



GermanStemCellNetwork

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Stem Cell Research and Diseases II

Annual magazine of the GSCN

2020/21

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Welcome Note



Organoid generation is a field in stem cell research, which is developing at a remarkably high pace. Organoids represent miniature imitations of organs grown from stem cells. These mini-organs can be used to study disease mechanisms, accelerate the search for new drugs, avoid animal testing and even develop personalized treatment options for patients. Stem cells are also used to simulate the natural development of organs. Organoid systems make it easier to analyse the status of each individual cell and their interactions. The Organoid Cell Atlas, which is part of the Human Cell Atlas project, captures the molecular signature of each individual cell in different organoids and thereby also of their constituent stem cells.

During the coronavirus pandemic, stem cell-derived organoids of the lung and other organ systems have helped scientists to analyse coronavirus infection pathways. The ACE2 enzyme has been shown to be the entry receptor for the virus while approaches for blocking the receptor have also been identified. The emergency measure of the Federal Ministry of Education and Research, which was launched to fund research on COVID-19, supported the quick formation of consortia and projects to do research in these areas. Yet, using organoids to analyse virus infections is nothing new. Organoids were used to shed light on the disease mechanisms causing Zika virus infection and Zika-associated underdevelopment of the brain or microcephaly. They were also used to expedite the development of new drugs to treat Zika. Furthermore, organoid models are being used to investigate bacterial infections, for example those leading to gastrointestinal diseases (Helicobacter).

Advances are also being made in the development of stem cell-derived treatments in humans.

Two research consortia coordinated by the University Medical Center Göttingen are developing ways to treat heart disease with synthetically generated cardiac tissue that is based on induced pluripotent stem cells and partially on genetic correction. The aim of these collaborative projects is to launch clinical trials for application in humans. Similar clinical trials to apply pluripotent stem cell derivatives in humans have already been launched at international level to treat other diseases, for example degenerative eye disorders such as macula degeneration and retinitis pigmentosa as well as diabetes and Parkinson's disease.

The German Stem Cell Network is an important platform for collaboration and exchange that enables Germany to make practical use of the opportunities offered by stem cell research for treating severe diseases and raise awareness of these novel approaches. I am therefore particularly delighted that the German Stem Cell Network and the Berlin Institute of Health concluded an agreement in early 2021 on their close and long-term collaboration to operate a platform for dialogue on stem cell research.

Thomas Rachel, MP
Parliamentary State Secretary
to the Federal Minister of Education and Research



We
are the
GSCN

Preface

Last year, Emmanuelle Charpentier and Jennifer A. Doudna received the Nobel Prize for Chemistry „for the development of a genome editing method.“ Drawing on the new „CRISPR/Cas9“ gene scissors technology, researchers can alter the genetic material of animals, plants, and microorganisms with extremely high precision and ease. To illustrate the revolutionary influence of this technology on stem cell research, it is worth taking a mental journey back a few years. Before genome editing it was very tedious and difficult to introduce gene modifications into mammal cells by homologous recombination. That was „state of the art“ in those days, hence M.R. Capecchi, M.J. Evans, and O. Smithies rightly won the Nobel Prize in 2007 for their discoveries of „Principles of introducing specific gene modifications in mice by the use of embryonic stem cells.“

In 2006, Shinya Yamanaka published a groundbreaking method for reprogramming mouse somatic cells into pluripotent stem cells (iPS cells or iPSCs), for which he received the Nobel Prize in 2012. In 2007, it was already possible to reprogram the cells of patients into iPSCs, so that different aspects of a disease could be investigated in the petri dish. The development of the Zinkfinger technology, the TALEN technology, and in particular the CRISPR/Cas9 technology have enabled the introduction and repair of mutations in iPSCs with relative facility! And it has since become possible to derive some extremely interesting structures from stem cells that are very similar to parts of human organs.

A White Paper on these so-called organoids was published late last year. That work was the fruition of the constructive collaboration among the German Stem Cell Network (GSCN), the Interdisciplinary Working Group (IAG) *Gene Technology Report* of the Berlin-Brandenburg Academy of Sciences and Humanities (BBAW), and the Berlin Institute of Health (BIH). These three institutions aim to raise public awareness of this exciting research field and stimulate an interdisciplinary public debate about organoids. The „BIH & GSCN Lecture“ with Jürgen Knoblich on brain organoids in November 2020 marked yet another successful public event. Discourses of this nature can provide decision-makers in the areas of politics and economics with valuable information and support into technologies and their potential for human welfare.

The tireless dedication and work of many researchers have given rise to a partnership between the GSCN and the BIH. Thanks to this partnership, the GSCN can look forward to a stable and strong future of continued support for many years to come. I owe a special debt to the GSCN, and I would like to especially acknowledge the support of former presidents Hartmut Geiger and Andreas Trumpp and the current Managing Director Daniel Besser. This partnership will enable these two groups to join their forces and foster

synergistic interactions on a new „stem cell research dialog platform.“ The platform will serve as a foundation for establishing and promoting joint activities such as conferences, workshops, training sessions for young scientists, or events for the general public.

The BIH has as its mission the discovery and creation of innovations in medicine for the improvement of the welfare and quality of life of humans. As a member of the Max Planck Society, I very much support and promote this endeavor. The work of my division relates first and foremost to basic research that is aligned closely with the underlying principle of the Max Planck Institute of „Insight must precede application.“ As new insights to improve human welfare and quality of life may arise through research in the field of stem cells, it is essential to maintain an open dialog with scientists whose goal is to transform such insights into medical applications.

I was very much looking forward last year to the GSCN conference in Ulm. Unfortunately, the meeting was only a virtual event due to the pandemic. Nonetheless, the digital conference was highly successful, and we are hopeful and cautiously optimistic that we can build on that success in person at the onsite conference at the Ulm research site on 6 – 8 October 2021.

I hope that you enjoy reading our annual magazine and gain insights and inspirations from the contributions for furthering your own research. Stem cells hold tremendous potential for the welfare and quality of life of human beings and I hope that you can help realize their immense potential and contribute to advancing research in this exciting field!

Best regards,



Hans Schöler
Active President





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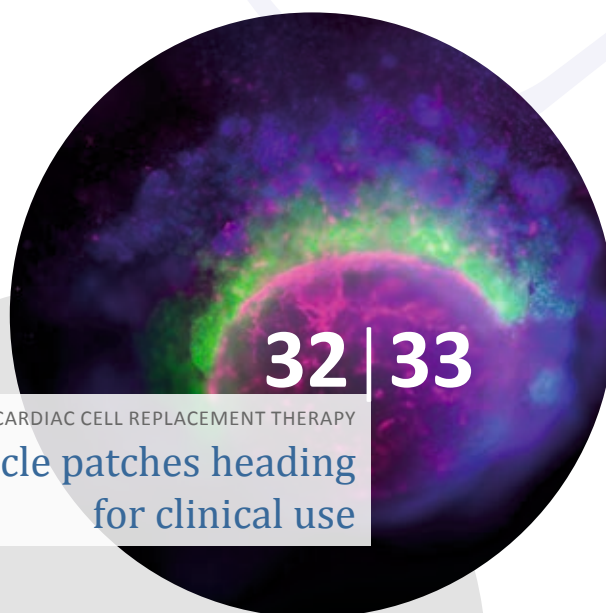


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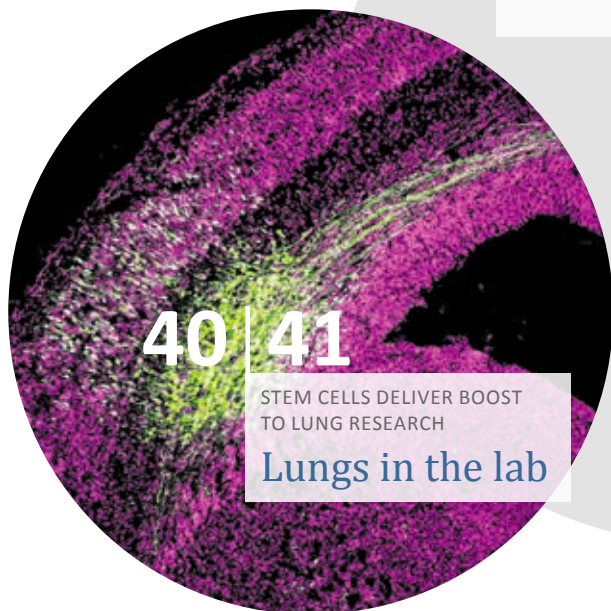
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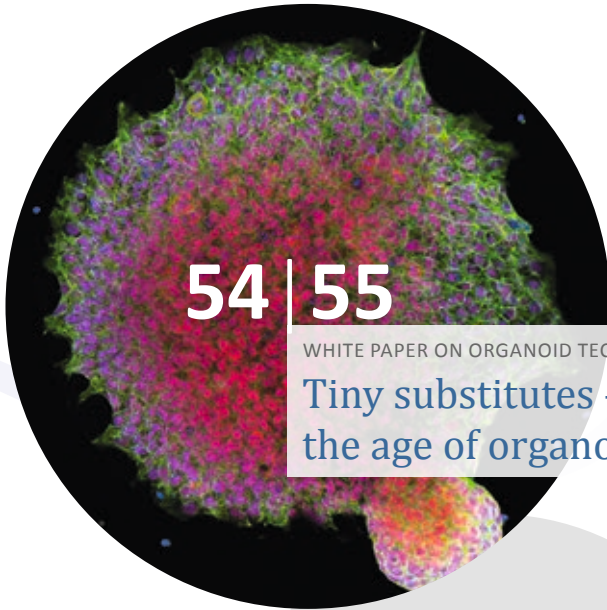
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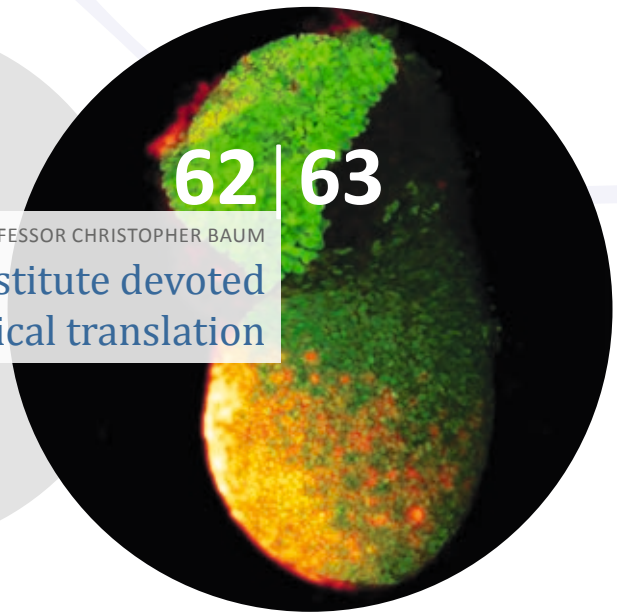
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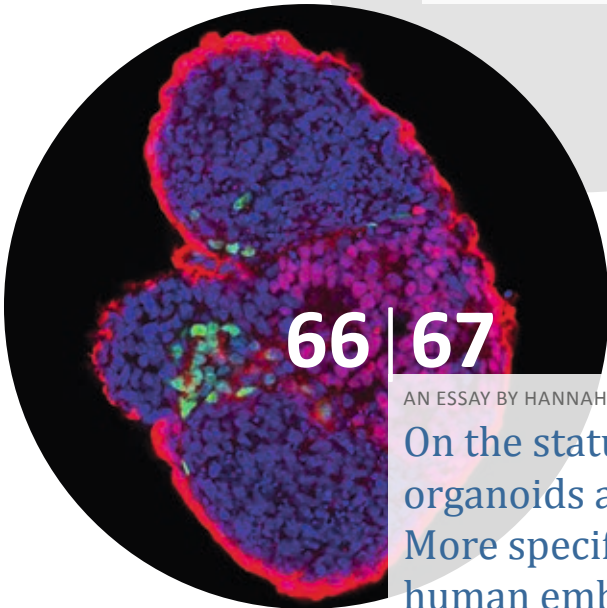
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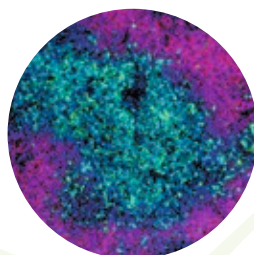
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A new phase for the GSCN:
Dialog Platform
Stem Cell Research

The new GSCN President Hans Schöler is starting a new phase with the stem cell network: beginning in 2021, the GSCN and the Berlin Institute of Health (BIH) will cooperate with each other on a long-term basis and establish the joint „Dialog Platform Stem Cell Research“. For Hans Schöler, the cooperation means new networks and a source for new energies. This fits in well with his hope to emerge from the pandemic times by 2021. The interview was conducted by Stefanie Mahler.

GSCN: On 1 January 2021, the GSCN entered a close partnership with the Berlin Institute of Health (BIH). The two organizations have co-founded the ‘Dialog Platform Stem Cell Research’, which will be attached to the BIH Center for Regenerative Therapies. What does this partnership mean for the GSCN?

Hans Schöler: Through this partnership, the GSCN is gaining a key strategic partner to achieve common goals. Both institutions pursue the goal of fostering the translation of academic insights into medical applications for the benefit of patients. The GSCN promotes and supports a network of German stem cell researchers across a range of disciplines and boasts a wide range of international connections. The BIH is involved in a much broader range of research, but also has a focus on stem cell research and associated technologies. We are both committed to the objective of fostering the translation of academic insights into practical applications and improving the environment for doing so. There is significant overlap between the GSCN and BIH, and the Dialog Platform Stem Cell Research, co-founded by the two organizations, pursues a shared objective. The platform is aimed at forging contacts between a wide range of scientists, promoting networking through conferences and workshops, and enhancing the way science is communicated using a range of formats, of which some have been previously developed by the GSCN. The BIH will benefit from greater depth and internationalization in stem cell research and enjoy networking benefits. The GSCN will gain long-term stability and financial security, which, by enabling to plan ahead with confidence, should endow the network with new vigor.

What are your goals for the Dialog Platform for the next two years of your presidency?

Over the next two years, we want to fill our partnership with the BIH with life. That will include integrating BIH scientists into GSCN working groups to form joint Dialog Platform working groups. We will be setting up and developing joint initiatives aimed at encouraging talented young researchers. These will range from travel awards and poster prizes to training courses. We also want to develop joint projects and organize both scientific and public events.

Photo: Max Planck Institute of Molecular Biomedicine



Hans Robert Schöler has been conducting research as Director of the Department of Cell and Developmental Biology at the Max Planck Institute for Molecular Biomedicine in Münster since 2004. He received his PhD degree from the Center for Molecular Biology at the University of Heidelberg in 1985. In 1999, he accepted a professorship in reproductive medicine at the School of Veterinary Medicine of the University of Pennsylvania, United States, and served in that position for five years. He also holds several full and associate professorships in Germany, the United States, and South Korea. Hans Schöler has received numerous prizes and awards, including the Robert Koch Prize, the Kazemi Prize, and the Max Delbrück Medal. He is an elected member of the German Academy of Sciences Leopoldina and numerous other academies. In 2010, the Hans Schöler Stem Cell Research Center (HSSCRC) was formally inaugurated in his honor at the Ulsan National Institute of Science and Technology in South Korea. Hans Schöler is on the board of the International Society for Stem Cell Research (ISSCR).

Specifically, we are already planning a joint session at the virtual 2021 ISSCR Annual Meeting and want to shape a joint BIH-GSCN presence within the international stem cell research world.

As President through to 2022, I hope to be able to help ensure that the partnership between the BIH and the GSCN is positive and constructive. Over these two years I am looking forward to a further White Paper, hopefully real-life conferences, and tangible mutual benefits.

We also want to take a more detailed, in-depth look at the issue of affirmative action programs for women, fine tune the conceptual basis for such programs and further develop modules aimed at encouraging talented young researchers.

My dream would be to help to remove or at least lower barriers that are impeding the translation of basic research into successful treatments.

How will the GSCN's autonomy be preserved in light of the GSCN's close partnership with the BIH?

In legal terms, the GSCN is a nonprofit organization. It operates as a network of scientists and is open to members. Members include natural persons people – the individual scientists and other people with an interest in stem cell research – and organizations – research institutes and companies involved in stem cell research. From a legal point of view, the GSCN and BIH have completely different structures, with the BIH in 2021 having become part of Charité – Universitätsmedizin Berlin. Through the Dialog Platform Stem Cell Research, we have successfully established a structure that enables us to work together while

maintaining the GSCN's autonomy as a scientific society. The interests of the GSCN will continue to be managed by an elected executive board in consultation with the larger GSCN management board, and its resolutions and activities will continue to be implemented by the GSCN office. As from 2021, however, this office will be largely financed by the BIH. The GSCN's autonomy is not impacted in any way – that was important to both organizations and is explicitly set out in the partnership agreement.

With a look to joint activities, the GSCN and BIH have co-founded the Dialog Platform for Stem Cell Research, which organizes and hosts workshops, conferences, and White Papers.

The coronavirus pandemic meant that the GSCN held most of its events online in 2020. How did you experience this, for example the virtual Annual Conference?

Looking back on 2020 and all those virtual conferences, workshops and meetings, there are, from my point of view, both advantages and disadvantages. For a conference like the 8th Annual GSCN Conference, I found it good that I could easily switch between sessions, put on a pair of headphones and really concentrate, and I found it easier to take notes than I do in most conference rooms. A further advantage is that it's easier to get international speakers on board for virtual lectures. I'm not sure, for example, that all of our keynote speakers would have been able to travel to Ulm for the conference. Speakers like Christine Mummery (Leiden NL), Bertie Göttgens (Cambridge, UK), Shahragim Tajbakhsh (Paris, FR), Jonathan Kimmelman (Montreal, CAN) and Marius Wernig (Stanford, US) are very much in demand and are often drowning in conference invites.

What I certainly missed, however, is the face-to-face discussions after sessions and having a beer with other scientists. And a meet-the-expert session is just a lot more fun when you're sitting around an actual table together. I also definitely missed the GSCN WunderBar at the ISSCR in June, originally scheduled to take place in Boston. It's a wonderful event which has become something of a tradition and enjoys a great reputation. Meeting up virtually just isn't the same, so I'm very much hoping that we will all be able to get together for the 9th GSCN Conference in Ulm. As the conference is not due to take place until October – specifically 6–8 October 2021 – I am cautiously optimistic that it will be able to go ahead. Networking is quite simply crucial, especially for younger researchers, but also with partners in the business sector. Being able to see the latest equipment in the flesh is incomparably better than viewing it virtually.

Which scientific achievements impressed you the most in 2020?

There have been quite a number of interesting advances well worthy of mention, but what has impressed me time and time again is the consistent progress Masayo Takahashi has been making. She has previously performed and published a number of clinical studies involving induced pluripotent stem cells (iPSC). She has published some excellent papers on retinal differentiation and on organoids derived from pluripotent cells. Right from the outset, she has taken the approach that reconstructing the photoreceptor layer will require tissue transplantation. In 2017, she and her team carried out the first successful procedure to transplant iPSC-derived retinal cells into the eye of a patient with advanced neovascular age-related

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macular degeneration. During the operation, a sheet of approximately 250,000 retinal pigment epithelial cells from donor-derived iPSCs was transplanted into the patient's eye.

Her next step is both logical and exciting – she is planning a clinical trial using organoids to treat patients with retinitis pigmentosa. She is planning to transplant tiny sheets of retinal progenitor cells cut from retinal organoids. The idea is that, once in the patient's eye, over a period of several months the retinal progenitor cells should mature into functional photoreceptors. She and her team published a paper demonstrating that this is in principle possible in 2018. Their experiments were able to demonstrate functional maturation of human ESC-derived retinal sheets (human embryonic stem cells) following transplantation in mice. Although there are other types of retinal cells that were not produced, this procedure could restore visual function in a retina in which complete photoreceptor degeneration has taken place. I am very much looking forward to seeing the results.

Regenerative medicine repeatedly touted as a vision for the future. Despite this, we still seem to be making slow progress in realizing rapid translation into practical applications and successful treatments. What, in your opinion, are the main obstacles to a more rapid translation process and how can they best be overcome?

I think we're still facing the same problems that were outlined in the German Stem Cell Network's 2018 white paper "Translational Medicine – from stem cells to future technologies". That White Paper described several key problems and potential solutions. The ongoing coronavirus pandem-

ic highlights the importance of being able to move quickly, and that's much easier if you remove unnecessary barriers on the one hand and promote the creation of structures conducive to this objective on the other. I'd like to highlight two examples here – one of unnecessary barriers and one of structures conducive to this objective.

One problem is restrictions on how stem cells can be used. Under the German Stem Cell Act (Stammzellgesetz), hESC-derived cells can be used in clinical trials, as these trials are considered a research activity. But if we got to the point where hES cells were to be routinely used to produce cell products for clinical applications, that would be prohibited under the Stem Cell Act. This restriction is significantly hindering the translation process. The ability to make non-research use of ES cells to manufacture cell products for developing treatments is simply indispensable. Otherwise, we are developing procedures in Germany which will only be able to be used overseas. If the Stem Cell Act is not amended on this point, our only hope is that one day we will be able to generate induced pluripotent stem cells which are equal in quality to hES cells.

It would be conducive to this objective if there were clinical trials units specializing in advanced therapy medicinal products (AMTPs) at German university hospitals. Stem cell researchers, clinicians and regulatory authorities coordinating closely at such clinical trials units would provide a major boost.

I am very much looking forward to seeing what new developments will arise in this exciting research field and, together with GSCN members, hope to be able to contribute to these developments.

Max Planck Institute for Molecular Genetics (MPIMG)

Research at the Max Planck Institute for Molecular Genetics (MPIMG) concentrates on genome analysis of man and other organisms. It is the overall goal of all MPIMG's groups to gain new insights into the development of diseases on a molecular level, thus contributing to the development of cause-related new medical treatments. Work at the MPIMG is characterized by a genome-wide approach to scientific questions. In this context, the very close connection between experimental and computational methods has become a major feature of all departments

and research groups at the institute in recent years. MPIMG researchers are interested in questions of epigenetic regulation and work on a better understanding of gene regulation networks for tissue formation and homeostasis, as their dysfunction may result in numerous diseases. In this context, stem cell research is gaining increasing importance.

Max Planck Institute for Molecular Genetics
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www.molgen.mpg.de



GSCN News

GSCN & BIH launch Dialog Platform Stem Cell Research

At the turn of the year, the GSCN entered into a close partnership with the Berlin Institute of Health (BIH). The two organizations will now work together to expedite the translation of stem cell innovations into clinical applications. To this end, they have co-founded the Dialog Platform Stem Cell Research, aimed at enhancing networking between national and international stem cell researchers. Joint activities will include conferences, workshops and mutual working groups. The legal structure of both organizations will, however, remain unchanged. The partnership means that the GSCN is now financially secure for the next four years.

White Paper on organoids

In November 2020, the GSCN and the Interdisciplinary Research Group (IAG) *Gene Technology Report* of the Berlin-Brandenburg Academy of Sciences and Humanities (BBAW) published a White Paper entitled "Organoids – from stem cells to future technologies". With this White Paper, they hope to raise public awareness of organoid research and to stimulate an interdisciplinary public debate on the issue. The White Paper includes a GSCN report on organoids, which offers an overview of the latest developments in the field and potential applications. The report includes viewpoints from national and international researchers, stakeholders from current projects, and companies involved in organoid research. This is followed by the working group's key points and recommendations on the use of organoids. To find out more, see the article on p. 55.

The white paper can be downloaded in PDF form in English or German from www.gscn.org.



The "GSCN Hilde Mangold Award" rewards outstanding female scientists and role models

Awarded annually, the GSCN Female Scientist Award has now been rebranded as the GSCN Hilde Mangold Award. The new name is in recognition of German embryologist Hilde Mangold (born 20 October 1898 in Gotha; died 4 September 1924 in Berlin). Mangold performed key experiments which paved the way for the discovery of the embryonic organizer, thereby playing a seminal role in the development of embryology. Her early death in a

tragic accident prevented her from being honored together with Hans Spemann when the latter was awarded the Nobel Prize for the discovery of the organizer effect in 1935.

The annual GSCN science prize is bestowed on outstanding female stem cell researchers. In addition to scientific achievement, the jury also aims to recognize the award winner's lifetime achievement as a role model for young female scientists. As before, women continue to be under-represented in stem cell research leadership positions at universities and research institutes.

European consortium for communicating gene and cell-based therapy information

Complementing the work of EuroStemCell, February 2021 will see the launch of a European consortium for communicating gene and cell-based therapy information to the general public. Sponsored by the EU, the project is entitled EuroGCT. The project is being led by the EuroStemCell team in Edinburgh and, with more than 47 European partner institutions from 16 countries, is a Europe-wide initiative. It is expected to attract significant interest from sections of the general public. The EuroStemCell website will remain in place and continue to provide helpful information on all aspects of stem cell research. The GSCN is an active partner in both EU projects.

A very different 2020 Non-PI Meeting went virtual

Very different, but normal for 2020 was the verdict on the 2020 Non-PI Meeting. The online event was held on 22 September. 13 participants attended from Germany and Switzerland. An online format meant that the meeting was able to go ahead despite the coronavirus pandemic. The four-hour get-together was planned as an open discussion



forum for young scientists to discuss technical and conceptual challenges relating to their research and solutions to methodological problems. Participants shared their thoughts on their research projects, key points in protocols and procedures, the latest technologies, cell culture reagents, and molecular biology. The meeting also offered opportunities for networking, exploring potential collaborations, and career planning. The meeting was organized by Germán Camargo Ortega (Basel, CH), Verena Börger (Essen), and Mona Vogel (Ulm) who were all very enthusiastic about the course of meeting. "The information shared at the meeting really is an invaluable asset for participants. It is indispensable for young scientists' careers and I'm sure will help them and their laboratories to advance towards their goals." The event concluded with a shared online escape room experience in the evening.

The next Non-PI Meeting will take place on 5 October, 2021 in Ulm. It will be a hybrid event, so that anyone will be able to take part online, even if they are not in Ulm. It's a great opportunity to talk to others in a similar position and solve problems!

UniStem Day 2020

UniStem Day 2020 was held on 6 March, 2020, just before the first lockdown. At the time there was great uncertainty as to whether it would be possible for events to continue, and if so, how they would be held. Many institutions canceled their planned UniStem Day events at short notice. Other in-



stitutions went ahead with their events only after putting in place suitable precautions and highlighting infection control measures, or with a much-reduced program. How the event was run varied greatly around the world, with many school classes and institutions canceling at short notice. Due to the subsequent lockdown and the focus on the pandemic, no reliable statistics for participant numbers are available. The GSCN events which did go ahead, for example in Berlin, were once again very successful.

GSCN affirmative action program for women

In 2020, the GSCN, through the Christiane Nüsslein-Volhard Foundation, supported Anna Döser with her research into tumor immunology in ovarian cancer.

The young mother is a physician performing her research at University Hospital Bonn. Commenting on the GSCN grant, she said, "The grant is aimed at giving female scientists with children the mobility and freedom they need to progress in their careers. Being relieved of domestic duties and having greater flexibility really did give me a fantastic feeling of freedom which I have been able to use for my research. Employing household assistance, for example, means that I no longer have to spend my evenings doing housework, but can instead spend time at my desk. This has freed up two or three evenings a week that I can use for work."



Anna Döser

Photo: Anna Döser, privat

Leibniz Institute on Aging – Fritz Lipmann Institute (FLI)

Research for better aging

The Leibniz Institute on Aging – Fritz Lipmann Institute (FLI) has dedicated to biomedical aging research since 2004. More than 350 employees from around 40 nations explore the molecular mechanisms underlying aging processes and age-associated diseases. The main aim of research at FLI is to delineate how aging leads to the development of tissue dysfunction and diseases in the elderly. If the understanding of the aging process contributes to the extension of healthy lifespan, the strains on society can be minimized and the society's future development

will be enriched by the wealth of knowledge and experience older people possess.

As one of 96 institutes of the Leibniz Association, the FLI is publically funded by the German Federal Ministry of Education and Research (BMBF) and the State of Thuringia.

Leibniz Institute on Aging –
Fritz Lipmann Institute (FLI)
Beutenbergstraße 11 · 07745 Jena
www.leibniz-flj.de



GSCN website relaunch

The GSCN has started the process of revamping its website. While the website boasts some excellent content, it has fallen behind the times technically. The English-language pages will feature a new format and new visuals. New format means that the website is now resized and the colors freshened up on smartphones and tablets, enhancing readability. In terms of content, much has changed, and at the same time very little has changed. Much in that we have streamlined and restructured many of the pages. Very little in that, if you dig down, you can still find the same treasure trove of content as before – our network can rest assured that this content has not been lost. The GSCN looks forward to the website continuing to be enthusiastically used by members, conference delegates, journalists, patients, and broad sections of society. Naturally, the website is still to be accessed at: www.gscn.org.

Photo: GSCN



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Understanding Stem Cells The conference for schools

German and English-language GSCN school materials updated

In 2020, the GSCN's material for schools, hosted at stammzellen-verstehen.de and understanding-stemcells.info, was updated with new content, and existing content was refreshed and adapted for use in online teaching. In January 2021, one teacher was enthusiastic enough to give us the following feedback, *"While looking for new material for my high school biology course in North Rhine-Westphalia, I quickly came across your website. I found the material and the website so interesting that I tried it out right away. So far (Basics and Ethics), the concept has also proved suitable for use for online learning and even for independent computer work (where the teacher is not present due to a teachers' meeting). In addition to the expertise with which the material has been prepared and the fact that it is very up to date, a key factor for me was that preparing a lesson using your material saved me a lot of time. It's very rare that I am satisfied with material from external sources. Because I have been benefiting from your material for two weeks now, I was eager to provide you with some feedback."* We hope that these words of praise from a teacher will encourage you to warmly recommend the material for schools to others!

GSCN Stem Cells for Life posters in English

In the beginning of 2021, the GSCN will be producing English versions of its Cells for Life poster series. The posters will then be available, together with a range of background information, at stemcells4life.info. Like the German-language version at zellenfuersleben.de, the posters are available for download free of charge on the GSCN website – enabling a complete exhibition on stem cells for use in institutions, schools or at public events to be produced in no time at all. So be sure to check it out!



