Annual Meeting of the International Stem Cell Conference (ISCCR) 2016

Impressions by Avni Baser, Phd Student, Martin-Villalba Lab, DKFZ, Heidelberg

First of all, I want to thank the German Stem Cell Network (GSCN) for this opportunity to present my data to the scientific community and have this unique experience of joining the worlds largest and most prestigious stem cell meeting. Indeed, it was a very fruitful time during which I got various input both regarding my current project, as well as my personal development.

Despite to huge number of attendees (>3000) it was fairly easy to get in touch with people of similar scientific interests. There was a very lively and interactive atmosphere, particularly during the poster sessions. I presented my research at the poster session the first night of the conference. Beforehand I was wondering how likely it is that many people will stop at my poster, given the fact that more than one thousand posters were exhibited during these days. In the end, I was talking one hour longer than the officially dedicated time, since there was a not ending stream of people who very interested in my project. One highlight was when a junior PI whose work I often cite was spending significant time at my poster to discuss details of my project and give me insights about their unpublished work addressing similar scientific questions. This way I got a good feeling for the stage of our work and missing pieces for publication in a high profile journal.

At the end of the first conference day I joined the junior investigator social networking night, which was another great chance to meet fellow students and postdocs from all around the world. Indeed, I got to know members of the Alvarez-Buylla lab, which did pioneering work on the field of neural stem cells.

The highlight of the next day was the talk by Shinya Yamanaka, nobel price winner and father of the iPS technology, which has its ten years anniversary. It was a great pleasure to finally experience the maybe most influential stem cell researcher of our time. It was amazing how ten years after the initial observation of induced pluripotency, iPS cells are now used routinely for multiple purposes including drug discovery and disease modeling. Professor Yamanaka talked about Nsun2, a protein he initially started working with during his postdoc time almost twenty years ago. He put the function of Nsun2 in a novel light, demonstrating that this RNA-binding protein is inhibiting the transition from ground state to the primed state of pluripotency in ES cells (referring to Austin Smiths work on 2i conditions) by being important for the translation of some key pluripotency factors.

For lunch, I joined the networking with leaders luncheon, an event that gave young investigators the chance to meet their favorite PIs. I preregistered for a seat at Arturo Alvarez-Buylla's lab and was already very excited about this meeting, since he is one of the most influential researchers of our (neural stem cell) field whose work we follow already over many years. Indeed, this was great experience since he shared a lot of personal impressions about what he thinks is important to become a successful scientist. He was telling us not to be afraid of scientific controversies and shared interesting stories of his early career. Interestingly, he even asked us for our opinion about some recent scientific challenges he is facing. We very much appreciated that he gave us the chance to be part of his research.

Later that day I joined the GSCN meet-up hub event, which was a good chance to meet GSCN members and interested people. I talked to some german postdocs from Harvard, who

were interested the work the GSCN is doing in Germany. In exchange, they gave me a good insight of the scientific environment in Boston.
The second poster session taking place that night was a good opportunity for me to walk around and talk to other scientists with similar background. I have meet students from Anne Brunet's lab from Stanford who are working on very similar questions as we do. It was great to discuss details of each other's projects resulting in good feedback for both sides.
The next day I was looking forward to my personal scientific highlights of the conference. First Mercedes Paredes, a postdoc of the Alvarez-Buylla lab, was describing a novel stream of newborn neurons to the prefrontal cortex in the human brain up to several years after birth. This is quite a big deal, since neurogenesis outside the hippocampus in the human brain is highly restricted and usually only taking place until some weeks after birth. It is surprising, that the community overlooked this stream so far and it will be very interesting for future studies to figure where these cells are originating.
Following this, Professor Alvarez-Buylla himself gave a presentation answering the key question of how neurogenesis is maintained throughout life. Using a series of elegant label-retaining assays he demonstrated that B1 cells (the neural stem cells of the adult subventricular zone) do rarely divide symmetrically but never asymmetrically. From this data suggests that long-term neurogenesis is mainly mediated by the initial pool of stem cells, which persist into adulthood and are depleted over time, concluding that "everything is planned from the embryo".
At night, I joined the social event of the GSCN at the Thirsty Bear, which was great fun. I have met very interesting people from around the world. One german PI from Guangzhou was sharing his experiences and challenges he is facing as a foreign scientist in China with us; very interesting insights considering the increasing number of high impact papers coming from China.

Altogether, these days were amazingly stimulating, meeting people whom we usually only know from publications. I am very thankful for the GSCN support and hope that I was able to give you a good overview about my impressions.

