White Paper

Organoids – from stem cells to future technologies

State of research, core statements and political recommendations for action on organoid techonology

Interdisciplinary Research Group *Gene Technology Report* of the BBAW
and the German Stem Cell Network (GSCN)

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Preface

Despite its close ties to stem cell research, organoid research in Germany has barely been aware in public consciousness. To date, discussion of this issue in German speaking countries has been predominantly confined to the scientific community. Organoids are three-dimensional cellular structures grown from stem cells in vitro. They mimic bodily organs, exhibiting similar cellular compositions and functions. Organoids can be used for basic research and offer great promise for medical research in an extremely wide range of fields, such as drug screening, toxicity tests, and individual drug-response. Through this White Paper, the Interdisciplinary Research Group (IAG) *Gene Technology Report* of the Berlin-Brandenburg Academy of Sciences and Humanities (BBAW) and the German Stem Cell Network (GSCN) hope to raise public awareness of this research field and stimulate an interdisciplinary public debate on organoids.

To this end, the 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. This is followed by the IAG's core statements and recommendations for action on the use of organoids.

Parallel with this white paper, the Interdisciplinary Resarch Group *Gene Technology Report* is also publishing two further works – "Organoide. Ihre Bedeutung für Forschung, Medizin und Gesellschaft" (edited by Sina Bartfeld, Hannah Schickl, Cantas Alev, Bon-Kyoung Koo, Anja Pichl, Angela Osterheider and Lilian Marx-Stölting) and a special issue of the *Journal of Molecular Medicine* entitled "3D Organoids", edited by Sina Bartfeld, Cantas Alev and Bon-Kyoung Koo.

We are grateful for the fruitful collaboration and would like to thank everyone who contributed to this white paper, especially all of the authors and interviewees. The IAG is indebted to the Friede Springer Foundation for its financial support and the BBAW for its long-standing support. The GSCN thanks the Berlin Institute of Health (BIH) for its financial support. Warmest thanks also go to Philipp Graf from BIOCOM AG and the central offices of the IAG and the GSCN for enabling the realization of this joint publication.

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REPORT

Tiny substitutes – the age of organoids

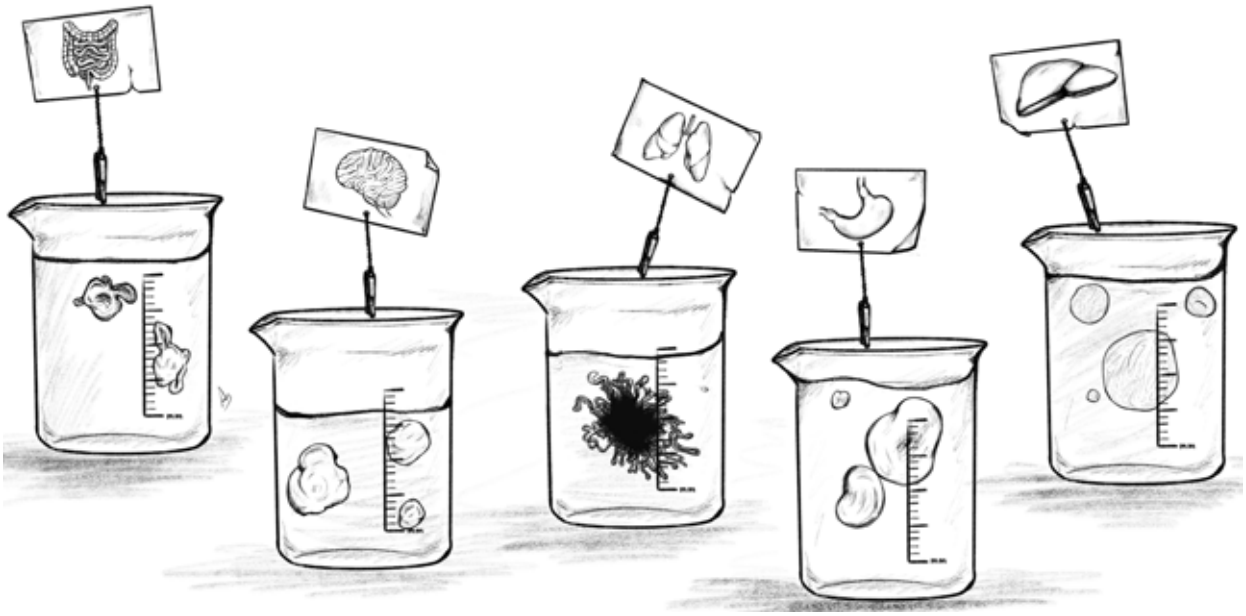
How tiny stem cell-derived 3D models are taking over biomedicine

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. In Germany too, stem cell researchers are enthusiastically adopting this new technology. 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. But these "mini organs" are far more than just test systems for new drug candidates. They also offer huge potential for diagnostics and regenerative therapies. Take a tour around the latest organoid research in Germany and its European neighbours.

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 millimetre 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 Organoids White Paper, 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



The organoid microcosm. With the help of stem cells, organoids can be produced for almost every human organ. The 3D cell structures, which are only a few millimetres in size, are fascinatingly complex.

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.

Miniaturized, stem cell-based biomedical research tools

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.

The two routes to building an organoid

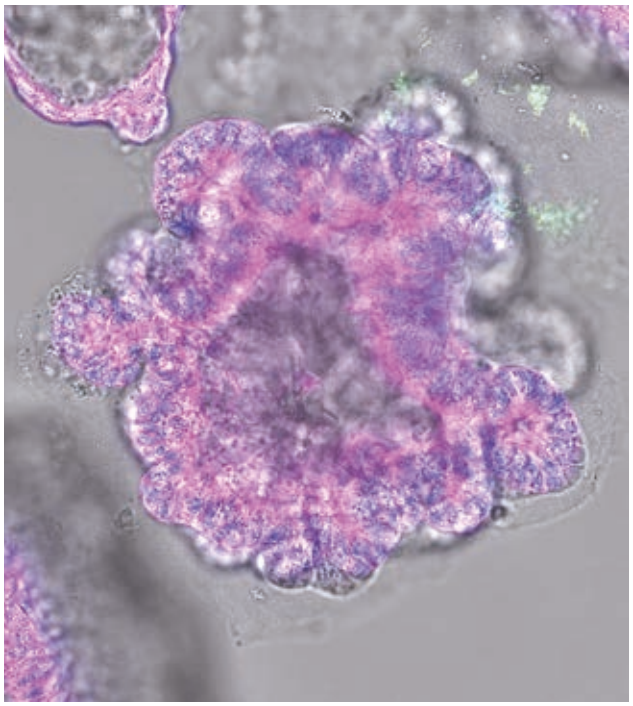
Stem cells are key components in creating organoid cultures, as they produce the cells required. The world of organoid research can be divided into two camps, involving two different techniques. One harnesses adult stem cells, the body's natural regenerative mechanism. These stem cells live in the tissues 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 Yamanaka** 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 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.



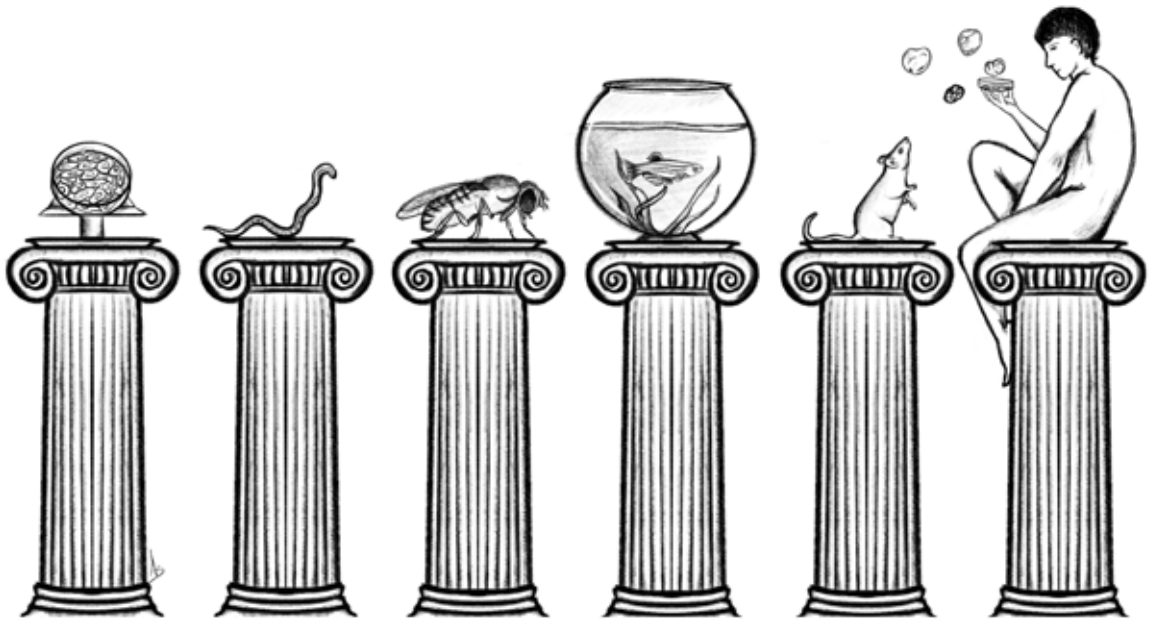
Human stomach organoids

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.