Photo: Sabine Wörmde, Uni Ulm

Bavarian research association ForInter

Human brain cell interaction

The research group ForInter aims to investigate the complex cell and molecular biological interactions of different cell types in the human brain in multidimensional, highly innovative cell culture systems. Our consortium is unique in Bavaria as an interdisciplinary research network of this kind. Under the leadership of the Friedrich-Alexander-Universität Erlangen-Nürnberg, scientists with basic biological and translational expertise in neurobiology and neurology, neuropathology, bioinformatics as well as legal and ethical aspects of genetic

engineering lay a foundation for application-oriented research of the human brain.

ForInter's new platform for functional analysis of the brain is intended to contribute in the long term to intervention strategies and therapies for diseases of the nervous system.

Funded by:
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2020 Conference Report

8th GSCN Annual Conference

23 – 25 September 2020

VIRTUAL 

In 2020, everything was new and different: what in spring 2021 seems like the best possible alternative to a physical conference, was a pioneering act in July 2020. Due to hygiene regulations and travel restrictions in the Corona Pandemic, the GSCN Annual Conference took place online. The goal behind it: To create the complete program with all elements as a digital likeness of an actual GSCN Annual Conference within three months. The online experiment succeeded: With 364 participants, 45 talks, 22 sessions, 22 exhibiting companies and 109 posters, the GSCN moved its conference online. The effort behind it was enormous for all parties involved: agencies, new techniques and new forms of communication had to be found and tested by the GSCN office, the speakers created online presentations, online posters could be enhanced with multimedia, companies moved their booths with new formats online – many questions and not always clear answers accompanied this joint expedition into virtual uncharted territory.

The Annual Conference was an excellent event, and everyone involved had a great time getting to grips with the new format. Of course, there were some technical glitches, such as the loss of some chairs or somewhat blurred images due to low network bandwidth at participants homes, and less communication among the conference participants and the companies. The biggest loss was certainly the lack of networking during the breaks and social meetings. Intensive exchange in conversation is simply more difficult in the net. In summary, it was a great conference – with considerable scientific output.

Headquarter in Berlin: 10 persons organized the GSCN Conference and were responsible for the technical and logistic issues of the virtual conference.



109

Poster

5

International
Keynote
Lectures

ethics

6

International
Highlight Talks

22

Sessions

10

National
Highlight Talksstem
cells

1

Non-PI Workshop

Extras

- Point-of-discussion: Sars-CoV-2/ COVID-19 and approaches with stem cells with Christine Mummery
- Membership Meeting
- Board meetings

1

ELSA Symposium

22

Industry exhibitors

3

GSCN Awards

50
Europe12
International302
Germany

364

Conference Participants

99 Students (27,2 %)

265 Regular (72,8 %)

networks

3

Meet-the-Expert-Tables

COVID-19

stem cell therapies

clinical studies

embryoids & organoids

2020 Conference Report

Five exciting international keynotes

On the morning of 23 Sept. 2020, more than 200 conferees had gathered in front of their screens to participate in the 8th virtual GSCN Annual Conference. They were warmly welcomed by GSCN President Hartmut Geiger and then introduced to the online systems used to broadcast the talks (Zoom) and present the posters and GSCN affiliates (iPoster) as well as to the web etiquette. After the technical briefings were done, the scientific program started.

The first keynote presentation of the scientific program was delivered by **Shahragim Tajbakhsh** from Institute Pasteur in Paris. The group of Shahragim Tajbakhsh has been using a combination of genetically modified mice and ex vivo artificial niches to investigate the heterogeneity and fate potential of adult skeletal muscle stem cells (MuSCs). MuSCs can be maintained through symmetric (SCDs) and asymmetric (ACDs) cell divisions, yet how and when these divisions occur in vivo in vertebrates is poorly understood. His group developed a clonogenic cell tracing method that demonstrates the asymmetric distribution of transcription factors along with old and new DNA in mouse muscle stem cells during skeletal muscle regeneration directly in vivo. Further, by combining single cell tracking and artificial niches ex vivo, they showed that cells can switch modes in consecutive divisions, suggesting that they are not dedicated to an obligate mode of cell division. Regarding stem cell heterogeneity, diverse properties and gene regulatory networks define MuSCs in different anatomical locations (e.g. head vs. limb). Although MuSCs derived from extraocular muscles (EOM) have a higher regenerative capacity than those derived from limb muscles, the molecular determinants that govern these differences remained undefined. The Tajbakhsh lab showed that EOM and limb MuSCs have distinct DNA methylation signatures associated with enhancers of location-specific genes,

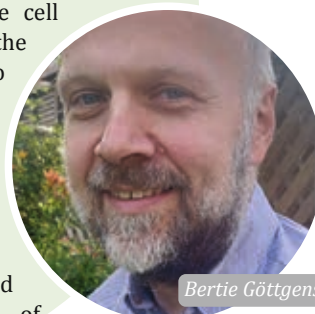
Shahragim Tajbakhsh

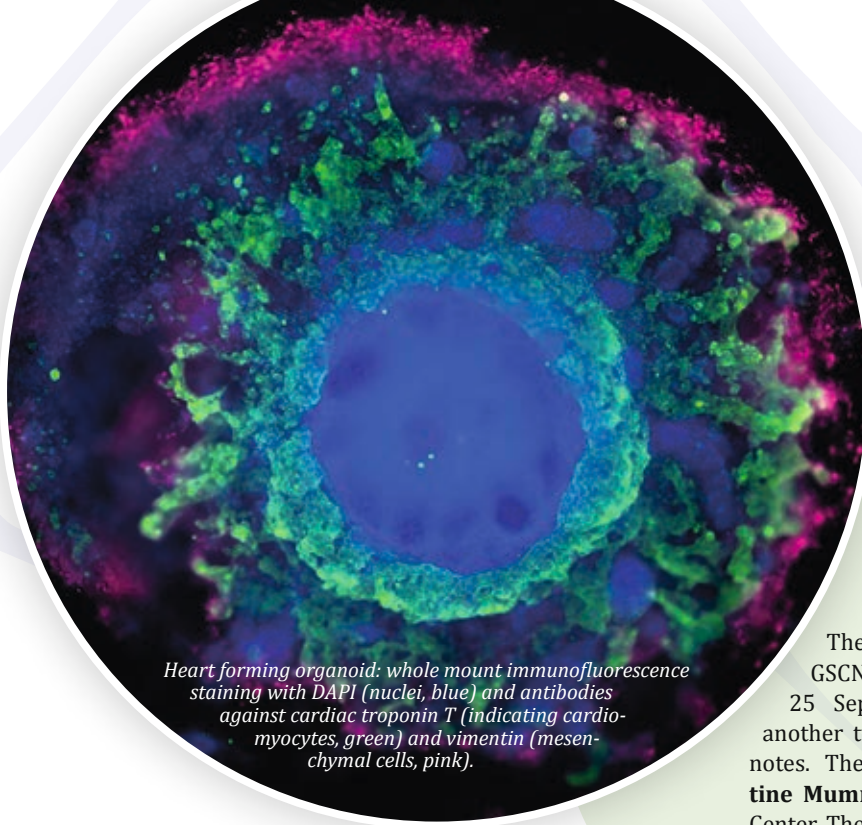


and that the EOM transcriptome is reprogrammed following transplantation into a limb muscle environment. Notably, EOM MuSCs expressed host-site specific positional Hox codes after engraftment and self-renewal within the host muscle. However, about 10% of EOM-specific genes showed engraftment-resistant expression, pointing to cell-intrinsic molecular determinants of the higher engraftment potential of EOM MuSCs. Taken together, these studies highlight the molecular diversity of distinct modes of division that muscle stem cells adopt in different scenarios that solicit a flexibility in cell plasticity.

The second keynote of the afternoon was given by **Bertie Göttgens** (Cambridge, U.K.). The Göttgens group uses a combination of experimental and computational approaches to study how blood stem cells develop, and how mutations in stem/progenitor cells can cause leukemia. Recent work has focused on applying single cell genomics technologies to the early stages of mouse embryo development, when the first blood cells are generated. Datasets of hundreds of thousands of cells have been generated for both wild type embryos, as well as embryos that carry mutations in key regulatory genes for early blood development. Integrated analysis of both single cell gene expression and open chromatin datasets has been instrumental to clarify the regulatory hierarchies of transcription factors responsible for early blood formation. In parallel studies on the adult blood system, the group has applied computer modeling to derive a mathematical framework that can capture experimental data generated by three different laboratories to obtain a quantitative description of the dynamical nature of blood stem cell function. This computational framework is not only useful to interpret normal blood stem cell behavior but is also being used to model the deleterious consequences of mutations that can corrupt normal stem cells to turn into leukemia stem cells.

Bertie Göttgens





Heart forming organoid: whole mount immunofluorescence staining with DAPI (nuclei, blue) and antibodies against cardiac troponin T (indicating cardiomyocytes, green) and vimentin (mesenchymal cells, pink).

Jonathan Kimmelman



Traditionally, the keynotes on the first conference evening provide the link to the discussion of ELSA issues around the GSCN Annual Conference and continue during the second day with the ELSA Symposium (see below). Thus, on Wednesday evening, the presentation by **Jonathan Kimmelman** (McGill University, Montreal, Canada) concluded the first day. Jonathan Kimmelman and his research group (STREAM) study ethical and social dimensions of clinical development of new treatment strategies. Kimmelman formerly chaired the ISSCR's ethics and public policy committee and co-chaired the ISSCR committee that developed Guidelines for Stem Cell Research and Clinical Translation in 2016. His work is guided by the premise that even the most technical aspects of research conduct are saturated with ethical judgments. Kimmelman's talk at GSCN built on his work uncovering various practices in preclinical and clinical research that frustrate the process of redeeming the public and patient investments in the enterprise of clinical development. He began by describing how initial research efforts aimed at addressing the COVID-19 pandemic laid bare numerous common research deficiencies, including poor study design, biased analysis and reporting, and a lack of coordination. He then used COVID19 research as a prism through which to view similar, recurrent challenges cell-based intervention research efforts. The talk closed by connecting these reflections with various policy statements on the ethical conduct of clinical research, including the ISSCR Guidelines for Stem Cell Research and Clinical Translation.

Christine Mummery



The final session of the GSCN conference on Friday, 25 September 2020 featured another two highly fascinating keynotes. The first was given by **Christine Mummery** (Leiden University Medical Center, The Netherlands). Her group has worked for many years creating models for cardiovascular disease based on pluripotent stem cells (hPSCs) and has used these for understanding disease mechanisms as well as detecting cardiotoxic effects of drugs and sensitivities associated with particular genotypes. Simple monolayer cultures of hPSC-cardiomyocytes or vascular cells have usually proven adequate for this purpose even though the cells are immature and fetal like. For example, by measuring contraction, action potential and calcium transients simultaneously in hPSC-cardiomyocytes, the group demonstrated that they could predict the toxic effects of a groups of test drugs with almost 80% accuracy, compared with less than 70% in primary rabbit cardiomyocytes. For some purposes though, immature cells in 2D culture are insufficient to capture disease phenotypes. Mummery gave two examples that showed the benefits of 3D culture of multicell type structures: the first, she combined cardiomyocytes, cardiac fibroblasts, and cardiac endothelial cells in "microtissues" consisting of just 5,000 cells. In these microtissues, the cardiomyocytes showed a remarkable degree of maturation including the formation of (post-natal) transverse tubules (T-tubules). By replacing each of the cell types in the microtissues with a diseased variant, she was able to show that cardiac fibroblasts carrying a PKP2 desmosomal gene mutation induce arrhythmia in microtissues in which the cardiomyocyte were normal and healthy. This indicated that fibroblasts in the heart can contribute to the phenotype in patients with arrhythmogenic cardiomyopathy. Mummery also gave an example of a vascular disease in which the vascular cells behaved identically as the healthy isogenic controls in 2D vascular networks but the lumenized vessels were distinctly abnormal in 3D microfluidic "Organ-on-Chip" models. These more complex cell systems based on hPSCs are paving the way forward for a new generation of disease models for understanding disease mechanisms and drug discovery.

The final presentation of the Annual Conference 2020 was yet another highlight lecture by **Marius Wernig** from the Institute for Stem Cell Biology and Regenerative Medicine at Stanford University. His lab of works on mechanism of cell lineage identity and on developing new approaches for cell therapies in the brain. Wernig discussed a recent project focused on Pelizaeus-Merzbacher disease, a fatal monogenetic leukodystrophy caused by mutations in the PLP1 gene. Wernig described how his lab used patient-derived induced pluripotent stem cells (iPSCs) and genetically corrected, isogenic cells to assess the impact of PLP1 mutations from two severely affected PMD patients. Genetically corrected iPSC-derived oligodendrocyte precursor cells (OPCs) showed functional correction in vivo as seen by restorative myelin formation after transplantation into myelin-deficient mice. These data provide proof of concept that a combination of reprogramming, gene engineering, and differentiation is a therapeutic path for myelin disorders and establish iPSC derived OPCs as viable platform for cell therapy in the brain. He further reported that PLP1-mutant, iPSC-derived iOPCs were formed normally but underwent apoptosis upon further differentiation. Unexpectedly, UPR and ER stress path-



Marius Wernig

ways were not activated as the mutant protein was transported to the cell membrane. Instead, it was found that mutant cells were critically sensitive to iron which caused secondary lipid oxidative stress. Gene-corrected OPCs were largely insensitive to increased iron. Pharmacological iron chelation rescued mutant cells in vitro and upon transplantation into hypomyelinating mice. OPCs from PLP-mutant jimpy mice also showed enhanced survival and differentiation upon iron chelation. These results suggest the intriguing possibility that simple iron chelation therapy might be beneficial at least for a subset of PMD patients. In a second approach, Wernig discussed his lab's investigations on the use of bone marrow transplantation to replace endogenous microglia with circulation-derived myeloid cells (CDMCs). The Wernig lab found that liberating microglial niche factors by microglia depletion is critical for robust differentiation and incorporation of CDMCs. Consequently, a combination of bone marrow transplantation conditioning and pharmacological depletion of microglia with a CSF1 receptor inhibitor resulted in near complete replacement. Wernig reported that current efforts center on the understanding of the cellular mechanisms of CDMC recruitment and to evaluate proof of principle therapeutic potential of this impressive brain reconstitution.

Photo: privat

Fraunhofer Institute for Cell Therapy and Immunology IZI



The Fraunhofer Institute for Cell Therapy and Immunology IZI investigates and develops solutions to specific problems at the interfaces of medicine, life sciences and engineering. One of the institute's main tasks is to conduct contract research for companies, hospitals, diagnostic laboratories and research institutes operating in the field of biotechnology, pharmaceuticals and medical engineering.

The Fraunhofer IZI develops, optimizes and validates methods, materials and products for the business units Cell and Gene Therapy,

Drugs and Diagnostics. Its areas of competence lie in cell biology, immunology, drug biochemistry, bioanalytics and bioproduction as well as process development and automation. The research focus is on developments in the field of immunoncology and infection research.

The institute works in close cooperation with hospital institutions and performs quality tests besides carrying out the GMP-compliant manufacture of clinical test samples. Furthermore, it helps partners obtain manufacturing licenses and permits.

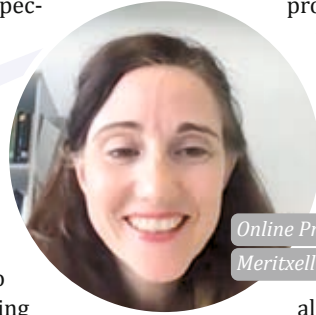


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The Presidential Symposium: GSCN Awards 2020 and Presidential Invite

In the afternoon of the second day of the conference, the Presidential Symposium brings further scientific highlights to the participants. The symposium includes a lecture by special invitation of the president and the three winners of the GSCN awards of the respective year.

In 2020, GSCN President Hartmut Geiger had invited **Meritxell Huch** from the Max Planck Institute for Molecular Cell Biology in Dresden to deliver a lecture. The Group of Meritxell Huch has developed liver and pancreas organoids from both mouse and human adult tissues and exploited them to gain basic molecular and cellular understanding of the biology of these two organs across scales. In her talk, Huch first described one of the molecular mechanisms involved in duct-mediated liver regeneration. The



Online Presenter
Meritxell Huch

group has recently learned that in liver cells, the transition from a unipotent to a bi-potent proliferative state requires the active de-methylation mediated by TET1 to transcriptionally activate the genes involved in regenerative program including components of the Erbb as well as YAP/TAZ hippo pathway. This activation is essential both in vitro, during organoid initiation and in vivo, during the damage-regenerative response. In addition, the group also described that the signaling that mediates this transition is derived, in part, from the portal mesenchyme. Switching gears to pancreatic system Huch also discussed their new protocol to establish human pancreas organoids from biopsies (even frozen tissue) and how these expand long term while retaining their genetic stability over time. This new human

Photo: GSCN

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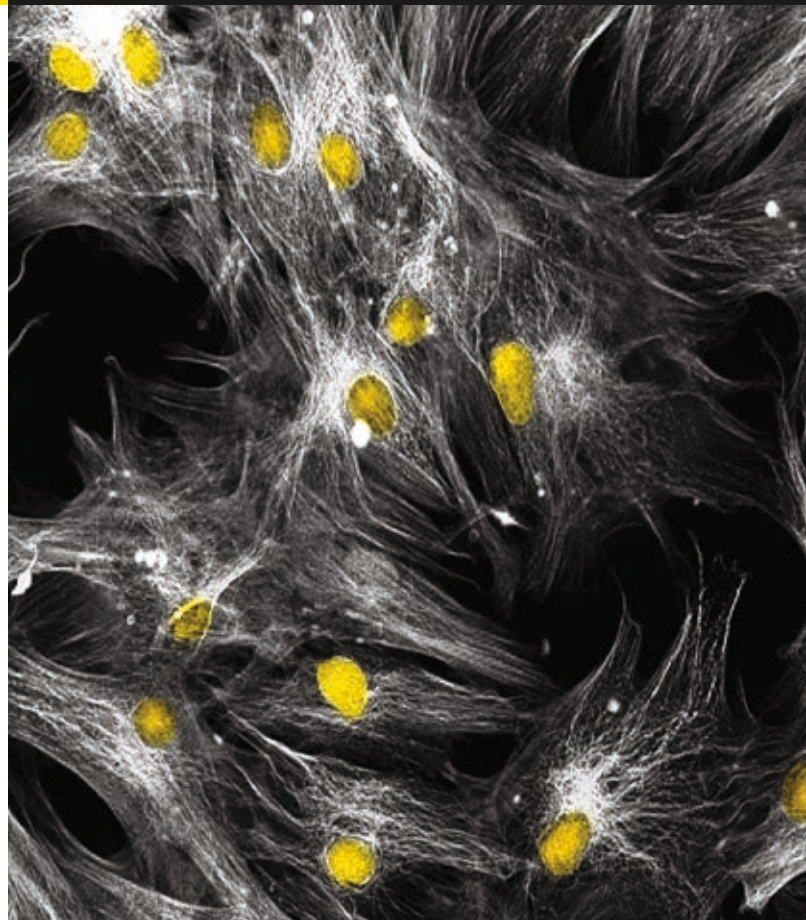
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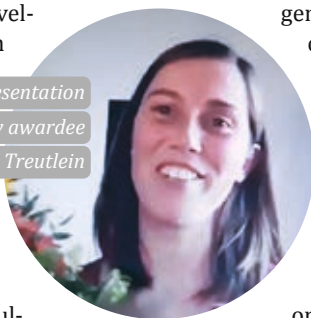
Simplifying Progress



pancreas ductal organoid culture medium also supports the growth of pancreas cells in a chemically defined fully biomimetic extracellular matrix. In summary, Huch shared the newest results of her research team on liver and pancreas organoids and their vision on how these can be used to gain basic understanding of the mechanisms of human organogenesis and repair.

The **GSCN 2020 Young Investigator Award** was presented to **Barbara Treutlein** for her seminal research on tackling differentiation on a single-cell level. Although being already a well-established researcher first at the MPI for Evolutionary Anthropology, Leipzig and since 2019 as Professor for Quantitative Developmental Biology at the ETH Zürich D-BSSE, Switzerland, it was just in 2012 that she finished her PhD at the LMU Munich, still making her eligible for the prestigious GSCN Junior Award. Her group uses and develops single-cell technologies in combination with stem cell based three-dimensional culture systems to study human organogenesis. In her talk, Treutlein first focused on their work on brain organoids to understand human-specific features of brain development. She first presented a single-cell transcriptomic analysis of human brain organoid development from pluripotency that revealed the emergence of diverse neuronal fates within the dorsal and ventral forebrain, mid-brain and hindbrain regions. Her group found that brain region composition varies in organoids from different iPSC lines, yet regional gene expression patterns are largely re-

Online presentation
by awardee
Barbara Treutlein



producible across individuals. They also compare human, chimpanzee and macaque cerebral organoid development using both single-cell RNA- and chromatin accessibility (ATAC)-sequencing and identify expression and gene regulatory features that are specific to humans. In the second part of her talk, she discussed new lineage recording strategies to explore dynamics during brain regionalization in organoids. She presented data from a new method called iTracer that couples reporter barcodes, inducible CRISPR/Cas9 scarring, and single-cell transcriptomics to analyze lineage relationships during organoid development. They used iTracer to infer fate-mapped whole organoid phylogenies over a scarring time course, and to reconstruct progenitor-neuron lineage trees within microdissected cerebral organoid regions. They show that the system is compatible with spatial transcriptomics, which revealed clonal enrichment in distinctly patterned brain regions. Finally, she showed new data from long term 4-D light sheet microscopy that enabled in toto temporal tracking of nuclei over 100 hours of cerebral organoid development. Altogether, the work sheds light on how fates emerge and mature during human brain organoid regionalization, and the techniques can be adapted in any pluripotent stem cell-derived cell culture system.

The **GSCN 2020 Female Scientist Award** was presented to **Edith Heard** (European Molecular Biology Laboratory, Heidelberg). The Award was presented for her important contributions to our understanding of X-chromosome inactivation. To achieve dosage compensation, one of the two X chromosomes is converted from the active euchromatic state into inactive heterochromatin during early female

Photo: GSCN

Max Delbrück Center for Molecular Medicine in the Helmholtz Association (MDC)

Excellent stem cell research at the MDC in Berlin

The Max Delbrück Center for Molecular Medicine is one of the world's leading biomedical research institutes. Many of the MDC's scientific teams at its two Berlin locations are using stem cells and organoids in their research. For example, they modify muscle stem cells using CRISPR-Cas to develop therapies for previously incurable muscle-wasting conditions. They are growing mini-tumors from cancer stem cells to test the efficacy of drugs. They are also attempting to cultivate egg cells from

reprogrammed skin cells of the northern white rhino in a bit to save the endangered species. One technology platform provides expertise on iPSC cell lines, another on organoids. „We offer excellent infrastructures and are further expanding our facilities,” says Professor Thomas Sommer, the Scientific Director of the MDC (interim). „Our organoid platform pools expertise and opens up new avenues to study the development of organs, such as the kidney, intestine and liver, or neuronal diseases.”

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Photo: Katharina Bohn/MDC

development. Unlike autosomes where both chromosomes are active, one of the two X chromosomes must be inactivated in females, otherwise there is early death of the embryo. Ensuring the right balance of proteins and nucleic acids in the cells of an organism is essential for life. In many organisms, males and females differ thanks to their sex chromosomes and this can lead to major imbalances in gene dosage. In mammals, males have one X and one Y chromosome, while females have two X chromosomes. However, the gene doses of one chromosome has to be sufficient to allow proper development and cellular function. Thus, in female cells one X chromosome becomes silenced at random and this silencing process is then propagated through cell divisions. The underlying mechanisms are of major importance for the function of embryonic stem cells

Online: Flowers
for the Awardee
Edith Heard



and for early developmental stages. This classic epigenetic process, results in the transcriptional silencing of over a thousand X-linked genes. A central role in this process is played by the non-coding RNA Xist which is the main effector in this process.

Xist together with its RNA binding partners induce the transcriptional silencing and early chromatin changes, both of which contribute to the initiation of gene repression. Heard showed in her presentation that an early loss of H3K27 acetylation via HDAC 3 is a central facilitator of the initiation of X-inactivation. Her research team also analyzed the function of the Xist RNA binding partner, SPEN, which turns out to be a key regulator of the initiation of gene silencing, via its SPOC domain which acts as a landing platform for multiple factors. SPEN is targeted to the



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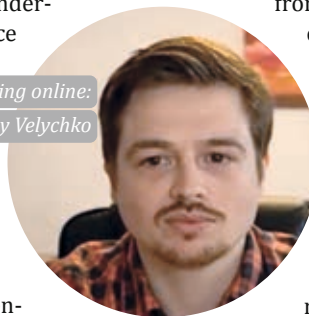
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X-chromosome by the Xist RNA and binds specifically to active promoters and enhancers but then disengages from chromatin as soon as transcriptional silencing begins. In addition to its early role in gene silencing on the X-chromosome, SPEN also acts to dampen expression of genes that escape from X-chromosome inactivation in differentiated cells where the inactive X is globally silent. The dampening of escaping genes by SPEM could be important for the maintenance of appropriate dosage of factors and protein complexes which are required in a specific stoichiometry. These findings have implications for our understanding of gene regulation and the importance of correct dosage in development and in disease including cancer and sex-biased metabolic autoimmune disorders.

The publication that was selected for the **Best Publication of the Year 2020** was Velychko, S. ..., Schöler, H.R. Excluding Oct4 from Yamanaka Cocktail Unleashes the Developmental Potential of iPSCs. 2019, *Cell Stem Cell*, 25, 737-753. **Sergiy Velychko** (Max Planck Institute for Molecular Biomedicine, Münster) reported in his award speech that

Presenting online:
Sergiy Velychko



Oct4 was thought to be the most irreplaceable factor of the Yamanaka cocktail, which can reprogram somatic cells to an embryonic stem cell-like state called induced pluripotent stem cells (iPSCs). The research group of Hans R. Schöler found that, contrary to this dogma, Oct4 can be omitted during the induction of pluripotency from mouse somatic cells; and Sox2, Klf4, and cMyc (SKM) combination is sufficient for the reprogramming process. Velychko et al. found that the simultaneous expression of Sox2 and cMyc

triggers immediate retroviral silencing independent

from the induction of pluripotency, which could explain the discrepancy with many previous studies that used retroviral delivery system to drive reprogramming. The ability of SKM to generate iPSCs challenges the recently proposed “seesaw model” of pluripotency, describing it as a tight equilibrium of opposing differentiation programs. While iPSC technology delivered a major breakthrough in stem cell research, multiple studies showed that the developmental potential of OSKM iPSCs does

not quite match that of ‘gold standard’ embryonic stem cells (ESCs). Velychko et al. showed that SKM delivers more faithful epigenetic reprogramming resulting in iPSCs with the highest developmental potential reported to date. Tetraploid complementation experiments revealed that SKM iPSCs were on average 20 times better in supporting full term development of all-iPSC mice; SKM all-iPSC mice were also significantly more likely to survive till adulthood when compared to OSKM all-iPSC animals. These results show that Oct4 overexpression is a double edge sword: it increases efficiency and kinetics of the reprogramming process, but on the other hand, its promiscuous genomic

From 2021 on it was decided by the GSCN Board to name this award the **“GSCN Hilde Mangold Award”** to commemorate one of the great German developmental biologists who discovered the Spemann-Mangold-Organizer. Hans Spemann received the 1935 Nobel Prize in Physiology or Medicine for this seminal finding. However, since Hilde Mangold tragically died in 1924 in an accident aged only 25, she could not be awarded.

Photo: GSCN

Fraunhofer Institute for Production Technology IPT

Innovative solutions for stem cell research and production

As a production engineering research institute, the Fraunhofer IPT offers many years of in-house experience in production processes, metrological systems, process automation and quality management. In cooperation with researchers from academia and industry, we use our know-how to develop technical systems for quality control, handling and processing stem cells. The fields of application range from manufacturing and research on structured surfaces for the guided differentiation through mechanotransduction to fully automated

platforms and processes for the adaptive production of stem cells. This way we develop innovative and tailored solutions together with our partners and customers.

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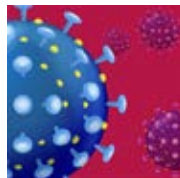


binding in somatic cells drives off-target gene activation and worsens the quality of iPSCs. The study brings about important ramifications for the future development and application of the iPSC technology.

Three more publications from July 2019 to June 2020 also got an honorary mentioning from the award committee showing the excellence of national stem cell research. These were:

- **Paczulla AM, ..., Lengerke C.** Absence of NKG2D ligands defines leukemia stem cells and mediates their immune evasion. 2019, *Nature*, 572, 254-259
- **de Laval B, ..., Sieweke MH.** C/EBP β -Dependent Epigenetic Memory Induces Trained Immunity in Hematopoietic Stem Cells. 2020, *Cell Stem Cell*, 26, 657-674
- **Collombet S, ..., Heard E.** Parental-to-embryo switch of chromosome organization in early embryogenesis. 2020, *Nature*, 580, 142-146.

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The GSCN Scientific Sessions

The GSCN annual conferences are not only characterized by the excellent scientific keynote lectures – these provide the framework for the conference – but especially the contributions in the parallel sessions of the GSCN working groups always clearly show the exciting research that is being done by GSCN members and other conference participants. Here is a selection of a few spotlights, but there are many more presentations that would deserve to be mentioned here.

Tianliang Sun (Novartis Institutes for BioMedical Research, Basel, Switzerland) presented data in the session “Somatic stem cells and development” showing the plasticity of liver epithelial cells during homeostasis, regeneration, and tumor formation. Using CRISPR screening in biliary epithelial cell (BEC) derived organoids followed by in vivo validation, YAP and mTOR are identified as key signaling pathways for establishing a ductular reaction (DR). Single cell analysis of EPCAM+ BECs within a DR further reveals novel heterogeneity within the BEC pool. Moreover, unlike in many other tissues, WNT responsive hepatocytes are not liver stem cells during homeostasis. Upon injury, WNT/beta-catenin signaling is activate throughout the liver and drive hepatocyte proliferation. Constitutive active WNT/beta-catenin pathway by deletion of its negative regulators ZNRF3/RNF43 leads to the formation of hepatocellular carcinoma.

