



GermanStemCellNetwork

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Stem Cell Research and Diseases III

Annual magazine of the GSCN

2021/22

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Preface

GSCN scientists were finally able to meet again in person last year at our stem cell conference. On the heels of 18 pandemic months, it was most rewarding to “meet up” with each other – and not just on computer screens. We were fortunate to be able to organize the 9th GSCN Conference in Dresden. The successful staging of this event at short notice was a Herculean effort amidst difficult and constantly changing conditions. First and foremost, the credit for this first goes to Daniel Besser and his amazing team at the GSCN Central Office, and of course to all the responsible people at the Center for Regenerative Therapies Dresden (CRTD) at TU Dresden. Thanks to a detailed hygiene plan, we were able to hold a safe and genuinely outstanding GSCN Conference in person from 6 to 8 Oct. 2021. The GSCN Conference went down as an absolute success: it featured six international keynote speakers, 68 presentations in parallel sessions, more than 100 posters, 26 industrial exhibitors, the GSCN Non-PI meeting, and the kick off of the GSCN Mentoring Program with five new chosen mentees. It was a fascinating, packed scientific program and I am particularly pleased that the new “GSCN Mentoring Group” project was very well received.

But there are also a number of other noteworthy initiatives now underway since I took over as GSCN President in 2020: as we had reported last year, it is thanks to the tireless efforts and the work of many that a GSCN partnership has been initiated with the Berlin Institute of Health (BIH), for which the GSCN sees a stable and promising future. The GSCN and BIH are now combining forces to create a “Dialog Platform Stem Cell Research”. The activities of the steering committee are up and running, the first working groups with initiators from the BIH and GSCN have been established and there are already joint projects underway in public outreach and the promotion of young researchers.

For example, the “BIH Lecture” series held in partnership with the GSCN proved an outstanding great success. On 28 May 2021, Masayo Takahashi, from RIKEN CDB in Japan, provided some fascinating insights into the current state and future vision of retina stem cell therapy – with the aim of making stem cell therapies available to patients. On 17 Dec. 2021, we invited Matthias Lütolf from the EPFL Lausanne and the Roche Institute for Translational Bioengineering, Basel to give a lecture on progress in the bioengineering of organoids, as part of the BIH Lecture series. Another highlight of the GSCN’s work has been the translation of the new ISSCR Guidelines into German, which will allow us to provide this essential information to scientists and decision-makers.



Following the successful conference in Dresden, we hope to be seeing you all in person from 13 to 16 Sept. 2022, at the 10th Annual Conference of the GSCN in Münster (North Rhine-Westphalia). This year, the conference will be extended by a day because we are eager to celebrate our anniversary at the 10th Annual Conference together with the Stem Cell Network NRW, which will be marking its 20th year – making it twice as old as the GSCN. In addition to stem cell research, the network also focuses on ethical, legal, and sociological aspects, in the interest of providing a responsible approach to the field. Please keep your fingers crossed that we will be able to celebrate this double-anniversary in the spirit it deserves and in person in Münster! I would like to take this opportunity right now to invite you very warmly to join us all.

As in previous years, we are delighted to present you with the new GSCN Annual Magazine on “Stem Cell Research and Diseases III”, focusing on neurosciences and blood stem cell research. I hope our latest issue will provide you with some new insights and valuable impulses.

Most cordially,

Hans Schöler
Active President



New guidelines bring current developments in stem cell research into focus

In 2021, the International Society for Stem Cell Research (ISSCR) has published an update of the "ISSCR Guidelines for Stem Cell Research and Clinical Translation" – with far-reaching changes. The German Stem Cell Network (GSCN) interviewed the current GSCN president Hans Schöler and the initiators of the GSCN working group "ELSA", Tobias Cantz (Hannover, Germany) and Sara Gerke (Carlisle, USA), to find out the significance of the new guidelines for Germany's stem cell researchers. Their conclusion: Harmonization of German regulation with regard to international developments is important for our research landscape.

What are the new implications for stem cell research in Germany and for the GSCN?

Hans Schöler: The guidelines generally deal with basic research but also with the clinical implementation of therapies based on stem cells in an international context. Since the publication of the previous guidelines in 2016, there have been a number of research findings worth discussing, such as embryo-like structures from stem cells, chimeric embryos, and fetuses of humans and animals or genome editing, such as the case of CRISPR-editing of human embryos by He Jiankui in 2018 that sparked global outrage.