“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. 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 post – no problem.”



Biological model system in close proximity to humans. Organoids as experimental 3D cell culture models bridge the gap between animal models – such as threadworms, fruit flies, zebra fish, mice – and humans.

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.

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.

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

Human brain organoids

(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.

Highly advanced bioanalytical techniques

To study the development of their organoids in detail, researchers resort to some very advanced biomedical techniques. In order to gain a detailed understanding of their cell biology, they rely on the most advanced, leading-edge light microscopy and high-resolution fluorescence microscopy techniques. Genome editing has also become an indispensable molecular biological tool. Thanks to designer nucleases like CRISPR/Cas9 – which won its developers the 2020 Nobel Prize for Chemistry – researchers can make targeted changes to organoid cell genomes, enabling them to investigate the effects of specific mutations.

Single-cell analysis is one of the most exciting recent advances in biotechnology. Next generation sequencing techniques make it possible to analyze even the faintest traces of genetic material or proteins from a cell. The best-known example is single-cell RNA sequencing. By looking at the population of messenger RNA (mRNA) molecules, this technique enables researchers to determine which genes are active in a single cell at a specific point in time. This can be used to determine the specific signature of a cell, its molecular profile.

Taking organoids as an example, developmental biologist **Barbara Treutlein** and her team have delivered an impressive demonstration of how the wide variety of new cell biology techniques can be combined to study tissue development and organogenesis. The researchers wanted to know how well 3D organoids produced from iPS cells model molecular processes involved in organ development in vivo.

“Both brain and liver organoids mirror in vivo gene expression patterns very narrowly,” says Treutlein. “However, they more closely resemble organ tissue during embryonic development than mature organs.” Treutlein believes that the combination of single-cell genomic analysis and stem cell-derived organoids opens up an exciting new field of research. “Being able to genetically modify organoids using genome editing means that we can now explore the mechanisms involved in human organogenesis in unprecedented detail,” enthuses Treutlein, who recently moved from the Max Planck Institute for Evolutionary Anthropology in Leipzig to the Department of Biosystems of ETH Zurich in Basel, where she is active as Professor of Quantitative Developmental Biology.

The translational medicine research institute, the Berlin Institute of Health (BIH), is also highly active in promoting the combined use of organoid technology and single-cell analysis. To this end, with the support of the Charité university hospital in Berlin and the Max Delbrück Center for Molecular Medicine (MDC), it aims to bring together a broad range of essential expertise. In view of the fact that organoids have the potential to revolutionize many different medical disciplines, the BIH has set up a dedicated Organoids and Cell Engineering Translation Hub. This is where the BIH research community links up to develop innovative methods and technologies.

The Berlin Institute for Medical Systems Biology (BIMSB, part of the MDC) is specifically dedicated to the continuing development of single-cell technologies and harnessing artificial intelligence to interpret results from these technologies. The institute is also home to Agnieszka Rybak-Wolf’s Organoid Platform. The Organoid Platform builds on the MDC and Charité’s extensive expertise in stem cell techniques and genome editing and will work closely with BIMSB founding director **Nikolaus Rajewsky**’s laboratory. Rajewsky is a specialist in novel sequencing techniques.

A human organoid cell atlas

Launched in summer 2020, the EU’s HCA|Organoid project is Europe’s contribution to the international Human Cell Atlas (HCA) project and aims to create a comprehensive human organoid cell atlas for use in biomedical research. A consortium of researchers from 18 countries is aiming to compile a reference database of gene activity in all human cell types featuring unprecedented resolution. The cell atlas, made up of molecular maps, is intended to establish a unique public resource – the Google Maps of human cell biology. This ambitious project has received funding from the philanthropic Chan Zuckerberg Initiative.

Engaging in the HCA|Organoid project, leading organoid researchers from Austria, the Netherlands, Germany and Switzerland will work on an open-access Organoid Cell Atlas. The consortium is funded by a €5 million grant from the EU. The project is being coordinated by the IMBA in Vienna. German participants are the Deutsche Krebsforschungszentrum (DFKZ) and the European Bioinformatics Institute (EMBL-EBI), both in Heidelberg. The project will start by producing brain organoids and intestinal organoids each from one hundred individuals. The organoids will then be

characterized using single-cell analysis, with the aim of mapping human genetic diversity and of establishing a comprehensive reference database for use in health research.

Understanding organ development in unprecedented detail

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 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.

Brain organoids raise ethical questions

Together with **Hans Schöler**, a stem cell researcher based in Münster and current President of the German Stem Cell Network (GSCN), Knoblich heads an interdisciplinary working group on brain or-

ganoids at the Leopoldina National Academy of Sciences. The group looks at issues such as whether these complex brain models might in future be able to develop something like pain perception or consciousness. “At our meetings, the assembled experts have unanimously been of the opinion that we are miles away from a structure that could in any way reproduce cognitive processes.”

In **Hannah Schickl**’s opinion, in Germany the debate on the ethics of these aspects of organoid research is still in its infancy. As a research assistant at the Berlin-Brandenburg Academy of Sciences (BBAW), Schickl coordinated the recently published volume “Organoide. Ihre Bedeutung für Forschung, Medizin und Gesellschaft” by the Interdisciplinary Research Group *Gene Technology Report*, in the course of which she took a particular interest in the debate on ethical and legal issues. The key points and recommendations for political action set out in the above volume form part of this White Paper.

As an analytical philosopher and bioethicist, Schickl considers the question of whether future, more complex brain organoids might potentially develop something like consciousness to be “vague”. Ethicists and philosophers grappling with this question currently have to rely on thought experiments. In addition, consciousness is a complex concept, and neither neuroscientists nor philosophers have succeeded in clearly defining what it is. While the phenomenon of consciousness remains theoretically unclear and until we have a way of measuring it in practice, any debate on the consciousness of cerebral organoids is destined to remain fairly abstract.

The fact that human brain development as a normative criterion feeds into the debate around legal issues on embryos such as termination of pregnancy and the 14-day rule raises a more specific question. “Either it alters our ethical and legal assessment already of existing (and not only future) human brain organoids or it alters our assessment of human brain development as a normative criterion. Brain organoids show once again that protection based on potential abilities cannot be sustained consistently. They should be given up as protection criteria – at least for a strong protection – in favor of actual abilities like e.g. sensitivity or consciousness.” Either way, this is a question which needs to be examined, says Schickl.

In Germany, legal academics are already undertaking research on the legal status of brain organoids. For the last year or so, academics from the Faculty of Law at the University of Passau have been examining the legal framework for existing and potential future organoid research scenarios. The team, headed by **Hans-Georg Dederer**, is part of the Interaction of Human Brain Cells (ForInter) research network, funded by a €4 million grant from the State of Bavaria. Which existing laws make up the legal framework for organoid research? Where is there a need for additional regulation of therapeutic applications? Do brain organoids need to be given legal protection, and if so, how far should this protection extend? These are the questions that Dederer’s team are seeking to address. Should they identify omissions or other shortcomings, they will also develop proposals for updating existing legislation.

Embryoids stoke intense international debate

Far more ethically and legally sensitive in Schickl's opinion is the issue of embryoids. Embryoids are produced when pluripotent stem cells in special cultures start to self-organize to form a 3D structure which resembles an embryo – both in terms of the cell types it contains and in its tissue organization. In a nod to the discipline of synthetic biology, embryoids are also known as synthetic embryos – produced not by the fusion of a sperm and egg cell, but from stem cells aggregating together in a culture dish. How embryoids should be classified ontologically (as human embryos or as novel entities), and what their normative status should be remain unanswered questions, as Schickl points out.

Animal embryoids capable of undergoing development have now been created. In addition, contrary to popular belief, pluripotent stem cells are, under certain circumstances, apparently capable of totipotency, so that they could give rise to a complete organism. Given that many legal regulations and guidelines treat totipotency as a key criterion in determining whether cells are worthy of protection, the significance of this research should not be underestimated. "The ethical and legal aspects of this are currently the subject of intense international debate." In Germany too, there is a need for a clear legal framework for embryoid research. Existing rules on human embryos in vitro are also in need of review.

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 Zika and 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. Affected babies were found to have microcephaly, meaning that their heads had failed to develop to a normal size.

By using brain organoids produced from pluripotent stem cells, biomedical researchers soon picked up the virus' trail. Using their in vitro tissue models, researchers were able to determine that the Zika virus infects neural stem cells and to study how this leads to microcephaly. And that's not all – screening potential active substances on brain organoids infected with Zika virus helped to identify a number of powerful drugs.

