues, the next generation of regenerative medicine must learn how to recreate, support, and replace complex organ functions. Our Lab has pioneered human organoid technologies, and advanced in vitro liver systems that reproduce human development, disease, drug responses, and regenerative processes. These discoveries have provided new ways to understand how organs form, fail, and recover. Building on these foundations, our group is now advancing organoid-based regenerative therapeutics toward real-world applications, including scalable organoid manufacturing, bioartificial liver systems, and computational approaches for predicting organ function and drug responses. In this talk, I'd like to summarize the state of art of hepato-biliary-pancreatic organogenesis research and illustrate how fundamental discovery-based science can evolve into potential disease modifying therapeutics, paving a way to challenge the limits of current medicine.

Yamaguchi, H., Yoneyama, Y., Ichimura, K. et al., Takebe T. (2026) Reversal of ACLF and ALF Using Whole Blood Extracorporeal System Combining HLA-Depleted Liver Organoids with Granulocyte-Monocyte Apheresis. Journal of Hepatology, 84, 293–307*

Al-Reza, H. Santangelo, C., Al-Reza, A., Iwasawa, K., Sekiya, S., Glaser, K., Bondoc, A., Merola, J., Takebe T. (2025) Multi-zonal Liver Organoids from Human Pluripotent Stem Cells. Nature, 641, 1258–1267*

Abstract No. K5

Using organoids to interrogate human development and cellular heterogeneity

Jason Spence

University of Michigan, Ann Arbor, USA

Understanding how human organs develop and mature requires experimental systems that faithfully capture the complexity of human tissues. Human pluripotent stem cell-derived and primary tissue-derived organoids have emerged as powerful platforms for modeling organ development, enabling researchers to study cell fate decisions, tissue patterning, and cellular heterogeneity in a human context. Our group has developed organoid systems for the human gastrointestinal tract and lung, and leverages these models alongside primary human tissue atlases to dissect the cellular and molecular mechanisms governing human organ development and maturation.

Our recent work combines single-nucleus RNA-sequencing, spatial transcriptomics, and organoid-based functional studies to characterize the cellular landscape of the early postnatal human lung. By profiling distal lung tissue from birth through the first two years of life, this work identified previously unappreciated heterogeneity within the alveolar epithelium, including functionally distinct states in the stem cell of the alveolus - the alveolar type 2 (AT2) cell. We observe that these cell states occupy discrete cellular niches with specific mesenchymal partners. Using AT2 organoid models, functional screens identified signaling cues that regulate these cell states, revealing roles for inflammatory signaling shaping AT2 cell states. Importantly, these AT2 cell states are correlated with clinical interventions in patients and are disrupted in pediatric lung disease, suggesting that the balance between specialized epithelial populations is critical for postnatal lung homeostasis. Together, this work illustrates how integrating high-resolution tissue atlases with organoid-based experimental models can reveal fundamental principles of human development and identify cellular mechanisms relevant to disease.

Presidential Symposium lectures: PS1 – PS4

GSCN Presidential Invite

PS1 Stem cells, embryos and embryo models: from science to ethical concerns
Janet Rossant

GSCN 2026 Young Investigator Award

PS2 Building towards understanding: from embryo models to principles of development (& back)
Jesse V. Veenvliet

GSCN 2026 Hilde Mangold Award

PS3 Studying diabetes with engineered stem cell islet organoids
Maike Sander

GSCN Publication of the Year 2025 - 2026 Award

PS4 Pluripotent stem-cell-based screening uncovers sildenafil as a mitochondrial disease therapy
Annika Zink

Abstract No. PS1: GSCN Presidential Invite

Stem cells, embryos and embryo models: from science to ethical concerns

Janet Rossant

The Hospital for Sick Children, University of Toronto, Canada

Understanding the processes and mechanisms underlying early human embryo development has potential for insights into important clinical issues such as early pregnancy loss, origins of congenital anomalies and developmental origins of adult disease, as well as fundamental insights into human biology. Direct analysis of human embryo material can be informative, but access is limited. In my research I have been able to isolate stem cells from different lineages of the mouse blastocyst that can be combined to model aspects of early development. Extension of these studies into human stem cell-based embryo models is providing accessible, scalable alternatives to studying the human embryo itself. These models can mimic the entire embryo or provide insight into specific aspects of development. Ethical concerns with stem cell models largely focus on the more complex integrated models of the early human embryo. However, future developments in all model systems may allow progress towards organ primordia with morphological similarities to human fetal material. Ongoing public engagement and ethical debate will be needed to set the limits of such research.

Abstract No. PS2: GSCN 2026 Young Investigator Award

Building towards understanding: from embryo models to principles of development (& back)

Jesse V. Veenvliet[1, 2, *], and *Team Stembryo*[#1]

[1] Max Planck Institute of Molecular Cell Biology and Genetics, Dresden
[2] Cluster of Excellence Physics of Life, TU Dresden & Center for Systems Biology, Dresden

*Presenting author

Embryo development is shaped by intrinsic factors like gene-regulatory networks (GRNs), as well as the cellular environment. The latter imposes mechanochemical, metabolic and geometrical constraints. How such boundary conditions contribute to the robustness of the formation of the mammalian body axes, a pivotal coordinate system for the future body plan, is a fundamental outstanding question. While the underlying GRNs are well-studied, how specific inputs from the physiological embryo microenvironment contribute to the robustness of axial patterning and morphogenesis remains largely elusive.This knowledge gap stems from the complexity of in vivo development, where genetic, mechanical, and biochemical processes are tightly coupled through feedbacks, and inherent constraints limit the range of accessible morphogenetic states (i.e., the developmental morphospace). Together, this hinders our ability to systematically and quantitatively dissect the role of specific, non-genetic, inputs. These limitations are lifted by stem-cell-based embryo models (SCBEMs, or "stembryos"), such as gastruloids and the trunk-like-structures we established, which combine scalability, modularity, and ease of measurement and manipulation with in vivo-like body axes formation. With my interdisciplinary team and in collaborations, we use live imaging, omics, genetics, biophysics, and data science, establishing experimental and computational frameworks for quantitative, multi-modal, multi-scale analysis of mouse and human SCBEMs. This enables a statistical, causal, and mechanistic understanding of how physiological constraints govern the robustness of mammalian body axes formation and provides fundamental biological insights that in turn allow us to develop more embryo-like SCBEMs. By combining quantitative mapping of the in vitro morphospace with targeted, mechanistic studies of the influence of metabolic and mechanochemical constraints, we address a fundamental outstanding question:

How do cells integrate and communicate with their dynamic physiological microenvironment to robustly build the body plan?

[#] *Alba Villaronga-Luque, Marc Trani-Bustos, Ryan Savill, Deniz Conkar, Lisa Bauer, Simone Gasparato, Yonit Maroudas-Sacks, Alexandra Schauer*

Abstract No. PS3: GSCN 2026 Hilde Mangold Award

Studying diabetes with engineered stem cell islet organoids

Han Zhu[1], *Gaowei Wang*[1], *Yesl Jun*[1], *Kim-Vy Nguyen-Ngoc*[1], *Somesh Sai*[2], *Jenna Kovsky*[1], *Michael Schlichting*[1, 2], *Medhavi Mallick*[1], and *Maike Sander*[1, 2,*]

[1] Department of Pediatrics, Pediatric Diabetes Research Center, UCSD, La Jolla, USA
[2] Max Delbrück Center, Berlin

*Presenting author

Human pluripotent stem cell-derived islet cells represent a valuable resource for diabetes research and cell therapies due to their unlimited supply. Studies have demonstrated the successful generation of glucose-responsive insulin-secreting pseudo-islets from stem cells (SC-islets) in vitro. SC-islets have now progressed to clinical trials for the treatment of type 1 diabetes, marking a significant step toward their therapeutic application. These SC-islets contain a heterogeneous mix of cells, including insulin-secreting beta cells, along with other endocrine cell types found in primary pancreatic islets. However, functional differences between SC-beta cells and primary human beta cells remain, limiting the full potential of SC-islets as a disease model.

To address these challenges, my laboratory has mapped gene regulatory networks of SC-islets and primary human islets, identifying key factors that could enhance the maturation and function of SC-beta cells in vitro. We have also developed an islet organoid model that incorporates vascular and stromal cells, integrating it into a microfluidic platform with perfused human microvessels. Notably, vascularization improved SC-beta cell function, underscoring the critical role of the islet niche in beta cell maturation. This advanced SC-islet organoid system provides a powerful platform for studying diabetes mechanisms and evaluating potential therapeutics.

Zhu, H., et al., Sander, M. (2023) Understanding cell fate acquisition in stem cell-derived pancreatic islets using single-cell multiome-inferred regulomes, Developmental Cell, 58: 727-743
Jun, Y., et al., Sander, M. (2025) Engineered vasculature induces functional maturation of pluripotent stem cell-derived islet organoids. Developmental Cell, 60: 2455–24691

Abstract No. PS4: GSCN Publication of the Year 2025 - 2026 Award

Pluripotent stem-cell-based screening uncovers sildenafil as a mitochondrial disease therapy

Annika Zink[1,] , Annika Wittich[2], Dao-Fu Dai[3], Marie-Thérèse Henke[4], Giulia Perdrotti[5], Sonja Heiduschka[1], Tancredi Massimo Pentimalli[6], Sofia Notopoulou[7], Caleb Jerred[1], Marta Suarez Cubero[8], Spyros Petrakis[7], Anu Suomalainen[9], Agnieszka Rybak-Wolf[6], Nikolaus Rajewsky[6], Frank Edenhofer[8], Pawel Lisowski[6], Antonio del Sol[10], Emanuela Bottani[5], Ole Pless[2], Markus Schuelke[4],* and *Alessandro Prigione[1]*

[1] University Hospital Duesseldorf, Heinrich Heine University
[2] Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Hamburg
[3] Johns Hopkins University School of Medicine, Baltimore, USA
[4] Charité - Universitätsmedizin Berlin
[5] University of Verona, Italy
[6] Berlin Institute of Medical Systems Biology (BIMSB), Max Delbrück Center, Berlin
[7] Institute of Applied Biosciences (INAB), Thessaloniki, Greece
[8] University of Innsbruck, Austria
[9] University of Helsinki, Finland
[10] University of Luxembourg

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Leigh syndrome (LS) is a severe and rare genetic form of mitochondrial disease that causes psychomotor regression and acute metabolic crises. Most individuals with LS have defects in mitochondrial energy production, resulting from pathogenic gene variants in over 100 genes in the nuclear DNA (e.g. SURF1) or mitochondrial DNA (e.g. MT-ATP6), involved in oxidative phosphorylation (OXPHOS). To accelerate drug discovery for LS, we employed a drug repurposing approach using induced pluripotent stem cell (iPSC)-derived neural progenitor cells (NPCs) from patients with LS to screen a library of 5,632 compounds that are potentially repurposable. We identified phosphodiesterase 5 inhibitors (PDE5i) as leads capable of normalizing mitochondrial membrane potential in LS NPCs. Among PDE5i, we prioritized sildenafil due to its safety profile in children and adults. Sildenafil was shown to restore key signaling pathways involved in nervous system development, promote neurite outgrowth in LS neurons, and normalize aberrant calcium responses in LS brain organoids under metabolic stress. Sildenafil extended lifespan in a mouse model of LS and rescued both metabolic and neurological phenotypes. Furthermore, sildenafil showed acceptable blood-brain barrier permeability, as demonstrated in an iPSC-derived model. Notably, chronic off-label treatment on an individual basis with sildenafil in six LS patients was well tolerated and associated with improved motor function and increased resilience to metabolic crises. These findings underscore the promise of iPSC-based drug discovery for rare, currently untreatable disorders and support sildenafil as a potential therapeutic candidate for LS.

Zink, A. et al. 2026, Pluripotent stem-cell-based screening uncovers sildenafil as a mitochondrial disease therapy, Cell, 189(6):1656-1679.e42. doi: 10.1016/j.cell.2026.02.008

Selected presentations

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Abstract No. T01

Super-SOX-mediated generation of pluripotent stem cells with enhanced developmental potential

Hans R. Schöler

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To date, the generation of iPS cells has been established for only a few model species; pluripotent stem cell lines exhibit inconsistent developmental potential. By exchanging structural elements between Sox2 and Sox17, we have developed a chimeric super-SOX factor[1], Sox2-17, which improved iPSC generation in five tested species: mouse, human, cynomolgus monkey, cow, and pig. Replacing alanine with valine at the interface between Sox2 and Oct4 resulted in a gain of function by stabilizing Sox2/Oct4 dimerization at the DNA, which enabled the generation of high-quality OSKM iPS cells capable of supporting the development of healthy mice derived entirely from iPS cells. Sox2/Oct4 dimerization proved to be a central driver of naive pluripotency. Temporary overexpression of Sox+Klf4 restored dimerization and enhanced the developmental potential of pluripotent stem cells across species, thereby providing a universal method for the naive reset in mammals. In this presentation, I will also describe a number of application areas in which Super-Sox could bring about—or has already brought about—significant progress, such as the rapid characterization of human oogonium-like cells.

[1] *MacCarthy CM, Wu G, et al. , Schöler HR, Velychko S (2024), Highly cooperative chimeric super-SOX induces naive pluripotency across species, Cell Stem Cell, 31, 127 - 147*

Abstract No. T02/P099

Mosaic gastruloids reveal a temporal restriction for developmental cell competition

Joshua D. Frenster[1, 2,*] , *Stephen Babin*[1], *Pablo Casani-Galdon*[1], *Joel Josende Garcia*[1], and *Alfonso Martinez Arias*[1]

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*Presenting author

The selective elimination of suboptimal cells is critical for maintaining developmental integrity during early mammalian embryogenesis. Toward this goal, cells undergo **Cell Competition**, a **non-autonomous quality control** in which "winner" cells outcompete viable but suboptimal "loser" cells based on relative fitness differences. Here, we use **mosaic 3D mouse gastruloids** to investigate cell competition dynamics. Introducing just two Trp53-deficient supercompetitor cells per gastruloid suffices to impair growth in neighboring wild-type cells through mitochondrial **apoptosis**. Competition is tightly restricted to a developmental transition-stage between primed pluripotency and early gastrulation and involves gene regulatory networks of pluripotency-exit. Heterochronic gastruloids from developmental stage-shifted cells, EpiGastruloids, and dynamic p53-degrons reveal that both winners and losers must reside within this permissive stage, during which acute relative p53 protein levels determine competitive outcomes. These findings advance our understanding of cell fitness evaluation and establish gastruloids as a powerful 3D-model for investigating developmental stage-specific cell competition in mammalian embryogenesis.

Abstract No. T03

HERVHLin coordinates LIN28A/let-7 activity to preserve genome stability during early human development

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Following embryonic genome activation (EGA) transposable elements become reactivated in well-defined transcriptional waves. The initial wave involves the activation of phylogenetically Young (<7MY old), potentially damaging actively transposing retrotransposable elements (REs), followed by older transpositionally inactive REs, including the human endogenous retrovirus H (HERVH). HERVHHigh cells represent a naturally occurring cell population in human pluripotent stem cell cultures (eFORM), which are the closest mimic of the inner cell mass (ICM). Increased retrotransposition of Young REs in HERVH-depleted human embryonic stem cells suggests that HERVH is a suppressor of retrotransposing elements. Based on the opposing expression to Young REs, we identified a subgroup of HERVH (N=101) with a tandemly repeated binding motif for LIN28 (referred to here as HERVHLin) that, as expected, strongly bind this conserved pluripotency factor and inhibitor of let-7 microRNA biogenesis. Since let-7 suppresses retrotransposition of LINE-1, knock-out clones of HERVHLin show increased LINE-1 activity, which can be restored by expressing a let-7 mimic or a construct containing the motif alone. HERVHLin modulates intracellular compartmentalization of LIN28, modulating an evolutionarily conserved pluripotency regulatory pathway and integrating let-7 into the genome protection programme of the human embryo. This co-opted HERVH event regulates the LIN28/let-7 axis, promotes genomic stability in human pluripotent stem cells and acts as a critical first line of defence for genome integrity during early human embryogenesis.

Abstract No. T04

HERVH-derived boundary elements shape 3D genome architecture in eFORM human stem pluripotent cells

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eFORM (embryo-forming) cells represent a transient, HERVH-high pluripotent state developmentally positioned between naïve and primed pluripotency and have been proposed as an in vitro counterpart of the human inner cell mass (1). Compared with primed human embryonic stem cells, eFORM cells retain an expanded repertoire of HERVH-derived topologically associating domain (TAD) boundaries. By integrating Hi-C with quantitative proteomics across primed and eFORM states, we identify 106 HERVH loci that function as robust TAD boundaries specifically in eFORM cells. Interestingly, these boundaries are absent in primed cells despite their comparable transcriptional activity, suggesting that HERVH transcription alone is not sufficient to drive boundary formation, a finding that contrasts with a previous study (2).Among the eFORM-specific TAD-forming loci is ESRG (Embryonic Stem Cell Related Gene), one of the most highly transcribed primate-specific long non-coding RNAs in pluripotent stem cells (3) and a widely used marker of pluripotency (4), although its functional contribution has remained unresolved (3, 5). Our findings suggest that HERVH-derived elements such as ESRG act not merely as transcriptional markers but as structural organizers of the pluripotent genome. Proteomic profiling further reveals coordinated remodeling of R-loop regulation, loop-anchoring complexes, and epigenetic regulators, consistent with a nuclear configuration that couples developmental plasticity with enhanced genome surveillance.

Collectively, these data define eFORM cells as a genomically distinct, inner-cell-mass-like pluripotent state characterized by HERVH-associated 3D genome organization, reinforced genome stability mechanisms, and structural features that may underlie early human developmental competence.

Z. Izsvák, J. Ma, M. Singh, L. D. Hurst, Co-option of an endogenous retrovirus (LTR7-HERVH) in early human embryogenesis: becoming useful and going unnoticed. Mob DNA 16, 27 (2025).

Y. Zhang, et al., Transcriptionally active HERV-H retrotransposons demarcate topologically associating domains in human pluripotent stem cells. Nat Genet 51, 1380–1388 (2019).

Abstract No. T05

A multi-individual iPSC resource from five non-human primate species for comparative biology and in vitro developmental studies

Vera Zywitza[1, 2, *], *Daniil Kachkin*[3], *Zeynep Hacer Ipek*[2], *Norman Krüger*[2], *Jeong-Eun Lee*[2, 3], *Marula Mathew*[3], *Antonella Molinari*[2, 4], *Schrade Lisa*[1], *Thomas B. Hildebrandt*[1, 3], *Katja Nowick*[3], and *Sebastian Diecke*[2]

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Induced pluripotent stem cells (iPSCs) from non-human primates (NHPs) provide a powerful platform for comparative and translational research, enabling the investigation of evolutionary, developmental, and biomedical questions in closely related species. Here, we present a collection of 12 iPSC lines derived from five primate species: bonobo (*Pan paniscus*), chimpanzee (*Pan troglodytes*), gorilla (*Gorilla gorilla*), orangutan (*Pongo pygmaeus*), and rhesus macaque (*Macaca mulatta*). Importantly, each species is represented by at least two independent individuals, allowing the assessment of both interspecies and intraspecies variability.

This panel of NHP-iPSC lines constitutes a valuable resource for studying the molecular basis of primate evolution, species-specific traits, and human disease susceptibility. Due to their close phylogenetic relationship to humans, NHP-iPSCs enable comparative analyses of gene regulation, cellular differentiation, and developmental processes in a controlled in vitro system. The inclusion of multiple individuals per species further increases the robustness of comparative studies by accounting for natural genetic variation.

Importantly, in vivo studies in non-human primates are highly restricted due to ethical considerations, limited accessibility, and the endangered status of several great ape species. Access to primary tissues is rare, and embryonic material for investigating developmental processes is largely unavailable. As a result, NHP-iPSCs provide a unique and ethically sustainable alternative for modeling early development and cell fate decisions in vitro. These cell lines, therefore, represent an essential resource for addressing questions that cannot be studied directly in humans or non-human primates in vivo.

Overall, this diverse NHP-iPSC collection expands the experimental toolkit for comparative primate biology and establishes a foundation for future studies in evolution, development, and disease-related mechanisms.

Abstract No. T06

Metabolic regulation of aged hematopoietic stem and multipotent progenitor cells

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ETH Zurich, Switzerland

Hematopoietic stem cells (HSCs) can respond to physiological and pathological challenges that shape their function throughout life. Understanding how HSCs adapt to tissue injury, metabolic perturbations, and aging is essential for uncovering mechanisms that regulate tissue repair and hematopoietic maintenance.

Myocardial infarction (MI) is a major global health challenge. Although emergency hematopoiesis supports tissue repair after MI, excessive myelopoiesis promotes inflammation, adverse cardiac remodeling, and impaired function. Using human sternal bone marrow (BM) samples from more than 150 cardiac surgery patients, including 49 with preserved cardiac function, we demonstrate that MI induces transcriptional and functional alterations in HSCs. Lineage tracing reveals that HSCs contribute to inflammatory myeloid cells infiltrating the injured heart, while pharmacological maintenance of HSC quiescence with the vitamin A metabolite 4-oxo-retinoic acid reduces inflammatory myelopoiesis, improves cardiac remodeling, and preserves long-term cardiac function. We are now translating these findings as a new therapeutic strategy for patients with MI.

Metabolic regulation is a critical determinant of HSC function, yet the metabolic landscape of human HSCs remains poorly defined. We established low-input targeted metabolomics and untargeted lipidomics approaches enabling integrated metabolomic, lipidomic, and transcriptomic profiling of human HSCs across differentiation, aging, and acute myeloid leukemia (AML). We identify choline metabolism as a hallmark of healthy HSCs that declines with aging and AML, and demonstrate that choline supplementation promotes lipid biosynthesis and enhances stem cell function.

Finally, integrated transcriptomic, epigenomic, metabolomic, lipidomic, and functional analyses of HSCs and MPP1–6 populations from young and aged mice reveal distinct age-associated adaptations across the hematopoietic hierarchy. Notably, MPP6 emerges as a unique progenitor population with a dormant, lymphoid-associated identity maintained during aging, providing new insights into mechanisms preserving hematopoietic function.

Abstract No. T07/P002

The development of simultaneous single-cell tRNA and mRNA profiling reveals dynamic tRNA programs in human hematopoiesis

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*Presenting author

Hematopoiesis is the tightly regulated regeneration of all blood cell types life-long. Transfer RNAs (tRNAs) play a central role in translation by decoding mRNA codons into amino acids, thereby shaping proteomic output. While tRNA abundance varies across tissues, its dynamics and functional relevance during hematopoietic differentiation remain largely unexplored.

We aimed to map tRNA expression and processing at single-cell resolution in human hematopoiesis and to determine how tRNA dynamics are associated with molecular programs of cell identity and differentiation trajectories.

We developed the first single-cell simultaneous tRNA and mRNA sequencing approach (sc-STM-seq), a scalable, polyadenylation-independent high-throughput method that captures full-length tRNAs alongside mRNAs in individual cells. We applied sc-STM-seq to human bone marrow mononuclear cells from healthy donors and performed integrative bioinformatic analyses.

sc-STM-seq enabled robust detection of full-length tRNAs and mRNA transcriptomes across thousands of single cells, with strong concordance to bulk tRNA-seq on prospectively isolated cell populations. We identified cell type-specific tRNA expression patterns and differential tRNA splicing across hematopoietic populations. During early hematopoietic stem and progenitor cell (HSPC) differentiation, tRNA expression exhibited dynamic, lineage-associated changes, including stemness-associated tRNAs (e.g. tRNA-SeC-TCA, tRNA-Gln-CTG) and differentiation-associated tRNAs (e.g. tRNA-Asp-GTC, tRNA-Lys-TTT). Extending these analyses to global differentiation trajectories confirmed lineage-specific and trajectory-dependent tRNA regulation, with distinct dynamics across monocytic, erythroid, B cell, and plasmacytoid dendritic cell lineages. Notably, tRNA-Asp-GTC was strongly associated with monocytic differentiation. Furthermore, tRNA expression profiles alone were sufficient to distinguish major hematopoietic cell types, particularly HSPCs, indicating that tRNA landscapes contribute to cellular identity.

Our study provides the first comprehensive single-cell atlas of tRNA expression in human hematopoiesis. We demonstrate that tRNA abundance and processing are dynamically regulated during differentiation and contribute to cellular heterogeneity and identity. These findings establish tRNA regulation as a previously underappreciated layer of gene expression control in blood cell development.

Abstract No. T08

Identification of a deeply dormant CD150neg hematopoietic stem cell population

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The Slam family marker CD150 has been widely used for the prospective isolation of hematopoietic stem cells (HSCs) for over two decades. In this study, we identify a rare population of CD150neg EPCRpos non-Slam-expressing HSCs (nSlam-HSCs) that exhibit all functional and molecular hallmarks of bona fide HSCs including multipotency, long-term repopulation, self-renewal and dormancy. Functionally, nSlam-HSCs sustain serial reconstitution of erythroid, megakaryocytic, myeloid and especially lymphoid lineages for at least 48 weeks, substantially exceeding the current 16-week gold standard used for HSC definition. Additionally, nSlam-HSCs can be successfully transplanted at the single-cell level at a level comparable to that of conventional CD150pos EPCRpos Slam-expressing HSCs (Slam-HSCs).

A distinguishing characteristic of nSlam-HSCs is their superior capacity to remain deeply dormant compared to Slam-HSCs. Remarkably, using the Scl-tTA; H2B-GFP mouse model to identify label-retaining cells (LRCs) after more than 200 days, we observed a substantially higher proportion of dormant LRCs among nSlam-HSCs (10 – 15%) compared to Slam-HSCs (2 – 3%). Additionally, while active Slam-HSCs (GFP– non-LRC) lost their stem cell activity and failed to engraft in transplantation, robust long-term multi-lineage reconstitution was still detected in active nSlam-HSCs. Consistent with their enhanced dormancy, nSlam-HSCs display reduced sensitivity to cell cycle activation induced by external stressors such as poly I:C, leading to increased resistance to proliferation-induced exhaustion.

Collectively, these findings refine the current understanding of HSC heterogeneity by defining a previously unappreciated nSlam-HSC population characterized by an exceptionally dormant phenotype. This work highlights the complexity of intra-organismal HSC diversity and its implications for stem cell maintenance, lineage differentiation and dormancy.

Abstract No. T09

Multiscale biological interactions define clinical trajectories in acute myeloid leukemia

Jan Barinka[1,], Sarah Gräßle[1], Magdalena Pajonk[2], Rosa Allesøe[3], Stefanos Bamopoulos[4], Maximilian Mönnig[2], Caroline Röthemeier[1], Lea Jopp-Saile[5], Dominik Vonficht[5], Eleni Besiridou[2], Jana Ihlow[1], Jan Braune[4], Evi Vlachou[6], Sergi Beneyto-Calabuig[3], Michael Kardorff[2], Selina Neunhäuser[2], Vincent Fregona[1], Simone Feurstein[2], Adriane Halik[1], Helen George[2], Judith Zaugg[6], Daniel Hübschmann[7], Michael Hundemer[2], Christoph Lutz[2], Andreas Trumpp[5], Lars Bullinger[4], Ulrich Keller[4], Carsten Müller-Tidow[2], Jörg Westermann[4], Frederik Damm[4], Jan Krönke[8], Tim Sauer[2], Lars Velten[3], Simon Raffel[2],* and *Simon Haas[1]*

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Cancer is characterized by complex interactions across genetic, cellular, and microenvironmental scales. However, a quantitative understanding of how these interactions shape clinical trajectories remains limited. Here, we present a multi-scale single-cell dataset from 184 treatment-naïve acute myeloid leukemia (AML) patients spanning all major genetic subtypes, together with an analytical framework to dissect interactions across biological scales. We show that distinct clinical outcomes are encoded by specific cross-scale, cross-compartment interactions present at diagnosis: response to induction therapy is governed by interactions between genetic alterations and leukemic differentiation state; relapse following chemotherapy is associated with non-genetic programs linked to metabolism; and relapse after allogeneic stem cell transplantation is driven by interactions between the immune microenvironment and residual healthy hematopoiesis. Together, our study provides a framework to resolve intra- and inter-patient heterogeneity in cancer and supports a model in which clinical trajectories in AML emerge from defined interactions across biological scales.

Abstract No. T10/P007

Molecular characterization and functional interrogation of dormant cancer stem cells in JAK2V617F-driven myeloproliferative neoplasms

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Polycythemia vera (PV) is a myeloproliferative neoplasm driven by hematopoietic stem cell (HSC) clones carrying activating JAK2 mutations, most commonly JAK2V617F, which cause constitutive JAK–STAT signaling and excessive blood cell production. Although JAK inhibitors and IFN-α can control symptoms, relapses after treatment discontinuation is common, suggesting persistence of disease-propagating cells.

Here, we focus on the role of hematopoietic stem cell states in sustaining PV. We use a JAK2V617F mouse model combined with an inducible H2B-GFP label-retention system to identify and isolate dormant mutant HSCs in vivo. This system distinguishes actively cycling stem cells, which dilute GFP during proliferation, from quiescent, long-lived HSCs that retain the label. This allows isolation of dormant mutant HSCs and direct comparison with actively cycling mutant counterparts.

We show that dormant, label-retaining mutant HSCs persist and remain identifiable for up to five months during disease progression, despite the pro-proliferative JAK2V617F mutation. Notably, these cells are resistant to the JAK2 inhibitor Fedratinib and IFN-α treatment. Transplantation experiments reveal that only dormant, label-retaining cells can re-initiate disease, identifying them as key drivers of disease propagation and likely reservoirs of therapy resistance.

Molecular profiling reveals that label-retaining mutant HSCs adopt a distinct transcriptional and epigenetic state compared with active mutant counterparts, with altered inflammatory and metabolic pathways. Furthermore, combining low-dose IFN-α with the Fedratinib synergistically reduces the dormant HSC compartment, identifying a potential therapeutic strategy to target these therapy resistant cells.

Together, our results identify a dormant mutant HSC population as the central reservoir of PV persistence and relapse, highlighting these cells as a critical target for therapies.

Abstract No. T11

Combining pooled single-cell screens and deep learning to identify phenotypes driven by oncogenes

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Cancer cells hijack developmental and stem cell programs to acquire the plasticity and adaptability that drive tumor growth and therapy resistance. In colorectal cancer (CRC), oncogenic mutations reshape these transcriptional programs, yet how individual driver mutations rewire cell states—and how this relates to clinical outcomes—remains poorly understood. I will discuss an approach to use pooled single-cell transcriptomic screen with single cell readout to identify oncogene-driven transcriptional programs and phenotypes. Specifically, we developed a barcoded library of oncogenic variants and transduced it as pool to cells, and performed single cell RNA-sequencing. Using an interpretable variational autoencoder-based factor model, we resolve ten conserved oncogene-driven transcriptional modules that capture core cancer cell states, including stem-like plasticity, inflammatory signaling, replicative stress, and epithelial-to-mesenchymal transition. We find that engagement of these modules is context-dependent, shaped by interactions between specific oncogenic drivers and the genetic background of the cell of origin. Applying these modules to patient tumor data, we show that module activity stratifies CRC patients into high- and low-risk groups, improving prediction of relapse-free survival beyond current classification schemes. Together, our findings provide a systematic, functional link between oncogenic signaling, stem cell-like transcriptional states, and clinical outcome, offering a generalizable framework for understanding how cancer cells co-opt stemness and plasticity programs, and a new lens for module-based patient stratification in precision oncology.

Hollek, V., Böhning, F., Florez Vargas, C. et al. Pooled single-cell screen in colorectal cancer defines transcriptional modules linked to oncogenes. Mol Syst Biol 22, 435–460 (2026). https://doi.org/10.1038/s44320-025-00186-2

Abstract No. T12/P012

Slow genes are soft genes: lineage memory and perturbation sensitivity share a common origin

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Isogenic cells in a common environment differ substantially in gene expression, and some of that variation is not transient noise but is inherited: sister cells resemble each other more than unrelated cells, sometimes for many divisions. Genes carrying such memory relax slowly relative to cell division, whereas most genes fluctuate within a fraction of a division. What distinguishes these genes functionally remains largely unresolved.

Across multiple lineage-barcoded single-cell RNA-seq datasets, four independent memory-callers (Coral, GEMLI, PowerSeek, and our own sister-pair concordance estimator) converged on a shared set of memory genes that cannot solely be explained by confounders such as expression level. Comparing these genes against perturbation data spanning hundreds to thousands of gene knockouts, we found that memory genes respond systematically more strongly than non-memory genes.

We propose that this follows from linear response theory. How long a gene's expression stays correlated with its own past state, and how strongly it responds to a sustained perturbation, are both set by its relaxation rate. That is, memory and perturbation-sensitivity are two readouts of the same quantity. For a stable Jacobian (the linearized gene-regulatory dynamics at steady state), the per-gene response ratio between memory and non-memory genes reduces to the ratio of their relaxation times, providing a parameter-free prediction that we test against the observed effect size.

Memory genes have modestly longer mRNA half-lives than non-memory genes, but the distributions overlap, and half-lives are short relative to the timescale of memory. By estimating relaxation and degradation rates in the same cells, we ask whether memory genes relax more slowly than their turnover and dilution allow, implicating self-reinforcing regulation rather than molecular stability. Finally, we test whether heritable expression is concentrated in a few collective modes and whether perturbation responses align with them, which would indicate an underlying shared network structure.

Goyal et al., 2023, Diverse clonal fates emerge upon drug treatment of homogeneous cancer cells, Nature
Filipczyk, Marr*, Hastreiter* et al., 2015, Network plasticity of pluripotency transcription factors in embryonic stem cells, Nature cell biology*

Abstract No. T13

Emergent cell-type order in epithelia: a hallmark of stem cell fate characteristics in homeostasis?

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Determining whether stem cells commit irreversibly to differentiation at division, or instead fluctuate reversibly through primed states ("licensing"), remains a major challenge in stem cell biology. Classical genetic lineage tracing can struggle to distinguish these scenarios in living homeostatic tissue, while direct live imaging is technically demanding. This raises the question of whether fixed-tissue data contain underused information about the underlying fate dynamics. Here, I test this idea using a stochastic lattice model of a self-renewing epithelial sheet -- representing, for example basal epidermis or mammary luminal epithelium -- in which cell division, local juxtacrine signalling and cell-fate choices interact. The model predicts distinct spatial signatures for different biological mechanisms. If fate is committed at division, symmetric divisions drive large patches of like cell types, unless neighbour signalling is laterally inhibiting. If fate choice is reversible and division-independent, spatial order appears only above a critical signalling strength: lateral induction produces macroscopic patches as well, whereas strong lateral inhibition can generate alternating patterns when symmetric divisions are rare. These results suggest that quantitative analysis of marker-defined spatial patterns in fixed samples could complement lineage tracing and live imaging, providing a practical route toward inferring self-renewal strategies and signalling modes in epithelial tissues.

Philip Greulich (2024), Emergent order in epithelial sheets by interplay of cell divisions and cell fate regulation. PLoS Comput Biol 20: e1012465.

Abstract No. T14

Epigenetic fidelity of hiPSC-derived T cell progenitors: accurate remodeling and aberrant DNA methylation imprints

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Generation of T cell subsets from hiPSCs has advanced greatly in recent years and offers great potential for therapeutic applications as a renewable source for adoptive T cell therapy. Yet, current protocols are still limited and mainly confined to selected functional subsets. Furthermore, it remains unclear how well hiPSC derived T cell progenitors compare to their physiological thymic counterparts, especially concerning their epigenetic fidelity.

Using two feeder-free protocols and five distinct hiPSC lines with different genetic backgrounds, we differentiated hiPSCs up to the CD4+ CD8αβ+ double positive T progenitor stage. We generated DNA methylation (DNAmeth) profiles of various sorted T progenitor populations, including hiPSC-derived CD34+ hematopoietic stem cell (HSC) intermediaries and paired these with differentiated cord-blood derived HSCs and ex vivo isolated primary human thymocytes for comparative assessment of in vitro-generated and ex vivo-derived T progenitors.

We reveal that the modes of hiPSC-HSCs generation are crucial for the efficiency and yield of T cell progenitor generation. On the epigenetic level, we show that a majority of important, physiological epigenetic remodeling events, that take place during thymic T cell development, are successfully recapitulated in the hiPSC-based in vitro system. This faithful remodeling was, however, overshadowed by an overall distorted DNAmeth signature in hiPSC-derived cells, which could be attributed to two parallel epigenetic imprints: a persisting hiPSC-inherent signature, mainly consisting of a global hypomethylation with limited impact on transcriptional profile, and a culture-induced imprint resulting in promoter-associated hypermethylation at relevant T cell differentiation genes impairing gene expression.

Our study demonstrates the strength of DNAmeth profiling to assess capacities and shortcomings of hiPSC-based T cell differentiation models, and can guide future improvements towards physiologically accurate, clinically relevant T cell products.

Abstract No. T15

SON maintains innate immune homeostasis in HSCs via splicing and retroelement control

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Hematopoietic stem cells (HSCs) maintain blood homeostasis through balanced self-renewal and differentiation. Chronic innate immune activation impairs HSC function in aging and disease, yet the intrinsic mechanisms that suppress aberrant inflammatory signaling remain poorly understood. We previously identified an m6A-SON axis governing HSC fate and inflammation control [1,2]. SON is a nuclear speckle component essential for RNA processing, and heterozygous SON loss-of-function mutations cause ZTTK syndrome, presenting with developmental delay and bone marrow failure.

Using conditional Mx1-cre Son knockout (cKO) mice, we demonstrate that SON loss severely disrupts hematopoiesis: bone marrow cellularity is reduced, platelet counts fall, myeloid progenitors are depleted, and phenotypic HSCs show an early differentiation block. Mechanistically, SON loss drives a twofold increase in double-stranded RNA, activating interferon-stimulated gene signatures and derepressing endogenous retroelements. Single-cell long-read sequencing, integrated with transcriptomic and chromatin accessibility profiling, enabled high-resolution analysis of phenotype-specific alternative splicing dynamics during HSC lineage commitment and improved definition of transposable element expression programs. This revealed that ISG induction is most pronounced along the HSC-to-megakaryocyte lineage, coinciding with increased retroelement chromatin accessibility. SON loss also alters HSC symmetric division patterns and causes widespread splicing abnormalities. Importantly, reverse transcriptase inhibitor treatment rescued SON cKO HSC function, establishing retroelement de-repression as a therapeutically actionable mechanism.

These findings establish SON as a key guardian of innate immune homeostasis in HSCs through splicing control and retroelement repression, with implications for bone marrow failure and aging.

Luo H, Cortés-López M et al. Cell Stem Cell, 2023. DOI: 10.1016/j.stem.2023.11.006
Cheng Y, Luo H, Izzo F et al. Cell Rep, 2019. DOI: 10.1016/j.celrep.2019.07.032

Abstract No. T16

Human pluripotent stem cell therapies to the heart and beyond: current status and challenges

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The clinical translation of human pluripotent stem cell (hPSC)-based therapies has advanced substantially in recent years. While directed derivation and production of organ-specific functional cell types from hPSCs is advancing rapidly, the frontier of challenges is shifting toward efficient engraftment and functional integration of transplanted cells in the diseased organ. This talk will provide insights into the state of the art in heart repair and examples from other organs, including the entire process: from cell production to transplantation; challenges in monitoring cell engraftment and functional integration; and aspects of allogeneic versus autologous therapy approaches.

Cyrys K, Zweigerdt R. Scalable process technologies for human pluripotent stem cells (hPSCs) expansion and differentiation. Adv Drug Deliv Rev. 2026, 235:115904. doi: 10.1016/j.addr.2026.115904. PMID: 42162620

Ina Gruh, et al. Robert Zweigerdt, Ulrich Martin (2026), Human iPSC-cardiomyocyte-aggregate cell therapy in non-human primates and correlation of heart recovery with contractile and electrophysiological cardiomyocyte properties, Nature Comm, accepted

Abstract No. T17/P062

Decoding neurovascular dysfunction in ADHD: patient-specific iPSC-derived blood-brain barrier (BBB) models uncover hidden metabolic drivers beyond PARK2 genetics

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Neurovascular dysfunction is emerging as a critical but underexplored component of psychiatric disease. In attention-deficit/hyperactivity disorder (ADHD), rare copy number variations (CNVs) in *PARK2*, a key regulator of mitochondrial quality control, suggest a mechanistic link between mitochondrial stress and blood-brain barrier (BBB) impairment. Yet, whether and how patient-specific genetic risk translates into human BBB dysfunction remains unresolved.

Here, we leverage human induced pluripotent stem cell (hiPSC)-derived brain capillary endothelial-like cells (BCECs) from adult ADHD patients carrying *PARK2* CNVs to establish a patient-specific BBB platform with direct translational relevance. Combining functional barrier measurements with high-resolution metabolic and mitochondrial profiling, we dissect genotype- versus environment-driven effects on BBB physiology.

Unexpectedly, *PARK2* CNVs exerted only subtle baseline effects: BCECs with *PARK2* duplications displayed reduced barrier integrity and heightened oxidative stress sensitivity, but largely preserved mitochondrial architecture and bioenergetics. Instead, we identified a dominant and previously underappreciated driver of BBB phenotype: Time in culture. Prolonged culture induced a striking collapse of barrier function alongside a coordinated metabolic rewiring from glycolysis to oxidative phosphorylation, accompanied by reduced lactate production and altered cellular energy balance.

These findings challenge a purely genetics-centered view of BBB dysfunction in ADHD and reveal that metabolic state transitions can overshadow disease-associated phenotypes *in vitro*. Our work establishes culture-dependent metabolic remodeling as a key confounder and opportunity in human BBB modeling.

By uncovering a dynamic interplay between genetic vulnerability and metabolic state, this study positions patient-specific BBB models as a powerful platform to interrogate neurovascular mechanisms in psychiatric disorders and to identify context-dependent therapeutic targets.

Abstract No. T18/P064

"Heps in a Bag", an engineered hepatic patch against acute liver failure

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*Presenting author

The liver plays a central role in protecting vital organs such as the brain and kidneys by detoxifying drugs and alcohol, secreting essential proteins such as albumin, and regulating glucose and lipid metabolism. Currently, treatment options for liver disease are limited to whole-organ transplantation or supportive care, with the hope that the liver can regenerate before the onset of multi-organ failure. Cell-based therapies using primary hepatocytes have shown promising results, particularly in paediatric patients. However, these approaches require large numbers of cells and are constrained by the scarcity of donor organs.

Hepatocytes produced from human Induced Pluripotent Stem Cells (hiPSCs) could provide an advantageous alternative. However, current protocols based on directed differentiation are challenging to scale up. To address these limitations, we partnered with the company Clexbio to develop a hepatic patch based on their novel encapsulation method, VivoSet, a platofrm that enables the self-assembly of human extracellular matrix (ECM) constructs.

We have combined the VivoSet system with hepatocytes generated from hiPSCs using forward programming (FoP-Heps). The resulting FoP-Heps display key hepatic functions such as Albumin secretion, Urea detoxification and CyP activity at level comparable to those observed in primary human hepatocytes (PHH). Importantly, forward programming bypass variability between hiPSC lines and transcriptomic analyses confirm the similarity of FoP-Heps with primary cells.

FoP-heps produced in bioreactor using hypo-immune hiPSC lines were encapsulated using the VivoSet approach to engineer a hepatic patch. The embedded cells rapidly organize into mini-liver tissue while maintaining their functional characteristics. The resulting construct maintains functional characteristcs for more than 30 days in vitro. Finally, the hepatic patch was implanted in animal models and human Albumin secretion could be detected for more than 7 days suggesting that such approach could confer hepatic functions necessary for a therapeutic effect in the context of acute liver failure.

Abstract No. T19

Off-the-shelf immune-shielded iPSC-derived CAR γδ T cells as novel cell therapy to treat hepatocellular carcinoma

Judith Hartmann[1], *Tabea Erdmann*[1], *Jessica Nolte*[1], *Lea Renneberg*[1], *Stefanie Kober*[1], *Theresa Klisch*[1], *Thomas Aleyt*[1], *Marion Philippe*[2], *Caroline Stienne*[2], *Philip Hublitz*[1], *Karine Pingris*[2], *Celine Poussereau Pomie*[2], *Michael Esquerre*[2], *Katrin Ridders*[1], *Andreas Scheel*[1], *Matthias Austen*[1], *Audrey Holtzinger*[1], and *Stephanie Sontag*[1,*]

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Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related mortality worldwide. Therapeutic options for advanced disease remain limited and yield poor long-term outcomes. While chimeric antigen receptor (CAR) T cell therapies have transformed the treatment of hematologic malignancies, their success in solid tumors is constrained by limited tumor infiltration, functional exhaustion, antigen heterogeneity, and, in allogeneic settings, allorejection.

To address these limitations, we developed allogeneic induced pluripotent stem cell (iPSC)-derived CAR γδ T cells (CAR iγδ T cells) as a standardized, fully controllable "off-the-shelf" therapy for HCC. This platform combines scalable, cost-effective manufacturing with precise genome engineering at the iPSC stage. Targeted introduction of a γδ T cell receptor (TCR) and a proprietary HCC-directed CAR enables the generation of CAR iγδ T cells that inherently infiltrate solid tumors, avoid graft-versus-host disease through HLA-independent recognition, and exhibit multimodal cytotoxicity. Additionally, immune-shielding, tumor microenvironment (TME) resistance editing, and an integrated safety switch enhance persistence, prevent allorecognition, and allow controlled therapeutic intervention if required.

We established a scalable, xeno-free differentiation process to generate highly pure CAR iγδ T cells without enrichment. The final immune-shielded, armored cells display a predominantly naïve, non-exhausted phenotype and exhibit robust trimodal killing via NK receptors, the γδ TCR, and the CAR against HCC cell lines *in vitro*. Importantly, our immune-shielding strategy protects from human NK and T cell-mediated killing and prevents cytokine release by these effector cells.

Collectively, our approach integrates precise genome engineering with scalable bioprocessing to deliver a GMP-compliant, broadly accessible, and cost-competitive CAR iγδ T cell therapy for HCC. By combining trimodal cytotoxicity with immune-shielding and TME resistance, this strategy addresses tumor escape, allorejection, and T cell exhaustion, supporting durable tumor clearance. Our platform is highly flexible and can be rapidly adapted to other tumor types and target antigens.

Abstract No. T20/P080

Engineering basal cells to modulate epithelial-macrophage interactions in COPD

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Chronic obstructive pulmonary disease (COPD) is the third leading cause of death worldwide and is characterized by chronic airway inflammation, tissue destruction and impaired regeneration capacity, with current treatments being limited to symptomatic management. Chronic exposure to noxious factors can disrupt and exhaust lung stem cell niches, impairing basal stem cell self-renewal and differentiation capacity, while dysregulated epithelial-immune cell interactions sustain a pro-inflammatory microenvironment that further limits tissue repair. This project aims to generate and characterize engineered basal stem cells with enhanced regenerative and immunomodulatory properties, capable of giving rise to airway epithelial cells that regulate inflammatory responses, to investigate and modulate epithelial-immune crosstalk in COPD-associated inflammation. Engineered airway organoids will be used as a model system to investigate these interactions.

Candidate targets and pathways with potential regenerative and immunomodulatory functions were identified through dataset analysis and validated by pharmacological induction in murine airway organoids, alongside immunostaining in murine and human lung tissues across different treatment and disease stages.

Furthermore, to characterize the immune cells involved in COPD, with a particular focus on macrophages, the functional phenotype of bone marrow-derived macrophages isolated from young and aged mice with and without 4-month cigarette smoke exposure was analyzed. Moreover, to reconstruct the stem cell-macrophage interaction niche ex vivo, an organoid-macrophage co-culture system with long-term culturing conditions was developed.

Together, these results provide a foundation for developing an organoid-based cell therapy approach that enables epithelial regeneration, immune-compatible engraftment and long-term functional tissue repair in a mouse model of COPD.

Abstract No. T21

Attenuation of stem cell aging to target aging-associated diseases

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Aging of adult stem cells is a central driver of tissue dysfunction and the onset of aging-associated diseases. There are a number of key molecular and cellular mechanisms underlying stem cell aging, including recently identified changes in pH in the niche and its impact on hematopoietc stem cell function. Similarly, mesenchymal stroma/stem cells in BM show changes in function upon aging. Strategies to attenuate or reverse stem cell aging in vivo are novel therapies that will restore aged stem cell function in vivo to attenuate aging-associated diseases driven by aged stem cells.

Abstract No. T22/P137

A human brain organoid model of ageing identifies chromatin-mediated control of transposable elements during neural ageing

Elisa Gabassi[1,*], *Sara Campagnol*[1], *Lisa Fellner*[1, 2], *Stefan Salzmann*[1], *Julia-Anna Ulz*[1], *Nicole Amberg*[3], *Theresa Lindlbauer*[1, 2], *Katharina Günther*[1], *Nina Grill*[1, 2], *Nikita Arnst*[1], *Samuel Aguirre*[4], *Marian Martínez-Balbás*[4], *Romana Höftberger*[3], *Ahmad Salti*[5], *Christopher Esk*[1], and *Frank Edenhofer*[1]

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Studies of human brain ageing have been constrained by limited access to patient-derived tissue and by the inability of induced pluripotent stem cell (iPSC) models to retain age-associated signatures. To address this limitation, we developed an inducible 3D human brain organoid model based on progerin overexpression aimed to recapitulate key hallmarks of ageing and to identify novel ageing regulators. Induced ageing in organoids resulted in epigenetic instability, characterised by a 40% reduction in H3K9me3-enriched heterochromatin, a two-fold increase in DNA damage, mitochondrial dysfunction, lipofuscin accumulation, and increased cellular senescence. Notably, ageing-associated phenotypes were partially reversible following pharmacological intervention.

To explore the molecular basis of these changes, transcriptomic profiling identified a distinct age-associated gene expression programme that closely mirrored profiles observed in aged human *post-mortem* cortical tissue, including downregulation of synaptic genes such as *SYN1* and *CALM2*, and known ageing regulators, including *SIRT1* and *HSPA8*. Among dysregulated genes, a histone demethylase was consistently reduced in both aged organoids and human cortical samples. ChIP-seq analysis identified enrichment of genomic regions containing motifs recognised by the KRAB zinc-finger protein ZNF93, a regulator of transposable element repression. Consistent with disruption of this regulatory pathway, aged organoids exhibited a 20% increase in transposable element expression, accompanied by re-localisation of ZNF93 from the nucleus to the cytoplasm, suggesting impaired chromatin recruitment downstream of reduced histone demethylase expression.

Together, these findings establish inducible ageing organoids as a human-specific model for investigating epigenetic instability and transposable element dysregulation during brain ageing, with implications for understanding neurodegenerative disease mechanisms and evaluating therapeutic interventions.

Abstract No. T23/P142

Extreme heterogeneity in hematologic aging is predominantly driven by stochastic variation, not by environmental nor genetic variation

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Organismal aging is thought to arise from cumulative genetic and environmental interactions, complicating mechanistic dissection. However, the degree of heterogeneity has been largely unexplored.

Here, we generated a multi-layered hematopoietic dataset using a large cohort (>100 individuals) of young (2 months), middle aged (18 months) and old (>24 months) inbred female C57BL/6 mice house under specified pathogen free conditions, to gain a comprehensive characterization of the aging process across blood, bone marrow, spleen, and transplantation assays.

While we recapitulate the expected age-related hematopoietic traits across the cohort, aged mice showed pronounced phenotypic heterogeneity: with some 24-month-old mice displaying parameters comparable to young controls, while others showed extreme aging outcomes. Surprisingly, a cohort-wide correlation analysis of the aged individuals discounted the previously accepted cause-effect relationships between hematopoietic stem cell (HSC) functionality (measured by transplantation output), HSC expansion, myeloid bias and anemia, with these outcomes being spread across different individual mice, suggesting that hematopoietic aging does not follow a single trajectory.

To investigate the molecular basis of this variability, we derived cell type-specific aging scores from bone marrow scRNA-seq data in a subset of the cohort, capturing transcriptomic dysregulation in hematopoietic and niche populations. Aging scores varied widely among aged individuals. To link aging traits with molecular data we performed intercellular communication analysis and identified distinct inflammatory signaling axes in the bone marrow niche associated with specific aging phenotypes. Elevated neutrophil-derived Oncostatin M signaling in a subset of mice seemed to remodels the AdipoCAR-HSC niche axis and drives myeloid bias, while in another subset of mice IL1 signaling from neutrophil to AdipoCAR correlated with anemia.

Our findings challenge the notion of a linear ageing process and rather indicate that hematopoietic aging proceeds through multiple independent routes, shaped by distinct inflammatory cell-cell communication axes within the bone marrow.

Abstract No. T24

Ontogenetically distinct bone marrow macrophages regulate HSC integrity and megakaryocyte-biased expansion

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Current understanding of hematopoietic aging centers on the paradox of an expanding hematopoietic stem cell (HSC) pool with diminished functional potential. Throughout life, HSCs rely on specialized interactions with their niche to maintain stemness. While bone marrow macrophages are known to be essential for establishing the HSC niche in new born mice, their role in maintaining these niches during aging remains poorly understood. Here, we show that embryo-derived macrophages (eMps) maintain close contact with HSCs in young mice. During aging, this direct interaction deteriorates and the majority of eMps are replaced by HSC-derived adult macrophages (aMps). This shift contributes to HSC heterogeneity and the expansion of megakaryocyte-biased (CD41+) HSCs which do not possess reconstitution capacity after transplantation. Notably, the depletion of eMps in young mice results in a premature accumulation of CD41+ HSCs that the presence of aMps cannot mitigate. Our findings reveal, that ontogenetically distinct macrophages inherit specialized functions within the bone marrow niche to preserve HSC integrity throughout the aging process.

Abstract No. T25

Clonal trajectories of adult B-ALL in medullary sites and brain infiltration at single-cell resolution

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B-cell precursor acute lymphoblastic leukemia (B-ALL) exhibits extensive cellular heterogeneity, yet the mechanisms governing its organization and evolution remain incompletely understood. This study aims to investigate the hierarchical trajectories of B-ALL by combining lentiviral barcoding and multiome single cell data to unveil the temporal and spatial dynamics of leukemic differentiation at clonal and single-cell resolution *in vivo*.

Single-cell analyses identified interconnected leukemic populations occupying distinct cellular states. Lineage tracing revealed that individual clones contribute to multiple cellular compartments, while functional transplantation assays and computational modeling supported the existence of a differentiation hierarchy within adult B-ALL. Together, these findings indicate that leukemic heterogeneity arises through the interplay of clonal evolution and hierarchical organization.