With best regards,
Avni Baser

ISSCR 2016 Annual Meeting, San Francisco, 22-25 June

GSCN working group: "Stem cells in regenerative therapies"

Cristina Golfieri, German Center for Neurodegenerative Diseases (DZNE), Dresden

I am very grateful to the GSCN for having given me the chance to attend the International Society for Stem Cell Research (ISSCR) annual meeting 2016 in San Francisco last June. This is the second time I have the opportunity to join the ISSCR annual meeting and, as it happened last year, also this time I came back home absolutely thrilled about the event.

The ISSCR annual meeting convenes the best scientists worldwide in the field of stem cells, with speakers such as Austin Smith, Irving Weissman, Eleine Fuchs, Shinya Yamanaka, who (each of them from a different research perspective) set milestones in the field thanks to their breakthroughs and discoveries.
In addition to the aforementioned keynote speakers, the ISSCR annual meeting fosters young, but nevertheless, great scientists who have the chance to share their data and findings within the community. I think "*sharing*" and "*community*" are actually two keywords of this meeting. Despite being a big meeting (more than 4000 attendees) the atmosphere is always very informal in a community/family-like environment and I believe this is one of the features that make this a fabulous and extremely productive scientific event. At any level (from students to established group leaders) the common denominator is the ability to share unpublished data with the stem cell community in very well balanced and engaging presentations.
The community feeling was also promoted by several social and networking events organized during the meeting by both ISSCR and GSCN, from casual meet-up hubs to meet other attendees who share common interests to different kind of organized luncheon and, last but not least, the junior investigator networking social night.

Another feature of the ISSCR annual meeting that I would like to emphasize is the role played by the pharmaceutical industry supporting such major event in stem cell research. In fact, what I have experience as ISSCR member and attendee is that companies invest significantly, working together with academics, in order to provide better and innovative solutions in a fast and reliable way for many different aspects of our work, i.e. from optimizing cell culture, differentiation and expansion procedures, to automatized and clinical applicable GMP solutions. Examples worth mentioning: the innovation showcases from Milteny Biotec and Stemcell Technologies. The former developed complete workflows for a standardized and clinically relevant preparation of hiPSC-derived cardiomyocytes, whereas the latter presented both a new system to scale up the hiPSC production in 3D suspension cultures and a protocol to robustly revert primed hPSC to naïve-like states

This year the organizers gave a particular emphasis on the career development of the attendees. For the first time a career fair took place during the meeting and gave the possibility to meet companies looking for talented scientists. Further, attendees (upon previous registration) had the chance to meet experts over lunch to discuss about specific topics and career path. Several PhD students, postdocs and I for example had lunch with Kristian Tryggvason (CEO and founder of BioLamina) who gave us an overview of his career path together with useful tips and advices to move to an alternative career outside academia. Moreover, the organizers gathered a group of people who took different paths during their career (start-up, academic, biotec company, commercialization and business development, IP and grant office) to set up a career panel discussion focusing specially on PhD careers beyond the academic setting. Most of us (PhD students and postdocs) are every day facing the dilemma of which career to pursue and some of us are not even aware of the possibilities that do exist outside the academic world. Therefore I found the interest from the ISSCR towards this topic extremely considerate and helpful.

In the field of stem cells and regenerative therapies many exciting and promising new data have been shown. Many efforts are being done in order to get new insights and improve the cell maturation process in the dish, which still remains one of the biggest issues in the field of stem cells and regenerative therapies as well as disease modeling. Christine Mummery and Chulan Kwon gave very interesting talks on that topic regarding PSC-derived cardiomyocytes. Indeed an area that I find extremely promising and fast moving forward is cardiac development and regeneration. Exciting data were presented by Stephanie Protze from the McEwen Center for Regenerative Medicine in Toronto who were able for the first time to generate and isolate in a transgene-independent manner functional hiPSC-derived sinoatrial node pacemaker cells in a dish, opening the door for a possible development of functional hiPSC-derived pacemakers in a clinical

setting. Yang Lei (Pittsburgh University) presented not least thrilling results showing the reconstruction of a whole decellularized mouse heart, including muscle and vessles and which is able to spontaneously contract and is drug-responsive, with hiPSC-derived cardiovascular progenitors.
In the field of neuro-regeneration Mark Tuszynski from the University of California, San Diego, showed regeneration of corticospinal axons in large numbers after transplantation of caudalized neural stem cells in the lesion site, which are able to synapse to host cells. Dr. Tuszynski's results are paving the way to move cell replacement approaches in spinal cord injury to clinic.