Jay Gopalakrishnan from the laboratory for centrosomes and cytoskeleton biology, Heinrich-Heine-University of Düsseldorf, presented the use of human brain organoids in modeling glioma invasion behavior in the session on “Organoids: new models for diseases”. His laboratory used patient-derived glioma stem cells and imaged their invasion patterns and their interactions with neurons of host organoids. Notably, the organoids-based invasion assay could distinguish the invasion behavior of primary versus recurrent gliomas exemplifying the use of brain organoids as a 3D substrate for a personalized glioma invasion assay. Besides revealing the biology of glioma stem cells, the described assays promise to conduct drug screening assays to identify candidate drugs that perturb glioma stem cell invasion.

Jennifer Steens (University Hospital Essen) presented data in the session “Stem cells in regenerative therapies: mesenchymal stromal cells” showing that lung resident mesenchymal stem cells (LR-MSCs) are located within the vascular stem cell niche, the so-called vasculogenic zone of adult lung arteries. Primary isolated LR-MSCs presented typical MSC characteristics in vitro and were phenotypically and functionally indistinguishable from MSCs derived from the vascular wall of adult human blood vessels (VW-MSCs). Moreover, LR-MSCs expressed the VW-MSC specific HOX genes (HOXB7, HOXC6, HOXC8) suggesting that LR-MSCs should be considered as VW-MSCs. Besides, immunofluorescent analyses of non-small cell lung cancer (NSCLC) samples revealed the mobilization and activation of LR-MSCs in NSCLC progression indicating that LR-MSCs may act as tumor supporting cells. These findings provide new insights into the role of MSCs in normal lung physiology as well as in pulmonary diseases.

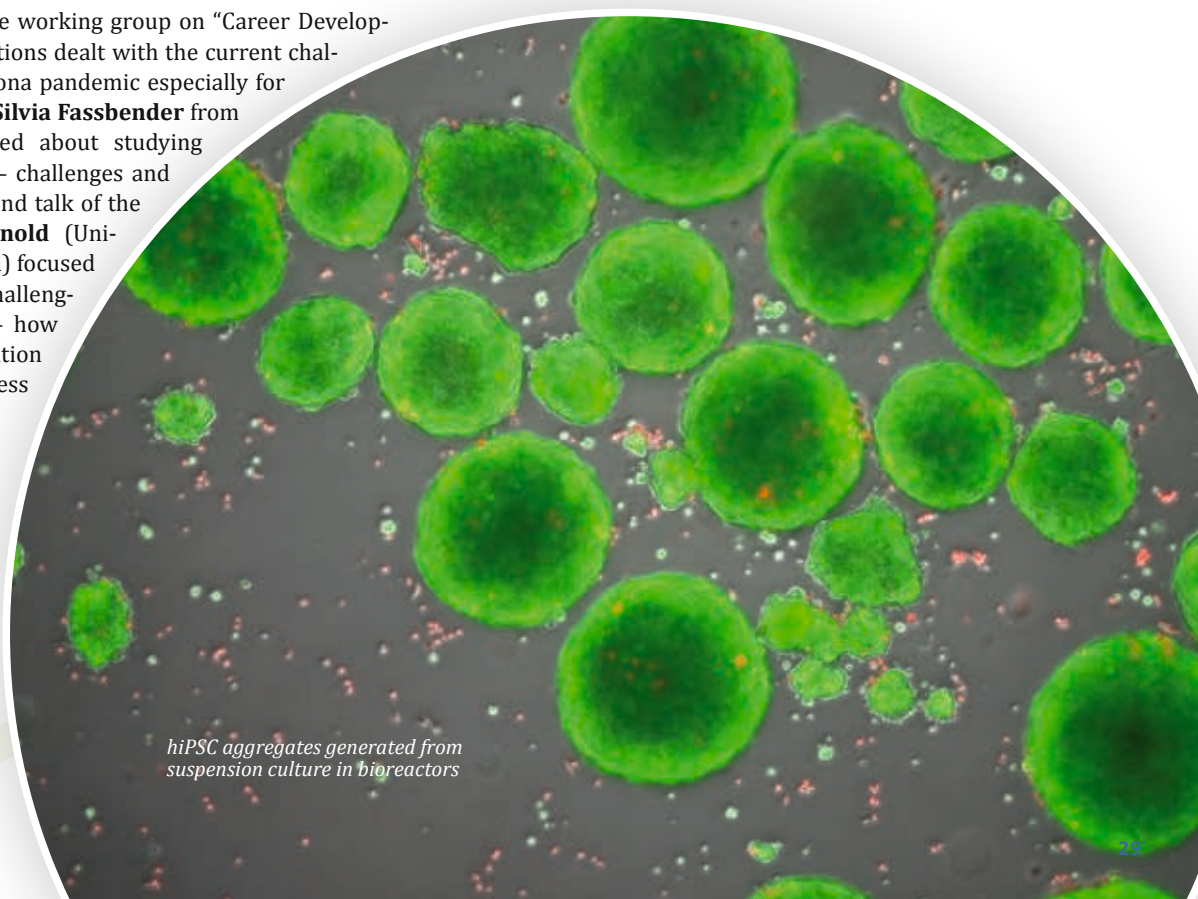
Matthias Pawlowski from the Department of Neurology at the University Hospital Münster presented data in the session “Pluripotency and reprogramming” showing that human pluripotent stem cells can be rapidly converted into microglia, the resident immune cells of the central nervous system (CNS). The method relies on inducible, transient overexpression of master transcription factors from genomic safe harbor sites and enables the manufacture of pure cultures of microglia in less than three weeks without relying on cell enrichment steps. The microglia are characterised by expression of typical microglia markers on mRNA- and protein-level, cluster with primary human microglia in RNA-seq analysis and display typical physiological microglia-functions. When cocultured with human, tau-mutant cortical neurons, microglia display increased production of reactive oxygen species and a disease-associated dystrophic phenotype, thus enabling large scale drug discovery tests for neurodegenerative disease.

The GSCN Strategic Sessions

The GSCN Working Group: “Technologies in Stem Cell Research” had assembled a highly interesting session on spatial resolution transcriptome analyses a technology that becomes increasingly important, for example in the assembly of the Human Cell Atlas. The three speakers in the session were **Simon Haas** from the Max-Delbrück-Center (MDC)/Berlin Institute for Molecular Systems Biology (BISMB) in Berlin who recently joined the institute coming from the DKFZ & HI-STEM in Heidelberg. Haas talked about single-cell and spatial multi-omics approaches of the bone marrow stating that their pioneering work will also help other to develop similar approaches in different tissues. **Nikos Karaiskos** (from MDC/BISMB in Berlin as well) followed suit and talked about spatial transcriptomics: recent advances and how to solve puzzles. He focused on their work on differentiation in *Drosophila* and Zebrafish as well as description of different cell types in mammalian tissue like the liver or the intestine using spatial information on transcriptional profile with a technology called novoSpaRc (de novo Spatial Reconstruction of Single-Cell Gene Expression). Finally **Mats Nilsson** (SciLifeLab, Stockholm University) talked about high resolution anatomical mapping of gene expression using targeted in situ sequencing. He focused on the development of the nervous system in mice and the different cell lineages in the mouse brain. Nilsson also represented the efforts of a Swedish consortium in the Human Cell Atlas initiative.

In the session by the working group on “Career Development” two presentations dealt with the current challenges with the Corona pandemic especially for young researchers. **Silvia Fassbender** from TU Darmstadt talked about studying in times of Corona – challenges and solution. In the second talk of the session **Daniel Hunold** (University of Greifswald) focused on motivation in challenging times: Corona – how to boost your motivation and reduce your stress NOW.

In the session on “Clinical trials and regulatory affairs” **Peter Bader** (University Hospital for Children and Adolescent Medicine Goethe University Frankfurt) presented his experience and views in the use of mesenchymal stromal cells for immunomodulatory effects in several clinical settings. His talk entitled “Mesenchymal stromal cell (MSC) therapy for the treatment steroid refractory graft versus host disease (GvHD) and severe COVID-19 diseases?” In Bader’s talk he showed the difficulties with these therapies especially due to the different quality of different preparations. The treatment of GvHD with MSCs is in the meantime well established and clinical studies are proceeding. He also gave an outlook of possible treatment with MSC for COVID-19 although these studies are still in its infancy. The second talk of the session was delivered by **Núria Montserrat Pulido** from Institute for Bioengineering of Catalonia, Barcelona. Her talk was entitled “Engineering solutions from human pluripotent stem cells differentiation: from organoid derivation to disease modeling applications”. She presented approaches to elucidate mechanisms of SARS-CoV-2 infections in human cells using organoids also focusing on the function of ACE2 as the entry receptor of SARS-CoV-2. She also gave an outlook on improving the culture techniques to generate organoids with matured cell types and additional cell types of the different tissues.



hiPSC aggregates generated from suspension culture in bioreactors

ELSA-Symposium

The interdisciplinary exchange on ethical, legal, and social aspects (ELSA) of stem cell research was continued during the 8th GSCN Annual Conference with a virtual symposium, organized by Sara Gerke (Cambridge, USA) and Tobias Cantz (Hannover) during 23 and 24 September 2020, in order to promote active communication and scientific exchange between stem cell researchers, ethicists, and lawyers. This year's program included presentations on data privacy in personalized (regenerative) medicine by **Fruzsina Molnar-Gabor** (Heidelberger Akademie der Wissenschaften) and on human germline editing in the era of

CRISPR-Cas by **Sebastian Schleiden** (PTHH Vallendar und Fernuni Hagen) and provided the basis for intensive online discussions with the approximately 35 participants of the online symposium. Preceding this ELSA discussion round, a keynote lecture was integrated in the main conference program, in which **Jonathan Kimmelman** (McGill University, Montreal, Canada) discussed appropriate clinical translation frameworks for stem cell-based therapies in reflection to disputable activities of clinical studies targeting the COVID-19 pandemic.

Poster Prizes

Poster awards and 500 Euro, sponsored by the GSCN member Takara and Thermo Fisher Scientific went to:

- **Dirk Loeffler**, ETH Zurich, D-BSSE, Basel, Switzerland: "Asymmetric cell division modulates human hematopoietic stem cell fates" (Session „*Hematopoietic stem cells and application*“)
- **Elisa Donato**, DKFZ & HI-STEM, Heidelberg: "Identification of molecular and functional roles of leukemic stem cells that drive DNMT3A mutant AMLs with distinct clinical outcomes" (Session „*Stem cells in disease: cancer stem cells*“)
- **Julia Dahlke**, Hannover Medical School (MHH): "Implementing and validating efficient genetic safety switches for future application of iPSC-derived cell transplants" (Session „*Stem cells in regenerative therapies*“)
- **Undine Haferkamp**, Fraunhofer IME Screeningport, Hamburg: "Interfacing human induced pluripotent stem cell-derived neurons with designed nanowire arrays as a future platform for medical applications" (Session „*Stem cells in regenerative therapies*“)

Wrap-up and outlook to 2021

Many presentations and of course the organization of the GSCN Conference 2020 dealt with the Corona virus pandemic. It significantly changed our lives throughout 2020 and into 2021. In order to give the virtually assembled scientists at the GSCN Annual Conference arguments for the daily debate on research with stem cells in the treatment of COVID-19 and the mechanism of infection of the SARS-CoV-2 viruses, the GSCN working group "Patient Information (Stem Cell Therapies)" with Ira Herrmann (Bonn) and Richard Schäfer (Frankfurt) had organized a session „Points-of-discussion“. **Christine Mummery**, who has organized the ISSCR COVID-19 networking meetings and thus an exceptionally good overview of the worldwide activities in this field, discussed with the participants. For almost an hour, an intensive exchange on research was maintained and the various possibilities to gain new insights into the COVID-19 disease with stem cells were explored.

Just as, of course, no social events were possible, the obligatory public event in 2020 could not be realized. Hopefully, the international efforts on vaccination programs will be a resounding success in 2021 and conferences and scientific meetings with personal contacts, social events and high-profile events will soon be possible again.



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Alfonso Martinez Arias (Barcelona, ESP) · Janet Rossant (Toronto, CAN) ·
Takanori Takebe (Cincinnati, USA) · Sara Wickström (Helsinki, FIN)

Presidential Symposium

GSCN Awardees: Young Investigator, Hilde Mangold Award, Publication of the Year

Early registration deadline: 25 June

Abstract submission deadline for oral presentations: 25 June

Oral presentations chosen from the best abstracts

Scientific sessions

- Pluripotency and reprogramming
- Somatic stem cells and development
- Hematopoietic stem cells
- Stem cells in diseases: cancer stem cells
- Stem cells in regenerative therapies
- Stem cells in regenerative therapies: mesenchymal stromal cells
- Stem cells in disease modeling and drug development
- Organoids: new models for diseases
- Computational stem cell biology

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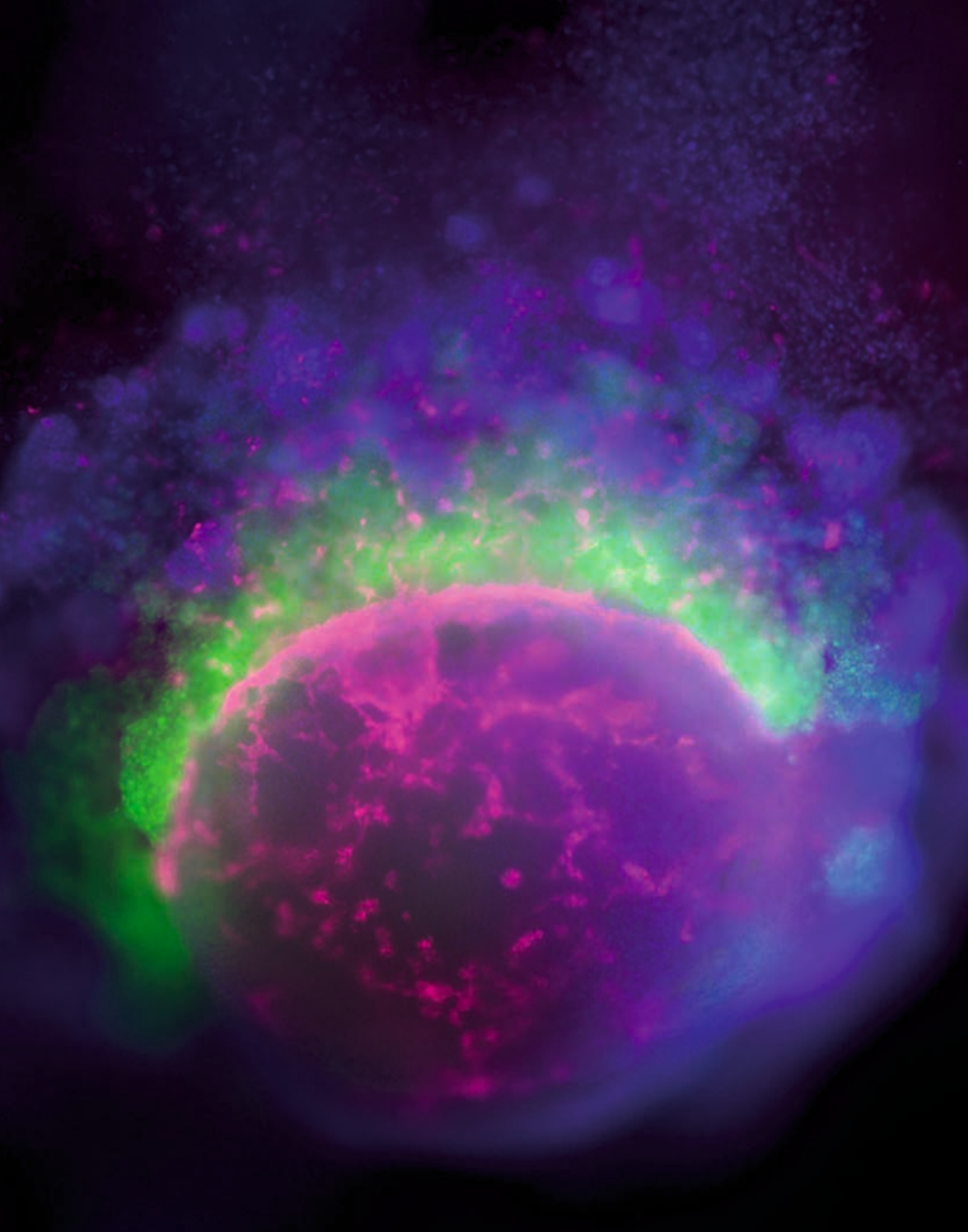
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Human pluripotent stem cell-derived heart-forming organoids (HFOs) resemble early heart and foregut development with a vascular network. Whole mount immunofluorescence staining for NKX2.5-eGFP (indicating cardiomyocytes, green), nuclei (DAPI, blue) and CD31 (endothelial cells, pink)

Cardiac cell replacement therapy

Muscle patches heading for clinical use

Using pluripotent stem cells, it's now possible to mass produce mature human heart muscle cells. These cells can be used for regenerative therapies aimed at restoring damaged heart muscle after events like heart attacks. Remarkable results have been achieved in animal models by infusing large numbers of individual cardiomyocytes or transplanting more complex bioartificial tissue patches. One of the first clinical trials in the world has now commenced in Germany.

Suturing pulsating muscle patches onto damaged hearts sounds like a very bold idea. But that's exactly what Wolfram-Hubertus Zimmermann is planning. The Göttingen-based stem cell researcher and his team have recently commenced a clinical trial to put this remarkable treatment strategy to the test in patients with cardiac insufficiency. They are the first ever research group to test this approach.

For Zimmermann and his team, the study, abbreviated as BioVAT-HF, represents a major milestone, "After 25 years of research, we have now reached the clinical trial stage." Zimmermann is director of the Institute of Pharmacology and Toxicology at University Medical Center Göttingen and has pioneered the use of stem cells for the treatment of heart failure. Heart failure often develops as a result of scarring of the heart tissue after a heart attack. This reduces the heart's ability to pump blood. A heart attack can result in the death of more than a billion heart muscle cells. In contrast to many other tissues, the ability of adult heart muscle to regenerate is very limited. The result is that the wall of the heart in the area of the infarct becomes thinner and no longer functions properly. A heart that has been weakened in this way does not heal.

Wolfram-Hubertus
Zimmermann



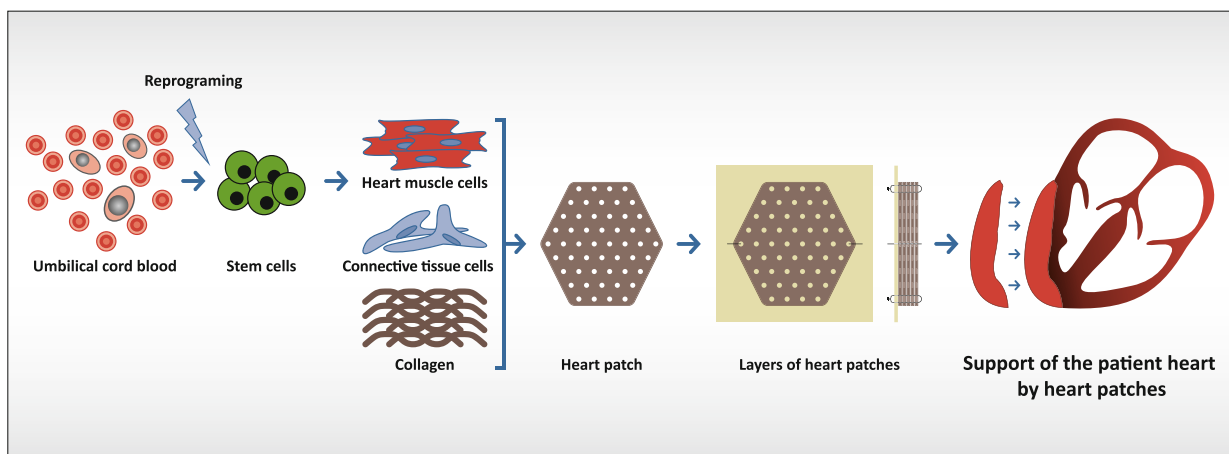
Physicians prescribe a wide range of drugs to reduce strain on the damaged heart and minimize problems down the line. But what these drugs can't do is reverse the damage to this vital muscle tissue. Some – but by no means all – patients with severe heart failure may be able to benefit from a mechanical cardiac assist device or a heart transplant.

"No other approach is able to achieve what we are looking to achieve with stem cell therapy," explains Zimmermann, "We hope to be able to actually repair damaged heart muscle."

A band-aid for the ventricular wall

The material they will use consists of cultured tissue patches developed through a joint project between University Medical Center Göttingen, the German Center for Cardiovascular Research (DZHK) and Repairon, a private company co-founded by Zimmermann. The technology is also known as tissue engineering. The researchers use reprogrammed pluripotent stem cells to produce human heart muscle cells (cardiomyocytes) and cardiac connective tissue cells. These are then embedded in a supportive bovine collagen gel. In the lab, these patches, which are around 4 cm x 4 cm in size and about 1 mm thick, can be seen to contract rhythmically.

Over the last few years, Zimmermann's team has exhaustively tested this bioartificial heart muscle. First in the laboratory and in rodents, and then – working with the German Primate Center in Göttingen – going on to transplant them also into rhesus macaques. According to Zimmermann, these experiments showed that the replacement muscle was not only able to survive in the heart and increase heart wall thickness after an infarction (in the macaques



Ulrich Martin and Robert Zweigerdt (right) with their bioreactor system for the production of cardiomyocytes in large quantities



this was demonstrated over a period of six months) but was actually able to restore normal contraction and pumping ability. While the collagen gel was gradually broken down and replaced by natural materials produced by the transplant recipient, the transplanted cells appear, says Zimmermann, to have integrated into the surrounding tissue to form a functional composite tissue.

Earlier this year, the team recruited the first patients for clinical trials of their lab-grown heart muscle. The study will enroll a total of 53 women and men with severe heart failure who have exhausted all other treatment options. At heart centers in Göttingen, Bad Oeynhausen, and Lübeck, patients will receive one or more (depending on individual circumstances) bioartificial heart muscle patches. Through a small incision in the left side of the chest, cardiac surgeons will suture the tissue patches directly to the ventricle. The hope is that this will strengthen the heart muscle and enable the heart to pump more effectively.

Zimmermann and his team expect to have statistically meaningful results in about three years' time. These are likely to be eagerly awaited internationally. The Göttingen study is much larger and more ambitious than the handful of previous pilot projects in which stem-cell derived cardiomyocytes were tested on patients in countries like Japan and China. A successful outcome from the Göttingen project would be a shot in the arm for the entire field.

Mass producing cardiomyocytes

The idea of using cell-based therapies to regenerate damaged heart muscle is far from new. Researchers experimented with injecting adult stem cells and precursor cells from bone marrow into heart muscle two decades ago, for example. These experiments, in rodents, suggested that this does indeed aid healing after a heart attack. In clinical trials, however, this kind of cell transplantation was found to improve heart function only marginally. In view of the modest results achieved, a 2017 editorial in influential journal *Nature Biotechnology* deemed it "A futile cycle in cell therapy".

So why should today's cell replacement therapy strategies be any more effective? Researchers argue that one obvious difference from those early methods lies in the nature of the cells used. "I was always skeptical about the utility of transplanting adult stem cells and precursor cells after a heart attack," says Ulrich Martin, head of the Leibniz Research Laboratories for Biotechnology and Artificial Organs (LEBAO) at Hannover Medical School. This is because

these tissue stem cells, generally taken from the patient's own blood or bone marrow, simply fail to give rise to new heart muscle after transplantation. The modest beneficial effects observed with cell transplantation are attributable to cellular and signaling substances. These are posited, for example, to stimulate angiogenesis in the heart muscle or aid survival of heart muscle cells at the margins of the infarct zone. These kinds of effects are referred to as paracrine effects.

In contrast to these 'first generation' cells, explains Martin, the 'second generation' cells used today are real, functioning cardiomyocytes. By using molecular differentiation processes, cardiomyocytes can be obtained from both embryonic and induced pluripotent stem cells (iPS cells). This technique was, as Martin emphasizes, simply not available in the early days of cardiac cell therapy.

Twenty years ago, when Martin began his research into how simian embryonic stem cells differentiate into cardiac muscle cells, "We were happy if we could just get a few cells in our Petri dish to twitch," he recalls. "With today's cellular technologies we are really working at a completely different level."

As part of the German Federal Ministry of Education and Research-funded iCARE project, Martin's team has developed a procedure for producing human cardiomyocytes in accordance with defined standards. The starting material is a simple blood sample containing immature blood precursor cells known as CD34-positive cells. The researchers use a virus to introduce transcription factors (genetic control elements) into these cells. These restore the cells to a completely undifferentiated state, turning them into pluripotent stem cells. The underlying principle was discovered by Japanese Nobel Laureate Shinya Yamanaka. The researchers then select suitable cell lines, which are expanded on a large scale in bioreactors, and further developed into ma-

ture cardiac muscle cells under specific growth conditions. Nowadays, it is even possible to produce ventricular and atrial cardiac cell subtypes, which have different properties and explains Martin, perform different tasks in the beating heart.

Martin and his colleagues have now tested the therapeutic potential of these cultured cells in long-tailed macaques. In this animal model, injecting human cardiomyocytes into the ventricular wall following an infarction caused pumping ability (determined by measuring the ejection fraction) to return to normal within just a few weeks. Histological examination also identified large areas of new heart muscle fibers. The team transplanted around 50 million cardiomyocytes into each animal. "Our hearts are larger," says Martin, "so in humans you would probably need at least ten times that number." With their high-performance, fully controllable bioreactor systems, it is now possible to culture

enough cells for one patient in a volume of just one liter. If everything proceeds according to planning, their technique could be ready for clinical testing in about three years.

Lots of different strategies, but is there a silver bullet?

While the experiments being carried out by these two teams in Germany and other groups internationally are highly promising, researchers are still grappling with a number of unanswered questions. The macaque experiments described above have demonstrated that transplanted cardiomyocytes can survive in the heart for several months. But what about the many years they would need to survive if used in humans? How would the transplanted cells stand up to normal, everyday activities, like climbing stairs?

In addition, a key question for all cell therapies is whether to use cells which are immunologically identical to the pa-

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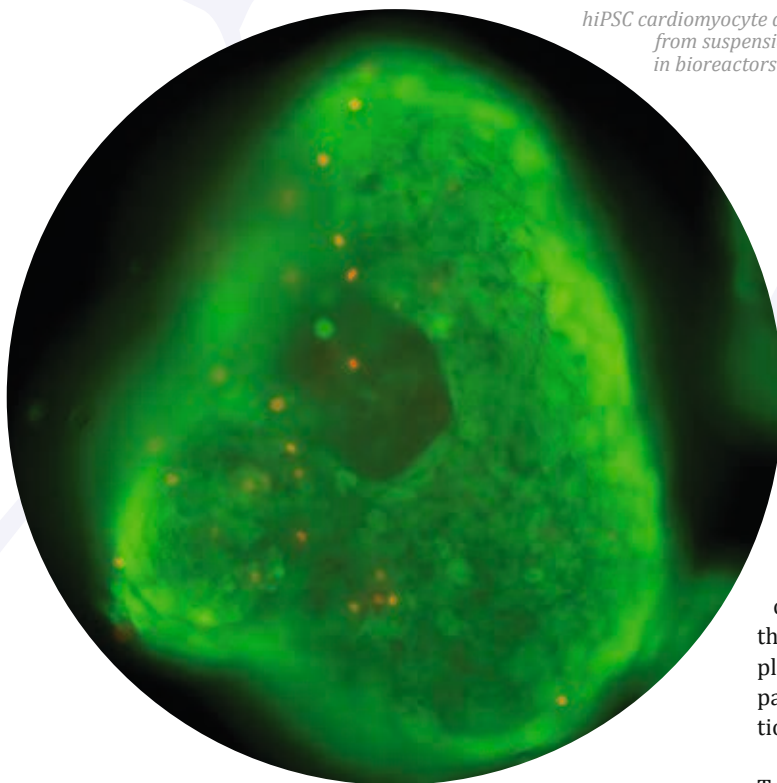
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tient's own cells or non-identical donor cells. To produce immunocompatible cardiomyocytes, it is in principle possible to obtain reprogrammed pluripotent stem cells (iPS cells) for each patient from his or her own cells. As well as developing universally transplantable cell products, Martin and his team are aggressively pursuing this approach. Autologous cell transplants, derived from the patient's own cells, are, notes Martin, particularly desirable for younger patients, as they dispense with the need for a lifetime of immunosuppressant drugs.

However, as Martin admits, this approach is considerably more expensive and laborious. At present, it takes six to seven months to go from induced stem cells to sufficient heart muscle cells for transplantation. Given the need for cell maturation, explains Martin, the extent to which this period can be reduced through improvements to the production process is also limited. Autologous therapies would therefore probably only be an option for people with long-

term heart failure and would not be an option for treating acute myocardial infarction.

"Naturally, autologous cell transplantation is the solution we are all dreaming of. But is it realistic in practice?" wonders Zimmermann. Instead, his team is pursuing the strategy of using a defined, existing stem cell line to produce heart cells and creating standard, off-the-shelf tissue patches. This approach means that transplants are instantly available. It also, however, means that patients in the Göttingen stem cell trial have to take additional drugs to prevent the donor cells from being rejected.

To reduce the impact of this problem, it might in future be possible to establish stem cell banks and select donor cells with a similar antigenic profile to the recipient – as is already done for bone marrow donation. This is known as HLA matching. It is also possible to genetically modify stem cells so that they feature fewer or weaker surface antigens, though this approach is not yet ready for primetime.

No less important than the search for the best immunological strategy is the question of the best cell transplant design from a bioengineering perspective. Some teams use suspensions of hundreds of millions or even billions of individual cardiomyocytes, others are transplanting cell aggregates. In aggregates, heart muscle cells are joined together via cellular bridges, forming clusters of several hundred cells.

An entirely different approach involves more complex transplants produced using tissue engineering techniques. It is, for example, possible to embed multiple cell types in three-dimensional gels enriched with extracellular pro-

Photo: Wiebke Trieber, LEBAO, MHH

REBIRTH – Research center for translational regenerative Medicine

From regenerative biology to reconstructive therapy

REBIRTH has, under the nationwide Excellence Initiative, been funded as a cluster of excellence since 2006. The aim of the internationally renowned Research center for translational regenerative Medicine is to develop innovative therapies for the heart, liver, lungs and blood, and to translate these into clinical use. This involves collaboration – in Hannover and at participating partner institutions – between physicians, physicists, chemists, biologists, engineers, legal professionals and ethicists, the main research priorities being stem cell biology, the reprogramming of cells for cell therapy, disease models and tissue engineering.