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.

Tools of pandemic research. Organoids as infection models help to understand what viruses such as SARS-CoV-2 or Zika do in the body and how the spread of the pathogens can be stopped with drugs.

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 battlegrounds 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 diarrhoea, 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 Cologne 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, involves 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.

A further BMBF-funded coronavirus research project, involving lung organoids produced from iPS cells, is currently underway at Ruhr-Universität Bochum. With the help of organoids, virologist **Stephanie Pfänder** and molecular biologist **Thorsten Müller** are aiming to develop a reliable model for use with high-throughput analyses. The project goes by the name Organ-Sars. In her experiments, Pfänder makes the coronavirus glow green. This is achieved by inserting a sequence coding for a green fluorescent protein into the SARS-CoV-2 genome. "We will be drawing on high-resolution microscopy to investigate interactions between the virus and organoid, and to study mechanisms of infection," explains Pfänder. The Bochum-based team are also planning to deploy their model system in testing antiviral drugs.

"Mini tumors" for personalized cancer treatment

Stem cell-based 3D model systems are also increasingly important in cancer research. Würzburg-based organoid researcher **Sina Bartfeld**, for example, is using stomach organoids to study the carcinogenesis of stomach cancer. Just under 50% of stomach ulcers are caused by infection with one of two pathogens. The *Helicobacter pylori* bacterium is responsible for up to 40 percent of cases, while the Epstein Barr virus (EBV) accounts for up to 10 percent. In both cases, however, we don't yet understand how the infection contributes to the development of cancer. "By experimentally infecting organoids in the lab, we can simulate the interaction between the pathogens and their human host cells and investigate these interactions in more detail."

Her experiments have shown that different cell types react differently to infection. Bartfeld's team is currently trying to determine whether Helicobacter pylori attaches to all cell types in the stomach or whether there is a specific target cell. How EBV causes cancer is also an extremely interesting question. "Currently, it is not clear exactly how EBV infects cells of the gastric mucosa," notes Bartfeld. Long term, she hopes to achieve a better understanding of why some patients develop cancer while others stay healthy.

Organoids also have potentially interesting applications in personalized medicine. Personalized medicine involves using molecular biology and clinical data for a specific patient to try to find the optimum therapy for that patient. Bartfeld has, for example, succeeded in producing organoids

not just from healthy tissue, but also from tumor tissue from patients who have had their stomach removed due to cancer. “Our experiments have shown that these organoids can in principle be used to test possible drugs. Other groups are now investigating whether drug tests involving organoids are able to predict how the patient will respond to those drugs in practice. The hope is that patient-specific tumor organoids could in future be used to determine which drugs are effective against that tumor and which are ineffective. We’ve still got a long way to go before we get to that point, however,” says Bartfeld.

Large collections of cancer organoids make the vast complexity and diversity of cancer amenable to laboratory experiments. Tumor organoids can be frozen, stored, thawed and multiplied as required. The result is living biobanks. Hubrecht Organoid Technology (HUB) in the Netherlands has compiled an extensive tumor organoid archive. HUB provides researchers with free access to cellular material and associated molecular biology and clinical data. How useful these tumor organoids will prove in practice for finding new active substances and for precision medicine remains to be seen. Numerous clinical observational studies are currently underway to find out.

Henner Farin heads a junior research group at Georg-Speyer-Haus in Frankfurt as part of the German Cancer Consortium (DKTK). Like Sina Bartfeld, he is a protégé of Hans Clevers’ Dutch organoid foundry who has made his way back to Germany. In Frankfurt, Farin creates intestinal tumor organoids and uses them to research mechanisms of carcinogenesis. “The conventional method for isolating and culturing tumor cells from patients produces cell lines that have little in common with the original tumor,” explains Farin.

Identifying a tumor’s individual weak points

If, however, the cancer tissue is taken to grow organoids, a very genetically stable tumor model can be created. “We can use this to study in detail the genetic differences between individual tumors and work out what this means in terms of their characteristics.” The researchers recently employed the CRISPR/Cas9 ‘molecular scissors’ system to switch off tumor suppressor genes in organoids. “Genetic screens will in future enable us to identify a tumor’s individual weak points, which we can successfully target with a suitable therapy,” describes Farin.

Stem cell researcher **Kai Kretzschmar** specializes in producing cancer organoids from patient tissue. Kretzschmar also came to Germany recently from Hans Clevers’ lab in Utrecht and, since early 2020, has been establishing a junior research group at the University Hospital of Würzburg. As a postdoc, Kretzschmar worked on optimising protocols for producing cancer organoids. Researchers are becoming increasingly adept at reproducing components of the microenvironment (the mix of cells in the immediate vicinity of the cancer cells).

“Mixing colon cancer organoids with immune cells in a culture dish is a good model for studying the interplay between them,” says Kretzschmar. This raises the possibility of new models for drug testing. “Long-term, these co-cultures could also be used to test the efficacy of novel immunotherapies.” Working at the Mildred Scheel Early Career Center for Cancer Research (MSNZ), Kretzschmar now wants to focus on the oral mucosal epithelium and is aiming to employ organoid technology in modeling the carcinogenesis of head-neck cancer.

A new perspective on neurodegenerative diseases

Neurodegenerative diseases are one area of research where organoid disease models are proving genuinely groundbreaking. The advent of human 3D cell cultures means that neuroscientists now have a disease model which is much more realistic than the traditional Petri dish cell culture lawns and animal (e.g. mouse) models. There is barely a neuroscience-oriented stem cell research team in the country that isn’t using organoids for disease research.

Hans Schöler’s team at the Max Planck Institute for Biomolecular Medicine is using brain organoids to study topics including the mechanisms underlying Parkinson’s disease. **Julia Ladewig** at the Hector Institute of Translational Brain Research in Mannheim is employing brain organoids to investigate the molecular and cell biological causes of developmental and mental health disorders such as autism and schizophrenia, as well as potential therapeutic targets in these disorders. These tiny balls of cells in a Petri dish can also be used to test potential psychotropic drugs. Based on brain-like cell culture models, **Beate Winner** at Universitätsklinikum Erlangen is trying to unravel the pathogenesis of rare neurological disorders. And **Oliver Brüstle** at the LIFE & BRAIN Center in Bonn has joined forces with the Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) to study CNS drug metabolism in cerebral organoids.

Benedikt Berninger’s team at the University of Mainz Institute of Physiological Chemistry has also opted for cerebral organoids in testing promising new approaches in regenerative medicine. The direct transformation of glial cells is one strategy for replacing lost nerve cells in the brain. “We are using these ‘mini-brains’ as a platform for studying the reprogramming of glial cells into nerve cells,” explains Berninger. **Magdalena Götz**’s team at Helmholtz Zentrum München is also researching this strategy with the help of brain organoids.

Stem cell-based 3D disease models for neurological research are becoming ever more complex and ever more sophisticated. **Mina Gouti**’s team at the Max Delbrück Center for Molecular Medicine in the Helmholtz Association (MDC) has recently developed a process for generating extremely highly developed, functioning neuromuscular organoids. Derived from pluripotent stem cells, the organoids spontaneously form nerve cells, skeletal muscle and even motor end plates. Motor end plates are the points of contact between nerve cells and muscles and the point at

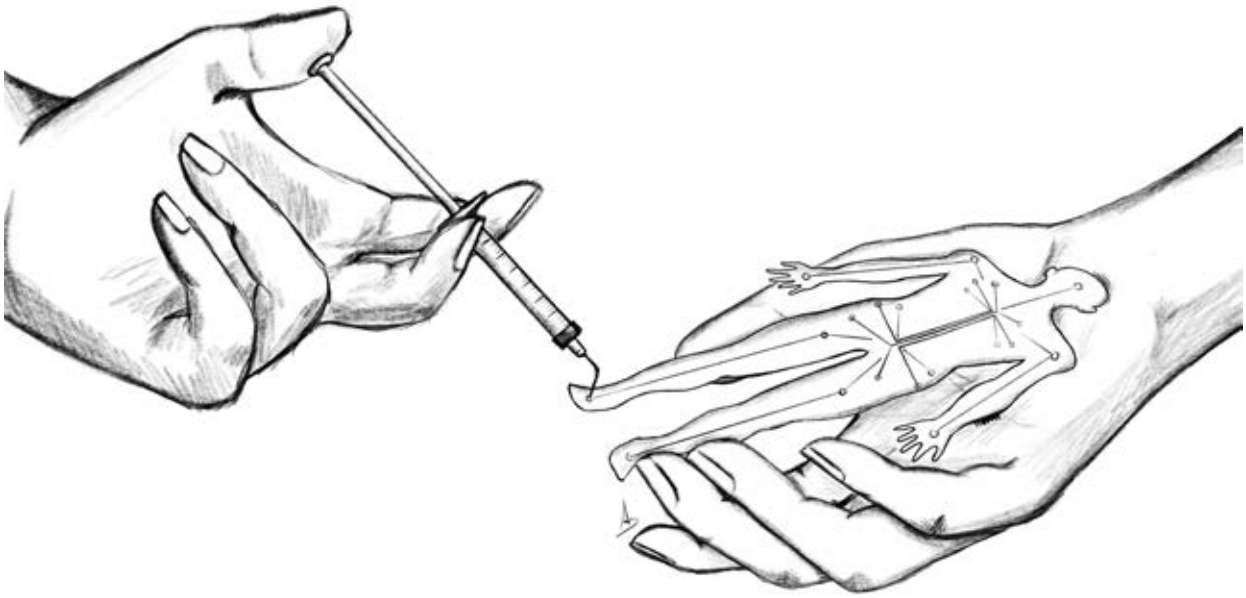
which the signals which cause muscles to move are transmitted to the muscle. To Gouti's astonishment, the self-organizing cellular structures have formed functional networks. After 40 days, the motor neurons in the organoids were actually able to trigger muscle contraction.

