

4th Annual Conference of the German Stem Cell Network
from 12 – 14 September, 2016 in Hannover

Novel trends and technologies in stem cell research

This year's GSCN Annual Conference in Hannover proved once again to be the most important annual meeting for stem cell researchers in Germany. Around 400 scientists met in the Lower Saxon capital for three days of intense communication and exchange on recent developments in the field. The top themes were the latest trends and techniques in organoid technologies, which are maturing at a rapid pace, the "new" discovery of extracellular vesicles, and tissue engineering. Ethical considerations were a major topic in a symposium held in parallel to the conference. A new component of this year's GSCN meeting was a technology transfer exchange.

Once a year, the German Stem Cell Network (GSCN) brings together researchers from across Germany for a few days of intensive scientific exchange. This year's three-day conference was held at Hannover Medical School (MHH) and revolved around new techniques, results and knowledge in stem cell research. The researchers made the most of the plentiful opportunities for lively discussion and debate at the poster presentations, sessions, plenary symposia and evening events. An industry exhibition was held in parallel, giving researchers the chance to network with corporate lab suppliers and specialists in cell culture technology and molecular biology. The event has grown from year to year and in 2016 it consisted of 35 booths spread over several stories.

On Monday, Minister-President of Lower Saxony Stephan Weil, opened the conference with a warm welcome and proved to be very well-informed on stem cell issues. Following brief opening addresses by MHH President Christopher Baum and GSCN President Uli Martin, the conference started off with some exciting news. Keynote

speaker Alexander Meissner announced that he is leaving the Broad Institute in Cambridge (US) and coming to Berlin in

2017. As director of the Max Planck Institute of Molecular Genetics he will be in an excellent position to contribute to German stem cell research. In his lecture, he presented interesting new data on mechanisms of epigenetic regulation in stem cells and over the course of their development. It turns out that few CpGs show changes in their methylation patterns during normal early embryonic development. Regions generally lie far above of developmentally regulated genes, and yet play important roles in their expression. In the second opening keynote of the conference, Sean Morrison from UT Southwestern, Texas (US), reported on findings in blood stem cells and their interactions with the perivascular stem cell niche. Morrison presented the latest data on the function of the chemokine CXCL12 in Tcf21-positive stromal cells and their role in establishing a niche for hematopoietic stem cells. The leptin receptor regulates the differentiation of stem cells of the bone in osteoblasts and adipocytes in the bones of the limbs. Leptin/Leptin-R activates the Jak2/Stat3 signaling pathway and promotes adipogenesis. Morrison also addressed new findings on the role of osteolection (CLEC11a) in the maintenance of the adult skeleton. The findings shed light on the regulation of bone homeostasis and how the niche for hematopoietic stem cells is established and maintained in the bone marrow.

On the first evening of the conference, Hiroshi Nagashima from Meiji University in Tokyo, Japan, gave a lecture on the generation of human organs in pigs. This branch of research has become increasingly important in the last few years due to the shortage of donor organs available for transplantation. However, the ethical implications of these technologies remain controversial. Hiroshi Nagashima's presentation focused on his lab's efforts to grow a human pancreas in a pig model. By changing the gene expression of Pdx1-Hes1 (the Pdx1 gene plays a key role in the formation of the pancreas), a genetic model was developed in which the animals no longer form a pancreas of their own. Exogenous stem cells from normal pigs, which differentiate into pancreatic cells, were able to completely form the organ during embryonic development, allowing the genetically modified pigs to survive. The team is now planning to generate models for other organs. The long-term objective is to use human cells to generate "humanized" organs in pigs, but this still requires a number of technological and



Alexander Meissner



Sean Morrison





ethical issues to be resolved. Another important lecture on a new animal model was held by Thomas Eschenhagen from the Medical Center Hamburg-Eppendorf (UKE) as part of the Presidential Symposium. Eschenhagen presented data from his working group on the transplantation of engineered heart tissue (EHT) differentiated from induced pluripotent stem cells (iPS cells) and endothelial cells in guinea pigs. The animals were transplanted with human EHT seven days following injury to the cardiac muscle. After 28 days under immunosuppression, the transplanted cardiac muscle tissue in the scarred tissue had grown, vascularized and formed some electrical connections. The findings show that human 3D heart tissue can be built into the injured heart and raises hopes that this could lead to new therapies in treating heart attacks.