We further investigated how leukemic populations respond to therapeutic pressure and distinct tissue microenvironments. Clonal analyses demonstrated dynamic remodeling of leukemic populations during treatment, characterized by shifts in clonal dominance and cellular composition. Profiling of medullary and extramedullary sites revealed organ-specific patterns of clonal selection, with distinct subclones preferentially expanding within the central nervous system (CNS). Ongoing studies employing serial transplantation and single-cell profiling aim to determine the stability of these cellular states and identify underlying mechanisms.

Overall, this study demonstrates the integration of lineage tracing and single-cell multiomics to resolve the clonal and cellular architecture of B-ALL. These findings provide new insights into the relationships between differentiation, clonal evolution, and microenvironmental adaptation during leukemia progression and therapeutic response.

Abstract No. T26

Starting matters: quality and reproducibility in PSC-based research

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Pluripotent stem cell (PSC)-based models have become indispensable tools for studying human development and disease and are increasingly used in drug discovery. Yet, despite major advances in differentiation technologies, standardization and quality control of the pluripotent starting population remain surprisingly inconsistent. Differences in PSC quality can profoundly affect differentiation outcomes and may be mistaken for disease-associated phenotypes, contributing to contradictory findings and limited reproducibility across studies.

This Spotlight Discussion will address a critical question for the field: How can we ensure that observed phenotypes reflect biology rather than variability in the starting cells? Experts from stem cell core facilities will discuss practical approaches to PSC quality control and experimental design, including appropriate metrics for isogenic studies, the use of sister and mock-edited clones, statistical power, and emerging challenges such as X-chromosome and XIST erosion. Particular attention will be given to how broadly accessible commercial differentiation systems are changing the field by enabling laboratories with limited prior PSC experience to establish complex stem cell models.

An additional perspective from drug discovery will highlight why robust, standardized, and reproducible stem cell systems are essential if PSC-derived models are to generate reliable and actionable data beyond academic proof-of-concept studies.

Following short impulse presentations, the speakers will engage in an open panel discussion and Q&A. The session aims to raise awareness, exchange practical experience, and stimulate discussion on minimum quality standards and experimental principles needed to improve reproducibility and confidence in PSC-based research.

Abstract No. T27

Microglia modulate neurodevelopmental responses to micro- and nanoplastic exposure in human brain organoids

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Brain development is shaped by tightly regulated genetic programs and environmental influences. Micro- and nanoplastics (MNPs) are increasingly detected in human tissues, including the brain, yet their impact on neurodevelopment remains poorly understood. Using complementary human iPSC-derived systems, we demonstrate that chronic MNP exposure disrupts human neurodevelopment across structural, transcriptional, metabolic, and functional levels, while microglia emerge as key modulators of tissue vulnerability. In high-throughput brain organoids, chronic MNP exposure impaired growth, disrupted ventricular zone organization, and reduced neural progenitor density. Single-nucleus RNA sequencing revealed altered neurodevelopmental trajectories, impaired radial glia maturation, diminished microcephaly-associated progenitor signatures, and the emergence of stress-associated neuronal states. Mature cortical neurons exhibited increased oxidative phosphorylation signatures, indicative of metabolic adaptation under chronic exposure. Exposure of human fetal brain explants to fluorescent particles identified microglia as a major cellular site of particle accumulation, motivating the generation of cerebral organoids containing organoid-grown microglia (oMGs). oMGs efficiently internalized MNPs and largely rescued MNP-induced growth deficits. While MNP exposure continued to alter ventricular zone organization and progenitor cell cycle dynamics, spatial transcriptomics revealed cell-type-specific stress responses and metabolic adaptations, and lipidomic profiling demonstrated extensive sphingolipid, phospholipid, and acylglycerol remodeling. oMG co-culture selectively normalized MNP-induced alterations in ceramides and PUFA-enriched phospholipids without affecting the basal lipid profile. iMGL monocultures confirmed microglial-intrinsic ceramide accumulation and metabolic reprogramming, including suppression of mitochondrial oxidative phosphorylation, fatty acid oxidation, and amino acid uptake alongside strong upregulation of de novo fatty acid synthesis. Finally, calcium imaging of long-term organoids demonstrated reduced signal frequency and amplitude alongside increased network synchronization, indicating impaired maturation of neuronal activity. Together, these findings establish that chronic MNP exposure disrupts human neurodevelopment at structural, transcriptional, metabolic, and functional levels, while microglia shape tissue resilience through particle sequestration and modulation of lipid and metabolic homeostasis.

Abstract No. T28

Dissecting the pathogenesis of Canavan disease using neuroglial organoids

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Canavan disease (CD) is a fatal leukodystrophy caused by mutations in the ASPA gene encoding aspartoacylase, an enzyme which degrades N-acetyl-L-aspartate (NAA) to aspartate and acetate. CD is characterized by spongiform white matter degeneration, intramyelin vacuolization, and swollen astrocytes with enlarged, structurally abnormal mitochondria. NAA accumulation and acetate deficiency are thought to disrupt osmotic and energy homeostasis, impair myelination, and alter histone acetylation, but the precise molecular mechanisms remain unclear. In this study, we adapted a protocol reported by Marton et al. (Nature Neurosci. 2019) to differentiate human induced pluripotent stem cell (iPSC) ASPA knock out (KO) and isogenic control (WT) lines into human oligodendrocyte-enriched late-stage neuroglial organoids, which were cultured for up to 150 days. Immunofluorescence and electron microscopic analysis depicted robust trilineage neural differentiation including myelinating oligodendrocytes. ScRNAseq data delineated 27 neural subpopulations with mostly ventral regionalization stretching from telencephalic to midbrain levels. These subpopulations encompass a broad spectrum of stem and progenitor cells up to differentiated derivatives of all three neural lineages. Aspa protein expression was clearly detectable by day 150, and ASPA-deficient organoids faithfully recapitulated accumulation of NAA. Interestingly, CD organoids showed an increase in glial progenitor populations with time, suggesting an impact of Aspa deficiency on glial maturation. Furthermore, CD organoids displayed differential expression of transcripts relating to oxidative phosphorylation, mitochondrial metabolism and acetylation across specific glial and neuronal cell populations. Considering the transcriptional alterations relating to oxidative phosphorylation and autopsy findings showing mitochondrial defects in astrocytes, we further employ 2D cultures of iPSC-derived astrocytes to assess mitochondrial morphology and function. We expect these model systems to provide deeper mechanistic insights into the role of Aspa and NAA in glial cell maturation, homeostasis and disease manifestation.

Marton RM, Miura Y, Sloan SA, Li Q, Revah O, Levy RJ, Huguenard JR, Paşca SP. Differentiation and maturation of oligodendrocytes in human three-dimensional neural cultures. Nat Neurosci. 2019 Mar;22(3):484-491

Abstract No. T29/P039

Patient-specific iPSC-derived sensory neurons as a gateway to individualized neuropathic pain modeling and treatment

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Small Fibre Neuropathy (SFN) is a chronic neuropathic pain disorder. Current treatment options are limited and highly individual, therefore highlighting the need for novel personalized therapeutic strategies.

We formed an interdisciplinary consortium within which we generated clinical, genetic and smart-watch-based biometric data from 24 SFN patients and 24 healthy controls over one year. Peripheral blood cells from seven SFN patients and seven healthy controls were reprogrammed into iPSCs. More than 100 iPSC lines underwent quality control by assessing genetic integrity, pluripotency marker expression and differentiation capacity into neural crest-like cells (NCLCs). These parameters were integrated into a weighted quality score (iQ-Score) to identify optimal iPSC-lines for downstream disease modelling and drug screening.

Patient-specific NCLCs were differentiated into sensory neurons by lentiviral-mediated NGN1 expression and matured for 67-70 days. Neuronal activity was measured using multielectrode array recordings.

Sensory neurons exhibited spontaneous activity. Surprisingly, SFN patient derived neurons showed reduced overall mean spike firing rates, whereas their firing frequency within bursts was significantly elevated.

A library of 88 clinically approved pain-related drugs was used for SFN patient-specific drug screenings. To quantify drug effects, we generated high dimensional MEA response vectors integrating the neurons´ firing and bursting behaviour for each compound. Vectors served as drug response fingerprints. These vectors were projected into a disease space defined by patient-derived and control-derived baseline signatures, allowing us to quantify drug induced shifts away from the patient specific pain state in the healthy direction. A defined subset of drugs shifted the SFN patient specific disease signatures towards the healthy region. These compounds represent candidate modulators for normalizing disease-associated functional patterns.

In summary, we established a scalable, medium throughput patient specific iPSC-based platform for modelling neuropathic pain and assessing drug responses. This approach provides the foundation for future personalized therapeutic decision-making for neuropathic pain patients.

Abstract No. T30

In vitro/in silico reciprocal modeling of human neuronal networks reveals presynaptic vesicle dynamics underlying epileptiform activity

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Epilepsy is among the most common neurological disorders, yet the underlying mechanisms remain poorly understood. This also relates to the pathognomonic slowing of rhythmic activity that often precedes seizure termination. Here we used spontaneously developing networks of human pluripotent stem cell-derived glutamatergic neurons (iGlutNs) generated via NGN2 forward-programming to address this question. Recordings of iGlutN networks on multi-electrode arrays revealed a nested "network super-burst" (NSB) phenomenon emerging in mature cultures (>7 weeks). NSBs comprise a train of sub-bursts with progressively lengthening inter-burst intervals (~250–600 ms), closely mirroring the 4–2 Hz rhythmic slowing seen in human absence and tonic-clonic seizures. Notably, NSBs persisted despite GABA receptor blockade, indicating that disinhibited excitatory networks alone can generate this epileptiform pattern. To dissect the underlying mechanism, we developed a computational model of excitatory networks incorporating a two-pool presynaptic vesicle hierarchy: a slowly-recovering reserve pool (RP) feeding a readily-releasable pool (RRP). This model recapitulated NSB dynamics, predicting that NSB strength tracks RP recovery while individual sub-burst dynamics track RRP recovery. These computational predictions were subsequently confirmed in wet lab in vitro experiments via matching recovery time constants. Specifically, pharmacological slowing of RP-to-RRP vesicle translocation with cytochalasin-D dose-dependently attenuated NSBs and right-shifted recovery, as predicted in silico. Further simulations revealed an intrinsic tonic-clonic bi-stability in excitatory networks, governed by the RRP recovery time constant — offering a novel, inhibition-independent explanation for the tonic-to-clonic transition characteristic of generalized seizures. Our findings establish in vitro/in silico reciprocal modeling of human neuronal networks as an informative reductionist approach for dissecting presynaptic contributions to epileptiform dynamics.

Abstract No. T31

Cooperative GNAS–KRAS signaling shapes intraductal papillary mucinous neoplasm phenotype and grade

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Intraductal papillary mucinous neoplasms (IPMNs), cystic precursors to pancreatic ducal adenocarcinoma (PDAC), frequently harbor activating mutations in GNAS and/or KRAS, yet the functional crosstalk remains largely unresolved. To dissect diverging and converging roles of the two oncogenes, we equipped human patient-derived $GNAS^{R201C}$ or $GNAS^{WT}$ induced pluripotent stem cells (iPSCs) with an inducible $KRAS^{G12D}$ cassette.

The cells were differentiated into pancreatic duct-like organoids (PDLOs) and analyzed in vitro or after maturation on an ex vivo porcine urinary bladder (PUB) scaffold. Endpoint analyses included global transcriptomic and proteomic analyses, histopathological grading, mucin subtyping, proliferation, senescence, and DNA-damage responses following irradiation.

Results: While $GNAS^{R201C}$ was sufficient to activate a mucinous program and uniquely induced MUC2 and CDX2, cooperation with $KRAS^{G12D}$ amplified dysplasia. Phenotypic mapping indicated intestinal traits as GNAS-dependent, whereas KRAS contributed toward gastric/pancreatobiliary IPMN-like features. Mechanistically, $KRAS^{G12D}$ triggered p53/p21 oncogene-induced growth arrest in a $GNAS^{WT}$ background. In contrast, $GNAS^{R201C}$ lowered p53 abundance and activity, blunted irradiation-evoked DNA-damage responses, and upregulated histone deacetylases potentially promoting p53 destabilization. Meta-analysis showed that TP53 mutations are underrepresented in GNAS-mutant IPMN lesions and PDAC.

Conclusion: Thus, $GNAS^{R201C}$ disabled the p53/p21 checkpoint to unleash KRAS-driven dysplasia. This human iPSC-PDLO/PUB platform mechanistically links genotype to IPMN subtype and reveals a potential therapeutic entry via HDAC blockade in GNAS-mutant disease.

Abstract No. T32/P040

Unveiling the genetic landscape of UV-induced cellular responses: A CRISPR whole genome screening approach

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Ultraviolet (UV) radiation is a major environmental stressor affecting human skin and the primary risk factor for cutaneous squamous cell carcinoma, yet many genetic determinants of cellular UV sensitivity and resistance remain unknown.

To address this knowledge gap, we performed a genome-wide CRISPR/Cas9 loss-of-function screen in human keratinocytes, enabling systematic and unbiased identification of genes regulating cellular responses to UV-induced stress. We identified 929 growth-essential genes and 21 genes associated with UV sensitivity and resistance, including established nucleotide excision repair genes among the strongest UV-sensitizing hits, and uncovered 11 novel candidate genes associated with cellular UV response.

To enable functional validation of candidate genes, human iPSC-derived skin organoids were established as a physiologically relevant model of human skin. As a proof of concept, CRISPR/Cas12-mediated knockout of Filaggrin resulted in altered epidermal organization and stratification, supporting the use of skin organoids for downstream validation of screening hits.

Overall, this study identifies novel candidate regulators of cellular UV response and establishes an integrated platform combining genome-wide CRISPR screening with human iPSC-derived skin organoids for their functional validation, providing a powerful framework to dissect mechanisms of UV sensitivity, skin homeostasis, and photocarcinogenesis.

Abstract No. T33/P045

ELAPOR2 controls pancreatic endocrine differentiation through cell cycle regulation

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The pancreas is an essential organ for endocrine regulation of glucose metabolism, and its proper development depends on tight coordination between pancreatic progenitor expansion, specification, and the balance between endocrine and exocrine lineages. Our group previously described Inceptor, also known as ELAPOR1, a protein which can regulate endocrine differentiation in human models. Interestingly, Inceptor has a paralog protein named ELAPOR2. In previous studies, ELAPOR2 was described as a regulator of proliferation throughout skin development, expressed throughout all germ layers, but its specific role in the pancreatic endoderm remains poorly understood. Therefore, we aimed to better determine the function of ELAPOR2 in human pancreatic progenitor proliferation and cell fate allocation. Using stem cell differentiation to model human pancreas development and endocrine differentiation, we show that, in pancreatic progenitors, loss of ELAPOR2 directly affected critical receptor signaling with established function in pancreas development. This observation correlated with an increased cell cycle length in ELAPOR2 knockout (KO) pancreatic progenitors, which facilitated the stabilization of NGN3, the major transcription factor to promote endocrine differentiation. ELAPOR2 KO lines displayed increased total ratios of β-cells by the end of differentiation. In reverse, overexpression of ELAPOR2 decreased the numbers of NGN3 expressing cells midway through endocrine induction and ultimately decreased the percentage of β-cells in our final differentiation product. These findings reveal that ELAPOR2 is a regulator of pancreatic progenitor proliferation and fate commitment. Our results identify a new molecular player in the regulatory network governing pancreas formation, which could be further explored to deepen our understanding of proper formation of the pancreatic endocrine lineage.

Siehler, J., Bilekova, S., Chapouton, P. et al. Inceptor binds to and directs insulin towards lysosomal degradation in β cells. Nat Metab 6, 2374–2390 (2024). https://doi.org/10.1038/s42255-024-01164-y

Ansarullah, Jain, C., Far, F.F. et al. Inceptor counteracts insulin signalling in β-cells to control glycaemia. Nature 590, 326–331 (2021). https://doi.org/10.1038/s41586-021-03225-8

Abstract No. T34

Human iPSC models for safer drug discovery through predictive teratogenicity assessment

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Human induced pluripotent stem cell (iPSC)-derived models offer an opportunity to make drug discovery safer and more predictive by identifying human-relevant liabilities before late-stage development. Teratogenicity is a clear example: conventional in vivo studies are resource-intensive, use high animal numbers, and are typically performed after substantial investment. At this stage, detection teratogenicity can terminate programs or restrict clinical development, particularly for women of childbearing potential. Earlier human-relevant approaches are therefore needed to guide compound design and candidate selection.

We developed a scalable human iPSC-based high-throughput screening platform for predictive teratogenicity assessment. The platform comprises four iPSC-derived models representing all three germ layers and captures a broad spectrum of developmental mechanisms. Benchmarking against approximately 150 reference compounds demonstrated an accuracy of 83%. Fully automated, miniaturized workflows combined with high-content imaging enable quantitative, multiparametric phenotyping and the screening of thousands of compounds per month, generating datasets suitable for computational modeling.

Beyond binary hazard identification, the platform supports medicinal chemistry decisions during drug discovery. In one project, profiling more than 500 compounds across multiple chemical series enabled identification of physicochemical properties associated with teratogenic hazards. These experimental data were used to build a quantitative structure-activity relationship (QSAR) model for structure-based prediction of teratogenic activity, providing actionable guidance for designing compounds with improved safety profiles.

Together, this human iPSC-based platform demonstrates how stem cell-derived models can support safer drug discovery through early, scalable, and predictive safety assessment. By combining human-relevant in vitro biology, automated screening, and computational modeling, the approach enables proactive teratogenicity risk mitigation, reduces reliance on late-stage animal testing, and reduces the risk of program termination late in the development process.

Abstract No. T35

Fabry iPSC-derived dorsal root ganglia (DRG) model

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Fabry disease is a lysosomal storage disorder characterized by a genetic deficiency of α-galactosidase A, resulting in the accumulation of globotriaosylceramide (Gb3). A hallmark of the disease is severe neuropathic pain, yet the molecular mechanisms by which Gb3 accumulation leads to nociceptor dysfunction is poorly understood. Here, we establish an iPSC-based dorsal root ganglion (DRG) -like culture as a Fabry disease model. We differentiated iPSCs from two Fabry patients and genetically corrected controls via an axial stem cell intermediate into mixtures of DRG sensory neurons and supporting glia. Our model demonstrates functionality and the relevant DRG markers (e.g. *TRPV1, TUJ1, POU4F1, SOX10*). Recordings of neuronal activity with High-density multi-electrode arrays (HD-MEA) uncovered patient-specific network dysfunctions such as hyperactivity and recruitment-driven burst remodeling. Transcriptomic comparison revealed a cohort of shared downregulated genes that point to a Fabry-specific stress state. More generally, we are providing an integrated Fabry disease DRG-like culture model linking organellar dysfunction changes with cellular electrophysiology and currently testing how these potential pain-relevant modulatory factors can reverse the hyperactivity phenotype.

Abstract No. T36

Intersectional genetics for precise manipulation and tracing of lung and skeletal muscle stem cells

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Most organs in mammals rely on adult stem cells for repair and regeneration but some do not. For example, the heart does not contain dedicated stem cells to replace lost cardiomyocytes but needs to change the state of existing cardiomyocyte to allow proliferation. Liver repair is done by existing hepatocytes but resorts to liver progenitor cells and oval cells in case of chronic or severe in injury. In contrast skeletal muscle completely relies on specialized muscle stem cells (MuSCs). In the lung the situation is more complicated. Several cell types such as secretory Club cell or alveolar type II cells (AT2 cells) have major roles in lung function but can also proliferate and give rise to other cell types, essential acting as stem cells. In addition, the lung has distinct stem cell populations such as basal cells and bronchioalveolar stem cells (BASCs).

It is often difficult to genetically manipulate and trace different stem cell populations because of the lack of uniquely expressed markers. We have tackled this problem by developing different tools, employing intersection genetics techniques. We have manipulated and traced different stem cell population in the lung but also generated mouse lines allowing targeting of different populations of smooth muscle cells (Wang et al, 2026). Intersectional genetics also allowed us to assess the proliferation status of stem cells in mice. We are analyzing whether MuSCs indeed exist in a dormant, quiescent state during a lifetime or are occasionally activated over an extended time period to refurbish their state. In addition to the need to maintain quiescence, MuSCs, as all other stem cells, require an intricate system of quality control to maintain genome stability. We have deciphered several of the underlying mechanism, which prevent transcription-replication collisions and maintain nuclear lamina integrity (Georgieva et al, 2025).

Georgieva AM, Sreenivasan K, Ding D, Villeneuve C, Wickström SA, Günther S, Kuenne C, Gärtner U, Guo X, Zhou Y, Yuan X, Braun T. Regulation of NSL by TAF4A is critical for genome stability and quiescence of muscle stem cells. 2025 Nat Commun., 16, 8726

Wang L, Staps M, Günther S, El Agha E, Bellusci S, Kuenne C, Du J, Schneider A, Braun T. Cell Type-Specific Targeting of Different Smooth Muscle Cell Populations by Intersectional Genetics. 2026, Circulation. doi: 10.1161/CIRCULATIONAHA.125.076318

Abstract No. T37/P168

Characterization of naïve human neuroepithelial stem progenitor cells with unlimited self-renewal and broad neurogenic potential

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Cell lines derived from early embryonic stages have significantly contributed to our understanding of mammalian development, yet they predominantly reflect late developmental stages, following neural tube closure. The current human neural stem/progenitor cell (NSPC) models, such as rosette-like or radial glial-like cells, either represent later neurodevelopmental phases or fail to sustain long-term clonal self-renewal. Here, we report the successful isolation and long-term expansion of a tissue-derived human NSPC population that transcriptomically mirrors the human neuroepithelium at five weeks of in vivo embryonic development. These embryonic neural stem/progenitor cells (eNSPCs) display a distinct naïve, non-polarized, pre-rosette phenotype, distinct from previously described rosette-like and radial glial-like NSPC models. Notably, eNSPCs exhibit virtually unlimited self-renewal capacity and retain multipotent differentiation potential into diverse neural lineages of both the central and peripheral nervous systems—including dopaminergic neurons, V2a progenitors and interneurons, and neural crest derivatives. Multimodal analyses on both RNA and protein level, including single-cell RNA sequencing, immunocytochemistry, flow cytometry amd ATAC-sequencing, revealed that eNSPCs constitute a homogeneous population of multipotent stem cells, rather than a mixture of committed neural progenitors, with distinctive expression of early neurodevelopmental markers, lack of lineage commitment and broad differentiation potential. In comparison with other previously established NSPC models, eNSCPs exhibit a distinct transcriptomic profile that corresponds to earlier human developmental stages. Together, these findings establish eNSPCs as the earliest stabilized human NSPC model reported to date and highlight their value for studying early human neurodevelopment, lineage specification, disease modelling, and regenerative medicine.

Abstract No. T38/P163

Lymphatic vasculature reprograms liver epithelium in assembloids and patients

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Understanding how microenvironmental cues can hijack epithelial cell identity is central to regenerative medicine. Biliary atresia, an infant liver biliary epithelial disease, offers a compelling disease model in which niche signaling drives epithelial fate regression, a phenomenon with broad implications for organoid-based disease modeling and stem cell biology.

Using a large, multi-center patient cohort (n=46), we integrated single-nuclei RNA sequencing (snRNA-seq), spatial transcriptomics (10X VisiumHD & Stereo-Seq), multiplexed immunofluorescence, and 3D light-sheet microscopy to resolve the hepatic lymphatic niche at single-cell and spatial resolution. To dissect niche-epithelial crosstalk, we employed human organoid and stem cell platforms: intrahepatic cholangiocyte organoids (ICOs), iPSC-derived hepatocytes (iHeps), and multicellular fetal liver-like organoids (FLOs), the latter recapitulating the cellular complexity of the developing liver.

Results:
snRNA-seq revealed profound transcriptional dysregulation of lymphatic endothelial cells (LECs) in patients with poor outcomes, corroborated spatially by LEC hyperplasia and 3D remodeling of the intrahepatic lymphatic network. Among upregulated LEC-derived mediators, the chemokine CCL21 emerged as a key niche signal enriched in patients requiring transplantation. To interrogate how this pathological secretome reshapes epithelial identity, we exposed FLOs to BA tissue-conditioned media, observing cholangiocyte dedifferentiation and delumenization into $CK19^{+}$ ductular-reactive conglomerates — faithfully modeling the in vivo ductular-epithelial reaction in a dish. Targeted CCL21 treatment of ICOs and iHeps consistently upregulated SOX9 and LGR5, respectively, activating biliary progenitor and hepatic stemness programs - especially in patients with an inflammatory disease phenotype. Direct co-culture of patient-derived hepatic LECs with ICOs recapitulated this epithelial fate regression, establishing a lymphatic-to-epithelial axis of niche-driven reprogramming.

Conclusion:
We identify CCL21-high lymphatic endothelial cells that reprogram liver epithelium in immune-mediated liver epithelial disease toward a progenitor/reactive state, impairing epithelial function. Primary assembloid and iPSC-based fetal tissue-like organoids faithfully model this niche-epithelial crosstalk, offering tractable systems for dissecting fate decisions in the developing and diseased liver.

Abstract No. T39/P169

Liver regeneration is programmed in the epigenetic landscape of cholangiocytes during fetal development

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Liver regeneration during chronic disease involves transdifferentiation of intrahepatic cholangiocytes into hepatocytes. This process implies that cholangiocytes have a unique capacity to switch of cellular identity in extreme conditions. The molecular mechanisms which establish this cellular plasticity in the human liver remain unclear. To address this question, we first assessed the transdifferentiation capacity of adult intrahepatic and gallbladder cholangiocytes using organoids. Despite a shared transcriptome, gallbladder organoids failed to activate hepatocyte markers, indicating a limited regenerative capacity. In parallel, we profiled genome-wide histone modifications and DNA methylation in intrahepatic and gallbladder organoids and their foetal progenitors. Our integrated analysis revealed epigenetic features associated with a permissive state at hepatocyte marker loci in intrahepatic cholangiocytes. In particular, intrahepatic cholangiocyte organoids showed increased H3K27ac enrichment and decreased DNA methylation at hepatocyte genes compared with gallbladder organoids. These hepatocyte markers are activated upon transdifferentiation of intrahepatic cholangiocytes to hepatocytes, suggesting that both histone marks and DNA methylation establish a competence towards hepatocyte fate. Notably, this signature is already present in hepatoblasts, the foetal progenitors of both hepatocytes and cholangiocytes during liver organogenesis. In contrast, this signature is absent in foetal gallbladder cholangiocytes, indicating that adult liver regeneration is developmentally programmed. To confirm the functional importance of epigenetic programming, small molecule inhibitors of epigenetic modifiers were added in culture conditions inductive for transdifferentiation in vitro. Under these conditions, adult gallbladder organoids induced hepatocyte markers upon transdifferentiation, supporting the role of epigenetic mechanisms in cholangiocyte plasticity. Together, our findings show that cellular plasticity of intrahepatic cholangiocytes is epigenetically programmed during foetal development to enable regenerative processes in the adult liver.

Abstract No. T40/P143

Liver regeneration during chronic liver disease: SOX4 and KLF6 play a role in liver cell plasticity

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Liver regeneration in the context of acute liver injury has been extensively studied. However, the regenerative processes occurring during chronic liver diseases are not fully understood yet. Previous investigations performed by our group have revealed that hepatocytes and cholangiocytes can transdifferentiate into one another during chronic injury. This process is marked by the production of biphenotypic cells expressing markers specific for the two cell types. The aim of this study is to identify the main factors that drive such cellular transdifferentiation during chronic disease progression.

We performed single nuclei RNA sequencing on liver biopsies of patients at different stages of the disease. That allowed us to identify a set of transcription factors that potentially play a role in the transdifferentiation process between hepatocytes and cholangiocytes. We identified 2 transcription factors, SOX4 and KLF6, as potentially crucial for acquiring the plasticity necessary for such cellular transdifferentiation. The expression of SOX4 and KLF6 in transdifferentiating cholangiocytes/hepatocytes was confirmed in vivo by immunostaining of human tissue slides. We then established two in vitro approaches to confirm the functional importance of these factors in transdifferentiation using patients'-derived intrahepatic cholangiocyte organoids (ICOs) and primary cells-derived hepatocyte organoids (HepOs). Both cell types can be transdifferentiated in vitro into biphenotypic cells, recapitulating the process observed in vivo. Through loss of function experiments conducted on ICOs, we showed the importance of SOX4 and KLF6 for the maintenance of cholangiocyte identity. When these 2 transcription factors are silenced, cholangiocytes are more prone to express hepatocyte markers upon transdifferentiation.

Overall, our experiments have identified two plasticity factors, SOX4 and KLF6, which could play an important role in regenerative processes occurring during MASLD progression.

Abstract No. T41

PluripotencyScreen - a new epigenetic framework to quantify cell fate decisions of pluripotent stem cells

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The differentiation potential of induced pluripotent stem cells (iPSCs) can vary substantially among lines, underscoring the need for a robust and quantitative quality control assay that enables standardized comparison of differentiation capacity across laboratories. Here we describe PluripotencyScreen, a DNA methylation (DNAm) based assay that uses cell type-specific signatures to quantify pluripotent, endoderm, mesoderm, and neuronal ectoderm states and enables deconvolution of mixed populations. We established and validated PluripotencyScreen on genome-wide DNAm profiles generated with six defined differentiation conditions and additional commercially available trilineage differentiation kits. Using the computational framework CimpleG, cell type-specific DNAm signatures were derived, consisting of two CG dinucleotides per cell-type, enabling rapid targeted analysis with digital PCR or pyrosequencing. These epigenetic signatures can be transformed into pluripotent and germ lineage scores to track differentiation. The ectoderm score, for example, clearly correlates with the fraction of PAX6 positive cells in undirected differentiated samples and was sensitive enough to reveal differentiation impairments, e.g. after genetic knockout of YAP1. The assay can be performed with fixed cells and on individual embryoid bodies to enable material-efficient analysis in parallel to immunofluorescence analysis. Furthermore, it is compatible with dried cell pellets on filter paper which enables easy sample preparation and shipment. This method was validated on 48 PSC samples from six independent laboratories using different reprogramming methods, with results largely consistent with their known differentiation potential. Together, these optimization and validation studies demonstrate that PluripotencyScreen provides a practical and broadly applicable tool for the stem cell community.

Abstract No. T42/P092

Modeling primate atherosclerosis using iPSC-derived macrophages

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Atherosclerosis is a chronic inflammatory disease characterized by lipid-driven plaque formation within the arterial wall and is one of the leading causes of death worldwide. Early stages of plaque development involve macrophages, which become lipid-laden foam cells upon uptake of oxidized low-density lipoprotein (oxLDL).

While the cellular and molecular mechanisms of atherogenesis have been extensively studied in mice and humans, far less is known about how these processes differ across primate species and how they have evolved. Non-human primates (NHPs), particularly chimpanzees, are of special interest in this context due to their close evolutionary relationship to humans and reported differences in susceptibility to atherosclerotic plaque formation.

Here, I present an in vitro model of foam cell formation from induced pluripotent stem cell (iPSC)-derived macrophages. It enables the differentiation of NHP iPSCs into macrophages and the investigation of their oxLDL uptake in vitro. The use of fused human-chimpanzee iPSCs — a tetraploid composite cell line containing human and chimpanzee genomes — enables the investigation of regulatory activity within a shared trans-regulatory environment. This allowed us to identify gene expression differences between human and chimpanzee macrophages during oxLDL uptake, attributable to independent cis-regulatory changes between species. These changes were significantly enriched, especially in the cholesterol efflux pathway, with chimpanzee macrophages exhibiting elevated expression of multiple efflux-associated genes upon oxLDL exposure. These results indicate evolutionary changes in the regulatory architecture of lipid-handling pathways. Ongoing functional assays will determine whether these transcriptional differences translate into altered cholesterol efflux capacity.

This system provides a framework for investigating how regulatory development influences human susceptibility to atherosclerosis and could ultimately reveal conserved and species-specific mechanisms relevant to future prevention and treatment strategies.

Abstract No. T43/P108

CTCF insulates gene expression to safeguard migratory myogenic progenitor cells

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During embryogenesis, multipotent progenitors present in the dermomyotome compartment of the somite generate multiple lineages including skeletal muscle, dermis and endothelial cells of the vasculature. The transcriptional programs governing these fate choices, coordinated by paired box transcription factor PAX3, are well established. How genome organization contributes to lineage specification remains poorly understood. CTCF, a key architectural protein that maintains chromatin domain boundaries to insulate gene expression, also cooperates with myogenic determination factor MYOD in muscle differentiation. However, the functional requirement for CTCF during cell fate specification *in vivo* has not been defined. Here we show that genetic inactivation of *Ctcf* in *Pax3*-expressing multipotent progenitors disrupts the specification of migratory myogenic progenitors, while closely related lineages, such as non-migratory myogenic progenitors and vascular endothelial cells, are spared. Our findings demonstrate a cell-autonomous requirement for CTCF's insulator function in safeguarding migratory myogenic progenitors from inappropriate enhancer–promoter interactions and aberrant gene expression. This model is illustrated by aberrant activation of *Ikaros* in the somitic mesoderm, through inappropriate usage of neighbouring enhancers associated with somite expression, resulting in impaired myogenic differentiation. Our findings define CTCF as a context-dependent regulator of cell fate specification, ensuring the emergence of the migratory myogenic progenitors of the *Pax3* lineage.

Abstract No. T44

Bioengineered muscle tubuloids: a human stem-cell–based model of neuromuscular development and innervation

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The formation of functional skeletal muscle is a complex, multistep process driven by the coordinated crosstalk between diverse cell populations with distinct differentiation potentials. Reproducing this cellular heterogeneity and spatial organization in vitro remains a major challenge. Here, we present a three-dimensional (3D) culture system that integrates a custom-engineered hydrogel platform with primitive neuromesodermal progenitors (NMPs), generating a new class of multicellular constructs that we term muscle tubuloids. These structures recapitulate key features of developing muscle, including the emergence of innervated, anisotropically aligned skeletal muscle fibers - an organization level that has been difficult to achieve so far in vitro.

Human pluripotent stem cell–derived NMPs were embedded into hydrogel fibers produced using a 3D wet-spinning biofabrication system and directed toward neuromyogenic differentiation over a 50-day culture period. Within these fibers, NMPs self-organized into elongated tubular structures that began spontaneous contractions by day 14. Analysis of gene expression profiles revealed that cells within the tubuloids express myogenic markers (PAX7, MyHC, TTN) and neurogenic markers (PAX6, CHAT, MAP2). Immunofluorescence staining confirmed the presence of aligned, well-organized skeletal muscle fibers supported by a network of motoneurons and functional neuromuscular junctions inside tubuloids.

These findings demonstrate that 3D hydrogel-based culture of NMPs enables synchronized, spatially patterned co-development of muscle and nerve tissue, mimicking native muscle architecture. The muscle tubuloid platform provides a new model for studying human muscle biology and holds promise for advancing research into neuromuscular disorders that remain difficult to treat.

Abstract No. T45

Multi-omics profiling reveals MAGEL2-driven defects in human corticogenesis shared across Prader-Willi and Schaaf-Yang syndromes

Jannis Buecking[1], *Baran Enes Güler*[1,*], *Michael Eibl*[1], *Azmal Syed Ali*[2], *Tobias Walczuch*[1], *Tobias Beschauner*[1], *Susanne Theiss*[1], *Melanie Spanjaard*[1], *Katrin Hinderhofer*[1], *Freya Herrmann-Sim*[1], *Celine E. de Esch*[3, 4], *Derek J.C. Tai*[5, 4], *Michael E. Talkowski*[5, 4], *Jeroen Krijgsveld*[6, 7], *Christian P. Schaaf*[1], and *Magdalena Laugsch*[1]

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Prader-Willi syndrome (PWS) and Schaaf-Yang syndrome (SYS) are related neurodevelopmental disorders with overlapping but distinct clinical presentations. SYS results from pathogenic variants in *MAGEL2*, a maternally imprinted gene regulating endosomal recycling, retromer trafficking, and actin dynamics, processes essential for neuronal maturation and cortical development. PWS arises from chromosomal deletions, imprinting defects, or uniparental disomy at chromosome 15q11-q13, a region encompassing several imprinted protein-coding genes and non-coding RNAs, including the *MAGEL2* gene. Both disorders share clinical features, including autism spectrum disorder, intellectual disability, hypotonia, and developmental delay, yet the contribution of MAGEL2 to their shared and distinct pathophysiology remains poorly understood.

To address this, we generated a comprehensive panel of CRISPR/Cas9-engineered isogenic human iPSC lines modeling key SYS mutations (including c.1996dupC and the perinatally lethal c.1996delC), heterozygous and homozygous *MAGEL2* deletions, and canonical PWS deletions (Type I and Type II) across two genetic backgrounds. We performed layer-resolved and integrated multi-omics analyses, including transcriptomics, proteomics, and ubiquitinomics across 14 hiPSC-derived cortical neuron models. To integrate multiple data modalities by reducing them into shared or distinct latent factors and finding strongly associated features (transcripts or proteins), we employed Multi-Omics Factor Analysis (MOFA). The results uncover disrupted protein homeostasis as the dominant shared molecular signature across SYS and PWS, with less pronounced convergent changes in transcription and ubiquitination. Moreover, we demonstrate shared functional deficits in corticogenesis, including impaired neuronal proliferation, migration, and maturation, as well as altered synaptic morphology, establishing MAGEL2 as a key regulator of overlapping pathophysiology. To our knowledge, this work provides the first comprehensive findings and integrative human cortical multi-omics framework for SYS and PWS. Taken together, the findings position MAGEL2 as a central coordinator of vulnerable developmental processes in human corticogenesis, extending the relevance of our study beyond rare syndromes to common neurodevelopmental disease mechanisms.

Strategic sessions presentations

14th GSCN Conference
German Stem Cell Network

9 – 11 September 2026

Max Delbrück Center
Berlin

Strategic sessions presentations: S1 – S7

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S5	Engineering mutation-specific and mutation-agnostic gene therapy approaches and their delivery *Dong-Jiunn Jeffery Truong*
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Abstract No. S1

Driving multimodal AI in precision medicine

Ulrike Weirauch[1,2,], Michael Rade[1], Till Braun[3], Markus Kreuz[1], David Fandrei[1,4], Christina Katharina Kuhn[1], Dennis Löffler[1], Conny Blumert[1], Christoph Kämpf[1], Alexander Scholz[1], Regina Demlova[5], Stefan Franke[6], Thomas Neumuth[6,7], Holger Fröhlich[8], Andreas Kremer[9], Carl Steinbeißer[10], Marco Herling[4], Michael Hudecek[1,11], Stephan Fricke[1,12], Ulrike Köhl[1,2,7], Maximilian Merz[13]*, and *Kristin Reiche[1,7,14]*

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AI-based tools enable the modeling of complex physiological and pathological processes and treatment outcomes by integrating multimodal data. The knowledge and models generated allow for tailored decision-making for individual patients in their current status. A key concept is the virtual twin (VT), a digital patient representation used to simulate patient-specific trajectories for precision medicine.

In the CERTAINTY project, we develop a multi-scale, patient-specific VT for multiple myeloma patients eligible for CAR T cell therapy. CAR T cells are living therapies with a stochastic biological nature. Integrating molecular/cellular data into the VT improves prediction of treatment response and adverse events.

Since molecular data from CAR T cell patients remain limited, we implemented a digital molecular medicine approach for immunomonitoring of CAR T cell patients, we established a pipeline that combines multi-modal single-cell next-generation sequencing (NGS) with advanced bioinformatics analysis. This enables comprehensive characterization of molecular/cellular signatures and the kinetics of therapeutic response and toxicity. In patients with multiple myeloma receiving BCMA-directed CAR T cells, we identified time-dependent cellular and molecular patterns as well as product-dependent effects driving differences in efficacy and toxicity [1].

Focusing on safety, we investigated a case of secondary CAR+ T-cell lymphoma after BCMA-directed CAR T-cell therapy by determining CAR transgene integration sites and analyzing molecular features of the patient's T-cell compartment over time and to revealing the evolution of the malignant T-cell clones [2]. Further analyses identified key pathogenic mechanisms and actionable therapeutic vulnerabilities. Additionally, we developed a data processing pipeline tailored to single-cell multiomics data, including CAR-engineered cell products, ensuring harmonized and reproducible bioinformatic workflow.

The generation of high-dimensional molecular and cellular data in clinical studies and routine practice using standardized immunomonitoring strategies, supports the implementation of trustworthy AI-based decision-support tools like VTs for clinicians and patients in precision medicine.

[1] Rade, M., et al., A longitudinal single-cell atlas to predict outcome and toxicity after BCMA-directed CAR T cell therapy in multiple myeloma. Cancer Cell 44, 586-603.e9; 10.1016/j.ccell.2025.10.014 (2026)

[2] Braun, T., et al., Multiomic profiling of T cell lymphoma after therapy with anti-BCMA CAR T cells and GPRC5D-directed bispecific antibody. Nature medicine 31, 1145–1153; 10.1038/s41591-025-03499-9 (2025)

Abstract No. S2

Translating regulatory expectations into context-specific genome-editing safety assessment

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The clinical translation of genome editing requires regulatory frameworks capable of addressing both sequence-level off-target activity and loss of genome integrity. The EMA Expert Meeting Report on Genome Editing Technologies and the recent FDA draft guidance on NGS-based safety assessment collectively support a tiered strategy: nomination of potential off-target sites using complementary methods; fit-for-purpose qualification of analytical assays; testing in clinically relevant human cells under representative editing conditions; quantitative characterization of intended and unintended on-target outcomes; and comprehensive analysis of structural and chromosomal abnormalities. However, key questions remain regarding the transferability of safety data across editor platforms, guide RNAs, and target-cell populations. To address these questions, we compared Cas9 nuclease with a panel of adenine and cytosine base editors in primary T cells, hematopoietic stem and progenitor cells, and fibroblasts. CAST-Seq and targeted deep sequencing were used to assess chromosomal rearrangements and sequence-level editing outcomes. We identified distinct editor-, deaminase-, guide RNA-, and cell type–dependent genotoxicity profiles. Cas9 predominantly caused large on-target deletions and inversions, whereas a hyperactive cytosine base editor showed broad mismatch tolerance, extensive off-target editing, and frequent chromosomal rearrangements. Cas9 activity was not a reliable surrogate for the corresponding base-editor off-target profile. Moreover, off-target frequencies, editing outcomes, and translocation patterns and persistence varied across cell types, despite a largely conserved spectrum of nominated sites. Optimized editor architectures substantially reduced genotoxicity. These findings argue against platform- or cell-independent safety assumptions. Regulatory assessment should integrate sequence-level and structural-variant analyses, relevant primary cell systems, donor variability, and editor-specific assay performance. Methods developed in our lab provide a sensitive framework for comparing candidate editors, prioritizing safer designs, and generating evidence suitable for mechanism-informed genetic risk assessment and early regulatory interaction.

Abstract No. S3

The off-target turn: how genotoxicity shaped tools, tests, and policy

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Genome editing and gene and cell therapies have progressed from theoretical concerns about genome perturbation to clinical technologies whose safety depends on precise, biologically informed genotoxicity assessment. Early lessons from insertional oncogenesis prompted the transition from γ-retroviral vectors to self-inactivating lentiviral vectors, while the emergence of ZFNs, TALENs, CRISPR nucleases, base editors, prime editors, and epigenome modifiers has enabled increasingly programmable and predictable genome modification. However, rapid methodological evolution, differences in editor design, guide architecture, sequence context, cell state, and delivery continue to complicate data harmonisation, cross-study comparison, and translational interpretation.

We established an integrated framework for characterising genomic aberrations in edited hematopoietic stem and progenitor cells, T cells, and induced pluripotent stem cells using complementary nuclease platforms. Orthogonal assays combined in silico prediction, targeted sequencing, digital PCR, HR CAST-seq, SCRIBE-seq, TQ-rhAmpSeq, multiplex digital PCR, karyotyping, and broad structural-variant analyses. This workflow enabled sensitive, quantitative assessment of on-target and off-target outcomes, including indel spectra, large deletions, loss of heterozygosity, persistent double-strand breaks, cut-and-repair cycles, translocations, co-translocations, donor DNA-bridged rearrangements, and unintended guide RNA contamination. HR CAST-seq and, to a lesser extent, TQ-rhAmpSeq improved rare-event detection by 10- to 1000-fold compared with standard approaches, while CLEAR-time digital PCR provided kinetic and structural insight into repair processes.

These findings demonstrate that genomic outcomes are shaped by both editor and cellular context and that no single assay can adequately capture the full spectrum of editing-associated risk. Experience from exagamglogene autotemcel (exa-cel; Casgevy) and emerging metabolic liver disease programmes further illustrates the importance of indication-specific risk–benefit assessment and integrated process understanding. As regulators increasingly support risk-based frameworks and iterative analytical updates, comprehensive genotoxicity assessment must evolve alongside editing modalities and delivery systems. Harmonised, high-sensitivity, orthogonal workflows will be essential to support robust safety evaluation and the responsible translation of durable, genome-guided therapies.

Abstract No. S4

Polymeric gene delivery agents, an emerging class of RNA nanocarriers

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*Presenting author

The growing number of emerging gene-based therapies has increased the demand for delivery systems with greater complexity, functionality, and robustness to effectively transport therapeutics to cellular targets. In particular, mRNA-based therapeutics have gained significant attention following the success of the COVID-19 Moderna and BioNTech vaccines, which utilize lipid nanoparticles as delivery vehicles for antigen-encoding mRNA.

Despite their proven clinical efficacy, current lipid-based delivery systems face several limitations. These include physicochemical constraints that hinder long-term storage and reconstitution, intrinsic immunostimulatory properties, and challenges associated with precise tissue targeting and controlled intracellular release of mRNA payloads. As a result, cationic polymers have emerged as a promising class of nanocarriers that offer advantages such as low cost, reduced immunogenicity, enhanced stability, and high modularity, addressing many of the shortcomings associated with lipid-based systems.

When functionalized appropriately for nucleic acid binding, polymeric carriers can readily form RNA–polymer complexes. The wide variety of available monomers and polymerization strategies enables the synthesis of polymers with diverse physicochemical and biological properties tailored to specific therapeutic applications and cargo requirements. This structural diversity is reflected in an equally broad range of nanoparticle morphologies, spanning electrostatically aggregated polyplexes to highly stable, crosslinked nanogels.

Furthermore, rational polymer design enables the incorporation of advanced functionalities. Stimuli-responsive features, such as disulfide linkages or acid-labile motifs, facilitate controlled RNA release in response to intracellular conditions encountered during cellular uptake and transfection. In addition, the conjugation of targeting ligands, including antibodies, peptides, and small-molecule motifs, enables active targeting of specific tissues and cell types. These advances significantly expand the potential of polymer-based RNA delivery systems and support their translation toward in vivo therapeutic applications.

L. Kaps, L. Nuhn [...], R. Zentel – Macromol. Rapid. Commun. 2015, 37, 924−933

P. Komforth, J. Imschweiler, [...] L. Nuhn – Biomacromolecules 2025, 26, 387−404

Abstract No. S5

Engineering mutation-specific and mutation-agnostic gene therapy approaches and their delivery

Dong-Jiunn Jeffery Truong[1,*], *Julian Geilenkeuser*[1], *Niklas Armbrust*[1], *Kai Fenzl*[2], *Julia Kornienko*[2], *Lars Steinmetz*[2], and *Gil Gregor Westmeyer*[1]

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Although advanced CRISPR editing tools such as base editors and prime editors have recently expanded genome-editing capabilities, their clinical use remains constrained by the lack of delivery systems that are both highly efficient and compatible with transient editor activity. Viral vectors such as adeno-associated viruses (AAVs) can support strong, long-term gene transfer, making them useful for gene therapies that replace deficient genes with functional copies. However, they are less suitable for delivering gene editors because prolonged expression increases off-target and bystander editing and elicits anti-editor immune responses. A safe alternative, therefore, requires a delivery approach that is transient yet highly efficient. Recent advances in engineering cell-derived enveloped particles help address this need by packaging and transferring genome-editing proteins and guide RNAs as preassembled RNPs. By systematically engineering particle assembly, cargo recruitment, and membrane fusion, we developed a highly efficient and modularly programmable platform for delivering diverse CRISPR effectors with high efficacy across multiple cell types, including in vivo corrections in mouse models of inherited retinal disease.

In contrast, mutation-specific gene-editing therapies can be difficult to adopt clinically and economically for genetically heterogeneous disorders. To address this challenge, we developed a mutation-agnostic, mechanism-driven strategy that uses a computationally designed chaperone to restore function to a pathogenic variant after protein translation. In mouse models of dilated cardiomyopathy (DCM), cardiotropic recombinant AAV delivery of these chaperons not only stopped disease progression but also restored cardiac function in advanced disease in both juvenile and adult mice. These findings demonstrate that inherited genetic disorders can be rescued post-translationally through artificial, de novo-designed binders.

Abstract No. S6

Viral vector-based gene therapies: current successes, limitations and technologies shaping the future

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Recombinant viral vectors derived from adeno-associated viruses (AAVs) have emerged as the leading technology for gene transfer in the field of translational virology. More recently, an unprecedented efficiency of AAV-driven genome editing without the need for endonucleases has been reported, further expanding the clinical applicability of this "simple" vector system. It also provides new hope for bridging the gap between currently available strong diagnostic powers and therapeutic benefit / improved health outcomes, especially in the underserved therapeutic area of rare and ultra-rare genetic disorder.

However, despite exciting in vivo preclinical data from multiple animal models and evidence of early clinical success, data accumulated from hundreds of AAV-based gene therapy trials convincingly demonstrate that current generation rAAV vectors remains unable to efficiently transduce human cells. This lack of clinical predictability is most probably an outcome of suboptimal AAV bioengineering mythologies applied to date as well as the use of biologically- and clinically-non predictive preclinical models in gene therapy development and validation studies. For AAV-based gene therapy to achieve its full potential and continue to fuel the healthcare revolution, novel vectors optimised for targeting human tissues are needed.

In his talk, Dr Lisowski will introduce and provide an overview of rAAV vecotorology and vector selection strategies aiming at identification of novel variants with desired (pre)clinical properties. The talk will highlight impacts of the selection process and selection system utilized on the function of identified candidates. Dr Lisowski will provide examples of how rAAV and genome editing tools can be combined to increase the efficiency and translational potential of both technologies. Finally, he will explain how the current technology can be applied to change lives of millions of children affected by rare genetic disorders, including sharing some exciting data from recently initiated AAV-CTNNB1 clinical trial in Slovenia.

Abstract No. S7

Scientific mobility in a changing world

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International collaboration is a fundamental part of modern science. Therefore, researchers are often expected to demonstrate a high degree of mobility, with PhD and postdoctoral training spanning multiple institutions and frequently multiple countries. For decades, North America, and particularly the United States, has been a primary destination for postdoctoral research.

In this career development session, we would like to discuss with scientists at different career stages the evolving scientific relationship between Germany, Europe, and the United States. We will explore questions such as: What is the current landscape for pursuing a postdoc in the U.S.? How is mobility shaping scientific careers today? How does the strong concentration of key scientific resources in the U.S. influence global research perspectives, and what could be the alternatives?

Company presentations

14th GSCN Conference

German Stem Cell Network

9 – 11 September 2026

Max Delbrück Center
Berlin

Company presentations: C01 – C13

C01 Streamlining advanced in vitro models: principles and tools for stem cell-derived NAMs
Katharina Debowski

C02 Enabling the future of cell therapy: from discovery to the clinic
Beau le Roy

C03 Next-generation synthetic peptide growth factors/cytokines for regenerative medicine and cell therapy
Kazuki Shigematsu

C04 Closing the analytical gap in cell therapy manufacturing: automated at-line flow cytometry for QC from research to GMP release
Félix A. Montero-Julian

C05 Integrating patient data and hiPSC microglia to model Alzheimer's disease for drug discovery
Bastian Zimmer

C06 3D bioreactor stem cell culture: consistent from R&D to commercial manufacturing
Philipp Nold

C07 Characterizing human PSC-derived cerebral organoids across imaging, cytometry, and sequencing
Hannah Johannsen

C08 Unlocking the future of gene-modified cell therapy with non-viral lipid-based transfection
Nadia Mazzaro

C09 Watching stem cells live: continuous live-cell imaging in iPSC and organoid research
Ceren Güneş

C10 Interrogating inflammatory signaling in human iPSC-derived pancreatic ductal organoids with a fully defined animal component-free matrix
Joel Cresser-Brown

C11 Advancing human relevant models: from AI-driven automated culture to high-content imaging and machine learning analysis - an end-to-end solution for iPSC and organoid workflows
Robert Storm

C12 Building more relevant and reliable human iPSC-derived neuronal models with the new neurobasal PhysioPlus medium
David Kuninger

C13 Innovative approaches and tools for investigating stem cell-based tissue culture
Francesca Aglialoro

Abstract No. C01

Streamlining advanced in vitro models: principles and tools for stem cell-derived NAMs

Katharina Debowski

STEMCELL Technologies Germany GmbH

Human pluripotent stem cell (hPSC)-derived models and organoids have transformed our understanding of complex biology. However, as these systems become increasingly integrated into drug discovery and regulatory safety testing, they encounter the framework of new approach methodologies (NAMs). A fundamental distinction exists between an exploratory academic assay, designed to uncover novel scientific insights, and a validated, qualified methodology, which serves as a highly standardized tool for formalized decision-making.

In this talk, we will highlight the key differences that distinguish a standard in vitro model from one designed as a decision-enabling tool. While basic research and formalized safety testing serve different primary purposes, emphasizing core principles like reproducibility, protocol transferability, and batch-to-batch consistency offers universal advantages. Prioritizing these elements helps mitigate internal experimental noise, strengthens data robustness for high-impact publishing, and facilitates smoother data integration during collaborative industry partnerships.

The rigorous consistency required for NAM qualification highlights the critical role of foundational cell quality and defined microenvironments. STEMCELL Technologies supports this dialogue by providing resources that extend beyond standard cell culture consumables. By offering highly standardized iPSC lines, fully defined differentiation systems, and robust organoid technologies, alongside technical support, educational resources, and training workflows, we help to minimize experimental drift and enhance protocol reproducibility.