This year, the annual meeting gave special attention on translational stem cell-based research with promising applications in the clinic. Stefan Irion from the Memorial Sloan Kettering Cancer Center in New York and Alessandra Biffi from the Dana Faber/Boston Children Cancer and Blood Disorders Center in Boston, gave two amazing examples on, respectively, cell therapy for Parkinson disease and on hematopoietic stem cell based gene therapy for the treatment of lysosomal storage disorders.
I believe that those kind of talks, combined with the several patients and patients advocates' speeches that were hosted this year at the annual meeting, were inspiring for all of us and proved how important is our research.

Poster sessions were very interactive with engaging discussions and, most likely, future collaborative projects. The organization did an amazing job with the design of the room, by combining snack areas close to the poster (although the temperature of the room was very unfriendly). Of note, each presenter had the possibility to visit posters from the same areas of research, which is normally impossible without skipping your presentation slot because vey often all the posters from the same field are assigned to the same time slot. Among the posters I would like to refer the work presented by Dr. Sarah Decembrini from the University of Lausanne, who is developing a micro-culture arrays to standardize and control the generation of retinal organoids in order to increase homogeneity and reproducibility (which is still a big issue in the field) and with high throughput capacities.

I would like to thank once again the GSCN for having awarded me a travel grant to attend this fabulous conference and, to conclude, I would like to cite the words from Sally Temple (now president of ISSCR): "Good science makes good medicine. Good stem cell science makes good regenerative medicine" and this was definitely the take home message of the ISSCR annual meeting 2016.

Travel award report

GSCN working group “Stem cells in disease modeling & drug development”

Dear GSCN committee,

First of all, I would like to express my thanks for awarding me with this travel grant and giving me the opportunity to attend the outstanding meeting of the ISSCR 2016 in San Francisco.

The overall slogan of this year’s annual meeting was “Translate Promise to Progress” and I think in several fascinating talks and presentation this catchphrase could be addressed. Several presented projects in different fields are already in a clinical trial phase or will soon start with a clinical intervention. ***(Malin Parmar / Heather Young / Roger Barker / Stefan Irion)***

Nevertheless, at least two important issues which need to be further addressed for successful translation of stem cells to the clinic were broadly discussed. One main topic was the discussion of potency of stem cells (naïve and primed state) and the important mechanisms of cell fate specification and determination. What are the key regulators to switch between naïve and primed state? ***(Austin Smith / Shinya Yamanaka)*** Does the naïve or primed state of stem cells affect the differentiation potential? How to generate a pure population of cells of interest? How can we establish efficient and reproducible protocols to generate the somatic cell type of interest? ***(Marius Wernig)*** How can we establish iPSC-based platforms for drug development? ***(Steven Finkbeiner)***

Another important aspect was the further understanding of the human genome and epigenome which can have huge impacts on clinical interventions and generation or differentiation of stem cells. How will the biological dark matter influence the genetics of the future? ***(Pier Paola Pandolfi)*** What functional consequence will the identification of additional non coding DNAs and RNAs have? ***(Andrew Field)*** How can we use non coding RNAs and/or specific chromatin remodeller to identify or generate specific cell types? ***(Kenneth Zaret / Benoit Bruneau)***

Especially the topic of generating the cell type of interest in a pure and reproducible manner is of importance for precise disease modeling and drug development. To establish this kind of protocols several groups showed transcriptomic data on single cell basis to verify the differentiation procedure. ***(Marius Wernig / Ana Martin-Villalba)*** With the help of single cell based approaches an in depth validation and characterization of a mixed cell population after differentiation including the cell type of interest can be achieved which will improve the quality and reproducibility of differentiation protocols in the future.

One of the most inspiring talks for me was the presentation by ***Shinya Yamanaka***. The first part of his talk “Reprogramming of Cells and Scientist” focused on a more personal level on the discovery of iPSCs and how this changed his scientific life. He said that “iPSC discovery reprogrammed myself” and let to “spending a lot of time in talking with people in government and industry and banks, and also spending a lot of time in fund raising.”. “But some portion of myself is refractory to reprogramming. That part tells me I should enjoy basic research”. This part was quite inspiring to me and is as well important for the translational aspect of stem cell research. iPSC technology is a great tool to model diseases and eventually identify novel targets for therapeutical approaches but further understanding of the basic mechanism of pluripotency, cell fate determination and disease mechanisms is essential for successful clinical translation.