Tobias Cantz: As a member of the ISSCR and when registering for its congresses and symposiums, we are asked to comply with the ISSCR guidelines. So, the new update of the guidelines affects us researchers very directly. For example, if I, as a researcher, disregard recommendations from the ISSCR, this would very likely be criticized by the research community and could be sanctioned if necessary.

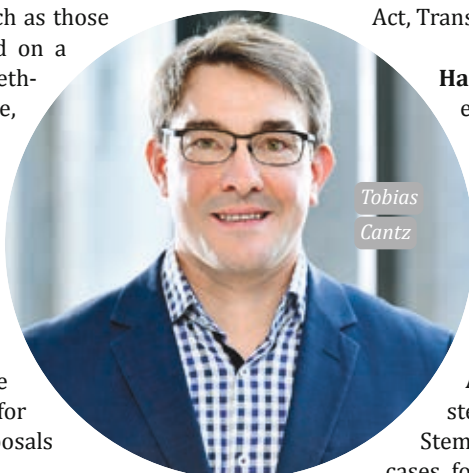
Sara Gerke: It should be emphasized that the ISSCR guidelines are non-binding recommendations. They are not legally binding. They can therefore not replace the respective national legal requirements. Nevertheless, as Tobias already pointed out, the ISSCR guidelines are of great importance and practical influence for researchers. Guideline recommendations such as those of the ISSCR, which build on a number of widely shared ethical principles in medicine, science, and research involving humans (e.g., the Nuremberg Code or the Declaration of Helsinki), can also complement existing legal frameworks (insofar as they comply with the applicable national laws) and can serve as a good starting point for the development of proposals for legal reforms.



Sara
Gerke



Hans
Schöler



Tobias
Cantz

There are relevant laws for stem cell research in Germany. Which regulations do the ISSCR guidelines expect internationally, and which oversight processes are suggested?

Sara Gerke: In Germany, the **Embryo Protection Act** primarily regulates in vitro fertilization and other aspects of reproductive medicine. It prohibits the use of in vitro embryos for research purposes. Therefore, for example, the derivation of human embryonic stem cells from living human embryos is legally excluded and punishable in Germany from the outset. The **German Stem Cell Act** regulates the import and use of human embryonic stem cells from abroad for high-level research projects in Germany. The Act is designed as a general ban subject to permission. So, the import and use of human embryonic stem cells require approval from the Robert Koch Institute, which considers the opinion of a central ethics committee for stem cell research (ZES) when making its decision. However, approval is only granted under very strict conditions. For example, researchers are from the start only allowed to use human embryonic stem cells generated before May 1, 2007. The Stem Cell Act does not apply directly to human induced pluripotent stem cell research. There is no separate law for research with these stem cells in Germany. However, research with human induced pluripotent stem cells in Germany is regulated in some aspects, for example, by provisions laid out in the Medicines Act, Transplantation Act, or Genetic Engineering Act.

Hans Schöler: The Stem Cell Act of 2002 is a good example that the slippery slope that was predicted at the time of its enactment did not materialize. Since it was set up around 20 years ago, the Central Ethics Committee for Stem Cell Research processed a total of 173 applications by the end of 2021, i.e., an average of 8–9 per year. Human induced pluripotent stem cells, first described in 2007, have made life much easier for researchers in Germany. As Sara explained, human induced pluripotent stem cells are not directly covered by the German Stem Cell Act. They only play an indirect role in rare cases, for example, if the application is intended to carry out research on both human embryonic stem cells and human induced pluripotent stem cells. Another example is when one wants to research human induced pluripotent stem cells primarily, for example, when modeling diseases, but want to use human embryonic stem cells as a Gold standard of comparison.