In Gouti's view, this 3D cell culture model opens up the possibility of completely new approaches to investigating diseases involving the death of motor neurons. One such disease is amyotrophic lateral sclerosis (ALS), a currently incurable disease that causes muscle weakness and loss of movement. Gouti's team are now planning to grow neuromuscular organoids from iPS cells from people with ALS. These organoids will offer a new means of observing the early stages of the disease in vitro, and new options for testing the effects of different drugs.

Blazing a trail for personalized medicine – test systems, drug screening and regenerative therapies

As models for human disease processes, organoids have become extremely popular tools for translational medicine – the process of transferring innovative research findings from the laboratory to the clinic.

By acting as surrogate organs, the hope is that these pinhead-sized balls of cells will respond to drugs in the same or a similar way to the real organ in the body. The big advantage they offer is that, using advanced stem cell technologies, it is possible to create an individualized disease model for every patient. This opens up entirely new possibilities for pharmaceutical research. These 3D tissue models can be harnessed to test active substances and investigate their efficacy. They pave the way for personalized medicine.



Vision human-on-a-chip. More and more model organ systems can be interconnected via microchannels on a chip. The multi-organ chips are suitable for drug testing in the pharmaceutical industry.

Test systems for pharmaceutical research

Cystic fibrosis is one area where organoid-based drug testing is already part and parcel of clinical practice. Cystic fibrosis occurs due to a genetic mutation which causes a change in a membrane channel. This means that the channel is no longer able to correctly regulate the balance of water and salt in epithelial cells, resulting in a build up of thick secretions. This particularly affects the lungs, but also impacts on the pancreas and gut. This misfiring membrane channel can be caused by a wide variety of different genetic mutations, some of them quite rare. As a result, until now it has often been hard to predict whether one specific drug will be effective in a particular patient.

Working with Hans Clevers' laboratory, a team of Dutch paediatricians has now demonstrated that, by testing the drug on patient-specific organoid cultures produced from rectal mucosal tissue, it is possible to predict the success of drug treatment with very high accuracy. "Since last year, Dutch health insurers have been paying for individualized organoid diagnostics," notes Clevers. These organoid tests mean that doctors can now better target this expensive cystic fibrosis drug to those patients who will benefit from it. "For cystic fibrosis, organoids have become an integral component of the Dutch health system," says Clevers.

Innovative approaches to testing and screening new drug candidates based on 3D cell cultures are also on the agenda for translational medicine institutes in Germany. That includes the Hector Institute for Translational Brain Research (HITBR), a partnership between the Central Institute of Mental Health (ZI) in Mannheim and the DKFZ in Heidelberg. The HITBR team's goal is to identify new therapeutic targets in severe psychiatric disorders and validate them for the development of new psychotropic drugs.

Translational medicine company ISAR Bioscience GmbH, located in Munich's Planegg district, is working on stem cell and organoid technologies for drug screening. Austrian biotech company a:head was spun off from the IMBA in 2019 with the aim of establishing cerebral organoids as a platform for research into new drugs for treating brain diseases.

Tumor organoids too offer huge diagnostic potential, and this potential is increasingly being exploited for healthcare applications. Danish-German company 2cureX, for example, is employing tumor organoids from cancer patients to test the effects of cancer drugs prior to use. This enables them to determine which drug or combination of drugs is most effective against the specific tumor. In vitro tests like these should provide doctors with a better basis for decision-making, reduce side effects and help make treatments work faster.

Improving control with organ-on-a-chip

If organoids do turn out to be suitable as drug testing systems, in future they could find use in preliminary testing prior to legally-required animal experiments. Only active substances which pass the organoid test would go on to be tested in animals. This one step alone would drastically reduce the number of experiments performed on rats and mice.

But before they can be put to work in testing and enable better comparison between them, these living 3D cell culture systems need to be made more robust and consistent. Already a number of teams are working on the next generation of organoids. One option for achieving this is combining stem cell techniques with organ-on-a-chip technology. This involves culturing the organoids on small microscope slides known as microfluidic biochips. The organoids are supplied with nutrients by way of extremely fine fluid channels that act as an artificial vascular system.

“The aim is to place the organoid in a micro-physiological environment which simulates as closely as possible the environment in the human body,” says **Peter Loskill**, bioengineer at the Fraunhofer Institute for Interfacial Engineering and Biotechnology (IGB) in Stuttgart and at the University of Tübingen. “By combining organoids and organ-on-a-chip systems, we are bringing complex self-organization into a controlled technical environment,” explains Loskill. In developmental biology, where Petri dishes fall short, high-tech is stepping in.

Retina on a chip as a model for toxicity testing

The retina-on-chip model Loskill has developed with Tübingen-based stem cell researcher **Stefan Liebau** is a good example of the bioengineering approach. Based on iPS cells, the researchers have created retinal organoids which possess almost all important cell types and form complex, multi-layered tissue. Nonetheless, they still lack a number of key features, among them retinal pigment epithelium, a layer of cells which sits in close contact with the light-sensitive photoreceptors in vivo. The absence of a circulatory system also means that they lack a continuous supply of nutrients.

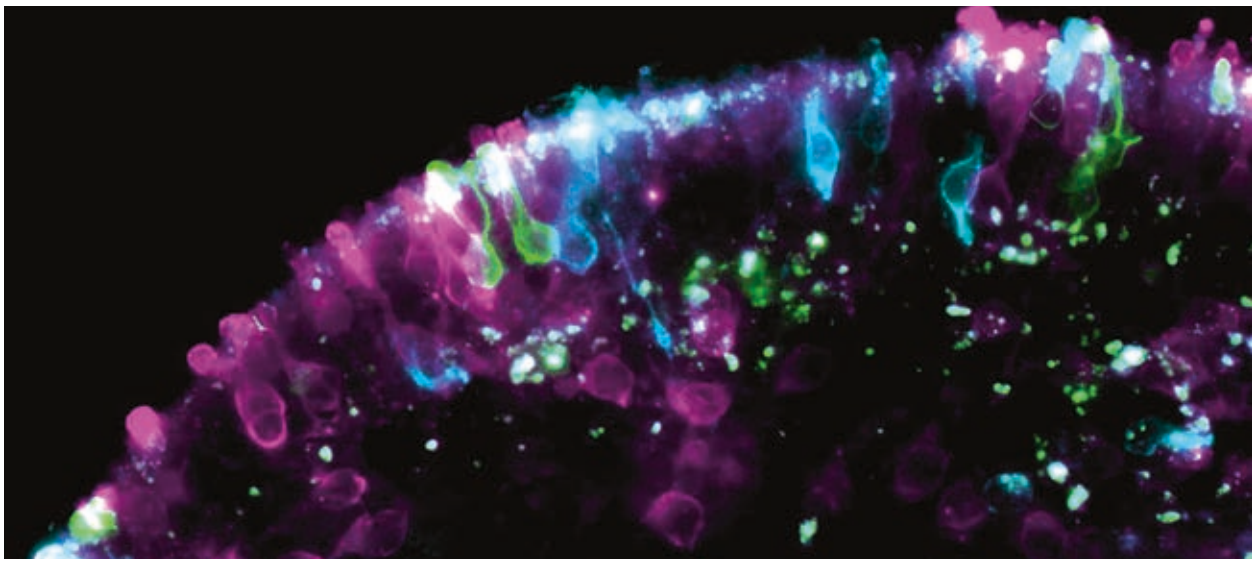
This is where the Fraunhofer engineers’ expertise comes into play. First the researchers seed a layer of retinal pigment epithelium in small indentations on small microscope slides equipped with biocompatible membranes. Next, they place retinal organoids on top of this epithelium. The system includes a microchannel, which acts as an artificial vascular system and, by way of pump system, can be used to bathe the material with nutrient solutions, immune cells or drugs. The chip therefore mirrors physiological conditions in the human retina in a number of ways and represents a powerful alternative to animal models.