This talk will provide an overview of the principles underpinning stem cell-derived NAMs and discuss tools provided by STEMCELL Technologies that enable the alignment of advanced in vitro research with these standards.

Abstract No. C02

Enabling the future of cell therapy: from discovery to the clinic

Beau le Roy

Acro Biosystems

no abstract available

Abstract No. C03

Next-generation synthetic peptide growth factors/cytokines for regenerative medicine and cell therapy

Kazuki Shigematsu

PeptiGrowth Inc.

Conventional sources of growth factors and cytokines, such as fetal bovine serum (FBS) and recombinant proteins, have been widely used in regenerative medicine, organoid and cell therapy fields. Despite their widespread use, concerns related to stability in cell culture, animal-derived materials, scalability, and high costs, as well as occasional lot-to-lot inconsistency, remain significant barriers to their broader application.

PeptiGrowth Inc. has established a platform of fully chemically synthesized peptide-based growth factors (PG-peptides) as an alternative to conventional growth factors and cytokines. Designed to mimic the biological activities of native proteins, PG-peptides achieve equivalent performance in receptor activation, cell proliferation, and cellular differentiation while containing no animal-derived components. In addition, their synthetic nature enables improved usability, extended shelf life, consistent product quality, and lower costs across research and development, manufacturing, and quality control.

We have currently launched 14 products (e.g., VEGF, FGF2, KGF and IL-15), and plan to launch IL-2 and IL-7 this year, 2026. We are also in the process of adding GMP-grade products for each item so that they can be used in clinical trials as well. We have generated many successful data across a wide range of applications, such as development of liver, nerve and lung alveolar organoids, pancreatic beta cells, iPS-derived NKT cells, and astrocytes using PG-peptides in the same manner as conventional growth factors and cytokines.

This presentation will introduce PG-peptide platform, a series of fully chemically synthesized peptide-based growth factors and cytokines, and demonstrate how these products can support research and manufacturing in regenerative medicine, organoid and cell therapy.

Abstract No. C04

Closing the analytical gap in cell therapy manufacturing: automated at-line flow cytometry for QC from research to GMP release

Félix A. Montero-Julian

Biomerieux, Accellix

Quality control remains one of the most significant constraints on the scale-up of stem cell–derived and engineered cell therapies. Characterization of cellular identity, purity, viability, and potency has long depended on centralized flow cytometry — a model that requires specialized operators, manual sample preparation, and turnaround times poorly matched to the tempo of GMP manufacturing. For autologous and short–shelf-life advanced therapy medicinal products (ATMPs), this delay directly affects batch disposition, cost, and patient access.

This presentation examines how cartridge-based, automated flow cytometry, repositioned at-line and adjacent to the manufacturing process, can resolve this bottleneck. By integrating standardized reagents, automated sample handling, and operator-independent analysis within a single closed system, the Accellix platform delivers reproducible, audit-ready cellular characterization without dependence on a centralized cytometry core.

Drawing on applications spanning pluripotent stem cell and hematopoietic workflows through CAR-T, NK, and TCR-engineered products, the talk will address how decentralized QC supports process development, in-process monitoring, and release testing under evolving FDA and EMA expectations. Particular attention will be given to assay standardization, data integrity, and the comparability challenges inherent in the clinical-to-commercial transition.

The aim is to position at-line analytics not as an incremental convenience, but as enabling infrastructure for scalable, reproducible, and regulatory-aligned manufacturing of next-generation cell therapies.

Abstract No. C05

Integrating patient data and hiPSC microglia to model Alzheimer's disease for drug discovery

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Drug discovery increasingly depends on human-relevant models that translate patient biology into experimentally tractable systems. At Evotec, we combine patient-derived molecular data with human induced pluripotent stem cell (hiPSC) technology to build in vitro disease models that better reflect complex human pathophysiology and support the discovery of more effective therapies. Alzheimer's disease (AD) provides a powerful example, as disease-relevant microglial states are difficult to capture in conventional model systems.

We generated a large-scale single-nucleus RNA sequencing atlas of human cortex by integrating newly generated and published datasets comprising 3.63 million nuclei from AD patients, cognitively normal controls, and cognitively resilient individuals. Genetic enrichment and high-resolution subclustering identified microglia as a major cellular compartment linked to AD risk and revealed a continuum of homeostatic, transitional, and disease-associated states. Disease- and lipid-associated microglia were strongly associated with AD pathology and cognitive decline, including subtypes linked to amyloid-related processes and lipid metabolism/tau-associated signatures.

To translate these patient signatures into a functional model, we exposed hiPSC-derived microglia to disease-relevant perturbations. Ferric ammonium citrate induced a disease- and lipid-associated microglial program with upregulation of AD risk genes including APOE and TREM2, activation of lipid metabolic pathways, impaired amyloid-β phagocytosis, reduced lysosomal degradation, and increased lipid droplet accumulation.

We then used this patient-anchored hiPSC model for pharmacological intervention. The GSK3 inhibitor LY2090314 reduced inflammatory and lipid-associated signatures, enhanced lysosomal and metabolic pathways, restored phagocytic and degradative functions, and shifted microglia toward a lysosome-enriched homeostatic phenotype.

Together, this work illustrates how Evotec integrates patient data and stem cell technology to create translational in vitro disease models. Linking human disease signatures to functional hiPSC phenotypes enables more predictive drug discovery and may ultimately support the development of better therapies for complex diseases such as AD.

Abstract No. C06

3D bioreactor stem cell culture: consistent from R&D to commercial manufacturing

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In recent years, we saw an advent of revolutionary stem cell approaches which require both research and development as well as manufacturing capabilities. In both cases, achieving sufficient numbers of functional stem cells in a standardized and reproducible process is crucial. Yet, these goals are hard to achieve with conventional methods, like 2D cell culture. An unnatural non-3D growing environment with limited growing space, uneven distribution of important culture components like nutrients and dissolved oxygen, but also less control over process parameters like pH or gassing pose bottlenecks to reach the full culture potential. Bioreactors can be a viable alternative for their ability to precisely control multiple process parameters, as well as enabling process intensification for a productive and regulated 3D cell culture. Learn in this talk how to achieve high cell densities of up to 33 × 106 cells/mL in bioreactors by process optimization and intensification approaches in R&D, and how to keep hardware and software environments consistent for the transition to commercial manufacturing.

Abstract No. C07

Characterizing human PSC-derived cerebral organoids across imaging, cytometry, and sequencing

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Organoids are becoming increasingly important models for studying human biology in a three-dimensional context, but their value depends on the ability to characterize them with readouts that capture structure, cell composition, and molecular state. Here, we present cerebral organoids generated from human iPSC lines under matrix-free conditions and analyzed them with complementary tools to explore organoid structure and cellular composition. Organoids were matured for up to 103 days and showed robust formation, reproducible size progression, and high viability after dissociation.

Characterization included cyclic immunofluorescence, 3D light-sheet microscopy, flow cytometry, and single-nuclei RNA sequencing. On a day 60 organoid section, cyclic immunofluorescence was performed on the MACSima™ Platform and showed clear spatial organization and distinct marker-defined cellular patterns within the organoid. 3D light-sheet microscopy on the UltraMicroscope Blaze was used to analyze cleared whole organoids and provided an intact 3D view of organoid architecture. For flow cytometry, samples were prepared by combined enzymatic and mechanical dissociation, which preserved high viability and enabled analysis of shifts in the cellular profile between day 60 and day 100 over time. Single-nuclei RNA sequencing followed nuclei extraction and enrichment by high-speed microfluidic cell sorting, further resolving the major cellular populations present in the model.

Together, these data show how complementary imaging, cytometric, and sequencing-based tools can be used in a practical and flexible way to generate a comprehensive view of organoid structure and cellular composition.

Abstract No. C08

Unlocking the future of gene-modified cell therapy with non-viral lipid-based transfection

Nadia Mazzaro

Scientific Support, Sartorius

The success of translational cell therapy hinges on seamless integration of drug discovery into the operational and regulatory demands of clinical manufacturing. This session explores how early decisions made during research and development can reduce downstream barriers when moving to GMP-compliant, clinical-scale production. Attendees will gain insight into aligning best practices with regulatory expectations, adopting industry standards to support translation from academia, and leveraging collaborations to accelerate the path from laboratory discovery to patient-ready cell therapies.

Join this session to:

- Understand common translational challenges when progressing cell therapies from discovery to clinical manufacturing.

- Learn best practices in advancing cell therapy programs in alignment with regulatory expectations.

- Explore how partnerships and collaborations support clinical viability and accelerate translational success.

Abstract No. C09

Watching stem cells live: continuous live-cell imaging in iPSC and organoid research

Ceren Güneş

Countstar

Stem cell cultures and organoids are highly dynamic systems, making continuous observation valuable for understanding growth, morphology, and differentiation. Live-cell imaging enables researchers to capture these processes over time, providing insights that endpoint assays miss while minimizing disruption to the culture.

In this presentation, we will demonstrate how **Countstar's Spica M6** continuous live-cell imaging system can support iPSC and organoid research through automated image acquisition and quantitative analysis. We will present applications spanning cell health monitoring, label-free cell counting, organoid tracking, and the generation of reproducible time-lapse datasets with minimal hands-on intervention.

The Spica M6 combines advanced optics and multiple fluorescence channels to accommodate a wide range of complex assays—from 2D stem cell cultures with diverse morphologies to organoids, drug screening, and long-term organoid tracking. Its Stellar AI analysis is trained specifically for these demanding samples, ensuring that analytical capability keeps pace with biological complexity rather than limiting it.

This session offers practical guidance for integrating continuous live-cell imaging into your stem cell workflows, from routine culture monitoring to differentiation studies and organoid development, supporting more informed experimental decisions and improved reproducibility. For those interested in seeing it live, come by **booth 13**, where we can showcase the Spica M6 in action.

Abstract No. C10

Interrogating inflammatory signaling in human iPSC-derived ductal organoids with a fully defined animal component-free matrix

*Joel Cresser-Brown**, *Xi Lu*, *John Leerar*, *John Leerar*, *Ashley Oliver*, *Bhamini Purandare*, *Callie Sagarsky*, *Surashree Kukarni*, *Jodi Hagen*, *Francisco Ramirez*, *Didarul Bhuiyan*, and *Chris Heger*

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Pancreatitis is a leading cause of gastrointestinal hospitalization, yet the mechanisms underlying the development of this condition remain poorly understood. Mechanistic studies have been limited by the availability of physiologically relevant in vitro models. Aberrant ductal inflammatory signaling is increasingly recognized as a key contributor to pancreatic injury. Induced pluripotent stem cell (iPSC) derived pancreatic ductal organoids (PDLOs) may provide a scalable and genetically tractable platform for modeling inflammation in the pancreas under both healthy and diseased context. However, most organoid systems rely on basement membrane extract (BME), which is an undefined matrix where residual peptides, transcription and growth factors may confound experimental outcomes and reduce reproducibility. Here, we evaluated a fully defined and synthetic hydrogel (Cultrex™ Synthetic Hydrogel) as an alternative extracellular matrix for culturing PDLOs. Organoid formation efficiency, morphology, and growth kinetics were compared directly between BME and synthetic hydrogel. PDLOs cultured in the synthetic hydrogel expanded robustly, formed organized cystic structure, and maintained ductal identity, as demonstrated by expression of canonical ductal markers including SOX9 and KRT19. Organoid function was verified using a forskolin induced swelling assay. To model inflammatory injury, PDLOs were stimulated with TNF-α and IL-1β and activation of stress and damage pathways were assessed by the presence of markers such as NF-κB, STAT3, and cleaved caspase-3. Cell identity and pathway activation were quantified for protein analysis using Simple Western™ and a multiplexed spatial assay on the COMET™ platform. The results demonstrate that iPSC derived PDLOs combined with the synthetic hydrogel provides a controlled, reproducible platform for interrogating ductal inflammatory signaling and enabling more precise mechanistic studies for pancreatitis.

Abstract No. C11

Advancing human relevant models: from AI-driven automated culture to high-content imaging and machine learning analysis - an end-to-end solution for iPSC and organoid workflows

Robert Storm

Molecular Devices (Germany) GmbH

The increasing adoption of stem cell-derived models, organoids, spheroids, and other complex 3D culture systems promises more physiologically relevant biology for disease modeling, drug discovery, and regenerative medicine. However, widespread implementation remains challenged by variability in culture methods, operator-dependent decision making, limited scalability, and difficulties in establishing reproducible workflows across laboratories. Consistency in both culture and phenotypic analysis is essential for generating robust and transferable biological insights.

Here we demonstrate an integrated approach combining automated cell culture, intelligent monitoring, and advanced high-content imaging to address these challenges. The CellXpress.ai Automated Cell Culture System (1) enables standardized, around-the-clock culture, maintenance, monitoring, and propagation of stem cells and 3D biological models using image-based, AI-assisted decision-making. Quantitative image analysis can be used to guide workflow progression, reducing subjectivity and improving experimental consistency.

To further characterize complex phenotypes, the ImageXpress HCS.ai platform can provide accessible, high-end, laser-based spinning-disk confocal imaging with the throughput required for modern 2D and 3D assays. A key advantage of this integrated workflow is the shared, deep-learning-enabled image analysis environment that operates across both systems. This framework supports automated decision-making during culture, as well as high-content analysis of intermediate or endpoint confocal imaging, creating a seamless workflow from cell maintenance to biological discovery. Together, these technologies help researchers increase reproducibility, standardization, scalability, and confidence in stem cell and organoid research.

(1) Sirenko O, Michlmeier A, et al., CellXpress.ai: Machine learning powered system for automation of complex 2D and 3D cell culture workflows. SLAS Technology 39 (2026) 100427. https://doi.org/10.1016/j.slast.2026.100427

Abstract No. C12

Building more relevant and reliable human iPSC-derived neuronal models with the new neurobasal PhysioPlus medium

David Kuninger

Thermo Fisher Scientific

Human iPSC-derived neuronal models are increasingly used to investigate nervous system development, disease mechanisms, and therapeutic responses, and the composition of the neuronal culture medium is an important determinant of neuronal maturation, network development, and experimental reproducibility. This presentation will discuss the role of physiologically relevant culture conditions in supporting robust neuronal function and introduce Neurobasal™ PhysioPlus Medium, a newly developed medium designed to better reflect the extracellular environment of the central nervous system. Across primary and human iPSC-derived neuronal cultures, Neurobasal PhysioPlus Medium, used with B-27™ Plus Supplement, supported greater neuronal survival compared to traditional systems, earlier onset of spontaneous network activity, and electrophysiological properties consistent with enhanced neuronal maturation. These findings highlight how optimization of the neuronal culture environment can improve the relevance and reliability of human in vitro neuronal models.

Abstract No. C13

Innovative approaches and tools for investigating stem cell-based tissue culture

Francesca Aglialoro

Corning Life Sciences

Stem cell-based tissue culture provides valuable models for investigating human development, disease, therapeutic responses, and regenerative biology. As the adoption of three-dimensional (3D) cell culture continues to grow, increasing attention has been directed toward specialized low-attachment culture surfaces, such as ultra-low attachment (ULA) platforms, which promote cell aggregation, self-organization, and the formation of biologically relevant spheroids and organoids. Building on this concept, Elplasia® microcavity plates enable the scalable and reproducible generation of highly uniform spheroids and some specific organoids. Corning® Matrigel® remains a cornerstone technology for recreating a basement membrane-like microenvironment that supports stem cell self-renewal, differentiation, organoid formation, and tissue morphogenesis.

Robust culture performance also depends on optimized media systems that support reliable cell expansion while preserving critical cellular characteristics across research and translational workflows. In this context, specialized Corning® mesenchymal stem cell (MSC) media are designed to promote cell growth, viability, and phenotype maintenance, helping to improve consistency and reduce variability as processes advance toward larger-scale applications.

Together, these tools create powerful, integrated platforms for investigating stem cell behavior, cell-cell interactions, and tissue development, enabling the generation of more predictive and physiologically relevant tissue models that accelerate translational research and therapeutic innovation.

Poster presentations

14th GSCN Conference
German Stem Cell Network

9 – 11 September 2026

Max Delbrück Center
Berlin

Poster session I: P001 – P087

Wednesday, 9 September

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P012 – P016: Computational stem cell biology page 128
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Note: posters P064 – P087 will be displayed in the MDC.C Foyer – Mezzanine

Even numbers: 16:30 - 17:30 h
Odd numbers: 17:30 - 18:30 h

Poster session II: P088 – P171

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P136 – P142, X1: Stem cells in aging & disease (cancer stem cells) page 264, X1
P143 – P172: Tissue-derived stem cells & organoids page 272

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Odd numbers: 18:00 - 19:00 h

Poster sessions I: P001 – P087

(the TXX number indicates an accompanying oral presentation)

P001 – P011: Basic, translational & applied hematopoiesis

P001 From data to dynamics: mechanistic modeling reveals heterogeneity and quiescence of hematopoietic stem cells
Ingmar Glauche

P002/T07 The development of simultaneous single-cell tRNA and mRNA profiling reveals dynamic tRNA programs in human hematopoiesis
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P003 2D and 3D in vitro models for human mast cells in the skin reveal complex interactions with dermal fibroblasts
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P004 Intermittent fasting remodels hematopoietic stem cells during obesity through coordinated transcriptional and regulatory reprogramming
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P005 Allele-specific transcriptional rebalancing preserves OCT4 dosage in heterozygous human iPSCs
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P006 Emergency megakaryopoiesis as a key driver of chronic inflammatory diseases
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P007/T10 Molecular characterization and functional interrogation of dormant cancer stem cells in JAK2V617F-driven myeloproliferative neoplasms
Elif Saf

P008 Continuous generation of functional human iPSC-derived NK cells in a scalable hematopoietic organoid system
Fawaz Saleh

P009 Feeder-free expansion of iPSC-derived NK cells to clinical scale
Daniel Terheyden-Keighley

P010 CD34+ cells cultured in a GMP compliant automated engineering process reflect manual culture based on transcriptomic and epigenetic characterization
Vithurithra Tharmapalan

P011 Functional perturbation of tRNAs to investigate regulatory roles in human hematopoietic differentiation
Anna-Sophia Wiegand

Abstract No. P001

From data to dynamics: mechanistic modeling reveals heterogeneity and quiescence of hematopoietic stem cells

Ingmar Glauche[1,*], *Yuri Garcia Vilela*[1], *Lars Thielecke*[1], and *Artur César Fassoni*[2]

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Hematopoietic stem cells (HSCs) maintain lifelong production of blood by balancing self-renewal and differentiation. However, certain aspects of their divisional dynamics, namely the role of quiescence and the intrinsic heterogeneity of the HSC pool, are not completely understood. High-resolution clonal tracking provides a powerful resource to investigate such dynamics as the data captures patterns of clonal persistence, dilution and late clonal emergence. Here, we apply mechanistic mathematical modeling to longitudinal clonal data from non-human primates to investigate the divisional dynamics of HSCs, particularly the role of quiescence and the intrinsic heterogeneity of the stem cell pool.

We show that models treating HSCs as a single, homogeneous population can explain the gradual loss of clonal diversity, but fail to reproduce clone size distributions and the long-term persistence of small and late-appearing clones. To address this, we propose a stochastic, two-compartment model in which HSCs transition reversibly between an actively cycling state and a quiescent, potentially niche-bound state. Compared to the simpler one-compartment model, this advanced framework provides a substantially improved fit for different metrics, consistently captures clone size distributions and explains the delayed activation and sustained coexistence of small and large clones.

These results provide quantitative evidence that heterogeneity within the HSC pool, particularly the existence of a reversible quiescent state, is critical to account for clonal aspects of long-term hematopoiesis. Our findings highlight how clonal data can uncover underlying regulatory mechanisms and supports a central role for niche-mediated HSC quiescence in maintaining stable and diverse blood production over time.

Abstract No. P002/T07

The development of simultaneous single-cell tRNA and mRNA profiling reveals dynamic tRNA programs in human hematopoiesis

Marius Külp[1,*], *Mireia Osuna Lopez*[2], *Stefan Günther*[3], *Tessa Schmachtel*[1], *Hendrik Schultheis*[3], *Mario Looso*[3], *Björn Häupl*[1], *Thomas Oellerich*[1], *Vladimir Benes*[2], *Halvard Bonig*[4], and *Michael A. Rieger*[1]

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Hematopoiesis is the tightly regulated regeneration of all blood cell types life-long. Transfer RNAs (tRNAs) play a central role in translation by decoding mRNA codons into amino acids, thereby shaping proteomic output. While tRNA abundance varies across tissues, its dynamics and functional relevance during hematopoietic differentiation remain largely unexplored.

We aimed to map tRNA expression and processing at single-cell resolution in human hematopoiesis and to determine how tRNA dynamics are associated with molecular programs of cell identity and differentiation trajectories.

We developed the first single-cell simultaneous tRNA and mRNA sequencing approach (sc-STM-seq), a scalable, polyadenylation-independent high-throughput method that captures full-length tRNAs alongside mRNAs in individual cells. We applied sc-STM-seq to human bone marrow mononuclear cells from healthy donors and performed integrative bioinformatic analyses.

sc-STM-seq enabled robust detection of full-length tRNAs and mRNA transcriptomes across thousands of single cells, with strong concordance to bulk tRNA-seq on prospectively isolated cell populations. We identified cell type-specific tRNA expression patterns and differential tRNA splicing across hematopoietic populations. During early hematopoietic stem and progenitor cell (HSPC) differentiation, tRNA expression exhibited dynamic, lineage-associated changes, including stemness-associated tRNAs (e.g. tRNA-SeC-TCA, tRNA-Gln-CTG) and differentiation-associated tRNAs (e.g. tRNA-Asp-GTC, tRNA-Lys-TTT). Extending these analyses to global differentiation trajectories confirmed lineage-specific and trajectory-dependent tRNA regulation, with distinct dynamics across monocytic, erythroid, B cell, and plasmacytoid dendritic cell lineages. Notably, tRNA-Asp-GTC was strongly associated with monocytic differentiation. Furthermore, tRNA expression profiles alone were sufficient to distinguish major hematopoietic cell types, particularly HSPCs, indicating that tRNA landscapes contribute to cellular identity.

Our study provides the first comprehensive single-cell atlas of tRNA expression in human hematopoiesis. We demonstrate that tRNA abundance and processing are dynamically regulated during differentiation and contribute to cellular heterogeneity and identity. These findings establish tRNA regulation as a previously underappreciated layer of gene expression control in blood cell development.

Abstract No. P003

2D and 3D in vitro models for human mast cells in the skin reveal complex interactions with dermal fibroblasts

Duncan Miller[1, 2,*], *Mengjie Hu*[1,2], *Yanyan Luo*[1,2], *Stefan Frischbutter*[1,2], *Frank Siebenhaar*[1,2], and *Jörg Scheffel*[1,2]

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Background
Primary human skin mast cells (hsMCs), isolated in vitro or used within ex vivo skin biopsies, are invaluable for studying skin-relevant allergens, pathologies, and novel therapeutics. However, they are often limited in availability and quantity, and hampered by inter-donor variability.

Peripheral blood stem cell-differentiated mast cells (PSCMCs) and human induced pluripotent stem cell-differentiated mast cells (hiPSC-MCs) provide more readily available MCs, although following in vitro derivation may not exhibit the same phenotype as freshly isolated hsMCs.

Aims
Establish 2D and 3D culture systems to enhance mast cell (MC) phenotypes in vitro, and identify factors which regulate MC survival and function in a skin-relevant context.

Methodology
PSCMCs or hiPSC-MCs were cultured in 2D directly with primary human dermal fibroblasts (HDFs), or incorporated into 3D skin organotypic cultures (OTCs) comprised of primary HDFs and keratinocytes. MCs were then tested and characterised for survival, marker expression, and function.

Results
Compared to control conditions, MCs cocultured with HDFs exhibited a shift in expression of several classic surface markers and a more diverse cytokine release profile. HDFs supported higher MC viability when exogenous SCF was reduced, and hiPSC-MC response to IgE stimulation was increased. MCs in 3D skin OTCs exhibited viability and functionality after a one-week period.

Conclusions
These versatile culture systems enhance in vitro MC phenotypes and reveal complex interactions in the skin. They can be applied to a broad range of disease modelling and compound testing studies. Refinement of this approach continues, with a view towards incorporating additional cell types.

Abstract No. P004

Intermittent fasting remodels hematopoietic stem cells during obesity through coordinated transcriptional and regulatory reprogramming

Bipasha Nandi Jui[1,*], *Francisco Garcia-Carrizo*[1], *Masoome Oveisi*[1], *Marina Leer*[1], *George Soultoukis*[1], *Sabrina Gohlke*[1], *Kyung Mok Kim*[2], *Björn von Eyss*[2], and *Tim J. Schulz*[1, 3]

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Obesity promotes hematopoietic stem cell (HSC) dysfunction through metabolic stress, resulting in compositional changes and increased activation. Intermittent fasting (IF) generally improves metabolic health, but the molecular mechanisms underlying its effects on HSCs remain poorly understood. Here, we investigated how IF remodels the HSC compartment in the New Zealand Obese (NZO) mice, a polygenic model of metabolic syndrome under ad libitum (AL) food access, using flow cytometry, bulk and single-cell RNA sequencing, and consensus regulatory network analysis.

IF reduced body weight and normalized blood glucose levels in mice, although animals remained severely obese. In the bone marrow, it attenuated expansion of the activated short-term HSC (ST-HSC) compartment. Bulk RNA sequencing identified enrichment of Gene Ontology (GO) terms related to "leukocyte proliferation" and "positive regulation of cell activation" in AL-fed mice, whereas terms "fatty acid metabolic process" and "response to xenobiotic stimulus" were enriched following IF. Single-cell RNA sequencing identified an LT-HSC-enriched cluster with increased lipid metabolism and detoxification-related biological processes following IF. Conversely, an AL-specific ST-HSC subpopulation was enriched for cytoplasmic translation and oxidative phosphorylation. Across both datasets, gene set scoring demonstrated increased quiescence, autophagy, and fatty acid metabolism, together with reduced senescence following IF.

To identify conserved regulatory mechanisms, we computationally integrated transcription factor (TF) activity and target-gene enrichment from the bulk and single-cell datasets. Consensus analysis identified five TFs, TEAD1, STAT3, AHR, IRF9, and STAT2, with TF-target gene interactions in both datasets. Among these, previous studies have linked AHR signaling to HSC quiescence, maintenance, and xenobiotic detoxification. Canonical AHR target genes, including Cyp1a1, Cyp1b1, Ugt1a6a, and Nqo1, were significantly upregulated in IF samples (all $P < 0.05$), indicating activation of an AHR-regulated detoxification program that may support HSC quiescence and long-term maintenance. Together, these findings identify candidate regulatory modules underlying restoration of HSC homeostasis during intermittent fasting.

Hatori M et al. Time-restricted feeding without reducing caloric intake prevents metabolic diseases in mice fed a high-fat diet. Cell Metab. 2012;15:848-860.

Kim Y et al. Time-restricted feeding reduces monocyte production by controlling hematopoietic stem and progenitor cells in the bone marrow during obesity. Front Immunol. 2022;13:1054875.

Abstract No. P005

Allele-specific transcriptional rebalancing preserves OCT4 dosage in heterozygous human iPSCs

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Biological systems exhibit remarkable robustness against genetic mutations, yet how early embryonic cells buffer against the loss of highly dosage-sensitive genes remains a central paradox. The master pluripotency regulator OCT4 (*POU5F1*) operates under exceedingly strict dosage constraints in human pluripotent stem cells (hPSCs); slight deviations trigger rapid differentiation or developmental failure. Consequently, how hPSCs survive heterozygous loss-of-function mutations in such critical regulators is largely unknown.

Building on our recent discovery of allele-specific transcriptional rebalancing (ASTR), a cis-acting mechanism preserving gene dosage following heterozygous gene disruption, we investigated whether a similar compensatory response safeguards core pluripotency networks. Using prime editing, we generated isogenic hPSC lines carrying heterozygous premature termination codon mutations in *OCT4*. Strikingly, preliminary allele-specific expression analyses reveal that total *OCT4* transcript abundance is maintained. Despite selective depletion of mutant transcripts, the intact wild-type allele dynamically increases its transcriptional contribution to rescue gene dosage. Current work utilizes allele-resolved transcriptomics, single-cell RNA-seq, and targeted CRISPR modifier screens to define the molecular machinery driving ASTR and determine how disrupting these pathways compromises developmental competence.

By extending ASTR from a housekeeping gene to a master developmental regulator, this project aims to establish allele-specific transcriptional buffering as a fundamental mechanism of cellular resilience, providing new insights into developmental robustness and variable disease penetrance.

Abstract No. P006

Emergency megakaryopoiesis as a key driver of chronic inflammatory diseases

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Many chronic inflammatory diseases (CIDs) are associated with dysregulated hematopoiesis and a persistent state of low-grade inflammation. Yet, the cause for this disturbance and its link to chronic inflammation remain unknown. Dysregulated Emergency Megakaryopoiesis (EM) may be central to this inflammatory shift since life-threatening thrombocytopenia caused by infections triggers EM to push dormant bone marrow hematopoietic stem cells (HSCs) to bypass hierarchical stages to expedite platelet production. This impairs HSC versatility and function over time, resulting in expansion of platelet-biased HSCs. We hypothesize that repeated or persistent exposure to inflammation dysregulates EM, causing long-term platelet-biased hematopoiesis and resulting severe health risks. We will investigate the effects of sterile and virus-induced thrombocytopenia, as well as immune training, on human and mouse HSCs using flow cytometry, transcriptomics and other functional assays. We will disrupt EM in mouse models to assess platelet bias and resulting development of hyperinflammation and susceptibility to CIDs. This project will decipher the role of dysregulated EM and platelet-biased HSCs in chronic inflammation. Beyond that, it will pave way for novel therapeutic strategies to prevent CIDs and immune system aging.

Abstract No. P007/T10

Molecular characterization and functional interrogation of dormant cancer stem cells in JAK2V617F-driven myeloproliferative neoplasms

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Polycythemia vera (PV) is a myeloproliferative neoplasm driven by hematopoietic stem cell (HSC) clones carrying activating JAK2 mutations, most commonly JAK2V617F, which cause constitutive JAK–STAT signaling and excessive blood cell production. Although JAK inhibitors and IFN-α can control symptoms, relapses after treatment discontinuation is common, suggesting persistence of disease-propagating cells.

Here, we focus on the role of hematopoietic stem cell states in sustaining PV. We use a JAK2V617F mouse model combined with an inducible H2B-GFP label-retention system to identify and isolate dormant mutant HSCs in vivo. This system distinguishes actively cycling stem cells, which dilute GFP during proliferation, from quiescent, long-lived HSCs that retain the label. This allows isolation of dormant mutant HSCs and direct comparison with actively cycling mutant counterparts.

We show that dormant, label-retaining mutant HSCs persist and remain identifiable for up to five months during disease progression, despite the pro-proliferative JAK2V617F mutation. Notably, these cells are resistant to the JAK2 inhibitor Fedratinib and IFN-α treatment. Transplantation experiments reveal that only dormant, label-retaining cells can re-initiate disease, identifying them as key drivers of disease propagation and likely reservoirs of therapy resistance.

Molecular profiling reveals that label-retaining mutant HSCs adopt a distinct transcriptional and epigenetic state compared with active mutant counterparts, with altered inflammatory and metabolic pathways. Furthermore, combining low-dose IFN-α with the Fedratinib synergistically reduces the dormant HSC compartment, identifying a potential therapeutic strategy to target these therapy resistant cells.

Together, our results identify a dormant mutant HSC population as the central reservoir of PV persistence and relapse, highlighting these cells as a critical target for therapies.

Abstract No. P008

Continuous generation of functional human iPSC-derived NK cells in a scalable hematopoietic organoid system

Fawaz Saleh[1], *Lucas Rebuffet*[2], *Roland Jacobs*[1], *Agnes Bonifacious*[1], *Berislav Čuvalo*[1], *Emilio Valdivia*[1], *Adrien Mazuel*[2], *Reinhold Förster*[1], *Britta Eiz-Vesper*[1], *Greta Meyer*[1], *Svenja Gaedcke*[1], *Sabine Buyny*[1], *Dominik Schmiedel*[3], *Duck Cho*[4], *Marco Carvalho Oliveira*[1], *Christine Falk*[1], *Adan C. Jirmo*[1], *Gesine Hansen*[1], *Eric Vivier*[2], and *Nico Lachmann*[1]

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Induced pluripotent stem cell (iPSC)-derived natural killer (iNK) cells offer an off-the-shelf platform for cancer immunotherapy, but scalable production and consistent functionality remain key challenges. Deeper analytical and bioprocess insights into scalable manufacturing is needed to improve the quality, consistency, and affordability of these cellular products. Here we presents a scalable manufacturing bioprocess that enables continuous generation of phenotypically stable iNK cell intermediates with emerging functional properties across small- (3 mL) to moderate-scale (50mL) benchtop bioreactors. Guided mesodermal induction followed by cytokine-driven hematopoietic specification, yielded $CD45^{+}CD3^{-}CD7+CD56^{+}$/- iNK subsets with dynamic surface-marker expression and reproducible yields across production scales, achieving approximately 50-fold amplification per input iPSC. Phenotypic and functional stability without scale-dependent differences in iNK subset composition or receptor expression, including KIR profiles. Differentiation generated transcriptionally distinct iNK populations, whereas expansion preferentially enriched $CD56^{+}$ subsets and increased expression of activating receptors (DNAM-1 and NKG2D), alongside dynamic regulation of inhibitory receptors. The resulting iNK cell populations displayed heterogeneous developmental states with transcriptional programs resembling primary NK cells, including activation-associated and cytokine-induced memory-like signatures. Bioreactor-based production supported sustained sequential harvests without compromising phenotype, cytotoxic function, or subset diversity. Expansion enhanced lytic activity, target-cell apoptosis, degranulation, expanded iNK cells maintained cytolytic effector molecule secretion comparable to expanded primary NK cells and displayed migratory behavior comparable to donor derived peripheral blood NK cells. Collectively, this bioprocess establishes a continuous, scalable platform for manufacturing iNK cells that preserves phenotypic diversity, transcriptional complexity, and functional competence across production scales, supporting cost-effective manufacturing of next-generation cell-based immunotherapies.

Abstract No. P009

Feeder-free expansion of iPSC-derived NK cells to clinical scale

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Natural killer (NK) cells are members of the innate immune system; however, they also have a bridging function to the adaptive immune system, killing cells targeted by B cell antibodies. This antibody-dependent cellular cytotoxicity (ADCC) can be exploited in combinatorial therapy using therapeutic antibodies, which is especially relevant for heavily pre-treated patients with compromised immune systems due to first-line chemo/radiotherapy.

NK cells from allogeneic sources have been proven to be safe, enabling large-scale manufacturing from a single donor for off-the-shelf therapies. Traditional donor-derived NK cell manufacturing faces challenges such as donor-to-donor variability and inefficient gene delivery, leading to inconsistent production. iPSC-derived NK cells offer a consistent, practically unlimited source material with the advantage of precise, one-time gene-editing. However, current methods using iPSCs often depend on embryoid body-based differentiation and cancerous feeder cells, creating additional complexities for clinical scalability.

An iPSC-derived NK cell platform was developed to address these challenges by enabling feeder-free expansion at clinical scale. This process uses defined media to expand and bank NK precursor cells at small scale before transitioning to cost-effective media for large-scale expansion. The developed protocol successfully expands up to several 100,000 NK cells per input iPSC in a feeder-free process. The resulting NK cells exhibit high purity, robust activation marker expression, and potent cytotoxic activity against target cells. In addition, we demonstrate the advantage of gene-edited NK cells by enhancing ADCC, resulting in the elimination of solid tumors in vitro. This platform provides a highly scalable, GMP-compatible, and feeder-free process sufficient for economically viable clinical applications.

Abstract No. P010

CD34+ cells cultured in a GMP compliant automated engineering process reflect manual culture based on transcriptomic and epigenetic characterization

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Hematopoietic stem and progenitor cells (HSPCs) are rare bone marrow resident cells responsible for self-renewal and differentiation, thereby sustaining hematopoietic homeostasis. *Ex vivo* cell and gene therapies for hematological malignancies have emerged as promising therapeutic strategies, particularly when combined with automated and closed platforms that support reproducibility and reduce operator dependent variation. Preserving the cells as closely as possible to their uncultured state is critical, and understanding culture associated changes may help to optimize clinical translation.

In this study, we compared CD34+ HSPCs cultured with the Hematopoietic Stem Cell Engineering Large Scale (HSCT-LS) Process in the CliniMACS Prodigy automated system with manually cultured CD34+ cells. A two day culture process showed comparable results between both conditions in terms of cell recovery, colony formation in CFU assays, and engraftment potential in NSG mice. In addition, lentiviral transduction of CD34+ cells showed similar transfection efficiencies in Prodigy cultured and manually cultured cells.

To further assess culture associated effects, we analyzed samples cultured for 2 days in the Prodigy and in parallel manual conditions, alongside uncultured CD34+ cells from five donors. DNA methylation analysis using the EPIC array revealed significant differences between day 0 uncultured and day 2 cultured cells, while Prodigy cultured and manually cultured CD34+ cells showed no significant methylation differences. RNA sequencing showed overall close transcriptional similarity between the two culture conditions, with hardly any differentially expressed genes.

Taken together, these results show that the CliniMACS Prodigy automated culture system closely mirrors conventional manual culture and supports reproducible HSPC processing for clinical applications.

Abstract No. P011

Functional perturbation of tRNAs to investigate regulatory roles in human hematopoietic differentiation

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Transfer RNAs (tRNAs) deliver amino acids to the protein synthesis machinery, acting as adaptor molecules that translate mRNA into protein. Although long considered ubiquitously present, tRNA abundance has been shown to influence elongation speed and, consequently, nascent protein levels and folding. The balance between tRNA supply and demand is therefore critical for efficient protein translation and for adaptive responses in developing cells.

We have previously characterized tRNA supply across hematopoietic populations, revealing dynamic changes associated with lineage specification. Building on these findings, we now systematically investigate how individual tRNAs influence differentiation and translational control in human hematopoietic stem and progenitor cells (HSPCs).

To elucidate the role of individual tRNA genes, we will perform the first lentiviral overexpression screen of distinct tRNA isodecoders in primary HSPCs. In parallel, we will use Cas9-expressing THP-1 and SEM cells to conduct a targeted knockdown screen with gRNA libraries covering all annotated tRNA genes, employing a destabilized fluorescent protein as a reporter of translational output.

Together, these complementary approaches aim to generate a comprehensive map of tRNAs that modulate differentiation and translation efficiency in hematopoietic cells. Our findings are expected to uncover previously unrecognized regulatory layers linking tRNA abundance to hematopoietic differentiation.

P012 – P016: Computational stem cell biology

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Abstract No. P012/T12

Slow genes are soft genes: lineage memory and perturbation sensitivity share a common origin

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Isogenic cells in a common environment differ substantially in gene expression, and some of that variation is not transient noise but is inherited: sister cells resemble each other more than unrelated cells, sometimes for many divisions. Genes carrying such memory relax slowly relative to cell division, whereas most genes fluctuate within a fraction of a division. What distinguishes these genes functionally remains largely unresolved.

Across multiple lineage-barcoded single-cell RNA-seq datasets, four independent memory-callers (Coral, GEMLI, PowerSeek, and our own sister-pair concordance estimator) converged on a shared set of memory genes that cannot solely be explained by confounders such as expression level. Comparing these genes against perturbation data spanning hundreds to thousands of gene knockouts, we found that memory genes respond systematically more strongly than non-memory genes.

We propose that this follows from linear response theory. How long a gene's expression stays correlated with its own past state, and how strongly it responds to a sustained perturbation, are both set by its relaxation rate. That is, memory and perturbation-sensitivity are two readouts of the same quantity. For a stable Jacobian (the linearized gene-regulatory dynamics at steady state), the per-gene response ratio between memory and non-memory genes reduces to the ratio of their relaxation times, providing a parameter-free prediction that we test against the observed effect size.

Memory genes have modestly longer mRNA half-lives than non-memory genes, but the distributions overlap, and half-lives are short relative to the timescale of memory. By estimating relaxation and degradation rates in the same cells, we ask whether memory genes relax more slowly than their turnover and dilution allow, implicating self-reinforcing regulation rather than molecular stability. Finally, we test whether heritable expression is concentrated in a few collective modes and whether perturbation responses align with them, which would indicate an underlying shared network structure.

Goyal et al., 2023, Diverse clonal fates emerge upon drug treatment of homogeneous cancer cells, Nature
Filipczyk, Marr*, Hastreiter* et al., 2015, Network plasticity of pluripotency transcription factors in embryonic stem cells, Nature cell biology*

Abstract No. P013

Cell-type-level negative matrix factorization (NMF) competes with deep learning for integrative spatial transcriptomics embeddings

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Cellular embeddings derived from single-cell transcriptomics data are essential for downstream tasks like label transfer and feature imputation, particularly for imaging-based spatial Transcriptomics (e.g., Xenium), where gene panels are restricted. However, using deep representation learning to adequately capture whole-tissue transcriptome diversity results in non-linear “black box” models. This prohibits a direct association between measured genes and learned latent features, compounding interpretability and verifiability issues in downstream pipelines such as spatial neighbourhood enrichment analysis.

Biological complexity multiplies across organizational levels (from cell state to tissue to organism), therefore we propose restricting cellular embedding discovery to only cell-state variability. By applying non-negative matrix factorization (NMF) to build separate latent spaces for each cell type, our framework ensures competitive performance on downstream tasks while retaining interpretability due to inherently additive gene programs.

We benchmark a selection of representation learning methods of varying complexity (PCA, NMF, scVI, MOFAFLEX) on their ability to learn ST latent spaces from reference scRNA-seq data. Models were evaluated on these core metrics across a range of hyperparameters and preprocessing pipelines: disentanglement, enrichment with prior biological knowledge, feature prediction performance, latent space structure, cell coverage, and embedding sparsity. Ultimately, we observe that cell-type-level NMF yields competitive performance against more complex non-linear methods on all metrics in our benchmarking suite, proving that superior performance does not necessitate sacrificing interpretability.

Abstract No. P014

Recovering full-transcriptome variance in spatial transcriptomics through cell-type-aware probe panel design

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Imaging-based spatial transcriptomics achieves single-cell resolution but requires the design of gene-specific probe panels informed by single-cell RNA sequencing (scRNA-seq) data. While modern panels can profile thousands of genes, larger panels come at the cost of reduced per-transcript coverage, making compact, study-specific panel design critical for downstream analysis and transcriptome reconstruction. However, selecting an informative gene subset remains challenging, as it must capture both cell-type identity and within-cell-type heterogeneity.

We present a two-level gene selection framework combining random forests and non-negative matrix factorization (NMF). At the first level, differentially expressed genes are identified to distinguish between cell types. At the second level, per-cell-type NMF captures continuous gene expression variation within each cell type. Together, these two levels ensure that the selected panel preserves the transcriptomic variance of the full scRNA-seq reference. We benchmark our approach against state-of-the-art panel design methods and demonstrate competitive performance in transcriptome reconstruction across diverse cell types.

Abstract No. P015

Longitudinal single-cell profiling identifies treatment-associated bone marrow remodeling in multiple myeloma

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The bone marrow (BM) microenvironment regulates multiple myeloma (MM) progression, therapeutic response, and hematopoietic recovery, yet how distinct treatment pathways reshape BM cellular ecosystems over time remains poorly understood. We performed longitudinal single-cell RNA sequencing of BM biopsies from 8 MM patients undergoing either a high-dose melphalan with autologous stem cell transplantation(ASCT) or Chimeric antigen receptor (CAR-T) cell therapy treatment. Samples were collected at baseline, across treatment, and during serial follow-up.

Following treatment initiation, both groups showed broadly comparable marrow composition despite substantial inter-patient heterogeneity. Divergence emerged during follow-up. The transplant-based pathway showed greater recovery of lymphoid and B-lineage programs, including precursor B-cell states and a more mature immune marrow landscape. In contrast, the CAR-T therapy showed reduced B-lineage progenitor programs during follow-up, accompanied by sustained progenitor- and myeloid-skewed states. Notably, hematopoietic stem and progenitor cell compartments, including lymphoid-primed multipotent progenitors, were relatively enriched in the CAR-T cell therapy treated patients compared with patient who received high dose melphalan-ASCT treatment, consistent with differential effects on stem-cell reserve and lineage regeneration. Granulocyte–monocyte progenitors displayed treatment-associated late remodeling, with stronger attenuation of chemokine and TNF/NF-κB inflammatory programs in patients treat with CAR-T therapy. Mesenchymal stromal cells showed a metabolic–inflammatory dissociation, with reduced TNF, interferon, and RAS signaling but increased oxidative-phosphorylation programs at late follow-up. Stromal cells in the CAR-T treatment further exhibited extracellular-matrix remodeling, collagen/laminin/integrin, chemokine, *IL-10*, and IGF signaling signatures, compatible with an immunosuppressive, metabolically supportive niche.

Together, our data reveals distinct hematopoietic, immune, and stromal trajectories across treatments and provide a framework for investigating how bone marrow niche remodeling relates to long-term disease control and immune recovery in multiple myeloma.

Abstract No. P016

Extracto: an AI pipeline for scalable synthesis of stem cell differentiation protocol knowledge

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Abstract

Stem cell differentiation literature contains decades of experimental knowledge, yet it remains unharmonized and non-interoperable at scale. Protocols are reported in heterogeneous prose across thousands of papers, making it difficult to systematically compare how growth factor composition, concentration, and timing govern cell fate decisions. Here, we present Extracto, an AI-driven platform that extracts, harmonizes, and structures differentiation protocols into a machine-readable database. Developed through iterative prompt engineering and human-in-the-loop curation, Extracto was trained and validated on approximately 200 protocols curated by a distributed community of student researchers. The platform routes parsed PDF text through a multi-stage large language model pipeline that extracts biological states, readouts, and protocol steps; aligns these on a shared temporal axis; and maps compounds and concentrations onto a canonical protocol framework. Our results demonstrate that iterative AI extraction combined with community-based curation can transform complex experimental methods into structured, interoperable biological data at scale.

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Abstract No. P017

Using an iPSC model to investigate blood-brain barrier dysfunction in childhood Batten disease

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CLN3 Batten disease is a paediatric neurodegenerative disease caused by mutations affecting the functionality of lysosomes in brain cells leading to neurodegeneration and eventually pre-mature death. There are no approved treatments for CLN3 Batten disease with the blood-brain barrier (BBB) posing a major challenge for drug delivery to the brain. The BBB maintains strict low permeability to many substances in the peripheral circulation to protect the brains unique environment. However, the potential dysfunction of the BBB from disease neurodegeneration has not been well-characterised in Batten disease research despite its key relevance to treatment design, delivery, and efficacy.

The aim of this study was to generate and use a patient-derived induced pluripotent stem cell (iPSC) model of BBB cells to characterise disease-specific changes in CLN3 Batten disease. Neuroinflammation is a well-recognised characteristic of neurodegenerative diseases; therefore, disease phenotype experiments were done at both baseline and induced inflammatory conditions by adding cytokines to the cell model microenvironments. Phenotyping experiments included measurements of BBB monolayer permeability (fluorescent dye delivery), staining and imaging of lysosome toxin accumulation, and lysosomal and BBB marker expression (qPCR). Additionally, drug repurposing candidate compounds were also tested as additional conditions to possibly identify a new drug with therapeutic potential.

Preliminary data from the iPSC BBB model suggests increased permeability in CLN3 Batten disease model and exacerbation of this under inflammatory conditions. These changes were significantly different to the healthy control model, which showed low permeability and only mild changes in response to the inflammatory environment. These findings potentially indicate that the BBB in CLN3 Batten disease is dysfunctional at baseline and vulnerable to neuroinflammatory conditions. Further replication of these experiments is currently underway to further validate these findings. A dysfunctional BBB is a key consideration to the design and delivery of future treatments.

Abstract No. P018

Brain organoid technologies to model human brain diseases

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Understanding the human brain in both healthy and diseased states remains one of the most formidable challenges in modern science. Progress in this field has long been constrained by the limited accessibility of human brain tissue and the ethical considerations surrounding its use.

In recent years, three-dimensional human brain organoids have emerged as a transformative experimental model that addresses many of these limitations. Generated from human pluripotent stem cells, brain organoids are genetically tractable and can reproduce essential features of early brain development, including cellular diversity, spatial architecture, and functional characteristics that closely resemble those of the developing fetal brain.

We will provide an overview of recent developments in the brain organoid platform and showcase several exemplary projects that illustrate how this technology can be leveraged to model human brain disorders. These examples encompass both neurodevelopmental and neurodegenerative diseases, underscoring the potential of brain organoids to deepen our understanding of brain pathology and support the development of innovative therapeutic strategies.

Abstract No. P019

Allele-specific transcriptional rebalancing preserves gene dosage at the expense of adaptive reserve

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Cellular resilience to deleterious genetic variation is a fundamental property of diploid life. Heterozygous loss-of-function (LoF) variants are pervasive in human genomes, yet many affect essential genes without overt phenotypic consequences, implying robust cellular buffering mechanisms whose molecular basis remains poorly defined. Here, we identify allele-specific transcriptional rebalancing (ASTR) as a cis-acting mode of cellular resilience that preserves gene dosage following heterozygous LoF mutations in the essential cytoskeletal gene *ACTB*. Using isogenic iPSC models bearing complementary frameshift and coding-sequence-deletion mutations, we show that mutant transcripts are rapidly cleared by RNA surveillance while total expression is preserved through selective transcriptional upregulation of the intact allele, producing pronounced allelic imbalance with low cell-to-cell noise.

Nascent RNA labeling, long-read allele phasing and single-cell transcriptomics demonstrate that allelic bias emerges during RNA maturation rather than at transcription initiation, and that compensation is locus-restricted, mutation-class sensitive, and independent of canonical cytoskeletal regulators including SRF and the biallelic-enforcement factor MSL2. Single-cell profiling reveals selective depletion of a stress-associated cellular state, and pharmacological profiling of iPSC-derived neural progenitors shows heightened transcriptional sensitivity to environmental perturbations, indicating that this buffering, while sufficient at baseline, comes at a measurable cost in cellular robustness. Allele-specific transcriptional rebalancing therefore defines a distinct tier of genetic buffering operating in cis, between canonical transcriptional adaptation and post-transcriptional RNA surveillance, and provides a framework for gene dosage robustness and the variable penetrance of heterozygous LoF variants in human cells.

Abstract No. P020

Characterizing major depression risk gene NEGR1 in human iPSC-derived astrocytes

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Genome-wide association studies have repeatedly implicated *NEGR1* (Neuronal Growth Regulator 1) as a risk locus for major depressive disorder. NEGR1 encodes a GPI-anchored cell-adhesion molecule of the IgLON family. Although its roles in neurodevelopment and synaptic organization are increasingly appreciated, its function in human glia, and the mechanisms linking it to disease risk, remain largely unexplored. Astrocytes are now understood as active participants in the stress- and immune-related processes implicated in mood disorders, making them a compelling context in which to interrogate NEGR1 function.

Here we apply an established iPSC-astrocyte differentiation protocol together with NEGR1 modulation to ask how NEGR1 dosage shapes the astrocytic response to disease-relevant challenges. Using paired transcriptomic and secretomic profiling across inflammatory and glucocorticoid stimulation, we examine how NEGR1 modulates this response in order to identify the pathways through which it acts.

Abstract No. P021

Identification of neuronal subtype-specific splice variants in iPSC-derived cell models of ALS and FTD

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Amyotrophic lateral sclerosis (ALS) is characterised by the premature degeneration of upper and lower motor neurons. Many patients have cytoplasmic inclusions positive for the TDP-43 protein independent of the aetiology. TDP-43 is a nucleic acid-binding protein and is involved in gene regulation and the processing of RNA. Mutations in TARDBP, encoding TDP-43, can cause age-related TDP-43 aggregation and nuclear depletion, leading to pathogenic alternative mRNA splicing.

To discover neuron-specific TDP-43 targets, we used bulk RNA-sequencing to identify splice variants in our ioGlutamatergic and ioMotor Neurons carrying the heterozygous or homozygous M337V mutation in TARDBP. We used MAJIQ to compare the splice variants of TDP-43 WT/WT, TDP-43 M337V/WT and TDP-43 M337V/M337V neurons at different time points.

Comparative analysis of wild-type versus TDP-43 mutant cells revealed splice variants both unique to, and shared between, neuron subtypes. At day 30 of the culture, we identified multiple different splicing events when comparing wild-type to TDP-43 mutant cells. Previously reported splicing targets or ALS/FTD associated genes including SETD5, PRUNE2, CALD1 and DPP6, along with novel targets, were identified in this analysis.

Our data demonstrate that our iPSC-derived ALS/FTD cell models provide a platform to delineate TDP-43 function and identify cell-specific target transcripts of TDP-43, and are valuable tools to study ALS/FTD and screen for drugs that can modulate the progression of these devastating diseases.

Abstract No. P022

Investigating the role of autonomic neurons in Takotsubo cardiomyopathy in a human 3D innervated cardiac muscle model

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Takotsubo Cardiomyopathy (TTS) is an acute, transient dysfunction of the left ventricle that occurs in the absence of obstructive coronary artery disease. Although often reversible, 22% of patients experience life-threatening symptoms in the acute phase. Increasing evidence supports a central role of the neuro-cardiac axis in disease progression. As TTS is frequently triggered by emotional or physical stress resulting in increased catecholamines and receptor sensitivity, it is now considered as a brain-heart syndrome that warrants further investigation into the involvement of the autonomic nervous system in TTS patients.

Studies of patient-specific TTS iPSC-cardiomyocyte models suggest a genetic predisposition to this syndrome.

To investigate the contribution of autonomic neurons to TTS pathophysiology in vitro, we utilised patient-specific iPSC to generate sympathetic neuronal organoid (SNO). Preliminary data suggest that the TTS SNO express characteristic sympathetic markers, including *PHOX2B*, dopamine beta-hydroxylase (*DBH*) and tyrosine hydroxylase (*TH*), supporting their identity of sympathetic neurons.

To further investigate neuro-cardiac interactions in TTS, we will utilise a 3D innervated engineered heart muscle (iEHM) generated by fusing SNO with engineered human myocardium (EHM). The resulting iEHM forms functional neuro-cardiac junctions, enabling controlled manipulation of neuron-to-cardiomyocyte response by optogenetic and pharmacological stimulation. To explore how neuronal stress can influence the cardiac phenotype, we generated a neuron-specific optogenetic TTS-patient hiPSC line expressing ChReef under the Synapsin promoter (Synapsin-ChReef). This approach allows selective activation of neurons, thereby isolating the neuronal component of stress signalling and its downstream effects on cardiac function.