Participating Partners:

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- Institute of Farm Animal Genetics, Friedrich Loeffler Institute, Mariensee
- Fraunhofer Institute of Toxicology and Experimental Medicine, Hannover



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teins. This is the approach being taken by Zimmermann's team in Göttingen. Another option is to produce wafer-thin cell sheets. In future, it may also be possible to produce bioartificial heart muscle tissue using 3D printers. These would use 'bio-inks' containing living cells.

A core idea in tissue engineering is to partially replicate natural tissue structures in the laboratory, thereby encouraging cell-cell interactions and self-organization of transplanted tissue in the heart. Currently, however, the thickness of these engineered tissues is limited by the need to ensure that they have an adequate supply of oxygen and nutrients. In addition, transplantation of tissue patches, for example, is a surgical procedure. Single-cell approaches, by contrast, allow cardiomyocytes to be injected into the heart muscle using a catheter procedure. What all these approaches have in common is that they are all aimed at replacing dead heart muscle.

Pigs as an animal model

To Michael Laflamme, one thing is clear, "We need to keep an open mind as to which strategy is best." Laflamme is a regenerative heart medicine expert at the McEwen Stem Cell Institute in Toronto and a scientific advisor to US-Canadian company BlueRock Therapeutics (owned by Bayer AG). BlueRock's mission is to develop clinical stem cell-based therapies in a variety of medical fields. In Laflamme's view, right now cardiac muscle replacement approaches are just in too great a state of flux. A further problem is that some effects in humans cannot be completely predicted by animal experiments.

"We have been working with a whole zoo of experimental animals, ranging from mice and rats to guinea pigs and monkeys," explains Laflamme. "Experiments on macaques, for example, have been excellent for researching immuno-

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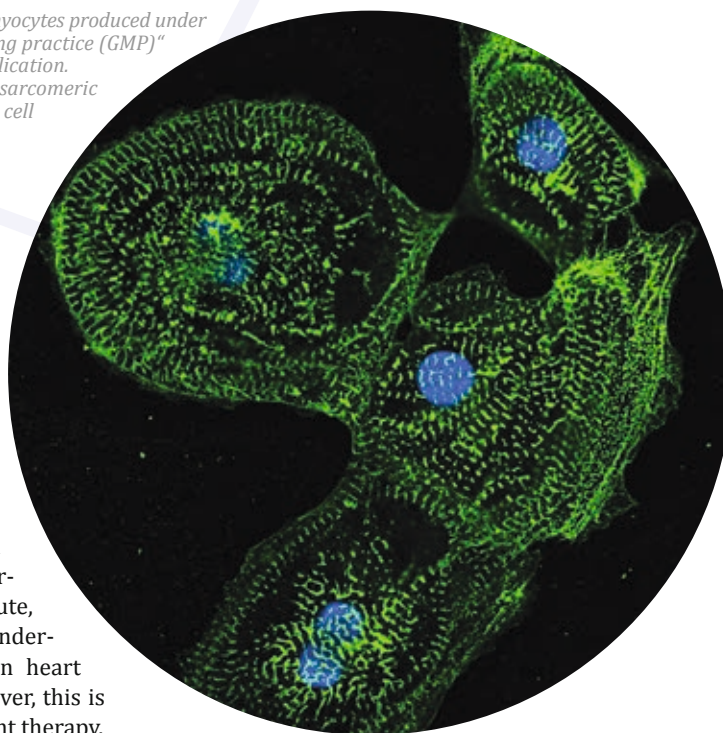
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Culture of cardiac myocytes produced under „Good manufacturing practice (GMP)“ for therapeutic application. Immunostaining of sarcomeric Actinin (green) and cell nuclei (blue)



logical aspects of cell transplantation, as they have a very similar immune system to humans.”

However, as Laflamme points out, assessments of specific aspects of cardiac function and electrical cardiac excitation have proved less reliable. Macaques such as rhesus macaques weigh just five to 15 kilograms. Their hearts are much smaller than human hearts and beat up to twice as fast as their human counterparts. Rat hearts beat over 300 times per minute, mice hearts around 600 times. This makes understanding the effects of cell transplantation on heart rhythm much harder. In Laflamme’s view, however, this is a key issue for successful cardiac cell replacement therapy.

The human heart’s natural rhythm is the result of regularly generated electrical signals arising in a collection of special cardiomyocytes in the right atrium – the sinoatrial node – and then spreading through the heart, stimulating it to produce coordinated contractions. To help the heart pump blood effectively, transplanted heart muscle cells have to be able to integrate into this electrical conduction system. This is known as electromechanical coupling. But transplanted cells can also form autonomous foci of excitation, disrupting the normal heart rhythm.

To look at this issue more closely, Laflamme’s team has been transplanting human cardiomyocytes into pigs. Pig hearts are very similar to human hearts, notes Laflamme. They beat around 90 times per minute and are an excellent model system. “Almost every major cardiac intervention was first tested in pigs.”

And indeed, in a study published in 2019, the researchers found that transplanted human cardiac muscle cells made pig hearts beat much faster and caused arrhythmias. Electrophysiological investigations showed that these dangerous ventricular tachyarrhythmias arose precisely at the boundary between the transplanted and native heart muscle tissue. What was really interesting, however, was that within four weeks the arrhythmias had disappeared and the pig heart had reverted to a normal sinus rhythm.

According to Laflamme, one obvious interpretation, supported by molecular analysis, is that the transplanted cardiomyocytes in the pig heart tissue are undergoing further maturation, in the process of which their electrical behavior normalizes. Laflamme’s team has now commenced a new pig study which, to reduce the risk of cardiac arrhythmias, involves introducing a more homogeneous, more ma-

Photo: Malte Tirbury, Med. Uni Göttingen

Leibniz Institute for Zoo and Wildlife Research (IZW) in the Forschungsverbund Berlin e.V.

Evolutionary wildlife research for conservation

The Leibniz Institute for Zoo & Wildlife Research (IZW) is an internationally renowned research institute of the Leibniz Association. With the mission of „understanding and improving adaptability“ it examines evolutionary adaptations of wildlife and its resilience to global change, and develops new concepts and measures for conservation. To achieve this, the IZW uses its broad interdisciplinary expertise in evolutionary ecology and genetics, wildlife diseases, reproductive biology and management in a close dialogue

with stakeholders and the public. The Department of Reproduction Management, headed by Prof Dr Thomas B Hildebrandt, develops cellular techniques for conservation. This new approach is an essential, promising option for highly endangered wildlife. For this purpose, the IZW builds up international networks on „cellular techniques“, including international expert meetings of the world’s leading scientists in the field of „cellular techniques“, and develops new methods of securing and preserving wildlife tissue samples.



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ture cell population. To reduce arrhythmias, it might also be possible to give anti-arrhythmic drugs for a short period after cell transplantation.

Laflamme believes that insights like these will be crucial to overcoming obstacles to successful cell therapies and for developing and optimizing the different approaches being taken. He expects his team's strategy to be at the point where it can undergo clinical trials in three to four years' time and believes that within a decade the field as a whole may have advanced to the point where regenerative stem cell treatments will be an option for a large number of patients. At the same time, Laflamme argues, there is still a need for basic research in this area using a range of animal models. It is quite plausible that different approaches, transplantation methods, and product designs will turn out to have different strengths and weaknesses.

This is a view shared by Wolfram-Hubertus Zimmermann, "There's not going to be a one-size-fits-all solution for every patient." Instead, he believes that different methods will likely be needed for different conditions and that treatment for a locally circumscribed infarct, for example, will differ from treatment for diffuse damage to cardiomyocytes throughout the heart. "It's important to have a number of different approaches," stresses Zimmermann.

Overall, reckons Zimmermann, regenerative heart medicine has made some big advances and, with several novel concepts, is now on the cusp of clinical use. The next few years will be a moment of truth for regenerative medicine, as applications enter clinical trials. The Göttingen study by Zimmermann and his team represent a first step towards this goal.

Text: Martin Lindner



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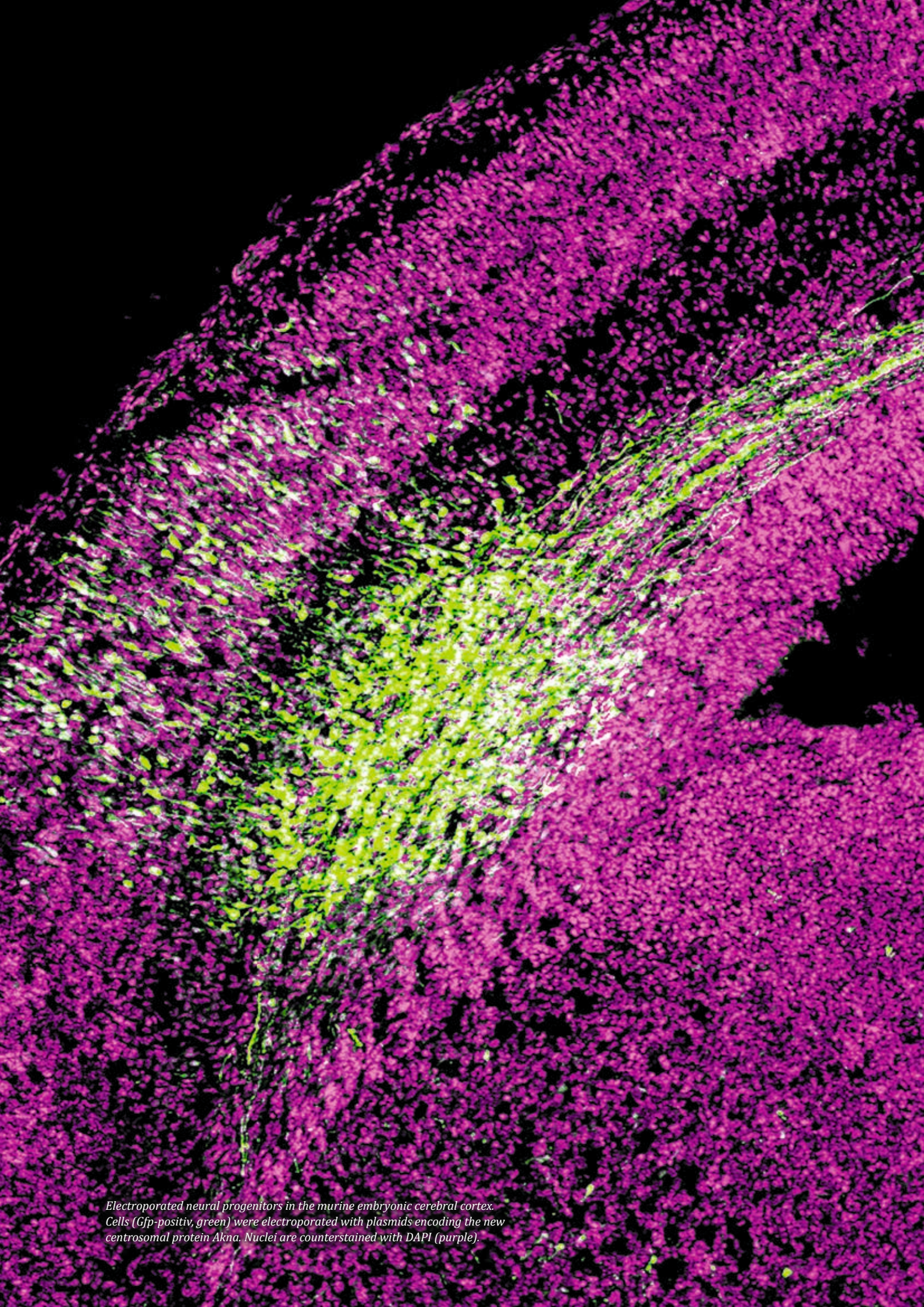
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Electroporated neural progenitors in the murine embryonic cerebral cortex. Cells (Gfp-positiv, green) were electroporated with plasmids encoding the new centrosomal protein Akna. Nuclei are counterstained with DAPI (purple).

Stem cells deliver boost to lung research

Lungs in the lab

Mimicking the complex structure of human lungs in the lab is a challenging undertaking, which stem cell engineers have only recently succeeded in achieving. Three-dimensional tissue cultures – lung organoids – in particular promise better ways of testing drugs and the ability to develop innovative treatments for conditions such as flu and COVID-19. The next few years could also see cellular immunotherapy and regenerative treatments for chronic diseases such as COPD and cystic fibrosis become reality.

Pneuma is what the ancient Greeks called the human breath, but also the vital force. With their complex architecture and function, the lungs still exert a strong fascination today. The airways are branched like a tree, and are home to an estimated 200 billion cells, consisting of more than 40 different cell types. The very tiniest branches of this tree open out into around 300 million alveoli – tiny sacs with extremely thin walls featuring a dense network of capillaries. With a total surface area the size of a tennis court, this is where the blood gets enriched with oxygen and gets rid of carbon dioxide, which is then exhaled. The lungs are a living interface between the body and the environment.

Researchers have now learned how to reproduce this system – in part at least – in a Petri dish. In doing so, they have discovered methods for better testing drugs, ways of providing patients with more specific treatments, and maybe even ways to regenerate damaged lungs.

Hans-Willem Snoeck is a stem cell expert at Columbia University in New York. Regarding the state of his research field, he believes that “We still have a lot of work ahead of us, of course, but in the last decade we have made tremendous progress.” Snoeck has pioneered the science of recreating lung tissue in the laboratory. During embryonic development, lungs develop from two lung buds which grow from the upper part of the digestive tract (the foregut). As the embryo develops, these buds develop into the right and left lung. As the lungs develop, the bronchial system forms finer and finer branches, and then finally the delicate alveoli.

It is this process that has long proved elusive for researchers in the lab, explains Snoeck. While it has been possible to induce embryonic stem cells to develop into intestinal or liver precursor cells since the mid-2000s, “We simply did not know how to culture human lung cells.” But that has changed fundamentally in the meantime.

Living 3-D models of lung development

In 2017, Snoeck’s team unveiled a three-dimensional tissue culture – an organoid – created from pluripotent stem cells. This tissue culture was able to model lung development in a scaled-down form through to the second trimester of pregnancy. When the New York-based researchers transplanted the human organoids into mice or cultured them in vivo for a prolonged period, they formed, over a period of several months, a kind of miniature bronchial tree and primitive alveoli. The lung organoids even responded to disease processes caused by viruses or genetic modification in a similar way to real lungs. The organoids broadly recapitulated lung development and disease processes.

As impressive as this is, at the same time Snoeck readily admits that his tissue models are a long way from mimicking the lungs in all their complexity. “An organoid that reproduces the human lungs in their entirety,” says Snoeck, “does not yet exist.” A number of international research groups have now managed to culture lung organoids from a variety of stem cell types (both pluripotent and adult). But these are generally limited to mirroring specific bronchial or alveolar tissue structures. Snoeck’s team has also been able to detect only some, not all, lung cell types in its organoids – and these cells were not always in a mature state.

The specialized epithelium that lines the airways and alveoli is made up of multiple cell types and is known to play a key role in lung function and disease. In the bronchi, this epithelium produces protective mucus, which is swept towards the throat by microscopic hair-like protuberances from the cell called cilia. Alveolar cells (pneumocytes), by contrast, act to lower surface tension in the alveoli and prevent the lungs from collapsing and facilitate gaseous exchange between the blood and inhaled air.

Currently, explains Snoeck, organoid models only partially reproduce this ingenious cellular differentiation process, which progresses from the trachea, to the large and small bronchi, to the alveoli (proximodistal specification). Moreover, an ideal lung organoid would also need to incorporate more than just the epithelium. It would need to incorporate the various connective tissue cell types, immune cells and the dense network of capillaries essential to lung function – all in a single model system.

Recently, however, researchers have taken a significant step towards achieving precisely this goal – not with human organoids, but with mouse models. “Our models are really very similar to mouse lungs,” explains Susanne Herold, stem cell specialist and Professor for Pulmonary Infections at Giessen University Hospital. In a study published



Hans-Willem
Snoeck

Lung organoid derived from type II human pneumocytes

last year, Herold and her colleagues grew complex organoids with branched bronchial and alveolar structures and specific bronchial and alveolar cell types from adult mouse lung stem cells.

A special aspect here: the researchers co-cultured epithelial stem cells and lung connective tissue cells. Moreover, in order to achieve a more complete range of cell types in their organoids, they also transferred lung-specific immune cells – alveolar macrophages – into the mature organoids. “Examining tissue sections from our organoids,” explains Prof. Herold, “we find that they are often barely distinguishable from real mouse lungs.” Her team is now planning to incorporate pulmonary vascular cells into these organoids to create a capillary network. This will result in a living 3D model for use in research on the alveolar blood-air barrier. “The challenge then is to understand how the insights gained from our mouse model apply in humans,” adds Herold.

New approaches to drug therapy

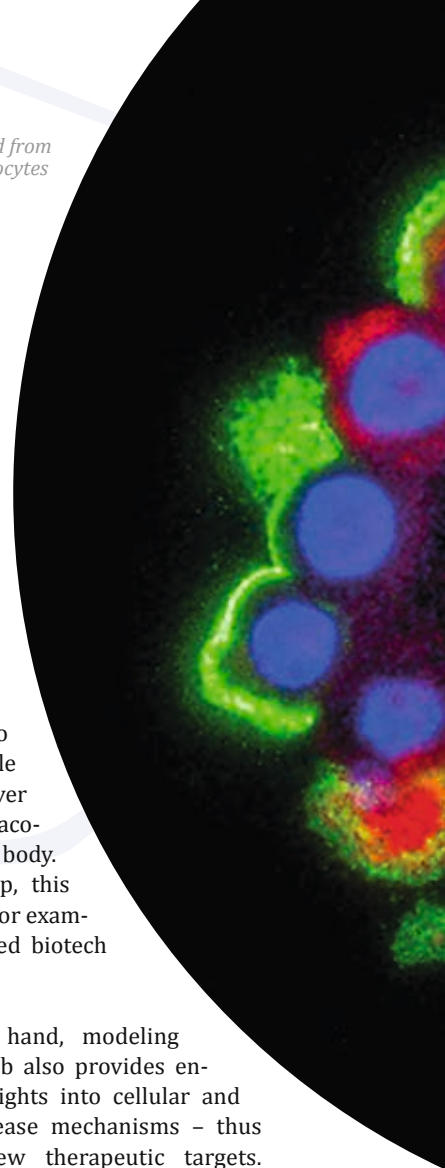
In the meantime, clinical applications for organoid research are already starting to emerge. On the one hand, organoid models enable innovative pharmacological tests.

In a 2019 study, a team led by South Korean cancer specialist Se Jin Jang at Asan Medical Center in Seoul showed that it is possible to produce personalized organoids from the cells of patients with lung cancer, and that these can then be used to test for sensitivity to a range of anti-cancer drugs. This approach could pave the way for better targeted, personalized cancer therapies. To standardize these

drug tests for laboratory use, organoids can be cultivated on small test slides known as microfluidic biochips. These use very fine fluid channels to simulate a vascular system and enable controlled biochemical analysis. It is even possible to combine organoids from multiple organs, for example, lung and liver organoids, and model pharmacological interactions within the body. Known as multi-organ-on-a-chip, this is the approach being taken, for example, by the Berlin-based biotech company TissUse.

On the other hand, modeling lungs in the lab also provides entirely new insights into cellular and molecular disease mechanisms – thus leading to new therapeutic targets. When Hans-Willem Snoeck and his team genetically modified their organoids, introducing changes associated in humans with pulmonary fibrosis (a condition involving pathological proliferation of connective tissue and stiffening of the lungs), the researchers discovered that tissue remodeling was controlled by the signaling protein interleukin-11 (IL-11). When interleukin-11 synthesis was blocked, the organoids no longer showed symptoms of fibrosis. Preclinical testing is now being carried out to determine whether suitable blocker substances could also halt the serious disease in patients, as Snoeck reports.

Susanne Herold



Photos: privat, med. Klinik II, Gießen / Yiyen Yao, University Hospital of the Saarland

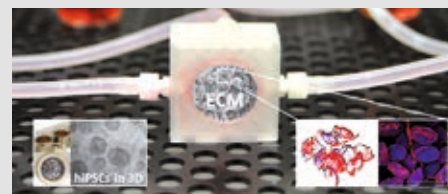
Chair of Tissue Engineering and Regenerative Medicine

Human organ models meets stem cell process engineering

The Chair Tissue Engineering & Regenerative Medicine, University Hospital Würzburg is working closely together with the Translational Center Regenerative Therapies, Fraunhofer Institute for Silicate Research Würzburg. Our research focuses on human organ models that find their application as alternative test systems to animal experiments. Basis of our models are either synthetic or biological carrier structures combined with primary- or iPSC-derived cells. Culturing of our models in specific bioreactors mimics *in vivo*-like microenvironmental

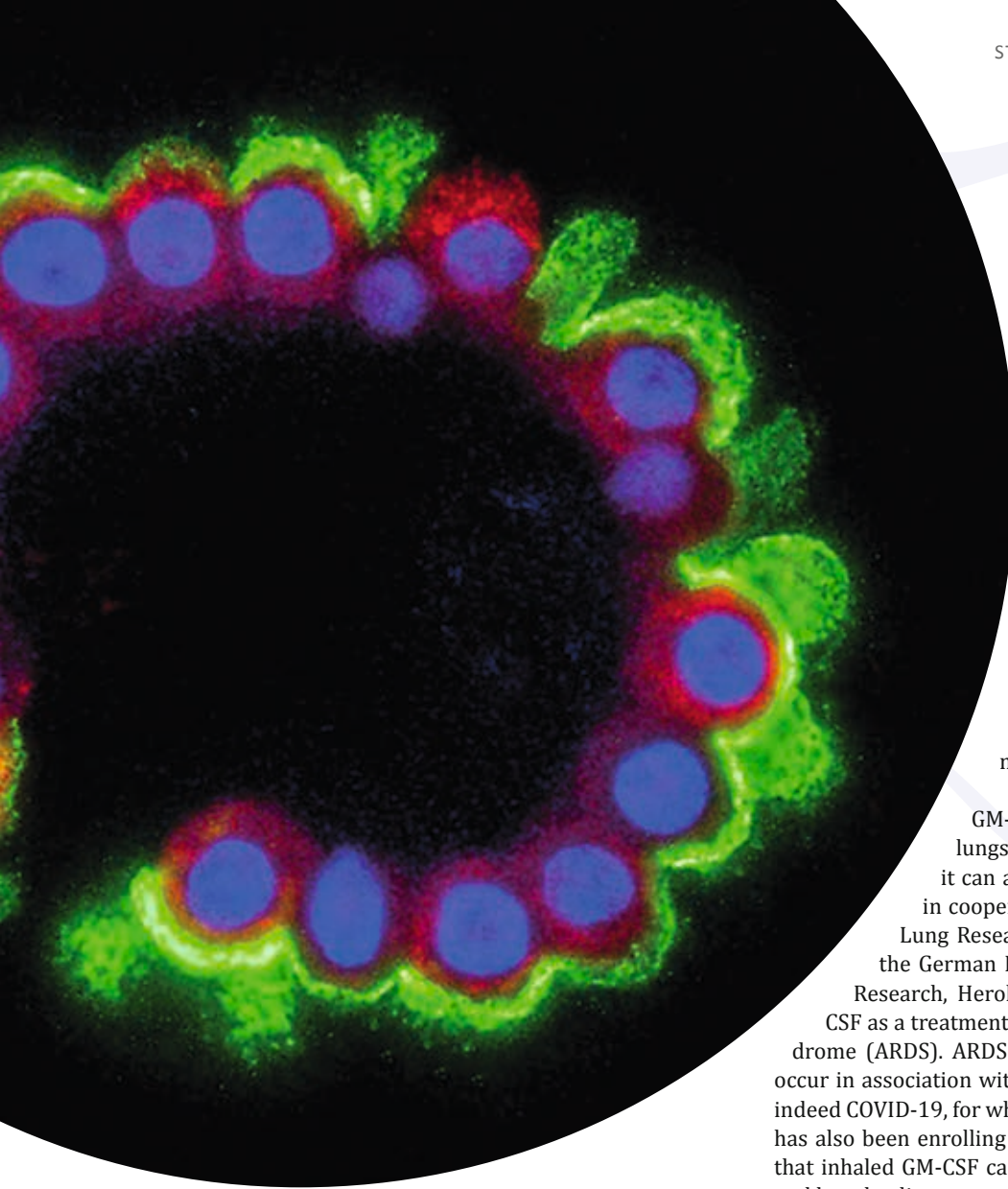
conditions *in vitro*. Since January 2021, we collaborate with the Fraunhofer Project Center for Stem Cell Process Engineering Würzburg, whose core institutes (Fraunhofer Institute for Biomedical Engineering IBMT and the Fraunhofer Institute for Silicate Research ISC) form a competence center in the field of stem cell process engineering. Our common goal is to transfer stem cell processes through automation solutions to an industrial scale and to improve the fields of cell expansion, differentiation and cryopreservation using novel materials.

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an immune response, and also appears to stimulate repair processes in lung tissue. After infection with an influenza virus, GM-CSF plays a role in triggering the coordinated proliferation of alveolar epithelial cells, explains Herold. “We can follow these processes in our organoid models.”

GM-CSF is naturally synthesized in the lungs, but, for therapeutic purposes, it can also be inhaled as a drug. In 2017, in cooperation with the German Center for Lung Research (DZL) and with funding from the German Federal Ministry of Education and Research, Herold initiated a clinical trial of GM-CSF as a treatment for acute respiratory distress syndrome (ARDS). ARDS is a serious condition which can occur in association with bacterial or viral pneumonia, or indeed COVID-19, for which reason, since last year, the trial has also been enrolling coronavirus patients. The hope is that inhaled GM-CSF can promote both pathogen defense and lung healing.

Alveolar phagocytes

“Using organoids to investigate signaling pathways is an extremely promising approach,” agrees Susanne Herold. One project being carried out by her team involves using tissue cultures to study viral lung infections. Pneumonia generally involves numerous cellular interactions and signaling molecules, notes Herold. One such signaling molecule is GM-CSF, which stimulates alveolar macrophages to mount

In pursuing this dual strategy of supporting the immune defenses and supporting tissue regeneration in the lungs, researchers are also now investigating cell therapy approaches. The alveolar macrophages are the focus of interest. These phagocytic cells live in the alveoli and form part of the innate immune system. They perform important

Center for Regenerative Therapies Dresden (CRTD)

Research Center of the TU Dresden

The Center for Regenerative Therapies Dresden (CRTD) of TU Dresden is academic home for scientists from more than 30 nations. Their mission is to discover the principles of cell and tissue regeneration and leveraging this for recognition, treatment and reversal of diseases. Research at the CRTD links the bench to the clinic and brings together scientists and clinicians. Expertise in stem cell research, developmental biology, genome editing and tissue regeneration aims at the potential cure

of diseases such as Alzheimer's and Parkinson's, haematological diseases such as leukaemia, metabolic diseases such as diabetes, and eye and bone diseases.

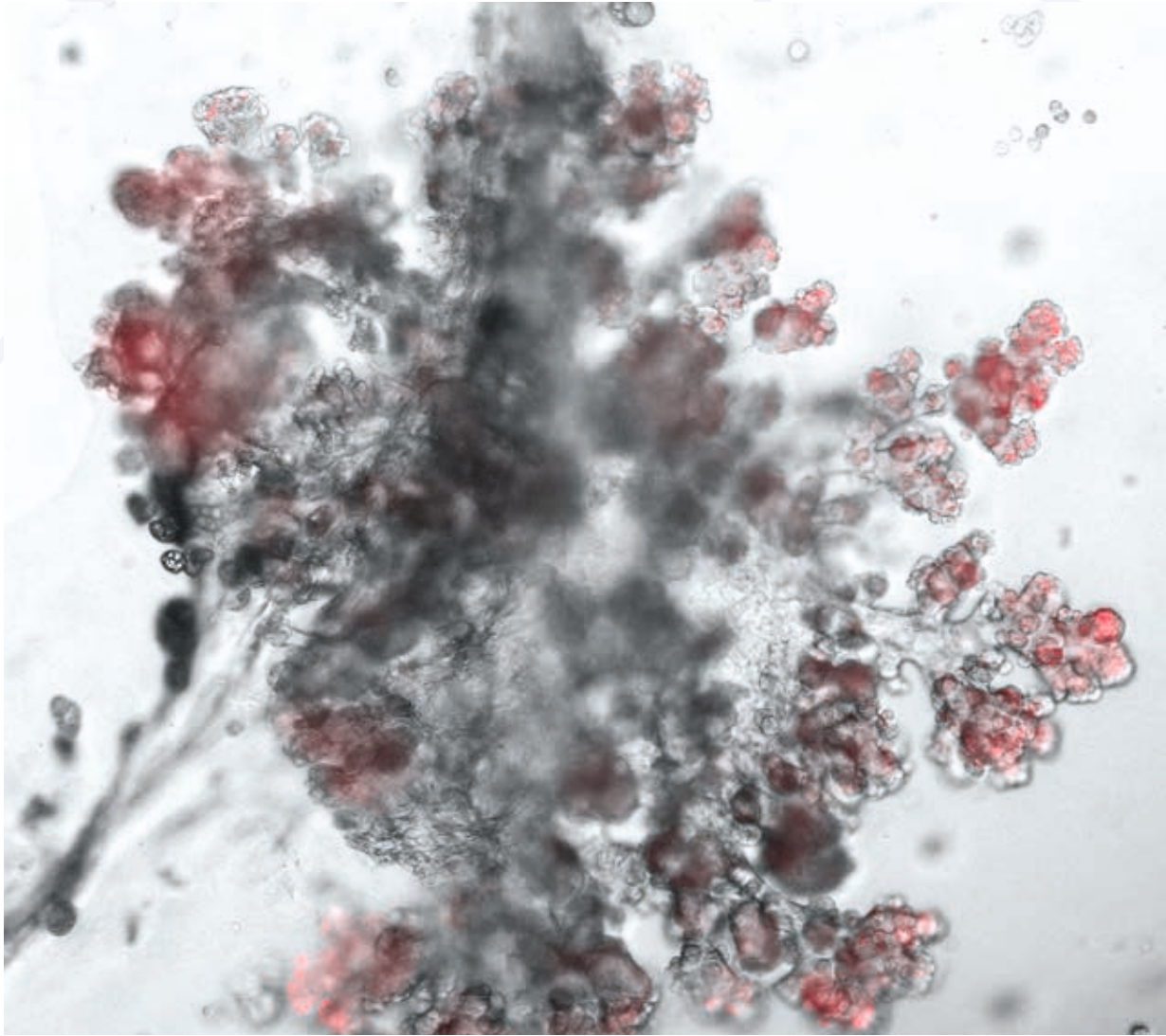
Between 2006 and 2019, CRTD has been funded as a Cluster of Excellence by the DFG. Since 2016 the CRTD is part of the central scientific unit Center for Molecular and Cellular Bioengineering (CMCB) of the TU Dresden and plays a central role within the research priority area Health Sciences, Biomedicine and Bioengineering of the TU Dresden.