“This allows us, for example, to test new drugs to see if they have any retinal side effects,” explains Loskill. The Fraunhofer researcher is already working with a number of pharmaceutical companies, which are deploying the retina-on-chip system primarily for toxicity testing. “Lots of novel drug candidates cause side effects involving the eye,” explains Loskill. “Our retina model is very good for examining and testing such effects.”

Jena-based start-up Dynamic42 GmbH is another organ-on-a-chip specialist. Dynamic42 is a contract research organization which was spun off from **Alexander Mosig**’s working group at Jena University Hospital in 2018. In addition to sophisticated microphysiological 3D liver and intestinal organ models, the Jena bioengineers have also developed a human alveolus model, an alveolus-on-a-chip. The model is already being employed as a test system for coronavirus research. Dynamic42’s particular area of expertise is in reconstructing blood flow in modeled organ systems, including blood-borne immune cells.

Berlin-based TissUse GmbH in turn specializes in combining multiple organoid systems on a biochip. Founded in 2010 as a spin-off from the Institute for Biotechnology at TU Berlin, TissUse’s vision is to build a ‘human-on-a-chip’. The team, headed by research director and founder **Uwe Marx**, has already developed a number of multi-organ chips.

Their organ models largely consist of ‘spheroids’, clumps of cells that are somewhat less complex than conventional organoids. The models are housed in tiny chambers on a plate the size of a microscope slide. A fluid-filled system runs through the structure mimicking a circulatory system. “Our multi-organ chips are excellent test benches for testing drugs and chemicals for the pharmaceutical and cosmetics industries,” says Marx. With a high relevance in physiological terms. Backed by millions of euros in funding from the Federal Ministry of Education and Research’s GO-Bio initiative, aimed at encouraging start-ups, the Berlin company has gradually combined more and more organ systems.



Fluorescent staining of a retinal organoid.

The most advanced product is a four-organ chip consisting of intestine, liver, kidney and a skin module. The tissue engineering company is planning to unveil a ten-organ chip in the near future.

A combination of organ chips and 3D cell cultures is also the focus for "Der Simulierte Mensch" (the simulated human), a research centre currently under construction in Berlin's Wedding district. The new research building, due for completion in 2023, will be the centerpiece of a new joint Charité and TU Berlin biotechnology and medical technology campus. The new €34 million building is jointly funded by the federal and state governments. The centre was initiated by TU biotechnologists **Roland Lauster** and **Andreas Thiel** from the BIH Center for Regenerative Therapies and will enable life science researchers and engineers to work together under one roof to develop the next generation of human model systems – enabling research in fields such as personalized immunotherapy, for example.

Regenerative medicine – organoids as cell production platforms

The core concept in regenerative medicine is the use of cells to heal disease. Stem cells represent a potentially inexhaustible source of cells for replacing or restoring the function of injured or destroyed tissue. Stem cell-based tissue replacement therapies have proven to be extremely complex. The path leading from experimental use of stem cell products to extensive applications in medical practice is long and winding and takes many years.

But in regenerative medicine too, stem cell-derived organoids have a valuable role to play. Take pancreatic organoids for example. The two most significant pancreatic diseases are diabetes and pancreatic cancer. Diabetes results from the death of insulin-producing beta cells. That makes it a promising candidate for cell replacement therapy and has led to an intensive international research effort in this area. Is it possible to make use of natural regenerative processes within the pancreas? How can we culture high quality beta cells? Working with pancreatic organoids, these are the questions that developmental biologist **Anne Grapin-Botton** is grappling with at the Max Planck Institute for Molecular Cell Biology and Genetics in Dresden. **Meritxell Huch** is another researcher from Hans Clevers' Utrecht talent factory to have found a home at the Max Planck Institute in Dresden. Her laboratory combines developmental biology approaches to the differentiation of liver and pancreatic organoids with the carcinogenesis of liver cancer and beta cell production in the pancreas.

Using organoids to blaze a trail for laboratory-grown replacement organs is the goal of the eISLET research project. A partnership between four research groups at the Helmholtz Zentrum München, the project is led by **Heiko Lickert** and **Matthias Meier**. The objective is to develop an organoid-based cell replacement therapy for diabetes. In spring 2020, the eISLET consortium was one of the winners in a BMBF pilot innovation competition aimed at promoting disruptive innova-

tions. Over the next three years, the researchers will be able to invest €1 million in projects aimed at producing alpha and beta cells from iPS cells. These cells are essential for the formation of fully functional pancreatic islets of Langerhans. The idea is to produce cell biologically and physiologically accurate islets of Langerhans which are functionally comparable with islets in vivo.

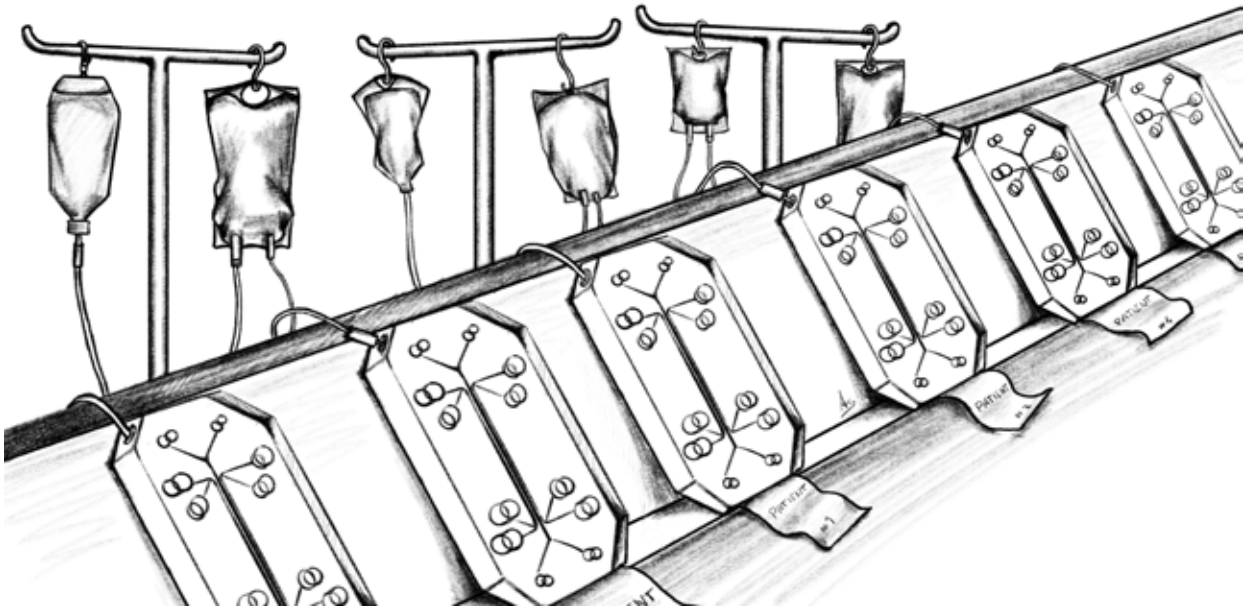
A number of cell replacement therapies for ophthalmic disorders are also currently undergoing clinical testing. Treating retinal disorders by transplanting photoreceptor cells is now becoming a realistic scenario. The availability of retinal organoids has played a key role in this development, and it is these organoids which are the area of expertise of Dresden-based stem cell researchers **Mike Karl** and **Marius Ader** at the Center for Regenerative Therapies (CRTD) at TU Dresden. 3D retinal cultures can be produced in the laboratory from human iPS cells and, under the right conditions, form large quantities of photoreceptor cells. “Organoids can act as a kind of production platform for human photoreceptors,” says Mike Karl. At the German Center for Neurodegenerative Diseases in Dresden and the CRTD, Karl and his team have been working to further advance and standardize this technology. An organoid culture can produce 300,000 photoreceptor cells, explains Karl. For patients with macular degeneration, Karl thinks that transplantation of just a few hundred thousand cones – the photoreceptors responsible for high-resolution color vision – might be sufficient to achieve a therapeutic effect.

Future scenarios – the next generation of organoids

Less than 15 years have passed since the first organoids were cultured in stem cell laboratories. As our journey of discovery through the German research scene makes clear, these 3D models, just a few millimetres in size, have already proven their huge potential for biomedical research. They are already enriching the medicine and life sciences toolbox on a number of health research fronts. More human-like than animal models, they could in future complement animal experiments.

“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



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. Another vision for the future: clinical studies using organ chips.

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.

Internationally, this kind of approach is being pioneered by **James Wells**. Working at Cincinnati Children's Hospital Medical Center, the developmental biologist has succeeded in producing intestinal organoids with a rudimentary nervous system which have even been observed to make peristalsis-like movements. Organoid builders have also created intestine models with a functional immune system.