By combining patient-specific iPSC disease modelling with organoid-driven tissue engineering, this model provides a tractable system to dissect disease mechanisms TTS and related brain-heart syndromes, and to explore potential therapeutic strategies.

Abstract No. P023

Patient-derived skin organoids to study cutaneous melanoma initiation and progression

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Cutaneous melanoma is the most aggressive form of skin cancer, arising from the malignant transformation of melanocytes. Although the common melanoma driver mutation *BRAF*^{V600E} initially promotes proliferation, it usually triggers oncogene-induced senescence (OIS) as a protective barrier against malignant transformation. However, inherited cancer-predisposing variants and secondary genetic alterations can facilitate escape from the senescent state, enabling melanoma development and progression.

Here, we generated a patient-derived induced pluripotent stem cell (iPSC) hair-bearing skin organoid model to study melanoma initiation and progression. Dermal fibroblasts obtained from a patient with familial melanoma were reprogrammed into iPSCs (MEL1) by overexpressing the Yamanaka factors. In parallel, a control iPSC line (HC) was generated from dermal fibroblasts of a healthy donor. Both iPSC lines expressed pluripotency markers and, in a trilineage assay, successfully differentiated into all three germ layers. Genomic integrity was confirmed by karyotyping and copy-number variation (CNV) analysis, showing no major chromosomal abnormalities. Next-generation sequencing identified a pathogenic germline stop-gain variant in the ATM gene in the MEL1 line. Both HC and MEL1 lines were subsequently differentiated into hair-bearing skin organoids.

To model melanoma initiation, we are currently genetically engineering iPSCs to enable melanocyte-specific, doxycycline-inducible expression of *BRAF*^{V600E} in patient-derived skin organoids. Following oncogene induction, OIS and potential OIS escape will be evaluated to determine how the patient-specific genetic background influences the response to oncogenic BRAF-MAPK signaling. This model will enable comprehensive mechanistic investigation of melanoma initiation and progression in a physiologically relevant human microenvironment and may support translational evaluation of therapeutic strategies.

Abstract No. P024

SAHA-mediated increase of chaperone expression reduces Z-alpha 1 antitrypsin polymers in a patient specific-iPSC based liver model for alpha-1-antitrypsin deficiency

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Alpha-1-antitrypsin deficiency (AATD) is a genetic disease affecting the lungs and the liver. The serine protease inhibitor (Pi) alpha-1-antitrypsin (AAT) is secreted by hepatocytes to protect tissues, especially the lungs, from overshooting immune reactions. The most severe AATD-phenotype is caused by the so-called Z-mutation within the *SERPINA1* gene. This Glu342Lys substitution causes misfolding and polymerisation of AAT, leading to its accumulation in the endoplasmic reticulum (ER) of hepatocytes and increasing their susceptibility to ER-stress. Besides a lung phenotype, adult patients suffer frequently from liver fibrosis/cirrhosis with no approved treatment so far.

In this project, we collect and bank urine derived MSCs from AATD-patients, carrying the homozygous Pi*ZZ genotype, and reprogram them into iPSCs. To model AATD, these iPSCs are differentiated into hepatocyte-like cells (HLCs). Healthy and patient derived iPSCs could be differentiated into HLCs as documented by immunofluorescence (IF) and qRT-PCR for hallmark hepatocyte markers.

Healthy and diseased HLCs could be distinguished by comparing AAT and Z-AAT levels in IF. HLCs were treated with the potential therapeutics Carbamazepine (CBZ), SAHA, Kifunensine (KIF), and Cysteamine (CYS). Of these, CBZ and SAHA could significantly reduce Z-AAT polymers. Transcriptome analyses revealed major differences in metabolism and signalling between control and AATD HLCs and indicated increased stress levels affecting intracellular organelles. Importantly, the transcriptomes of control and patient-derived cells separated into distinct clusters with respect to the expression of chaperone encoding genes. Treatment with SAHA induced increased expression of various chaperones which might contribute towards reduced ZAAT polymers.

These results give an insight into the potential of patient-specific HLCs generated from iPSCs as a suiting model for research on the individual genetical and molecular background of AATD. We will further exploit its functionality as a drug testing system and to increase our understanding of ZAAT polymer formation.

Abstract No. P025

Stem cell based disease modeling platform for NEDAMSS phenotypic screening and drug discovery

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Neurodevelopmental Disorder with regression, Abnormal Movements, Loss of Speech and Seizures (NEDAMSS) is an ultra-rare neurodevelopmental and neurodegenerative disorder caused by pathogenic variants in the IRF2BPL gene. IRF2BPL is an atypical single-exon gene encoding a protein containing polyglutamine/polyalanine (polyQ/polyA) tracts, structural features thought to contribute to its condensation properties and phase behavior. Recent work has identified disrupted liquid-liquid phase separation (LLPS) as a potential mechanism underlying IRF2BPL-associated disease. Consistent with this model, we observed aberrant cytoplasmic localization and reduced nuclear IRF2BPL in patient-derived astrocytes. However, the structural determinants of this mislocalization phenotype, and its consequences for human cortical development, remain incompletely understood.

To address these questions, we (i) evaluated the effects of truncating variants located at distinct positions on protein mislocalization and condensate formation in hiPSC derived astrocytes with introduced IRF2BPL mutant variants, (ii) established and characterized a micropatterned cortical organoid model of IRF2BPL variant and (iii) performed preliminary functional assessment of the model using spontaneous calcium imaging.

A panel of isogenic hiPSC lines carrying introduction of three truncating IRF2BPL variants (c.499C>T, c.762dupC, and c.1693C>T) into one healthy background was used to develop a quantitative high-content astrocyte phenotyping assay based on IRF2BPL immunofluorescence and segmentation-derived perinuclear-to-nuclear intensity measurements. In parallel, a micropatterned cortical organoid model was established from the c.499C>T line and characterized by immunohistochemistry and spontaneous calcium imaging at day 40.

Together, this work establishes a unique panel of isogenic hiPSC models representing IRF2BPL variants located at distinct positions within the protein, enabling systematic comparison of genotype-dependent cellular phenotypes. Combined with quantitative high-content imaging in astrocytes and micropatterned cortical organoids, these models provide a versatile framework for mechanistic studies and future therapeutic screening in NEDAMSS.

Dell'Oca, Marco, et al. "NEDAMSS syndrome-related truncating and missense mutations are associated with aberrant liquid-liquid phase separation of IRF2BPL." Nature Communications 17.1 (2026): 3301.
Bauersachs, Daniel, et al. "Novel human neurodevelopmental and neurodegenerative disease associated with IRF2BPL gene variants—mechanisms and therapeutic avenues." Frontiers in Neuroscience 18 (2024): 1426177.

Abstract No. P026

Establishing human cerebellar organoids to model Leigh syndrome for mechanistic insight and therapeutic discovery

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Leigh syndrome (LS) is a severe, early-onset mitochondrial disorder characterized by progressive neurodegeneration and high childhood mortality. Variants in more than 100 genes involved in oxidative phosphorylation can cause the disease, with *SURF1* being the most frequently affected gene. Although the cerebellum is consistently affected in LS patients, the mechanisms underlying its pathology remain poorly understood due to the lack of physiologically relevant human disease models. Existing animal models fail to recapitulate key disease features, highlighting the need for patient-specific in vitro systems.

This project aims to establish human induced pluripotent stem cell (iPSC)-derived cerebellar organoids as a translational model to investigate disease mechanisms in LS and to provide a platform for therapeutic testing. Building on previous work from our group demonstrating disease-specific phenotypes and successful drug screening in cortical and midbrain organoids, this project extends these approaches to the cerebellum (Zink et al., 2026).

Cerebellar organoids of control iPSCs were generated to establish and optimize a differentiation protocol published by Atamian et al. (2025) during the first 30 days. Preliminary immunofluorescence analysis identified KIRREL1-positive ventricular zone progenitors and ATOH1-positive rhombic lip progenitors, confirming successful induction of early cerebellar identity. These initial results provide an important first step for the subsequent generation of SURF1 patient-derived cerebellar organoids and their application as a human model system. Future studies will characterize developmental abnormalities in these organoids using molecular, cellular, and functional analyses and evaluate the therapeutic potential of candidate compounds for LS treatment.

Zink, A., Dai, D.-F., Wittich, A., Henke, M.-T., Pedrotti, G., … Prigione, A. (2026). Pluripotent stem-cell-based screening uncovers sildenafil as a mitochondrial disease therapy. Cell, 189(6), 1656-1679.e42. https://doi.org/10.1016/j.cell.2026.02.008

Atamian, A., Birtele, M., Hosseini, N., & Quadrato, G. (2025). Generation and long-term culture of human cerebellar organoids from pluripotent stem cells. Nature Protocols, 20(6), 1584–1615. https://doi.org/10.1038/s41596-024-01093-w

Abstract No. P027

Chronic acetaminophen exposure alters neural rosette cell-type composition and proliferation-differentiation dynamics in human cortical organoids

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Since 2013, epidemiological studies suggest that prenatal acetaminophen exposure (APAP; paracetamol) may increase offspring risk of neurodevelopmental disorders, including ADHD and ASD. However, evidence remains contested. We therefore investigated chronic APAP exposure in human cortical organoids, an *in vitro* model that reduces environmental confounding and enables experimental access to prenatal human brain development.

Organoids from two donors were generated following Yoon et al. (Nat.Methods 2019) and exposed to DMSO, 82.5µM or 165µM APAP for four and eight weeks, modelling repeated chronic rather than single-dose exposure. Viability assays confirmed sub-toxic exposure concentrations, and LC-MS/MS confirmed the presence of APAP in organoid lysates.

Based on the observed APAP-associated organoid volume reduction, we performed bulk RNA-sequencing, spatial transcriptomics and whole-mount light-sheet microscopy (LSFM) to assess underlying cellular and molecular changes. Bulk RNA-sequencing showed a mild, synchronous APAP-associated transcriptomic shift. Spatial transcriptomics resolved APAP-associated changes within individual neural rosettes, revealing altered cell-type composition with increased neural stem cell proportions in the apical compartment (+14.8%; 35.5% to 50.3%) and reduced immature neuron proportions in the basal compartment (-22.4%; 58.2% to 35.8%). The APAP-associated transcriptomic response was consistent across rosette rings. APAP upregulated p53-associated apoptosis and stress-response genes, including TP53, CDKN1A and BAX, with enrichment of intrinsic apoptosis, ER-stress and hypoxia–glycolysis pathways. Concordantly, whole-mount LSFM revealed increased cleaved Caspase-3$^+$/SOX2$^+$ cell density in APAP-exposed rosettes (5-fold; 1,503 vs. 291/mm^3), while cleaved Caspase-3$^+$/HOPX/TBR2$^+$ progenitor and NeuN$^+$ neuron densities were unaffected.

At 165µM APAP, the overall Ki-67$^+$/Hoechst$^+$ proliferating cell fraction increased from 11% to 14%. LSFM revealed unchanged proliferating SOX2$^+$ NSC density, whereas proliferating HOPX/TBR2$^+$ intermediate progenitor density increased under APAP exposure (1.7-fold; 14,175 vs. 23,932/mm^3).

Although reductionist and thus not fully predictive of organismic developmental neurotoxicity, this model indicates that chronic APAP exposure affects neuroepithelial expansion, composition and proliferation-differentiation dynamics, supporting further *in vitro* and *in vivo* studies.

Yoon, S.-J. et al. Reliability of human cortical organoid generation. Nature Methods 16, 75–78 (2019)

Abstract No. P028

iPSC-derived cortical brain organoids for the study of pathomechanisms and therapeutic approaches in Leigh syndrome

Sonja Heiduschka[1,], Isabella Tolle[1], Shattom Ghosh[2], Annika Zink[1], Louis Neu[3], Laura Petersilie[3], Jochen Dobner[4], Caleb Jerred[1], Andrea Rossi[4], Christine R. Rose[3], Michal Minczuk[2],* and *Alessandro Prigione[1]*

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Human induced pluripotent stem cells (iPSCs) substantially contribute to the 3R principle (replace, reduce, refine) in biomedical research. They can be differentiated into cell types of interest while preserving the human genomic background and patient-specific mutations. Three-dimensional neuroectodermal differentiation gives rise to cortical brain organoids (cBO) that recapitulate early stages of human brain development. They represent a promising model system to investigate Leigh syndrome (LS), a rare mitochondrial disorder with no effective treatment options due to its poorly understood pathomechanism. LS is caused by nuclear or mitochondrial DNA mutations impairing mitochondrial energy production. Using iPSCs and brain organoids, two therapeutic approaches were assessed: Treatment with the PDE-5 inhibitor Sildenafil, identified in a screen of repurposable compounds in neural cells [1], and mitochondrial DNA editing using double-stranded DNA deaminase toxin A-derived cytosine base editors (DdCBE).

cBO were generated from LS patient iPSCs with mutations in the mitochondrial gene *MT-ATP6*. Patient cBO displayed reduced growth, premature loss of neural progenitor proliferation and altered pathways related to synapses. Cultured patient cBO slices showed an increased calcium response after chemically-induced metabolic stress. Sildenafil treatment of patient cBO shifted the expression profile towards control-like conditions and normalized the calcium response. To address the underlying cause of LS, patient iPSCs were transfected with plasmids containing DdCBE constructs for the correction of *MT-ATP6* mutation m.8993T>C, resulting in a shift of heteroplasmy levels towards a healthy threshold and thereby generating an isogenic control line. Future studies will employ this line for cortical brain organoid generation and phenotype characterization, while DdCBE delivery directly into organoids via transduction will be explored as a potential gene therapy strategy.

Collectively, these findings demonstrate the potential of iPSC-derived models for investigating mitochondrial genetic disorders such as LS and for evaluating novel therapeutic and gene-editing approaches.

[1] Zink, Dao-Fu*, Wittich*, Henke*, Pedrotti*, Heiduschka*, et al. (2026): Pluripotent stem-cell-based screening uncovers sildenafil as a mitochondrial disease therapy. Cell 189(6):1656-1679.e42.*

Abstract No. P029

Development of iPSC-derived models for glutaric aciduria type 1 (GA1) and their cellular and molecular profiling

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Glutaric aciduria type 1 (GA1) is a rare neurometabolic disease with autosomal recessive inheritance caused by pathogenic variants in mitochondrial glutaryl-CoA-dehydrogenase (GCDH) which catalyzes the oxidative decarboxylation of glutaryl-CoA in the L-lysine degradation pathway. In GA1, glutaryl-CoA is converted to the neurotoxins glutaric acid (GA), 3-hydroxy glutaric acid (3-OH-GA) and glutaconic acid, as well as to non-toxic glutarylcarnitine. Untreated individuals present with acute or insidious striatal injury between 3-36 months of age, resulting in moderate to severe complex movement disorders with predominant dystonia. Treatment is based on low-lysine diet, carnitine supplementation, and emergency treatment to avoid catabolic crisis. Metabolic therapy is burdensome for patients and families, lacks efficacy in a significant number of patients, and does not prevent progression of white matter changes and kidney disease, indicating a significant unmet medical need. To understand the molecular pathomechanisms of GA1 and to facilitate future drug screens, we generated glutamatergic neurons from GA1 patient iPSCs by transduction of a doxycycline inducible expression system for the neurotrophic transcription factor neurogenin 2 (Ngn2).

GA1 Ngn2-iPSC lines underwent iPSC characterization and were differentiated into glutamatergic neurons. We demonstrated impaired mitochondrial function in GA1 Ngn2 neurons, including reduction of mitochondrial membrane potential and slightly enhanced levels of reactive oxygen species. We observed the characteristic accumulation of the neurotoxic metabolites GA and 3-OH-GA in patient neurons compared to healthy controls. Taken together, we demonstrate that the established iPSC-based model recapitulates disease-specific phenotypes. Future work includes analysis of neuronal morphology and implementation of additional forward reprogramming protocols for GABAergic neurons using Ascl1. We established a valuable tool for understanding disease physiology and to identify novel therapeutic options in a drug repurposing screen within the scope of the Horizon SIMPATHIC (Accelerating drug repurposing for rare neurological, neurometabolic and neuromuscular disorders by exploiting SIMilarities in clinical and molecular PATHology) consortium.

Abstract No. P030

Human iPSC-derived 2D and 3D neural models advance neurodevelopmental and therapeutic studies of Leigh syndrome

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Leigh syndrome (LS) is a rare pediatric mitochondrial disease, characterized by neurodevelopmental dysfunction and neurodegeneration. Disease prognosis is typically poor, with no cure and approximately 50 % of patients dying by the age of 3. LS is highly heterogeneous with more than 110 identified monogenic causes and substantial phenotypic variability driven by factors including mitochondrial heteroplasmy, compensatory mechanisms, and metabolic stress. Furthermore, LS research has been limited by disease rarity (1:40,000) and insufficiency of animal models. Human induced pluripotent stem cell (iPSC) models address these limitations through the generation of disease-relevant tissues with an isogenic human genetic background, enabling investigation of LS pathophysiology and therapeutic discovery.

Here, we model the largest genetic subgroup of LS, comprising mitochondrial complex I defects, using isogenic iPSCs harboring an *NDUFS1* mutation. These iPSCs are used to generate neural progenitor cells (NPCs), 2D midbrain dopaminergic neurons (mDANs), and 3D midbrain organoids (MBOs) to model neurodevelopmental and midbrain pathology observed in patients. Initial analyses revealed disrupted 2D neuronal development, abnormal neuronal morphology, electrophysiological dysfunction, and reduced mitochondrial membrane potential (MMP). To explore the neurodevelopmental implications of these phenotypes, MBO electrophysiology was investigated longitudinally using high-density microelectrode array (HD-MEA), identifying reduced neuronal bursting activity and accelerated deterioration of electrical activity. To advance the fundamental goal of establishing LS treatments, NPCs were treated with the mitochondrial disease drug candidate alverine citrate, which partially restored MMP. Together, these investigations demonstrate the efficacy and versatility of iPSC-derived 2D and 3D neural models for advancing the understanding of LS pathophysiology and accelerating critical therapeutic discovery.

Jerred, C. et al. Generation of an iPSC line IUFi004-A-13 with homozygous NDUFS1 mutation for the study of Leigh syndrome. Stem Cell Res 94, 104002 (2026).

Zink, A., Lisowski, P. & Prigione, A. Generation of Human iPSC-derived Neural Progenitor Cells (NPCs) as Drug Discovery Model for Neurological and Mitochondrial Disorders. Bio Protoc 11, e3939 (2021).

Abstract No. P031

Multimodal analysis of human PSC-derived cerebral organoids generated under matrix-free conditions

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Human pluripotent stem cell-derived cerebral organoids provide a useful model for studying aspects of human brain development and for illustrating multimodal approaches to organoid characterization. Here, we generated cerebral organoids from human iPSC lines under matrix-free conditions and used complementary analytical approaches to examine their structural, cellular, and transcriptional features. Organoids were matured for up to 103 days and showed robust formation, reproducible size progression, and high viability after dissociation.

Characterization was performed using cyclic immunofluorescence, 3D light-sheet microscopy, flow cytometry, and single-nuclei RNA sequencing. Cyclic immunofluorescence on a day 60 organoid section revealed SOX2-, PAX6-, Ki67-, TUBB3-, MAP2-, NeuN-, and Podoplanin-positive populations and enabled phenotyping of proliferative and non-proliferative neural progenitors as well as mitotic and post-mitotic MAP2-positive neurons. Three-dimensional light-sheet microscopy provided spatial insight into ventricular-like zones, apical membrane organization, dorsal forebrain progenitor cells, and immature neuronal structures in intact organoids. Flow cytometry at day 30 and day 100 showed high viability after dissociation and progressive changes in marker composition, including reduced SOX2/PAX6, Ki67, and SSEA-1 and increased PSA-NCAM over time. Single-nuclei RNA sequencing of a day 100 organoid further resolved mesenchymal cells, astrocytes, neuroblasts, late neuroblasts, mature neurons, and both GABAergic and glutamatergic neuronal subtypes.

Together, this study demonstrates the value of combining complementary imaging, cytometric, and sequencing-based methods for extended analysis of cerebral organoids and provides a detailed overview of their structural organization and cellular diversity.

Abstract No. P032

Tyrosine hydroxylase deficiency influences mitochondrial function and neuronal morphology

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Tyrosine hydroxylase (TH; gene ID 7054) is the rate-limiting enzyme in dopamine biosynthesis. It converts L-tyrosine to L-DOPA, which is further metabolized to dopamine. TH deficiency (THD), which is one cause of DOPA-responsive dystonia (DRD), presents as an autosomal recessive disease as an early-onset, progressive levodopa responsive dystonia-parkinsonism syndrome. THD presents as an early-onset movement disorder reaching from a progressive hypokinetic rigid syndrome with dystonia up to a complex encephalopathy with neonatal or early infancy onset and a reduced response to levodopa. With patient-specific induced pluripotent stem cells (iPSCs) we investigated the pathological features of THD and changes in cellular metabolism in THD neural progenitor cells (NPCs) and Ngn2 neurons.

Electron microscopy images of THD NPCs show structural changes in mitochondrial morphology accompanied by a reduction in mitochondrial membrane potential (MMP) as measured via tetramethylrhodaminemethylester (TMRM) staining. Interestingly, ROS levels are not significantly altered in THD NPCs. In contrast, in Ngn2-inducible glutamatergic neurons we report a slightly enhanced MMP compared to healthy controls. ROS-levels are lower in the THD Ngn2 neurons as compared to healthy control Ngn2 neurons. Additionally, THD neurons exhibited differences in neurite branching with a more prominent axonal staining with a significantly reduced number of dendritic trunks compared to healthy wildtype Ngn2 neurons.

Taken together, THD NPCs show impaired mitochondrial function, whereas THD Ngn2 neurons present with morphological changes also present in more common neurodegenerative diseases. Currently, a proteomics study on isolated mitochondria from THD NPCs is ongoing together with the analysis of mitochondrial fusion and fission and mitophagy to better understand the pathological changes observed in mitochondria.

Abstract No. P033

Towards high throughput screening for compounds allowing readthrough of premature termination codons based on genetically engineered primary ciliary dyskinesia patient-specific hiPSCs

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Primary Ciliary Dyskinesia (PCD) is a rare genetic disease characterized by impaired mucociliary clearance in the airways, leading to recurrent respiratory infections, bronchiectasis and ultimately lung failure. The disease is caused by mutations in genes essential for ciliary function, resulting in defective ciliated cells. More than 50 genes have been implicated in PCD, and mutations across these loci give rise to a broad spectrum of clinical phenotypes, none of which currently have a curative treatment. Notably, approximately 25% of all PCD-causing mutations are premature termination codons (PTCs), which represent a potentially targetable class through PTC suppression therapies.

In this study, DNAI1-dTomato reporter hiPSCs were generated using Cas9-mediated gene editing and subsequently differentiated into proximal airway epithelia in air-liquid interface (ALI) cultures, where dTomato-expressing motile ciliated cells developed. A second reporter line carrying a patient-specific PTC in exon 9 was generated in homozygosity. Upon ALI differentiation, these cells formed immotile ciliated cells with a markedly reduced dTomato mean fluorescence intensity (MFI). Western blot and PCR analyses revealed, in addition to the canonical transcript variant, an unexpected exon-skipped isoform lacking the PTC, which accounts for the observed dTomato expression.

To assess the system's utility for drug screening, PTC suppressors were applied intermittently to 96-well ALI cultures, and dTomato MFI was quantified over time. G418 combined with SRI-41315, among other conditions, significantly increased MFI levels compared with the DMSO control. Additionally, differentiation into respiratory ciliated cells was achieved in submerged 384-well cultures through combined Notch and BMP inhibition, establishing a platform suitable for high-throughput screening.

Abstract No. P034

Modeling Kleefstra syndrome 1 in human cortical organoids: deciphering the role of EHMT1 in neurodevelopmental timing

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Kleefstra syndrome 1 is a rare neurodevelopmental disorder characterized by impaired intellectual development, microcephaly, heart defects and facial abnormalities caused by deletions or pathogenic mutations in the *EHMT1* gene. EHMT1 is a histone H3K9 methyltransferase associated with transcriptional repression. Recently, EHMT1 has been recently found among a set of epigenetic modifiers that regulate the pace of neuronal maturation, suggesting that altered neurodevelopmental timing is a central driver of Kleefstra syndrome 1 phenotypes.

To systematically dissect how EHMT1-dependent chromatin regulation controls human cortical development, we established a set of human induced pluripotent stem cell (iPSC) models. Using CRISPR/Cas9 gene editing, we engineered isogenic heterozygous iPSC lines carrying patient-specific point mutations in key functional domains of EHMT1: C1073Y (disrupting catalytic SET domain activity) and P809L (weakening ANK domain binding to methylated H3). Additionally, iPSC lines with heterozygous deletion of *EHMT1* were generated to serve as a reference for reduced gene dosage.

These engineered lines are currently being differentiated into 3D human cortical organoids. To capture developmental shifts in lineage progression, we aim to employ quantitative imaging, chromatin profiling and single cell transcriptomics at key developmental points. By comparing domain-specific mutations and knockout of *EHMT1* with healthy iPSC lines, we aim to understand whether developmental timing defects in Kleefstra syndrome 1 stem from altered catalytic activity, chromatin targeting or gene dosage of EHMT1.

Abstract No. P035

Beyond the brain: the role of the liver in neurodegenerative disorders

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The liver performs a variety of functions, including metabolism of amyloid beta (Aβ), which is accumulated in the brain in Alzheimer's disease (AD). With the rise in the aging population, the prevalence of AD has been increasing worldwide. Several studies showed a correlation between the occurrence of AD and fatty liver disease. Given the liver's major roles in the body, it may be involved in AD pathogenesis.

To address this, we analyzed single-cell transcriptomic data generated from liver tissues obtained from 106 donors with different degrees of fatty liver disease to determine the expression of genes associated with AD. These analyses showed a reduction in the expression of genes associated with Aβ degradation, such as ABCA1 and ADAM10, while the expression of MAPT, which encodes tau protein, was upregulated in steatotic livers. Immunofluorescence on human liver tissue sections supported the transcriptomic data, as Aβ and p-Tau protein accumulation were enhanced in steatotic livers. Finally, we used isogenic iPSC lines harboring either PNPLA3I148M or PNPLA3KO to generate 3D hepatocytes and cerebral organoids. We treated hepatocytes with oleic acid or palmitic acid to induce metabolic dysfunction-associated steatotic liver disease (MASLD) or metabolic dysfunction-associated steatohepatitis (MASH)-like phenotypes, respectively. The conditioned media collected from these cells were used to culture cerebral organoids to determine whether the secretome from MASLD/MASH hepatocytes can induce AD-like phenotypes. hiPSC-derived 3D hepatocytes showed upregulation of Aβ when treated with oleic acid. Interestingly, cerebral organoids cultured in unconditioned media showed increased cell death when compared to those cultured in conditioned media.

These results show that both in vitro and in vivo steatotic hepatocytes displayed increased expression of factors associated with AD. Furthermore, hepatocytes appear to protect neuronal cells against cell death. Therefore, this study provides novel evidence that the liver could play an important and direct role in neurodegenerative disorders.

Abstract No. P036

Modeling PURA syndrome in neural progenitor cells and cerebral organoids using PURA KO and patient-derived iPSCs

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The neurodevelopmental disorder PURA syndrome is caused by heterozygous *de novo* mutations in the *PURA* gene. The disorder is characterized by intellectual disability, hypotonia, epilepsy and other symptoms, which vary considerably among the more than 840 reported patients.

The *PURA* gene encodes a nucleic acid-binding protein. Studies in HeLa cells and mouse models have implicated PURA in several cellular processes, including RNA metabolism and transport, processing (P-) bodies and immune responses. However, human-derived models to investigate the role during neurodevelopment and to elucidate the molecular mechanisms underlying PURA syndrome are still lacking.

To address this, we generated human homozygous knock-out (KO) iPS cell lines and patient-derived iPS cell lines carrying the most recurrent pathogenic PURA mutation (Phe233del), together with their respective isogenic controls. These iPSC lines were differentiated into neural progenitor cells (NPCs) and cerebral organoids. Morphological analyses did not reveal differences between KO, patient-derived, and isogenic control cell lines. Ongoing molecular and functional analyses are aimed at identifying cellular pathways and mechanisms affected by PURA deficiency and by the disease-associated variant, providing new insights into the role of PURA in human neurodevelopment and the pathogenesis of PURA syndrome.

Abstract No. P037

From HTS to patient-specific phenotyping: CBF-based assessment of CFTR modulators in hiPSC-derived airway epithelia

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Cystic fibrosis (CF) is a common genetic disorder that affects over 100,000 people worldwide. It is caused by mutations in the CFTR gene, which encodes a chloride and bicarbonate channel. These mutations impair secretory organs, particularly the lungs, where defective mucociliary clearance (MCC) leads to progressive lung disease as the primary cause of death in CF patients. The identification of a class of drugs termed CFTR modulators has led to substantial advances in the field of CF therapy. However, these drugs are not yet available for all CFTR mutations, and therefore, not all patients can benefit from them. In order to advance available treatment options for CF, we use hiPSC-derived airway epithelium to model CF using an assay measuring the ciliary beat frequency (CBF) as key determinant of impaired MCC. We aim to establish this assay as an automatable, mid- to high-throughput platform using modulator-induced rescue of CBF as the readout. It has already been demonstrated that the CBF assay provides a stable, automatable platform that reflects the CF lung disease phenotype in hiPSC-derived airway epithelium. This is achieved by rescuing the CBF after treatment with CFTR modulators, thus validating its application in the screening for new CFTR modulators. Standardization through scripted data analysis is already reducing manual workload and ensures reproducibility. Although full high-throughput deployment requires further automation and formal performance benchmarking, the current data support the use of the CBF assay for evaluating approved modulators and for testing and prioritising of carefully scoped, HTS-derived, chemistry-refined candidates. The ultimate goal will be to expand therapeutic options for patients with rare CFTR mutations and allow for patient specific theratyping of CFTR modulators.

Abstract No. P038

Human 3D Neuromuscular Organoids to Model TDP-43 related mechanisms in ALS

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Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease characterized by motor neuron degeneration, skeletal muscle atrophy and paralysis. While traditional monoculture systems and assembled co-cultures of neurons and muscles have provided valuable insights into ALS biology, they fail to capture the early cross-tissue interactions and bidirectional signalling at the neuromuscular junctions (NMJs) that are critical for physiological relevance. To address this limitation, we established self-organized neuromuscular models that recapitulate key embryonic developmental principles offering a major advantage for studying human neuromuscular biology and disease pathophysiology. We established 3D neuromuscular organoids (NMOs) (Martins et al, 2020) and 2D self-organizing neuromuscular junctions (Urzi et al, 2023) from induced pluripotent stem cells (iPSCs) via bipotent neuromesodermal progenitors (NMPs). These systems self-organize into spinal cord neurons and skeletal muscle and form functional NMJs, enabling detailed analysis of ALS-related phenotypes.

Here, we generated NMOs from isogenic iPSC lines carrying heterozygous and homozygous TDP 43M337V mutations alongside the parental KOLF2.1J line to investigate disease mechanisms. By integrating automated high content image analysis, functional assays, and bulk and single cell molecular readouts, we map the temporal and spatial relationships between TDP 43 mislocalization, motor neuron vulnerability and muscle maturation. Collectively, our findings demonstrate that NMOs reproduce key aspects of ALS pathology in the absence of external stress. This establishes NMOs as a developmentally accurate and scalable human platform for the mechanistic dissection of ALS and for preclinical evaluation of therapeutic strategies.

Abstract No. P039/T29

Patient-specific iPSC-derived sensory neurons as a gateway to individualized neuropathic pain modeling and treatment

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Small Fibre Neuropathy (SFN) is a chronic neuropathic pain disorder. Current treatment options are limited and highly individual, therefore highlighting the need for novel personalized therapeutic strategies.

We formed an interdisciplinary consortium within which we generated clinical, genetic and smart-watch-based biometric data from 24 SFN patients and 24 healthy controls over one year. Peripheral blood cells from seven SFN patients and seven healthy controls were reprogrammed into iPSCs. More than 100 iPSC lines underwent quality control by assessing genetic integrity, pluripotency marker expression and differentiation capacity into neural crest-like cells (NCLCs). These parameters were integrated into a weighted quality score (iQ-Score) to identify optimal iPSC-lines for downstream disease modelling and drug screening.

Patient-specific NCLCs were differentiated into sensory neurons by lentiviral-mediated NGN1 expression and matured for 67-70 days. Neuronal activity was measured using multielectrode array recordings.

Sensory neurons exhibited spontaneous activity. Surprisingly, SFN patient derived neurons showed reduced overall mean spike firing rates, whereas their firing frequency within bursts was significantly elevated.

A library of 88 clinically approved pain-related drugs was used for SFN patient-specific drug screenings. To quantify drug effects, we generated high dimensional MEA response vectors integrating the neurons´ firing and bursting behaviour for each compound. Vectors served as drug response fingerprints. These vectors were projected into a disease space defined by patient-derived and control-derived baseline signatures, allowing us to quantify drug induced shifts away from the patient specific pain state in the healthy direction. A defined subset of drugs shifted the SFN patient specific disease signatures towards the healthy region. These compounds represent candidate modulators for normalizing disease-associated functional patterns.

In summary, we established a scalable, medium throughput patient specific iPSC-based platform for modelling neuropathic pain and assessing drug responses. This approach provides the foundation for future personalized therapeutic decision-making for neuropathic pain patients.

Abstract No. P040/T32

Unveiling the genetic landscape of UV-induced cellular responses: A CRISPR whole genome screening approach

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Ultraviolet (UV) radiation is a major environmental stressor affecting human skin and the primary risk factor for cutaneous squamous cell carcinoma, yet many genetic determinants of cellular UV sensitivity and resistance remain unknown.

To address this knowledge gap, we performed a genome-wide CRISPR/Cas9 loss-of-function screen in human keratinocytes, enabling systematic and unbiased identification of genes regulating cellular responses to UV-induced stress. We identified 929 growth-essential genes and 21 genes associated with UV sensitivity and resistance, including established nucleotide excision repair genes among the strongest UV-sensitizing hits, and uncovered 11 novel candidate genes associated with cellular UV response.

To enable functional validation of candidate genes, human iPSC-derived skin organoids were established as a physiologically relevant model of human skin. As a proof of concept, CRISPR/Cas12-mediated knockout of Filaggrin resulted in altered epidermal organization and stratification, supporting the use of skin organoids for downstream validation of screening hits.

Overall, this study identifies novel candidate regulators of cellular UV response and establishes an integrated platform combining genome-wide CRISPR screening with human iPSC-derived skin organoids for their functional validation, providing a powerful framework to dissect mechanisms of UV sensitivity, skin homeostasis, and photocarcinogenesis.

Abstract No. P041

Deciphering the regulatory role of long non-coding RNA in pancreatic development and diabetes

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Gene regulatory networks play a vital role in pancreatic development and function. However, pathomechanisms associated with the non-coding genome are just starting to be discovered. Our recent work demonstrated that mutations in the ONECUT1 gene are responsible for a new neonatal diabetes syndrome in homozygous patients, whereas heterozygous carriers develop early-onset diabetes. Stage-specific characterization of in vitro differentiated human embryonic stem cells (hESCs) revealed that ONECUT1 plays an important role in transcriptional regulation during pancreatic progenitor formation and the initiation of the endocrine developmental program. Nonetheless, the complex regulation of ONECUT1 expression is only partly uncovered.

While investigating the ONECUT1 locus, we found a variant most strongly associated with T2D (rs2440374), located within the lncRNA RP11-209K10.2 (lncRNA-RP11), 11 kbp from ONECUT1. The GTEx Portal shows decreased lncRNA-RP11 expression in the pancreas in the presence of the T2D-associated allele. This SNP also disrupts a binding motif for transcription factor NKX2.2, essential for endocrine pancreas development and islet-cell fate. Therefore, we hypothesize a regulatory role for this non-coding region.

Our omics data revealed transcription factor binding peaks in the promoter region of lncRNA-RP11. Since promoters of lncRNAs can also act as enhancer elements regulating neighbouring genes, we anticipate that the lncRNA-RP11 promoter might regulate ONECUT1. To test this, we deleted only the lncRNA-RP11 promoter. These hESCs will be differentiated into pancreatic endocrine cells to evaluate effects on ONECUT1 expression and lineage specification.

Although no differences in differentiation efficiency have been detected to date, increased expression of pancreatic progenitor markers such as ONECUT1 and NKX6.1 suggests a potential repressive role for this regulatory element.

This characterization will provide insights into the role of the lncRNA-RP11 locus in endocrine development and pathophysiology, improving understanding of diabetes-related transcriptional regulation.

Abstract No. P042

Development of an iPSC-based high-throughput drug screening in hereditary pulmonary arterial hypertension

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Pulmonary arterial hypertension (PAH) is a severe cardiopulmonary disease resulting in death for many patients within a few years of diagnosis. PAH involves progressive remodelling of the pulmonary vasculature, resulting in increased resistance, pulmonary arterial pressure and terminal right heart failure. The incomplete understanding of its primary pathomechanisms continues to present a significant challenge for therapeutic development. We aim to develop a high-throughput drug screening platform based on human induced pluripotent stem cells (iPSCs) focussing on hereditary PAH (hPAH). The most frequently mutated gene in hPAH is bone morphogenetic protein receptor type 2 (BMPR2), whose canonical signalling through Smad1/5/8 induces anti-proliferative genes such as Inhibitor of Differentiation 1 (ID1). BMPR2 dysfunction disrupts signalling balance, decreasing Smad1/5/8 and increasing Smad2/3 activity, thereby promoting resistance to apoptosis, proliferation and extracellular matrix production in smooth muscle cells (SMCs). To establish a scalable drug screening tool, we introduced an eGFP reporter into the ID1 locus of wild-type (WT) and patient-derived iPSCs. In addition, we created a BMPR2 knockout in WT-ID1eGFP iPSCs. All lines were differentiated towards induced SMCs (iSMCs). Reporter activity was assessed using flow cytometry and plate reader measurements in a 96-well format. Pilot experiments demonstrated phenotype-dependent differences in the ID1eGFP signal following stimulation with PAH-associated molecules. This project integrates PAH-relevant reporter lines to monitor BMP signalling in iSMCs. We aim to determine whether our platform provides a scalable basis for high-throughput drug screening to identify novel therapeutic candidates for hPAH.

Abstract No. P043

Towards serum-reduced culture conditions for patient-derived stem cells and cancer stem cell models

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Stem cells cultured under traditional in vitro conditions offer great opportunities for basic and translational research. However, the culture conditions differ significantly from the physiological environment and can therefore pose limitations, especially for demanding cell types. Fetal bovine serum (FBS) is widely used in human cell culture, yet batch-to-batch variability and undefined composition compromise reproducibility and quality. In addition, FBS can distort human physiology in vitro and raises animal-welfare concerns. We used a Taguchi Orthogonal Design to generate test media with reduced FBS, compensated by defined addition of biomolecules in different combinations in a synthetic basal medium. After short-term cultivation, proliferation was comparable to standard medium in primary human cardiac stem cells (hCSCs), primary lung cancer stem cells (LCSCs) and HeLa cells. Further analysis in HeLa cells showed that migration remained detectable, whereas chemosensitivity was differentially affected. However, the tested formulations did not support long-term cultivation. Ongoing work will expand the factor set, systematically optimize biomolecule concentrations and test different culture flask coatings to develop an easy-to-use, defined FBS-reduction medium for various cell types in basic and medical research.

Abstract No. P044

Modeling pancreatic cancer evolution in forward-programmed human stem cell–derived organoids

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Pancreatic ductal adenocarcinoma (PDAC) is one of the most difficult-to-treat cancers, with a 5-year survival rate below 12%. This poor prognosis is largely due to late diagnosis and the lack of reliable biomarkers that would enable early therapeutic intervention. Despite its clinical urgency, the early development of PDAC remains poorly understood because of its complex and heterogeneous nature. The absence of robust human model systems that faithfully mimic pancreatic cancer initiation severely limits both research and treatment development. Therefore, this project aims to develop human pluripotent stem cell-derived organoid models that recapitulate the evolution and diversity of pancreatic tumors, with the goal of facilitating early biomarker discovery and the evaluation of novel therapeutic strategies.

To this end, we genetically manipulate human stem cell-derived pancreatic duct-like organoids (PDLOs) to express common PDAC-associated mutations, including KRAS, TP53, SMAD4, and CDKN2A, in a controlled, forward-programmed manner. To dissect the individual and combinatorial effects of these mutations on early tumor evolution, we employ our established doxycycline-inducible piggyBac overexpression system for KRAS G12D and extend this approach to include both the G12D and G12C KRAS variants. For tumor suppressor gene inactivation, we adapted a CRISPR/Cas9-based gene-editing protocol to our organoid platform. Morphological characterization and transcriptomic analyses will provide new insights into how molecular events occurring at precursor stages influence subsequent cancer phenotypes.

Breunig M, Merkle J, Melzer MK, et al. Differentiation of human pluripotent stem cells into pancreatic duct-like organoids. STAR Protoc. 2021;2(4):100913. Published 2021 Dec 8. doi:10.1016/j.xpro.2021.100913

Allgöwer C, Mulaw MA, Nagai J, et al. An oncogenic KRAS-driven secretome involving TNFα promotes niche preparation prior to pancreatic cancer onset. Mol Cancer. 2026;25(1):29. Published 2026 Feb 3. doi:10.1186/s12943-025-02541-1

Abstract No. P045/T33

ELAPOR2 controls pancreatic endocrine differentiation through cell cycle regulation

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The pancreas is an essential organ for endocrine regulation of glucose metabolism, and its proper development depends on tight coordination between pancreatic progenitor expansion, specification, and the balance between endocrine and exocrine lineages. Our group previously described Inceptor, also known as ELAPOR1, a protein which can regulate endocrine differentiation in human models. Interestingly, Inceptor has a paralog protein named ELAPOR2. In previous studies, ELAPOR2 was described as a regulator of proliferation throughout skin development, expressed throughout all germ layers, but its specific role in the pancreatic endoderm remains poorly understood. Therefore, we aimed to better determine the function of ELAPOR2 in human pancreatic progenitor proliferation and cell fate allocation. Using stem cell differentiation to model human pancreas development and endocrine differentiation, we show that, in pancreatic progenitors, loss of ELAPOR2 directly affected critical receptor signaling with established function in pancreas development. This observation correlated with an increased cell cycle length in ELAPOR2 knockout (KO) pancreatic progenitors, which facilitated the stabilization of NGN3, the major transcription factor to promote endocrine differentiation. ELAPOR2 KO lines displayed increased total ratios of β-cells by the end of differentiation. In reverse, overexpression of ELAPOR2 decreased the numbers of NGN3 expressing cells midway through endocrine induction and ultimately decreased the percentage of β-cells in our final differentiation product. These findings reveal that ELAPOR2 is a regulator of pancreatic progenitor proliferation and fate commitment. Our results identify a new molecular player in the regulatory network governing pancreas formation, which could be further explored to deepen our understanding of proper formation of the pancreatic endocrine lineage.

Siehler, J., Bilekova, S., Chapouton, P. et al. Inceptor binds to and directs insulin towards lysosomal degradation in β cells. Nat Metab 6, 2374–2390 (2024). https://doi.org/10.1038/s42255-024-01164-y

Ansarullah, Jain, C., Far, F.F. et al. Inceptor counteracts insulin signalling in β-cells to control glycaemia. Nature 590, 326–331 (2021). https://doi.org/10.1038/s41586-021-03225-8

Abstract No. P046

A microphysiological system with integrated real-time assessment of cell viability and drug response

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Recent advances in drug development, including targeted, biological, and immunotherapies, have improved therapeutic potential but require precise prediction of treatment responses for each individual patient. Testing of safety and efficacy of potential drug candidates remains one of the most challenging tasks in medicine due to their biological complexity, variability, and the high failure rate in drug development process. Microphysiological systems such as organ-on chips have the potential to better mimic the physiological conditions, reduce animal testing, and therefore improve the therapeutic outcome.

Here, we combine several recent technological advances. We integrate different cell models, such as patient-derived 3D cell cultures (organoids) from colorectal carcinomas that recapitulate the architecture and heterogeneity of the original tumor, liver cells for hepatotoxicity testing, and skin models for investigating cosmetics-induced inflammatory responses. The integration of induced pluripotent stem cell (iPSC) derived models is currently being established. Microfluidic perfusion enables long-term measurements and defined exposure of cytostatic drugs, such as mimicking plasma concentration profiles of the patient's medications. Oxygen microsensor particles are embedded in cavities along the channels together with the cells to assess cell viability in real time. In parallel, cell-based sensors can be used to detect inflammatory responses.

By combining real-time sensor technology with microfluidics, we are able to examine growth behavior during and after drug exposure, which provides insights into the regeneration of tumor growth. This provides a valuable opportunity to evaluate and anticipate the effectiveness of cancer therapies before they are administered.

Abstract No. P047

Modeling the impact of genetic variants on metabolism and epigenetics with hiPSC-derived hepatocytes

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Metabolic dysfunction-associated steatotic liver disease (MASLD) is one of the most common liver diseases worldwide. MASLD is a progressive disease: the first step of MASLD progression is characterized by the accumulation of fat (steatosis) in hepatocytes, the main parenchymal cell type of the liver. MASLD can then escalade into inflammation, fibrosis, cirrhosis and hepatocellular carcinoma or liver failure.

Risk factors for MASLD include lifestyle such as diet, but there is also a strong genetic component with several disease associated gene variants identified. Furthermore, patient data show aberrant epigenetic profiles, including differentially methylated genes linked to metabolism. Thus, MASLD progression seems to involve interplays between genetic factors, change in metabolism and modifications of epigenetic profiles.

Here, we propose to investigate these mechanisms using hepatocytes generated by forward programming hiPSCs (FoP-hepatocytes). The resulting cells are grown in the presence of free fatty acids to model steatosis. This *in vitro* platform can be used to define the effect of cell autonomous defects. Using CRISPR editing, we have generated isogenic hiPSCs lines carrying genetic variants of *PNPLA3*, which are associated with MASLD progression. The resulting cells were differentiation into FoP-hepatocytes in the presence of oleic and palmitic acid. Cells carrying mutated *PNPLA3* showed increased steatosis and resistance to lipid toxicity. We are currently studying the impact of this genetic modification on lipid metabolisms and DNA methylation.

Taken together, our results describe a new approach to investigate the mechanistic interplays between genetic variants, metabolic activity and epigenetic regulations in chronic diseases.

Abstract No. P048

Induced sensory neurons: on the road to authenticity

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When recreating a human cell type from induced pluripotent stem cells (iPSCs), we aim to generate an authentic representation of its *in vivo* counterpart. However, *in vitro* cultures often fall short of this goal. Here, we aimed to generate human sensory neurons from iPSCs that recapitulate three key features of native sensory neurons: (i) their transcriptional profile, (ii) their specialized functionality, and (iii) their characteristic pseudounipolar morphology, a hallmark feature that is typically absent from standard iPSC-derived sensory neuron cultures.

To generate sensory neurons, an inducible cassette encoding *NGN1*, *BRN3A*, and *ISLET1* (NBI) was homozygously integrated into the AAVS1 safe-harbor locus of iPSCs. These transcription factors form a micronetwork that plays a central role in sensory neuron development by initiating neurogenesis, activating terminal differentiation programs, and repressing non-neuronal gene expression. Seven days of induction efficiently generated induced sensory neurons (iNBI-SNs). To assess molecular authenticity, we performed single-nucleus transcriptomic profiling at DIV63 and compared their transcriptional profile with a human dorsal root ganglion (DRG) reference atlas revealing greatest similarity to mechano- and nociceptive sensory neuron subtypes.

To assess functional authenticity, we examined hallmark physiological properties of sensory neurons. iNBI-SNs formed functional connections with excitatory CNS neurons and more than 98% of cells displayed TTX-resistant sodium currents. Additionally, iNBI-SNs generated from genetic chronic pain patient iPSCs exhibited a pathological firing pattern.

Finally, we addressed morphological authenticity. We found that iNBI-SNs acquire a pseudounipolar morphology upon co-culture with rodent DRG cells. This morphological transition was characterized by a short stem axon that bifurcates into a presumptive peripheral and central axon, and was accompanied by faster conduction in the peripheral axon branch.

Together, these findings demonstrate that combining forward programming of sensory neurons with niche-dependent maturation through DRG co-culture provides a valuable model for studying sensory neuron development, physiology and disease.

Abstract No. P049

Establishment of 3D tissue culture for leukemia drug screening

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Leukemia, especially Acute Myeloid Leukemia (AML), is a significant cause of mortality worldwide. Leukemia research and drug development relies heavily on animal models, which is problematic not only for ethical reasons but also for interspecies differences.

The culture of primary bone marrow cells has been central to basic research for almost 50 years. However, the potential for application has been severely limited due to complex and time-consuming cultivation as well as vast donor variation. Besides, these cultures are characterized by very limited hematopoietic activity. All of the above is compounded when neoplastic HSCs come into play, given low ex vivo survival rate.

The 3D tissue culture presented here consists of three different stromal cells and CD34+ hematopoietic stem cells (HSCs), which self-assemble in 96-well plates to form floating spheroids. This model system has already been shown to perform robustly with HSCs from healthy donors and donors with AML or MDS (Myelodysplastic Syndrome). In all instances, allogeneic stroma cells have supported CD34+ HSC growth and hematopoiesis. Using flow cytometry analyses, we have seen consistent formation of myelopoietic and erythropoietic progenitors over the course of 4 weeks, while colony-forming assays have confirmed that HSCs and progenitor cells emerging from the tissue model are capable of producing mature blood cells.

Current efforts to improve standardization and scalability will allow this model to aid in the discovery of novel treatment options and support drug screening in the context of personalized medicine.

Abstract No. P050

An LNP-enabled hiPSC-cardiomyocyte platform for functional analysis of cardiac β-adrenergic receptor signaling

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Current models for cardiac β-adrenergic signaling rely either on easily transfectable heterologous systems with limited physiological relevance or on complex cardiac models requiring viral transduction or transgenic engineering. Human iPSC-derived cardiomyocytes (hiPSC-CMs) offer a physiologically relevant alternative but are often experimentally demanding. Here, we coupled our iPSC and LNP platforms to create a model that combines physiological relevance with simplified and scalable experimental accessibility. We demonstrate its usefulness for drug research by quantifying β_1/β_2 receptor selectivity of the β-blocker landiolol.

β-adrenergic receptor (βAR) signaling is the major regulator of cardiac contractility through modulation of intracellular cAMP levels in cardiomyocytes. While β_1ARs dominate cardiac sympathetic responses, the contribution of β_2AR to cAMP signaling and functional regulation in human cardiomyocytes (CM) remains incompletely understood.

Our 2D iPSC-CM model was generated via bi-phasic Wnt-signaling modulation resulting in a highly pure cardiomyocyte population (>90% $cTnT^+$), verified by expression of typical cardiomyocyte markers and functional properties. To monitor intracellular cAMP dynamics in real time, we created a robust, efficient, and non-toxic lipid nanoparticle (LNP) formulation containing FRET-based cAMP biosensor-encoding mRNA. Using this formulation, we successfully transduced >80% of iPSC-CMs. Our model exhibited the expected cAMP response to epinephrine, but this cAMP signal was primarily β_2AR-mediated, indicating a β_2-dominant neonatal receptor expression phenotype. To study βAR subtype selectivity, we further leveraged the LNP technology by co-transducing the β_1AR. In this model, epinephrine exhibited higher potency and efficacy in cAMP signaling with clear β_1AR and β_2AR components. The β_1AR co-transfected model showed sensitivity to landiolol inhibition, while the endogenous β_2AR component was largely unaffected.

In summary, our platform bridges the gap between heterologous expression systems and animal models, which may have limited translational relevance for human cardiac adrenergic signaling. The model provides an in-depth understanding of β-blocker effects on cardiac function.

Abstract No. P051

An axonal model of FUS-ALS pathogenesis identifies a novel therapeutic strategy

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Amyotrophic Lateral Sclerosis (ALS) is a fatal neurodegenerative disease characterized by the progressive loss of motor neurons (MNs), where axonal degeneration precedes soma loss generally termed as “dying back”. Among the genetic causes of ALS, mutations in FUS results in one of the most aggressive forms of the disease and are associated with juvenile and paediatric onset cases. One of the important and longstanding question we wanted to address in this work is why MN axons are particularly vulnerable, and how this vulnerability is exacerbated by mutant FUS. Using iPSC-derived MNs, cultured in microfluidic chambers to physically isolate axons from soma, compartment specific transcriptomic profiling revealed that mutant FUS axons display a pronounced dysregulation of mitochondrial genes, while the soma remained largely unchanged from isogenic WT MNs. This was further verified using TMRE assay displaying mitochondrial membrane potential defects in the axons of mutant FUS MNs. Building on this mitochondrial phenotype, axonal degeneration was modelled by challenging MNs with lactate as metabolic energy source, which selectively resulted in degeneration of mutant FUS axons and and established a tractable readout for axon degeneration of iPSC derived FUS-ALS models. We also observed from immunofluorescence assay that FUS granules accumulate in the mutant FUS MN axons. This granule accumulation potentially resulted in axonal translation repression in mutant FUS axons, which we hypothesize to drive mitochondrial defects. Building on these findings, this work advances and validates a novel therapeutic strategy that exploits FUS's physiological RNA-binding function. Strikingly, exogenous “decoy” RNA delivered at high concentrations was sufficient to competitively sequester mutant FUS, restore axonal translation, and rescue mitochondrial function in axons of mutant FUS MNs, providing proof-of-concept that competitive engagement of mislocalized FUS by RNA can protect axons from degeneration.

Abstract No. P052

Humanized mouse models 2.0: deep immune profiling through integrated in vivo and ex vivo approaches to advance immuno-oncology drug development

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Background

Humanized mouse models are indispensable for the preclinical evaluation of next-generation immunotherapies, including immune checkpoint inhibitors (CPIs), engineered immune cell therapies, and immune-cell engagers. We previously demonstrated that peripheral blood mononuclear cells (PBMCs), defined T- and NK-cell subsets, and CD34+ hematopoietic stem cells (HSCs) can be used to establish functional human immune systems in immunodeficient mice. Recent advances in next-generation NOG strains expressing human cytokines and lacking murine Fcγ receptors further enhance the translational relevance of these models.