CATEGORY 1	CATEGORY 2	CATEGORY 3
1A – Exempt from review by a specialized oversight process – Most <i>in vitro</i> pluripotent stem cell research – Most <i>in vitro</i> organoid research – Transfer of human stem cells into postnatal animal hosts	2 – Reviewed by a specialized oversight process – Procurement of embryos, or gametes for the creation of embryos, for <i>in vitro</i> research – Derivation of cell lines from human embryos – Genetic alteration of embryos or gametes – <i>In vitro</i> culture of human embryos for research until the formation of the primitive streak or 14 days from fertilization, whichever occurs first – Human cells transplanted into nonhuman embryos that are gestated in a non-human uterus – Integrated stem cell-based embryo models – Transferring human embryos following MRT into a human uterus	3A – Not allowed; currently unsafe – Heritable genome editing – Transferring mtDNA-modified (not including MRT) embryos into a uterus – Using gametes differentiated from human stem cells for reproduction
1B – Reportable, but not typically reviewed by a specialized oversight process – Non-integrated stem cell-based embryo models – <i>In vitro</i> culture of chimeric embryos (human cells into non-human embryos) – <i>In vitro</i> gametogenesis without fertilization or generation of embryos		3B – Not allowed; lacks compelling scientific rationale or is ethically concerning – Gestating human stem cell-based embryo models – Human reproductive cloning – Breeding human-animal chimeras where there may be human germ cells – Transferring human-animal chimeric embryo(s) to a human or ape uterus – Transferring human embryo(s), irrespective of origins, to an animal uterus

New categorization of research projects in the updated ISSCR guidelines

Tobias Cantz: For the proposed oversight processes, the ISSCR guidelines categorize research activities from “exempt or only reportable” (category 1A / 1B) to “review and approval by an expert panel” (category 2) to “ban – currently unsafe or without a compelling scientific rationale, ethically concerning” (category 3A/B). Some of these oversight processes and prohibitions are reflected in our regulations in a fairly similar way, but some are not. However, there are discrepancies not only here but probably in many other countries as well.

This means that the ISSCR guidelines cannot be easily integrated into the respective regulatory framework. What adjustment processes would be necessary here in Germany?

Tobias Cantz: With regard to clinical research, the local ethics committees at the medical institutions have an important oversight function. For preclinical research with stem cells and other patient materials, an assessment committee could already be set up for work with human induced pluripotent stem cells. However, aspects that are not directly related to patients may remain under the radar, especially when working with freely available stem cell lines that were not generated in the respective institutes.

Sara Gerke: Embryonic Stem Cell Research Oversight (ESCRO) committees have long been known in the United States. In many institutions, these committees now also function more generally as Stem Cell Research Oversight (SCRO) committees, which also review certain research activities involving stem cells other than human embryonic

stem cells, such as research projects with human induced pluripotent stem cells intended to create gametes. I am not aware of committees in this form in Germany. This is probably due to the fact that there was less reason to establish them due to the restrictive legislation on human embryonic stem cells. In addition, work with imported human embryonic stem cells is already being approved by the Robert Koch Institute, which considers the opinion of the Central Ethics Committee for Stem Cell Research. However, there are very widespread close interactions between humanities scholars and stem cell researchers, as can be seen in many research projects on the ethical, legal, and social aspects (ELSA) of stem cell research. Not least because of this, we founded the “ELSA” working group at the GSCN to promote mutual exchange on normative aspects.

Hans Schöler: The German researchers are doing their homework very well in this regard. The Berlin-Brandenburg Academy of Sciences, for example, has dealt intensively with research on organoids and has also made recommendations for a regulatory framework (2020). The Leopoldina has also published up-to-date statements on reproductive medicine (2019) and research with embryos (2021). Many stem cell researchers are also – as Sara has already mentioned – very actively involved in the public debate and in professional exchange. But the existing legal provisions in the Embryo Protection Act of 1990 and the Stem Cell Act of 2002 do not adequately reflect these novel aspects, and looking at the ISSCR guidelines, we see that some things are simply forbidden here, which is why there are then also no oversight processes. However, other things remain largely unregulated, so that we already see gaps in the recommendations of the guidelines in Germany.

How could the regulatory framework be adapted to make stem cell research in Germany fit for the ISSCR guidelines?

Hans Schöler: From the field of reproductive medicine, we hear calls for the statutory rules to be revised in an amended law on reproductive medicine. For example, many people find it incomprehensible that people have to go abroad to examine their embryos because preimplantation genetic diagnosis in Germany is extremely restrictive. I don't want to judge ad hoc whether newer aspects of research with human in vitro embryos should then be regulated again in such a law or whether these aspects would not be better embedded in a more comprehensive new regulation of stem cell research. But I do wish that our Acts from 1990 and 2002 would be further developed and that our legal framework be harmonized with those of the most important international research partners in stem cell research.