The need for ingredients such as nutrient media and the growth factors that organoids require to develop means that growing organoids in the laboratory is currently still a very expensive process. Innovation is called for in areas such as the gel-like 3D matrices in which stem cells are embedded to enable them to form organoids. As an alternative to the Matrigel which predominates at present, bioengineers are working to develop novel hydrogels with defined characteristics. The global organoid research community is also trying to improve networking, and to standardize and improve the consistency of laboratory protocols for generating these tiny 3D objects. This would make them even more useful as biomedical research and translational medicine tools.

Sina Bartfeld is enthusiastically involved in this process. Her team has recently produced organoids from stomach, small intestine and large intestine tissue to create a kind of 'miniature gastrointestinal tract organ bank'. She 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."

Interdisciplinary Research Group *Gene Technology Report*

Sina Bartfeld, Stephan Clemens, Tobias Erb, Heiner Fangerau, Boris Fehse, Jürgen Hampel, Ferdinand Hucho, Martin Korte, Stefan Mundlos, Jens Reich, Silke Schicktanz, Jochen Taupitz, Jörn Walter, Eva Winkler and Martin Zenke

Core statements and recommendations for action on organoids

The core statements from the Interdisciplinary Research Group *Gene Technology Report* are structured as follows: The first part comprises a summary of the current state of affairs, a prospective look at the significance of organoids for future research and health care, and an overview of the legal situation and ethical considerations. The second part explores derived recommendations for action for policymakers.

Core statements on organoid technology

Organoids derived from stem cells

Organoids are three-dimensional organ-like groups of cells in which different cell types have self-organized in a way that approximates the type of organization seen in the corresponding bodily organ. They have three characteristic features – self-organization, multicellularity and functionality. The range of organs on which research can be carried out using organoids is growing rapidly and includes the brain, gut, kidney, stomach, pancreas, lungs, liver, prostate, oesophagus, gallbladder and the female reproductive tract. In addition, research is also being carried out on embryo-like organoids (embryoids).

Organoids are created either from pluripotent stem cells or from tissue-specific adult stem cells. Adult stem cells are present in a very wide variety of tissues and are responsible for renewing the cells in these tissues. They are only able to produce those cell types that are present in the tissue from which they originate. Intestinal epithelial stem cells, for example, only produce intestinal epithelial cells (i.e. the epithelium and glandular tissue that lines interior and exterior body surfaces), and do not produce muscle or nerve cells. They are therefore multipotent. Pluripotent stem cells, by contrast, are able to give rise to every one of the more than 200 different cell types in the human body. Pluripotent stem cells are obtained either from human embryos (human embryonic stem cells or hES cells) or by 'reprogramming' somatic cells to produce human induced pluripotent stem cells (hiPS cells). These somatic cells can be obtained from healthy donors or from donors with disease.

Both types of stem cell, adult and pluripotent, can be used to grow organoids in vitro. In the case of adult stem cells, researchers attempt to mimic the natural environment in the tissue from which the stem cell is obtained. In the case of an intestinal epithelial stem cell, for example, researchers would add the same signaling molecules as would be present in the intestinal environment in vivo. The stem cell reacts to these signaling molecules by dividing and forming new intestinal epithelium, just as in the body. Because of its similarity to the actual in vivo organ, the structure created in culture using these techniques is called an 'organoid'. The principle is similar for pluripotent stem cells, with researchers once again attempting to mimic the stem cell's natural environment in a culture dish. However, because these stem cells can differentiate into a much wider range of cell types, researchers have to mimic a series of developmental steps in vitro. To achieve this, researchers make use of our knowledge of embryonic development. Defined signaling molecules are added in a series of sequential steps – the same signaling molecules which ensure that pluripotent stem cells follow a specific development pathway in the body. Just as stem cells in an early embryo develop into the gut wall only after passing through a number of previous developmental stages, it likewise takes several weeks for pluripotent stem cells to develop into intestinal stem cells, and to in turn give rise to an intestinal organoid.

Adult and pluripotent stem cells differ in the way they are used to produce organoids and each has its own advantages and disadvantages. At present, organoids produced from adult stem cells can only be produced from epithelial cells and remain purely epithelial in character. An adult intestinal epithelial stem cell, for example, will always produce intestinal epithelium, and will never produce connective tissue. This is not the case for organoids derived from pluripotent stem cells. They can also contain other cell types, are more complex and are more heterogeneous. Intestinal organoids produced using pluripotent stem cells, for example, do indeed contain connective tissue. This means that pluripotent stem cells can differentiate into organoids as diverse as intestinal organoids, brain organoids and embryoids. It is not currently possible to make brain organoids or embryoids using adult stem cells. The two techniques also differ in certain ethical and legal respects. Despite these differences, there is considerable overlap in terms of their application.

The role of organoids in biomedicine

Basic research and developmental biology

Organoids offer great promise for a number of life sciences fields. In the basic research field, they can provide insights into how organ formation is controlled in vivo, into cell differentiation and into how tissues and organs are able to persist as stable structures (homeostasis). This is especially useful in the case of tissues that are difficult or impossible to access in vivo, such as the brain. One major advantage of organoids over two-dimensional cell cultures is that they contain a wide range (ideally all) of the cell types that make up the organ in vivo. This means they can be used

to study complex processes such as interactions between cells. It also means they are better than two-dimensional cell cultures – and in some cases even than animal models – at modeling disease states. Take, for example, the case of pathogens which specifically infect humans and have no animal host. Already today, organoids represent a better model for studying such infectious diseases than animals.

Disease models

Due to their potential as disease models, hiPS cells have long been a beacon of hope for basic research and personalized medicine. The basic approach involves obtaining and multiplying cells from a patient with a specific illness, enabling researchers to research the specific pathology directly and to identify appropriate medicines for that specific patient. Thanks to organoids, this is already clinical reality. The use of organoids complements the use of pure iPS cells with two decisive developments: Firstly, organoids can now be used directly to multiply adult stem cells from any patient. Secondly, three-dimensional cultures allow the production of complex structures, allowing better modeling of disease. As a result, organoids also enable research into diseases with a genetic origin, human-specific infections, and infections where the pathology in animal models differs from that in humans, with the result that satisfactory system models have not been available to date. One potential clinical application is in companion diagnostics for personalized medicine. This involves testing the efficacy of a drug directly on organoids produced from the patient's own stem cells. In principle, this could be done using either adult or iPS cells. In practice, however, because adult stem cells are directly accessible, it is these which are actually being used in the clinical diagnostics. In the Netherlands, an organoid-based patient-specific therapy is already being employed in the treatment of cystic fibrosis, with the cost of these organoid-based diagnostic tests being reimbursed by health insurers. Organoids are also becoming more and more important in cancer research. Tumor organoids, for example, can be used to screen a wide range of substances in the search for new cancer drugs. In addition, patient-specific tumor organoids could in future enable clinicians to investigate the development of tumor resistance to specific cancer drugs. Clinical trials in this area are already showing a great deal of promise. The ability to use organoids as individual disease models enables organoids to make a valuable contribution to the field of personalized medicine.

Genetic engineering

Organoids can also be genetically modified. A variety of techniques are available (e.g. genome editing with CRISPR/Cas9) enabling the genetic modification of organoids. Genome editing refers to techniques in which large or small stretches of DNA (DNA: deoxyribonucleic acid) are selectively deleted from the genome or replaced by alternative DNA sequences. By way of this technique, a single genetically modified cell can be used to produce clonal organoids containing specific genetic changes in order, for example, to investigate the effect of a specific mutation or to correct a pa-

tient-specific mutation. This is a multi-stage process – stem cells are first genetically modified by way of genome editing, then multiplied in a cell culture, and induced to undergo differentiation into the target organoid in the next step. During differentiation into the organoid, the modified stem cell genome is passed on to the daughter cells.

Regenerative medicine and organoid transplantation

One future clinical application involves transplanting organoids or cells derived from them into humans, which is known as cell replacement therapy, stem cell therapy or regenerative medicine. This could involve either autologous transplants using cells donated by the target patient him or herself, or allogeneic transplants entailing cells donated by someone else. In this case, the role of organoid technology would be to produce the right type of cell in sufficient quantities for transplantation. By way of additional genetic engineering techniques, it might in future be possible to correct disease-causing mutations, enabling the production of healthy organoids for transplantation. Initial experiments involving animal models are already delivering promising results, but further studies on organoid functionality in vivo are needed.

Biobanks

Living biobanks have been set up for hiPS cells. This involves freezing donated hiPS cells and sorting them into groups with specific characteristics, such as just patients with disease x, all patients who have undergone operation y, or healthy donors. The cells can be thawed out as required and induced to multiply or differentiate into organoids. It is also now possible to freeze adult stem cells in organoid form. Organoid biobanks for a number of organs have already been set up at various sites around the world. There are, for example, biobanks for intestinal organoids, liver organoids, and kidney and urinary tract organoids. Each can contain organoids from several hundred patients. Depending on the scientific or medical issue a researcher is interested in, they can thaw out either specific groups of organoids or entire biobanks. These biobanks are particularly expedient for drug testing. The stored organoids can be used to screen for new drugs or to determine how effective a drug is in specific patient groups. They can also be deployed in toxicology testing.