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Occurrence of alveolar epithelial cells type II (red) in the distal structures of a murine bronchioalveolar lung organoid

cleansing functions, eliminating inhaled pathogens or foreign bodies and taking care of metabolic waste products. If alveolar macrophage activity is inhibited – for example by autoantibodies to GM-CSF – lipid secretions (pulmonary surfactant) accumulate in the alveoli. Pulmonary surfactant is normally responsible for regulating surface

tension in the alveoli. When present in excess, however, it impedes oxygen uptake, leading to coughing and shortness of breath. This condition is known as pulmonary alveolar proteinosis. Macrophages are also known to release signaling molecules that draw other immune cells into the alveoli, and in this respect, they function as immunological relay

Photo: Ana Ivonne Vazquez-Armendariz, med. Clinic II, Gießen

The Collaborative Research Center SFB 873

Maintenance and differentiation of stem cells

The Collaborative Research Center SFB 873 “Maintenance and Differentiation of Stem Cells in Development and Disease” at Heidelberg University works towards defining the regulatory principles underlying the balance between maintenance, expansion and differentiation of stem cells in diverse systems on a mechanistic level. To this end the SFB873 studies a wide spectrum of experimental models ranging from plants to human to elucidate the inherent properties of specific stem cell systems, but also to uncover common and divergent principles behind regulatory regimes and molecular signa-

tures. Our consortium brings together internationally recognized researchers, with unique scientific strengths in cell biology, biophysics, developmental biology, molecular medicine or modeling. With our research we hope to advance our understanding of principles underlying stem cell function and lay the foundation for translational approaches.

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stations. Recent research suggests that these cellular interactions contribute to the runaway alveolar inflammation seen in coronavirus infection.

The function of alveolar macrophages, however, is not limited to immune defense. "They are also involved in tissue regeneration and help maintain alveolar structure," explains Robert Bals, lead pulmonologist at Saarland University Medical Center in Homburg. It may even be possible to use alveolar macrophages specifically to trigger regenerative processes by cell transplantation, for example in chronic obstructive pulmonary disease (COPD).

Indeed, these cells offer the very practical advantage that they live on the interior surface of the alveoli and can



Robert Bals

be obtained comparatively easily in patients with lung lavage. Bals' idea is to culture specific macrophage subpopulations in the lab and equip them with novel genetic properties. This would enable them to be trained against specific pathogens or to enhance their regenerative properties. They could then be reintroduced into the patient's airways via bronchoscopy. "This kind of cell therapy is already feasible in laboratory animals," explains Bals. He expects these techniques to be ready for early-stage clinical testing within a few years.

A remarkable paper by stem cell specialist Nico Lachmann at Hannover Medical School takes a similar tack. In the 2018 study, however, Lachmann's team did not use macrophages from patients' lungs, but instead produced the phagocytes from a human pluripotent stem cell line in

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Lung Organoid

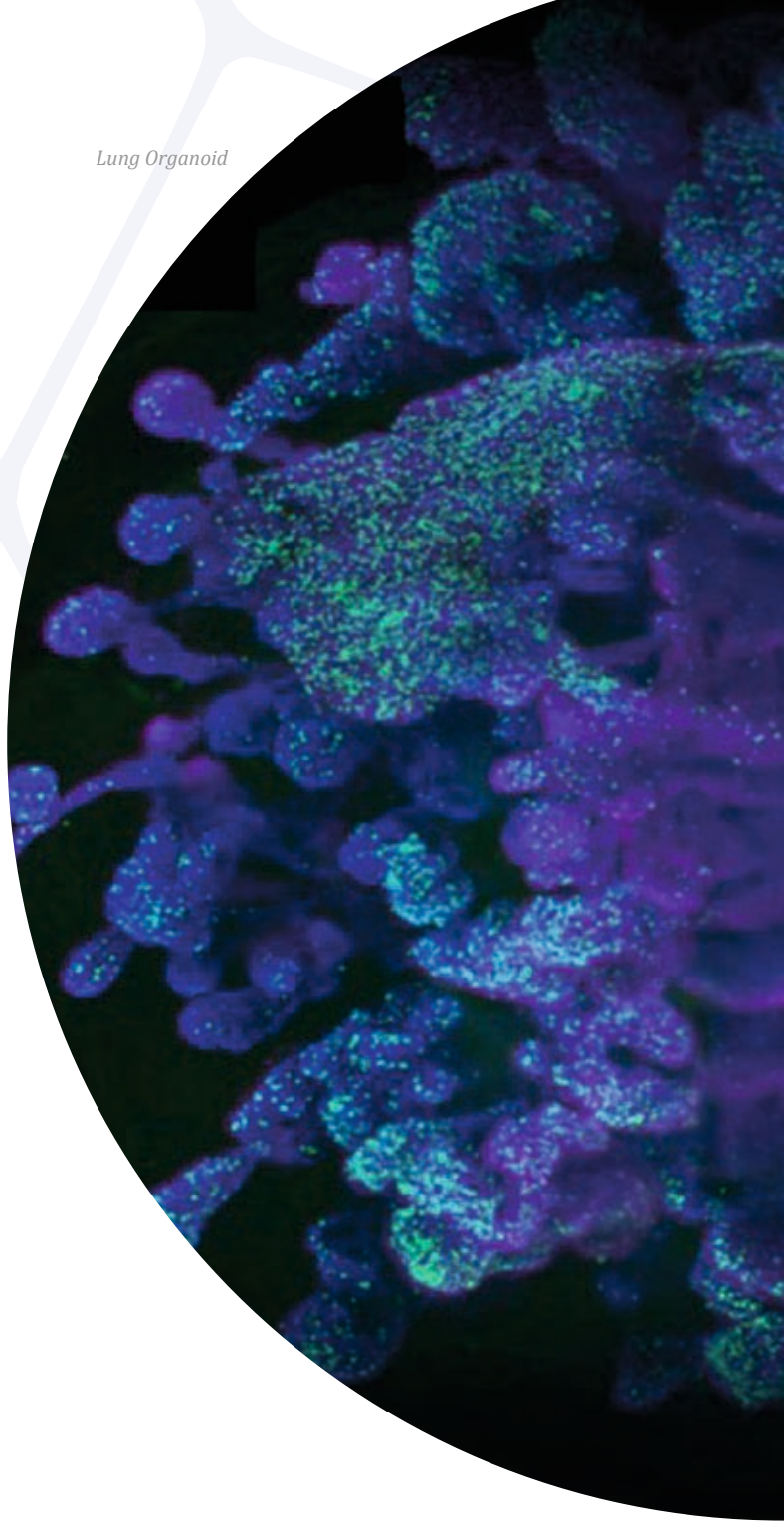
industrial-grade bioreactors. The macrophages mass produced by the researchers had much in common with mature alveolar immune cells. When instilled into the lungs of immunodeficient mice, they were able to successfully fight off infection by *Pseudomonas aeruginosa*, a bacterium that causes difficult to treat infections in patients with COPD and cystic fibrosis.

The future of cell therapy – can we fix damaged lungs?

Most experts now view macrophage therapy as a realistic potential treatment, but the stem cell research community is also grappling with a bigger question. Will we in future be able to replace respiratory epithelium – and thereby actually repair damaged lungs?

In this context, cystic fibrosis is a textbook example. The disease occurs due to a genetic mutation leading to a change in a membrane protein, the CFTR chloride channel. The mutation means that the channel is no longer able to correctly regulate the balance of water and salt in epithelial cells, which results in a buildup of viscous secretions. This particularly affects the lungs, but also affects the pancreas and gut. The cilia lining the epithelium have difficulty clearing this thick bronchial mucus, resulting in chronic cough and frequent chest infections. Occasionally a lung transplant may even be required.

In a highly regarded study published last year, a team led by Matthew Porteus at the Children's Hospital at Stanford University demonstrated that the CRISPR/Cas9 technology can be used to correct airway basal stem cells from patients with cystic fibrosis in the laboratory, and that these can then be used to culture a functional epithelial layer.



Fraunhofer Institute for Translational Medicine and Pharmacology ITMP

Fraunhofer is the largest application-oriented research organization in Europe with over 25,000 employees and operates more than 70 institutes and research facilities in Germany. ScreeningPort is a department of the Fraunhofer Institute for Translational Medicine and Pharmacology ITMP located in Frankfurt and Hamburg. Fraunhofer ITMP conducts health research in line with the Fraunhofer 4D concept (Drugs, Diagnostics, Devices, Data), which aims to optimize inter- and transdisciplinary health research in order to improve patient treatment

qualitatively and economically. One focus of ITMP ScreeningPort is on assay development for biochemical and cell-based formats, on development and application of efficacy and toxicity assays based on human pluripotent stem cells, on assay minituration, high-throughput and high-content screening, and on chemi- and bioinformatics. The indication focus is on infectious and immune-related diseases.

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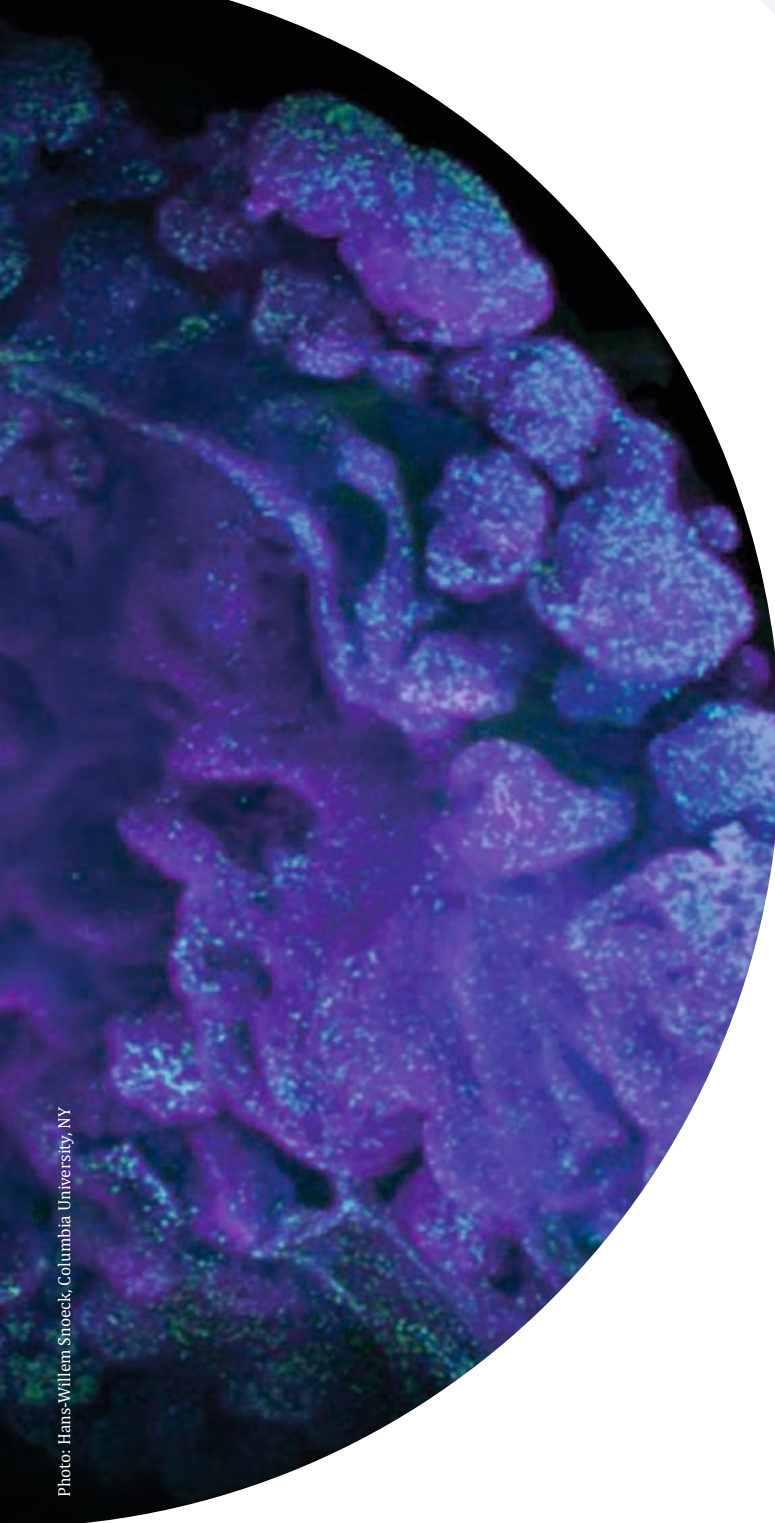


Photo: Hans-Willem Snoeck, Columbia University, NY

“At the moment, however, it’s unclear whether these corrected epithelial cells would continue to grow if returned to the lungs,” notes pulmonologist Robert Bals. One difficulty lies in the simple fact that to transplant new, healthy cells, you first have to clear some space for them in the airways.

This is the problem being addressed by tissue engineer Gordana Vunjak-Novakovic’s working group. Vunjak-Novakovic works at Columbia University in New York and is also collaborating with Hans-Willem Snoeck. “Our aim is to combine stem cell techniques and bio-engineering methods,” explains Snoeck. Some years ago, they performed experiments in an animal model that showed that, using a chemical solution instilled via a catheter, it is possible to remove the lung epithelium without damaging the supporting connective tissue and the critical vascular network. These ‘naked’, decellularized lungs can then be repopulated with new epithelial cells produced from human stem cells. Vunjak-Novakovic and her team are now testing this bold strategy on lungs from organ donors which are not suitable for transplantation for reasons such as chronic lung disease or a long-term smoking history. The aim is to upgrade the damaged donor lungs so that they can then be used for organ transplantation. In the long term, the researchers speculate, it may even be possible to decellularize the lungs in the body of patients themselves and replenish them with healthy epithelium.

Whether – and when – this vision might become reality is hard to foretell. However, the New York tissue engineer’s experiments certainly provide some fascinating insights into the astonishing nature of the human respiratory organ.

Text: Martin Lindner

Helmholtz Zentrum München

German Research Center for Environmental Health

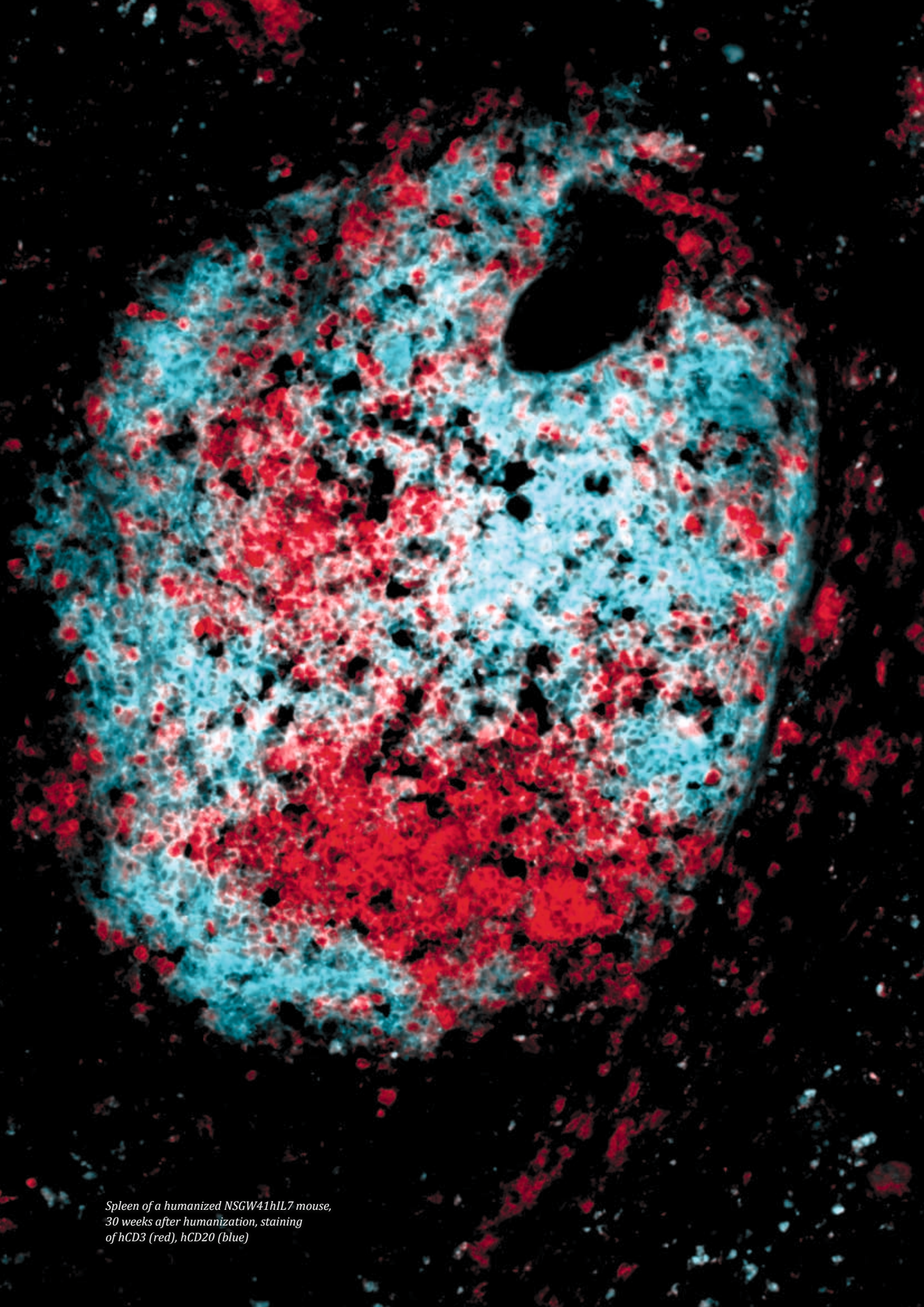
The Helmholtz Zentrum München (HMGU) is a key player for the Helmholtz Association within the research field “Health” aiming to understand how our cells interact with the environment.

Thus, the Institute of Epigenetics and Stem Cells (IES) at the HMGU is on the mission to unravel the mechanisms underlying stem cell and cell fate identity and to understand the processes behind cell reprogramming and genome stability.

Under the leadership of Maria-Elena Torres-Padilla, the 34 fellows from 17 different nationalities are devoted to the studies of how cells package their genome, how they protect their chromosomes and how they acquire fitness to be able to generate cells that can make any cell type in the organism. The IES consists of four research groups and a Microscopy Core that follow original and complementary research lines to enable pioneering discoveries at IES.



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*Spleen of a humanized NSGW41hIL7 mouse,
30 weeks after humanization, staining
of hCD3 (red), hCD20 (blue)*

Stem cells and immunological memory

Defense training in the bone marrow

Contrary to a dogma in medicine, the body's non-specific defense system apparently also forms a memory for pathogens and vaccines. As new research shows, the genetic program of blood stem cells in the bone marrow can be modulated in this process. The innate immune response to the same as well as other germs is rendered more effective as a result. This opens the door for innovative vaccination strategies.

When two French physicians developed a vaccine against tuberculosis exactly one hundred years ago, they had no way of knowing that their vaccine would also help for very different infections – perhaps even for COVID-19 now. The achievement of Albert Calmette and Camille Guérin from the Pasteur Institute was remarkable enough anyway: the physicians spent more than a decade cultivating the bovine tuberculosis pathogen in culture media of bile and potatoes, before finally creating an attenuated vaccine bacillus. In 1921, a baby in a hospital in Paris received the live vaccine for the first time. Since then, doctors have injected billions of children around the world with the “Bacille Calmette-Guérin”, BCG for short, to protect them against the most dangerous cases of tuberculosis.

However, there is now growing evidence that the famous vaccine influences the stem cells in the bone marrow – thereby strengthening the natural immune response as a whole. In fact, various studies suggest that the body already responds to some vaccines and infectious agents on the level of its stem cell populations. Here, the contact between human and microbe imprints on the innate defense system as a memory trace.

“These insights are fundamentally important,” says Maziar Divangahi, tuberculosis researcher and stem cell expert at McGill University in Montreal, Canada. “This is because they change our understanding of the immune system and potentially open the door to new vaccine strategies.”

It is known that an infection or vaccination creates an immunological memory in the body. So-called memory cells develop from pathogen-specific B and T cells of the immune system. These cells can be activated more quickly upon renewed contact with the same pathogen to produce specific antibodies and initiate cellular defense mechanisms. Experts speak of adaptive or acquired immunity.

On the other hand, there is an innate and evolutionarily much older component of immunological response. It is conveyed among other things by various scavenger cells

and components of blood plasma and it can be triggered within minutes. However, it is non-specific. According to the conventional dogma, only the adaptive immune system is capable of learning – while the innate immune system has no memory at all.

Tuberculosis as a model: how immune stem cells learn

This is precisely what new research now seems to refute. “We actually came across our findings by accident,” comments Divangahi. At first, he and his team just wanted to compare the different effects of the BCG vaccination when the bacillus is injected under the skin or into a vein.

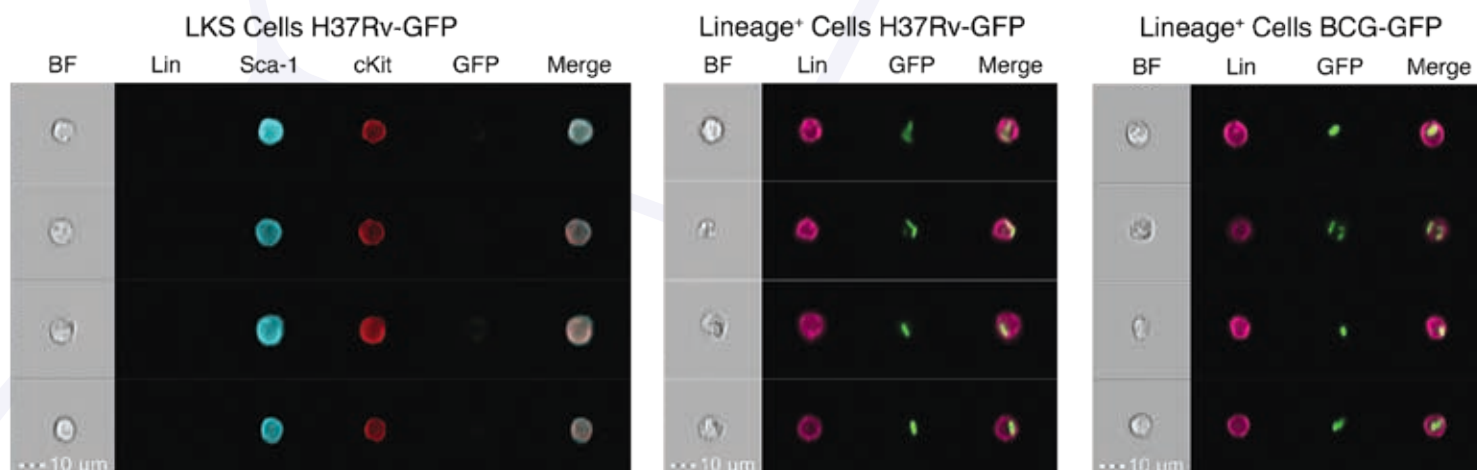
But the researchers were astounded when they scrutinized the bone marrow of an intravenously vaccinated mouse: the BCG bacteria had migrated there – and the blood cell precursors, also known as hematopoietic stem cells (HSCs), had significantly multiplied as a result. “It is important to know that blood stem cells are responsible for the replenishment of all immune cells,” underlines Divangahi. On the one hand, the B and T lymphocytes of the specific defense system (lymphoid cells) differentiate from the HSCs via various precursor cell lines. On the other hand, cell populations such as the so-called monocytes (myeloid cells) also develop. They patrol the blood as part of the innate defenses and can migrate into the tissues when an infection occurs, developing further into scavenger cells (macrophages). Originally, macrophages are derived from specific embryonic progenitors rather than monocytes and live as independent cell populations in various organs. Sometimes, however, they seem to die off, for example in the case of infections, and are then replaced by blood monocytes.

In fact, as the team demonstrated in a series of experiments, the BCG bacteria in the bone marrow do not only stimulate the blood stem cells to increasingly produce exactly such myeloid cell lines. Rather, particularly powerful, reprogrammed monocytes and macrophages develop that fight disease-causing tubercle bacilli more effectively both in the Petri dish and in the animal model. Even when the researchers transplanted the hematopoietic stem cells from vaccinated test animals into other mice, the rodents were better able to keep pulmonary tuberculosis at bay thanks to the more efficient scavenger cells that were formed.

No less remarkable is that the tuberculosis pathogens themselves apparently have the exact opposite immunological effect. As Divangahi’s research group showed in a



Maziar Divangahi



Mycobacterium tuberculosis (H37Rv-GFP) was unable to infect Lin⁻ c-Kit⁺ Sca-1⁺ (LKS) cells, whereas Lin⁺ cells were readily infected, as evidenced by ImageStream.

study published last year, the disease germs also migrate to the bone marrow when mice are infected via the blood or respiratory tract. There, the pathogens suppress the formation of myeloid scavenger cells – thereby weakening the innate immune defense of the infected test animals.

“Migration to the bone marrow is probably an evolutionarily old strategy of the tuberculosis bacteria,” says Divangahi. “It seems like a hijacking of the immune system.” Just as a person’s natural defense system is made more effective with a BCG vaccination via the detour of blood stem cells, tuberculosis pathogens use the same route to undermine the innate immune response.

The mechanisms involved were traced by the researchers down to the molecular details. Divangahi explains that so-called epigenetic changes occur in the blood stem cells when the body is infected with tuberculosis or vaccinated with BCG. These are chemical modifications of DNA that affect the activity of individual genes. In tuberculosis, epigenetic reprogramming is triggered by the messenger sub-

stances IFN- α and IFN- β (type I interferons) – while the opposing IFN- γ (type II interferon) plays a key role in BCG vaccinations. According to Divangahi, the different epigenetic programs are retained, even in serial bone marrow transplants from one test animal to the next, and these influence the new scavenger cells that develop in the recipient organism.

The real reason for the paradoxical effects of tubercle bacteria on the one hand and vaccine bacilli on the other, probably lies in a certain region of the microbial genome. Among experts, it is also known as “Region of Difference 1”. Tubercle bacilli have this gene region, but the BCG vaccinal strain does not. If it is removed from the disease-causing pathogens, they behave immunologically very similarly to vaccine bacilli, says Divangahi. Experts therefore assume that Albert Calmette and Camille Guérin – unknowingly – achieved exactly this gene loss when they cultivated the BCG vaccine strain with their bile-potato cultures a hundred years ago. A handful of genes are likely to play a role in determining which memory trace the microbes leave behind in bone marrow stem cells.

Photo: Maziar Divangahi, McGill University

German Cancer Research Center (DKFZ)

Research for a life without cancer

The German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ), located in Heidelberg, is a member of the Helmholtz-Association and is the largest biomedical research institute in Germany.

At the DKFZ, more than 1,000 scientists work together in order to develop novel strategies aimed at improving the prevention, diagnosis and treatment of cancer. Several research laboratories investigate normal and cancer stem cells (CSCs) as well as their respective niches. The goal is to develop strategies to monitor and

target CSCs in primary cancers and metastasis.

Together with the Dietmar Hopp Foundation, the DKFZ is a shareholder of HI-STEM, the nonprofit Heidelberg Stem Cell Institute and organizes the biannual Heinrich-Behr-Conference on „Stem Cells and Cancer“, which attracts international experts in the field.

With the Heidelberg University Clinic, the DKFZ has established the National Center for Tumor Diseases (NCT), to clinically translate innovative basic cancer and stem cell research discoveries into clinical therapies.

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Activating the non-specific defense system

"Up until now, immunologists have mainly investigated how contact with microorganisms affects differentiated immune cells, such as B and T cells, and what happens at the site of the infection," says Elvira Mass, a researcher studying the development of the immune system at the Life and Medical Sciences Institute (LIMES) of the University of Bonn. "We are now beginning to understand the effects of infection on immune stem cells as well."

It is now indisputable that the innate defenses can also develop a kind of memory, confirms Mass. "Even a short stimulus sometimes causes the non-specific defense to react quite differently at a later point in time." As opposed to the classic, adaptive immunity of B and T cells, specialists refer to this phenomenon as "trained immunity".



Elvira Mass

This memory formation cannot just be a result of the short-lived scavenger cells that patrol the blood, says Mass. Rather, it is apparent that for longer-term learning processes, the hematopoietic stem cell populations themselves must also be involved, presumably responding to quite different stimuli. Animal experiments have shown, for example, that a certain cell wall component of many fungi, the beta-glucan, stimulates the bone marrow precursor cells of the blood monocytes and that this is accompanied by an improved non-specific immune defense, e.g. against staphylococcal bacteria or tubercle bacilli.