Methods

Humanized mice were generated by transplantation of CD34+ HSCs, PBMCs, or purified immune cell subsets into NOG and next-generation strains. Human immune cell reconstitution and lineage-specific differentiation were monitored longitudinally by flow cytometry. Cell line-derived xenografts (CDXs) and patient-derived xenografts (PDXs) were implanted subcutaneously or orthotopically. Tumor growth was assessed by caliper measurements and bioluminescence imaging (BLI). Deep immune profiling was performed using multiparametric flow cytometry and 3D light-sheet fluorescence microscopy to characterize immune cell infiltration and spatial distribution within tumors and lymphoid organs.

Results

NOG-EXL mice achieved the highest levels of human immune cell engraftment, reaching up to 80% human leukocytes and displaying enhanced myeloid differentiation. Humanized NOG, hIL-6 NOG, and FcResolv™ NOG mice demonstrated long-term survival exceeding 400 days. CDX and PDX models were successfully established with engraftment rates above 70% and maintained growth kinetics comparable to non-humanized controls. Immunotherapeutic interventions generated distinct responder and non-responder phenotypes associated with differential immune cell infiltration. Flow cytometry enabled comprehensive monitoring of immune reconstitution and treatment responses, while light-sheet imaging provided high-resolution spatial visualization of tumor-infiltrating lymphocytes.

Conclusions

The integration of advanced humanized mouse models with complementary in vivo and ex vivo immune profiling technologies provides a robust and predictive platform for translational immuno-oncology research and the preclinical assessment of emerging immunotherapies.

Abstract No. P053

Next-generation electrophysiology for functional characterization of human neural organoids and assembloids

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Human-induced pluripotent stem cell (hiPSC)-derived 3D neural models (e.g. organoids, assembloids, etc.) are crucial tools for replicating human brain development and studying neurological disorders like Alzheimer's and Parkinson's disease. High-density microelectrode arrays (HD-MEAs) offer a label-free, non-invasive approach to real-time, high-resolution electrophysiological recordings from neural organoids, assembloids, and tissue explants.

We used the MaxOne and MaxTwo HD-MEA platforms, each featuring 26.400 electrodes per well, to record extracellular action potentials from various 3D neural models across different scales, ranging from cell population networks down to single-cell and subcellular levels. We showcased the flexible selection of recording electrodes, enhancing the data's reproducibility and statistical power. Key parameters, including firing rate, spike amplitude, and network burst profile, were extrapolated. The AxonTracking Assay was employed to trace action potential propagation along axonal branches and analyze conduction velocity, latency, and axonal morphology. This breakthrough assay enables high-resolution analysis of disease models targeting axon initial segment, development, and conduction.

The here presented HD-MEA platforms' capability for targeted electrode selection improves data consistency and enables more comprehensive statistical insights. Furthermore, automated data visualization and metric extraction make these systems a robust and user-friendly choice for in-vitro disease modeling and drug testing in both acute and longitudinal studies.

Abstract No. P054

Advanced murine and human lung organoid systems for vascularized disease modeling

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Over the last decade, lung organoid models have evolved toward increasing cellular, structural, and functional complexity, enabling more faithful modelling of lung development and disease. In our previous work, we established a robust protocol for generating murine bronchioalveolar lung organoids (BALO) by FACS-based isolation and co-culture of bronchoalveolar epithelial stem cells and resident mesenchymal cells from adult mouse lungs. After 21 days, BALO self-organize into bronchiolar and alveolar-like regions containing basal, secretory, ciliated, alveolar type 1, and alveolar type 2 epithelial cells. To increase model complexity, we incorporated flow-sorted pulmonary endothelial cells into differentiated BALO by microinjection, leading to the formation of endothelial networks over the alveolar compartment and enabling the study of epithelial-endothelial responses to injury ex vivo. We further use BALO exposure to urban particulate matter (UPM) as an environmental injury model to investigate cellular responses to air pollution-related stress. In parallel, human iPSC-derived lung bud tip organoids with integrated endothelial compartments demonstrate that endothelial cells enhance organoid growth, complexity, and distal epithelial organization. Building on these platforms, we are integrating iPSC-derived macrophages into human lung organoids to model epithelial-vascular-immune interactions and identify immune cell-specific molecular pathways driving lung disease initiation, progression, and resolution.

Abstract No. P055

A physiologically relevant basal medium enables robust maintenance and functional maturation of human PSC-derived neuronal cultures

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Human pluripotent stem cell (PSC)-derived neuronal cultures are increasingly used to investigate human neurobiology, model neurological disease, and evaluate therapeutic strategies. As these models mature, the neuronal culture environment plays an essential role in supporting neuronal health, functional maturation, and physiologically relevant activity. Although conventional neuronal maintenance media effectively sustain cell survival, their nutrient and metabolite composition differs substantially from that of the native brain extracellular environment, which may influence neuronal physiology and long-term network function.

Here, we evaluate Neurobasal™ PhysioPlus Medium, a physiologically relevant basal medium developed to support the maintenance and maturation of human PSC-derived and primary neuronal cultures. The medium was assessed across a diverse range of PSC-derived neuronal applications, including two-dimensional monolayer cultures and three-dimensional neuronal models, to characterize its ability to support long-term neuronal health and function. Endpoints included neuronal survival, neurite outgrowth, and maturation marker ICC quantitation, as well as assessment of electrophysiologic properties by both whole-cell patch clamp recordings and spontaneous activity by MEA during extended culture.

Across multiple neuronal model systems, Neurobasal™ PhysioPlus Medium supported robust neuronal survival while promoting progressive maturation and sustained spontaneous activity throughout long-term maintenance. The medium demonstrated broad applicability across both 2D and 3D neuronal cultures, supporting functionally mature neuronal networks under physiologically relevant culture conditions.

These findings demonstrate that Neurobasal™ PhysioPlus Medium provides a versatile foundation for the maintenance and maturation of human PSC-derived neuronal cultures. By combining physiological relevance with robust neuronal health and sustained functional activity, this medium enables the development of more biologically representative in vitro neuronal models for basic neuroscience, disease modeling, and therapeutic research.

Abstract No. P056

Sanguibacter biliveldensis - a novel bacterial species as a source of secondary metabolites with antitumoral activity in HeLa cells and primary human glioblastoma stem cells

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Proteasome inhibitors are effective for treating certain malignancies; however, development of resistance in cancer cells, commonly mediated by cancer stem cells, remains a major limitation. Greater structural diversity of inhibitors may help overcome this. Plant-pathogenic bacteria are a promising source, as secretion of proteasome-inhibitory secondary metabolites - often biosynthesized by nonribosomal peptide synthetases (NRPS) - is a known strategy to modulate host defense. We isolated and identified the novel plant pathogen *Sanguibacter biliveldensis*. Cell-free supernatants showed cytotoxic effects in HeLa cells and primary human glioblastoma stem cells. In a HeLa cell-based model, the bioactivity of ethyl acetate extracts was demonstrated, and the active components were narrowed down to specific fractions by flash chromatography. Mass spectrometry revealed a markedly altered metabolite profile of extracted supernatants under induction conditions versus non-induction control. This enables identification of the bioactive compound and assessment of its potential proteasome-inhibitory activity.

Targeting Key Signaling Pathways in Glioblastoma Stem Cells for the Development of Efficient Chemo- and Immunotherapy

Sanguibacter biliveldensis sp. nov., a Gram-positive mesophilic bacterium isolated from plant lesions

Abstract No. P057

Modeling human heart atlas-derived disease mechanisms in iPSC-based cardiac systems

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Cardiovascular target discovery is limited by access to disease-relevant human tissue and by model systems that often fail to capture patient biology. To address this, we established an integrated discovery and validation framework that connects a high-resolution human Heart Atlas with scalable induced pluripotent stem cell (iPSC)-derived cardiac models.

The Heart Atlas integrates more than 2 million single cells from public datasets with over 130 proprietary spatial transcriptomics and proteomics profiles from human left ventricular tissue, supported by curated clinical and histopathological data. This multimodal resource maps molecular, cellular, and spatial remodeling across health, early risk states, and advanced cardiovascular disease. AI-based modeling was used to identify disease-associated pathways, cell states, and candidate drivers linked to cardiac structure and function.

Atlas-derived hypotheses were tested in a genetically diverse iPSC-cardiac platform comprising iPSC-derived cardiomyocytes, cardiac fibroblasts, 2D co-cultures, and 3D cardiac spheroids. Scalable differentiation workflows were combined with CRISPR/Cas9 genome editing and RNA interference to introduce disease-relevant variants or perturb prioritized targets. Functional consequences were assessed using contractility, calcium transient, and electrophysiological assays, complemented by molecular profiling.

This approach enables human tissue-derived disease biology to be modeled and functionally interrogated in defined iPSC systems. Spatial and single-cell atlas data support target prioritization based on disease context, cell-type specificity, and localization, while iPSC-based perturbation experiments provide causal evidence for target function and mechanism.

Together, this integrated Heart Atlas and iPSC-cardiac platform provides a scalable translational strategy to identify, prioritize, and validate cardiovascular disease mechanisms. By linking patient tissue signatures with functional stem cell models, the framework increases confidence in therapeutic relevance and supports more predictive early-stage cardiovascular drug discovery.

Abstract No. P058

Immune-competent human iPSC-derived fetal liver organoids as a platform for metabolic and alcohol-associated liver injury modelling

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Fatty liver disease constitutes a major global health burden, and recent studies have revealed that the role of alcohol co-consumption has been substantially underestimated. In recognition of metabolic dysfunction and alcohol consumption, metabolic dysfunction and alcohol-associated liver disease (MetALD) is a new nomenclature while its mechanisms remain incompletely understood. Our group established immune-competent fetal liver organoids (FLOs) containing both hepatic and myeloid compartments, enabling the investigation of immune-mediated liver injury in a human multicellular context.[1]

Here, we explore the application and further optimization of this FLO platform for metabolic and alcohol-associated liver disease modelling. Using oleic acid/palmitic acid (OA/PA) treatment, FLOs developed lipid accumulation accompanied by neutrophil expansion and NETosis. Importantly, pharmacological inhibition of IL-8 signaling reduced NETosis and lipid accumulation, highlighting the utility of FLOs for studying immune-mediated lipotoxic stress and inflammatory crosstalk.[1]

To further improve hepatic function, we evaluated maturation conditions with supplementation of OSM, HGF, and dexamethasone. These conditions increased CYP3A4 enzymatic activity, suggesting enhanced functional maturation of the hepatic compartment. In addition, FLOs expressed alcohol-metabolizing enzymes such as ADH1B, indicating their potential suitability for future alcohol-associated injury modeling.

Together, these findings support immune-competent FLOs as a tractable and versatile human organoid platform with potential applications in metabolic and alcohol-associated liver injury modelling.

1. *Rezvani M, Quach S, Lewis K, et al. Modeling immune lineage co-development in human pluripotent stem cell-derived liver organoids. J Hepatol. 2026;84(5):946-961. doi:10.1016/j.jhep.2025.11.018*

Abstract No. P059

Differential characterization of oxidative and nitrosative stress-induced blood-brain barrier dysfunction in human iPSC-derived endothelial models

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The blood-brain barrier (BBB) is a highly specialized vascular interface that regulates the exchange of molecules between the bloodstream and the central nervous system. Brain microvascular endothelial cells form the principal physical barrier of the BBB. Its weakening integrity is implicated in neurodegenerative disease progression, with functional impairment by oxidative/nitrosative stress serving as a likely critical pathway [1].

We seek to elucidate how different types of oxidative/nitrosative stress induce endothelial barrier dysfunction and whether antioxidant treatment can mitigate these effects. To that end, human induced pluripotent stem cell-derived endothelial-like cells (hiECs) and brain microvascular endothelial-like cells (hiBMECs) are exposed to three chemically distinct stressors: hydrogen peroxide (H_2O_2), tert-butyl hydroperoxide (tBHP), and DETA NONOate. These agents trigger oxidative and nitrosative stress via distinct pathways, causing protein oxidation, lipid peroxidation, and DNA damage, thereby disrupting tight junctions, increasing permeability, and leading to endothelial barrier dysfunction. To evaluate potential therapeutic strategies, the antioxidants edaravone, SB3-CT, and dimethyl fumarate (DMF) are assessed for their ability to preserve or restore barrier integrity.

Transendothelial Electrical Resistance (TEER) measurements and permeability assays with fluorescent tracers, including dextran Texas Red (70 kDa), dextran Cascade Blue (10 kDa), and sodium fluorescein, were used to monitor changes in barrier integrity following stressor exposure and antioxidant treatment. Preliminary data indicate that exposure to varying concentrations of the selected stressors impairs endothelial barrier integrity, as reflected by reduced TEER and increased permeability in both cell models. By identifying distinct patterns of endothelial dysfunction induced by different stressors, this work may help link specific stress profiles to disease-relevant mechanisms and support the development of more targeted therapeutic strategies.

[1] Kim S, Jung UJ, Kim SR. Role of Oxidative Stress in Blood–Brain Barrier Disruption and Neurodegenerative Diseases. Antioxidants (Basel) 2024; 13: 1462.

P060 – P087: Stem cells in regenerative therapies

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Kathrin Zbinden

Abstract No. P060

Effects of obesity and weight loss on the vasculogenic potential of adipose stromal/stem cells in a microphysiological device

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Human adipose stromal/stem cells (ASC) are promising for tissue repair and regeneration, particularly in vascular pathologies. However, obesity-related adipose tissue expansion impairs ASC vasculogenic functions through chronic inflammation, altered differentiation, and disrupted angiogenesis. As most obesity research relies on animal models that do not fully recapitulate human physiology, this study aimed to analyse the effects of obesity and weight loss on human ASC using a 3D microphysiological in vitro model. Such systems better mimic human biology than conventional 2D cultures, providing an improved platform to study ASC behaviour and disease mechanisms.

ASC were isolated from adipose tissue of the same donors undergoing bariatric surgery, collected before weight loss (obASC), after weight loss (wlASC), and from normal BMI donors (nASC). Cells were cocultured with human umbilical vein endothelial cells in a commercial microphysiological device. Vessel length, average diameter, and area were quantified. Pericyte coverage was assessed by immunostaining for αSMA and CD31, and fourteen vasculogenic genes were analysed to evaluate ASC vasculogenic potential.

Both obASC and wlASC cocultures exhibited reduced vessel length compared to nASC cocultures. Weight loss did not restore this parameter; rather, vessel length was further reduced in wlASC compared to obASC cocultures. The pericytic gene CSPG4 was significantly upregulated in both obASC and wlASC cocultures compared to nASC, although no differences in pericytic coverage area were detected with immunostainings. ANGPT1 was significantly downregulated and KDR upregulated in obASC and wlASC cocultures compared to nASC. Additionally, the endothelial marker CD31 was significantly increased in both groups. COL4A1 expression was upregulated in obASC cocultures compared to nASC, but significantly decreased in wlASC compared to obASC, reaching expression levels similar to nASC.

In conclusion, obesity impairs ASC vasculogenic functions, and these alterations persist after weight loss, potentially limiting the therapeutic utility of ASC in vascular diseases.

Abstract No. P061

Scalable 3D closed stirred-tank reactor enabling multi-lineage differentiation for cell therapy

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De-risking the manufacturing of iPSC-derived progeny remains a key challenge for enabling robust, safe, and cost-effective cell therapies. To address this, we developed a fully closed, GMP-compliant manufacturing strategy for iPSC expansion in stirred-tank reactors (STRs), supporting robust, scalable, and xeno-free cell production for clinical translation. Lineage-specific differentiation protocols were subsequently integrated to generate macrophages, T cells, and insulin-secreting islet-like clusters (ILCs).

This work is based on a perfusion-enabled STR expansion process using a GMP-grade iPSC line, with controlled pH and dissolved oxygen. The process was optimized to facilitate scale-up without compromising cell growth, aggregate size distribution, or product quality, while achieving a 10-fold iPSC amplification rate within 4 days.

Expanded iPSCs were transferred to three cell type-specific differentiation procedures in our established STR format.

1) Macrophage differentiation was conducted by predominantly perfusion-based hematopoietic progenitor cell (HPC) differentiation and macrophage maturation from HPC aggregates. This continuous, automated, and GMP-compatible STR process yielded macrophages with >90% purity.

2) For the generation of lymphoid-potent iPSC-derived CD34+ hematopoietic progenitor cells (iCD34+ HPCs), we established a semi-automated STR differentiation process that efficiently yields iCD34+ HPCs that can be directly used for T cell differentiation without an enrichment step.

3) ILC production followed similar principles, as automated media change strategies are combined with perfusion-feeding, resulting in a 90% closed and automated process requiring minimal operator interaction. The produced ILCs display a favorable cell composition with a high beta cell fraction and robust response to KCl depolarization.

Collectively, the developed processes enable scalable, automated manufacturing of large iPSC starting material, supporting efficient and reproducible differentiation into multiple therapeutic cell types. This streamlined, GMP-compliant approach provides a robust foundation for industrial-scale cell therapy production, ensuring consistency and efficiency.

Abstract No. P062/T17

Decoding neurovascular dysfunction in ADHD: patient-specific iPSC-derived blood-brain barrier (BBB) models uncover hidden metabolic drivers beyond PARK2 genetics

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Neurovascular dysfunction is emerging as a critical but underexplored component of psychiatric disease. In attention-deficit/hyperactivity disorder (ADHD), rare copy number variations (CNVs) in *PARK2*, a key regulator of mitochondrial quality control, suggest a mechanistic link between mitochondrial stress and blood-brain barrier (BBB) impairment. Yet, whether and how patient-specific genetic risk translates into human BBB dysfunction remains unresolved.

Here, we leverage human induced pluripotent stem cell (hiPSC)-derived brain capillary endothelial-like cells (BCECs) from adult ADHD patients carrying *PARK2* CNVs to establish a patient-specific BBB platform with direct translational relevance. Combining functional barrier measurements with high-resolution metabolic and mitochondrial profiling, we dissect genotype- versus environment-driven effects on BBB physiology.

Unexpectedly, *PARK2* CNVs exerted only subtle baseline effects: BCECs with *PARK2* duplications displayed reduced barrier integrity and heightened oxidative stress sensitivity, but largely preserved mitochondrial architecture and bioenergetics. Instead, we identified a dominant and previously underappreciated driver of BBB phenotype: Time in culture. Prolonged culture induced a striking collapse of barrier function alongside a coordinated metabolic rewiring from glycolysis to oxidative phosphorylation, accompanied by reduced lactate production and altered cellular energy balance.

These findings challenge a purely genetics-centered view of BBB dysfunction in ADHD and reveal that metabolic state transitions can overshadow disease-associated phenotypes *in vitro*. Our work establishes culture-dependent metabolic remodeling as a key confounder and opportunity in human BBB modeling.

By uncovering a dynamic interplay between genetic vulnerability and metabolic state, this study positions patient-specific BBB models as a powerful platform to interrogate neurovascular mechanisms in psychiatric disorders and to identify context-dependent therapeutic targets.

Abstract No. P063

Production of CAS9 expressing hiPSCs for genetic screen

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Metabolic dysfunction-associated steatotic liver disease (MASLD) is a chronic disease linked to diabetes and characterized by lipid accumulation in hepatocytes. The disease progresses through stages of steatosis, hepatocyte injury, fibrosis, inflammation and cirrhosis, leading to liver failure or hepatocellular carcinoma. End stage of MASLD can only be treated with liver transplantation. Despite affecting approximately one-fourth of the global population, and with incidence rates expected to rise over the coming years, there are currently no approved drug to prevent lipid accumulation in the liver. Therefore, there is great interest to identify novel druggable targets to halt or to reverse MASLD progression.

To address this challenge, we aim to develop a scalable CRISPR-knockout screening strategy to identify regulators of lipid metabolism using human induced pluripotent stem cells (hiPSCs) forward programmed hepatocytes (FoP-Heps). However, stable expression of CAS9 remains difficult to achieve especially during differentiation thereby limiting the development of such screen. To overcome this, we have generated hiPSC lines expressing CAS9 under the control of different constitutive or tissue specific promoters. We then monitored transcript and protein levels during hepatocytes production and validated CAS9 activity. We also confirmed that gene targeting did not affect pluripotency or differentiation.

These engineered cell lines lay the groundwork for developing CRISPR screens to uncover novel regulators of lipid metabolism in MASLD, which could serve as new therapeutic targets. Of note, our gene expression strategy might be applied to different cell types and enable CRISPR knock out screens in a diversity of cell types.

Abstract No. P064/T18

"Heps in a Bag", an engineered hepatic patch against acute liver failure

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The liver plays a central role in protecting vital organs such as the brain and kidneys by detoxifying drugs and alcohol, secreting essential proteins such as albumin, and regulating glucose and lipid metabolism. Currently, treatment options for liver disease are limited to whole-organ transplantation or supportive care, with the hope that the liver can regenerate before the onset of multi-organ failure. Cell-based therapies using primary hepatocytes have shown promising results, particularly in paediatric patients. However, these approaches require large numbers of cells and are constrained by the scarcity of donor organs.

Hepatocytes produced from human Induced Pluripotent Stem Cells (hiPSCs) could provide an advantageous alternative. However, current protocols based on directed differentiation are challenging to scale up. To address these limitations, we partnered with the company Clexbio to develop a hepatic patch based on their novel encapsulation method, VivoSet, a platofrm that enables the self-assembly of human extracellular matrix (ECM) constructs.

We have combined the VivoSet system with hepatocytes generated from hiPSCs using forward programming (FoP-Heps). The resulting FoP-Heps display key hepatic functions such as Albumin secretion, Urea detoxification and CyP activity at level comparable to those observed in primary human hepatocytes (PHH). Importantly, forward programming bypass variability between hiPSC lines and transcriptomic analyses confirm the similarity of FoP-Heps with primary cells.

FoP-heps produced in bioreactor using hypo-immune hiPSC lines were encapsulated using the VivoSet approach to engineer a hepatic patch. The embedded cells rapidly organize into mini-liver tissue while maintaining their functional characteristics. The resulting construct maintains functional characteristcs for more than 30 days in vitro. Finally, the hepatic patch was implanted in animal models and human Albumin secretion could be detected for more than 7 days suggesting that such approach could confer hepatic functions necessary for a therapeutic effect in the context of acute liver failure.

Abstract No. P065

Maximizing gene editing efficiency for enhanced clinical-grade iPSCs via sequential factor delivery

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Human induced pluripotent stem cells (iPSCs) represent a transformative platform for cell therapy across various applications. Realizing their full potential, however, requires precise genetic engineering, such as the modification of immunomodulatory receptors to enhance immune compatibility, and the integration of safety switches facilitating the development of reproducible, cost-effective off-the-shelf therapies. In cancer treatment, the introduction of chimeric antigen receptors (CARs) enables the generation of immune cells with superior therapeutic efficacy. Yet, efficient manipulation of iPSCs remains a technical hurdle, impeding broader clinical translation.

Using Catalent's GMP-compliant iPSC lines, we have systematically refined CRISPR-Cas-mediated genome editing protocols. Based on the sequential delivery of donor plasmids and RNPs, the approach achieves targeted knock-ins of full-length transgenes at efficiencies exceeding 50%, without relying on cell sorting, antibiotic selection, or viral vectors. This method enables identification of positive clones through small-scale random picking. We demonstrate the platform's versatility by generating iPSCs carrying clinically relevant transgenes, including safety switches, immunomodulatory proteins, or CARs. This integrated platform provides a versatile and scalable system for producing gene-edited, GMP-grade iPSCs with enhanced safety and functionality, supporting the advancement of allogeneic iPSC-based therapies.

Abstract No. P066

GMP iPSC derived CAR macrophages with immune shielding for off-the-shelf treatment of fibrosis

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Fibrosis is a progressive process in the etiology of many diseases with often severe or fatal consequences. While current therapies may slow disease progression, reversal remains an unmet medical need. Macrophages have emerged as promising candidates for cell-based immunotherapies due to their intrinsic anti-fibrotic activity, tissue infiltration, and immunomodulatory capacity. Early clinical data from autologous macrophage trials, such as the MATCH01 trial in liver fibrosis, demonstrate safety and therapeutic potential. However, autologous approaches are limited by donor variability, restricted gene editing, and high manufacturing costs. iPSC-derived macrophages (iMACs) offer an off-the-shelf alternative with defined genotype and scalable production.

Unedited iMACs demonstrated inherent anti-fibrotic activity in liver fibrosis models, including normalization of myofibroblast phenotype and reduced expression of fibrosis-associated markers, including collagen and α-smooth muscle actin. To further enhance therapeutic efficacy, we introduced targeted gene edits enabling immune shielding and additional anti-fibrotic functions. Using a GMP iPSC line, a feeder- and serum-free 3D manufacturing process generated functional macrophages with >90% purity. The workflow includes GMP-grade reagents and cryopreservation for off-the-shelf use. A scalable protocol in stirred-tank bioreactors has been established, achieving ~10-fold expansion per iPSC input. We generated immune-shielded iMACs with HLA inactivation to block killing by T-cells and the expression of an NK-inhibitory mechanism to suppress NK killing. We developed high-efficiency CAR constructs targeting a validated fibrosis-associated antigen by integrating novel high-affinity binders into a CAR backbone optimized for robust surface expression in iMACs. Edited clones were validated for genetic integrity, proper transgene integration, and pluripotency. CAR-iMACs exhibited stable CAR expression throughout differentiation and showed enhanced antigen-specific phagocytosis of fibrotic target cells.

We present a GMP-compatible platform to produce highly pure, immune-shielded CAR-iMACs at scale, generating off-the-shelf cell products combining enhanced phagocytic and anti-fibrotic functions with immune evasion, supporting clinical development for fibrosis, e.g., in the liver and lung.

Abstract No. P067

Gingival mesenchymal stem cells ameliorate cartilage repair in a monosodium iodoacetate-induced rat model of knee osteoarthritis

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Background: Knee osteoarthritis (OA) is a prevalent degenerative musculoskeletal disorder affecting both younger and older populations. Current clinical management mainly relies on analgesics, nonsteroidal anti-inflammatory drugs, intra-articular lubricating agents, and, in advanced cases, joint replacement surgery. Although these interventions provide symptomatic relief and may slow disease progression, they do not fundamentally target the underlying pathological mechanisms of OA or effectively prevent its progression. Therefore, increasing attention has been directed toward disease-modifying therapies, particularly cell-based approaches, which may offer regenerative potential.

Aim: This study aims to evaluate the potential of gingival mesenchymal stem cells (GMSCs) to repair articular cartilage deterioration in a monosodium iodoacetate (MIA)-induced rat model of osteoarthritis using biological, quantitative real-time polymerase chain reaction. Western blot, radiological, and histological analyses.

Methods: Thirty 9-week-old male Sprague-Dawley rats were randomly assigned into three groups: control, osteoarthritis (OA), and transplanted OA group (OA + GMSCs). OA was induced by intra-articular injection of 50 µL saline containing 2 mg monosodium iodoacetate (MIA). Rats in the OA + GMSCs group received intra-articular injections of 50 µL GMSCs suspension containing 1×10^6 cells once weekly for three weeks. The control group received intra-articular injections of 50 µL saline.

Results: GMSC treatment exerted antioxidant and anti-inflammatory effects and was associated with improved cartilage structure. Radiological assessment showed improvement in joint morphology, while histological analysis demonstrated enhanced cartilage architecture and reduced degenerative changes. At the molecular level, GMSC treatment reduced the expression of catabolic markers, including MMP-3, MMP-13, ADAMTS5, and collagen type X, while restoring the expression of anabolic and chondrogenic markers, including SOX9, aggrecan, and collagen type II. These findings suggest that GMSCs may promote cartilage repair through modulation of inflammatory, catabolic, and chondrogenic pathways.

Conclusion: These findings demonstrate the beneficial effects of GMSC transplantation in an MIA-induced rat model of osteoarthritis.

Abstract No. P068

Archimedes One: a dynamic adherent bioreactor enabling scalable stem cell manufacturing for regenerative medicine

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The cell therapy field is experiencing sustained clinical progress. Suspension-based platforms (e.g., stirred-tank bioreactors) enable scalable, reproducible GMP manufacturing that supports multiple approved products. Adherent cell therapeutics, such as iPSC-derived dopaminergic progenitors for Parkinson's disease, are often forced into these suspension-format processes to leverage established infrastructure, compromising adherent cell behavior. Alternatively, they rely on legacy 2D systems, complex hollow-fiber bioreactors, or space-intensive robotics. This can cause batch-to-batch variability from inconsistent environmental control (nutrients, gas transfer, shear, attachment conditions), labor-intensive processing, and harvesting procedures that compromise cell integrity and yield. These limitations delay clinical translation and complicate cost-of-goods reduction essential for commercial scalability.

To close this gap, we developed Archimedes One, building on the proven CellScrew technology. This dynamic adherent bioreactor combines large-scale, surface-based cultivation with the process control of conventional bioreactors. The closed, pre-assembled, single-use consumable is 3D-printed from plant-based polylactic acid (PLA), providing 10,000 cm² of growth surface within a compact footprint. Functionally analogous to a perfusion reactor for adherent cells, it enables continuous/semi-continuous media exchange with homogeneous, low-shear distribution suitable for sensitive cell types. The system is compatible with standard biocontrollers for full pH, dissolved oxygen, and temperature regulation. Automated harvesting by mechanical knocking replaces manual detachment, reducing enzyme use and operator-dependent variability. Harvesting efficiencies exceed 94% across Vero B4, HeLa, HEK293, and CHO-K1 cells.

Archimedes provides a scalable, controlled manufacturing solution for adherent stem cell-based therapies. Structured early access programs and comparative evaluations against established adherent workflows are underway to characterize performance across cell types, including iPSCs and MSCs. In parallel, continued collaboration and engagement in the development of standardized performance benchmarks and pragmatic regulatory frameworks is important to accelerate platform maturity. Together, these efforts aim to facilitate broader adoption, reduce manufacturing risk, and support the efficient clinical and commercial translation of next-generation adherent regenerative therapies.

Abstract No. P069

From research to GMP: scalable adherent iPSC and MSC culture for regenerative cell therapy manufacturing

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Despite two decades of research since the first derivation of iPSCs, only two iPSC-derived therapies have received conditional regulatory authorisation to date, both granted by Japan's MHLW in early 2026. This translational gap reflects not a deficit in biological understanding, but persistent unmet needs in scalable, standardised, and GMP-aligned manufacturing, including reproducible expansion, closed-system processing, and process scalability from research through clinical production. These bottlenecks are shared across adherent cell therapy programmes such as those targeting Parkinson's, where current processes rely on manual 2D systems and scale-up demands a shift toward high-complexity automation or adaptation into suspension.

The CellScrew®, a single-use adherent cultivation system 3D-printed from plant-based polylactic acid (PLA), provides 850 to 10,000 cm² of growth surface within a compact footprint. Its architecture of concentric cylinders and Archimedean screws promotes culture homogeneity through low-shear rotational mixing, supporting uniform nutrient and oxygen distribution. Feasibility studies using HEK293 (1), CHO-K1 and fibroblasts confirmed robust adherent growth and compatibility with standard downstream workflows. Human iPSCs expanded under clinically relevant media and matrix conditions retained pluripotency across SOX2, OCT3/4, NANOG, and TRA-1-60, with 91.7% TRA-1-60+ cells by flow cytometry, and subsequently underwent cardiac lineage specification yielding >98% cTnT+ cardiomyocytes at day 9. MSC lines from multiple tissue sources demonstrated robust adhesion and proliferation under serum-containing, chemically defined, and xeno-free conditions, with Laminin-521 coating further improving attachment under serum-free conditions.

Collectively, the dynamic low-shear environment supports scalable expansion cell banking, intermediate and final manufacturing steps, with applicability extending to cardiac and neural lineages, macrophages, and ocular cell therapies requiring defined adherent manufacturing conditions. Availability in research-use and GMP-compatible formats ensures process continuity across development phases, with translation toward fully closed automated manufacturing being advanced through the Archimedes One bioreactor, currently evaluated in an Early Access Program to generate comparative cross-application data.

1) Boshof, B., Hüppner, A., Eichberg, J. et al. Characterization and evaluation of a novel polylactic acid-made bioreactor for large-scale adherent cell expansion. Appl Microbiol Biotechnol 110, 155 (2026). https://doi.org/10.1007/s00253-026-13880-4

Abstract No. P070

Off-the-shelf immune-shielded iPSC-derived CAR γδ T cells as novel cell therapy to treat hepatocellular carcinoma

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Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related mortality worldwide. Therapeutic options for advanced disease remain limited and yield poor long-term outcomes. While chimeric antigen receptor (CAR) T cell therapies have transformed the treatment of hematologic malignancies, their success in solid tumors is constrained by limited tumor infiltration, functional exhaustion, antigen heterogeneity, and, in allogeneic settings, allorejection.

To address these limitations, we developed allogeneic induced pluripotent stem cell (iPSC)-derived CAR γδ T cells (CAR iγδ T cells) as a standardized, fully controllable "off-the-shelf" therapy for HCC. This platform combines scalable, cost-effective manufacturing with precise genome engineering at the iPSC stage. Targeted introduction of a γδ T cell receptor (TCR) and a proprietary HCC-directed CAR enables the generation of CAR iγδ T cells that inherently infiltrate solid tumors, avoid graft-versus-host disease through HLA-independent recognition, and exhibit multimodal cytotoxicity. Additionally, immune-shielding, tumor microenvironment (TME) resistance editing, and an integrated safety switch enhance persistence, prevent allorecognition, and allow controlled therapeutic intervention if required.

We established a scalable, xeno-free differentiation process to generate highly pure CAR iγδ T cells without enrichment. The final immune-shielded, armored cells display a predominantly naïve, non-exhausted phenotype and exhibit robust trimodal killing via NK receptors, the γδ TCR, and the CAR against HCC cell lines *in vitro*. Importantly, our immune-shielding strategy protects from human NK and T cell-mediated killing and prevents cytokine release by these effector cells.

Collectively, our approach integrates precise genome engineering with scalable bioprocessing to deliver a GMP-compliant, broadly accessible, and cost-competitive CAR iγδ T cell therapy for HCC. By combining trimodal cytotoxicity with immune-shielding and TME resistance, this strategy addresses tumor escape, allorejection, and T cell exhaustion, supporting durable tumor clearance. Our platform is highly flexible and can be rapidly adapted to other tumor types and target antigens.

Abstract No. P071

Advancing cell dissociation in bioprocessing with CellTrypase: a novel, high-purity trypsin-like enzyme for GMP workflows

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GMP-compliant manufacturing of advanced cell-based therapies, viral vaccines and vectors for gene therapies requires stringent control of raw materials to ensure safety, consistency, and regulatory compliance.

Cell dissociation is a critical step in these workflows, yet conventional trypsin solutions often lack defined purity levels and only partially comply with GMP standards. Increasing regulatory and quality expectations have accelerated the adoption of recombinant alternatives1,2,3,4. Recombinant trypsin-like enzymes, like TrypLETM,5 have emerged as a preferred solution because they enable efficient but more gentle cell dissociation.

CellTrypase is a recombinant trypsin-like enzyme of fungal origin that combines highest purity with robust performance across diverse cell systems. Its GMP-compliant manufacturing process excludes materials of animal origin, antibiotics, and TSE/BSE-risk components, ensuring consistently high purity, traceability and alignment with global regulatory standards.

Benchmarking against the current GMP-grade industry standard demonstrated that CellTrypase offers superior purity. It also delivers comparable detachment efficiency, high viability, and stable yields over multiple passages, with slightly reduced dissociation times in production cell lines and induced pluripotent stem cells (iPSCs). CellTrypase thus sets a new standard for safe, consistent, and highest quality cell dissociation in modern GMP workflows.

U.S. Food and Drug Administration. (2010). Guidance for industry: Characterization and qualification of cell substrates and other biological materials used in the production of viral vaccines for infectious disease indications. Rockville, MD: U.S.

European Medicines Agency. (2014). Guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials (EMA/CHMP/BWP/814397/2011). Amsterdam, Netherlands: European Medicines Agency.

Abstract No. P072

A new animal component free culture medium for three dimensional expansion of human pluripotent stem cells (hPSCs)

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Human pluripotent stem cells (hPSCs) are a key resource for regenerative medicine, disease modeling and cell-based therapies due to their unlimited self-renewal and ability to differentiate into all somatic lineages.

Conventional two-dimensional (2D) culture systems, however, impose physical and biochemical constraints that limit scalability and a cost efffective production.

Animal component–free (ACF) cell cultivation offers improved safety and consistency by eliminating the risk of contamination with animal-derived pathogens and reducing batch-to-batch variability. It also enhances regulatory compliance and reproducibility, as defined, chemically controlled media better support standardization in research and clinical applications.

To support upscaling approaches and clinical workflows, we developed an ACF medium optimized for three-dimensional (3D) culture of hPSCs that support maintenance and proliferation while preserving pluripotency.

Presented data consists of morphological 2D and 3D, flow cytometric and proliferative analysis.

hPSC clones cultured with our new medium optimized for 3D cultivation exhibit robust viability, uniform sized spheroids, and sustained expression of key pluripotency markers (SSEA4, Tra-1-60, OCT4, NANOG), shown for several clones over 10 passages.

Functional assays demonstrate preserved differentiation capacity into ectodermal, mesodermal and endodermal lineages. It supports 3D cultivation formats from a manual lab scale (e.g. 6well plates) to small scale and fully controlled bioreactor systems.

Overall, our new 3D ACF medium facilitates robust, scalable and ethically responsible stem cell culture of high quality hPCSs for clinical workflows.

Abstract No. P073

Three-dimensional expansion of human pluripotent stem cells (hPSC) with a new animal component free culture medium in an innovative bionic bioreactor

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For this proof-of-concept study the complementary expertise of Miltenyi Biotec and BioThrust are combined to demonstrate the three-dimensional (3D) expansion of human pluripotent stem cells (hPSCs) in a ComfyCell Incu bioreactor (BioThrust) cultivated in the new StemMACS™ PSC-Brew 3D ACF, human (Miltenyi Biotec).

The simplified single-use 300 mL bioreactor (SU300) was designed to support the transition from conventional 2D to 3D cell culture, with focus on essential process functions during early development. An important characteristic of the system is the membrane stirrer material and geometry, which enables exceptional gas transfer kinetics coupled with gentle hydrodynamics, facilitating high density hPSC cultivation with minimal shear stress exposure.

The new StemMACS PSC-Brew 3D ACF, human cultivation medium enables robust and scalable stem cell culture of high quality hPSCs in a high density culture while enhancing regulatory compliance and reproducibility.

We were able to demonstrate that the system provides a highly reproducible and stable culture environment, characterized by a consistently high cell viability as well as the formation of spheroids with a narrow and uniform size distribution. Cultivation schedule could be adapted between five and seven days, resulting in an expansion factor between 20 and 50 respectively. Additionally, the cultured hPSCs maintained a strong and sustained expression of key pluripotency associated markers, SSEA4, TRA-1-60 and OCT4, confirming preservation of their pluripotent state.

Comprehensive media analysis further indicated that the cultivation conditions secure optimal nutrient availability even under high cell density conditions, supporting efficient cell growth and metabolic activity. Additionally, the process was associated with minimal accumulation of potentially toxic or differentiation-inducing metabolic by-products, highlighting a well-balanced metabolic environment.

Collectively, these results underscore that the combination of the ComfyCell Incu bioreactor and StemMACS PSC-Brew 3D ACF medium is suitable for controlled, efficient and high-quality expansion of pluripotent stem cells in 3D culture format.

Abstract No. P074

Generating immune stress-resistant β cells for cell replacement therapy

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Type 1 diabetes (T1D) is an autoimmune disorder resulting in the destruction of insulin-producing β cells. In clinical trials, stem cell-derived β (SC β) cells have been shown to restore glycaemic control in T1D patients after transplantation of *in vitro* generated stem cell-derived islets (SC-islets), circumventing the shortage of cadaveric islets. $CD4^+$ T cells play a crucial role in the manifestation of autoimmunity as well as in graft rejection, in the case of transplanted islets. Recurrent autoimmunity still poses a threat to the transplanted SC-islets. This study aims to generate SC-islets resistant to immune-related stress.

Collaborators in the Pasquali laboratory established a co-culture system using EndoC-βH1 cells / human islets and activated CD4+ T cells. Activating Transcription Factor 3 (ATF3) was identified as a possible target gene involved in this immune-related stress response. ATF3 single nucleotide polymorphisms (SNPs) are associated with T1D in Genome Wide Association Studies (GWAS).

To test whether ATF3-loss of function could have beneficial immunomodulatory effects, we generated an ATF3 knock out iPS cell line through CRISPR/Cas9 mediated deletion and subsequent insertion of an H2B-Venus reporter in the previously published insulin mCherry reporter iPSC line. We differentiated this double reporter ATF3-knockout cell line into SC-islets and confirmed reporter activation by various stress stimuli, using flow cytometry. We identified inflammatory cytokines, released by $CD4^+$ T cells, to be the most effective inducer of ATF3-mediated stress response. We are currently testing concentrations of these cytokines and assessing the viability of the ATF3 knock out cells. Overall, our results suggest that manipulation of ATF3 may influence β cell response to immune-related stress.

By generating SC β cells resistant to immune-related stress, we strive to advance the field of β cell replacement therapy for T1D.

Abstract No. P075

Exploring the therapeutic potential of hiPSC-derived basal cells in the context of primary ciliary dyskinesia

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Primary ciliary dyskinesia (PCD) is a genetic disorder affecting motile airway cilia. Mutations in more than 50 genes disrupt cilia assembly and function, leading to impaired mucociliary clearance, recurrent infections, and progressive lung damage. Current treatments are symptomatic and do not restore epithelial function. Regenerative approaches using human induced pluripotent stem cell (hiPSC)-derived airway epithelial cells may address these deficits, but key translational challenges remain, including scalable animal-free cell production and identifying the proportion of functional cells required for therapeutic benefit.

To explore the therapeutic potential of hiPSC-derived airway epithelial cells in PCD context, we develop a co-culture system composed of hiPSC-derived airway basal cells (iBCs) and PCD patient-derived nasal epithelial cells (PCD NECs). To support this approach, we generated a healthy reporter hiPSC line, enabling tracking and quantification of hiPSC-derived cells and optimized and scaled up the iBC differentiation protocol. In parallel, we established a PCD NEC biobank, which includes the seven most frequently mutated PCD genes. To establish baseline functional properties, we thoroughly characterized iBC- and PCD NEC-derived airway epithelia, including ciliary beating frequency, cilia length, cell type composition, and mucociliary transport. Subsequent co-cultures of iBCs and PCD NECs at defined ratios will be performed to explore ratio dependent and PCD phenotype-dependent effects on MCC restoration.

This work will provide important insights into the feasibility and design parameters of future iBC-based cell therapies for PCD and beyond this for other chronic airway diseases, such as cystic fibrosis and COPD.

Abstract No. P076

Direct reprogramming of blood cells into isthmic region-like neural progenitor cells for cell replacement therapy

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Current strategies for generating neural progenitor cells (NPCs) for cell replacement therapy (CRT) largely rely on pluripotent stem cell (PSC)-based differentiation. Although powerful, this approach involves prolonged culture timelines, cellular heterogeneity, and safety concerns related to residual pluripotent cells. Direct lineage reprogramming offers an alternative approach, converting somatic cells into lineage-restricted NPCs without passage through a pluripotent state. Building on our induced neural plate border stem cell (iNBSC) technology (Thier et al. 2019), we generated isthmic neural progenitor cells (istNPCs) using defined neural transcription factors (BKSZ). Unlike conventional OKSM-mediated reprogramming, this approach does not employ the oncogene MYC. istNPCs are a CNS-restricted population resembling the midbrain–hindbrain boundary (MHB), the isthmic organizer, a developmental signaling center patterning adjacent midbrain and hindbrain territories. istNPCs self-renew, are clonal, xeno-free, and bioreactor-scalable. Bulk RNA sequencing revealed a transcriptomic profile consistent with isthmic organizer identity. At the protein level, regional markers including GBX2, FGF8, EN1, and PAX2 confirmed a predominantly posterior isthmic identity. Controlled modulation of developmental signaling pathways shifted istNPCs toward a more anterior phenotype, demonstrating patterning plasticity within the MHB domain and allowing full representation of the isthmic organizer region. Consistently, istNPCs differentiated into MHB neuronal subtypes, including dopaminergic and serotonergic neurons, *in vitro* and *in vivo*, making them a promising tool for CRT in e.g. Parkinson's disease (PD). Moreover, caudoventral patterning generated OLIG2-positive pMN-like progenitors that differentiated into mature MBP-positive oligodendrocytes within 30 days. Safety assessments showed no detectable pluripotency markers by immunofluorescence or RT-qPCR, and no abnormal growth or tumor formation *in vivo*. Overall, direct reprogramming of human somatic cells into clonal, self-renewing, xeno-free, bioreactor-scalable istNPCs represents a versatile platform for studying early human brain development and a promising step toward rapid, efficient generation of regionally specified NPCs. istNPCs may therefore support CRT for neurological disorders, including PD and demyelinating diseases.

Thier MC, Hommerding O, Panten J, Pinna R, García-González D, Berger T, et al. Identification of Embryonic Neural Plate Border Stem Cells and Their Generation by Direct Reprogramming from Adult Human Blood Cells. Cell Stem Cell. 2019;24(1):166–82.e13.

Abstract No. P077

Contamination control strategy for advanced therapy medicinal products (ATMPs)

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Emerging technologies for the manufacture of Advanced Therapy Medicinal Products (ATMPs) are increasingly enabling end-to-end, automated production. These innovative systems are predominantly designed as closed systems and are steadily evolving toward the standards established for traditional pharmaceutical manufacturing. This trend aligns with the principles outlined in Annex 1 of the EU-GMP Guidelines Part I, which serves as a valuable reference for developing future-ready facilities and equipment.

In accordance with EU-GMP Part IV, ATMP manufacturers can expect the introduction of new standards as the European Medicines Agency (EMA) works to align Part IV with Annex 1. A key element of this alignment is the implementation of a Contamination Control Strategy (CCS). The CCS functions as a master document and a critical quality management tool within the pharmaceutical quality system of aseptic manufacturers.

Microbial contamination of raw or starting materials remains one of the primary risks in aseptic processing. To mitigate such risks, a multilayered network of preventive measures—referred to as contamination controls—is applied. These include both organizational and technical controls such as process design, material enclosure, effective sealing mechanisms, and controlled air quality systems.

Together, these contamination controls form the foundation for ensuring aseptic processing, as summarized and managed within the CCS. The strategy provides a structured, holistic framework for listing, evaluating, and continuously managing contamination risks while measuring the effectiveness of implemented controls.

This presentation will focus on establishing a CCS and integrating the equipment necessary for medicinal product manufacturing. It will outline the relevant regulatory background, introduce participants to the concept and objectives of the CCS, and highlight current and emerging trends shaping regulatory expectations in ATMP manufacturing.

Abstract No. P078

TGFβ-dependent epithelial-mesenchymal plasticity in immortalized adult human epicardium-derived cells

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The adult epicardium contributes to cardiac homeostasis and injury-associated remodeling, but stable human in vitro models for investigating epicardial activation remain limited. Here, we characterized immortalized epicardium-derived cells (iEPDCs) generated from the adult human atrial auricle and investigated their TGFβ-dependent epithelial-mesenchymal plasticity. iEPDCs from five adult donors were cultured under epithelial-maintaining conditions using the TGFβ receptor inhibitor SB431542 or stimulated with TGFβ3. Cellular morphology, epicardial and epithelial-mesenchymal marker expression, and transcriptomic changes were analyzed by immunocytochemistry and bulk RNA sequencing.

iEPDCs displayed distinct epithelial-like and mesenchymal-like cellular states depending on TGFβ signaling. SB431542-treated cells showed epithelial-like morphology and increased expression of the epicardial and epithelial-associated markers WT1, MSLN, and CRIP1. In contrast, TGFβ3 treatment induced mesenchymal-like morphology, reduced nuclear WT1, MSLN and CRIP1 expression, and increased the mesenchymal-associated markers VIM and CD105/ENG. Transcriptomic analysis revealed clear treatment-dependent clustering and extensive remodeling of protein-coding gene expression. Pathway enrichment under mesenchymal-like conditions included extracellular matrix organization, focal adhesion, PI3K-Akt signaling, and wound healing, whereas epithelial-maintaining conditions were associated with epithelial-related signaling pathways.

Together, these findings demonstrate that immortalized adult human iEPDCs retain TGFβ-responsive epithelial-mesenchymal plasticity across multiple donors. Their combined phenotypic and transcriptomic characterization supports their use as an in vitro platform for studying mechanisms of human epicardial activation and cardiac remodeling.

https://doi.org/10.3390/cells15141313

Abstract No. P079

Comparison of different experimental models of stem cell secretome therapy in BAC-induced limbal stem cell damage

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Chronic ocular exposure to preservatives, such as benzalkonium chloride (BAC), leads to disruption of corneal epithelial homeostasis and reduced regenerative capacity of limbal stem cells (LSCs). The effectiveness of regenerative therapies may depend on the stage of cellular damage at which treatment is initiated. The study aimed to compare the cytoprotective and reparative effects of stem cell secretomes in two experimental models: simultaneous exposure to BAC and conditioned medium (CM), and CM treatment after BAC-induced LSC damage.

CM derived from human adipose-derived stem cells (ADSCs), human amniotic epithelial cells (hAECs), and immortalized human amniotic cells (hACs) were used to evaluate their effects on BAC-exposed LSCs. In the first model, LSCs were simultaneously exposed to BAC and CM for 48 h. In the second model, cells were exposed to BAC for 48 h and then incubated with CM for an additional 48 h. Cell viability, migration, proliferation, apoptosis, and the expression of genes related to these processes, as well as inflammatory markers, were evaluated using MTT assay, scratch assay, CFA, flow cytometry, and RT-qPCR.

BAC at a concentration of 0.0002% reduced LSC viability, migration, and proliferation, while increasing apoptosis. In the simultaneous exposure model, BAC+CM48 groups exhibited lower viability, proliferation, and migration compared to the control and CM48 groups ($p<0.05$), but significantly higher values than the BAC48 group ($p<0.05$). In the reparative model, CM administration following BAC exposure partially restored cellular parameters to levels approaching those of the control group.

BAC induced toxic effects on LSCs. ADSC-CM, hAEC-CM, and hAC-CM showed cytoprotective activity toward BAC-exposed LSCs, with ADSC-CM demonstrating the strongest protective potential. Stem cell secretomes exerted stronger cytoprotective effects during simultaneous exposure to BAC and CM than reparative effects following BAC-induced damage, suggesting that their protective activity may be more effective than their regenerative potential.

Abstract No. P080/T20

Engineering basal cells to modulate epithelial-macrophage interactions in COPD

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Chronic obstructive pulmonary disease (COPD) is the third leading cause of death worldwide and is characterized by chronic airway inflammation, tissue destruction and impaired regeneration capacity, with current treatments being limited to symptomatic management. Chronic exposure to noxious factors can disrupt and exhaust lung stem cell niches, impairing basal stem cell self-renewal and differentiation capacity, while dysregulated epithelial-immune cell interactions sustain a pro-inflammatory microenvironment that further limits tissue repair. This project aims to generate and characterize engineered basal stem cells with enhanced regenerative and immunomodulatory properties, capable of giving rise to airway epithelial cells that regulate inflammatory responses, to investigate and modulate epithelial-immune crosstalk in COPD-associated inflammation. Engineered airway organoids will be used as a model system to investigate these interactions.

Candidate targets and pathways with potential regenerative and immunomodulatory functions were identified through dataset analysis and validated by pharmacological induction in murine airway organoids, alongside immunostaining in murine and human lung tissues across different treatment and disease stages.

Furthermore, to characterize the immune cells involved in COPD, with a particular focus on macrophages, the functional phenotype of bone marrow-derived macrophages isolated from young and aged mice with and without 4-month cigarette smoke exposure was analyzed. Moreover, to reconstruct the stem cell-macrophage interaction niche ex vivo, an organoid-macrophage co-culture system with long-term culturing conditions was developed.

Together, these results provide a foundation for developing an organoid-based cell therapy approach that enables epithelial regeneration, immune-compatible engraftment and long-term functional tissue repair in a mouse model of COPD.

Abstract No. P081

AccuBase™: a GMP-grade protein-format cytosine base editor (CBE) enabling safer, high-performance gene editing

Tal Shamia

Synthego, Cologne

Base editing enables precise single-base changes without inducing double-strand breaks. AccuBase, Synthego's GMP-grade cytosine base editor, is an engineered protein-based editor designed to provide the precision, safety, and quality required for CRISPR-based therapeutics.

By converting C•G base pairs to T•A, AccuBase can introduce stop codons for efficient gene knockout, disrupt splice donor or acceptor sites to promote exon skipping, and silence genes with precise control. It can therefore achieve outcomes similar to CRISPR nucleases while reducing the risks associated with double-strand breaks, including indels, chromosomal rearrangements, and persistent DNA damage.

Unlike mRNA-based editors that require intracellular translation, AccuBase is delivered as a ready-to-use ribonucleoprotein complex. This enables immediate editing and a short intracellular half-life, limiting exposure to a brief, controlled window. The transient format helps minimize genomic side effects and reduces activation of DNA-damage pathways such as p53.

AccuBase has demonstrated high knockout efficiency in primary T cells without compromising viability or editing precision. It also supports multiplex editing across several loci, with virtually no detectable chromosomal translocations, large indels, or off-target single-nucleotide variants. These characteristics allow therapeutic developers to perform multiple precise edits in a single step while maintaining stringent safety requirements.

The therapeutic potential of AccuBase has also been demonstrated in edited natural killer cells, where an AccuBase RNP-based program received IND clearance and advanced into clinical development for solid tumors.

Combined with Synthego's GMP-grade guide RNAs and comprehensive quality documentation, AccuBase provides an integrated, GMP-compliant editing solution that can be incorporated into clinical manufacturing workflows. By addressing efficiency, multiplexing, off-target risk, and regulatory readiness, AccuBase offers a safer and more controlled alternative to mRNA-based cytosine base editors.