Toxicology

Before a drug is tested on people, extensive testing needs to be carried out to ensure the drug is free of toxic effects, which entails animal models. A complementary or even alternative option could be to test candidate drugs on organoids taken from biobanks. The generally accepted approach involves testing a number of organoids in parallel, and focusing on organs that are commonly affected by drug toxicity (liver, kidney, intestine, etc.). Research on how organoid tests compare to animal experiments in predicting drug efficacy in patients is currently ongoing. Hopes are high that it will in future be possible to test drug toxicity and efficacy based on organoids, either supplementing the results from animal experiments or dispensing with the need for ani-

mal toxicity experiments completely. Organs-on-chips are another promising approach for drug testing. In future, this technique could enable multiple different organoids to be linked together on a chip to form a miniature 'human-on-a-chip'.

Limitations of current organoid research

Although organoids bear a striking similarity to organs, especially compared to conventional cell cultures, as models, at present, they are still strongly reductive, and are far less complex than the corresponding organ. Real intestines, for example, do not consist solely of the inner mucous membrane layer (made up of epithelium), but are also surrounded by connective tissue and muscle layers, enmeshed in a network of nerves and blood vessels, and populated with microorganisms. While connective tissue is present in organoids grown from pluripotent stem cells, they still lack many other components of in vivo organs, as well as the local environment within the body, which also exerts an effect on organ function. One disadvantage – at present at least – is that it is not yet possible to replicate many of these interactions. Researchers are therefore working to produce more complex organoids, such as intestinal organoids with a functioning enteric nervous system. Producing organoids that more closely resemble in vivo human organs is just one of a number of research goals. One advantage of current, reductionist models is that they can be used to study specific aspects of an organ or organ function, or specific effects on specific cell types. Organoids therefore represent a major step forward in biomedicine and a major research advance.

Ethical aspects of organoid research – brain organoids, embryoids and human-animal chimeras

Organoid research raises numerous ethical issues, and these are the subject of intense debate. These are particularly relevant in areas such as embryo research, research involving hES cells, the creation of human-animal chimeras and research entailing donor material and data from biobanks. Organoids, particularly brain organoids and embryoids, also throw up a whole range of highly specific new issues. The global debate on the ethical issues raised by organoids is still in its infancy.

Existing brain organoids are still a long way from having the complexity of a human brain. There has, however, been repeated speculation about the possibility that future, more complex brain organoids or fused organoids from different brain areas ('assembloids') could develop awareness, how, if they did, could we measure this, and what ethical and legal protection they might be entitled to. If we assume that many higher animals also develop some form of consciousness, this would then apply to both human and animal-derived brain organoids. In humans, brain de-

velopment has a major bearing on the point at which in vitro and in vivo embryos are subject to ethical and legal protection, even at very early stages of development. This raises the question of whether brain organoids should be subject to similar protection and what degree of development would be required for a brain organoid to be afforded such protection. In addition, the issue of human brain organoids transplanted into living mammals (e.g. rats, mice and potentially larger mammals) for the purpose of studying how they interact with other tissues in vivo raises particular ethical questions. Such animals are known as human-animal chimeras. This raises questions not just about the legal significance of species boundaries, familiar from other areas of stem cell research, but also about whether this might make chimeras more intelligent or more capable of suffering, and what implications this might have. In addition, the creation of human-animal chimeras also needs to be viewed in the context of the cultural history of how we look at the distinction between humans and animals and areas where this distinction is blurred. This applies in particular to public education and media work.

The question as to how human life comes into being remains opaque for research to date. How does a single fertilized egg cell transform itself into something as complex as an embryo? For ethical, religious or cultural reasons, many countries prohibit or restrict research on human embryos in vitro. In recent years, murine and human pluripotent stem cells have been used to create complex, organized structures similar to very early stage embryos. Research on mouse stem cells is considerably more advanced than research on human stem cells. Within the foreseeable future, some researchers believe we will be able to create structures which are indistinguishable from an embryo. These are variously known as synthetic embryos, embryoids or blastoids, and are not to be confused with embryoid bodies, which are undifferentiated aggregates of pluripotent stem cells. Embryoid bodies are less complex and organized and can form a preliminary stage of embryoids. In view of their similarity to human embryos and in keeping with regulations on research involving human embryos in many countries, embryoids are not currently cultured for more than 14 days. How embryoids should be classified ontologically (like human embryos or something else altogether?), what they should be called and what their legal status should be remain unanswered questions.

To arrive at consensual political and legal solutions to these ethical questions, an interdisciplinary and broad public debate will be necessary.

The legal status of organoid research

Although there are no specific legal regulations on the production and use of organoids in Germany, they do fall within the scope of both constitutional and non-constitutional law. Given the origin of the material from which they are produced, organoids are likely to fall within the scope of the Stem Cell Act (*Stammzellgesetz*), which regulates the import and use of human embryonic

stem cells. In Germany the preparation of hES cells is prohibited by the Embryo Protection Act (*Embryonenschutzgesetz*). Under the Stem Cell Act, since 2002, it has been legal to carry out research on hES cell lines produced in another country and imported into Germany, but only in justified exceptional cases, under strict conditions and only for research purposes. There are growing calls for the Stem Cell Act to be fundamentally revised. The rules on cut-off dates and the laborious approval process have been much criticized. Both are also problematic under constitutional law. Furthermore, in the event that specific treatments involving the use of hES cells were to become available, the fact that the use of hES cell lines is limited to research purposes would become untenable, since it would mean specifically preventing patients in Germany from accessing such treatments.

The legal status of embryoids in particular depends on whether or not they are classified as human beings with a developmental capacity similar to that of human embryos. In this case they might be considered to be in possession of human dignity and deserving of the protection afforded to human life. Whether they are covered by the Embryo Protection Act as it stands is entirely unclear. Legal policymakers certainly need to consider whether such emphatic legal protection is justified given that the way they are produced differs from a natural embryo, with no fertilization involved, that they come into being in a context entirely unrelated to reproduction, and potentially also in view of the fact that they are produced with the intention of terminating their development at a very early stage. The question of whether future, highly developed brain organoids should be subject to the same rules as embryos also remains a matter of debate in legal policymaking circles.

Human-animal chimeras largely fall through the regulatory cracks. Section 7 of the Embryo Protection Act prohibits their creation only in the event that they contain material from human embryos, or that a human embryo capable of differentiation is produced by fertilising a human egg cell with animal semen or by fertilising an animal egg cell with human semen. Transferring a human embryo produced as above to a woman or animal and transferring a human embryo to an animal are also prohibited. The corpus of German law does not contain any other regulations specifically relating to human-animal chimeras; the animal protection law regulates animal experimentation only generally. There are a number of potential applications involving the production of human-animal organoids or even complete hybrid organisms (e.g. by implanting human organoids into animals or by implanting animal organoids into humans), and these have elicited calls for further regulation. A key demand is that any such research should have to be evaluated by an ethics committee which specializes in these particular issues. It cannot be assumed that the bodies responsible for approving animal experiments and the ethics committees which support them possess sufficient expertise to evaluate issues specific to human-animal chimeras.

With regard to the German *Persönlichkeitsrechte* (the right to live as one pleases, protected under the German Basic Law), and the highly sensitive nature of health and genetic data, the use

of organoids derived from cells and tissues from healthy people or people with specific diseases present a variety of data protection challenges. In the context of providing medical treatment (e.g. involving the diagnostic or therapeutic use of organoids), the legal basis for processing sensitive personal, health and genetic data is clearly determinable, since such treatment is generally carried out in the context of a contract for treatment. There are, however, a range of legal principles which could apply when using such patient data for research purposes. This applies also to how products of research are treated subsequently, for example in the context of storage in an organoid biobank. This pits academic freedom against *allgemeine Persönlichkeitsrechte* (the general right to live as one pleases) and the basic rights granted under European data protection legislation. These rights are protected under both German constitutional and European Union law. Data protection requires informed consent, with the consequence that research projects must be carefully scoped. Academic freedom, by contrast, requires wide-ranging, straightforward access to data and materials, even for quite vaguely formulated research projects. Both of these rights and freedoms enjoy legal protection and have to be carefully weighed against each other. Striking the right balance between these two conflicting interests would be made easier if the relevant data protection supervisory authorities were to issue some guidance. This would provide researchers with greater legal clarity. In view of the wide range of applicable legislation, such guidance would make an important contribution to determining which legislation applies and providing greater legal clarity.