Both areas – basic research and clinical translation – require a better understanding of the complex cellular and molecular clues underlying pluripotency and lineage-specific differentiation. This complexity is further extended by the diversity of 2D and 3D culture platforms applied in the field. Focusing on the transition of pluripotent stem cells (PSCs) into definitive blood cells, in his keynote lecture,

*“New treatments
for cardiac
infarction”*

Peter Zandstra presented impressive progress on how the design of “in vitro niches” combined with computational modeling of “stem cell behavior” can be applied to direct PSC differentiation into hemogenic mesoderm, and ultimately mature T-cells. Moreover, once blood progenitors have emerged, successful maintenance of these progenitors in a “blood forming niche” was demonstrated, reminiscent of the endogenous hematopoietic stem cell niche in the body. In conclusion, Peter highlighted how engineering principles and theoretical modeling can be successfully applied to the very practical challenges of translational stem cell research, providing important stimulation to the field.

Pete Coffey’s lecture was canceled due to illness; two young researchers jumped in with excellent presentations. Boris Greber from the Max Planck Institute for Molecular Biomedicine in Münster gave a lecture entitled “Principles of cardiac induction in human pluripotent stem cells” and Chao Sheng from the Institute of Reconstructive Neurobiology of the University of Bonn spoke on “Blood-derived stable induced neural stem cells: Preservation of age-related DNA methylation patterns and application to disease modeling.”

The REBIRTH Cluster of Excellence

From regenerative biology to reconstructive therapy



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

Participating Partners:

- Hannover Medical School
- Leibniz University of Hannover
- Hannover Laser Centre
- University of Veterinary Medicine Hannover, Foundation
- Helmholtz Centre for Infection Research Braunschweig
- Max Planck Institute for Molecular Biomedicine, Münster
- Institute of Farm Animal Genetics, Friedrich Loeffler Institute, Mariensee
- Fraunhofer Institute of Toxicology and Experimental Medicine, Hannover



REBIRTH Cluster of Excellence

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A pioneering feature of the GSCN conferences is the amount of the program dedicated to talks by up-and-coming young scientists. GSCN working groups select a program of presentations from the best abstracts for concurrent sessions. The participants of the online evaluation of the conference were full of praise for this approach, with 79 percent rating the structure of the conference as “very good” or “excellent”. “For the 2017 conference in Jena, we will try to organize even more plenary sessions alongside the Presidential Symposium and the keynotes,” said GSCN managing director Daniel Besser, “but the basic structure of the conference is our trademark and also provides a great opportunity for young researchers to present their data. The survey clearly

“Young scientists play a major role”

confirms this view.” In 2016, 184 abstracts were submitted for the conference and evaluated by a jury. The chosen papers were organized into a total of 14 sessions reflecting current trends and top themes in stem cell research. The field of organoids is still developing exponentially and becoming increasingly differentiated into subfields for each organ.

Beside a complete session on organoids in “Technologies in stem cell research”, Alexander Kleger (University Medical Center, Ulm) presented a novel approach to direct human pluripotent stem cells towards pancreatic organoids (POs) resembling acinar and ductal progeny in the session “Tissue engineering and organoids”. Upon orthotopic transplantation into the murine pancreas, these POs formed normal pancreatic ducts and acinar tissue resembling fetal human pancreas. By applying this differentiation platform to model pancreatic facets of cystic fibrosis (CF), the group was able to demonstrate that pancreatic commitment occurred unhindered in CF patient-derived iPS cells both in vitro and in vivo. Interestingly, the cells mirrored the CF-phenotype on a functional and global gene expression level and can thus be used for drug screenings and the testing of new therapeutic approaches.]. Further, Rasmus Freter (LICR, Oxford, UK) introduced his stem cell reporter OSCAR in the working group session “Somatic stem cells and development”. The lab has shown previously that adult stem cells of at least seven different lineages show decreased rates of mRNA transcription, marked by dephosphorylated RNA polymerase II. Using a phosphorylation-sensitive yellow fluorescent protein (YFP) that loses fluorescence in activated