Abstract No. P082

The role of neural stem cells in vascular remodelling

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The adult central nervous system (CNS) critically relies on the proper function of its vasculature in homeostasis and disease. A crucial function of the cerebrovasculature consists of forming the blood-brain barrier with highly specialized endothelial cells that precisely control the local cerebral microenvironment. The subventricular zone (SVZ) stem cell niche, the largest neurogenic niche in the mammalian brain, is characterized by a 'leaky' vasculature, with reduced coverage by pericytes and astrocytic endfeets, thus allowing SVZ neural stem / precursor cells (NSPCs) to sense peripheral factors under homeostasis and disease. However, whether NSPCs communicate with the SVZ niche vasculature affecting their properties in peripheral inflammation is unknown. Here, we show that the SVZ serves as a vulnerable area that reacts early to neuroinflammation in the experimental autoimmune encephalomyelitis (EAE) mouse model of multiple sclerosis. Our preliminary results demonstrated that EAE-induced peripheral inflammation evoked early environmental changes in the SVZ niche, with increased fibroblast growth factor-2 expression in NSPCs, as well as increased intercellular adhesion molecule 1 and occludin tight junction protein expression in endothelial cells. Furthermore, expression of inhibitor of DNA binding (Id) proteins in NSPCs is increased during the pre-onset phase of EAE. Targeted depletion of Id2 and Id3 in adult SVZ NSPCs resulted in improved vascular barrier properties, with increased expression of laminin extracellular matrix protein and occludin tight junction protein. Consequently, this response protected the SVZ niche from neuroinflammation-induced alterations. We propose that EAE-induced neuroinflammation triggers SVZ environmental changes, regulating Id protein expression in NSPCs, thereby altering NSPC functions promoting vascular remodelling. Together, our data described endogenous SVZ NSPCs as primary signaling mediators between the periphery and the CNS, and highlighted their therapeutic potential in CNS inflammatory diseases.

Abstract No. P083

From developmental benchmarking to epigenetic improvements of iPSC-Tregs to enable off-the-shelf adoptive Treg therapy products

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Immunosuppressive regulatory T cells (Tregs) are a promising modality in adoptive T cell therapy to reduce post-transplant graft rejection and treat autoimmune disorders, but their broader clinical application is currently limited by challenges in manufacturing highly pure, stable, and scalable Treg products. iPSCs provide an attractive platform to address these constraints, as they possess limitless self-renewal capacity, can be differentiated into standardized “off-the-shelf” products, and are highly amenable to precise engineering. However, current iPSC-to-T-cell differentiation protocols, particularly for iPSC-derived Tregs, are limited, often yielding heterogeneous populations with incomplete maturation and function that diverge from physiological T cells developed in the thymus.

This project focuses on the comparative molecular profiling of iPSC-derived T cell populations and their physiological in vivo Treg counterparts. First, we will collect early Treg precursors and mature Tregs from the human thymus, and generate a comprehensive roadmap of physiological Treg development via transcriptomic and DNA methylation profiling, as we have done before for other T progenitor subsets (Hamm et al., 2025). Second, we will use artificial thymic organoids (ATO) and feeder cell-free differentiation systems to differentiate iPSCs to Tregs through defined developmental stages, isolate stage-matched iPSC-derived T cell progenitor populations, and profile them in parallel. This comparison will identify stage-specific defects and misregulated regulatory elements between both differentiation systems and our ex vivo controls. These data will be used to identify current molecular discrepancies in iPSC-derived Tregs, which will enable the development of improved feeder-free iPSC-Treg differentiation protocols that are efficient and yield Tregs that closely resemble natural thymic Tregs in their molecular, epigenetic, and functional properties.

Hamm et al., DNA methylomes undergo distinct waves of remodeling during thymic T cell development and do not acquire a proliferation-induced imprint. Cell Rep. 2025 Aug 26;44(8):116092. doi: 10.1016/j.celrep.2025.116092. Epub 2025 Aug 2. PMID: 40753575.

Abstract No. P084

Inducing an acomys-like regenerative phenotype in murine and human macrophages

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Skin is the largest organ of the body and serves as an essential structural and immunological barrier. In most mammals, including humans, wounds heal after injury through the production of a thick collagen-enriched scar, which can cause permanent functional impairment of the skin.

In contrast, spiny mouse (*Acomys spp*.) skin regenerates without scarring. Recent studies have shown that macrophages are essential during the earliest phases of regeneration in the *Acomys* ear pinna. We therefore aimed to recreate the phenotype and gene-expression profile of these cells for their potential application in murine and human wound-healing models.

Using single-cell transcriptomics together with immunostaining of dorsal skin from the house mouse (*Mus musculus*) and *Acomys dimidiatus*, we identified a macrophage population with distinct properties in spiny mice. Based on its gene-expression profile, this population may play a role in the remodelling of the wound matrix after skin injury. To recreate the *Acomys* wound microenvironment in vitro, we supplied primary murine and human myeloid cells with similar growth factors and cytokines, promoting an *Acomys*-like macrophage phenotype, as indicated by mRNA and protein expression.

We aim to further investigate the regenerative potential of these bona fide pro-regenerative macrophages under fibrotic conditions using different *in vitro* and in vivo murine and human wound-healing models. This approach may provide a new strategy to reduce scar formation in human skin.

Abstract No. P085

Cold storage, warm hearts: optimizing hiPSC-cardiomyocyte cryopreservation for tissue engineering and regenerative medicine

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Building upon protocols established by Miller *et al.* (2020, Current Protocols in Stem Cell Biology), we aimed to optimize the cryopreservation of human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs). Traditional post-thaw viability and **"Recovery Rate"** (the ratio of live cells immediately post-thaw to initially frozen cells) often fail to predict the long-term functional survival required for complex tissue engineering, such as Engineered Heart Tissues (EHTs).

Using a VIA Freeze controlled-rate system (-1°C/min), we evaluated freezing densities (1-40 million cells/mL) and volumes (0.25–1.0 mL of DMSO-based cryoprotectant). We assessed the real-world utility of **"Regrowth Rate"** (the ratio of live cells after one week of culture to initially replated cells) as a prognostic indicator for downstream applications.

Controlled-rate freezing significantly outperformed passive cooling methods (Mr. Frosty), yielding an average regrowth rate of 143.9% versus 92.7%. Density optimization revealed a critical threshold: while ultra-high densities (22–40 million cells/mL) depressed Regrowth Rate (57.4%), a concentration of 4 million cells/mL in a 0.5 mL volume (2 million cells/vial) maximized yields. Using this optimized protocol, an initial batch of 1 million frozen hiPSC-CMs yielded a 73.25% post-thaw Recovery Rate. Subsequent cultivation resulted in a 388.9% Regrowth Rate over one week, ultimately yielding 2.85 million viable hiPSC-CMs—a net 2.85-fold expansion overall.

Tracking regrowth over a 7-day culture period with three medium changes proved highly reliable for predicting cellular fitness and successful EHT casting. Ongoing research validates these parameters across diverse wild-type hiPSC lines and earlier developmental stages (cardiac progenitor and mesodermal cells). Parallel initiatives are evaluating DMSO-free cryoprotectants and prototyping novel cryo-block hardware to further standardize heat-transfer rates. In this poster presentation, we will detail these optimized parameters and demonstrate how Regrowth Rate serves as a superior metric for hiPSC-CM quality control and regenerative medicine applications.

Simple Workflow and Comparison of Media for hPSC-Cardiomyocyte Cryopreservation and Recovery https://doi.org/10.1002%2Fcpsc.125

Abstract No. P086

Beyond regeneration: stem cell-derived EVs at the crossroads of fertility and gynecologic cancer

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Mesenchymal stromal/stem cells, among clinically relevant adult stem cell populations, and their extracellular vesicles (EVs) are recognized as mediators of tissue homeostasis, repair, and disease-associated remodeling. In female reproductive biology, these active nanocarriers contribute to endometrial regeneration, embryo–endometrium communication, implantation competence, and reproductive potential. However, the same regenerative and stromal communication networks may acquire different consequences under aging, inflammation, or genetic susceptibility, positioning stem cell-derived EVs at a critical interface between fertility and gynecologic disease.

In reproductive medicine, EVs offer a cell-free paradigm for refractory infertility-associated conditions, including Asherman syndrome and thin endometrium. By transferring regulatory microRNAs, functional proteins, and bioactive cargo, mesenchymal stromal cell-derived EVs may promote angiogenesis, attenuate fibrosis, modulate inflammation, and support epithelial–stromal repair. Through these mechanisms, they hold translational potential for restoring endometrial receptivity and improving the environment required for conception.

Conversely, in women with reproductive aging or inherited cancer predisposition, such as BRCA1/2 mutations, the stromal microenvironment may undergo epigenetic and functional reprogramming. High-risk mesenchymal stromal/stem cell niches have recently been associated with DNA damage, epithelial survival, and malignant transformation in the fallopian tube, suggesting that high-grade serous ovarian carcinoma may emerge not only from epithelial genetic alterations but also from a permissive stromal field. In established gynecologic malignancies, EV-mediated communication among cancer-associated fibroblasts, mesenchymal stromal cells, tumor cells, and immune components contributes to invasion, metastasis, chemoresistance, and immune modulation across ovarian, endometrial, and cervical cancers.

By examining this dual nature, the review bridges regenerative medicine and gynecologic oncology through cellular crosstalk. Understanding why vesicular signals support repair in one context but pathological remodeling in another may open avenues for biomarker discovery, early detection, targeted therapy, and safer EV-based reproductive interventions. Ultimately, decoding this balance may reposition stem cell-derived EVs into precision-guided translational approaches for fertility preservation and gynecologic cancer prevention.

Chatterjee, M., Gupta, S., Mukherjee, T., Parashar, D., Kumar, U., Maitra, A., & Das, K. (2024). The role of extracellular vesicles in the pathogenesis of gynecological cancer. Frontiers in Oncology, 14, 1477610. https://doi.org/10.3389/fonc.2024.1477610

Garcia, G. L., Orellana, T., Gorecki, G., Frisbie, L., Baruwal, R., … Coffman, L. G. (2025). Aged and BRCA-mutated stromal cells drive epithelial cell transformation. Cancer Discovery, 15(6), 1203–1224. https://doi.org/10.1158/2159-8290.CD-24-0805

Keyword: MSC-derived EVs

Abstract No. P087

Enhancing intramuscular engraftment of stem cell-derived islets

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The autoimmune disease type 1 diabetes is characterized by the loss of insulin-producing β-cells, requiring lifelong exogenous insulin therapy to maintain glucose homeostasis. An alternative is the transplantation of cadaveric islets, which are limited in application by islet supply. Stem cell-derived islets (SC-islets) can be produced in unlimited quantities with high yield of insulin producing β-cells. A remaining problem, however, is the significant loss of endocrine cells, including β-cells, within the first days following transplantation. Cell death is promoted by the lack of vascularization, resulting in the accumulation of metabolic waste, nutrient deprivation, and hypoxia in the freshly transplanted graft.

This study aims to increase the survival of endocrine cells by preconditioning SC-islets *in vitro* to the subsequent transplantation environment by metabolic and pharmaceutical modulation as well as by improving the peri-transplantation medium.

We developed an *in vitro* model that simulates key aspects of the early post-transplantation environment by exposing SC-islets to 1% oxygen (hypoxia) and 10% medium (nutrient deprivation). Furthermore, by using reporter iPSC-derived SC-islets, we can assess β-cell survival and insulin production. Our work is ongoing in screening of preconditioning strategies, pharmacological interventions, and peri-transplantation media.

Initial results indicate that hypoxia has a greater impact on SC-islet loss than nutrient deprivation. We identified lowering of nutrient availability improves hypoxia resistance. Further, acute administration of amino acids and cholesterol can support survival.

Candidate interventions identified *in vitro* will subsequently be evaluated *in vivo* following transplantation into the gastrocnemius muscle of mice. Our findings could pave way for more effective application of cell replacement therapy for diabetes.

Poster sessions II: P088 – P171

(the TXX number indicates an accompanying oral presentation)

P088 – P135: Pluripotency, differentiation & PSC-derived models

P088 Development of a scalable stirred-tank bioprocess for large-scale manufacturing of human iPSC-derived cardiac organoids
Ebru Aksoy

P089 Generation of vascularized human induced pluripotent stem cell (hiPSC) derived lung organoids
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P090 Improving reproducibility and scalability in human organoid culture using AI-engineered proteins and a defined synthetic hydrogel
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P091 Patient-derived hiPSC sensory neurons reveal increased neuronal activity in paroxysmal extreme pain disorder
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P092/T42 Modeling primate atherosclerosis using iPSC-derived macrophages
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P093 Synthetic peptide growth factors and cytokines enable generation of iPSC-derived immune cells
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P094 Community driven-consolidation of the vast expanse of stem cell differentiation protocol literature
Rafaella Buzatu

P095 Promoting survival and maturation of ASCL1-induced basket cell-like neurons by tuned ASCL1 expression and MEF2C overexpression
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P096 Mapping the marker landscape of early germ layer differentiation for stem cell quality control and experimental planning
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P097 Nuclear and chromatin architecture & mechanics in stem cell fate regulation
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P098 Understanding the mechanisms controlling human pancreas organogenesis using a new in vitro platform
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P099/T02 Mosaic gastruloids reveal a temporal restriction for developmental cell competition
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P100 Genetically engineered research tools based on extensively characterized control hiPSCs
Christian Freund

P101 Human induced pluripotent stem cell differentiation for in vitro skin modelling
Ronja Friede

P102 Foreign mitochondria, fragile stem cells: a hidden challenge for human naïve stem cell culture
Ana Lourdes Gama Manon

P103 Deciphering the role of NR2F1 in craniofacial and brain development: from locus-specific regulation to genome-wide impact
Maren Gehringer

P104 Establishment of human immune-competent induced pluripotent stem cell-derived lung organoids to model alveolar macrophage niche during development and disease
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P105 GMP-compliant iPSC banking and robust cardiac differentiation platform for clinical translation
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P106 Characterizing COQ4-associated neuronal phenotypes using CRISPR-edited hiPSC derived neurons
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P107 Beyond viability: evaluating post-thaw recovery in iPSC-derived and 3D cell culture workflows
Mariya Hrynchak

P108/T43 CTCF insulates gene expression to safeguard migratory myogenic progenitor cells
Sören Hüttner

P109 Synthetic peptide growth factors enable defined 3D culture of human iPSCs in hydrogel systems
Bärbel Icheln

P110 A high-throughput disease modeling system offers large-scale investigation of rare genetic diseases
Amy Vivien Job

P111 Improving cross-species comparability of human and cynomolgus macaque iPSCs
Antonia Keßler

P112 Generation of functional oligodendrocyte progenitor cells through serial replating of iPSC-derived NPC spheres
Kee-Pyo Kim

P113 Electroporation of cortical organoids for functional investigation of neurogenesis
Annika Kolodziejczyk

P114 Differentiation of human pluripotent stem cells to steroid-producing adrenal cells
Katrin Koehler

P115 Effect of microfilaments on embryoid body morphogenesis and early neuronal induction
Merle Küstner

P116 Modelling the molecular basis of human speech evolution
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P118 A hiPSC-derived endothelial cell model with kallikrein activity for hereditary angioedema
Yanyan Luo

P119 The impact of cohesin on human head and face development
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P120 An insight into gorilla (Gorilla gorilla) induced pluripotent stem cells
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Lisa Münchhalfen

P122 Analyses of the impaired endothelial blood-brain barrier and senescence-associated molecular phenotypes in Rett syndrome
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P124 Membrane-stirrer bioreactor platform enables record-breaking human iPSC expansion at clinically relevant scales
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P125 PSC suspension culture eases the transition to 3D differentiation workflows
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P126 Embryonic macrophages direct hepatocyte expansion in liver development
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P127 Effective cryopreservation of retinal organoids via vitrification preserves retinal identity and developmental potential across differentiation stages
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P128 FLT3L and SR1 regulate development and immunostimulatory function of human PSC-derived dendritic cells
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P129 Investigating the impact of endocrine chemical disruptors on liver development using hiPSCs
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P130 Full-length laminin-521 recreates the native stem cell niche to support human pluripotent stem cell survival, migration, and expansion
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P131 Engineering the CDX2/PDX1 locus in human stem cells to study lineage-specific gene regulation
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P132 Benchmarking the matrix transition: a standardized screening and validation framework for cerebral organoid cultures
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P135 Biobanking and stem cell technologies across species for conservation and basic research
Vera Zywitza

Abstract No. P088

Development of a scalable stirred-tank bioprocess for large-scale manufacturing of human iPSC-derived cardiac organoids

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Scalable manufacturing of human induced pluripotent stem cell (hiPSC)-derived cardiac organoids remains a major bottleneck for their translational application. We established an in-house cardiac organoid differentiation protocol and successfully scaled the process from a 100 mL to a 1 L working volume in stirred-tank bioreactors.

Dissolved oxygen (DO) and pH were continuously monitored throughout differentiation to characterize process dynamics during scale-up. Daily morphological assessment, flow cytometry and whole-mount immunostaining were used to evaluate organoid development and differentiation.

With the optimized process, we could reliably produce about 70,000 spontaneously beating cardiac organoids. Online monitoring helped us understand how DO and pH changed during differentiation, which will help us improve the process further. Flow cytometry and whole-mount immunostaining showed that cardiac organoid differentiation was successful after scaling up, and the organoids kept their shape and function even after increasing the working volume tenfold.

This study presents a scalable stirred-tank process for making hiPSC-derived cardiac organoids and establishes a basis for standardized large-scale production to support future regenerative medicine applications.

Abstract No. P089

Generation of vascularized human induced pluripotent stem cell (hiPSC) derived lung organoids

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Lung organoid models derived from human and murine stem cells have become a powerful tool to study lung development and disease. Recently, the cellular and structural complexity of lung organoid models has increased significantly. However, a lung organoid system with a vascular compartment is still missing. Here, we describe a method to generate hiPSC-derived lung bud tip organoids with an integrated endothelial compartment. hiPSC were differentiated into CXCR4, CKit, FOXA2 and SOX17 expressing endoderm, further polarized into anterior foregut endoderm followed by the induction of lung progenitors. Lung progenitors were then enriched by sorting for NKX2.1+ cells. In parallel, hiPSC were differentiated into functional, tube forming CD31+CD144+CD34+CD105+ endothelial cells (ECs). Co-culture of sorted NKX2.1+ lung progenitors with ECs resulted in the formation of complex branched lung organoids containing NKX2.1+SOX2+SOX9+ lung bud tip progenitors, as well as differentiated cells, such as MUC5A+ goblet cells and SFTPC+ alveolar epithelial type 2 cells (AEC2). After a few days, organoids were surrounded by complex, lumen forming endothelial networks, closely interacting with the organoid. Co-culture of the sorted lung progenitors with ECs significantly increased organoid size, indicating epithelial-endothelial cell crosstalk.

To study the role of the lung vascular compartment during cancer, the vascularized organoids were microinjected with either non-small-cell-lung cancer or melanoma cells. Seven days after microinjection, tumour cells were engrafted, forming several tumours within the organoid. Furthermore, injected melanoma cells exhibited characteristic angiotropism by closely aligning with the endothelial network around the organoids.

In summary, we were able to generate complex hiPSC-derived lung organoids containing a vascular compartment which can be used to study epithelial-endothelial interactions and tumour-lung-endothelial cell interactions.

Abstract No. P090

Improving reproducibility and scalability in human organoid culture using AI-engineered proteins and a defined synthetic hydrogel

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Three-dimensional cell and organoid culture systems are key platforms for therapeutic screening and disease modeling. These models rely on animal-derived matrices, notably basement membrane extract (BME), and unstable growth factors such as FGF-10 and Wnt-3a1. These reagents pose manufacturing challenges, poor reproducibility, high costs, and no opportunities for clinical translation due to risk of contaminants. To address these limitations, a two-pronged strategy was used: (1) a novel variant of FGF-10 and a Wnt/RSPO (R-Spondin) agonist4 with improved thermostability and solubility were developed through AI-driven protein engineering and mutation library screening and (2) a fully defined matrix, Cultrex Synthetic Hydrogel, was adopted to replace BME.

Human adult intestinal, liver, and lung organoids and iPSC-derived pancreatic duct-like organoids (PDLOs) were cultured with these reagents. The data revealed robust growth across multiple organoid types while maintaining key markers and morphology. The Wnt-agonists more efficiently induced β-catenin signaling at reduced concentrations relative to wild-type Wnt-3a. Further, thermostable FGF-10 supported healthy organoid culture without needing additional supplementation. These findings support the advantages of combining thermostable FGF-10 and Wnt agonists with a synthetic hydrogel to generate supportive growth environments for diverse organoid models.

Abstract No. P091

Patient-derived hiPSC sensory neurons reveal increased neuronal activity in paroxysmal extreme pain disorder

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Paroxysmal Extreme Pain Disorder (PEPD) is a rare inherited pain syndrome caused by gain-of-function variants in *SCN9A*, encoding the voltage-gated sodium channel Nav1.7. Previous studies in heterologous expression systems have linked PEPD-associated variants to impaired channel inactivation, enhanced resurgent sodium currents, and increased neuronal excitability[1,2].

Here we investigate patient-specific human induced pluripotent stem cell (hiPSC)-derived sensory neurons (iSNs) carrying the heterozygous missense variant Nav1.7 p.V1299F. The patient presents with typical clinical PEPD symptoms, including recurrent episodes of severe pain and skin flushing. We generated an isogenic wild-type hiPSC line using CRISPR/Cas12a-mediated genome editing and differentiated hiPSCs into iSNs by forced NGN1 overexpression. iSNs were electrophysiologically analyzed using whole-cell patch-clamp.

Patient-derived iSNs showed increased spontaneous activity compared with isogenic control neurons (33%, n= 66 vs. 20%, n = 54). Furthermore, patient-derived neurons exhibited a significantly reduced rheobase and a trend toward higher action potential firing frequencies in response to current injection. Ongoing voltage-clamp experiments aim to determine whether these changes are associated with altered Nav1.7 channel properties, particularly enhanced resurgent sodium currents.

In summary, patient-derived sensory neurons recapitulate features of the PEPD gain-of-function phenotype, including increased neuronal activity and reduced rheobase. This hiPSC-based model provides a human platform to study the contribution of mutant Nav1.7 channels to pain pathophysiology and to explore novel therapeutic strategies.

Theile, J. W., Jarecki, B. W., Piekarz, A. D. & Cummins, T. R. Nav1.7 mutations associated with paroxysmal extreme pain disorder, but not erythromelalgia, enhance Navβ4 peptide-mediated resurgent sodium currents. J. Physiol. 589, 597–608 (2011).

Dib-Hajj, S. D. et al. Paroxysmal Extreme Pain Disorder M1627K Mutation in Human Nav 1.7 Renders DRG Neurons Hyperexcitable. Mol. Pain 4, 1744-8069-4–37 (2008).

Abstract No. P092/T42

Modeling primate atherosclerosis using iPSC-derived macrophages

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Atherosclerosis is a chronic inflammatory disease characterized by lipid-driven plaque formation within the arterial wall and is one of the leading causes of death worldwide. Early stages of plaque development involve macrophages, which become lipid-laden foam cells upon uptake of oxidized low-density lipoprotein (oxLDL).

While the cellular and molecular mechanisms of atherogenesis have been extensively studied in mice and humans, far less is known about how these processes differ across primate species and how they have evolved. Non-human primates (NHPs), particularly chimpanzees, are of special interest in this context due to their close evolutionary relationship to humans and reported differences in susceptibility to atherosclerotic plaque formation.

Here, I present an in vitro model of foam cell formation from induced pluripotent stem cell (iPSC)-derived macrophages. It enables the differentiation of NHP iPSCs into macrophages and the investigation of their oxLDL uptake in vitro. The use of fused human-chimpanzee iPSCs — a tetraploid composite cell line containing human and chimpanzee genomes — enables the investigation of regulatory activity within a shared trans-regulatory environment. This allowed us to identify gene expression differences between human and chimpanzee macrophages during oxLDL uptake, attributable to independent cis-regulatory changes between species. These changes were significantly enriched, especially in the cholesterol efflux pathway, with chimpanzee macrophages exhibiting elevated expression of multiple efflux-associated genes upon oxLDL exposure. These results indicate evolutionary changes in the regulatory architecture of lipid-handling pathways. Ongoing functional assays will determine whether these transcriptional differences translate into altered cholesterol efflux capacity.

This system provides a framework for investigating how regulatory development influences human susceptibility to atherosclerosis and could ultimately reveal conserved and species-specific mechanisms relevant to future prevention and treatment strategies.

Abstract No. P093

Synthetic peptide growth factors and cytokines enable generation of iPSC-derived immune cells

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Manufacturing of cell therapy products typically relies on recombinant growth factors, cytokines, and serum-derived supplements to support cell expansion and differentiation. While these biologics have enabled significant advances, their batch-to-batch variability and dependence on animal- or cell-derived systems present challenges for process standardization, scalability, and reproducibility. Developing chemically defined alternatives that replicate essential signaling pathways is therefore important for more controllable cell manufacturing.

Here, we investigated synthetic peptide growth factor and cytokine mimetics as substitutes for conventional biologics. These peptides are designed to activate signaling pathways analogous to those triggered by native factors while offering advantages in chemical definition and stability.

As a demonstration, human iPSCs were differentiated into natural killer T (NKT) cells via a hematopoietic stem and progenitor cell (HSPC) intermediate. Synthetic peptide growth factors corresponding to Wnt3a, TPO, and VEGF were used to induce differentiation into HSPCs, followed by differentiation into NKT cells. Peptide conditions accelerated differentiation, shortening the process by one day to completion within 10 days, while approximately doubling cell yield without altering HSPC surface marker expression. The resulting NKT cells showed functional properties comparable to those generated using recombinant factors. Moreover, terminal maturation of NKT cells was achieved using an IL-15 alternative peptide, which promoted robust expansion and maturation comparable to recombinant IL-15.

These findings demonstrate that synthetic peptide mimetics can support differentiation and expansion of iPSC-derived immune cells in a defined system without serum or recombinant proteins, highlighting their potential for standardized cell therapy manufacturing.

Abstract No. P094

Community driven-consolidation of the vast expanse of stem cell differentiation protocol literature

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Humanity's knowledge of induced and embryonic pluripotent stem cell (i/ePSC) differentiation spans a vast and largely empirical literature that remains heterogeneous and poorly standardized. Unifying this fragmented knowledge could yield crucial insight into the molecular logic of stem cell differentiation decisions. As a first step towards this goal, we establish a community-driven harmonization effort to consolidate differentiation protocols for human i/ePSCs. We developed an online community platform to organize differentiation steps and experimental readouts into a harmonized database, populated using AI-assisted text extraction and curated by community volunteers. The platform captures protocol steps, durations, reagents, culture media, vendors, compund concentrations, and differentiation readouts. We applied this framework to ~200 curated articles, enabling systematic comparison of protocols across the literature and connecting them into a longitudinal branching differentiation landscape. Together, this work establishes a searchable database linking protocol parameters to cellular phenotypic outcomes, enabling data-driven and AI-assisted optimization of i/ePSC differentiation.

Abstract No. P095

Promoting survival and maturation of ASCL1-induced basket cell-like neurons by tuned ASCL1 expression and MEF2C overexpression

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Efficient fate conversion of non-neuronal cells by overexpression of neurogenic transcription factors (TFs) such as Ascl1 holds promise as a source of induced neurons (iNs) for basic and translational research purposes. Our ability to promote iN survival and to instruct the acquisition of molecular, morphological and functional properties typical of endogenous neurons is, however, still limited. Overexpression of a mutant form of Ascl1 (Ascl1SA6) converts cortical glia to an inhibitory neuron-like state characterized by marker expression and functional features typical of cortical fast-spiking interneurons such as Parvalbumin-positive Basket cells, while retaining broadly immature morphological characteristics. To test the hypothesis that persistent overexpression of Ascl1SA6 and lack of expression of TFs responsible for developmental subtype specification may hinder iN maturation, we modulated Ascl1SA6 expression and overexpressed Mef2c, a TF essential for Parvalbumin-positive interneuron specification and whose expression is maintained in mature neurons. Overexpression of Mef2c alongside Ascl1SA6 generated iNs displaying markedly more complex morphologies and progressively decorating the soma and dendrites of nearby iNs with extensive arborizations, resembling endogenous Basket cells. Crucially, however, while Ascl1SA6 was necessary for efficient reprogramming, its expression at high levels interfered with the acquisition of Mef2c-induced features. To test if reducing Ascl1SA6 expression following reprogramming initiation, alone or in combination with Mef2c overexpression, might suffice to promote iN maturation, we employed a published microRNA-based self-regulating system, thus negatively coupling acquisition of neuronal identity and Ascl1SA6 expression. In vitro experiments show Ascl1SA6 expression to be significantly and selectively dampened among iNs, with a concomitant long-term increase in iN survival. Ongoing experiments are assessing if and how these effects may be compounded by concomitant Mef2c overexpression.

Reprogramming astroglia into neurons with hallmarks of fast-spiking parvalbumin-positive interneurons by phospho-site–deficient Ascl1; 10.1126/sciadv.adl5935

Abstract No. P096

Mapping the marker landscape of early germ layer differentiation for stem cell quality control and experimental planning

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Human pluripotent stem cell quality control may be perceived as a necessary obstacle delaying visionary researchers from performing transformative experiments. However, when carefully designed and streamlined, it can provide valuable biological insight into stem cell identity, differentiation capacity, and experimental reproducibility. We recently reported the need to curate and update marker gene lists for gene expression-based quality control assays and extensively validated hiPSCore, a machine learning-based functional pluripotency classifier. In parallel, we established an expanded set of validated marker genes for early induced pluripotent stem cell quality control.

Building on these studies, we substantially expanded the hiPSCore database by incorporating additional cell lines, differentiation states, culture media, and matrix compositions, thereby enabling a broader and more practical assessment of pluripotency and early differentiation competence across diverse experimental conditions. We further demonstrate that hiPSCore can reduce time and costs in the development of advanced three-dimensional model systems for drug testing by identifying suboptimal differentiation trajectories before resource-intensive experiments are initiated. Finally, we show that hiPSCore is broadly applicable to quality control scenarios, including cell lines reported to fail conventional pluripotency assays.

Together, our findings highlight that stem cell quality control is not an end in itself, but a powerful strategy to improve experimental success, reduce unnecessary costs, and uncover biologically meaningful variation in pluripotent stem cell differentiation potential.

Dobner, J., Diecke, S., Krugmann, J. et al. Reassessment of marker genes in human induced pluripotent stem cells for enhanced quality control. Nat Commun 15, 8547 (2024). https://doi.org/10.1038/s41467-024-52922-1

Defining early human developmental identity: A curated, cross-platform marker framework Jochen Dobner, Alessandro Prigione, Andrea Rossi bioRxiv 2026.03.26.714482; doi: https://doi.org/10.64898/2026.03.26.714482

Abstract No. P097

Nuclear and chromatin architecture & mechanics in stem cell fate regulation

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Cells continuously sense and respond to a dynamic combination of biochemical and mechanical cues from their microenvironment. These signals integrate at the nuclear periphery, where they regulate genome organization and influence cell state. The mechanisms by which mechanical and biochemical cues integrate to drive stem cell state transitions remain incompletely understood.

Here, I investigate how dimensionality and biochemical signals jointly regulate the exit from primed pluripotency in human induced pluripotent stem cells. I show that transitioning cells from a 2D, ECM-adherent culture to a 3D, ECM-free environment accelerates the exit from primed pluripotency and induces a symmetry-breaking event characterized by the emergence of nuclear YAP- and E-cadherin-high cell clusters. Furthermore, the transition to a 3D topology triggers a significant reduction in nuclear volume accompanied by sustained remodeling of chromatin architecture, ultimately promoting cell state specification. Remarkably, re-establishing 2D culture after 3D aggregation preserves both the symmetry-broken phenotype and the associated chromatin landscape, suggesting the establishment of a persistent mechanical memory.

Together, these findings demonstrate that topological and biochemical cues remodel nuclear architecture and chromatin organization to direct stem cell state dynamics.

Stephens, R. K., & Miroshnikova, Y. A. (2024). Nuclear periphery and its mechanical regulation in cell fate transitions. Current opinion in structural biology, 87, 102867. https://doi.org/10.1016/j.sbi.2024.102867

Pecori, F., & Torres-Padilla, M. E. (2023). Dynamics of nuclear architecture during early embryonic development and lessons from liveimaging. Developmental cell, 58(6), 435–449. https://doi.org/10.1016/j.devcel.2023.02.018

Abstract No. P098

Understanding the mechanisms controlling human pancreas organogenesis using a new in vitro platform

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Understanding early pancreas organogenesis is essential to reveal the mechanisms resulting into developmental disorders and to develop regenerative therapies. However, early pancreas organogenesis remains relatively unexplored, especially in humans, due to ethical and technical reasons. As a result, much of our current knowledge has been built on studies in mouse models, and the mechanisms by which signaling pathways and transcriptional networks coordinate to establish distinct lineages in humans remain to be fully uncovered. Here, we established a novel human induced pluripotent stem cell (hiPSC)-derived foregut culture system that recapitulates a critical window of early lineage specification, simultaneously giving rise to multiple progenitor populations with pancreatic (*SOX9, PDX1, NKX6.1*), biliary (*CK19, CK7*), and hepatic (*HNF4a, AFP*) identity. Using this platform, we investigated the effect of oxygen tension in early pancreatic organogenesis. By systematically modulating oxygen levels (hypoxia 5% O2 vs. normoxia) we demonstrate that low oxygen tension inhibits early pancreatic lineage specification. To further validate these observations, we pharmacologically stabilized hypoxia-inducible factors (HIFs) with an HIF-prolyl hydroxylase inhibitor and confirm that specific progenitor fates can be selectively promoted or suppressed by manipulating signalling pathway downstream of hypoxia. These changes in cell identity are accompanied by a modification of cell size and number suggesting an involvement of cell cycle regulations and/or mechanosensing mechanisms. To confirm these hypotheses, we are currently performing single cell RNA analysis during pancreatic differentiation using different oxygen tension conditions. Finally, pancreatic progenitors generated in these culture conditions can form organoids which self-organized into branching structure resembling early pancreatic bud. Overall, our results provide a new hiPSC-derived differentiation system to investigate how oxygen levels and HIF-driven gene programs contribute to the network of signals that guide further pancreatic development. This platform opens new possibilities for understanding how the local environment can influence cell fate choice during early human organogenesis.

Abstract No. P099/T02

Mosaic gastruloids reveal a temporal restriction for developmental cell competition

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The selective elimination of suboptimal cells is critical for maintaining developmental integrity during early mammalian embryogenesis. Toward this goal, cells undergo **Cell Competition**, a **non-autonomous quality control** in which "winner" cells outcompete viable but suboptimal "loser" cells based on relative fitness differences. Here, we use **mosaic 3D mouse gastruloids** to investigate cell competition dynamics. Introducing just two Trp53-deficient supercompetitor cells per gastruloid suffices to impair growth in neighboring wild-type cells through mitochondrial **apoptosis**. Competition is tightly restricted to a developmental transition-stage between primed pluripotency and early gastrulation and involves gene regulatory networks of pluripotency-exit. Heterochronic gastruloids from developmental stage-shifted cells, EpiGastruloids, and dynamic p53-degrons reveal that both winners and losers must reside within this permissive stage, during which acute relative p53 protein levels determine competitive outcomes. These findings advance our understanding of cell fitness evaluation and establish gastruloids as a powerful 3D-model for investigating developmental stage-specific cell competition in mammalian embryogenesis.

Abstract No. P100

Genetically engineered research tools based on extensively characterized control hiPSCs

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The Leiden hiPSC Centre offers control hiPSC lines LUMC0099iCTRL and LUMC0065iCTRL generated from a healthy female and male donor with an updated informed consent including various research applications. In addition to the standard characterization (pluripotency status, functional pluripotency, cell identity, karyotype) these lines have undergone microbiology testing, transcriptome analysis, WGS and HLA typing, have been registered at hPSCreg (LUMCi004-A and LUMCi031-A, respectively) and have been used successfully in various research projects by multiple users.

Furthermore, we equipped both lines with STRAIGHT-IN landing pads in safe harbor loci AAVS1 and CLYBL allowing for efficient integration of large DNA payloads. Currently we use these STRAIGHT-IN hiPSCs for developing various research tools for a wide range of applications such as

1) hiPSCs with a Doxycycline-inducible transcriptional activator or repressor (CRISPRa/i): Preliminary data showed that targeting SOX2 in CRISPRi hiPSCs leads to a reduction of pluripotency markers Nanog and TRA-1-60 assessed by FACS after 3 days,

2) hiPSCs with Doxycycline-inducible transcription factors for forward programming: in a proof-of-concept doxycycline-induced overexpression of transcription factor MyoD1 was able to efficiently differentiate hiPSCs into myogenic progenitors based on morphology and expression of MHC and

3) hiPSCs equipped with the split-fluorescence system for efficient generation of reporter hiPSCs. In a first step, the sequence of the large fragment of mNeongreen (mNG2) was integrated into AAVS1 where it is constitutively expressed but non-fluorescent. We then targeted histone H2B with the short mNG2 fragment using a ssODN. Expression of H2B in undifferentiated cells led to a fully functional mNG2 resulting in hiPSCs with green, fluorescent nuclei. We are currently further validating the system. In addition, we are adding more colors and are generating hiPSCs with two colors which can be used for the generation of dual reporters.

Abstract No. P101

Human induced pluripotent stem cell differentiation for in vitro skin modelling

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The skin, one of the most important organs of the human body, protects internal tissue from external influences. In case of disorders, personalized medicine can support efficient treatment. Patient-specific skin equivalents can be used for drug testing and the investigation of disease progression. However, skin equivalents from isolated primary cells lack complexity and are limited in number, due to the demanding maintenance and amplification of primary keratinocytes. Therefore, human induced pluripotent stem cells (hiPSC), as an abundant cell source, can be used to derive skin cells and to generate personalised skin equivalents.

Protocols for the differentiation of hiPSCs towards dermal fibroblasts and epidermal keratinocytes were established, followed by characterisation of the derived cells. Both, hiPSC-derived keratinocytes (hiPSC-dK) and hiPSC-derived fibroblasts (hiPSC-dF), were characterised by qPCR and immunofluorescence (IF) staining and compared to primary cells. Functionality was further evaluated in terminal differentiation of hiPSC-dK and in 3D-models. Terminal differentiation was induced by increasing the extracellular calcium levels, resulting in involucrin/keratin 1-positive cells, validated in qPCR and IF staining. Functional skin equivalents were generated using microporous scaffolds, promoting adhesion, proliferation, and the synthesis and secretion of extracellular matrix (ECM) proteins. hiPSC-dF were seeded on these scaffolds. After 14 days of culture, formation of a dermal equivalent was observed, and the secretion of ECM proteins was investigated via IF staining. hiPSC-dK were seeded onto dermal and stratified at air-liquid interface for 21 days. Stratification resulted in the formation of the epidermal layers stratum basale (keratin 5/14-positive cells) and stratum spinosum (involucrin/keratin 1-positive cells).

In conclusion, we developed an in vitro skin model that consists solely of hiPSC-derived skin cells and has the potential to be a patient-specific disease model.

This model provides the foundation for inclusion of early-stage hiPSC-dK, potential epidermal stem cells, leading to a more physiological skin model in the future.

Abstract No. P102

Foreign mitochondria, fragile stem cells: a hidden challenge for human naïve stem cell culture

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Human pluripotent stem cells (hPSCs) rely on tightly regulated mitochondrial function to maintain pluripotency, metabolic balance, and differentiation potential. Although feeder layers such as mitotically inactivated mouse embryonic fibroblasts (iMEFs) remain widely used, it has remained unclear whether xenogeneic mitochondria can transfer to hPSCs and influence their bioenergetic state. Here, we addressed this gap by investigating both direct and indirect mitochondrial transfer from iMEFs to hPSCs through imaging, flow cytometry, species specific PCR, nanoparticle tracking analysis, and metabolic flux assays. We discovered that iMEFs transfer mitochondrial material to hPSCs through contact-dependent tunneling nanotube–like structures, but mainly and through extracellular vesicle–associated mitochondria (EVM) enriched in conditioned medium. The transfer, of EVMs yielding a high frequency uptake of mouse mitochondria in recipient cells, which was and detectable by mouse COX2 mtDNA expression in recipient cells. Although the xenogeneic mtDNA is gradually lost over subsequent passages, its transient presence coincides with disrupted mitochondrial membrane potential, reduced oxidative ATP production, compensatory glycolysis, and selective changes in lineage associated gene expression. These findings establish xenogeneic mitochondrial transfer as a biologically meaningful modifier of stem cell function, revealing a previously underappreciated source of variability in feeder based systems. This work highlights and supports the importance of xenofree, defined culture conditions to preserve mitochondrial stability, minimize culture-derived variability, improve experimental reproducibility, and strengthen the translational robustness of hPSC based applications.

Abstract No. P103

Deciphering the role of NR2F1 in craniofacial and brain development: from locus-specific regulation to genome-wide impact

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NR2F1 is a developmental transcription factor with essential roles across multiple tissues, including the brain, visual system, and craniofacial structures. Heterozygous mutations or deletions of *NR2F1* cause Bosch-Boonstra-Schaaf optic atrophy syndrome (BBSOAS), an autosomal dominant neurodevelopmental disorder characterised by developmental delay, visual system and craniofacial abnormalities.

The pleiotropic role of NR2F1 is well established; however, its molecular pathway in brain and neural crest tissues remains to be elucidated. To address this, we CRISPR/Cas9-engineered human induced pluripotent stem cell (hiPSC) lines carrying an *NR2F1* deletion, leading to reduced *NR2F1* expression. Time-resolved transcriptomic analysis of hiPSC-derived neural progenitor cells (NPCs) and early cortical neurons (CNs) to mimic brain development, as well as cranial neural crest cells (CNCCs) modelling craniofacial structures, identified key biological processes sensitive to *NR2F1* dosage and reflecting BBSOAS phenotypes/characteristics. These processes include genes that shape specific programs related to neurodevelopment (*SOX1*), craniofacial programs (*COL2A1*), as well as shared (*CDON, MSX2*) features, highlighting the relevance of *NR2F1* dosage in BBSOAS.

To further assess the role of *NR2F1* dosage, we investigated the role of cis-regulatory elements neighboring *NR2F1*, including the adjacent to *NR2F1* divergently transcribed long non-coding RNA (lncRNA) *lncNR2F1*. CRISPR/Cas9 deletion of *lncNR2F1* resulted in altered *NR2F1* expression across NPCs/CN and CNCCs, suggesting the presence of a cis-regulatory element located within the *lncNR2F1* locus. Transcriptomic analysis revealed both *lncNR2F1*-specific and some overlapping features, with those affected by *NR2F1* loss. To dissect NR2F1 targets affected by *NR2F1* deletions and *lncNR2F1* deletions, we are performing time-resolved ChIP-seq from NPC/CN and CNCC. We aim to determine *NR2F1* dosage-dependent regulatory networks across brain and craniofacial tissue types. Our data will provide novel insights into BBSOAS pathophysiology that may contribute to improved molecular diagnosis and facilitate the development of novel therapeutic approaches.

Abstract No. P104

Establishment of human immune-competent induced pluripotent stem cell-derived lung organoids to model alveolar macrophage niche during development and disease

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In the last decade, human organoids have become useful models for lung development, physiology, and disease modeling. However, these systems often lack the tissue-specific immune cell compartment. The crosstalk between the lung epithelium and alveolar macrophages is crucial for proper lung function during homeostasis and disease. This study aims to establish a reliable protocol to generate human induced pluripotent stem cell (hiPSC)-derived immune-competent lung organoids for disease modeling. For this purpose, hiPSCs were differentiated into definitive endoderm, verified by the expression of C-Kit, CXCR4, FOXA2, and SOX17. Endodermal cells were further differentiated into anterior foregut endoderm and subsequently into NKX2.1-expressing lung progenitors. NKX2.1+ progenitors were purified via cell sorting of NKX2.1GFP reporter or CD26lowCD47high cells. To generate hiPSC-derived precursor macrophages (pre-Macs), embryoid bodies were formed, differentiated into mesoderm, and subsequently into hemogenic endothelium. The resulting myeloid-cell-forming complexes generated CD45, CD14, CD11b, and CD163 expressing pre-Macs as shown by flow cytometry. Lung bud tip organoids or alveolospheres were generated by culture of NKX2.1+ lung progenitors in the presence or absence of pre Macs. Immunofluorescence staining of the co-cultures revealed that the pre-Macs engrafted into the lung bud tip organoids. Moreover, co-cultures of lung progenitors and pre-Macs resulted in higher organoid formation efficiency compared to lung progenitors alone. These data indicate that the crosstalk between epithelial cells and macrophages is beneficial for organoid growth and survival. Our ultimate goal is to utilize the immune-competent organoids to investigate the interplay between lung epithelial cells and alveolar macrophages within lung development and disease.

Abstract No. P105

GMP-compliant iPSC banking and robust cardiac differentiation platform for clinical translation

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Background: iPSC-based cardiac therapies require genomically stable GMP starting materials and robust, scalable differentiation protocols. We have recently validated a new single-cell passaging-based banking process and refined our cardiac platform toward clinical readiness.

Methods: Single-cell passaging with Rho kinase inhibition (ROCKi) generated GMP master banks from cord blood (R34 EU; R35/R36 US; R38 pipeline). QC included karyotyping, ddPCR, WGS, and cancer-gene sequencing. The cardiac platform features WNT/BMP/FGF/TGFβ co-stimulation, optimized media changes, 3D compatibility, single-cell dissociation/re-aggregation, GMP reagents, and EHT contractility assays. Cryopreservation efficiency was assessed post-dissociation.

Results: The new GMP iPSC lines met all release criteria with acquried pluripotency, normal karyotypes, no critical cancer mutations, and low overall mutation burden. Interestingly, ROCKi served to mitigate - not enhance - selective pressure on the cells, thereby contributing to preserved genomic integrity. This conclusion was based on competition experiments between wild-type iPSCs and mutant clones with duplicated chr20q11, thereby providing formal evidence for the claim.

In the cardiac induction protocol, all lines displayed >90% cardiomyocyte (CM) purity indicating *bona fide* cell line-indepence. The weekend-free platform further showed high batch-to-batch robustness and scalability. Recent advancements include the incorporation of a cryopreservation step following single-cell dissociation of the primary CM aggregates, and successful transition to GMP reagents, and development of contration force-based potency assay.

Conclusions: Validated GMP iPSC banking plus the optimized cardiac platform deliver genetically stable, high-purity, functional cardiomyocytes with GMP compatibility and cryopreservation readiness—providing a streamlined path to clinical cardiac cell therapy.

Abstract No. P106

Characterizing COQ4-associated neuronal phenotypes using CRISPR-edited hiPSC derived neurons

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Mitochondrial dysfunction is increasingly recognized as a major contributor to both neurodevelopmental and neurodegenerative disorders. Coenzyme Q10 (CoQ10) is a central component of the mitochondrial electron transport chain and a key determinant of cellular ATP production, redox balance, and mitochondrial homeostasis.

Pathogenic variants in COQ4, a gene encoding an essential enzyme in the endogenous CoQ10 biosynthesis pathway, cause primary coenzyme Q10 deficiency¬¬ 7 (OMIM #616276) and have been associated with severe neurological phenotypes. However, the precise effects of COQ4 mutations on human neuronal development, maturation and network function remain incompletely understood, and clinical benefit from CoQ10 supplementation is often limited, underscoring the need for more informative human cellular models.

Here, we apply CRISPR/Cas9-engineered isogenic human iPSC lines carrying homozygous pathogenic COQ4 variants alongside matched controls to examine neuronal differentiation, mitochondrial integrity and functional network behavior in a human-relevant system. Using a multimodal approach, we aim to evaluate how COQ4 dysfunction shapes cellular phenotype and emergent network activity during neuronal maturation. That approach includes morphological and immunofluorescent assessment of neural progenitor and neuronal markers, quantitative RT PCR profiling of neuronal and synaptic genes, mitochondrial membrane potential measurements, and high-density microelectrode array recordings. Beyond characterizing disease-relevant phenotypes, this platform is designed to support translational follow-up: it can be used to screen pharmacological interventions and test candidate compounds for their capacity to rescue mitochondrial and electrophysiological deficits.

Collectively, these studies seek to facilitate mechanistic insight and preclinical evaluation to further potential therapeutic avenues for COQ4-associated neurological disease.

Abstract No. P107

Beyond viability: evaluating post-thaw recovery in iPSC-derived and 3D cell culture workflows

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While immediate post-thaw viability is an important quality indicator, the practical success of cryopreservation in induced pluripotent stem cell (iPSC), stem cell-derived, progenitor cell, cardiomyocyte, and 3D culture workflows is often determined by whether usable cultures can be re-established after thawing. Relevant indicators include attachment, morphology, recovery behavior, expansion, and, where applicable, functional readouts.

Across stem-cell-related cryopreservation settings, Bambanker™, an FBS-free, ready-to-use cryopreservation medium, has been used with undifferentiated human iPSCs, iPSC-derived dopaminergic neurospheres, neural progenitor cell workflows, hiPSC-derived cardiomyocytes, and 3D organoid models.

In iPSC-derived dopaminergic neurospheres, Bambanker™ cryopreserved cells retained dopaminergic marker expression, dopamine secretion, and electrophysiological activity. Following transplantation into 6-OHDA-lesioned rats, cryopreserved cells survived, differentiated into mature dopaminergic neurons, and improved abnormal rotational behavior. Other stem-cell-related workflows highlight additional post-thaw assessment needs, including morphology and lineage marker expression in progenitor cell models, contractility and electrophysiological profiling in cardiomyocyte models, and growth recovery and structural integrity in 3D organoid models.

Together, these examples highlight the relevance of evaluating cryopreservation outcomes beyond immediate viability alone, particularly when working with valuable and sensitive stem-cell-related models. This poster shows application examples for Bambanker™ in iPSC-derived, progenitor, cardiomyocyte, and 3D cell culture cryopreservation workflows, with the aim of supporting practical medium selection for post-thaw culture recovery and downstream usability.

Abstract No. P108/T43

CTCF insulates gene expression to safeguard migratory myogenic progenitor cells

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During embryogenesis, multipotent progenitors present in the dermomyotome compartment of the somite generate multiple lineages including skeletal muscle, dermis and endothelial cells of the vasculature. The transcriptional programs governing these fate choices, coordinated by paired box transcription factor PAX3, are well established. How genome organization contributes to lineage specification remains poorly understood. CTCF, a key architectural protein that maintains chromatin domain boundaries to insulate gene expression, also cooperates with myogenic determination factor MYOD in muscle differentiation. However, the functional requirement for CTCF during cell fate specification *in vivo* has not been defined. Here we show that genetic inactivation of *Ctcf* in *Pax3*-expressing multipotent progenitors disrupts the specification of migratory myogenic progenitors, while closely related lineages, such as non-migratory myogenic progenitors and vascular endothelial cells, are spared. Our findings demonstrate a cell-autonomous requirement for CTCF's insulator function in safeguarding migratory myogenic progenitors from inappropriate enhancer–promoter interactions and aberrant gene expression. This model is illustrated by aberrant activation of *Ikaros* in the somitic mesoderm, through inappropriate usage of neighbouring enhancers associated with somite expression, resulting in impaired myogenic differentiation. Our findings define CTCF as a context-dependent regulator of cell fate specification, ensuring the emergence of the migratory myogenic progenitors of the *Pax3* lineage.

Abstract No. P109

Synthetic peptide growth factors enable defined 3D culture of human iPSCs in hydrogel systems

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Growth factors derived from conventional sources (e.g., serum or recombinant expression) have supported advances in regenerative medicine and cell therapy, but their instability, batch variability, and animal-derived components limit reproducibility and scalability. Chemically defined alternatives that can recapitulate essential signaling pathways are therefore needed to establish more controllable stem cell culture systems.

Synthetic peptide growth factor mimetics represent a promising approach to replacing conventional biologics. These peptides are designed to activate native receptor signaling while offering advantages in stability, chemical definition, and manufacturing consistency.

Here, we evaluated a synthetic FGF2 alternative peptide (FGFR1c agonist) for human induced pluripotent stem cell (iPSC) culture in both two-dimensional and three-dimensional hydrogel environments. iPSCs were expanded in xeno-free medium supplemented with the peptide and subsequently cultured within a synthetic hydrogel matrix to establish 3D cultures. Under these conditions, the peptide supported robust cell proliferation while maintaining pluripotency markers, including OCT4 and LIN28.

In 3D hydrogel culture, iPSCs grown with the synthetic peptide exhibited enhanced growth compared with cultures using heat-stable recombinant FGF2, despite the peptide being used at lower concentrations. The hydrogel-based system enabled high-density expansion and uniform cell morphology while preserving stem cell characteristics, demonstrating compatibility between synthetic peptide signaling and defined extracellular matrices. These findings indicate that synthetic peptide growth factors can function effectively in complex 3D environments, not only in conventional 2D culture systems.

This study highlights the potential of combining chemically defined peptide growth factors with synthetic hydrogels to establish scalable and reproducible platforms for pluripotent stem cell expansion. Such defined culture systems may facilitate the development of standardized manufacturing processes for regenerative medicine and cell therapy applications.

Abstract No. P110

A high-throughput disease modeling system offers large-scale investigation of rare genetic diseases

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Rare genetic diseases cause 72% of all rare diseases known worldwide. However, individual disease modeling remains a challenge due to limited scalability and non-consistent reproducibility.

Here, we introduce you to a patient-specific, large-scale disease modeling system based on the generation of high-quantity human brain organoids (Hi-Q organoids). This established modeling platform is used to investigate alterations in the brain, as presented in rare neurodevelopmental disorders. Therefore, we achieved to collect more than 20 patient-derived cell lines as a base for our Hi-Q organoids. The genetically manifested phenotypes in our affected individuals range from normal brain imaging but present intellectual disability, to brain malformations and primary microcephaly. By applying our disease modeling system, we can provide a robust, large-scale palette of brain-like tissue, by which we enable functional analysis across different genetic backgrounds, as well as the identification of common biological mechanisms and potential corresponding therapeutic targets.

Abstract No. P111

Improving cross-species comparability of human and cynomolgus macaque iPSCs

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Cross-species comparisons are essential for understanding human development and the evolution of gene regulatory networks, yet, they require orthologous cell types across species that are largely inaccessible *in vivo* due to ethical and practical constrains. Somatic cell reprogramming into induced pluripotent stem cells (iPSCs) enables the generation and experimental manipulation of these cell types from diverse species *in vitro* and has revolutionized cross-species comparisons. The cynomolgus macaque, a well-established non-human primate model for early development, represents an ideal system for investigating the evolution of gene regulatory networks due to its phylogenetic distance from humans. However, limited numbers of cell lines and substantial variability among iPSC lines currently constrain cross-species comparability.