Tobias Cantz: Maybe not everything has to be evaluated by a central committee like the Central Ethics Committee for Stem Cell Research based at the Robert Koch Institute. Similar to animal testing projects, ethical evaluations could also be made by local committees. In many places, such interactions are already common practice. For example, in large re-

search networks, accompanying normative research on ethical and legal issues is often conducted so that corresponding consulting possibilities are already provided there.

Sara Gerke: As already mentioned, Embryonic Stem Cell Research Oversight (ESCRO) and Stem Cell Research Oversight (SCRO) committees are commonplace in the USA. These have the advantage that they usually consist of experts in the fields of stem cell research, biology, genetics, bioethics, and law. For example, most ESCRO committees have expanded their work over the years so that they are now also examining other scientifically and ethically complex research projects with human induced pluripotent stem cells, such as gamete research, or with human neural stem cells. They are thus very flexible and can adapt to current developments in stem cell research. In Germany, we have exclusively the Central Ethics Committee for Stem Cell Research based at the Robert Koch Institute, which specializes in research with imported human embryonic stem cells. I can imagine that it would be helpful in Germany if either SCRO committees were established at the medical institutions or, alternatively, if the local ethics committees took on this task additionally so that ethically unacceptable research projects that are not directly related to patients – as Tobias has already mentioned – do not possibly stay under the radar.



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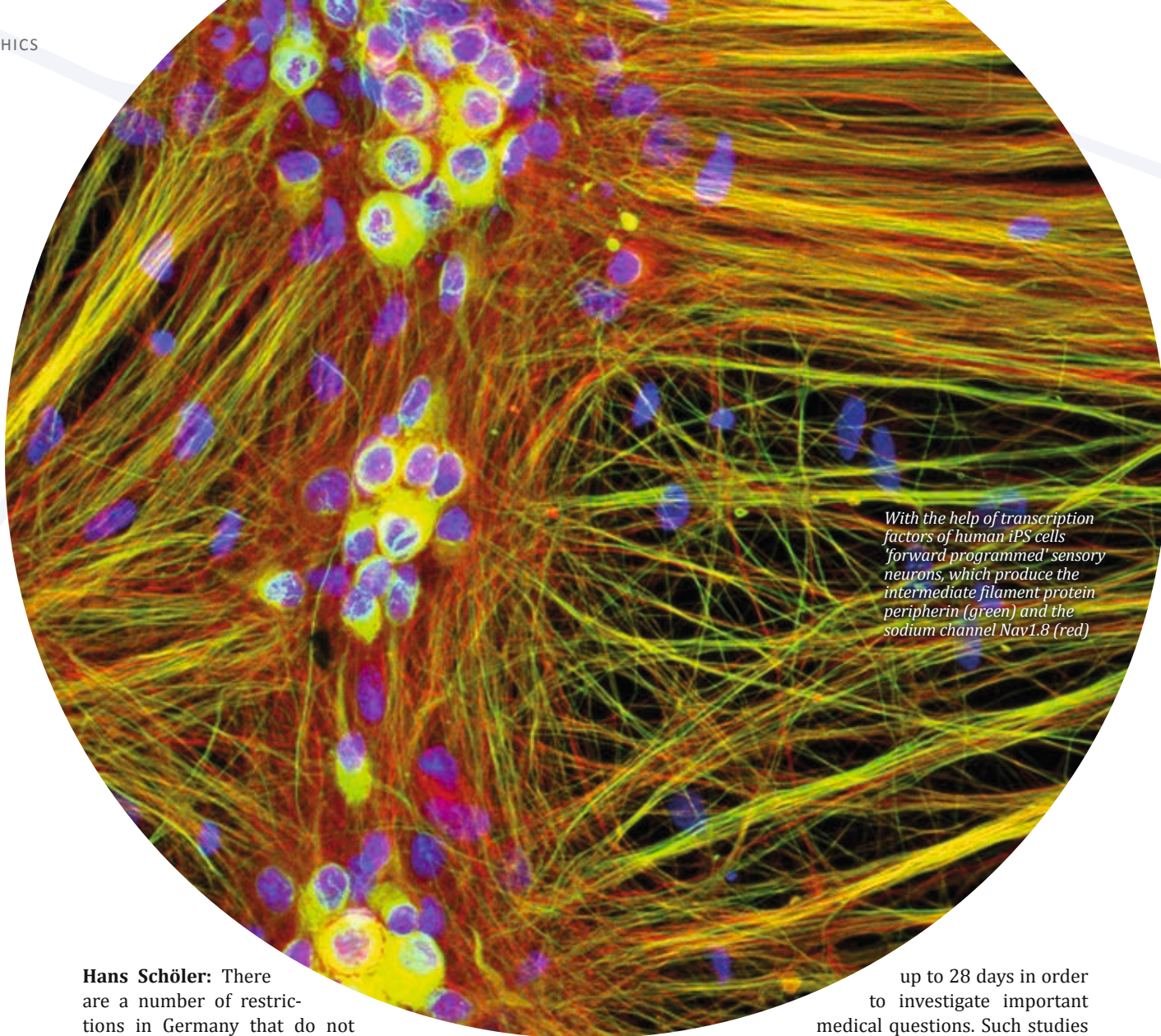
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Hans Schöler: There are a number of restrictions in Germany that do not allow researchers here to keep up internationally. One example is research on surplus human embryos, which is not permitted in Germany under the Embryo Protection Act. Research on such embryos is possible in a number of countries such as Denmark, Sweden, the USA or Japan. In some countries, as outlined in the ISSCR guidelines, even the 14-day rule is currently being questioned. One would like to examine whether it would not make more sense to allow researchers to cultivate embryos in vitro for