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

Excellent stem cell research at the MDC in Berlin

The MDC is a biomedical research center in the north of Berlin. Many of its research groups work with stem cells, which often serve as a model system for the investigation of the molecular causes of diseases of the cardiovascular system, the nervous system or the immune system, cancer and developmental disorders. Also, the application in therapy is being investigated. The center's Scientific Director Prof. Martin Lohse says: „We are very well-connected with clinical researchers and offer excellent infrastructures for stem cell research and animal ex-

periments. This makes the MDC an excellent place for working with stem cells. We will even expand our expertise in the field in the near future.“ The Berlin Institute for Health (BIH), which was founded by MDC and Charité, will also strengthen its stem cell research by recruiting scientists for the areas of humanized models systems and cell engineering. A core facility for induced pluripotent stem cells (iPS cells) is maintained by both MDC and BIH and provides the scientific staff with support and expertise in obtaining and modifying iPS cell lines.

MDC MAX-DELBRÜCK-CENTRUM FÜR MOLEKULARE MEDIZIN IN DER HELMHOLTZ-GEMEINSCHAFT



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cells, it was possible to visualize dormant adult stem cell induction and differentiation in intestinal organoids using timelapse microscopy and FACS.

This reporter will be useful for the identification and isolation of pure dormant stem cells from many tissues as well as the screening of culture conditions for the expansion of immature stem cells *in vitro*.

MSCs have been applied in many clinical trials to treat various diseases. In contrast to the original hypothesis that MSCs home and integrate into affected tissues, in many diseases they seem to exert their therapeutic functions in a paracrine rather than a cellular manner. In the session "Stem cells in regenerative therapies" Verena Börger (University hospital Essen) presented data showing that extracellular vesicles from MSCs, such as exosomes and microvesicles, can exert comparable therapeutic functions in several disease models as the MSCs themselves. The researchers are currently focusing on improving their MSC-EV production and quality assurance platform with the aim of applying for a MSC-EV production license in near future.



Hiroshi Nagashina

The program of the GSCN annual conference covered the whole thematic spectrum of the working groups from cancer stem cells to pluripotency.

Birte Baudis (Institute for Neurophysiology, Cologne) reported in the session "Stem cells in regenerative therapies" on the immunologic properties of murine embryonic stem cell (ESC)-derived cardiomyocytes (CMs) in immunocompetent mice mismatched for major (MHC) or minor histocompatibility antigens (mHAg). She found that eight weeks after transplantation the survival of ESC-CMs transplanted under the kidney capsule was comparable in both experimental groups and in immunodeficient mice. Surprisingly, the immunization of mice with the mHAg expressed by ESC-CMs did not reduce the CM survival although it induced mHAg-specific cytotoxic T cells (CTLs) and caused rejection of control cancer cells

that expressed the same mHAg. *In vitro* analyses demonstrated that this apparent "immunological privilege" of ESC-CMs *in vivo* could be

due to very low levels of MHC molecules expressed on the surface of ESC-CMs and their reduced susceptibility to lysis by CTLs. Aline Bozec (Erlangen, Germany) reported in the session "Stem cells and aging, genome stability and epigenetics" on how a high fat diet changes the hematopoietic stem cell (HSC) bone marrow niche. Mechanistically, diet-induced changes of the intestinal microbiota, particularly gram⁺ bacteria, induced a switch of mesenchymal stem cells from osteoblasts to adipocytes, which consequently alter HSC differentiation.

Center for Regenerative Therapies Dresden (CRTD)

DFG Research Center and Cluster of Excellence at the TU Dresden

At the DFG Research Center for Regenerative Therapies Dresden (CRTD), Cluster of Excellence at the TU Dresden scientists are seeking to understand the mechanisms of regeneration using model organisms to translate the results to man and to develop novel regenerative therapies for thus far incurable diseases. The center's major research areas are focused on hematology/ immunology, diabetes, neurodegenerative diseases, bone regeneration and technology development. Currently, seven professors and twelve group leaders are working at the CRTD. They are integrated into a network of over 80 member labs at

7 different institutions in Dresden. In addition, 21 partners from industry are supporting the research projects. The synergies in the network allow for a fast translation of results from basic research to clinical applications.