A team led by Andreas Schlitzer and Mihai Netea, who are colleagues of Mass from the Bonn LIMES Institute and the Radboud University Medical Center in Nijmegen, published

Photo: private, LIMES, Uni Bonn



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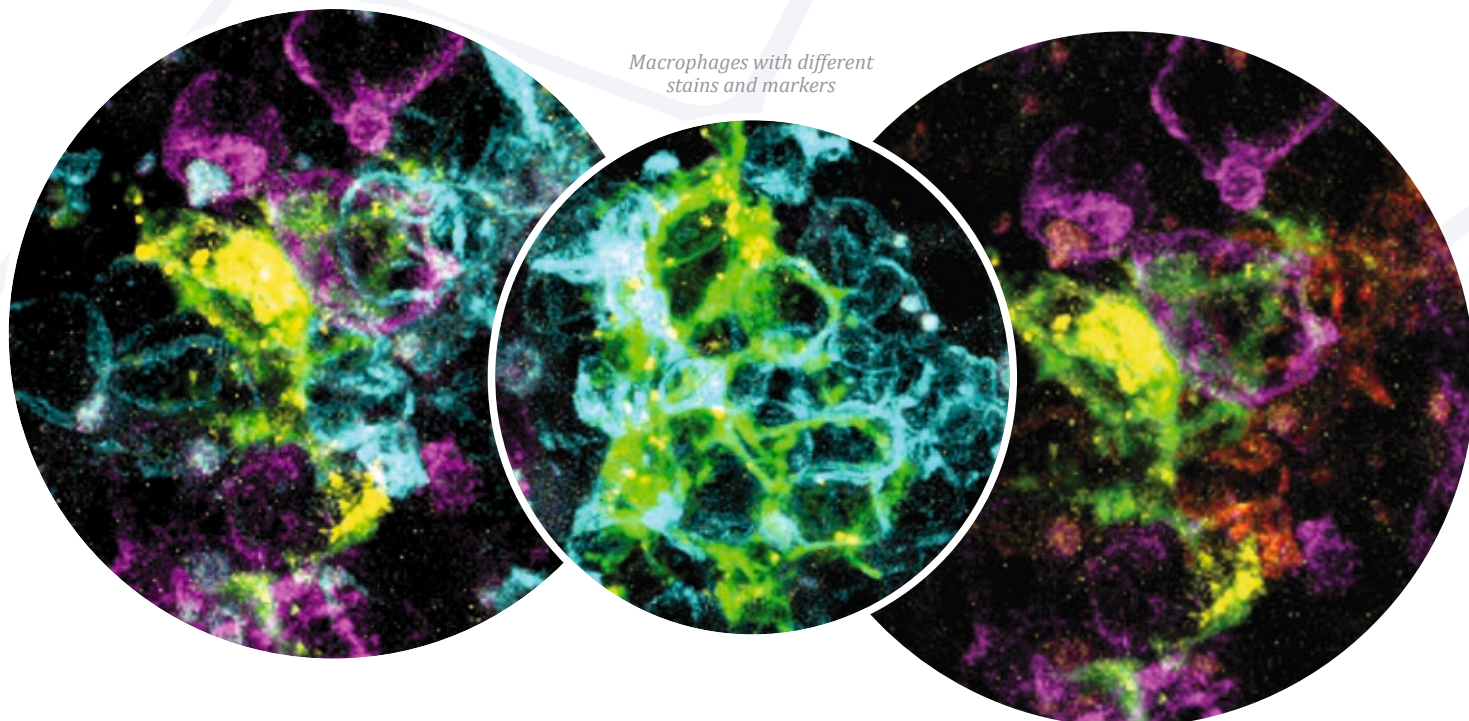
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Macrophages with different stains and markers

a study last year that points in the same direction. The researchers had administered a BCG vaccine to the skin of volunteers, and three months later examined their bone marrow and immune cells in the blood. In a result reminiscent of the animal experiments conducted by Divangahi's group, altered genetic activity was found both in the blood monocytes and in their hematopoietic precursor cells. The scavenger cells also released more inflammatory messengers, so-called cytokines, which render the natural immune defense more powerful overall. According to the authors of the study, it is possible that BCG components or the body's own signal substances travel to the bone marrow via the bloodstream from the puncture site in the skin in order to initiate reprogramming of the blood stem cells.

These relationships could also explain why vaccinations – in addition to their pathogen-specific effects on B and T cells – sometimes lead to a broad activation of the non-specific immune defense. Epidemiological studies in developing countries have shown that BCG-vaccinated newborn also die less frequently from other infections, regardless of the milder courses of tuberculosis. For example, according to model studies, BCG could stimulate the body's natural immune response to yellow fever or malaria. Likewise, live vaccines against measles or polio seem to protect against additional pathogens.

Photos: Amir Kayvanjoo, AG Mass, LIMES, Uni Bonn

Institute of Reconstructive Neurobiology

From disease modeling to stem cell therapies

The Institute of Reconstructive Neurobiology at the University of Bonn Medical Faculty focuses on the use of pluripotent stem cells for the study and treatment of neurological disorders.

Based on a broad technology portfolio including cell reprogramming, neural differentiation, direct cell fate conversion, stem cell industrialization and neurotransplantation, the Institute develops stem cell-based model systems for disease-related research and drug development as well as novel cell therapy regimens. It closely

interacts with LIFE & BRAIN GmbH, a translational hub of the University of Bonn Medical Faculty providing stem cell products and services for pharma, biotech and academia.

Institute of Reconstructive Neurobiology
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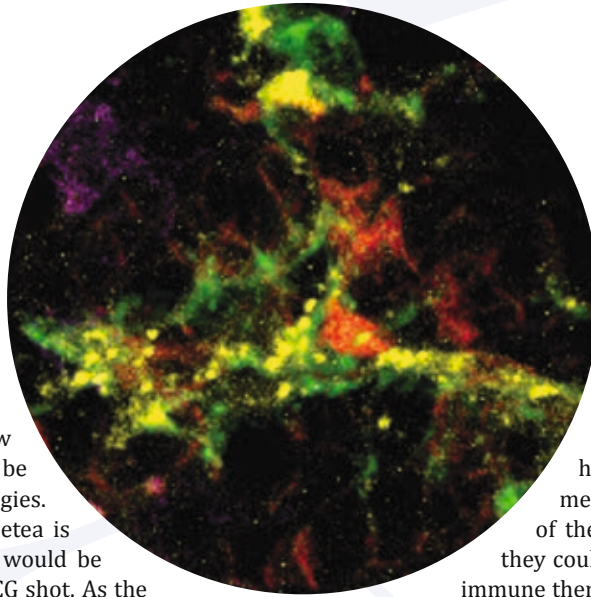
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Institute of Reconstructive Neurobiology



New vaccination strategies being put to the test

Researchers are already exploring how non-specific immune memory can be targeted for new vaccination strategies. For example, a team led by Mihai Netea is researching whether elderly people would be better protected overall through a BCG shot. As the interim results of the clinical study called ACTIVATE suggest, respiratory tract infections in particular are less common among people who have been vaccinated. In addition, various international working groups are currently investigating whether BCG is also suitable for the prevention of COVID-19. It may even be possible to genetically modify the vaccine bacillus so that it carries coronavirus antigens on its surface – thus activating both the non-specific and the adaptive immune system at the same time.



Stained macrophages

However, even independent of an application to COVID-19, these approaches are likely to help elucidate the fundamental learning capacity of the natural defense – and they could pave the way for new immune therapies. “In the future, we may be able to use pharmacological substances to influence blood stem cells in a very specific manner,” says Divangahi. For example, how can a non-specific immune response be triggered, maintained, or modulated? How do innate and acquired defense mechanisms interact? “We have only just begun to look at these questions,” says Divangahi. “But in the long run, this will lead to a more complex and complete picture of our immunological memory.”

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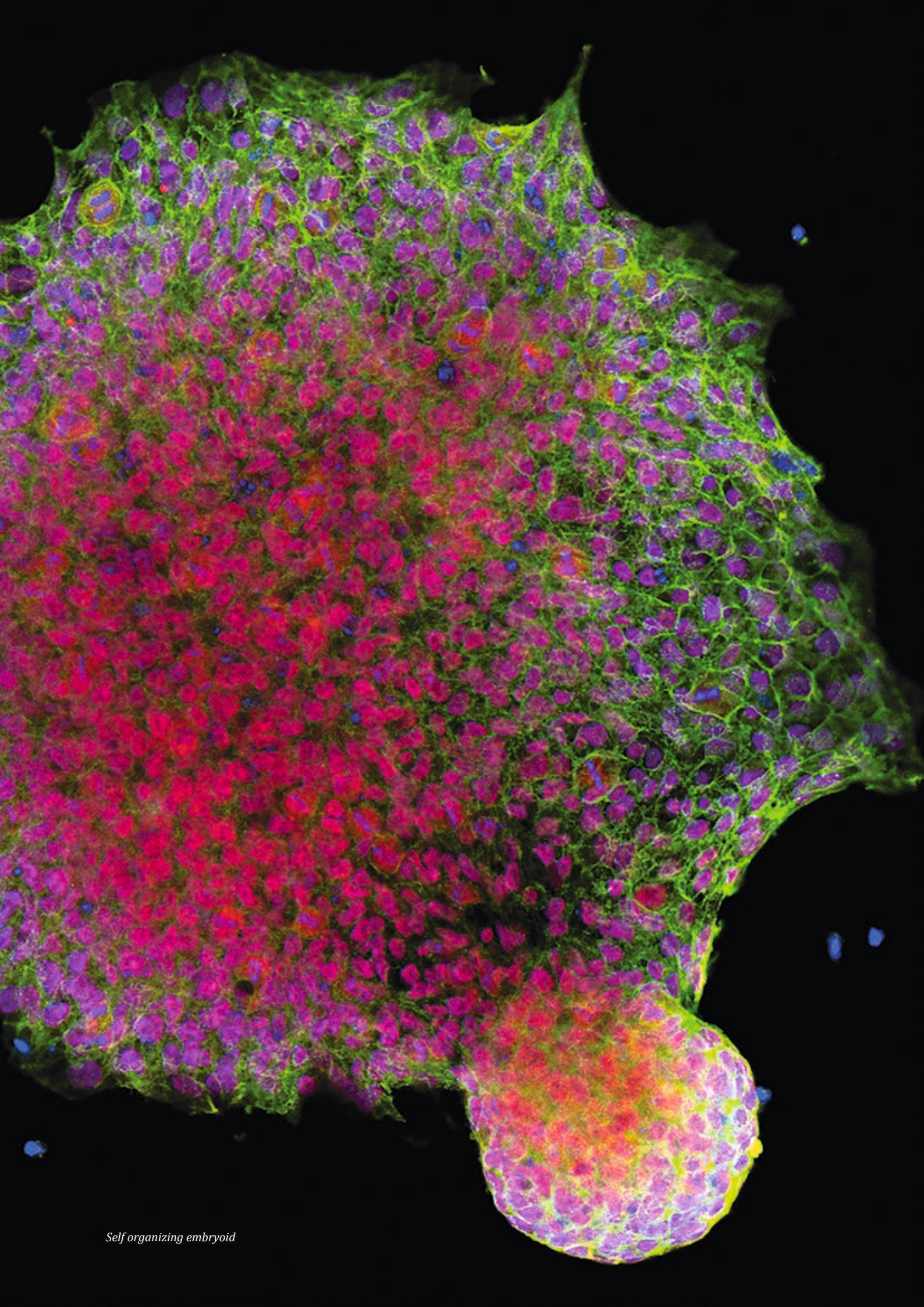
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Self organizing embryoid

White Paper on organoid technology

Tiny substitutes – the age of organoids

They may be just the size of a mustard seed, but over the last few years organoids have advanced to stardom status in the health research field. Thanks to sophisticated 3D tissue culture techniques, it is now possible to use stem cells to grow self-enclosed reductionist model versions of brains, intestines, or hearts. Although organoids are less complex, they model their in vivo counterparts so closely, that organoids offer completely new ways of performing research into developmental biology and disease processes. From the coronavirus pandemic, to cancer, to genetic disorders, organoids are already in use at many different frontiers in medicine. Together with the Berlin-Brandenburg Academy of Sciences and Humanities (BBAW), the GSCN has published a comprehensive White Paper on the current state of research and the potential of organoid technology.

Through the White Paper “Organoids – from stem cells to future technologies”, the Interdisciplinary Research Group (IAG) *Gene Technology Report* of the Berlin-Brandenburg Academy of Sciences and Humanities (BBAW) in cooperation with GSCN hope to raise public awareness of this research field and stimulate an interdisciplinary public debate on organoids. The 45-page publication was published in November 2020. The IAG’s has drafted core statements and recommendations for action on the use of organoids. And a GSCN report on organoids offers a tour of the latest developments in this major research field and of current and potential future applications. The focus is on current organoid research projects and companies, with viewpoints from a range of researchers and stakeholders. The following text is a shortened excerpt of the GSCN report.

Sina Bartfeld heads a junior research group at the Institute for Molecular Infection Biology at the University of Würzburg. Every time she looks down her stereo microscope and sees her “mini-stomachs” – each just a few days old – she is always enraptured. “Organoids are just so beautiful,” she opines. Barely half a millimeter across, these delicate, hollow balls consist of just a single layer of cells. Tiny blebs bulge out from their edges. “In addition to a variety of differentiated cell types, they also contain stem cells, which provide a constant supply of new cells,” explains Bartfeld. It takes less than two weeks to produce these stomach models.

Bartfeld is one of a rapidly growing band of researchers who are using organoids to transform biomedicine. From intestines, pancreases and hearts to livers, lungs and brains, simplified miniature versions of almost every organ in the human body are currently blossoming in cell culture labs around the world. And these tiny in vitro models don’t just look like their real life human or animal counterparts. They also mirror astonishingly closely the

biological processes taking place in them. “What’s fascinating is just how complex these structures are, and what they reveal to us about real life,” says Bartfeld.

This report, part of the White Paper on organoids, aims to provide an insight into current research on organoids globally, and in Germany, Austria and Switzerland in particular. It offers a guided tour of an extremely dynamic research field. An astonishing 3D microcosm is currently being created in stem cell labs the world over. To explore this microcosm, researchers are deploying some of the most powerful life sciences technologies currently available. The use of organoids as model systems closes a major gap in biomedical research, paving the way for new therapeutic approaches, innovative drugs, and potentially to reducing the use of animal experiments in healthcare research.

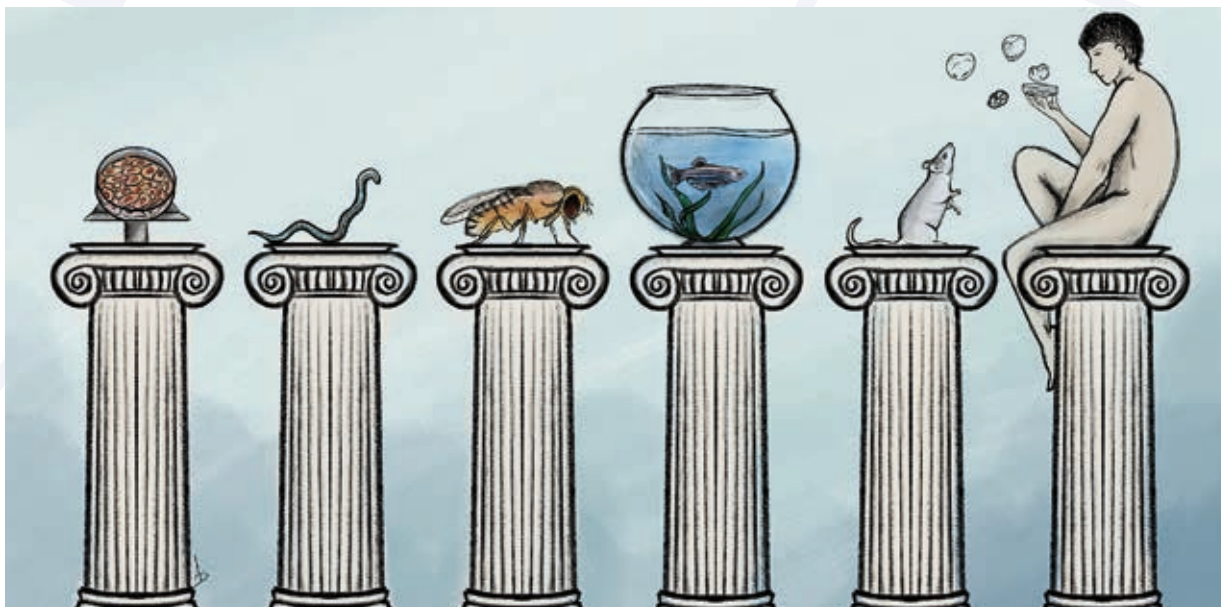
The two routes to building an organoid

Produced from stem cells, organoids are miniature three-dimensional balls of cells with structures which mimic those of an organ. Though microscopic in scale, they nonetheless mirror the architecture and many of the functions of their macroscopic counterparts with impressive fidelity. 3D cell cultures are by no means a new trend. Tissue engineers have been experimenting with 3D aggregates composed of a mixture of cell types for decades. But the decisive breakthroughs in organoid research date back to just over ten years ago. That’s when researchers succeeded in awakening the intrinsic ability of these cell aggregates to self-organize.

Stem cells are key components in creating organoid cultures, as they produce the cells required. The world of organoid research can be divided into two camps, involving two different techniques. One harnesses adult stem cells, the body’s natural regenerative mechanism. These stem cells live in the tissues of the body and produce a constant supply of new cells to replace cells that are worn out or damaged. The other source of cells are pluripotent stem cells. These cells are able to develop into almost any of the more than 200 different cell types in the human body. The term covers both embryonic stem cells (ES cells) and induced pluripotent stem cells (iPS cells). The latter can be obtained by transforming fully differentiated skin cells using a set of four transcription factors – a reprogramming technique which won Japanese scientist **Shinya Yamanka** the Nobel Prize.

Adult stem cells back in the limelight

Before taking up her current post at the University of Würzburg, Sina Bartfeld worked as a postdoc at the Hubrecht Institute in Utrecht in the Netherlands, where she



Biological model systems in close proximity to humans.

was part of a research group led by Dutch stem cell researcher **Hans Clevers**. Clevers is one of the pioneers of and catalysts for the current cell culture boom. From the crucible of the Hubrecht Institute, organoid technology has spread to research labs the world over.

“Using techniques developed in Hans Clevers’ lab, we can recreate the adult stem cell niche in a culture dish,” explains Bartfeld. This trick was first performed in 2009 by **Toshiro Sato**, working in Hans Clevers’ lab in Utrecht, using tissue from the small intestine. One of the keys to the team’s success was identifying the LGR5 protein as a stem cell surface marker that could be used to easily isolate adult stem cells from intestinal tissue removed during surgery. This marker can also be used to sniff out adult stem cells in other parts of the body, where they are involved in producing new tissue.

Further progress was achieved through refinements in cell culture techniques. By adding Matrigel, a gel-like substance secreted by mouse cancer cells, researchers were able to closely recreate the microenvironment inhabited by adult stem cells – their niche. This 3D matrix provides

a highly agreeable environment for cells. After that, all that’s required is the addition of growth factors and a few other cell types and the adult stem cells begin to do in a Petri dish what they do in the wall of the intestine – to renew themselves and organize themselves into zones corresponding to villi or crypts. They grow in vitro into a highly simplified “miniature intestine”.

Publication of these results in *Nature* in 2009 led to an explosion of activity in the field, explains Bartfeld. Having been very much overshadowed by iPS cells, adult stem cells found themselves back in the limelight. Many of her Utrecht colleagues at this point moved on to working on specific organ systems.

Fascinating self-organization

“What’s fascinating about organoids is that they self-organize and then continue growing,” says Bartfeld. “We emulate the signals and the environment in the body in a culture dish – the rest is all down to the stem cells.” A major advantage is, that “this culture technique gives us an inexhaustible source of human cells from a specific tissue.

Abb.: Andreia Sofia Batista Rocha, IMBA Vienna

Heidelberg Institute for Stem Cell Technology and Experimental Medicine (HI-STEM)

HI-STEM gGmbH is a non-profit public-private partnership between the German Cancer Research Center (DKFZ) and the Dietmar Hopp Foundation (DHS). Located within the DKFZ in Heidelberg, HI-STEM performs cutting-edge research on stem cells and translates these results into novel clinical applications. This includes the development of novel diagnostic tools and innovative therapies to monitor and target leukemic and solid tumor stem cells as well as metastatic disease. Professor Dr. Andreas Trumpp and seven Research Group Leaders direct an international research team of more than fifty employees.

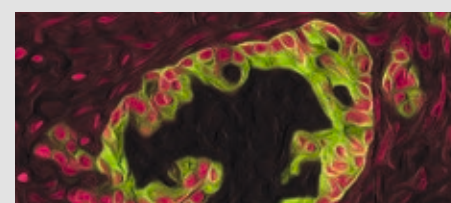
The HI-STEM Research Groups:

- Hematopoietic and Leukemic Stem Cells (A. Trumpp)
- Stem cells at the interface of hematopoiesis, immunity and cancer (Simon Haas)
- Pattern Recognition and Digital Medicine (Daniel Hübschmann)
- Experimental Hematology (Mick Milsom)
- Stress induced activation of HSCs (Marieke Essers)
- Cancer Stem Cells and Metastasis (Martin Sprick & A. Trumpp)
- Metastatic Niches (Thordur Oskarsson)
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Plus, the cells are not genetically modified.” A further bonus is that the technique for obtaining and culturing these cells is easy to learn, and the organoids are also easy to handle. “Freeze them, thaw them, pop them in the mail – no problem.”

Nevertheless, there are limits to what organoid builders can achieve using adult stem cells. Some current organoids don't contain the full spectrum of cell types. “The main limitation is that we can only grow epithelial cells,” explains organoid pioneer Hans Clevers. Epithelial tissue lines surface on the inside and outside of the body, and are found in places like the skin, gastrointestinal tract, and lungs. The body contains three other tissue types which can't be mimicked using adult stem cells – connective tissue such as bone and fat, muscle tissue, including heart muscle, and nervous tissue.

Pluripotent stem cells – all-rounders bridge the gaps

Cell biologists can overcome this shortcoming by using pluripotent stem cells. That's because, with the right cocktail of growth factors, both iPS and ES cells can be transformed into almost any cell type in the human body.

One of the first scientists to describe the use of pluripotent stem cells to form 3D organoids was Japanese researcher **Yoshiki Sasai**, who sadly passed away long before his time. His observation, published in the journal *Cell Stem Cell* in 2008, was that, if by allowing embryonic stem cells to form a clump of cells before undergoing differentiation into nerve cells, the clump of cells begins to organize itself into a structure that resembles the early stages of brain development. Once again, the key to success was a gel-like 3D matrix.

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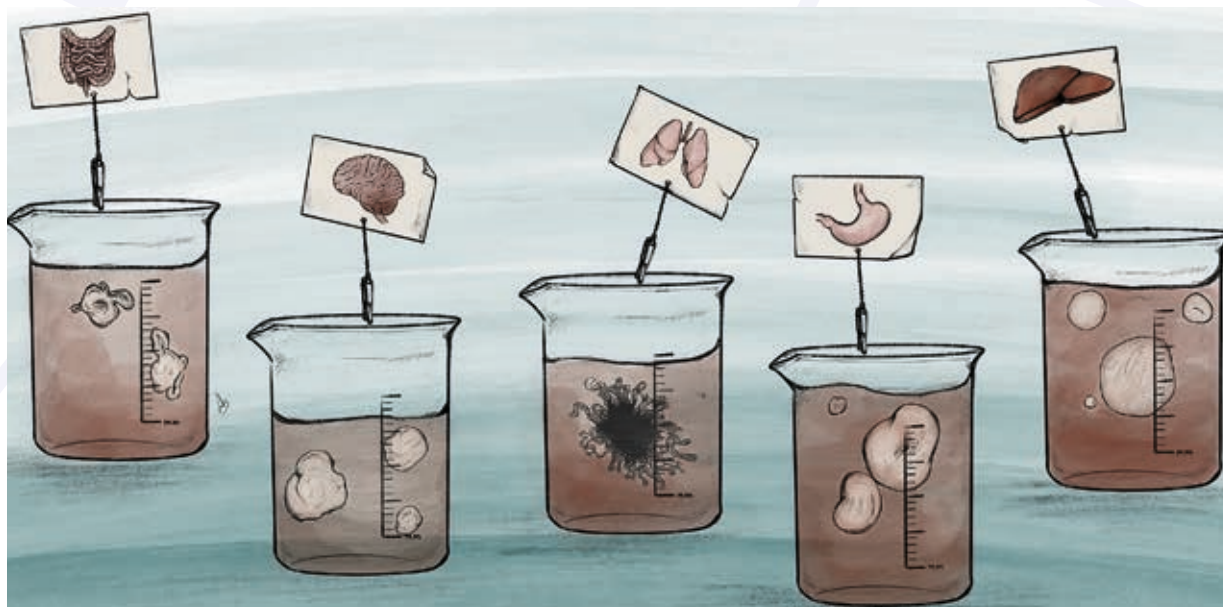
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The organoid mirocosm: Organoids can be produced for almost every human organ.

In response, developmental biologists worldwide set to work developing 3D cell cultures for a wide range of organ systems, ranging from the central nervous system to the kidneys and pancreas. But the organoid that has made the biggest splash in recent years has been the pea-sized brain models created in **Jürgen Knoblich's** lab at the Institute of Molecular Biotechnology of the Austrian Academy of Sciences (IMBA) in Vienna by researcher **Madeline Lancaster**. Neuronal progenitor cells produced from iPS cells began to aggregate to form cerebral organoids almost of their own accord. The external structure and molecular biology of these tiny balls of neural tissue resembles that of an embryonic brain.

Making brain organoids

Biologist **Agnieszka Rybak-Wolf** is another researcher who specializes in using iPS cells to grow cerebral organoids. She heads the newly set up Organoid Platform at the Max Delbrück Center (MDC) in Berlin. "In culture flasks the stem cells clump together to form three-dimensional cell aggregates. Using a special mix of growth factors, they are then induced to differentiate into neuronal

cells." If you embed this cell cluster in a 3D matrix, you can once again observe this fascinating process of self-organization. "If you get neural rosettes forming – they look a bit like flowers – that's a good sign," explains Rybak-Wolf. Now it's time to wait while the organoids grow to the size of a pea, mature and tissue organization becomes more complex. This can take three months or more. "The brain age of these organoids typically corresponds to around the 23rd to 28th week of gestation," as Rybak-Wolf explains.

But this time scale presents challenges for the researchers. Since, in becoming an organoid, pluripotent stem cells have to travel along a much longer developmental pathway than adult stem cells, these "mini-brains" in the laboratory can be highly variable. This variability is further exacerbated by the fact that cerebral organoids in a culture dish are derived from different pluripotent stem cells. Nutrient supply in 3D tissue cultures is a further difficulty. The lack of a vascular system means that the core of these pea-sized clumps is not directly supplied with oxygen or nutrients, so that if their growth is too strong much of this core tissue dies off.

Abb.: Andreia Sofia Batista Rocha, IMBA Vienna

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A new generation of biological model systems

Vienna-based stem cell researcher **Jürgen Knoblich** is convinced that human organoids represent a new generation of biological model systems that will enable human organ development and diseases to be researched in unprecedented detail.

“As experimental models, human organoids bridge the gap between animal models and humans,” says Knoblich. To understand stem cell biology and the key stages of organ development, developmental biologists have traditionally relied on model organisms such as nematodes, zebrafish and mice. It’s clear, however, that these animal models mirror tissue architecture, human genetics and human physiology only imprecisely.

The advent of organoids has now made it possible to rapidly mimic the process of human organ development in vitro by way of techniques that are not excessively technically complex. “This opens up new possibilities, particularly for organ systems that are difficult to perform experiments on, such as the brain.” The stem cell-derived cerebral organoids cultured in Vienna are especially useful for studying the details of early brain development. It’s not just in terms of genetics that these pea-sized balls of tissue better model the situation in humans. They also match up in terms of timing – the organoids grow and develop at the same pace as human embryos.

For Knoblich, organoids are therefore ideal for studying how neural stem cells and progenitor cells give rise to such a large variety of different neurons in this highly



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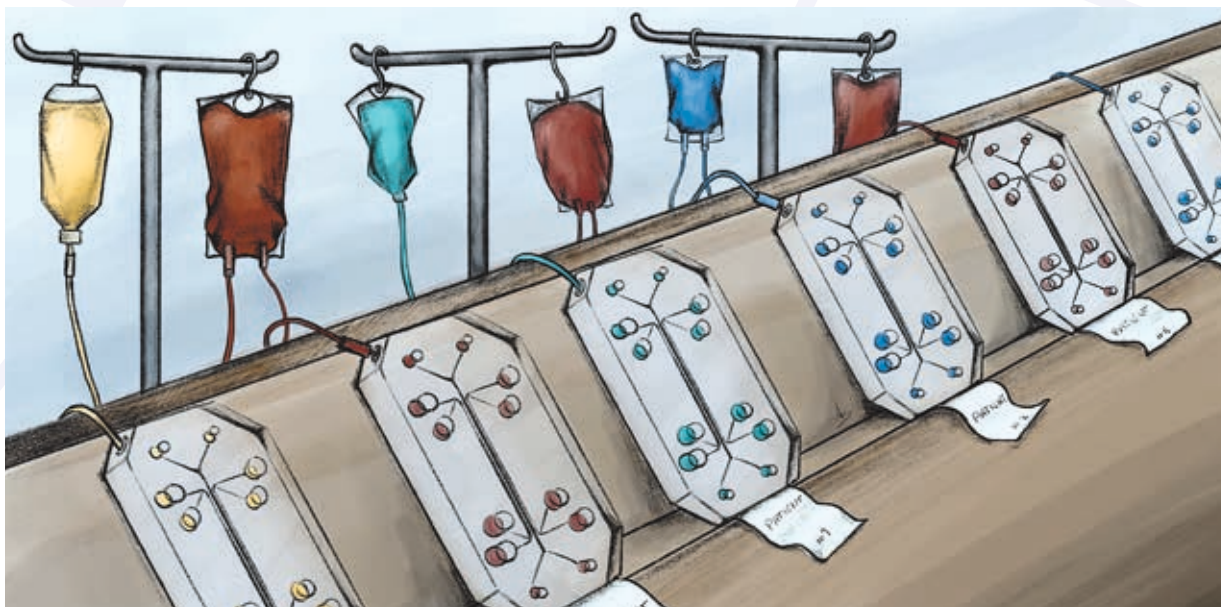
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The organoid clinic: In the future, multi-organ chips as a proxy for a patient could help to identify the best combination of active ingredients for the individual therapy.

complex environment, and how they interact with each another. And in fact, the cells in these cerebral tissue models form actual synapses. A number of laboratories worldwide have recorded neural network activity – so-called oscillations.

Knoblich urges caution in interpreting these observations, however. More research into the characteristics and relevance of this data is needed. To date, organoid systems have only been able to model tiny portions of the human body *in vitro* and have not been able to model interactions between different parts of the body. Brain organoids are a long way from realizing the highly complex tissue architecture and spatial organization of a real brain. “Modeling higher order brain functions is also not what the field is trying to do,” explains Knoblich. In addition, these tissue aggregates lack key cell types, such as microglia, other immune cells and blood vessels.

New disease models – drilling down on viruses, cancer and genetic disorders

But organoids don’t just offer new insights into developmental processes. They also give rise to exciting new opportunities for researching disease mechanisms. The spectrum ranges from infectious diseases and cancer to genetic disorders and neurodegenerative diseases.