Recommendations for action on the use of organoids

Recommendations for research funding

- Organoids are still a relatively new technology. As our understanding of this technology grows, new biotechnology, biomedical and clinical applications are likely to arise. There should therefore be targeted funding for research using organoids as disease models or biotechnological test systems (including organs-on-chips).
- Establish research networks: With any new technology, a variety of approaches will be tried. To establish common standards Germany-wide and facilitate significant synergies, there should be targeted funding for research networks that are working to establish, validate and standardize organoids as disease models and biological test systems.
- Drug research: One area in which organoids and organoid biobanks promise major benefits is drug research. Organoids are expected to make excellent models for preclinical efficacy and toxicity testing. This would involve testing new drugs on organoids corresponding to organs which play a major role in drug metabolism – such as the intestines, liver and kidneys – prior to performing human trials. These tests might also dispense with the need for some or all of the

animal experiments currently performed for this purpose. Organoids from biobanks could also be used to screen existing libraries of drug candidates to identify new drugs or subgroups of patients who respond to treatment. This would enable drugs to be targeted more precisely at those who would benefit from them. Better disease models are also useful in pharmaceutical research, where they can help in areas such as understanding and optimising drug mechanisms of action. There should therefore be targeted funding for pharmaceutical basic research and partnerships between research institutes and the pharmaceutical industry.

- Translation into clinical applications: Organoids hold huge potential in the field of personalized medicine. Following its successful use in the Netherlands, organoid-based personalized medicine should be made available to all cystic fibrosis patients in Germany as soon as possible. There should be targeted funding for translational medical research and for clinical trials involving other organoid-based personalized therapies, for example in oncology. Basic research should be carried out to explore the potential offered by transplantation of organoids or of tissues derived from them. The three-dimensional matrix required to culture organoids is not currently produced in accordance with good manufacturing practice (GMP). Since this is a requirement for use in humans, this means it is not currently possible to transplant organoid materials into humans. There should therefore be targeted funding for developing alternative matrices that can be produced in accordance with GMP.

- Genome editing: There should be thoroughgoing, long-term research into the use of genome editing in organoids. This technique offers the possibility of patient-specific therapies and drug development (personalized medicine) for currently untreatable diseases. Detailed research into the safety and risks of potential genome editing applications should be carried out. This is essential for properly evaluating the opportunities and risks involved in translation into clinical applications.

- Interdisciplinary research: In view of the fact that the development and use of organoids involves innovations that present far-reaching social, ethical and legal questions and will continue to raise further such questions in future, there should be targeted funding for interdisciplinary research projects examining these questions. There are hardly any ELSA research projects on organoids underway in Germany at present. In view of the large number of unanswered questions relating to the conceptual, ontological, ethical, legal and social implications of organoid research and organoid applications, researchers from the humanities and social sciences should make a significant contribution to this research.

Ethical and legal recommendations:

- Research involving hES cells: There is no prospect that organoid research using hiPS and adult stem cells will be able to take the place of research based on hES cells in the foreseeable future. In the current research environment, being able to access hES cell lines is essential for stem cell researchers in Germany. The restrictions on academic freedom and on research involving hES cells imposed by the Stem Cell Act are ethically controversial and not justified under constitutional law. We therefore strongly recommend that the cut-off date set by the Stem Cell Act should be abolished, or at least that a floating cut-off date should be introduced. To enable German patients to benefit from medical organoid applications developed in Germany, the import and use of hES cells needs to be permitted for diagnostic, preventive and therapeutic purposes, not just research purposes.

- Research on foetal tissue: Verifying and improving organoid models of the in vivo environment using organoids derived from adult and from pluripotent stem cells requires detailed comparative studies using both adult and foetal tissue. Such studies are dependent on access to foetal tissue that would otherwise be discarded. In German, the legal situation with respect to the use of foetal tissue and foetal cells for research purposes is unclear. No pregnancy should be terminated for the purpose of enabling cells and tissues from the aborted foetus to be used for research. Researchers should also have to obtain the pregnant woman's informed consent for the planned research project. Researchers are also expected to treat foetal tissue responsibly.

- Embryoids: Human embryonic development is a key area of biomedical research. Embryoids offer the ability to use stem cells to replicate embryonic developmental processes in vitro, greatly facilitating research in this area. Currently, a number of important ethical and legal questions on the use of embryoids remain unanswered. A clear legal framework for embryoid research needs to be created, and there needs to be a review of existing legislation on research involving human embryos. There is an urgent need to review the strict prohibition on research involving human embryos, for example. Such research should be permitted within certain limits in Germany, and at the very least – with the informed consent of the biological parents – with embryos that were created for reproductive purposes but will no longer be used for this purpose and would otherwise be discarded. Consideration should also be given to the potential future use of embryoids in a reproductive context. For the wellbeing of the people who might be born as a result, this needs to be explicitly prohibited.

- Brain organoids: With brain organoids, the question arises of whether they might in future be able to develop consciousness. From a theoretical perspective, it remains unclear what specific properties are intrinsic to the concept of consciousness (e.g. self-awareness, the capacity to feel/suffer, thought), nor is it clear how they can be measured in practice. A joint endeavour involving neuroscientists, developmental biologists and neuro-philosophers is needed to

clarify and demarcate terms and concepts relating to potential mental or cognitive properties of brain organoids. This debate needs to be based on a realistic assessment of what may be possible in future based on the current state of research. These insights should then be applied in clarifying whether and to what extent human and animal brain organoids and potentially animals into which they are transplanted should enjoy ethical and legal protection. The international scientific debate around organoids tends to focus on this specific point, but it is important that other ethical questions are not neglected. These include, for example, the potential of organoids to reduce the need for animal experiments, donor and patient education and consent for research, and the ontological, moral and legal status of the cells used to create organoids. This raises the question of whether the legal status of brain organoids should be adjusted to match that of human embryos, given that early stages of brain development serve as a cut-off point for the protected status of the latter.

- Information and consent for research: In view of the dynamic nature of organoid research projects, as well as the deployment of new technologies and the need for research data in biobanks to be widely availability and networkable, obtaining informed consent is not always feasible. The use of broad or dynamic consent would be one alternative. It is important to ensure that ethical standards are observed, and in particular that the fundamental right to privacy, and the right of patients and donors to decide how their data and samples should be used are maintained. Additional measures to improve transparency and data security, and build trust are therefore advised. Examples include clarifying data processing methods, protective measures to reduce data processing risks (e.g. technical and organizational limitations on access to data), setting up a website to inform study participants about specific research projects and providing them with the opportunity to object to the use of their data and materials. Consent should be sought in particular for highly sensitive areas of research. These include, for example, research involving hES cells, foetal cells and tissues, embryos, embryoids and brain organoids. With this in mind, efforts should be made to ensure that donors and patients are able to determine how their data and biomaterials are used to the maximum possible extent consistent with academic freedom.

- Less reliance on animal experiments: As disease models and for toxicology screening, organoids have the potential to complement animal experiments carried out in the context of basic research and by the pharmaceutical industry. Against the backdrop of the internationally recognized principle of the 3Rs (‘replacement, refinement, reduction’) and its implementation by EU directive 2010/63/EU on the protection of animals used for experiments and other scientific purposes, developing, validating and then using alternative methods is a high priority. Achieving this would, however, require changes to consumer protection legislation relating to tolerance and toxicology.

Recommendation on educating and involving the public:

- Science communication: Stem cell research offers huge potential and hopes are high that it will deliver major advances. In recent decades it has become clear that it is important to communicate research results and treatment options comprehensibly, clear-sightedly and realistically. The various entities involved in communicating this information – scientific institutions, individual researchers, businesses and professional associations – should make appropriate efforts to communicate their work to the wider public. The highest standards should be applied to communication about stem cells and organoids produced from stem cells, in keeping, for example, with the 2016 guidelines of the International Society for Stem Cell Research. To avoid creating unrealistic public expectations of the impending availability of stem cell-based treatments, communication should always be clear about the limits of and problems involved in research and development. Researchers and scientific institutions should also give consideration to a code of ethics for the proper communication of research results.

- Potential unproven therapies involving organoids or cells obtained from organoids: Around the world, patients are being offered a wide range of unproven stem cell-based treatments the safety and efficacy of which has not been verified in clinical trials. These represent a danger to patient health and damage the reputation of stem cell research. Steps need to be taken to ensure that organoids too do not become the subject of premature, scientifically unjustified uses without being properly licensed. The conditions that need to be met to obtain marketing authorization for drugs and other treatments should be reviewed and updated to establish appropriate criteria for and impose suitable limits on such treatments. International standards for regulating clinical applications should be developed and implemented.

- Initiating a broad public debate: The ethical and legal debate revolving around organoids is in its infancy. It is therefore important to initiate a broad, timely public discussion, in which the various interested parties and the general public are equally involved. National institutions can contribute to this debate, as can the provision of funding for research projects that look in detail at the ethical, legal, social and economic background to organoid research. It is important to ensure that public debate and media reporting is not colored by exaggerated accounts of future cures, but remains an objective, fact-based debate on the possibilities offered by and limitations of organoid research.

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