up to 28 days in order to investigate important medical questions. Such studies could also help to develop alternatives to the embryos created by fertilization. However, there is also a need for discussion about embryo-like structures derived from stem cells. These may answer developmental or medical questions, but what if these entities have the potential to develop into fetuses? Therefore, in my opinion, it is extremely important that the ISSCR guidelines are discussed in Germany with social representatives from a wide range of expertise.

Photo: Oliver Brüstle, Uni Bonn

Max Planck Institute for Molecular Genetics (MPIMG)

Research at the Max Planck Institute for Molecular Genetics focuses on the analysis of genome function and regulation, especially during embryonic development, differentiation, organ development and disease. A characteristic feature of the work at the MPIMG is the combination of experimental and computational methods: Genes and genomes are studied using automated methods, high-throughput technologies and various model systems, followed by computational analysis and interpretation of the results. MPIMG researchers are interested in questions of epigenetic regulation and work on a better understanding of gene regu-

lation networks for tissue formation and homeostasis, as their dysfunction may result in numerous diseases. In this context, stem cell research is gaining increasing importance. Founded in 1964 and situated in the southwest of Berlin in Dahlem, the MPIMG employs approximately 300 people and fosters a working culture of interdisciplinarity and innovation.

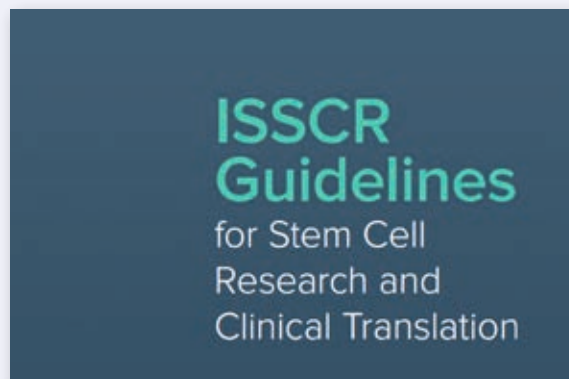
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www.molgen.mpg.de



What's new in the updated 2021 ISSCR guidelines?

The 2021 update of the ISSCR guidelines takes a closer look at new advances in stem cell-based embryo models, genome editing and chimeras, and the use of human induced pluripotent stem cells in research.

In recent years, there have been notable key developments in stem cell research and rapid progress in several areas of human embryo research, such as technologies for expanded in vitro culture. An international working group of about 50 experts from 14 countries in the scientific, clinical, policy, ethical, and legal fields has responded to these advances by revising the ISSCR guidelines. The changes include recommendations for the use of human embryo models, laboratory-derived gametes, and human-animal chimeras, as well as a proposal to modify the widely accepted two-week maximum for the growth of human embryos in culture. Although the guidelines themselves are



merely recommendations and not laws, they are considered a standard for international research and are used as a basis for scientists, physicians, and regulatory agencies, as well as the public. In addition, they can provide a basis for a regulatory framework in countries without existing regulatory systems.

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