The defining feature of any iPSC line is pluripotency, its ability to differentiate into all three germ layers. Yet, despite the fact that iPSC lines typically express the appropriate marker genes and display the expected colony morphology, they often differ substantially in their differentiation potential. This heterogeneity is known to be influenced by technical factors like cell type of origin, reprogramming method and culture conditions. In particular, part of the variability in the differentiation potential among iPSC lines is thought to be due to an incomplete reprogramming of the epigenetic state. Such factors may also exacerbate species differences, reducing the comparability of iPSCs across species.

To systematically address these challenges, we generated a panel of iPSC lines from both human and cynomolgus macaque cells using fibroblasts or urine-derived stem cells as primary cell source. Through comprehensive characterization of clonal lines, controlled comparison of culture conditions, and increased number of cell lines, we aim to identify conditions that maximize similarity in gene expression profiles between species. By minimising technical and epigenetic variability, this work seeks to enhance the power of cross-species comparisons.

Abstract No. P112

Generation of functional oligodendrocyte progenitor cells through serial replating of iPSC-derived NPC spheres

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Oligodendrocytes (OLs) are essential for myelin formation in the central nervous system, and their loss or dysfunction is a hallmark of various demyelinating and neurodegenerative disorders. Although oligodendrocyte precursor cells (OPCs) represent a promising cell source for remyelination therapies, existing protocols for generating OPCs from human-induced pluripotent stem cells (iPSCs) are often limited by prolonged culture duration, low efficiency, and cellular heterogeneity. Here, we report an efficient and reproducible platform for generating OPCs from iPSC-derived neural progenitor cells (iNPCs) through stage-specific modulation of developmental signaling pathways. Directed differentiation of iNPCs recapitulated key developmental transitions, progressing through OLIG2+/NKX2.2+ progenitors to CD140a+/O4+ OPCs within a significantly shortened timeframe compared to conventional approaches. Notably, iNPC-derived spheres functioned as a progenitor-like niche, enabling sustained OPC production through serial replating. Purified OPCs could differentiate into MBP+ oligodendrocytes and demonstrated myelination capacity both in vitro, via nanofiber ensheathment and in vivo following transplantation into shiverer (shi/shi) mice, where they formed myelin sheaths around host axons. Despite these advances, OPC differentiation and maturation efficiencies remained suboptimal, highlighting the need for further optimization. Collectively, our findings establish a scalable and time-efficient strategy for iPSC-derived OPC generation and underscore their potential for disease modeling and cell-based remyelination therapies.

Abstract No. P113

Electroporation of cortical organoids for functional investigation of neurogenesis

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Cortical organoids have become important tools for studying mammalian brain development, neurodevelopmental disorders, and brain evolution. Thus far, studies analysing gene function by overexpression or knockout have been instrumental in animal models to provide mechanistic insights into the regulation of neocortex development. Here, we present a detailed workflow for CRISPR/Cas9-mediated acute gene knockout by electroporation of sliced human cortical organoids (hCOs). The slicing of cortical organoids aids the identification of ventricle-like structures for injection and subsequent electroporation, making this a particularly well-suited model for acute genetic manipulation during neocortex development. We describe the design of guide RNAs and the validation of targeting efficiency *in vitro* and in cortical organoids. Electroporation is performed at mid-neurogenic stages, enabling the targeting of most major cell classes in the developing neocortex, including apical radial glia, basal progenitor cells, and neurons. The approach has been applied, for example, to explore the role of secreted proteins such as EPIREGULIN on neural development. Additionally, we show that this method can be utilised in primate cerebral organoids to study brain evolution. Taken together, the electroporation of cortical organoids represents a powerful technique to investigate gene function, gene regulation, and cell morphology during brain development.

Kolodziejczyk, A., et al. (2024). Electroporation of Sliced Human Cortical Organoids for Studies of Gene Function. J. Vis. Exp. DOI: 10.3791/67598.

Abstract No. P114

Differentiation of human pluripotent stem cells to steroid-producing adrenal cells

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Adrenal glands are the central stress organ in the human body producing hormones such as cortisol, aldosterone and adrenaline, thereby regulating stress responses, metabolism, blood pressure and fluid balance. Adrenal insufficiency is a life-threatening condition. It is associated with weight loss, low blood pressure, fatigue, seizures and metabolic disturbances. Current treatment approaches are based on hormone replacement therapies which, however, have significant limitations. Differentiation of human pluripotent stem cells (hPSCs) into steroid-producing cells could represent a therapeutic option for the treatment of adrenal insufficiency. The goal was therefore to generate human induced steroidogenic cells (hiSCs) derived from hPSCs.

We optimized a protocol for the directed differentiation into adrenal cells using activators of the wingless and int-1 (WNT), retinoic acid (RA), and bone morphogenic protein (BMP) signaling pathways. Lentiviruses were produced and utilized to introduce genes encoding steroidogenic factor 1 (SF-1), adrenocorticotropic hormone receptor (ACTH receptor; MC2R) – and its accessory protein (MRAP). To determine whether the differentiated cells are indeed steroid-producing adrenal-like cells, the expression of genes for pluripotency (*Oct4*), for early stage of adrenal development (*DAX1*, *GATA4*, *GATA6*, *WT1*, *DLK*, *OSR2*), and for adrenal gland (*NR5A1*, *MC2R*, *MRAP*, and *CYP11B1*) were analyzed. We pursued a strategy to achieve optimal outcome by generating a score based on both the expression of adrenal-compatible markers and negative influencing factors. We were able to demonstrate that hiSCs exhibit characteristics of adrenal cells. The induction of SF-1, MC2R and MRAP expression results in dose-dependent ACTH reactivity; however, this responsiveness could be further improved.

In conclusion, cell-based therapy could offer a physiologically relevant approach for improved treatment of adrenal insufficiency. HiSCs exhibit the ability to release adrenal hormones when stimulated by steroidogenic inducers. Further optimization is required to increase the proportion of adrenal cells within the population of differentiated cells and to boost steroid production.

Abstract No. P115

Effect of microfilaments on embryoid body morphogenesis and early neuronal induction

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Generating cerebral organoids with high structural complexity while maintaining experimental reproducibility remains a major challenge. Unguided differentiation protocols preserve important aspects of spontaneous brain-like self-organization but frequently exhibit substantial variability in embryoid body morphology, neuroectoderm formation and subsequent tissue organization. In contrast, strongly guided differentiation protocols improve standardization but may restrict developmental diversity. Microfilament-mediated elongation of embryoid bodies has previously been shown to influence cerebral organoid development, although its implementation remains technically demanding and difficult to scale.

Here, we present the MatriFilamentSystem® (MFS), a scaffold-based culture platform designed to provide physical guidance during early cerebral organoid development. The system combines integrated microfilaments with a thermoformed culture architecture, enabling controlled embryoid body formation, simplified handling and parallel organoid production without extensive biochemical patterning.

Early embryoid body morphology and neural induction were assessed by daily brightfield imaging, immunofluorescence staining and gene expression analysis. Compared with conventionally generated unguided organoids, MFS-derived embryoid bodies exhibited distinct changes in geometry and early tissue organization. During neural induction, scaffold-guided aggregates showed pronounced peripheral tissue organization and differences in the appearance of neuroepithelial regions.

Overall, the MFS provides an adaptable approach for improving experimental control in unguided cerebral organoid culture while preserving spontaneous self-organization. The platform may facilitate the systematic investigation of how early aggregate geometry, mechanotransduction and cell–cell adhesion influence human neural development in vitro.

Abstract No. P116

Modelling the molecular basis of human speech evolution

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Heterozygous loss-of-function mutations in the transcription factor FOXP2 lead to speech and language disorder. Two human-specific amino acid substitutions (T302N and N324S) occurred in the conserved FOXP2 protein after the human-chimpanzee split, suggesting a role of FOXP2 in the evolution of speech. Mouse models (Foxp2hum) with these human-specific substitutions showed enhanced synaptic plasticity in the form of stronger long-term depression (LTD) in the medium spiny neurons (MSN) of the striatum, decreased tissue dopamine levels, enhanced performance during certain learning tasks, and altered gene expression of striatal neuronal pathways during learning. To understand the molecular basis of speech development and evolution, we use homology-directed CRISPR-cas9 genome editing to create the two amino acid substitutions, which generates a "chimpanized" version of FOXP2 in human iPSC cell line. Additionally, we generate mouse iPSCs from Foxp2hum and WT mice. We will differentiate these cells into MSNs and subsequently perform RNA-seq to investigate to what extent human and mouse in vitro MSNs can recapitulate the differential expression found in the striatum of Foxp2hum mouse model.

Abstract No. P117

Characterization of NMDA receptor function in human NGN2 induced neurons

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Human induced pluripotent stem cell (hiPSC)-derived neurons provide a platform to study the function of human neurons. Many differentiation protocols have been developed to generate glutamatergic induced neurons (iNs), yet a key functional feature of mature glutamatergic neurons, NMDA receptor (NMDAR) function, has remained difficult to establish in these models, despite being well characterized in rodent systems. In particular, neurogenin-2 (NGN2)-driven iNs, in which the neural progenitor cell stage is skipped, show little to no NMDAR current (Nehme et al., 2018), in contrast to their robust AMPA receptor-mediated current. We have recently developed an NGN2 induction protocol (Dimitrov et al., 2025) to generate human glutamatergic iNs and observed substantial NMDA-evoked currents, indicating a more mature neuronal phenotype than previously reported. We hypothesized that these iNs would show a GluN2B-to-GluN2A switch, a developmental process required for proper synaptic maturation as shown in vivo (Monyer et al., 1994). We performed electrophysiology to assess NMDAR subunit composition and function across differentiation timepoints. These results support the use of iNs generated with this NGN2 protocol as a model for studying NMDAR function in human neurons.

Dimitrov et al., Proteomics-based receptor-ligand matching enhances differentiation maturity of human-stem-cell-derived neurons, Stem Cell Reports (2025), https://doi.org/10.1016/j.stemcr.2025.102604

Abstract No. P118

A hiPSC-derived endothelial cell model with kallikrein activity for hereditary angioedema

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Introduction
Hereditary angioedema (HAE) is a rare genetic disorder characterized by recurrent episodes of swelling caused by excessive bradykinin (BK) production due to dysregulation of the kallikrein-kinin system (KKS). Human endothelial cell-expressed bradykinin receptor 2 (B2R) is the primary target of bradykinin-mediated vascular leakage; however, physiologically relevant human models for studying endothelial responses within the KKS remain limited. We aimed to establish and characterize a human induced pluripotent stem cell-derived endothelial cell (hiPSC-EC) model suitable for investigating HAE-associated vascular dysfunction.

Methods
We established a protocol to differentiate human induced pluripotent stem cells (hiPSCs) into a pure population of endothelial cells (hiPSC-ECs). The resulting hiPSC-ECs were characterized by flow cytometry, immunofluorescence staining, and functional enzymatic assays to assess endothelial identity and KKS-related properties.

Results
The differentiation protocol consistently yielded a highly pure population of cells exhibiting classic cobblestone endothelial morphology. Characterization confirmed that the hiPSC-EC model expresses canonical endothelial markers, including CD31, CD144 (VE-Cadherin), and VEGFR2 (KDR), indicating a mature endothelial phenotype. IF staining revealed correct localization of VE-Cadherin at cell-cell junctions. Furthermore, hiPSC-ECs demonstrated significant expression of the bradykinin receptors B1R and B2R, key components of the KKS and critical for bradykinin function. Importantly, functional analysis confirmed that the hiPSC-EC model possesses measurable kallikrein activity.

Conclusions
We successfully established a hiPSC-derived endothelial cell model that recapitulates key endothelial and kallikrein-kinin system features relevant to HAE. This platform provides a promising tool for studying disease mechanisms and evaluating therapeutic strategies targeting bradykinin-mediated vascular dysfunction.

Abstract No. P119

The impact of cohesin on human head and face development

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Cohesin is a highly conserved multiprotein complex composed of the core ring components Structural Maintenance of Chromosomes (SMC1A, SMC3) and auxiliary proteins. Beyond the maintenance of genome integrity through sister chromatid cohesion and DNA damage repair, cohesin has an essential role in gene expression regulation by organizing 3D chromatin architecture, facilitating enhancer-promoter communication. Disruption of the transcriptional regulation caused by mutations affecting cohesin or cohesin-related proteins leads to Cornelia de Lange syndrome (CdLS), a congenital multisystem neurodevelopmental disorder characterized by heart defects and cognitive deficits, limb and craniofacial (head and face) malformations. Although the craniofacial abnormalities are essential aspects of the CdLS diagnosis, the relationship between the cohesin mutations and human craniofacial development has not been investigated. To address this, we aim to determine 3D chromatin and transcriptional programs in human induced pluripotent stem cells (hiPSC) and hiPSC-derived cranial neural crest cells (CNCC), which substantially contribute to craniofacial structures. Our previous time-resolved inference of gene regulatory networks (GRNs) underlying CNCC development using transcriptomic and chromatin accessibility mapped novel regulatory relationships, linking non-coding genetic variants associated with orofacial clefting to both known and novel putative target genes, otherwise missed in analyses based on a single timepoint. To elucidate how cohesin mutations alter GRNs in hiPSC and hiPSC-derived CNCC, we have generated CRISPR/Cas9-engineered hiPSC with SMC1A and SMC3 mutations. Subsequent transcriptomic, epigenomic, and chromatin conformation assays combined with bioinformatics analyses will allow us to investigate if mutations or other alterations of the identified GRNs (1) are linked to undiagnosed cases of individuals with craniofacial deformities, (2) are risk factors for multifactorial diseases, (3) contribute to the variability of a phenotype. Thus, insights gained from the rare disease CdLS may be translated to more common disorders, opening new opportunities for diagnosis and therapy.

Abstract No. P120

An insight into gorilla (Gorilla gorilla) induced pluripotent stem cells

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Humans and gorillas (*Gorilla gorilla*) share genetic, molecular, and developmental traits. Therefore, gorilla induced pluripotent stem cells (iPSCs), provide a powerful platform for disease modeling, regenerative medicine, evolutionary biology, and comparative biomedical studies. In this study, we generated three iPSCs lines from one male and two female gorillas [MPH-GorGor-C00001 (G1), MPH-GorGor-C00002 (G2) and MPH-GorGor-C00003 (G3)].

To do so, skin fibroblasts were subjected to Sendai virus-reprogramming. Treatment with and without enhancers (EPZ5676 and CBP30), feeder and feeder-free systems, as well as medium change with mouse embryonic fibroblasts-conditioned medium (MEFs-conditioned medium) before gradual transition to pluripotency medium (mTeSR or StemMACS) were evaluated. TRA-1-60 sorting was repeatedly performed and pluripotency was assessed by immunostaining and tri-lineage differentiation.

Overall, feeder systems and enhancer treatment improved reprogramming efficiency. MEFs-conditioned medium supported early pluripotency induction but caused colony deterioration after prolonged use, requiring gradual transition to pluripotency medium. In G2 and G3, StemMACS outperformed mTeSR. Repeated TRA-1-60 sorting improved stability of lines. Generated lines have normal karyotypes, express pluripotency markers and differentiate into cells of the three germ layers.

In conclusion, gorilla iPSCs establishment remains technically challenging, particularly during early reprogramming and pluripotency stabilization. Short treatment with MEFs-conditioned medium before transitioning to pluripotency medium, feeder systems, and enhancer treatment improved culture stability and reprogramming efficiency. For iPSCs growth, StemMACS outperformed mTeSR under our conditions. These findings support the successful derivation of stable gorilla iPSCs lines and contribute to the optimization of species-specific reprogramming protocols for translational and comparative biomedical research.

Abstract No. P121

Genetic Engineered-hypoimmunogenic human induced Pluripotent Stem Cells evade surveillance of the immune system in a murine xenotransplantation model

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Immunoreaction after transplantation, mainly caused by the interaction of cell surface proteins of the graft with receptors of immune cells of the host, is one of the major hurdles to overcome for stem cell-based therapeutic approaches. Xenotransplantation experiments and approaches play an important role in providing graft materials for transplantation and for basic transplantation research.

Deuse et al. (2019) showed that deleting the Major Histocompatibility Complex (MHC I and II) while overexpressing CD47 could effectively render grafts undetected by the allogeneic recipient's immune system.

We generated a hypoimmunogenic human iPSC line designed to evade immune recognition in a murine host. Using CRISPR/Cas9, MHC class I and II complexes were deleted, and murine CD47 was transgenically expressed via a piggyBac system. Hypoimmunogenic hiPSCs were transplanted into immunocompetent mice, and immune responses were assessed in vivo. Preliminary data indicate that hypoimmunogenic hiPSCs evade host immune surveillance and persist long-term, resulting in teratoma formation. Comparable graft persistence is observed in wild-type hiPSC transplants only under systemic immunosuppressive treatment, whereas wild-type hiPSCs transplanted without immunosuppression are rapidly rejected, preventing long-term follow-up.

Deuse , T., et al., Hypoimmunogenic derivatives of induced pluripotent stem cells evade immune rejection in fully immunocompetent allogeneic recipients. Nature Biotechnology, 2019. Mar; 37

Abstract No. P122

Analyses of the impaired endothelial blood-brain barrier and senescence-associated molecular phenotypes in Rett syndrome

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Background and Research Question:
Rett Syndrome (RTT) is a rare, X-Chromosome linked neurodevelopmental disorder caused by mutations in the MECP2 gene and affects almost exclusively girls. It is characterized by an initial period of normal development, followed by a regression phase between 6 and 18 months of age, where the child loses acquired skills, particularly in speech, hand function, and social interaction.

Although alterations in several components of the neurovascular unit, including neurons and astrocytes, have been described in RTT, the role of endothelial cells remains poorly understood. To address this gap, this study investigates blood–brain barrier (BBB) function using induced pluripotent stem cell (iPSC)-derived endothelial cells. RTT cells were compared with healthy cells and CRISPR/Cas-corrected isogenic cells.

Method:
Barrier integrity of BBB endothelial cells was assessed by transendothelial electrical resistance (TEER) measurements and sodium fluorescein permeability assays. Senescence-associated and proliferative phenotypes were evaluated by immunofluorescence staining and flow cytometric analysis of the proliferation markers PCNA and Ki-67. In addition, the expression of cell cycle- and senescence-related markers, including p21, γH2AX, RB, and p53, were evaluated using immunostaining, flow cytometry, and western blot analysis. Cell cycle distribution was further examined by propidium iodide-based flow cytometry.

Results:
The results indicate impaired BBB function in RTT-derived endothelial cells, accompanied by altered cell cycle regulation and a senescence-associated phenotype. Taken together, these findings provide novel insight into the vascular contribution to RTT pathogenesis and suggest that endothelial dysfunction may represent an important, previously underappreciated aspect of the disorder.

Abstract No. P123

UV-micropatterning for high-throughput generation of embryoid bodies

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Embryoid bodies (EBs) are three dimensional aggregates of pluripotent stem cells which self organize and exhibit multilineage differentiation potential, making them indispensable tools for drug screening, disease modeling, and regenerative medicine. Conventional EB production, however, relies on dissociating cells into single cell suspensions followed by centrifugation, forcing the cells to re-aggregate. We previously demonstrated that geometrically confined colonies of induced pluripotent stem cells (iPSCs) on micro-contact-printed vitronectin circles detached upon confluency to form size-controlled aggregates. Building on this concept, we developed an ultraviolet micropatterning approach (UV µ-pattern) that further improves the efficiency, uniformity, and scalability of EB generation. For this approach, glass slide inserts were initially coated with a protein-repellent layer, then locally exposed to UV light to degrade the repellent layer and to define patterns. Subsequently, the irradiated regions were coated with vitronectin, allowing localized iPSC attachment and after five to six days, reliable self-detachment as EBs. Compared with conventional U-bottom wells and the AggreWell™ system, UV µ-pattern EBs showed comparable morphology, maintenance of pluripotency, and robust multilineage differentiation towards endoderm, mesoderm and ectoderm. Gene expression profiles supported the notion that UV µ-pattern EBs have similar differentiation potential, with less evidence for hypoxia than observed for the AggreWell system. Furthermore, UV µ-pattern EBs were successfully used for differentiation towards cardiac lineage. Finally, we could demonstrate that this new method for EB generation could be implemented on an automated cell culture system, to facilitate gentle EB generation without the need for additional centrifugation steps. Overall, our new approach provides a cost-effective, scalable, and automation-friendly method for standardized EB generation.

Abstract No. P124

Membrane-stirrer bioreactor platform enables record-breaking human iPSC expansion at clinically relevant scales

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Human induced pluripotent stem cell (hiPSC) manufacturing remains a critical bottleneck limiting the clinical and industrial translation of stem cell-based therapies. Here, we present a novel membrane-stirrer bioreactor platform that achieves unprecedented hiPSC expansion under suspension culture conditions, demonstrated at both 300 mL and 2 L scales.

Process development began with systematic identification of key bioprocess limitations. Contrary to initial expectations, oxygen transfer was not the primary constraint; instead, medium composition emerged as the dominant limiting factor, with enriched formulations enabling substantially higher cell densities even under fed-batch conditions. This finding redirected process optimization toward intensified perfusion cultivation integrating real-time dissolved oxygen (DO) control, pH monitoring, controlled perfusion, and optimized nutrient feeding strategies.

The resulting intensified bioprocess effectively minimized nutrient depletion and metabolite accumulation while ensuring adequate oxygen transfer — enabled by the membrane-stirrer's exceptional mass transfer performance, as reflected in its high kLa values. Under fully controlled conditions, iPSC aggregates were expanded over 8-day (300 mL) and 5-day (2 L) cultivation runs, maintaining high viability, robust growth kinetics, and pluripotency-associated morphology throughout.

The platform achieved record viable cell densities of 44 × 10^6 hiPSCs/mL at 300 mL and 11 × 10^6 hiPSCs/mL at 2 L scale — the highest reported for hiPSC suspension expansion to date. Critically, scale-up from 300 mL to 2 L was accomplished without compromising process stability or culture performance. Harvested cells retained pluripotency marker expression above 90% and displayed homogeneous, highly circular aggregate morphology, confirming maintenance of cell quality at scale.

These results establish intensified perfusion-based bioprocessing as a robust and scalable strategy for clinically relevant hiPSC manufacturing, with the membrane-stirrer design as a key enabling technology for next-generation cell therapy production.

Abstract No. P125

PSC suspension culture eases the transition to 3D differentiation workflows

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Pluripotent stem cells (PSCs) have unlimited expansion capacity and can be differentiated into any cell type, making them powerful tools to study development and disease. The emergence of PSC-derived organoid cultures has further improved the physiological relevancy of these cell models. However, conventional PSC culture is based on adherent culture techniques that have limited scalability potential and require the dissociation and reaggregation of PSCs for many organoid differentiation methods. To address these workflow limitations, StemScale PSC suspension medium was developed to support PSC growth in suspension which can reduce hands-on time and enable rapid scale-up from small culture vessels to bioreactors while maintaining key stem cell attributes. Indeed, PSCs cultured for >30 passages maintained stemness marker expression, trilineage differentiation potential and a stable karyotype. Moreover, RNAseq indicated the global transcriptome of PSCs cultured in StemScale was highly concordant with conventional adherent medium PSC cultures. A cohort of 230 differentially enriched genes was detected in adherent cultures that were primarily associated with ECM and focal adhesin KEGG pathways. Suspension culture enriched genes were not associated with any KEGG pathway and principal component analysis suggested transcriptome differences were driven less by the culture medium and more PSC-line specific. Furthermore, we discuss how PSC suspension culture may ease the transition into 3D differentiation protocols leading to lineage dependent and lineage agnostic benefits. Differentiating PSCs in suspension may shorten the time to produce dopaminergic neurons from 35 to 25 days and electrophysiology suggested these cells also achieve a higher maturation level than their matched 2D controls. Likewise, PSCs could be differentiated into cytotoxic CD56+CD3-CD16+ natural killer cells, capable of killing patient derived tumoroids, in a more scalable manner. Overall, this data suggests PSC suspension culture is well-suited for scalable PSC workflows including 3D differentiation and for generating more reliable, reproducible, and human-relevant cell models.

Abstract No. P126

Embryonic macrophages direct hepatocyte expansion in liver development

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In liver development, hepatoblasts are epithelial progenitors that differentiate into hepatocytes or biliary epithelial cells (BECs). Despite their bipotential nature, hepatocytes vastly outnumber BECs, comprising approximately 80% of the adult liver. Embryonic macrophages populate the developing liver and become tissue-resident. However, their role in orchestrating epithelial output remains incompletely understood.

Here, we identify embryonic macrophages as promoters of epithelial progenitor expansion and hepatocyte development using a human fetal liver cell atlas, human immune-competent fetal liver organoids (FLOs), and complementary mouse models. Within the human fetal liver atlas, macrophage-to-hepatoblast interactions were most prominent during early development. In FLOs, HepPar1+ hepatocyte output positively correlated with IBA+ macrophage frequency. Pharmacological and genetic macrophage depletion through targeting of colony-stimulating factor 1 receptor (CSF1R) reduced cycling HNF4a+ hepatic and SOX9+ BEC progenitor populations. In addition, macrophage depletion reduced ALB+ PanCK- hepatocyte output and epithelial cluster expansion.

In vivo, Tnfrs11αCre/+ Csf1rfl/fl and Tnfrs11αCre/+ Spi1fl/fl mouse models deplete embryonic macrophages at embryonic day (E)12.5 and E14.5, respectively. Macrophage depletion at E12.5 but not at E14.5 decreased postnatal hepatocytes and periportal BECs, indicating that embryonic macrophages support progenitor cell expansion during early development. Despite reduced abundance, BEC structures were retained in vivo and in FLOs. Altogether, these findings highlight that fetal macrophages maintain epithelial progenitors and support hepatocyte development.

Mechanistically, ligand-receptor analysis identified TNF and LGALS9 as candidate mediators of macrophage-to-hepatoblast crosstalk. Surprisingly, combined TNF and LGALS9 exposure suppressed hepatocyte output in CSF1R KO FLOs, contrasting the pro-proliferative effects reported for TNFα in adult liver regeneration. These findings suggest that inflammatory signals may exert distinct functions during liver development. In summary, our findings identify embryonic macrophages as contributors to hepatocyte-dominant epithelial output during liver development.

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Abstract No. P127

Effective cryopreservation of retinal organoids via vitrification preserves retinal identity and developmental potential across differentiation stages

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Human pluripotent stem cell (hPSC)-derived retinal organoids are a powerful platform for disease modeling, drug screening, and gene therapy. However, their utility is limited by continuous culture demands and the lack of reliable biobanking strategies. Cryopreservation offers a promising solution, yet its impact on retinal organoid integrity remains poorly characterized.

We applied a vitrification protocol to retinal organoids at day 25 and day 65 of differentiation. D25-vitrified organoids assessed at day 65 showed well-preserved morphology, including retinal layer lamination and a bright neuroepithelium, comparable to age-matched controls. Immunohistochemical analysis confirmed retention of retinal progenitor identity, with expression of VSX2, KI67, and BRN3, consistent with age-matched non-vitrified controls, indicating that vitrification does not disrupt progenitor expression, architecture, or proliferation.

D65-vitrified organoids maintained until day 100 demonstrated continued growth, with typical retinal neuroepithelial layers and increased organoid diameter comparable to controls. Immunohistochemical characterization is ongoing to confirm retinal identity recovery post-thaw.

In parallel, MEDY-based (methylcellulose, ethylene glycol, DMSO, Y-27632) cryopreservation was applied at day 20 and assessed at day 65. Immunohistochemical analysis revealed partial preservation of retinal progenitor markers, with reduced VSX2 and KI67 expression compared to controls, while BRN3 expression was comparable to both vitrified and non-vitrified groups. These findings provide a comparative insight into the performance of two distinct cryopreservation approaches at early retinal organoid stages.

These results suggest vitrification as an effective biobanking strategy across retinal organoid differentiation stages, opening the door to large-scale production and storage for disease modeling, drug screening, and gene therapy applications.

Mojica-Perez S, Stokes K, Jacobs S, et al. Cryopreservation of human cortical organoids using vitrification. bioRxiv. 2025. doi:10.1101/2025.04.08.647634

Xue W, Li H, Xu J, et al. Effective cryopreservation of human brain tissue and neural organoids. Cell Reports Methods. 2024;4:100777.

Abstract No. P128

FLT3L and SR1 regulate development and immunostimulatory function of human PSC-derived dendritic cells

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Dendritic cells (DCs) are central regulators of adaptive immunity, and while their developmental pathways are well established, the mechanisms governing their functional specialization remain incompletely understood in humans. To address this, the field has increasingly shifted toward the development of human in vitro systems to better investigate the mechanisms regulating immune cell development and function. Here, we establish a feeder-free, fully defined human pluripotent stem cell-derived hematopoietic organoid system that enables sustained production of myeloid iDC subsets. Within this platform, we demonstrate that FLT3L signaling supports iDC development, while aryl hydrocarbon receptor modulation using SR1 promotes an activation-associated DC state. Supplementation of FLT3L alone or in combination with SR1 yielded comparable iDC subset composition, however SR1-conditioned iDCs displayed enhanced antigen uptake and processing capacity, consistent with an activation-associated transcriptional profile. To define the role of FLT3L signalling, we leveraged iPSCs carrying a loss-of-function FLT3L (FLT3LLOF) mutation. FLT3LLOF abrogated DC generation and impaired early hematopoietic specification, marked by loss of $KDR^{+}CD235a^{+}$ progenitors, identifying a developmental bottleneck upstream of iDC commitment. Functionally, SR1-derived iDCs induced robust activation of autologous T cells in response to cytomegalovirus (CMV) antigens, with sustained $CD8^{+}$ T cell proliferation, increased acquisition of memory phenotypes, and elevated secretion of pro-inflammatory cytokines, including MCP-1, IL-8, IL-6, and IL-18. Together, these findings demonstrate that FLT3L signaling is essential for early human hematopoiesis and DC development, while SR1 modulates their functional programming, and establish a platform for the generation of antigen-presenting DCs.

Abstract No. P129

Investigating the impact of endocrine chemical disruptors on liver development using hiPSCs

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Endocrine chemical disruptors (EDCs) are substances found in common products such as pesticides, cosmetics, plastics. EDCs can interfere with the endocrine system and the normal metabolic functions of the human body. In the liver, they are suspected to influence lipid metabolism which leads to an enhanced lipid accumulation and metabolic dysfunction-associated steatotic liver disease (MASLD). However, the impact of EDCs on the human liver development and the link to MASLD occurring later in life are still poorly understood. To study the impact of EDCs on liver development, we propose to use the HepBud platform which is based on the differentiation of human induced pluripotent Stem cells (hiPSCs) into self assembling liver buds. This approach models stages of liver development including liver bud formation, hepatoblast generation and then their differentiation into hepatocytes and cholangiocytes. We will differentiate hiPSCs in fetal and adult liver cell types (hepatoblast, hepatocytes and cholangiocytes) in the presence and in the absence of EDCs. In first results, live dead assay has shown that acute exposure of hepatoblast organoids to high dose of Bisphenol A (BPA) lead to rapid cell death thereby confirming the hepatoxicity of EDC. However, short-term treatment to PFOA did not display any toxicity thereby suggesting that the impact of EDCs could be more subtle and affect other aspect of hepatocyte biology. Accordingly, we are planning to evaluate the functional activity of the resulting liver cells after chronic exposure of low dose EDCs. We will especially focus on their capacity to metabolise lipids and to resist to toxic stress.

Overall, we hypothesis that EDCs affect liver development resulting in the production of cells which are less resistant to lipotoxicity and more susceptible to MASLD. Our experiments also establish hiPSCs as a replacement to animal models for studying the impact of pollutant on human fetal health.

Abstract No. P130

Full-length laminin-521 recreates the native stem cell niche to support human pluripotent stem cell survival, migration, and expansion

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Human pluripotent stem cells (hPSCs) require an extracellular matrix (ECM) for maintenance, proliferation, and differentiation. Laminins are a family of 16 distinct ECM proteins and represent a key component of the stem cell niche. Different laminin isoforms are expressed throughout development and are differentially expressed in across tissues, with specific isoforms either supporting stem cell maintenance or contribute to driving tissue-specific differentiation.

Laminins exert this influence by binding directly to both integrin and non-integrin receptors, as well as by sequestering and modulating the release of growth factors. Through these mechanisms, laminins direct intracellular signaling pathways and contribute to the local stem cell niche. In contrast, fragmented laminins lack many of these properties and are not naturally produced in healthy tissues.

Full-length laminin-521 has been shown to significantly enhance PSC survival and proliferation, all while enabling high-efficiency single-cell seeding with or without the addition of ROCK inhibitors. Previous studies have shown that hPSCs with a Laminin Alpha Chain 5 (LAMA5) knockout cannot survive and expand without exogenous supplementation of full-length laminin-521. In addition, we have demonstrated that PSCs cultured on full-length laminin-521 exhibit enhanced migratory capacity, effectively spreading to cover the entire culture surface, improving stability at high densities, and improving yields. In migration/gap-closure assays, PSCs cultured on laminin-521 spread evenly to cover nearly 100% of the culture surface, whereas fragmented laminins achieve only 29–44% coverage under the same conditions.

Importantly, these findings highlight the ability of full-length laminin-521 to recreate a more physiologically relevant cellular microenvironment. This capability is critical for advancing PSC culture techniques, improving differentiation protocols, refining disease modeling, and supporting the manufacture of groundbreaking cell therapies.

Abstract No. P131

Engineering the CDX2/PDX1 locus in human stem cells to study lineage-specific gene regulation

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Precise control of gene expression is crucial for lineage specification during development. The transcription factors CDX2 and PDX1 are master regulators of intestinal and pancreatic lineage commitment, respectively, and are expressed in a mutually exclusive pattern, which is crucial for correct lineage specification. Despite their distinct expression patterns, the genes reside at the same genomic locus and share a gene regulatory landscape. How this landscape ensures the selective activation of both genes remains poorly understood. To dissect how the cis-regulatory landscape controls lineage-specific gene expression, we combine state-of-the-art genetic engineering of hiPSCs with directed differentiations. We apply a synthetic genomics approach to insert synthetic wildtype and variant versions of the ~100kb CDX2/PDX1 locus at a safe-harbour site. Differentiation of engineered hiPSCs into CDX2 and PDX1-expressing cell types allows us to compare expression from endogenous and synthetic alleles simultaneously and identify the changes driven by variant synthetic loci. Using this strategy, we aim to dissect whether an intervening lncRNA subdivides the locus or whether enhancer-promoter specificity allows differential CDX2/PDX1 expression. In addition, we use our platform to rebuild the mouse Cdx2/Pdx1 locus in hiPSCs and examine whether the regulatory logic is conserved between species. Taken together, our approach establishes a framework for stem cell engineering to dissect the genetic control of cell fate decisions during lineage-specification.

Abstract No. P132

Benchmarking the matrix transition: a standardized screening and validation framework for cerebral organoid cultures

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Although Matrigel remains the conventional gold standard for extracellular matrices due to its versatility and high complexity, it still has serious drawbacks. Its murine tumor origin, batch-to-batch variability, and undefined composition increasingly drive the biomedical field to seek more reproducible alternatives. However, shifting away from Matrigel entails scientific and technical hurdles that hinder broader adoption.

To streamline this transition, we identified these challenges and, as a result, designed a standardized framework for matrix selection and evaluation. We introduce a matrix selection checklist to align model-specific needs with available resources. In parallel, we designed OSCAR, the organoid scaffold assessment radar, as a multi-parametric screening tool designed to systematically evaluate matrix properties. We validated this combined approach within cerebral organoid cultures by quantitatively tracking embedding efficiency, structural integrity, and general biocompatibility.

This systematic pipeline successfully narrowed down a selection of viable matrix alternatives, which we then further benchmarked using RNA sequencing and histological validation. Our findings confirm that this framework effectively guides researchers toward optimized, model-specific options. While demonstrated here in cerebral organoids, this modular strategy can be readily adapted across diverse 3D cell culture models to improve reproducibility and translational impact.

Abstract No. P133

Human oligodendrocyte differentiation from induced neural plate border stem cells in 30 days

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Human oligodendrocytes (OLs) myelinate axons and provide the metabolic support essential to central nervous system function. Their loss or dysfunction is central a wide range of demyelinating diseases such as multiple sclerosis. However, current hiPSC-based approaches for generating oligodendroglial cells for developmental & disease modelling is limited by low yields and long differentiation timelines of 75-100 days.

Here, we present a rapid oligodendroglial differentiation strategy based on induced neural plate border stem cells (iNBSCs), a directly reprogrammed human neural progenitor population. Patterning of iNBSCs using small molecules generated OLIG2$^+$/SOX10$^+$ oligodendrocyte progenitor cells (OPCs) within 3 weeks, and pre-myelinating O4$^+$/MBP$^+$ OLs within 30 days. The protocol was transferable to other neural progenitor lines, including iPSC-derived iNBSCs, demonstrating that its applicability was not restricted to directly reprogrammed iNBSCs.

Further, the selective use of 3D or 2D culture systems allow for selective enrichment of either mixed neuron/glia or pure oligodendroglial cultures, respectively. During differentiation, the resulting glial progenitors recapitulated surface-marker transitions observed in primary human tissue. Various growth factors drive commitment and differentiation during oligodendrogenesis. We examined how different receptor tyrosine kinase ligands influence the induction and expansion of early OPCs, and found that bFGF alone is sufficient, and more efficient than PDGF, at inducing an OPC population in our context.

Together, we show that rapid oligodendroglial specification is possible within 30 days, and that RTK ligand choice is a key determinant of OPC induction and expansion. Future studies will determine the transcriptomic & chromatin transitions during the gliogenic switch and oligodendroglial commitment, as well as functional maturation and myelination capacity of the resulting cells.

Abstract No. P134

Impact of LRP2 deficiency on human neuronal cell specification and forebrain patterning through SHH signaling pathway

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Pathogenic variants affecting developmental signaling pathways are a major cause of congenital brain disorders. Disruption of the Sonic Hedgehog (SHH) signaling pathway is a leading cause of holoprosencephaly (HPE), an incomplete separation of the cerebral hemispheres with marked phenotypic variability. Although the mechanisms underlying this variability remain unclear, modifier genes are thought to influence disease susceptibility and resilience.

Our previous studies identified LDL receptor–related protein 2 (LRP2), a primary cilium-localized co-receptor and modulator of SHH signaling, as a critical determinant of forebrain development. Lrp2 deficiency caused a fully penetrant HPE phenotype in C57BL/6N mice but was completely rescued on the FVB/N background, revealing a strong genetic modifier effect. We further identified candidate modifier genes such as *Unc-51 Like Kinase 4* (*ULK4*) and *Pituitary Tumor–Transforming Gene 1* (*PTTG1*) that enhance SHH signaling [1].

To elucidate the role of LRP2 in SHH-dependent forebrain patterning and disease mechanisms during human brain development, we differentiated *LRP2*$^{-/-}$ pathogenic human induced pluripotent stem cells (hiPSCs) and isogenic controls into dorsal and ventral neuronal precursor cells (NPCs) and forebrain organoids. LRP2-deficient NPCs exhibited aberrant cell specification and cellular morphology. LRP2-deficient forebrain organoids displayed patterning defects and impaired rosette formation compared to isogenic controls. Transcriptomic and immunocytochemical analyses of human neuronal cultures further revealed alterations in primary cilia morphology and dynamics following LRP2 loss.

In summary, our data establish LRP2 as a key regulator of early neuroectodermal patterning by controlling primary cilium-dependent SHH signaling, cellular polarity, and cell fate specification. Disruption of LRP2 alters ciliary structure, microtubule organization, and early brain patterning. The identification of SHH signaling modulators and microtubule-associated factors further supports a model in which ciliary components act as genetic modifiers, ameliorating or exacerbating developmental defects. Together, these findings will provide mechanistic insight into how cilium-associated regulators contribute to phenotypic variability in neurodevelopmental disorders.

[1] https://doi.org/10.1242/dev.199307

Abstract No. P135

Biobanking and stem cell technologies across species for conservation and basic research

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Biodiversity is declining at an alarming rate. Without targeted protection of the remaining genetic diversity, it is unlikely that species extinction can be halted in time. It is therefore increasingly important to preserve living cellular material from numerous species and individuals before they disappear entirely or the genetic pool required for the long-term survival of a species becomes critically depleted.

Since the 1990s, the Leibniz Institute for Zoo and Wildlife Research (Leibniz-IZW) has been developing a continuously expanding wildlife biobank. The biobank cryopreserves tissues, gametes, embryos, cell cultures, and pluripotent stem cells (PSCs) from more than 500 animal species, including mammals, birds, reptiles, amphibians, and fish. These biological resources are made available to researchers worldwide for conservation as well as basic and biomedical research.

Of particular importance are our PSC lines. Currently, the biobank contains two embryonic stem cell lines derived from the southern white rhinoceros and a total of 28 induced PSC lines (iPSCs), including multiple individuals and clones from seven different species, among them five non-human primates and three rhinoceros species.

Taken together, living cellular material represents a dynamic, functional, and shareable resource enabling a wide range of applications. Whereas fibroblasts can be directly applied in, among other fields, -omics analyses, aging research, and disease modeling, PSCs provide new opportunities to investigate embryogenesis and organogenesis, including developmental timing, comparative biology, and evolution, in line with the 3R principles.

While the primary aim of this biobank is to support conservation efforts and genetic rescue strategies, it also constitutes a valuable and versatile resource for a broad spectrum of fundamental biological research.

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Abstract No. P136

Modeling liver aging with tissue-derived organoids

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Aging is conventionally characterized as a progressive, time-dependent decline in physiological function but, more broadly, it represents a loss of regenerative capacity. The liver, the largest internal solid organ in mammals, is notable for its robust regenerative response to injury compared to other organs. Interestingly, the liver's regenerative ability also decreases with age. Traditional tissue-derived organoid models have been limited by their inability to fully replicate the liver's intricate cellular composition and architecture, restricting their utility for modeling liver homeostasis and disease in vitro. In my previous work, I have developed advanced organoid systems comprised of adult cholangiocytes and mesenchymal cells—and subsequently adult hepatocytes, cholangiocytes, and portal fibroblasts— to reconstruct the liver's periportal region and simulate key aspects of regeneration and fibrosis in a dish. These proof-of-concept studies paved the way for more sophisticated tissue-derived organoid models that better mimic hepatic tissue, enabling investigation of aging-related disruptions in stem cell–niche cell-cell interactions. Recently, I have established organoid (hepatocyte, cholangiocyte) and primary mesenchymal niche cell lines from young and aged mice. I am now employing complex organoid models composed of epithelium and mesenchyme to study aging-related phenotypes. My studies facilitate the identification of age-related signals that are diminished during aging, resulting in stem cell dysfunction—as evidenced by the reduced organoid formation efficiency observed in organoids derived from aged mice. The overarching aim of this research is to discover therapeutic targets that restore regenerative function in aged livers.

Abstract No. P137/T22

A human brain organoid model of ageing identifies chromatin-mediated control of transposable elements during neural ageing

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Studies of human brain ageing have been constrained by limited access to patient-derived tissue and by the inability of induced pluripotent stem cell (iPSC) models to retain age-associated signatures. To address this limitation, we developed an inducible 3D human brain organoid model based on progerin overexpression aimed to recapitulate key hallmarks of ageing and to identify novel ageing regulators. Induced ageing in organoids resulted in epigenetic instability, characterised by a 40% reduction in H3K9me3-enriched heterochromatin, a two-fold increase in DNA damage, mitochondrial dysfunction, lipofuscin accumulation, and increased cellular senescence. Notably, ageing-associated phenotypes were partially reversible following pharmacological intervention.

To explore the molecular basis of these changes, transcriptomic profiling identified a distinct age-associated gene expression programme that closely mirrored profiles observed in aged human *post-mortem* cortical tissue, including downregulation of synaptic genes such as *SYN1* and *CALM2*, and known ageing regulators, including *SIRT1* and *HSPA8*. Among dysregulated genes, a histone demethylase was consistently reduced in both aged organoids and human cortical samples. ChIP-seq analysis identified enrichment of genomic regions containing motifs recognised by the KRAB zinc-finger protein ZNF93, a regulator of transposable element repression. Consistent with disruption of this regulatory pathway, aged organoids exhibited a 20% increase in transposable element expression, accompanied by re-localisation of ZNF93 from the nucleus to the cytoplasm, suggesting impaired chromatin recruitment downstream of reduced histone demethylase expression.

Together, these findings establish inducible ageing organoids as a human-specific model for investigating epigenetic instability and transposable element dysregulation during brain ageing, with implications for understanding neurodegenerative disease mechanisms and evaluating therapeutic interventions.

Abstract No. P138

A novel human stem cell culture model for severe traumatic brain injury reflecting sexual dimorphism in heterotopic ossification

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Traumatic brain injury (TBI), which occurs more frequently in males than females, can cause critical primary and secondary injuries. In particular, severe TBI can induce heterotopic ossification (HO), the formation of ectopic bone in soft tissue outside of the skeletal system. The human mechanisms linking TBI to ectopic bone formation remain unclear. We therefore established an in vitro model using human adult stem cells to identify osteoinductive factors in sera of TBI patients. Supplementing osteoinductive medium with TBI serum led to highly increased osteogenic differentiation levels, with the most pronounced effect in male skeletal stem cells (SSCs). TGF-β1 emerged as an important factor contributing to these osteogenic processes, with significantly higher serum levels in male than in female TBI patients 14 days post-injury. Neutralizing TGF-β1 revealed a sexual dimorphism, markedly reducing osteogenic differentiation in male SSCs while no statistically relevant effect was detectable in female SSCs. These findings indicate that TGF-β1 may play a central role in the development of HO in males, whereas alternative signaling mechanisms may be relevant in female patients.

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Abstract No. P139

Understanding the role of H3K36 methylation in epigenetic aging

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Aging is associated with robust and reproducible changes in DNA methylation (DNAm), however the upstream chromatin mechanisms governing these methylation patterns are poorly understood. Histone 3 lysine 36 (H3K36) methylation, specifically H3K36me2/me3, recruit DNA methyltransferases, DNMT3A/B, to target regions. Therefore, we aimed to elucidate whether H3K36 methylation patterns change with aging and if this contributes to age-associated DNAm. H3K36me2 and H3K36me3 profiles were investigated in peripheral blood derived mononuclear cells of 5 old and 5 young donors. We observed significant changes in both marks, with particularly loss of H3K36me2 and gain of H3K36me3. Notably, these genomic regions were enriched in genes associated with leukocyte and immune function. We observed that subsets of both patterns overlap with each other, suggesting a shift toward H3K36me3 in aging. However, the changes in H3K36 marks did not reveal clear association with genomic regions with age-associated DNAm. To better understand how the H3K36 marks interact with DNAm, we generated CRISPR-Cas9 knockout of the histone methyltransferases, NSD1 and SETD2, which are responsible for depositing H3K36me2 and H3K36me3, respectively, in induced human pluripotent stem cells. In fact, NSD1 and SETD2 knockout clones showed corresponding decrease in either H3K36me2 or H3K36me3 patterns. NSD1 knockout resulted in a significant hypomethylation, but it was not considerably impacting age-associated DNAm. On the other hand, we did not see any evident DNAm changes in SETD2 knockout lines. Collectively, our work demonstrates an age-associated shift from H3K36me2 to H3K36me3, but these changes appear to be independent from age-associated DNAm.

Abstract No. P140

Divergent NF-κB responses distinguish TNF-α-sensitive and -resistant human cancer stem cells

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Cancer stem cells (CSCs) contribute to tumor initiation, metastasis, therapy resistance, and recurrence. We isolated and characterized primary human CSC populations from several solid tumor entities, including non-small-cell lung cancer (NSCLC), prostate cancer, and glioblastoma. Although the CSC populations clustered independently of tissue origin, full-length cDNA nanopore sequencing revealed significant enrichment of the GO term “NF-κB binding” across all investigated populations. Moreover, the NF-κB family member RELA was expressed in every population, suggesting a shared involvement of NF-κB signaling in CSC biology.

Immunocytochemical analyses confirmed broad RelA expression but revealed marked differences in basal nuclear localization, expression of RelB and c-Rel, as well as TNF-α-induced nuclear translocation. These molecular differences were accompanied by divergent functional responses. TNF-α reduced survival of prostate CSCs, particularly in populations with impaired RelA translocation. In contrast, TNF-α enhanced survival of glioblastoma and NSCLC CSCs. Treatment with PDTC reduced CSC viability and counteracted the cytoprotective effect of TNF-α, supporting a contribution of NF-κB signaling to CSC survival. However, non-malignant human cardiac stem cells were more sensitive to PDTC than the investigated CSCs, indicating limited tumor selectivity of untargeted pharmacological inhibition.

Our findings show that NF-κB does not constitute a uniform survival program across human CSCs. Instead, basal and inducible NF-κB states are associated with context-dependent TNF-α responses ranging from cytoprotection to apoptosis. Functional stratification of these response states may guide the development of cancer-specific strategies targeting NF-κB signaling while limiting adverse effects on non-malignant stem cells.

Abstract No. P141

Analysis of senescence in blood brain barrier endothelial cells derived from Alzheimer specific induced pluripotent stem cells

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Alzheimer's disease (AD) is the most common cause of dementia. Novel monoclonal anti-amyloid-β antibodies have so far only demonstrated therapeutic benefits in the early stages of AD and are associated with severe adverse effects such as cerebral edema. This highlights the need for additional therapeutic approaches. A pathological characteristic of AD is an alteration in the functionality of the blood–brain barrier (BBB), resulting in dysregulated amyloid-β transport. Furthermore, cellular senescence is increasingly discussed as a prodromal factor in the pathogenesis of AD. This raises the question of whether senescence in BBB endothelial cells represents a key pathogenetic mechanism in AD and whether senotherapeutic interventions, such as metformin and dasatinib/quercetin, may offer a potential therapeutic strategy.

To investigate senescence in AD, BBB endothelial cells were generated from induced pluripotent stem cells (iPSCs) derived from somatic cells of AD patients carrying an APOE4/4 genotype. The senescence-associated phenotype (SAP) and experimentally induced senescence with neocarcinostatin were compared between AD-derived and healthy control cell lines. Barrier integrity was assessed by measuring transendothelial electrical resistance (TEER) and permeability to sodium fluorescein. The SAP was characterized by immunofluorescence staining and flow cytometry, with analysis of proliferation markers, cell cycle regulators, and general senescence markers. In addition, a novel panel of 17 markers was established to analyze the senescence-associated secretory phenotype (SASP), enabling evaluation of paracrine, autocrine, and endocrine signaling effects.

The results demonstrate a pronounced SAP, including alterations in proliferation, cell cycle regulation, and general senescence markers, accompanied by a characteristic SASP signature.

This study underlines the importance of senescence in BBB endothelial cells with an APOE4/4 genotype. Targeting senescence, including the associated BBB alterations, by the use of senotherapeutic agents represents a promising scientific perspective and a potential therapeutic approach.

Abstract No. P142/T23

Extreme heterogeneity in hematologic aging is predominantly driven by stochastic variation, not by environmental nor genetic variation

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Organismal aging is thought to arise from cumulative genetic and environmental interactions, complicating mechanistic dissection. However, the degree of heterogeneity has been largely unexplored.

Here, we generated a multi-layered hematopoietic dataset using a large cohort (>100 individuals) of young (2 months), middle aged (18 months) and old (>24 months) inbred female C57BL/6 mice house under specified pathogen free conditions, to gain a comprehensive characterization of the aging process across blood, bone marrow, spleen, and transplantation assays.

While we recapitulate the expected age-related hematopoietic traits across the cohort, aged mice showed pronounced phenotypic heterogeneity: with some 24-month-old mice displaying parameters comparable to young controls, while others showed extreme aging outcomes. Surprisingly, a cohort-wide correlation analysis of the aged individuals discounted the previously accepted cause-effect relationships between hematopoietic stem cell (HSC) functionality (measured by transplantation output), HSC expansion, myeloid bias and anemia, with these outcomes being spread across different individual mice, suggesting that hematopoietic aging does not follow a single trajectory.

To investigate the molecular basis of this variability, we derived cell type-specific aging scores from bone marrow scRNA-seq data in a subset of the cohort, capturing transcriptomic dysregulation in hematopoietic and niche populations. Aging scores varied widely among aged individuals. To link aging traits with molecular data we performed intercellular communication analysis and identified distinct inflammatory signaling axes in the bone marrow niche associated with specific aging phenotypes. Elevated neutrophil-derived Oncostatin M signaling in a subset of mice seemed to remodels the AdipoCAR-HSC niche axis and drives myeloid bias, while in another subset of mice IL1 signaling from neutrophil to AdipoCAR correlated with anemia.

Our findings challenge the notion of a linear ageing process and rather indicate that hematopoietic aging proceeds through multiple independent routes, shaped by distinct inflammatory cell-cell communication axes within the bone marrow.

Abstract No. X1

Interplay between genetic and epigenetic alterations in liver cancer initiation

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Loss of epigenetic patterns and gain of somatic mutations are known to play a key role during the acquisition of cellular plasticity leading to epithelial carcinogenesis (Hannahan, 2022). Despite the importance of these mechanisms, their interplay remains to be fully uncovered. Interestingly, our group has shown that liver cells become more plastic during the progression of chronic liver disease. This process results in the production of bi-phenotypic cells sharing expression of hepatocyte and cholangiocyte markers (Gribben et al., 2024). More recently, the same cells have been identified in hepatocellular carcinoma and cholangiocarcinoma, suggesting a role for this cellular plasticity in the progression to liver cancer.

To investigate cooperation between epigenetic remodelling and acquisition of oncogenic mutations in liver cancer initiation, we are taking advantage of Intrahepatic Cholangiocyte (ICOs) and Hepatocyte Organoids (HepOs) derived from primary tissues. These organoids are genetically modified to carry cancer driver mutations using RNP-based CRISPR. We achieved knockout efficiencies of 85-95% in three different ICOs lines carrying mutations in tumour suppressor genes. In parallel, we are treating the same organoids with small molecules affecting the epigenetic machinery. Cellular plasticity in these organoid lines is currently being assessed, with preliminary results suggesting that P53 deletion could increase the transdifferentiation capacity of ICOs.

