

Poster presentations

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Wednesday, 9 September

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Abstract No. P001**From data to dynamics: mechanistic modeling reveals heterogeneity and quiescence of hematopoietic stem cells***Ingmar Glauche^{1,*}, Yuri Garcia Vilela¹, Lars Thielecke¹, and Artur César Fassoni²*¹IMB, TU Dresden²Universidade Federal de Itajubá, Brazil

*Presenting author

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**

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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**

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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**

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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***Priyamvada Philip*, Ibrahim Hawwari, and Bernardo Franklin*

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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**

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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***Daniel Terheyden-Keighley*, Thomas Berger, and Boris Greber*

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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

- P012/T12** Slow genes are soft genes: lineage memory and perturbation sensitivity
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Ida Büschel
- P013** Cell-type-level negative matrix factorization (NMF) competes with deep
learning for integrative spatial transcriptomics embeddings
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cell-type-aware probe panel design
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marrow remodeling in multiple myeloma
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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***Christian Eger^{1,*}, Helene Hemmer¹, and Dominic Grün^{2,3}*¹ Julius-Maximilians-Universität Würzburg² Institute of Systems Immunology - University of Würzburg³ CAIDAS - Center for Artificial Intelligence and Data Science, Julius-Maximilians-Universität Würzburg, Würzburg

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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, MOFABLEX) 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***Prachurjya Panda^{1,*}, Dominic Grün^{1,2}, and Leo Rasche³*¹ Würzburg Institute of Systems Immunology² CAIDAS - Center for Artificial Intelligence and Data Science, Würzburg³ University Hospital of Würzburg

*Presenting author

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- κ B 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***Tiago Scarano, Rafaella Buzatu, Christian Schröter, and Micha Drukker*

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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***Destiny Aranovitch^{1, 2, *}, Anthony White^{1, 2}, and Lotta Oikari^{1, 2}*¹ QIMR Berghofer, Herston, Australia² The University of Queensland, Brisbane, Australia

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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 brain's 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***Saman Ghodsi*, Vista Tirandazi, Luca Gentile, and Kerstin Bartscherer*

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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/mm³), 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/mm³).

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**

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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***Franklin Lo^{1, 2, *}, and Ludovic Vallier^{1, 2}*¹ Berlin Institute of Health (BIH) at Charité² Max Planck Institute for Molecular Genetics, Berlin

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The liver performs a variety of functions, including metabolism of amyloid beta (A β), 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 A β 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 A β 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 A β 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 therotyping 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.

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Abstract No. P045/T33**ELAPOR2 controls pancreatic endocrine differentiation through cell cycle regulation***Oswaldo Rodrigues Pereira**, Kei Kozawa, Johanna Siehler, Ingo Burtscher, and Heiko Lickert

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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.

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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 escalate 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 differentiated 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***Felix Schuster*, Alexei Sirbu, Tobias Benkel, Sarah Heil, and Martin J. Lohse*

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*Presenting author

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 (β AR) signaling is the major regulator of cardiac contractility through modulation of intracellular cAMP levels in cardiomyocytes. While β_1 ARs dominate cardiac sympathetic responses, the contribution of β_2 AR 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_2 AR-mediated, indicating a β_2 -dominant neonatal receptor expression phenotype. To study β AR subtype selectivity, we further leveraged the LNP technology by co-transducing the β_1 AR. In this model, epinephrine exhibited higher potency and efficacy in cAMP signaling with clear β_1 AR and β_2 AR components. The β_1 AR co-transfected model showed sensitivity to landiolol inhibition, while the endogenous β_2 AR 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 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***Michael Derr, Soojung Shin, David Kuninger, and Tim Wessel**

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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**

Kinga Wrona , Benjamin Fischer, Karsten Rinas, Menglin Zheng, Fabrizia Zopetti, Marie Frühauf, Guerin Darvas, Ramon Oliveira Vidal, Tobias Bohnenpoll, Sandra Lubitz, Philipp Skroblin, Uwe Andag, Lavanya M. Iyer, Sara Klas, and Bastian Zimmer*

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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 (H₂O₂), 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 α SMA 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***Ferhat Ali Yaman^{1, 2, *}, Merrit Romeike^{1, 2}, and Ludovic Vallier^{1, 2}*¹Berlin Institute of Health (BIH) at Charité, BIH Centre for Regenerative Therapies, Berlin²Max-Planck-Institute for Molecular Genetics, Berlin

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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***Fabian Bachinger^{1, 2,*}, Pablo Carasa³, and Ludovic Vallier^{1, 2}*¹ Berlin Institute of Health, BIH Centre for Regenerative Therapies, Berlin² Max Planck Institute for Molecular Genetics, Berlin³ Clexbio, Oslo, Norway

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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 platform 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 characteristics 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***Thomas Berge**, and *Boris Greber*

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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 $\gamma\delta$ 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 $\gamma\delta$ T cells (CAR $\gamma\delta$ 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 $\gamma\delta$ T cell receptor (TCR) and a proprietary HCC-directed CAR enables the generation of CAR $\gamma\delta$ 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 $\gamma\delta$ 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 $\gamma\delta$ 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 $\gamma\delta$ 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 alternatives^{1,2,3,4}. 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.

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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 effective 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 hPSCs 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- β H1 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)***Stefan Löffler*

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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***Lili Rusznyak^{1,*}, Deepesh Dhakad¹, Ali Önder Yildirim^{1,2}, and Maja Funk¹*¹ Helmholtz Munich² Ludwig-Maximilians-University, Munich

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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***Rena Taher^{1,*}, Yu-Hsuan Chu^{1,2}, and Christian Schachtrup^{1,3}*¹ Institute of Anatomy and Cell Biology, Faculty of Medicine, University of Freiburg² Faculty of Biology, University of Freiburg³ Center for Basics in NeuroModulation (NeuroModulBasics), Faculty of Medicine, University of Freiburg

*Presenting author

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 endfeet, 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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*Presenting author

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., Baruwala, 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.

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