The revolution in stem cell research ushered in by iPS cells means that biomedical researchers for the first time have direct access to ‘real’ human cellular material from both healthy people and individuals with disease, in almost inexhaustible quantities. Using ‘molecular scissors’, such as genome editing tool CRISPR/Cas9, they can make precise changes to stem cell genomes. It is thereby possible to produce disease model cells with tailored genetic modifications in a laboratory.

This enables organoid culture to serve as *in vitro* patient surrogates – cell-biological ‘avatars’. The hope is that these organoids will react to drugs in the same or a similar way as the actual organ in the human body. This would provide researchers with a more efficient way of

modeling and testing the effect of a drug without exposing patients to unnecessary side effects. That would enable medics to more accurately predict whether a patient would respond to a specific therapy. The ideal outcome would be treatment tailored to the cellular characteristics of the individual disease.

Pandemic research: how COVID-19 ravage the body

Organoids may be quite a recent development, but they have already proven themselves to be valuable tools for researching new infectious diseases and pandemic viruses. When the mosquito borne Zika virus emerged in 2016, doctors and virologists spent a long time puzzling out how the pathogen is able to cause severe brain malformations in unborn babies.

As models for researching the SARS-CoV-2 coronavirus, organoids are also currently at the forefront of the fight against the COVID-19 pandemic. The initial focus has been on the most important point of entry into the body, the respiratory tract.

Andreas Hocke’s team is using the latest molecular biology and imaging techniques to investigate how highly contagious viruses such as influenza and coronaviruses attack living lung tissue and what they do to it. Hocke is an infectious diseases researcher at the Charité in Berlin and a pioneer in developing alternatives to animal experiments. Ten years ago, he developed a 3D lung tissue model derived from human lung tissue removed during operations at the Charité. It is now an established translational research tool there. The big drawback is that these tissue fragments are short-lived and available in limited quantities only.

For the last 18 months, Hocke’s team has therefore been experimenting with lung organoids produced from adult stem cells. “They are easy to multiply, can be cultured for long periods and closely mirror the cellular context. They can even be used to model chronic disease processes,” explains Hocke. His team has now succeeded in infecting these lung organoids with SARS-CoV-2 and in learning

more about which cell types the virus seeks out in the lungs. The focus is on the ACE2 receptor. Like the SARS-CoV-1 coronavirus described in 2003, SARS-CoV-2 uses this cell surface receptor to attach to cells and inject them with its genetic material. “Our investigations lend weight to the observation that the virus infects alveolar cells less than first thought, but instead triggers a systemic inflammatory reaction which has an indirect destructive effect on the lungs,” says Hocke.

Hocke is fascinated by organoids, but he is also well aware of their limitations. “A lung organoid mirrors basic functions very closely, but it doesn’t breathe,” notes Hocke. “Nonetheless they complement our existing models and help to reduce animal experiments.”

Global anti-COVID alliances were initially entirely focused on the respiratory tract. But evidence soon began to accumulate that SARS-CoV-2 also affects many other organ systems, including the brain, kidneys, gut, liver, heart, pancreas and placenta. But are these really new viral battle-grounds within the body, or is this just collateral damage from a misdirected immune response? What does the virus do within the body? Organoid researchers around the world quickly started to expose their 3D cell cultures to the virus. They found that the COVID-19 pathogen does not just infect lung, liver, and kidney organoid cells. Around 30 percent of COVID-19 patients have diarrhea, and in some patients the virus can be isolated from stool samples. In addition to **Hans Clevers** in Utrecht, **Steeve Boulant** from the Deutsche Krebsforschungszentrum (DKFZ) in Heidelberg is also using intestinal organoids to study how the virus interacts with human intestinal cells. SARS-CoV-2 has also been found to directly infect blood vessel organoids, like the organoids produced in **Josef Penninger**’s laboratory at the Life Sciences Institute at the University of British Columbia in Canada. Working with researchers from Paris, Cologne, Münster and Bonn, **Jay Gopalakrishnan** from the Institute of Human Genetics in Düsseldorf is investigating how SARS-CoV-2 infects neuronal cells in brain organoids.

New alliance develops organoid infection models

“It remains unclear to what extent SARS-CoV-2 can directly infect and damage other organ systems or whether this damage is triggered indirectly by the immune system,” says Andreas Hocke. The diversity of human organoid models provides the perfect platform for infectious disease research. This is set to be put to the test by a new nationwide research alliance organized by the University Medical Network to Combat COVID-19, which is funded by the Federal Ministry of Education and Research (BMBF). The alliance, which goes by the name Organo-Strat, in-

volves partners from nine locations who have come together to develop a range of different organoid-based models of infection.

The alliance is being coordinated by Charité researcher Andreas Hocke. Sina Bartfeld’s group in Würzburg and DKFZ researcher Steeve Boulant are also on board. University medical faculties in Würzburg, Jena, Heidelberg, Tübingen, Münster, Marburg, Hamburg and Aachen are also involved in the initiative. Although the focus is firmly on SARS-CoV-2, the aim is for the organoid models created to serve as a platform for future pandemic research when new pathogens emerge. “We’re also going to use these organoid models of infection for preclinical testing to help identify potentially effective antiviral drugs,” explains Hocke.

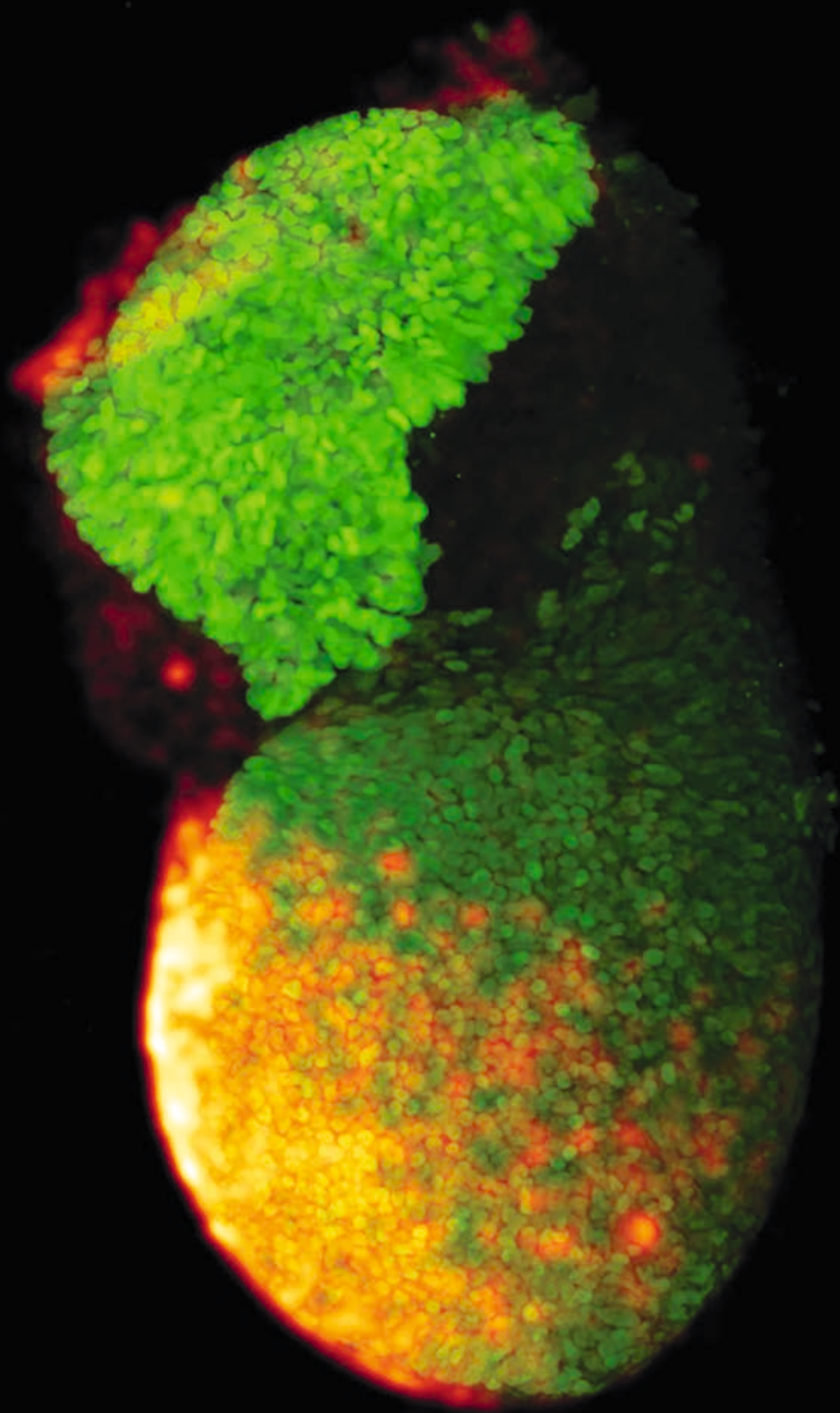
The next generation of organoids

“Fascinating as they are, we need to be clear that organoids are still strongly reductive models,” notes Würzburg infectious diseases researcher Sina Bartfeld. “They are significantly less complex than the corresponding organ.” Unlike organoids, real intestines (for example) do not consist of just the inner mucous membrane layer. They are also surrounded by connective tissue and muscle layers and enmeshed in a network of nerves and blood vessels. A brain organoid is not the same as a complete brain.

Bioengineers are leveraging many different factors to construct the next generation of increasingly complex organoid models. The big challenge for 3D cell culture is replicating a functional vascular system. Microfluidic channel systems on biochips are becoming increasingly proficient in mimicking blood flow, while 3D printing technologies enable the production of ever more sophisticated support structures for organoid construction. Meanwhile, tissue engineering specialists are hard at work on bringing together blood vessel organoids and other organ systems. Elaborate co-cultures made up of multiple cell types are also breaking new ground (*Find more on organ-on-chip technology in the long version of the White Paper report*).

The potential of organoid technology in medicine is huge: Sina Bartfeld is using these tiny surrogate organs to study how the layer of cells which lines the digestive tract responds to microorganisms and how it differentiates between benign and hostile residents. “Unraveling the complex interplay between immune cells, mucosal cells and microbes is extremely difficult,” notes Bartfeld. “Organoids help us to unlock the secrets of this hidden world.”

Text: Philipp Graf



A morphogen gradient: Embryonic day 7.0 of a mouse embryo stained against Cerberus 1 (anterior visceral endoderm) and Sox2 (in epiblast)

Interview with Professor Christopher Baum

The BIH: An institute devoted to medical translation

Since October 2020, molecular biologist and medical doctor Professor Christopher Baum has led the Berlin Institute of Health (BIH), which at the turn of the year became the translational research unit of Charité – Universitätsmedizin Berlin. In the interview, he talks about his goals for the medical translation institute. In 2021, the BIH and the GSCN founded the joint “Dialog Platform Stem Cell Research” with the aim of networking stem cell research more effectively, both nationally and internationally, and accelerating the translation of research findings in this area. Stefanie Mahler conducted the interview.

GSCN: In terms of translation, on which areas will the BIH focus in the coming years?

Christopher Baum: We have just established three so-called Focus Areas: “Translational Vascular Biomedicine” concentrates on the small blood vessels that play a role in many common diseases like heart attacks, strokes, diabetes and kidney diseases. In the Focus Area “Regenerative Therapies” the emphasis is on the novel cell-based and gene therapy treatment options as used in, for exam-

ple, immunotherapies. But we also want to leverage the body’s own regeneration processes, such as in patients with acute or chronic degenerative diseases. And the third Focus Area, “Single Cell Approaches for Personalized Medicine,” deals with novel single cell technologies and their clinical applications. We have just recruited four young junior group leaders in this area, each of whom works closely with a Charité clinician for the purpose of actually developing the technologies for the benefit of patients. Stem cell-based approaches are of key importance for all three Focus Areas.

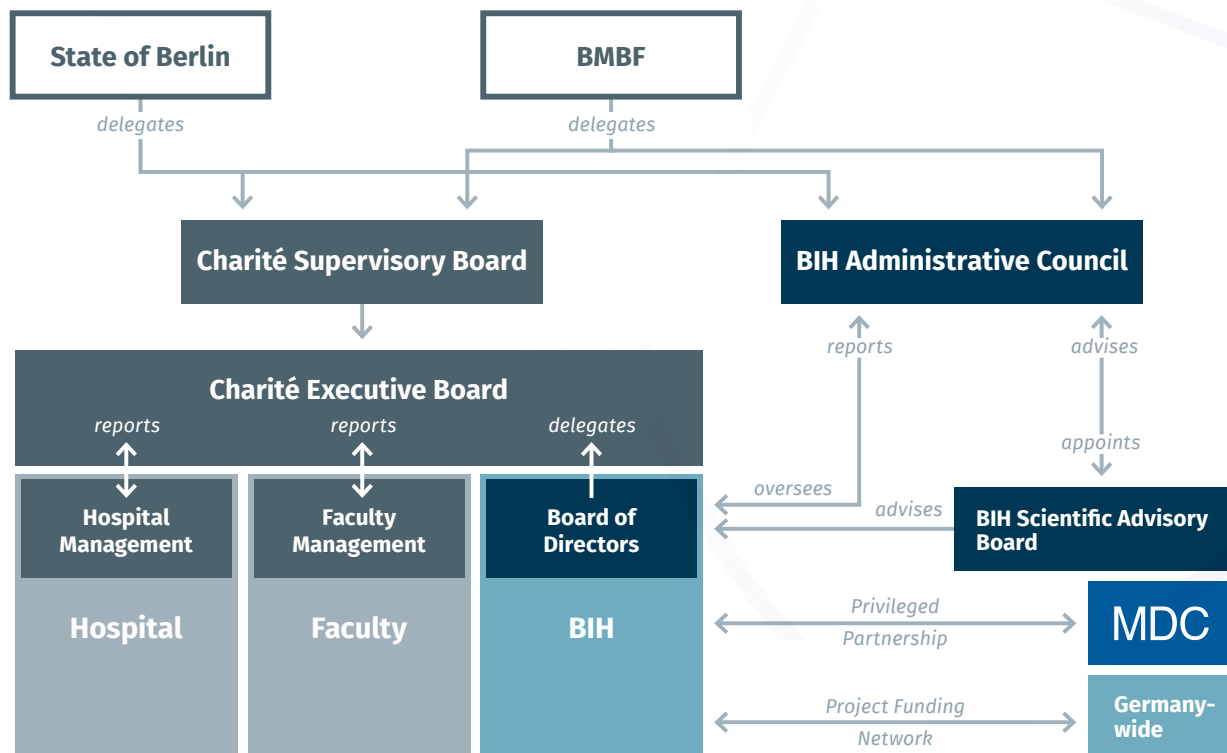
Moreover, the BIH has focused intensely on the digitalization of medicine since the outset. We develop and provide tools which make it possible to take full advantage of the enormous volume of data from biomedical research and clinical practice, obviously taking into account data protection issues. We also extract information from medical data for personalized therapy ourselves. And in the scope of the Digital Health Accelerator program, we support scientists and doctors who wish to put their digital health solutions into actual practice.

Prof. Christopher Baum

Chair of the BIH Board of Directors and Chief Translational Research Officer of Charité – Universitätsmedizin Berlin

Prof. Dr. med. Christopher Baum was born in 1962 in Marburg and studied philosophy (2 semesters in Mainz) and medicine in Essen, Freiburg and Hamburg. He received his doctorate (Dr. med.) in 1991 and habilitated in molecular medicine at the University of Hamburg in 1999. In the year 2000, he accepted a professorship in stem cell biology at the Hannover Medical School (MHH) and at the same time was associate professor of pediatrics at the Cincinnati Children’s Hospital in the USA. In Hannover, from 2006, he headed the Institute for Experimental Hematology, served as Ombudsperson for Good Scientific Practice and as Dean of Research, and in 2013 was elected President of the Hannover Medical School (MHH). In early 2019, Baum moved to the University of Lübeck as the first full-time vice president of medicine and board member of UKSH, Germany’s second-largest university hospital after Charité. Since October 2020, Christopher Baum has been chairman of the board of the Berlin Institute of Health (BIH). Scientifically, Christopher Baum became involved with gene therapy at an early stage. He developed gene vectors to insert genes into blood stem cells and uncovered the basics of the mutagenesis in gene therapy, which leads to blood cancer in patients treated with gene therapy. Based on this, he developed test methods to detect dangerous side effect before the transfer of the genetically modified blood stem cells.





Where would you like to see the BIH in five years; what goals would you like to achieve by then?

We would like to be perceived throughout Germany as an indispensable institute for medical translation. We are currently testing innovative instruments for promoting translational career and project development in the Berlin research environment. A key action area is the evaluation of translational projects: Is a project truly based on sufficiently reproducible research results? How great is the medical need and the anticipated benefit for patients? Have all regulatory aspects been considered and are all skills available in-house or in a suitable network? Any medically promising discovery must address such questions in the laboratory before further steps toward application and promotion are taken. But it goes without saying that the actual implementation of the first translational projects in five years, whether in the form of new diagnostic techniques, new treatment options or digital solutions that truly help patients, is also our goal.

What specific tasks in translation does the BIH hope to accomplish in the area of regenerative medicine (BIH Regeneration)? What will be the role of the technologies from stem cell research here?

One way in which the technologies from stem cell research are used in this area is the development of organoids, on which important research on the causes of or treatment options for diseases can be conducted – neurological diseases are an example. This includes novel techniques based on human cells, which should make it possible to reduce the number of animal experiments in research. Stem cell technologies are also used in the propagation, genetic modification and differentiation of autologous cells before the latter are given back to a patient. To this end, in Berlin we are pursuing projects in, for example, hematology, immunology and on the musculoskeletal system. And obviously our colleagues in the Single Cell Focus Area are also working with stem cell technologies, for instance when searching

BIH Center for Regenerative Therapies (BCRT)

The BIH Center for Regenerative Therapies (BCRT) was established as an interdisciplinary translational center with the goal of enhancing endogenous regeneration by cells, biomaterials, and factors which can be used to develop and implement innovative therapies and products. At the BCRT clinicians and researchers are working closely together on the medicine of the future: targeted, personalized medicine that depends on the early recognition of patients' individual healing potential. The primary focus of the BCRT is on diseases of the immune system, the musculoskel-

etal system, and the cardiovascular system supported by the interdisciplinary fields of tissue homeostasis & cachexia and molecular analysis/rare diseases for which currently unsatisfactory treatment options are available. According to our results, the analysis and control of inflammation/immunity plays a key role in the successful restoration of tissue homeostasis. Early cooperation with industry, health insurers and regulatory authorities as well as other external partners boosts the chances of innovation and exploitation of the new methods and provides access to flexible financing options.



BIH Center for Regenerative Therapies BCRT
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 Augustenburger Platz 1 · 13353 Berlin
www.bihealth.org/de/regeneration

Photo: Peer Schröder

for the “cell of origin” (i.e. the cause of a disease) or testing cell products for homogeneity.

Thanks to the German Stem Cell Network (GSCN), the BIH is now more involved in the German stem cell research scene – what hopes and what expectations do you see in this?

We are very excited about this cooperation. First of all, we are gaining a partner that is already networked throughout Germany, which also helps us to expand our network beyond Berlin. Secondly, we hope to have fruitful cooperation activities in the field of stem cell research in our own scientific units. And thirdly, GSCN stem cell researchers themselves may be interested in translating their findings into patient applications, and we would gladly assist them in doing so. Also, the BIH translational instruments specifically address complex medical products and should therefore be well suited for stem cell-based treatment methods.

ioSkeletal Myocytes

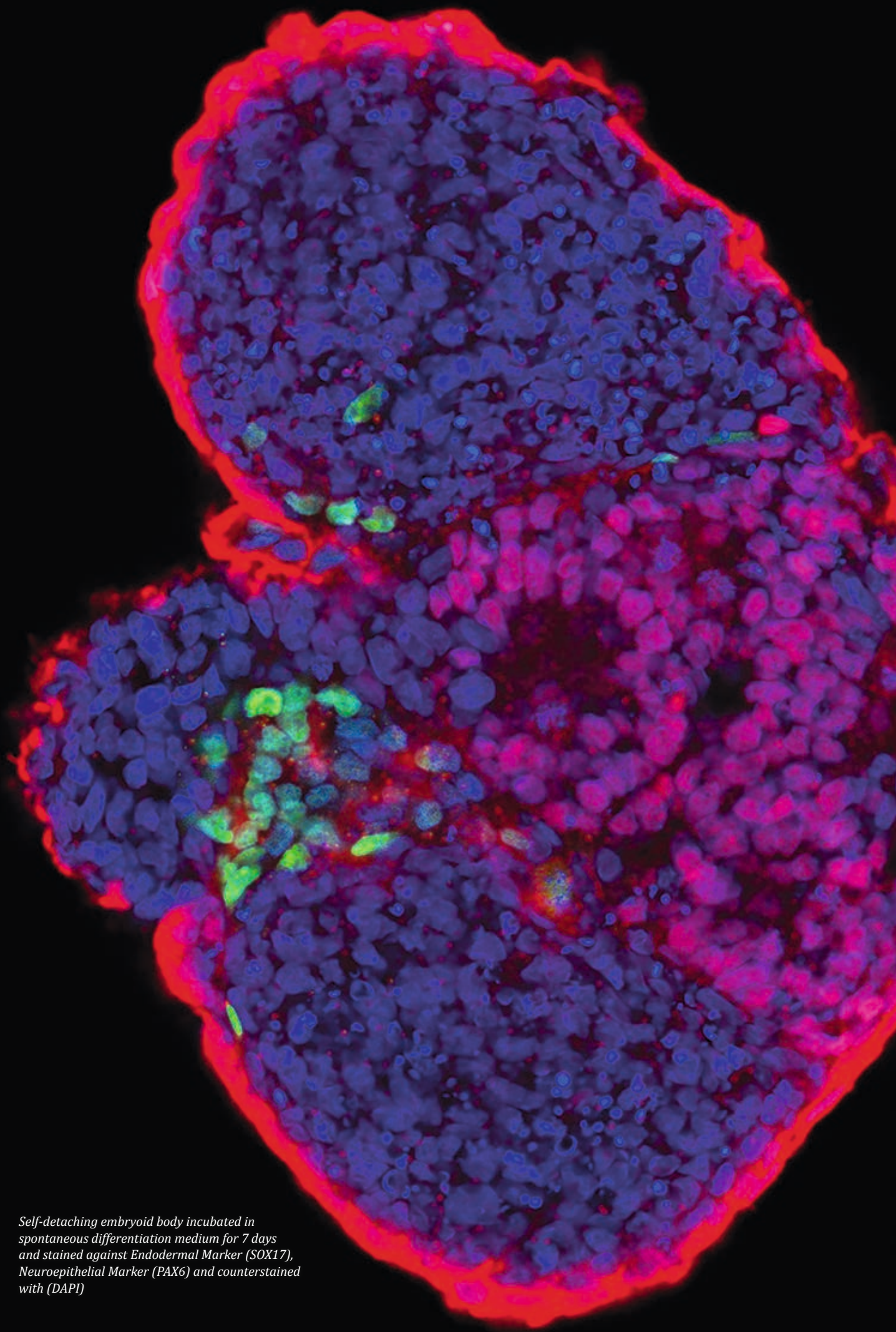
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Self-detaching embryoid body incubated in spontaneous differentiation medium for 7 days and stained against Endodermal Marker (SOX17), Neuroepithelial Marker (PAX6) and counterstained with (DAPI)

An essay by Hannah Schickl

On the status of brain organoids and embryoids. More specifically: the status of human embryos 2.0

The moral and legal (or normative) status of both human brain organoids and embryoids is dependent on the moral and legal status of human embryos. Brain organoids and embryoids could potentially force us to rethink the status of human embryos.

Organoid research – the use of stem cells to create three-dimensional organ cultures – has advanced rapidly since first coming to the fore a little under 12 years ago, and has already made the leap from the lab to clinical use. Given this, it is surprising that the ethical (and legal) debate around their use is relatively tractable. In Germany in particular, debate on the ethics of organoid research is, both among professionals and among the public, at best still in its infancy. This may be attributable in part to the fact that the only ELSA research currently being conducted consists of one legal subproject in Bavaria (“Interaction of Human Brain Cells/ForInter”, Hans-Georg Dederer, Chair of Constitutional and Administrative Law, Public International Law, European and International Economic Law at the University of Passau) as well as a working group at the German National Academy of Sciences Leopoldina, both on brain organoids. In addition, media interest in organoids in general currently remains relatively modest. Another conspicuous feature of the debate to date is that many articles limit themselves to offering an overview of potential ethical issues. In doing so, it is often assumed that organoid research merely rehashes well-worn ethical questions of established fields such as research and medicine in general, or stem cell research in particular. This has now become a popular assumption when it comes to the ethics of new fields of research and technologies, one example of this being genome editing. The fact that organoid research and its applications throw up numerous ethical questions which have previously been and are now being asked in related fields (such as research with human em-

bryonic stem cells, human-animal chimeras, genome editing, animal experiments, biobanks, data protection, types of informed consent, and distributive justice) does not mean that there are no ethical questions specific to it. Such questions arise in particular in relation to brain organoids and embryoids. These questions are not just new – some also have significant ethical and legal ramifications.

Hollow debate on the consciousness of brain organoids

Human brain organoids are cultured from human pluripotent stem cells. They are currently able to recapitulate various regions of the embryonic to mid fetal brain in vitro. This raises two sets of ethical questions, but curiously – both domestically and internationally – only one is the subject of serious debate. In Frankenstein-esque thought experiments, writers raise the concern that future, more mature, more complex brain organoids could develop consciousness in vitro. Concern for the well-being of human brain organoids is sufficiently well developed that it has been proposed that legal guardians should be appointed to represent the possible interests of these entities (analogous to guardians in child custody cases). This set of ethical questions poses a number of difficulties. Given that there is uncertainty over whether existing living organisms that are unable to communicate or are not understood possess consciousness (as, for example, remains the case for most animals, fetuses and newborn babies, patients in a coma, etc.), it is *biologically* very difficult – if not impossible – to anticipate whether brain organoids might be able to develop consciousness and, if they were able to, what form it would take. The vast majority of biologists consider it very unlikely. There is also a *practical*, methodological problem, especially for in vitro cultures, of measurability. It is also unclear from a *theoretical* point of view what we should be measuring. The term ‘consciousness’ covers a variety of different, graduated characteristics, states, and capabilities. When discussing consciousness in brain organoids, different writers therefore cite a wide variety of categories (e.g. perception, sentience, the ability to learn, self-awareness, etc.). Just as unclear is what the *consequences* of this should be, which is why most writers settle for calling for the question to be debated further and more widely – an approach which is scientifically somewhat unsatisfactory. Putting aside the fact that the debate remains vague on a

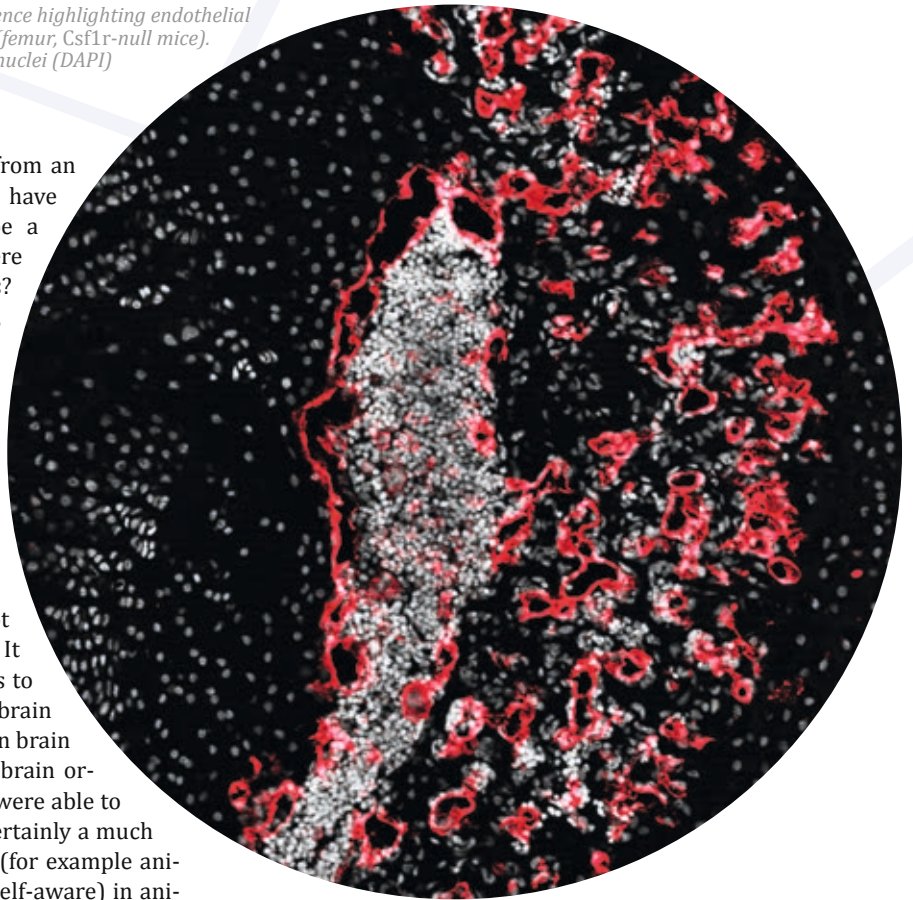
1 Preparatory work for this article can be found in the section *Ethische Fragestellungen im Zusammenhang mit der Organoidforschung* by the above author in the introduction to the volume *Organoide. Ihre Bedeutung für Forschung, Medizin und Gesellschaft* (edited by S. Bartfeld, H. Schickl, C. Alev, B.-K. Koo, A. Pichl, A. Osterheider and L. Marx-Stölting. Baden-Baden: Nomos 2020, p. 51–53. Available at: <https://www.nomos-elibrary.de/10.5771/9783748908326/organoide>) and an interview with the author in the white paper *Organoids – from stem cells to future technologies* (edited by the Interdisciplinary Research Group *Gene Technology Report* and the GSCN. Berlin 2020, p. 12–13. Available at: <https://www.gentechnologiebericht.de/publikationen/organoide-2020>).