Overall, this study will shed light on the molecular mechanisms that connect cellular plasticity with liver carcinogenesis. Such knowledge could help to develop new therapies promoting tissue regeneration while limiting tumorigenesis.

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Abstract No. P143/T40

Liver regeneration during chronic liver disease: SOX4 and KLF6 play a role in liver cell plasticity

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Liver regeneration in the context of acute liver injury has been extensively studied. However, the regenerative processes occurring during chronic liver diseases are not fully understood yet. Previous investigations performed by our group have revealed that hepatocytes and cholangiocytes can transdifferentiate into one another during chronic injury. This process is marked by the production of biphenotypic cells expressing markers specific for the two cell types. The aim of this study is to identify the main factors that drive such cellular transdifferentiation during chronic disease progression.

We performed single nuclei RNA sequencing on liver biopsies of patients at different stages of the disease. That allowed us to identify a set of transcription factors that potentially play a role in the transdifferentiation process between hepatocytes and cholangiocytes. We identified 2 transcription factors, SOX4 and KLF6, as potentially crucial for acquiring the plasticity necessary for such cellular transdifferentiation. The expression of SOX4 and KLF6 in transdifferentiating cholangiocytes/hepatocytes was confirmed in vivo by immunostaining of human tissue slides. We then established two in vitro approaches to confirm the functional importance of these factors in transdifferentiation using patients'-derived intrahepatic cholangiocyte organoids (ICOs) and primary cells-derived hepatocyte organoids (HepOs). Both cell types can be transdifferentiated in vitro into biphenotypic cells, recapitulating the process observed in vivo. Through loss of function experiments conducted on ICOs, we showed the importance of SOX4 and KLF6 for the maintenance of cholangiocyte identity. When these 2 transcription factors are silenced, cholangiocytes are more prone to express hepatocyte markers upon transdifferentiation.

Overall, our experiments have identified two plasticity factors, SOX4 and KLF6, which could play an important role in regenerative processes occurring during MASLD progression.

Abstract No. P144

Impact of developmental programming by maternal obesity on alveolar macrophage-epithelial cell interactions in lung development and function

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Lung development and function depend on coordinated interactions between alveolar epithelial type II cells (AECII) and tissue-resident alveolar macrophages (AMs). Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a well-established mediator of epithelial regeneration as well as AM survival and function. Maternal obesity alters key metabolic pathways, including glucose and lipid metabolism, and may thereby disrupt AECII–AM crosstalk. However, the molecular mechanisms underlying this disruption remain poorly understood. To elucidate these mechanisms, we established a 3D murine bronchioalveolar lung organoid (BALO) model by co-culturing FACS-sorted bronchioalveolar stem cells (BASCs) with lung-resident mesenchymal cells (rMCs). AMs were microinjected into BALOs to study AECII–AM crosstalk in an alveolar-like environment. Using this *ex vivo* immunocompetent model, we demonstrated functional AM–AECII interactions following influenza A virus (IAV) infection, as evidenced by the significant upregulation of IL-1β, IL-6, and TNF-α at 48 hours post-infection in the presence of AMs. To investigate the effects of maternal obesity on lung regeneration, adult offspring of high-fat diet-fed mothers (HFDm) and control diet-fed mothers (CDm) were infected with IAV. During the course of infection, HFDm mice exhibited reduced survival, increased weight loss, and depletion of epithelial and airway cell populations compared with CDm mice. Furthermore, AECII-derived alveolospheres generated from IAV-infected HFDm mice exhibited significantly reduced organoid-forming efficiency compared with those generated from CDm mice, indicating impaired AECII regenerative capacity. By combining this *in vivo* model of maternal obesity with *ex vivo* BALOs generated from adult offspring, we aim to elucidate the mechanisms underlying these defects and gain insight into how maternal obesity influences long-term respiratory health and susceptibility to chronic lung disease in adult offspring.

Abstract No. P145

Modeling spinal and bulbar muscular atrophy using patient-derived neuromuscular organoids

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Spinal and bulbar muscular atrophy (SBMA) is a rare X-linked neuromuscular disorder caused by a CAG expansion in the androgen receptor gene. Although traditionally considered a motor neuron disease, increasing evidence suggests that skeletal muscle pathology may contribute to motor neuron degeneration, potentially involving neuromuscular junctions (NMJs). However, whether early NMJ dysfunction contributes to non–cell autonomous motor neuron impairment in human SBMA remains unclear. Moreover, currently available human in vitro models lack the three-dimensional architecture required to preserve functional NMJs and muscle contractility, limiting their ability to capture key disease mechanisms.

To overcome these limitations, we established a patient-derived neuromuscular organoid (NMO) model of SBMA that recapitulates the essential cellular components of the NMJs, including spinal motor neurons, skeletal muscle fibers, and Schwann cells. NMOs self-organize in three dimensions and form functional NMJs that mature over time and drive skeletal muscle contraction. NMOs were generated from induced pluripotent stem cells derived from two brothers, one affected by SBMA and one unaffected.

Using this system, we observed an early impairment in spontaneous muscle contractility in SBMA-NMOs. Longitudinal analyses revealed progressive NMJ instability, indicating impaired maintenance of muscle–motor neuron connectivity. This neuromuscular dysfunction was associated with mitochondrial stress, reflected by reduced mitochondrial membrane potential and increased oxidative stress in both neuronal and muscle compartments. In addition, mitochondria exhibited increased fragmentation, consistent with reduced network connectivity and altered metabolic efficiency. Metabolic imaging using multiphoton fluorescence lifetime microscopy further indicated a shift of SBMA muscle fibers toward glycolytic, anaerobic metabolism.

Together, these findings demonstrate that patient-derived NMOs recapitulate early neuromuscular and metabolic alterations associated with SBMA in a human-relevant three-dimensional system, providing a valuable platform to dissect disease mechanisms and evaluate therapeutic strategies.

La Spada et al, Nature (1991), 352: 77-79
Faustino Martins et al, Cell Stem Cell (2020), 26: 172-186

Abstract No. P146

ECM-sensing modulates hepatocyte polyploidy in health and disease

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Hepatocytes are the main cell type of the liver and one of the very few cells that naturally sustain polyploidy. The human liver contains 40% of polyploid hepatocytes and this proportion increases with age and in diseases such as MASLD/MASH and liver fibrosis. Hepatocyte polyploidization, or whole-genome duplication, can occur through different routes. Failed cytokinesis gives rise to hepatocytes with multiple nuclei (cellular polyploidy) while endocycling and failed chromosome segregation result in hepatocytes with nuclei containing multiple copies of the genome (nuclear polyploidy). These mechanisms are regulated by the E2F family proteins and the first wave of polyploidization occurs through the insulin pathway. Having multiple copies of the genome could act as a protective mechanism against mutation and cancer initiation, increase the metabolic potential of hepatocytes or "prime" them to quickly produce new cells in case of an injury. However, how polyploidy impacts hepatocyte functions and liver regeneration have been a long-standing debate in the field.

In this project, we take advantage of primary human Hepatocyte organoids to investigate how ECM proteins and their downstream signaling pathways can affect the cell cycle of hepatocytes, modulate their ploidy level and affect their gene regulation and regenerative abilities. To do so, we gryw Hepatocyte Organoids in hydrogels with defined composition and in the presence of various inhibitors of ECM-receptors and found that Collagen-sensing impacts the ploidy level of Hepatocytes. Our first results hint at a role of the FAK/p53/p21 axis in this process, leading to an increased nuclear ploidy. We then aim to take advantage of this model to understand how gene expression is regulated in both cellular and nuclear polyploid cells, by combining sequencing and high-resolution imaging approaches.

Taken together, our results uncover how extra-cellular micro-environment can influence polyploidy and how such change can be linked to disease progression and fibrosis.

Abstract No. P147

Neural progenitors adjust their cell cycle speed and intercellular communication to ensure normal brain development

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During human brain development, cellular lineages are constantly altered by genetic or environmental perturbations, yet overall brain development in terms of growth and organization is largely maintained. Studies in brain organoids indicate that human neural progenitor cells (NPCs) can adjust progeny output in response to genetic or chemical tissue growth perturbation. How human NPCs carry out this replenishment response remains poorly understood. Here, we use a human chimeric brain organoid model of controlled, targeted depletion to dissect the cellular and molecular basis of replenishment. By combining microscopy, flow cytometry, time-resolved transcriptomics and lineage-resolved scRNA-sequencing, we demonstrate that tissue-perturbed organoids preserve overall cell type composition while undergoing a rapid expansion of replenishing, fast-growing lineages within ten days. This response is driven by accelerated cell-cycle progression and extensive rewiring of cell-cell communication, including developmental and extracellular matrix ligand–receptor pathways. Our findings reveal a compensatory strategy in which neural progenitors restore tissue homeostasis not via bulk self-expansion, but by dynamically adjusting proliferative behaviour and signalling interactions while broadly preserving developmental organization. These insights provide a framework for understanding tissue-mediated growth control and how human neural tissue withstands and repairs structural disruption, with implications for developmental neurobiology and regenerative strategies.

Abstract No. P148

Uncovering new CSF-contacting neuron subtypes as candidate regulators of the spinal cord stem cell niche

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In the adult spinal cord, the stem cell niche lies in the ependymal zone surrounding the central canal and consists of quiescent cells. Following injury, progenitor cells re-enter the cell cycle and contribute to scar-forming glia. However, the markers of cells involved in this response and the regulators governing niche activation remain poorly understood.

We focus on cerebrospinal fluid-contacting neurons (CSF-cNs), as a controversial and understudied player in this niche. Their cell bodies reside in the periependymal layer, while an apical process extends into the central canal. CSF-cNs are GABAergic, express variety of chemo- and mechanosensory receptors, retain immature features, and migrate during postnatal development. Although their genetic ablation causes only minor locomotor deficits at baseline, it impairs recovery after spinal cord injury. Together with evidence that CSF-cNs suppress ependymal proliferation through dynorphin-dependent signaling, this identifies them as candidate niche regulators. We therefore asked whether molecularly distinct CSF-cNs populations may perform roles in niche regulation.

We isolated nuclei from genetically labelled neonatal mouse CSF-cNs, performed single-nucleus RNA sequencing, and validated markers in vivo by RNAscope across developmental stages. We identified five transcriptionally distinct populations, including two previously unrecognized spatially restricted groups: a ventral *Dcn*$^+$ cluster and a caudal *Ren1*$^+$ cluster. Both identities were maintained throughout development. Notably, ventral CSF-cNs were also *Pdyn*$^+$, identifying a previously unreported source of dynorphin in proliferation control. We also identified a distinct *Ddc+* population, suggesting a link to monoaminergic regulation of glial activation and neuroinflammation. Several clusters shared overlapping transcriptional programs, indicating a maturation continuum rather than exclusively terminally differentiated subtypes.

Our study provides a molecular framework for CSF-cNs heterogeneity and identifies potential targets within the spinal cord stem cell niche. These findings establish a basis for testing how distinct CSF-cN states regulate ependymal quiescence, activation, and progenitor fate after injury.

Abstract No. P149

Apically accessible intestinal organoids composed of stroma and macrophages - A model to test ingested chemical substances

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The development of intestinal organoid cultures emerged as a potential replacement for animal experiments. However, the current state of organoid cultures is characterized by limitations in their capacity to accurately replicate in vivo conditions, which are attributed to the inaccessibility of the apical surface and the absence of stromal and immune cells. To overcome these constraints, we have developed a novel self-maintaining intestinal apical-out organoid (AOO) system that can be enriched with bone-marrow-derived macrophages. AOOs consist of a stromal-cell core covered by an epithelial layer and possess a constantly apically accessible surface. At an early stage, the epithelium exhibits regenerative properties. While covering the core the epithelium matures and finally comprises proliferative precursors, stem cells, and terminally differentiated secretory and absorptive cells. The AOOs display cellular turnover and allow continuous culture for several weeks. Embedded macrophages form inter-epithelial dendrites to sample environmental particles, migrate, and accumulate beneath the epithelial sheet in response to epithelial damage. This model underscores the utility of AOOs in analyzing tissue- and immune-cell responses to ingested and apically acting biological or chemical agents.

Abstract No. P150

Optimization of pluripotent stem cell spheroid growth in liter scale bioreactors via continuous medium perfusion

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The development of pluripotent stem cell (PSC) culture protocols in multi-liter bioreactors is important for efficiently scaling PSC yields to manufacturing levels. We have previously demonstrated that PSCs can be expanded as spheroids in 3 L stirred-tank bioreactors (SBRs). These systems use impellers that continuously mix the culture medium but also generate shear stress, which may negatively affect PSC growth. Additionally, protocols that rely on gravity sedimentation of PSC spheroids and manual aspiration of spent medium become impractical beyond ~3 L culture scale. SBRs can be combined with perfusion systems to continuously supply fresh medium and eliminate the need for manual medium exchange. Here, we describe our ongoing efforts to optimize PSC spheroid growth in perfusion-fed, multi-liter bioreactor cultures by balancing stir speed, shear stress, and medium exchange rates. PSCs were seeded into dual pitch blade horizontal impeller-based SBRs at low stir speeds (i.e., low RPM) to promote spheroid formation. The RPM was then gradually increased to prevent spheroid aggregation and maintain culture homogeneity. Unsurprisingly, shear stress was detrimental to spheroid growth at higher speeds; however, this effect was mitigated by the addition of Pluronic. Specifically, 0.1–0.2% Pluronic enabled the formation of larger, more uniform spheroids, resulting in increased cell yields. We further evaluated spheroid growth using tangential flow depth filtration (TFDF) and alternating tangential flow (ATF) perfusion systems for medium exchange. Both systems supported spheroid expansion with similar efficiencies. Under optimized conditions, we observed yields of up to 25 billion PSCs in 2 L cultures (~12×10^6 lls/mL; ~80-fold expansion) after 10 days, while maintaining high levels of pluripotency marker expression (>95% $OCT4^+$/$NANOG^+$ cells). Overall, these results demonstrate that PSC culture in perfused SBRs is a promising approach for meeting manufacturing-scale demands.

Abstract No. P151

Collagen-based biomaterials in organoid technology for regenerative medicine: Current advances and future perspectives

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Organoid technology, as an advanced 3D laboratory model, has become a revolutionary advance in research and a valuable tool for disease modeling, drug screening, and regenerative medicine, given the limitations of laboratory resources and ethical considerations. However, the reliance on Matrigel, given its tumor-derived origin and biosafety issues, still poses limitations to the development of therapeutic applications of organoids.In contrast, collagen-based biomaterials have been proposed as promising alternatives for organoid culture due to their biocompatibility, biodegradability, cell-remodeling ability, and structural similarity to natural extracellular matrix.This study was a narrative review of collagen-based biomaterials commonly used for organoid culture, including Matrigel and decellularized extracellular matrix. Collagen hydrogels, collagen-based composite scaffolds, gelatin methacrylate, recombinant collagen, and decellularized extracellular matrix in organoid culture were reviewed. Reports focusing on regenerative medicine applications, including liver, intestinal, lung, cardiac, neural, and musculoskeletal organoids, were analyzed. Particular attention was paid to extracellular matrix–cell interactions, mechanobiology, scaffold properties, and their potential for transfer to clinical tissue regeneration. Collagen-based biomaterials were shown to effectively promote organoid development, organization, stem cell retention, and tissue-specific differentiation. In addition to physiologically relevant chemical and mechanical cues, the use of collagen hydrogels and decellularized extracellular matrix–derived matrices promoted more advanced stages of organoid differentiation than did standard culture media. Composite collagen matrices enabled better tuning of stiffness, degradation, and activity, whereas bioengineered collagen derivatives enabled integration with bioprinting and organ-on-a-chip platforms. Importantly, across several tissue types, including liver, intestine, lung, heart, and neural tissue, the use of collagen matrices increased cell function and facilitated regeneration. Collagen-based biomaterials can be considered promising substitutes for extracellular matrices in future organoid-based regenerative medicine applications.

Farrell, L. et al. (2025). Organoids with a type 1 collagen scaffold to model bacterial cancer therapy. Cells, 14, 524. https://doi.org/10.3390/cells14070524

Feng, B. et al. (2023). Collagen-based biomaterials in organoid technology for reproductive medicine: composition, characteristics, and applications. Collagen and Leather, 5, 35. https://doi.org/10.1186/s42825-023-00142-6

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Abstract No. P152

Human iPSC-derived cerebral organoid model for investigating cellular senescence in APOE-associated Alzheimer's disease

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Aim:Cellular senescence is a hallmark of aging that contributes to Alzheimer's disease (AD) by promoting chronic neuroinflammation through the senescence-associated secretory phenotype (SASP). However, human models integrating patient-specific genetic risk with age-related cellular phenotypes remain limited. We aimed to establish a human iPSC-derived cerebral organoid model to investigate cellular senescence in APOE-associated AD and facilitate the evaluation of senescence-targeted therapies.

Method: Cerebral organoids were generated from patient-derived APOE4/4 late-onset AD iPSC lines and genetically matched APOE3/3 control iPSC lines using a robust differentiation protocol. Organoid development was assessed by immunofluorescence analysis of neural progenitor and cortical markers to confirm reproducible neural differentiation and cortical identity. Organoids were maintained under long-term culture conditions, and cellular senescence was induced using DNA damage paradigms.

Result: Robust and reproducible cerebral organoids were successfully established from both APOE4/4 and APOE3/3 iPSC lines. Organoids exhibited consistent cortical organization and reproducible expression of neural progenitor and cortical markers across independent differentiations. This platform enables comprehensive assessment of cellular senescence using complementary readouts, including senescence-associated β-galactosidase activity, expression of canonical senescence and DNA damage markers, and quantitative profiling of SASP-associated inflammatory mediators. Furthermore, the model provides a framework for evaluating senescence-targeted interventions, including senolytic and senomorphic compounds.

Conclusion: We established a patient-derived human cerebral organoid platform that integrates APOE-associated genetic risk with a disease-relevant three-dimensional brain model to investigate cellular senescence in Alzheimer's disease. This physiologically relevant platform enables mechanistic studies of genotype-dependent brain aging and supports the preclinical evaluation of senescence-targeted therapies.

Abstract No. P153

Spatiotemporal lineage progression of pancreatic cells during mouse development revealed by spatial transcriptomics

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The pancreas is an organ with dual functions: the exocrine pancreas produces and transports digestive enzymes to the small intestine, whereas the endocrine pancreas produces and secretes hormones to regulate blood glucose. Both exocrine and endocrine cells arise from pancreatic progenitor cells at distinct stages during development. The morphogenetic organization of a branched ductal network with terminal acini and nearby islets of Langerhans coincides with cell differentiation in the embryonic pancreas. Snapshots of emerging cell types have been captured by a variety of techniques, including single-cell RNA sequencing, in situ hybridization, and immunofluorescence, but each approach has limitations. Cell dissociation methods sacrifice spatial information and can lose fragile cell populations, while imaging based methods are restricted to a limited set of pre-selected genes or proteins.

Here, we apply high-resolution spatial transcriptomics (Visium HD) to map morphogenesis and differentiation of mouse embryonic pancreas during development (E10.5, E11.5, E12.5, E14.5, E16.5, E18.5). We optimized a protocol that preserves RNA quality in the later stages of pancreas (E16.5 and E18.5), overcoming the challenges posed by the high RNase activity in acinar cells and the slow penetration of fixative. Using cell segmentation on haematoxylin and eosin stained images, our preliminary data confirm lineage progression of pancreatic progenitors, early acinar progenitors, early and late islets, acinar cells, as well as surrounding mesenchyme. Ongoing integration of data across developmental stages and experiments will generate a comprehensive, spatially resolved atlas of pancreatic lineage progression. This atlas will serve as an unbiased benchmark for spatiotemporal studies of pancreatic development and may reveal previously unrecognised sub clusters within cell type-specific populations.

Abstract No. P154

Matrix stiffness as a modulator of cellular behavior: mechanical regulation in 2D and 3D systems

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The extracellular matrix (ECM) is a central regulator of cellular behavior, influencing processes such as adhesion, migration, differentiation, and tissue organization through biochemical and mechanical cues. Among its many properties, matrix stiffness has emerged as a key regulator of mechanotransduction pathways such as Notch, which governs vascular morphogenesis while also playing fundamental roles in stem cell maintenance, lineage specification, and organoid development. Although the influence of ECM stiffness has been extensively investigated in 2D culture, its contribution to 3D microenvironments relevant to organoid systems remains less defined due to the complexity of matrix design and limited tunability. This study investigates how matrix stiffness modulates endothelial behavior in different culture systems and highlights the importance of considering mechanical properties when establishing physiologically relevant organoid and in vitro models.

Using synthetic PDMS-based substrates in 2D and natural PhotoCol hydrogels in 3D, matrix stiffness was systematically modified and mechanically characterized. Cellular morphology, cohesion, sprouting, and mechanosensitive signaling, including Notch pathway activation, were assessed. In 2D, substrate stiffness influenced endothelial adhesion, morphology, and signaling. In 3D, spheroid architecture and sprouting behavior were strongly stiffness-dependent, with matrix mechanics either promoting coordinated outgrowth and migration or preventing sprouting and compromising structural integrity, accompanied by corresponding changes in Notch activity.

These findings demonstrate that endothelial self-organization is tightly regulated by the mechanical microenvironment and support a role for mechanosensitive pathways such as Notch in mediating these responses. Given the central role of Notch signaling in stem cell maintenance and differentiation, these results emphasize the importance of considering mechanical cues when developing physiologically relevant stem cell-derived organoids and advanced in vitro tissue models.

Abstract No. P155

From regenerative niches to organ reconstruction: a multi-scale framework for human liver regeneration

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The liver is unique among adult organs in its capacity to restore mass, architecture, and function following injury. Despite decades of research, the mechanisms coordinating regeneration across biological scales remain incompletely understood, especially in humans. A major challenge is to integrate the molecular, cellular, and spatial processes that determine regenerative success or failure.

To address this challenge, we are establishing a multi-scale framework for human liver regeneration that combines longitudinal human samples, patient-derived models, and experimental systems, enabling mechanistic interrogation of tissue repair. Our objective is to identify the cellular states, microenvironmental signals, and tissue-level interactions that drive regeneration and coordinate organ rebuilding.

Three-dimensional tissue reconstruction using light-sheet microscopy with a cell-type-resolved proteomic panel has enabled detailed characterisation of healthy and diseased human liver architecture, revealing the spatial organisation of the liver lobule, including the biliary network, vascular structures, and parenchymal compartment.

To investigate its singular organisation at molecular resolution, we developed a liver-specific spatial transcriptomic framework based on MERFISH. Using a custom-designed 1,000-gene panel, we resolved lobular architecture, metabolic zonation, and cellular identities in healthy livers. The sensitivity and specificity of this approach enable the reconstruction of inter- and intracellular communication networks and provide a foundation for characterising regenerative mechanisms at subcellular resolution.

To experimentally investigate the earliest events of liver repair, we established a tractable system of primary human hepatocyte-derived organoids from healthy adult and neonatal liver samples. Our model maintains the hepatocytes in a quiescent functional state while preserving their capacity to respond to regenerative stimuli and re-enter the cell cycle.

Together, these complementary approaches enable the characterisation of regenerative niches across scales, from molecular signalling and cellular interactions to tissue remodelling and organ reconstruction. Ultimately, this work seeks to define the principles governing human liver regeneration and provide a foundation for future regenerative medicine strategies.

Abstract No. P156

Transcription factor-guided co-differentiation of human iPSCs generates isogenic multilineage cardiac microtissues with a distinct endothelial identity

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Human vascularized cardiac tissues for disease modeling and drug screening typically require separately differentiating and mixing multiple cell types, often from different iPSC lines or donors, limiting isogenic applications and precluding developmental co-emergence between lineages. Self-organizing cardiac organoid approaches, conversely, offer limited control over cellular composition, and endothelial fractions remain below physiological levels. Here, we developed a lineage-biased co-differentiation protocol combining wildtype human iPSCs with doxycycline-inducible ETV2 and NKX3.1 lines at defined ratios, jointly differentiated toward cardiomyocytes with staged growth factor supplementation. Single-line differentiation confirmed that ETV2 or NKX3.1 overexpression redirects cell fate toward endothelial cells or mesenchymal progenitors, respectively, within the cardiomyocyte differentiation milieu. At day 14, co-differentiation produced multilineage cultures comprising approximately 50% cardiomyocytes, 20% endothelial cells, and 20% mesenchymal progenitor populations. Single-cell RNA sequencing revealed that endothelial cells emerging alongside cardiomyocytes exhibit a transcriptional identity distinct from endothelial cells generated by single-differentiation: canonical arterial markers (DLL4, EFNB2, GJA4, CXCR4) were downregulated, while ENG, MMP2, SPARC, VIM, NR2F1, NR2F2, APLN, and ESM1 were upregulated, a profile suggestive of cardiomyocyte-instructed adaptation toward a capillary-like or remodeling-competent phenotype. These cells were then harvested for cardiac organoid generation. After two weeks of cardiac organoid culture, co-differentiation-derived endothelial cells showed improved network integration, mural coverage by PDGFRβ+ cells, and cardiomyocyte-vessel proximity compared to organoids assembled from separately differentiated cell mixtures. GFP-labeling confirmed the ETV2 line as a substantial source of the endothelial population in the organoids. The resulting vascular density scaled tunably with ETV2-iPSC input ratio, demonstrating protocol controllability. This platform enables generation of isogenic multilineage cardiac tissues from a single differentiation, positioned for patient-specific vascularized disease modeling. Ongoing work integrates these cells into perfusable cardiac-on-chip platform to assess long-term vascular and contractile function against sequentially differentiated cell mixtures.

Abstract No. P157

Characterization of early human cortical neurogenesis in MCT8-deficient cerebral organoids

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Allan-Herndon-Dudley syndrome (AHDS) is a **rare X-linked disease** associated with severe cognitive and motoric developmental delay. It is caused by mutations in the *SLC16A2* gene, encoding for the thyroid hormone (TH) transporter MCT8. TH is critical for human brain development but, to date, the precise developmental effects of MCT8-deficiency on **human fetal neurogenesis** remain elusive. Against this background, we engineered **different MCT8-deficient hiPSC lines** and generated **cerebral organoids (hCOs)** to characterize cell type-specific effects of MCT8-deficiency on human cortex development. Using highly multiplexed **single cell RNA-seq**, we profiled the transcriptome of three MCT8-deficient hCO models *versus* isogenic controls under different TH culture conditions and at different time points. Quality of hCO cultures was stringently controlled by IF-based assessment of cytoarchitectural features at DIV 21, 46, 58 and 70. MCT8-deficient hCOs showed no differences in cortical architecture on DIV 46 yet a delay of TH-dependent upper layer neuron differentiation at DIV 58. When using scRNAseq to assess effects of MCT8 deficiency on cell type-specific gene expression at DIV 70, we observed both TH-dependent and TH-independent response patterns in neuronal progenitor cells and deep layer neuron subtypes. Interestingly, instead of an absent TH response, due to dysfunctional TH transport, so far defined as key driver of the pathology of AHDS in the CNS, we detected an enhanced TH response pattern caused by MCT8 deficiency. Current therapeutic strategies focus on compounds circumventing the transport defect and mimicking TH. Our experimental strategy (isogenic pairs, triplicate analyses) allowed new insights into the role of MCT8 deficiency in the neurodevelopmental pathogenesis of AHDS and strongly imply that new therapy approaches need to be developed that take our findings into account.

Abstract No. P158

Choroid plexus organoids as a model system for evaluating blood-cerebrospinal fluid barrier properties in healthy patient-derived induced pluripotent stem cells

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In diseases of the central nervous system, the cerebrospinal fluid (CSF) is a key target for studies on disease onset and progression, as well as treatment efficacy. One of the primary routes of access to the CSF is by crossing of the blood-CSF-barrier (B-CSF-B) of the choroid plexus (ChP). The ChP epithelium tightly regulates the barrier permeability, CSF secretion, and brain homeostasis. Emerging studies using organoids manage to reproduce the human B-CSF-B more accurately than humanized mouse models. In our study, we characterized patient-specific ChP organoid models as a mean evaluate B-CSF-B properties.

Therefore, embryoid bodies of healthy induced-pluripotent stem cell (iPSC) lines of different ages and genders were generated and differentiated into a 3D neuroepithelial tissue of ChP identity, which developed fluid-filled compartments. The integrity of the B-CSF-B was evaluated using immunofluorescence staining of epithelial markers that are essential for barrier function and CSF secretion, as well as permeability assays.

The ChP organoids exhibited morphologically consistent expansion of neuroepithelium from culture day 10 onwards, with observable development of fluid-filled compartments on day 25-30 across different cell lines and culturing methods. Immunostaining evaluated the presence of key markers of the ChP epithelium, such as Transthyretin (TTR) and tight junction proteins. The analysis further investigated proliferation and apoptosis within the organoids. Molecules with known barrier permeability properties showed the degree of barrier integrity and function within the organoids.

This investigation demonstrates the applicability of ChP organoids to assess the properties of the B-CSF-B within healthy patient-derived iPSC lines.

Abstract No. P159

Modeling an immune-competent 3D liver portal niche to study T cell–mediated alloimmune injury and tolerance induction

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Liver transplantation is the only curative treatment for end-stage liver disease, but prevention and treatment of allograft rejection, including acute T cell–mediated rejection (TCMR), still depend on systemic immunosuppression with long-term side effects. Acute TCMR occurs primarily in the portal region, where biliary epithelium, vasculature, and mesenchyme are densely organized, and is driven by alloreactive T cells that particularly target biliary epithelial cells (BECs). Regulatory T cells (Tregs) can promote immune tolerance, and increased Treg numbers correlate with graft acceptance, but their therapeutic potential and most relevant mechanisms remain unclear. Preclinical testing of Treg-based therapies relies largely on animal models, which have ethical and translational limitations, while current in vitro systems are mostly two-dimensional not capturing immune–tissue interactions.

Here, we establish a human organoid model of liver TCMR focused on the portal area as the primary injury site. The model combines BECs, endothelial cells, fibroblasts, and immune cells. To overcome the limited self-organization of non-stem-cell-derived primary cells, we enable tissue assembly under bidirectional flow in a rotating bioreactor. Incorporation of pre-enriched alloantigen-specific allogeneic PBMCs induces immune-cell migration into organoids, as shown by liver-cell imaging, upregulation of T-cell activation markers (CD137, CD154), and production of effector cytokines (TNFα, IFNγ). Those responses were suppressed by tacrolimus, validating the model's therapeutic relevance. We will use this platform to compare clinical-grade Treg products, including CRISPR-Cas9-edited FKBP12KO Tregs developed at our institute, engineered to preserve Treg activity during tacrolimus exposure. Treg function will first be evaluated in standard suppression assays; using our platform, we will then increase the complexity of functional testing. Unbiased omics approaches will be applied to define mechanisms of action, including the relevant components of direct cell–cell interactions and soluble mediators, such as CTLA-4-mediated inhibition and IL-10/TGF-β secretion, which can be individually perturbed to verify their contribution to tolerance.

Zarrinrad G et al. Clinical development of tacrolimus-resistant regulatory T cells to enable simultaneous immunosuppression and immune regulation. Mol Ther Adv. 2026 Apr 9;34(2):201735. doi: 10.1016/j.omta.2026.201735. PMID: 42147444; PMCID: PMC13175770.

Abstract No. P160

Of mice and men: can cellular plasticity vary between species?

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Recent findings in human suggest that transdifferentiation between hepatocytes and cholangiocytes is the primary regenerative process in chronically injured livers. Transdifferentiation is characterized by the direct conversion of one cell type into another. This form of cellular plasticity occurs in response to extracellular stimuli and does not involve an intermediate progenitor state. However, this process is limited to a small number of cells in patients and occurs only in end-stage disease. This contrasts sharply with observations in mouse models of liver injury which display large scale regenerative processes involving up to 40% of liver cells. This divergence in regenerative capacity suggests the existence of species-specific differences in cellular plasticity. To investigate this hypothesis, we derived intra-hepatic cholangiocyte organoids from both mouse and human livers, and characterized their plasticity by defining their ability to transdifferentiate into hepatocyte. Preliminary results suggest that mouse cholangiocytes display an increased capacity for transdifferentiation when compared to their human counterparts. We now aim to identify and validate the molecular mechanisms driving this divergence in cellular plasticity, with a focus on epigenetic regulation and gene regulatory networks. Finally, we will explore strategies to increase a plasticity-permissive state in human liver cells. This research could lead to new regenerative therapies in liver diseases, an area with a significant unmet medical need.

Abstract No. P161

Impact of epigenetic erosion on wild-type and P53-mutated cholangiocyte organoids

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Metabolic Dysfunction–Associated Steatotic Liver Disease (MASLD) affects 1.3 billion people worldwide and this chronic disorder is a major contributing factor to liver cancer [1]. The Vallier laboratory has found that cholangiocytes and hepatocytes can transdifferentiate between each other during MASLD progression[2]. This process is marked by the apparition of biphenotypic cells co-expressing cholangiocyte and hepatocyte markers. The apparition of these cells suggest an increase in cellular plasticity, which is likely induced by an epigenetic erosion driven by the diseased niche. On the other hand, bi-phenotypic cells are most abundant in end-stage disease, which carries a high cancer risk while they can also be found in both hepatocellular carcinoma and cholangiocarcinoma. Additionally, cancer-related genes such as *FOXO3* and *SOX4* are expressed in bi-phenotypic cells. Thus, we hypothesise that the epigenetic erosion associated with the emergence of bi-phenotypic sells could facilitate the progression toward tumorigenesis.

Here, we investigate this hypothesis by studying the impact of DNA methylation and Histone modification inhibition on the plasticity of wildtype and *P53*-mutated intrahepatic cholangiocyte organoids (ICOs) derived from primary tissues. For that we use small molecules and genetically engineered ICOs using RNP-based CRISPR. We then analysed the impact of these different conditions on cholangiocyte identity, proliferation and capacity to transdifferentiate in vitro.

Overall, this study will reveal the interplays between epigenetic regulations and somatic mutation in the development of cellular plasticity in pre-cancerous, late-stage MASLD. A deeper understanding of this process may ultimately contribute to improved strategies for the prevention and treatment of liver cancer associated with MASLD.

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Abstract No. P162

Molecular profiling of human intrahepatic cholangiocarcinoma across primary tissue and patient-derived tumoroids

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Intrahepatic cholangiocarcinoma (iCCA) is a highly aggressive primary liver cancer with a poor prognosis and limited treatment options. The pronounced molecular heterogeneity of iCCA across genomic, transcriptomic, and epigenetic levels represents significant challenges for accurate diagnosis and for the development of targeted therapies.

To address this challenge, we established a deeply characterized patient-derived biobank comprising matched tumoral and non-tumoral tissues, along with corresponding organoid and tumoroid models, to better understand the mechanisms associated with iCCA. Using a multi-omics strategy that combines single-nuclei RNA sequencing, whole-genome sequencing, and DNA methylation profiling, we systematically characterize the molecular and cellular landscape of iCCA in-vivo. Comparing tumoral tissues with matching non-tumoral tissues and healthy cholangiocytes identifies novel disease-associated cell populations, cancer cell trajectories as well as genes and regulatory programs that underlie tumor heterogeneity and progression.

Preliminary transcriptomic analyses reveal a pronounced inter-patient heterogeneity, with tumoral cells displaying different transcriptional states across tissue samples. Furthermore, genomic analyses identified recurrent chromosomal alterations and frequently affected genomic regions across the patient cohort. In parallel, different media are being evaluated to purify the tumoral cell population in culture and optimize culture conditions. Preliminary data suggest that tumoroids can proliferate in the absence of selected factors, whereas the growth of matched non-tumoral organoids is restricted under these conditions. Ongoing comparative analyses of primary tissues and their derived in-vitro models will clarify the extent to which tumoroids recapitulate patient-specific tumor features.

Collectively, this study identifies key molecular signatures associated with iCCA, reveals how to improve the fidelity of tumoroid-based models and establishes a robust platform for biomarker discovery and future precision oncology approaches.

Abstract No. P163/T38

Lymphatic vasculature reprograms liver epithelium in assembloids and patients

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Understanding how microenvironmental cues can hijack epithelial cell identity is central to regenerative medicine. Biliary atresia, an infant liver biliary epithelial disease, offers a compelling disease model in which niche signaling drives epithelial fate regression, a phenomenon with broad implications for organoid-based disease modeling and stem cell biology.

Using a large, multi-center patient cohort (n=46), we integrated single-nuclei RNA sequencing (snRNA-seq), spatial transcriptomics (10X VisiumHD & Stereo-Seq), multiplexed immunofluorescence, and 3D light-sheet microscopy to resolve the hepatic lymphatic niche at single-cell and spatial resolution. To dissect niche-epithelial crosstalk, we employed human organoid and stem cell platforms: intrahepatic cholangiocyte organoids (ICOs), iPSC-derived hepatocytes (iHeps), and multicellular fetal liver-like organoids (FLOs), the latter recapitulating the cellular complexity of the developing liver.

Results:
snRNA-seq revealed profound transcriptional dysregulation of lymphatic endothelial cells (LECs) in patients with poor outcomes, corroborated spatially by LEC hyperplasia and 3D remodeling of the intrahepatic lymphatic network. Among upregulated LEC-derived mediators, the chemokine CCL21 emerged as a key niche signal enriched in patients requiring transplantation. To interrogate how this pathological secretome reshapes epithelial identity, we exposed FLOs to BA tissue-conditioned media, observing cholangiocyte dedifferentiation and delumenization into $CK19^{+}$ ductular-reactive conglomerates — faithfully modeling the in vivo ductular-epithelial reaction in a dish. Targeted CCL21 treatment of ICOs and iHeps consistently upregulated SOX9 and LGR5, respectively, activating biliary progenitor and hepatic stemness programs - especially in patients with an inflammatory disease phenotype. Direct co-culture of patient-derived hepatic LECs with ICOs recapitulated this epithelial fate regression, establishing a lymphatic-to-epithelial axis of niche-driven reprogramming.

Conclusion:
We identify CCL21-high lymphatic endothelial cells that reprogram liver epithelium in immune-mediated liver epithelial disease toward a progenitor/reactive state, impairing epithelial function. Primary assembloid and iPSC-based fetal tissue-like organoids faithfully model this niche-epithelial crosstalk, offering tractable systems for dissecting fate decisions in the developing and diseased liver.

Abstract No. P164

Glucose uptake assay to study functional maturation of intestinal organoids

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Glucose enters cells via two transporter families: passive GLUTs and active SGLTs. These days SGLT1 and SGLT2 are getting more in focus as therapeutic targets especially for diabetes. To test potential drugs, a reliable glucose uptake assay is needed. Traditionally, radioactive glucose analogues like ^{14}C-AMG are used in glucose uptake assays but these have safety and cost drawbacks. The fluorescent probe 1-(N-(7-Nitrobenz-2-oxa-1,3-diazol-4-yl) amino)-1-deoxy-d-glucose (1-NBDG), unlike 2-NBDG, is transported by both GLUTs and SGLTs and remains stable under alkaline conditions, enabling simpler, safer assays. Using human SGLT1- and SGLT2-expressing cell lines, researchers developed and validated a high-throughput screening method with 1-NBDG, showing results consistent with traditional radioactive assays.

In this project, self-synthesized 1-NBDG is used to set up a functional glucose uptake assay in human small intestinal organoids. The assay is validated using known SGLT1 inhibitors with either an image based or a spectrophotometric readout. When testing different differentiation conditions, a disconnection between the results gained during functional testing with the 1-NBDG assay and gene expression levels were discovered. This result highlights the need for a reliable functional glucose assay in addition to RT-qPCR for drug discovery and basic research.

Abstract No. P165

Modeling long-term host-microbe interactions with human intestinal organoid monolayers

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Clinical studies have linked the presence of specific bacterial strains in the gut microbiome with beneficial outcomes, yet the mechanisms of action are often difficult to resolve. This is in part caused by the lack of human *in vitro* models that allow the mechanistic analysis of host-microbe-interaction, especially for a prolonged duration of time, such as weeks rather than hours. To investigate host-microbe-interaction *in vitro*, we use patient-derived intestinal organoids, which preserve gastrointestinal region specificity, epithelial cell heterogeneity, and innate immune features. By growing human intestinal organoids as monolayers and applying previously reported differentiation media, we generated an apically accessible intestinal epithelium composed of differentiated enterocytes and mucus-secretory cells. To enable long-term colonization, we focused on the probiotic bacterium *Limosilactobacillus reuteri* (*L. reuteri*). While contact with pathogenic bacteria, such as Enteropathogenic *Escherichia coli* (EPEC), leads to cell death within the first 3-6 hours, direct contact with *L. reuteri* induces only mild epithelial cell responses while maintaining barrier integrity. We observed that epithelial cell responses differ according to the enterocyte maturation state in the small intestine. This model will now be used to address the question, whether secreted mucus is necessary to physically separate the colonic epithelium from a lumen-like environment containing probiotics to support long-term co-culture. Our approach highlights adult stem cell-derived intestinal organoids as physiologically relevant models for dissecting strain-specific probiotic mechanisms across different regions of the host–microbe interface.

Abstract No. P166

CELLnROLL: a gentle, parallelized 96-well cell sorting platform for low-input organoid and co-culture applications

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CELLnROLL is a novel cell sorting platform designed to address the limitations of conventional technologies when working with low-input and fragile samples. Standard cell sorting approaches often require large cell numbers, extensive preprocessing, specialized instrumentation, and frequently expose cells to significant shear stress during operation. These constraints restrict their use in emerging models such as tissue-derived organoids and co-culture systems, where sample availability is limited, cells are often fragile, and preservation of physiological states is critical for downstream applications. As a result, researchers are often forced to pool multiple samples to reach sufficient input, which dilutes the signal and obscures biological variability.

Here, we present CELLnROLL, a parallel cell sorting platform implemented in a standard 96-well plate format. The system distributes sorting reactions across individual wells, enabling simultaneous processing of multiple samples, targets, or conditions in parallel. This parallelized design allows scalable handling of low cell numbers while maintaining compatibility with standard laboratory workflows and infrastructure. The platform is microfluidics-free, avoids high-shear flow conditions, and completes sorting in as little as 10 minutes, helping preserve cells in their native physiological state.

CELLnROLL is particularly suited for applications involving limited sample input. The platform has demonstrated the ability to perform sorting with as few as 5,000 cells per well without impacting viability. In negative isolation of T cells from 10,000 PBMCs, CELLnROLL achieved a purity above 94%, while positive selection experiments reached near 100% purity, sufficient for sensitive downstream applications such as proteomics and sequencing.

By combining parallelization, low-input compatibility, and rapid, gentle processing in a scalable 96-well plate implementation, CELLnROLL provides a practical alternative to traditional cell sorting technologies. The platform is designed to enable future applications in organoid research, co-culture systems, immune profiling, and other settings where limited sample availability and the need for parallel processing are critical.

Abstract No. P167

Charité PRIMARY TISSUE PIPELINE: a central service platform to provide access to primary tissue for stem cell-based and biomedical research

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Human model systems, such as organoids and engineered tissues, serve as proxies for specific aspects of organ function. Patient-derived tumor organoids can capture oncogenic signaling within a patient-specific background, which can reveal mechanisms of therapy resistance. Additionally, advances in omics-based transcriptome, proteome, and metabolome analysis technologies offer invaluable tools for uncovering disease mechanisms and optimizing therapies. When combined with clinical data, these methods can enhance the predictive value of preclinical research and expand the possibilities for personalized medicine, ultimately benefiting patients. A structured and comprehensive access to primary tissue is essential for these advancements.

As one of Europe's largest hospitals, Charité provides both patient care and performs extensive biomedical research. During surgeries and medical procedures, tissues and cells are excised and withdrawn from patients—though only partially utilized for diagnostics.

With the "Primary Tissue Pipeline", we have established a central facility at the Charité – Universitätsmedizin Berlin that facilitates access to primary tissue for Charité researchers as well as external and industry partner. It serves as an interface between Charité as a hospital and the biomedical research community. The pipeline supports specific research projects by initiating and coordinating the sampling of human tissue. Specifically, it contacts relevant clinical departments, recruits patients and suitable biosamples, supports with application for ethical votes and builds up a project-specific logistic for sampling. The initiative serves as a central point of contact and takes on a pilot function in order to make the best possible use of the existing infrastructures at Charité.

This initiative enhances the stem cell based models and direct tissue cultures, promoting personalized medicine and regenerative medicine by bridging the gap between healthcare and research, while reducing reliance on animal models.

Abstract No. P168/T37

Characterization of naïve human neuroepithelial stem progenitor cells with unlimited self-renewal and broad neurogenic potential

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Cell lines derived from early embryonic stages have significantly contributed to our understanding of mammalian development, yet they predominantly reflect late developmental stages, following neural tube closure. The current human neural stem/progenitor cell (NSPC) models, such as rosette-like or radial glial-like cells, either represent later neurodevelopmental phases or fail to sustain long-term clonal self-renewal. Here, we report the successful isolation and long-term expansion of a tissue-derived human NSPC population that transcriptomically mirrors the human neuroepithelium at five weeks of in vivo embryonic development. These embryonic neural stem/progenitor cells (eNSPCs) display a distinct naïve, non-polarized, pre-rosette phenotype, distinct from previously described rosette-like and radial glial-like NSPC models. Notably, eNSPCs exhibit virtually unlimited self-renewal capacity and retain multipotent differentiation potential into diverse neural lineages of both the central and peripheral nervous systems—including dopaminergic neurons, V2a progenitors and interneurons, and neural crest derivatives. Multimodal analyses on both RNA and protein level, including single-cell RNA sequencing, immunocytochemistry, flow cytometry amd ATAC-sequencing, revealed that eNSPCs constitute a homogeneous population of multipotent stem cells, rather than a mixture of committed neural progenitors, with distinctive expression of early neurodevelopmental markers, lack of lineage commitment and broad differentiation potential. In comparison with other previously established NSPC models, eNSCPs exhibit a distinct transcriptomic profile that corresponds to earlier human developmental stages. Together, these findings establish eNSPCs as the earliest stabilized human NSPC model reported to date and highlight their value for studying early human neurodevelopment, lineage specification, disease modelling, and regenerative medicine.

Abstract No. P169/T39

Liver regeneration is programmed in the epigenetic landscape of cholangiocytes during fetal development

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Liver regeneration during chronic disease involves transdifferentiation of intrahepatic cholangiocytes into hepatocytes. This process implies that cholangiocytes have a unique capacity to switch of cellular identity in extreme conditions. The molecular mechanisms which establish this cellular plasticity in the human liver remain unclear. To address this question, we first assessed the transdifferentiation capacity of adult intrahepatic and gallbladder cholangiocytes using organoids. Despite a shared transcriptome, gallbladder organoids failed to activate hepatocyte markers, indicating a limited regenerative capacity. In parallel, we profiled genome-wide histone modifications and DNA methylation in intrahepatic and gallbladder organoids and their foetal progenitors. Our integrated analysis revealed epigenetic features associated with a permissive state at hepatocyte marker loci in intrahepatic cholangiocytes. In particular, intrahepatic cholangiocyte organoids showed increased H3K27ac enrichment and decreased DNA methylation at hepatocyte genes compared with gallbladder organoids. These hepatocyte markers are activated upon transdifferentiation of intrahepatic cholangiocytes to hepatocytes, suggesting that both histone marks and DNA methylation establish a competence towards hepatocyte fate. Notably, this signature is already present in hepatoblasts, the foetal progenitors of both hepatocytes and cholangiocytes during liver organogenesis. In contrast, this signature is absent in foetal gallbladder cholangiocytes, indicating that adult liver regeneration is developmentally programmed. To confirm the functional importance of epigenetic programming, small molecule inhibitors of epigenetic modifiers were added in culture conditions inductive for transdifferentiation in vitro. Under these conditions, adult gallbladder organoids induced hepatocyte markers upon transdifferentiation, supporting the role of epigenetic mechanisms in cholangiocyte plasticity. Together, our findings show that cellular plasticity of intrahepatic cholangiocytes is epigenetically programmed during foetal development to enable regenerative processes in the adult liver.

Abstract No. P170

Modeling neurodevelopmental diseases in 3D dorsal forebrain organoids

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Human cortical development relies on tightly coordinated regulatory programs controlling progenitor proliferation, neuronal differentiation, migration, and maturation. Disruption of these processes contributes to neurodevelopmental disorders (NDDs), including Bosch-Boonstra-Schaaf optic atrophy syndrome (BBSOAS) and Schaaf-Yang syndrome (SYS). BBSOAS is caused by haploinsufficiency of the transcription factor NR2F1, whereas SYS results from mutations in the imprinted gene MAGEL2, linked to regulation of post-transcriptional pathways.

We previously established CRISPR/Cas9-engineered hiPSC models to study both conditions in 2D hiPSC-derived cortical neurons by integrating multi-omics approaches. Using transcriptomic, epigenomic, chromatin accessibility, and chromatin conformation data, we characterized NR2F1-associated regulatory networks and inferred NR2F1 dosage-dependent gene regulatory networks, revealing stage-specific functions of NR2F1 in progenitor maintenance and neuronal lineage specification. MAGEL2-related defects were mapped by transcriptomics, proteomics, and ubiquitinomics, identifying imbalances in progenitor proliferation, neuronal maturation, migration, and synaptic development. Although these 2D models provide novel insights into the pathophysiology of these conditions, some of which may reflect broader pathogenic pathways shared with other NDDs, they do not capture key aspects of tissue architecture and cellular heterogeneity.

We are therefore currently characterizing 3D dorsal forebrain organoids (DFOs) derived from isogenic hiPSC lines modeling BBSOAS and SYS to study genotype-phenotype relationships in a context that more closely resembles the developing human cortex. We will apply single-cell multi-omics (combined transcriptomic and epigenomic profiling from the same cell) to resolve cell-type-specific regulatory states of NR2F1. As a next step, we plan to extend these analyses by studying MAGEL2, with the goal of incorporating emerging single-cell proteomics methods for both disorders to link regulatory states to protein-level changes across cell types.

Abstract No. P171

Hormone-responsive reproductive organoid interfaces for interpreting stem cell-derived EVs effects

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Human reproductive success is governed by a temporally coordinated dialogue between a hormone-conditioned endometrial niche and an implantation-competent trophoblast lineage. Stem cell-derived extracellular vesicles (EVs) have increasingly been discussed as cell-free mediators of tissue repair, immunomodulation, angiogenesis, and endometrial regeneration. However, their biological effects are often evaluated outside spatially organized, hormone-responsive epithelial–stromal–vascular systems that more closely reflect the implantation microenvironment. This limitation restricts mechanistic interpretation, translational safety assessment, and the rational positioning of EV-based reproductive interventions.

In this review, hormone-responsive reproductive organoid and spheroid interface models are discussed as emerging platforms for interpreting the context-dependent actions of stem cell-derived EVs. Particular attention is given to estrogen- and progesterone-conditioned endometrial epithelial and stromal compartments, epithelial polarity, extracellular matrix remodeling, angiogenic support, inflammatory regulation, fibrosis-associated signaling, and trophoblast-facing epithelial competence. These model systems provide a biologically relevant framework for examining how EV cargo may influence endometrial receptivity, stromal remodeling, vascular support, and implantation-associated cellular communication.

Importantly, stem cell-derived EVs should not be regarded as uniformly regenerative biological agents. Vesicular signals capable of promoting repair, angiogenesis, and epithelial–stromal recovery may also modify stromal permissiveness, epithelial plasticity, or invasion-associated pathways under conditions of aging, chronic inflammation, genetic susceptibility, or tumor-adjacent remodeling. Therefore, reproductive organoid-based models may serve not only as platforms for regenerative screening but also as early safety filters for detecting undesired pro-remodeling or pro-invasive responses.

By integrating reproductive stem cell biology, EV-mediated communication, organoid engineering, and computational interpretation, hormone-responsive reproductive organoid interfaces may contribute to more precise, safer, and mechanistically grounded approaches for endometrial dysfunction, fertility preservation, and gynecologic disease prevention.

Keywords: Organoids; Stem cell-derived EVs; Endometrial receptivity; Reproductive niche; Hormone-responsive modeling

Abstract No. P172

Integrating computational and stem cell-derived modeling of metabolic liver disease identifies vitamin B2 networks as tractable targets

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Human-induced pluripotent stem cell (hiPSC)-derived models are a widely used technology for drug testing; however, they often operate in isolation from computational drug predictions, limiting their full potential. Here, we integrate hiPSC-derived modeling into computational frameworks to improve disease network identification. We apply this strategy to metabolic dysfunction-associated steatotic liver disease (MASLD), identifying vitamin B2 networks as therapeutic targets. First, we developed MetaLiver, a digital systems biology platform harmonizing a MASLD-specific knowledge graph, bulk and single-cell transcriptomic patient data. MetaLiver positioned vitamin B2 networks as one critical target for hepatocyte dysfunction in MASLD. To iteratively refine and validate these predictions, we established and incorporated a hiPSC-derived MASLD escalation model into MetaLiver. The model induces metabolic crisis in hepatocyte-like cells (HLCs) by compounding free fatty acid excess, disease-aggravating extra-hepatic signaling molecules, and immune cell co-culture. Exposed HLCs mimicked metabolic injuries when benchmarked to patient transcriptomes, including mitochondrial dysregulation, reproduced across three hiPSC donors. Consistent with MetaLiver´s prediction, metabolic crisis in HLCs disrupted vitamin B2 network gene expression, which was reversible by its effector metabolite flavin adenine dinucleotide (FAD). FAD supplementation rescued major MASLD hallmarks, e.g. steatosis, mitochondrial dysregulation, and pathologic transcriptional programs, including fibrogenic signaling. We validated the anti-steatotic and pro-mitochondrial effects in primary human hepatocytes. For translational exploration, FAD-affected network nodes identified the candidate compounds aspirin, norleucine, and 3P that recapitulated pro-mitochondrial effects. Ultimately, we identified vitamin B2 network hub genes, using Cox regression analysis on an independent patient cohort (n =460) for discriminating liver events. This 19-gene hub-signature outperformed the clinical fibrosis marker FIB-4, positioning these signature genes as critical bottlenecks. Our study demonstrates how integrating stem cell-derived models with computational drug prediction expedites therapeutic discovery and reveals previously unknown pathways. Importantly, MetaLiver enables integration of any iPSC-line transcriptomic data for donor-specific network and drug response predictions (digital twin).

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