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Not all the lectures in Hannover were dedicated to basic science – many focused on legal, ethical and philosophical aspects of stem cell research. A special symposium gave researchers the opportunity to discuss how artificially generated “totipotent” cells should be viewed in the context of current definitions of embryos in German law. “The symposium on “Totipotent non-embryos and non-totipotent embryos” certainly delivered on its provocative title,” said Martin Heyer from the Institute of Science and Ethics at the University of Bonn. „The exciting issues involved in the hotly debated topic of totipotency were discussed in depth and at a high level by the speakers and the audience. The fact that the event was part of the GSCN Annual Conference made it particularly successful.”



Thomas Eschenhagen

Following a lecture by Thomas Eschenhagen (UKE, Hamburg) on heart muscle cells in disease modeling, “Engineered human heart muscles for disease modeling and cardiac repair” (see above), the central Presidential Symposium presented the winners of the GSCN Awards. The winner of the Young Investigator Award 2016 Leo Kurian (University of Cologne) spoke about his lab’s work in the field of developmental biology on non-coding (Inc) RNAs and their significance in inducing the embryonic development of the heart. “I am delighted to be recognized by the German Stem Cell

Network. I would like to thank my lab, to whom the credit really belongs for the work we do and to GSCN for the award. This was my first GSCN meeting and in my opinion this is a great forum to learn about national research efforts and a great platform for networking. I am particularly impressed with the diversity of the groups and excited about the excellent science presented,” said Leo Kurian on receiving the GSCN award.

The GSCN Female Award 2016 went to Claudia Waskow (TU Dresden). “I am delighted about the award and regard it as an exceptional distinction for the work that my team and I have been able to conduct in the last few years,” said Claudia Waskow about the award that recognizes her outstanding scientific achievements. She held a lecture entitled “Generation and regeneration of human and murine hematopoietic stem cells”.

The GSCN Publication of the Year 2016 award went to Guangqi Song, Martin Pacher, Michael Ott and Amar Deep Sharma of the REBIRTH Center and the TWINCORE Center of the Hannover Medical School (MHH) for their publica-





tion “Direct Reprogramming of Hepatic Myofibroblasts into Hepatocytes In Vivo Attenuates Liver Fibrosis” published in the journal *Cell Stem Cell*. Guangqi Song held a lecture with the same title as the publication at the GSCN conference. Their article impressively demonstrates how Shinya Yamanaka’s work on reprogramming has given rise to a technology that now enables the direct conversion of a cell of one type into other cell types in the organism. These approaches could revolutionize the treatment of many severe diseases in the future.

Both poster sessions triggered lively discussion and debate. A total of 150 posters were presented in sections corresponding to the different working groups. The information displayed was studied with great interest. The poster awards provided by GSCN member company Peptrotech, went to:

- Antje Appelt-Menzel, University of Würzburg, TERM: “Establishment of a human blood-brain barrier co-culture model based on human multipotent and pluripotent stem cells mimicking the neurovascular unit”
- Christoph Hirche, German Cancer Research Center Heidelberg (DKFZ)/ HI-STEM gGmbH: “MCMV infection modulates cell cycle state and functionality of long-term hematopoietic stem cells in vivo”
- Alexander Kleger, Ulm University: “Human pluripotent stem cell-derived acinar/ductal organoids generate human pancreas upon orthotopic transplantation and allow disease modeling”
- Maike Kosanke, MHH Hannover: “Reprogramming enriches for subchromosomal variants that pre-exist at low frequency in parental cells”



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The scientific program of the conference was rounded off with a REBIRTH session addressing the whole range of ethical and legal aspects of stem cell research from basic research to heart development and the treatment of heart disease, with presentations by Nils Hoppe, Leibniz Universität Hannover, and Kai Wollert, Thomas Thum and Robert Zweigerdt from the Hannover Medical School. The GSCN

conference prides itself on further improving its format and its program of events every year. The Program Committee thus followed the call to offer even more “meet the expert” tables, where small groups are given the opportunity to fire questions at “experts” during the lunch breaks. This year’s experts were Ingo Roeder (TU Dresden), Hans Schöler (MPI Münster), Ana Martin-Vilalba (DKFZ Heidelberg), Marisa Karow (LMU Munich), Henner Farin (Goethe University Frankfurt) and Ina Gruh

(REBIRTH, Hannover). “We had a very interesting discussion with Hans Schöler,” said conference participant Sebastian Diecke. “We didn’t just talk about stem cell research but also about career-related issues, such as how best to acquire funding. It was a great opportunity to ask questions directly and get really helpful answers.”