Immunofluorescence highlighting endothelial cells in the bone (femur, Csf1r-null mice). red: CD31, grey: nuclei (DAPI)

number of levels, the biggest problem from an ethical perspective is why this should have *normative relevance*. Would it even be a problem if human brain organoids were able to develop human consciousness? Of the capabilities cited in the debate, all have been demonstrated in animals. Not all animals, but then they are not present in all people either. Being human is not a necessary (or sufficient) requirement for possessing forms of consciousness. Consequently, if forms of consciousness are to be regarded as having normative relevance (which some of them, such as sentience and self-awareness, certainly are), it is not because they are 'human consciousness'. It therefore follows that this debate, if it is to be had at all, should concern itself with brain organoids per se, rather than with human brain organoids. So would it be a problem if brain organoids, be they human or non-human, were able to develop consciousness? Probably. But certainly a much lesser problem than the use of animals (for example animals which have sentience and/or are self-aware) in animal experiments, livestock farming, or other spheres (e.g. zoos, etc.). If we let some of the anthropocentric hot air out of the overblown debate on consciousness, it turns out to be a somewhat hollow debate, in which there is little worthy of discussion.

Is human brain development status relevant?

There is, however, a second, more neglected set of questions concerning human brain organoids that is more worthy of examination. Human brain development as a criterion for determining at what point human embryos and fetuses should have full protection of life, particularly in the context of abortion, has been debated by ethics specialists and legal researchers since the 1980s. The key concept underlying this position is, in an analogy between the beginning and end of life, a 'brain life criterion', analogous to the 'brain death criterion'. The latter has been an established criterion since the 1970s and enjoys official legal status in most countries. What makes a human being a human being – or more precisely an individual – is his or her brain and the capabilities associated with it (e.g. consciousness, self-awareness, the ability to communicate, etc.). It follows that personal life must end once brain function has irreversibly ceased and begin with brain development (which advocates of this position consider to be about the 10th week after conception). In Germany, the criterion of brain development has no legal status. (This would have the consequence of prohibiting abortion well



before the 12th week of pregnancy). However, the internationally widespread '14-day rule', allowing human embryos to be cultured for up to the 14th day after fertilization, can be traced back to the fact that the appearance of the primitive streak is the first harbinger of the developing nervous system and brain (which forms the basis of the capacity to suffer). If thus human brain development in very early embryonic stages is considered of significance for the moral and legal status of human embryos, consistency requires that it is also considered of significance for human brain organoids, particularly as these organoids are already able to recapitulate significantly later developmental stages. This could be used to argue for a ban on research involving human brain organoids, but it could equally be used to argue for a change to the 14-day rule (increasingly being called for anyway). Certainly human brain development as a criterion for determining the normative status of brain organoids needs to be examined from both ethical and legal perspectives, and repercussions relevant to the status of human embryos and existing legal regulations need to be reviewed. Given that the brain life criterion represents a weak position that has not found general ethical or legal acceptance and has not been enshrined in legislation, and that the 14-day rule is rather based on the capacity to suffer (for which, to ensure a margin of error, an earlier time threshold was selected), examining this point is likely to prove relevant, less for the status of brain organoids, and more for the status of human embryos.

Is development potential or totipotency status relevant?

Embryoids are the subject of intense ethical and legal debate internationally, but, somewhat inexplicably, very little debate in Germany. Like brain organoids, human embryoids are produced from human pluripotent stem cells and replicate early stages of embryonic development (blastulation, gastrulation, and neurulation) *in vitro*. As with human parthenotes and before that clones, at the heart of the debate is the question of whether embryoids are human embryos and whether legal protections applying to embryos apply to embryoids (in particular the 14-day rule). The reason this question is asked is that the relevant (predominantly restrictive) laws and guidelines use the term 'embryo' in a normative sense, i.e. anything that constitutes a human embryo is protected, and anything that doesn't isn't. This legislative structure has the consequence that,

over the last few years, not only science but, increasingly, also courts and legislators have repeatedly had to revisit anew the question of what defines an embryo. While human entities resulting from somatic cell nuclear transfer are recognized as embryos, in 2014 Europe's highest court decided that human parthenotes are not embryos (European Court of Justice C-364/13, December 18, 2014) – a decision with which most ethicists agree and which many biologists (rightly) find peculiar (the ISSCR, for example, defines parthenotes as embryos). The reason human parthenotes are not considered to be embryos is a limited potential for development (to birth) and therefore absence of totipotency. In the ongoing international debate on embryoids, the ability to develop into a (born) human is again considered the key argument for or against embryoids being entitled to the same moral and legal status as human embryos. Initially, the idea that human embryoids should enjoy the status of embryos was widely and some-



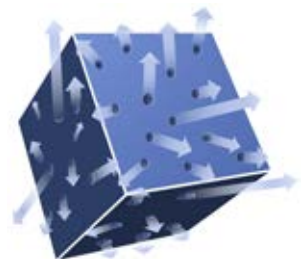
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times vehemently rejected. Rapid advances in embryoid development (especially mouse embryoids) caused some authors to revise their view and to now favor differentiating embryoids normatively into two types – those with and without the potential to develop into human beings (depending on whether or not extraembryonic tissue is present). Under this view, new and specific regulations are required only for the first category, and should be based on existing regulations for human embryos. The prevailing arguments in this ongoing debate are problematic in two respects in particular. Firstly, the question, “Are embryoids human embryos?” is not a normative question and must be considered separately from the question of the moral and legal status of embryoids. If we try to answer the two questions (what they are and how they should be protected) together, we run the risk of answering the former normatively, concluding that embryoids cannot – or even must not – be human embryos because they should not be protected like embryos. This fundamental mistake has already been made with respect to parthenotes and is now being repeated with respect to embryoids, particularly in the early stages of the debate. The more recent division of embryoids into two types places the emphasis on the question of how they should be protected and sets aside completely the issue of what they are. This avoids the counterintuitive conclusion that some embryoids are human embryos and some are not. The two questions are, however, completely unrelated – it may be that embryoids are not human embryos but should nonetheless be protected or equally vice versa. Embryos may enjoy legal protection, particularly in Germany, but also in many other countries, but there has been criticism of the ethical positions and arguments underlying this protection for decades, and this criticism is getting louder. Secondly – and building on the above – the

normative significance of development potential is ethically highly controversial. Indeed embryoid research is itself driving the debate on development potential as a normative criterion towards a significant turning point. It is not just embryoids that should be regarded as being capable of development or totipotent, but, under specific culture conditions, also the – according to the currently prevailing view – *pluripotent* stem cells from which they are derived. The key characteristic of embryoids is that the stem cells develop spontaneously through self-organization. In view of these new insights, some stem cell researchers now ascribe to pluripotent stem cells “a previously unsuspected capacity for totipotency” (Aach et al. *ELife* 2017; DOI: 10.7554/eLife.20674). Because totipotency, particularly in German embryo protection and stem cell research legislation, represents a key protection criterion, consistency requires that this insight should result in a ban on all research involving pluripotent stem cells, i.e. all stem cell research. The fact that embryoids require specific culture conditions is legally and ethically irrelevant, since every totipotent cell or totipotent cell aggregate requires a specific environment. Section 3(4) of the German Stem Cell Act (*Stammzellgesetz*) states accordingly that “any human totipotent cell which has the potential to divide and to develop into a human being if the necessary conditions prevail” should be protected. Whether or not these conditions are actually present is irrelevant; all that matters is whether the cell(s) would be capable of development if they were present. It might be expected that, at this juncture, the worlds of ethics, law and politics might, particularly in Germany, sit up and take notice. This has not, however, happened yet. In response to new scientific technologies and findings, those who oppose the potentiality argument have argued for years that development potential and toti-

Max Planck Institute for Heart and Lung Research (MPI-HLR)

The Max Planck Institute for Heart and Lung Research, located in Bad Nauheim, investigates developmental processes of organs in the cardiovascular system and the lung. A second focus is molecular and cellular processes during the formation of diseases in heart, blood vessels and lung, including remodeling processes in these organs. Scientists at the institute search for new approaches to support repair and regeneration of the affected organs.

The MPI closely cooperates with universities in Frankfurt, Gießen and Marburg. It is a major part of various federal and state excellence initiatives and contributes to two “Gesundheitsforschungszentren”.

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potency should not be normative criteria and that existing legislation based on these concepts is faulty. Recent research on embryoids showing that pluripotent stem cells are capable of totipotency is, however, the nail in the coffin for the normative (but note, not necessarily the biological) distinction between pluripotency and totipotency and can therefore no longer form the basis of (criminal) legislation. What is needed is not new legislation specifically for embryoids modeled on human embryo legislation, but rather the opposite. Embryoid research provides a concrete cause for fundamentally reconsidering existing embryo protection legislation, for giving priority to other normative criteria (e.g. – as is increasingly being argued – actual abilities such as sentience), and for permitting research on both embryos and embryoids.

There are calls for legislative change in this direction internationally, above all for changes to the 14-day rule (predominantly calls for it to be extended to, for example, 28 days). The argument here focuses on the difference in timing between embryoid and embryonic development, as a result of which the primitive streak in embryoids does not necessarily appear on day 15. Moreover, when we consider the above argument on the normative role of human brain development in the context of research on brain organoids, organoid research yields a number of points which tend to undermine the moral and legal status of human embryos, particularly in Germany, but also internationally – a sufficient number to seriously shake that status, and perhaps even to topple it completely.

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GSCN Annual Report



Boards

Executive Board

In accordance with Section 8(1) of the statute and rules of the German Stem Cell Network (GSCN) e.V., the Executive Board (presidium) consists of the Active President (chairperson), the Senior President (first vice chair), the Designated President (second vice chair), the Treasurer, and the Assessor. In the current association year (Sept. 2020 – Sept. 2021), the Executive Board is made up of the following members:

Active President (Chair)

Prof. Dr. Hans Schöler (MPI for Molecular Biomedicine)
office@mpi-muenster.mpg.de

Senior President (first vice chair)

Prof. Dr. Hartmut Geiger (Ulm University)
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Designated President (second vice chair)

Prof. Dr. Claudia Waskow (Leibniz Institute on Aging, Jena)
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Treasurer

Dr. Michael Cross (Leipzig University)
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Assessor

Prof. Dr. Andreas Trumpp (German Cancer Research Center Heidelberg)
a.trumpp@dkfz.de

Extended Board

In accordance with Section 9(1) of the statute and rules of the GSCN e.V., the Extended Board consists of up to 15 persons. In the reporting period, the Extended Board comprises the following members:

Prof. Dr. Dr. Thomas Braun (MPI for Heart and Lung Research, Bad Nauheim)
office.braun@mpi-bn.mpg.de

Prof. Dr. Oliver Brüstle (University of Bonn)
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Prof. Dr. Frank Buchholz (TU Dresden)
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Dr. Nina Cabezas Wallscheid (MPI of Immunobiology and Epigenetics, Freiburg)
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Prof. Dr. Ana Martin-Villalba (German Cancer Research Center Heidelberg)
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Dr. Elvira Mass (LIMES Institute, Bonn)
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Dr. Francesco Neri (Leibniz Institute on Aging)
francesco.neri@leibniz-fli.de

Prof. Dr. Wolfgang Wagner (RWTH Aachen)
wwagner@ukaachen.de

Long-serving board members Ingo Roeder and Michael Rieger stepped down from the boards in 2020. GSCN thanks them for their commitment and hopes that they will continue to support the network's interests and be available for activities as ordinary members.

Working group initiators

Scientific working groups

Pluripotency and reprogramming	Dr. Micha Drukker, Prof. Dr. Hans Schöler Prof. Dr. Mathias Treier mathias.treier@mdc-berlin.de
Somatic stem cells and development biology	Prof. Dr. Dr. Thomas Braun Prof. Dr. Federico Calegari (CRTD Dresden) federico.calegari@crt-dresden.de Prof. Dr. Ana Martin-Villalba Prof. Dr. Elly Tanaka (IMP Wien) elly.tanaka@imp.ac.at
Basic, translational and applied hematopoiesis	Prof. Dr. Claudia Waskow Prof. Dr. Timm Schroeder (ETH Zürich) tim.schroeder@bsse.ethz.ch
Stem cells in diseases (cancer stem cells)	Prof. Dr. Thomas Brabletz (University of Erlangen-Nuremberg) thomas.brabletz@fau.de Prof. Dr. Andreas Trumpp
Stem cells in regenerative therapies	Dr. Michael Cross Prof. Dr. Ulrich Martin Prof. Dr. Wolfgang Wagner
Stem cells in disease modeling & drug development	Prof. Dr. Oliver Brüstle Dr. Bert Klebl (Lead Discovery Center, Dortmund) klebl@lead-discovery.de Prof. Dr. Karl-Ludwig Laugwitz (Klinikum rechts der Isar, TU Munich) klaugwitz@med1.med.tum.de
Computational stem cell biology	Prof. Dr. Georg Füllen (IBIMA Rostock) fuellen@uni-rostock.de Dr. Carsten Marr (Helmholtz Zentrum München) carsten.marr@helmholtz-muenchen.de Prof. Dr. Ingo Röder (TU Dresden) ingo.roeder@tu-dresden.de
Strategic working groups	
Funding programs and policies	Prof. Dr. Ulrich Martin Vacant
Career development	Dr. Insa Schröder (GSI Helmholtz Center for Heavy Ion Research) i.schroeder@gsi.de Dr. Marieke Essers
Clinical studies and regulatory affairs	Dr. Andreas Kurtz (BCRT Berlin) andreas.kurtz@charite.de Prof. Dr. Torsten Tonn (Institute for Transfusion Medicine Dresden) t.tonn@blutspende.de Prof. Dr. Hans-Dieter Volk (BCRT Berlin) hans-dieter.volk@charite.de Dr. Zoltán Ivics (Paul-Ehrlich-Institut Langen) zoltan.ivics@pei.de
Public engagement and outreach activities	Prof. Dr. Tobias Cantz Ira Herrmann
Ethical, legal, and social aspects – ELSA	Prof. Dr. Tobias Cantz Sara Gerke (Harvard Law School, Boston, US) sgerke@law.harvard.edu
Patient information (e.g. stem cell therapies)	Ira Herrmann Richard Schäfer (Institute of Transfusion Medicine and Immunohematology, Frankfurt am Main) r.schaefer@blutspende.de
Technologies in stem cell research	Dr. Andreas Bosio (Miltenyi GmbH, Bergisch Gladbach) andreas.bosio@miltenyibiotec.de Dr. Sebastian Diecke (Max Delbrück Center, Berlin) sebastian.diecke@mdc-berlin.de Prof. Dr. Frank Emmrich (Fraunhofer IZI, Leipzig) frank.emmrich@izi.fraunhofer.de

Facts and figures

Meetings

Executive Board meetings

The Executive Board of the GSCN e.V. regularly holds meetings and video calls. These meetings are coordinated and organized by the Central Office. In 2020, the following Executive Board meetings and the General Assembly were also held online due to the coronavirus pandemic:

- 10 June 2020
- 6 Aug. 2020
- 21 Sept. 2020
- 8 Feb. 2021

Extended Board meetings

- 10 June 2020
- 21 Sept. 2020
- 8 Feb. 2021

General Assembly

- 23 Sept. 2020

Summary of members 2020

Total members		393
Natural persons	Full members	259
	Junior members	98
Legal entities	Research institutes	18
	Companies > 20 full-time employees	5
	Companies < 20 full-time employees	12
	Partner societies	1
Resignations by members in 2020		35
Exclusions of members in 2020		3
Members of working groups		
Scientific working groups	Pluripotency and reprogramming	204
	Somatic stem cells and development biology	155
	Basic, translational and applied hematopoiesis	87
	Stem cells in diseases (cancer stem cells)	160
	Stem cells in disease modeling & drug development	174
	Stem cells in regenerative therapies	211
	Computational stem cell biology	48
Strategic working groups	Funding programs and policies	146
	Career development	135
	Clinical studies and regulatory affairs	120
	Public engagement and outreach activities	65
	Patient information (e.g. stem cell therapies)	24
	Ethical, legal, and social aspects – ELSA	32
Technologies in stem cell research		221

As of 31 Dec. 2020

Member institutes

- Bavarian Consortium ForInter - BayFOR
- BIH Regeneration – BIH Center for Regenerative Therapies (BCRT), Berlin
- Center for Regenerative Therapies Dresden (CRTD)
- German Cancer Research Center (DKFZ), Heidelberg
- Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Hamburg, formerly IME, Aachen
- Fraunhofer Institute for Production Technology (IPT), Aachen
- Fraunhofer Institute for Cell Therapy and Immunology (Fraunhofer IZI), Leipzig
- Fraunhofer Translational Center for Regenerative Therapies (TERM), Würzburg
- Helmholtz Zentrum München, German Research Center for Environmental Health
- Institute of Reconstructive Neurobiology, University of Bonn
- ISAR Bioscience, Munich
- Leibniz Institute on Aging – Fritz Lipmann Institute (FLI) e.V., Jena
- Leibniz Institute for Zoo and Wildlife Research (IZW), part of the Forschungsverbund Berlin e.V.
- Max Delbrück Center for Molecular Medicine (MDC), Berlin-Buch
- Max Planck Institute for Heart and Lung Research (MPI-HLR), Bad Nauheim
- Max Planck Institute for Molecular Genetics (MPIMG), Berlin
- REBIRTH Cluster of Excellence, Hannover Medical School (MHH)
- SFB 873, COS, University of Heidelberg

Organizational members

- AMSBIO
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- HISS Diagnostics GmbH
- iota Sciences
- Miltenyi Biotec B.V. & Co. KG
- NIPPON Genetics EUROPE GmbH
- PELOBiotech GmbH
- PeproTech GmbH
- Proteintech Europe
- RheinCell Therapeutics GmbH
- Takara Bio Europe SAS
- Thermo Fisher Scientific – LSG

Partner societies

- German Society for Transfusion Medicine and Immunohematology (DGTI) e.V.

GSCN General Assembly

On 23 Sept. 2020, the Annual GSCN General Assembly 2020 was held during the 8th Annual Conference, with 96 participants. Due to the pandemic, it was an online meeting, with votes cast via online voting. The minutes and presentation to the General Assembly are available in the Membership Documents folder on the GSCN intranet, HumHub.

2020/2021 activities

A crucial activity for the GSCN is the contractually agreed cooperation with the Berlin Institute of Health (BIH) for the years until 2024. For the GSCN, the cooperation means that the “Dialog Platform Stem Cell Research” has been founded in partnership with the BIH. Both entities will use the platform to continue to advance stem cell research with the GSCN’s proven methods and formats. The aim is also to bring scientists from both institutions closer together, with improved networking on all working levels. The GSCN’s association status and affairs are not affected by the cooperation agreement.

For the GSCN, the year 2020/2021 was a year marked by the coronavirus pandemic. Due to the legal requirements, the GSCN limited its network and public outreach activities to online formats from mid-March 2020. Despite this restriction, the GSCN still managed to organize an impressive number of meetings – but compared with previous years, many meetings and events that traditionally form part of the GSCN’s annual calendar could not be held. However, the renouncement was also a successful learning experience – the GSCN was able to identify and use the digital space as a great meeting point and network opportunity. The GSCN’s aim for 2021 remains real-life encounters under safe health conditions, but the ability to meet digitally as a supplement will certainly continue to be used and expanded.

The network

The Annual GSCN Conference is the core element of the GSCN network. In 2020, the 8th Annual Conference was planned and prepared in Ulm, until Ulm University decided at the end of July that the health risk of a physical meeting was too high. The GSCN responded by organizing an online solution and entered previously uncharted territory – the internet as a conference location. And it was a complete success: from 23 to 25 Sept., 364 scientists came together online and met for 45 selected lectures and discussions from their home offices. While the speakers recorded their lectures as videos in advance, the subsequent Q&A sessions were always live. These were very lively and were guided by a second chair for Q&A, who managed the session in partnership with the first chair. The odd technical breakdown did happen, from a lack of bandwidth on home WiFi networks, to missing chairs who could not get back into their own sessions. But these problems were taken in good humor and did not hinder the scientific discussions in any way. Participants in the poster sessions also took advantage of the online options, using multimedia functionality to showcase their findings. They designed multimedia posters with videos and photos to present their data.

The industry exhibition was a particular experiment, featuring 22 exhibitors and including three gold supporters, six silver supporters and six bronze supporters. The companies also enriched their virtual stands with multimedia elements. Overall, the virtual annual conference was a great success, even if the opportunity to meet in-person was sorely missed.

The virtual **Non-PI-Meeting** was again held in conjunction with the GSCN Annual Meeting on 22 Sept. 2020, with 13 participants. The group discussed specialist matters, had good online conversations and held in-depth, substantive discussions. A particularly positive example was an in-depth discussion from all levels about difficult laboratory conditions, technical problems, and the differing approaches to handling the regulations of the coronavirus pandemic. The online model allowed for participation from Germany and Switzerland and is recommended as a hybrid option for future Non-PI meetings.

On the evening of the first day of the conference, Jonathan Kimmelman’s keynote kicked off the integrated **Symposium on Ethical, Legal, and Social Aspects (ELSA) of stem cell research**. This meeting, open to all conference participants, focused on current ELSA issues, with a special ethical look at how the clinical phases of Sars-CoV-2 drugs and vaccines are run. COVID and Sars-CoV-2 was also the topic at a new discussion session at the conference: in “Point of discussion”, it was all about SARS-CoV-2 / COVID-19 and research approaches with stem cells. The session was led by Christine Mummery (Leiden, NL).

In 2020, the following scientific prizes called the “GSCN Awards” were presented:

- The “GSCN 2020 Young Investigator Award” went to Prof. Dr. Barbara Treutlein from the Max Planck Institute for Evolutionary Anthropology, Leipzig and the Department of Biosystems Science and Engineering at the ETH Zürich in Switzerland.
- The “GSCN 2020 Female Scientist Award” was bestowed on Prof. Dr. Edith Heard, Director General of the European Molecular Biology Laboratory (EMBL) in Heidelberg.
- GSCN board members passed a resolution during their online meeting on 8 Feb. 2021 stating that this award will from now on be called the “GSCN Hilde Mangold Award”, thereby commemorating Hans Spemann’s famous staff member who assisted with the development of the Spemann-Mangold organizer that was recognized with a Nobel Prize.
- The “GSCN 2020 Publication of the Year Award” was awarded to Sergiy Velychko and Prof. Dr. Hans R. Schöler from the Max Planck Institute for Molecular Biomedicine in Münster for their publication “Excluding Oct4 from Yamanaka cocktail unleashes the

developmental potential of iPSCs”, 2019, published in the journal *Cell Stem Cell*, 2019 (Sergiy Velychko, et al., 2019, *Cell Stem Cell*, Vol. 25, Issue 6, Dec. 2019, 737-753.e4, doi:10.1016/j.stem.2019.10.002).

In 2020, the GSCN took part in many successful online events, with sessions, public events, and financial support:

- **IGDL Meeting** in Frankfurt am Main (5 to 6 March 2020) – just before the first lockdown in March 2020 – with a GSCN session with Marco Metzger (Würzburg), Andreas Radtke (Seattle), Ulrich Martin (Hannover), and Nina Cabezas-Wallscheid (Freiburg) and a joint GSCN session with the German Society for Extracellular Vesicles (GSEV) with the speakers Joost Sluijter (Utrecht), Dirk Herrmann (Essen), Gregor Fuhrmann (Saarbrücken), and Heide-Marie Binder (Salzburg).
- **Virtual ISSCR Annual Meeting 2020** (23 to 27 June 2020): GSCN Meet-Up Hub with online chat and interested participants.
- **DGTI Annual Meeting 2020** (16 to 18 Sept. 2020); joint GSCN-DGTI session with Axel Schambach (Hannover), Julia von Maltzahn (Jena), Halvard Bönig (Frankfurt), and others
- **EuroStemCell-Workshop** (11 to 12 Dec. 2020)
- **Public event “Brain in a dish”** – what exactly are organoids? Current developments, potential, and challenges in research. Online discussion from the interdisciplinary working group (IAG) *Gene Technology Report* in cooperation with the GSCN (23 Nov. 2020)
- **BIH lecture in cooperation with the GSCN** with Jürgen Knoblich (27 Nov. 2020)
- **GSCN travel scholarships** were awarded to only a few young scientists, given the travel restrictions and virtual conferences:
- **Maike Kosanke**, Hannover: Starting Single Cell RNA-Seq Analysis Course, Cambridge, England (1 to 5 June 2020, online)
- **Verena Börger**, Essen, ISCT 2020 virtual meeting, (28 to 29 May 2020)
- **Seraina Domenig**, Zurich, ISSCR Boston, virtual meeting (23 to 27 June 2020)
- **Praeploy Pongpamorn**, Hannover, ISSCR, Boston, virtual meeting (23 to 27 June 2020)

Reports on the experiences for all travel scholarships were written up and published on the GSCN website (www.gscn.org/en/EVENTS/GSCNTravelAwards.aspx). Particularly for young scientists, experiences at international conferences are incredibly important. The deadlines for applications for the travel award are again 31 May (July to September), 31 Aug. (October to December) and 30 Nov. (January to March). We hope that many scientists will continue to take advantage of this opportunity in the future, even though many conferences are certain to be held only online in the first half of 2021.

Science communication

A network organization’s public outreach activities above all involve organizing various formats to convey the group’s issues and topics to sectors in society in a targeted manner. With the GSCN focusing on stem cell research, this means political and other decision-makers, school students, patients, and interested members of the public.

The publication in November 2020 of the **White Paper** “Organoids – from stem cells to future technologies. State of research, core statements, and political recommendations for action on organoid technology” marked a major success for GSCN science communication. The White Paper was published by the GSCN, the Interdisciplinary Research Group (IAG) *Gene Technology Report* from the Brandenburg Academy of Sciences and Humanities (BBAW), and the Berlin Institute of Health (BIH). It consists of two parts: The GSCN wrote a synthesis report about the current state of organoid research, with a particular focus on Germany. The IAG wrote core statements and political recommendations for action on organoid technology. The White Paper was published online and in print form and was sent to decision-makers in science and politics. The White Paper was released in connection with the publication of a BBAW-IAG research report “Organoid” (Ihre Bedeutung für Forschung, Medizin und Gesellschaft) (“Organoids” (Their significance for research, medicine, and society) from Nomos Verlag, ISBN 978-3-8487-6711-3). The publication was accompanied by two successful online events with the BBAW and BIH: The **public event: “Brain in a dish – what exactly are organoids? Current developments, potential and challenges of research”**, an online discussion from the Interdisciplinary Research Group (IAG) *Gene Technology Report* in cooperation with the GSCN on 23 Nov. 2020 and the **BIH lecture with support from the GSCN** with Jürgen Knoblich on 27 Nov. 2020.

Another highlight in the GSCN’s science communication is the multimedia **“Stem Cells for Life” poster exhibition** (zellenfuersleben.de and stemcells4life.info). The GSCN developed ten posters/roll-ups with ten topics from stem cell research. These are available as print-ready files on the Internet and can be printed out by any institute, any teacher, and any interested institutions – as big DIN A0 posters or as roll-ups: But that’s not all. The posters also feature links/QR codes that make it easy for visitors to access the companion website. On the website, there are videos and factsheets that provide in-depth information, as well as a quiz to interactively check learning. Due to the coronavirus pandemic and the related cancellation of physical events, the exhibition has not yet been extensively featured, but was very popular in Berlin and Ulm.

The existing school material from the **GSCN's** stammzellen-verstehen.de and understanding-stemcells.info was updated in 2020 and adjusted to meet the needs of online learning. Some relevant feedback from a teacher in January 2021: *"When searching for new material for my advanced biology class for final-year school students in North-Rhine Westphalia, I immediately came across your site and found the material and the site so exciting that I tried it out right away. The concept (principles and ethics) worked both in distance learning and even in digital, self-directed work (teacher is not present, as a conference-based system is used). As well as the specialist treatment and the up-to-date nature of the material, a key aspect for me is the fact that preparation with the material has also resulted in significant time savings. I'm rarely satisfied with external material. But since I've been happily using your series for two weeks now, I wanted to report that back to you."*

The **UniStem Day 2020** was scheduled for 6 March 2020, immediately before the first lockdown, and came at a time of great uncertainty about whether and how events would be able to be held. Numerous locations decided at short notice to cancel their planned UniStem Days. At other locations, the events were held under strict hygiene rules, or with a reduced program. Around the world, the themed day was held in very different ways, as many school classes or institutes canceled at short notice. Given the subsequent lockdown and the focus on the pandemic, there are no reliable statistics about participant numbers. However, the GSCN events that were held were very successful – in Berlin, for example, 130 school pupils learned how stem cells could one day help with heart attacks, the fertilization of endangered species of animals, and with muscular dystrophy. They also watched twitching cardiac muscle stem cells and enhanced their knowledge about CRISPR/Cas9.

Other GSCN events in Berlin included:

- The MINT 400 forum, with the special event for the 2019 "Jugend forscht" (youth research) prize winners in Berlin (27 to 28 Feb. 2020)
- Online stem cell event with Charité medical students, Berlin (28 May, 19 and 26 Nov. 2020)

The GSCN maintains outreach programs for school students and the general public by producing its own **videos in German and English**. In 2020, video product was suspended due to the pandemic – however, the GSCN redesigned its YouTube channel: at www.youtube.com/c/GscnOrg all GSCN videos about stem cell researchers made since 2014 can be found in German and English.

The GSCN harnesses many channels for its communication: via HumHub, newsletters, Twitter, LinkedIn, its website and Facebook, the GSCN reaches its members and interested followers. Patients also contact us throughout the year, seeking advice and opinions on clinical studies and the prospects of stem cell therapies.

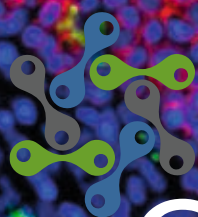
Finances

The GSCN is a non-profit organization and was funded in 2020 from **member contributions and project funding from the Berlin Institute of Health (BIH)**. Under Section 4 of the GSCN's statute and rules, the membership fees are set by rules adopted at the General Assembly. Membership fees are detailed on the GSCN's membership form.

The financial year is the calendar year. Membership fees are due at the start of the financial year. The Executive Board is responsible for producing the annual accounts and submitting them to the General Assembly. **Details of the association's finances** are provided at the General Assemblies.

In light of recent events, we would like to remind members again that GSCN memberships can be canceled easily and without the use of a particular form by e-mailing the Central Office (gscn.office@mdc-berlin.de). Notice must be given by 30 Nov. of any given year in order to cancel the membership for the following financial year (starting 1 Jan.).

*Immunofluorescence
of the white pulp of a
wild type mouse spleen*



GSCN

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