A new component of the conference was the Technology Exchange Workshop where researchers had the chance to present innovative technologies to industry. Selected projects were briefly presented and their potential for industrial application was then discussed. “It

“We will develop the Tech-Transfer-Exchange”



Peter Zandstra



High-ranking public event in Hannover at the conclusion of the conference (from left): Michael Manns, Nils Hoppe, Tobias Cantz, Stefanie Seltmann, Uli Martin and Axel Haverich discuss the potential use of stem cell therapies.

was exciting because we had some great projects and good discussions. Over time and once the event has become more widely known, this could develop into a real technology transfer exchange,” said Daniel Besser, who initiated the workshop. “We plan to work on developing it further.”

A range of strategic issues was also addressed and discussed at length during the conference in Hannover. Topics included the promotion of young scientists, clinical trials, regulatory issues and technologies in stem cell research. Alongside an excellent session on organoids by the working group “Technologies in stem cell research”, the session on “Clinical trials and regulatory affairs” proved to be one of the highlights of the conference. It consisted of three lectures on research translation. Felipe Prosper from the University Hospital Navarra, Pamplona, spoke about European funding for translation relating to therapies using stem cell derivatives, using his university as an example. This was followed by a lecture by Arnd Hoeveler from the European Commission, and then by Aliko Nichogiannopoulou from the European

German Cancer Research Center (DKFZ)

Research for a life without cancer

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

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

target CSCs in primary cancers and metastasis. Together with the Dietmar Hopp Foundation, the DKFZ is a shareholder of HI-STEM, the nonprofit Heidelberg Stem Cell Institute and organizes the biannual Heinrich-Behr-Conference on „Stem Cells and Cancer“, which attracts international experts in the field. With the Heidelberg University Clinic, the DKFZ has established the National Center for Tumor Diseases (NCT), to clinically translate innovative basic cancer and stem cell research discoveries into clinical therapies.



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Patent Office, Munich on the patenting of stem cell-based inventions. The discussion, which continued well into the following break and could have carried on a lot longer, generated much potential for discussion at future GSCN conferences.

“Wonderful evening in the zoo”

burgers from the barbecue and enjoyed the lush summer evening far away from the lecture halls. There was ample opportunity for networking fun, rounded off by dancing under the full moon and a nocturnal walk through magical settings with flares leading the way back through the zoo.

It's no surprise then that the evening was given a straight “Excellent” rating in the online evaluation. The get-together on the first evening of the conference was also a lively and relaxed occasion with good food and plenty of good discussion on a pleasant summer's evening.

A special highlight of the Hannover conference was the GSCN Networking Evening – which was held at the zoo! In pleasant summer temperatures, the conference participants strolled through the otherwise deserted zoo, admired the wolves and monkeys, and then, with a welcome drink in hand, enjoyed watching the feeding session of two polar bears. In a setting reminiscent of a Canadian logging town, the participants observed the seals and penguins, ate ham-



The final event of the GSCN conferences is traditionally a public event in the hosting city. On the Wednesday evening in Hannover, chief physicians Michael Manns and Axel Haverich together with Ulrich Martin, Tobias Cantz and lawyer Nils Hoppe – all from REBIRTH and the MHH – made up the panel hosted by Stefanie Seltmann, DKFZ press officer, to speak about the opportunities and the future of stem cell research. In the unusual setting of a former newspaper hall of the *Hannoversche Allgemeine Zeitung*, the GSCN showed its new movie portraits on the work of the panel participants. The portraits on Michael Manns and Tobias Cantz, as well as Ulrich Martin and Nils Hoppe are available in English and German on the GSCN website.



Max Planck Institute for Molecular Genetics

MPIMG

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

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

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GermanStemCellNetwork

5th Annual GSCN Conference

11 – 13 September 2017

Friedrich Schiller University Jena

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Presidential Symposium

Jürgen Knoblich (Vienna) · GSCN Awardees: Young Investigator,
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Scientific sessions

- Pluripotency and reprogramming
- Somatic stem cells and development
- Hematopoietic stem cells
- Stem cells in diseases: cancer stem cells
- Stem cells in regenerative therapies
- Stem cells in disease modeling and drug development
- Computational stem cell biology

Program committee

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