Another highlight of the ISSCR annual meeting was the poster session on every evening where hundreds of project were presented in parallel. Several encounters with poster presenters led to fruitful discussions, insights into adjacent fields of research, ideas for my own research, and potential contacts and cooperation for the future.

Apart from 'pure' science it was fantastic to join the GSCN WunderBar Evening. The German stem cell scientists met at the 'Thirsty Bear Brewing Company" and had a great evening with inspiring scientific as well as non-scientific discussions, great beer and tapas in a relaxed atmosphere which led to new cooperation and ideas and was a helpful way to meet new people and become more familiar with each other.

I really enjoyed the ISSCR conference in beautiful San Francisco and gained new insights and inspiration for my personal work and the future of stem cell research in general. I got a broad overview of all the novel developments and efforts in stem cell research which will for sure "translate promise to progress" in the next couple of years.

Kind regards,

Stefan Hauser

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Dr. Stefan Hauser
Postdoctoral Researcher

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Report for the GSCN travel award to the ISSCR 2016 annual meeting

GSCN working group: Pluripotency and Reprograming, including Direct Cellular Reprograming

August 4th, 2016

Dear GSCN committee,

First, I would like to express my sincere gratitude for the generous financial support for my participation at the ISSCR 2016 annual meeting. During the meeting, I had great opportunities to witness fascinating talks from the leaders in stem cell fields, present my own work to the whole society, exchange ideas and protocols with other scientists, and also enjoy all the wonderful social events organized by ISSCR and GSCN.

My research focuses are: 1) direct conversion of human somatic cells into neural stem cells, namely "iNSCs"; 2) characterization of the regional identity, self-renewal, and multipotency of iNSCs; 3) directed differentiation of iNSCs into specific neuronal subpopulations such as motoneurons and midbrain dopamine neurons; 4) exploring the potential discrepancies between direct cell fate conversion and classic iPSC reprogramming, especially changes of age-related epigenetic and genetic signatures during reprogramming. Therefore, I was particularly interested in talks and posters related to my studies and discussions with leaders of my field.

I was very fascinated by several talks in the relevant sections, for example, the talk from **Dr. Anne Brunet** (Stanford University), titled "**Epigenetic regulation of aging neural stem cells**". Neural stem cell decline may underlie age-dependent cognitive deterioration, and their previous studies across different species strongly suggest that epigenetic changes in chromatin states may be particularly important in aging neural stem cells. They are currently characterizing epigenetic changes, specifically changes at H3K4me3, in neural stem cells in the aging mouse cohorts. By using next generation RNA sequencing (RNA-seq), they are able to identify the genome-wide distribution of H3K4me3 in quiescent neural stem cells (qNSCs), young and old adult neural stem cells (aNSCs). Their unpublished results show that: 1) single cell RNA-seq libraries can be established from single NSCs FACS sorted from the SVZ of adult mice; 2) multiple states of aNSCs along the course of activation and differentiation can be identified; 3) there are more protein aggregates (Proteostat Dye) and lysosomes in the qNSCs than aNSCs, suggesting that qNSCs are more "aged" compared to aNSCs. The knowledge of the epigenetic network controlling neural stem cell homeostasis might help counter brain aging in long-lived species, including human.

I was also very impressed by the talk from **Dr. Moritz Mall** (Stanford University), titled "**active lineage-specific transcriptional repression is required for proper cell fate transitions**". Use of target cell-specific transcription factors (TFs) explains induction of the target cell program, but it is unclear how the same factors can silence multiple different donor programs. Using the induced neuron (iN) as exemplar, they found that neuronal reprogramming TF "Myt1l" can access most of its physiological targets in fibroblasts and act predominantly as repressor through recruitment of the Sin3/HDAC complex to silence many non-neuronal programs including the fibroblast-specific transcriptome. Their results suggest that active and sequence-specific repression mechanisms exist to generally suppress many un-related lineage programs enabling cell fate choice and

stability involved in development and disease.

There were also a number of interesting posters. For example, **Kilsoo Jeon**'s (NIEHS/NIH) work suggested that GLIS3 regulates anterior-posterior patterning in human PSC-derived neural stem cells via WNT signaling pathway. **Maroof Adil** (UC Berkeley) showed a scalable and efficient protocol for the generation midbrain dopamine neurons from human PSCs in a defined, 3D biomaterial platform. **Fatih Semerci** (Baylor College of Medicine) showed that Lunatic Fringe is a selective marker for hippocampal neural stem cells, and its expression is necessary for the maintenance of neural stem cells.

As a tradition of ISSCR, I had the opportunity to have a lunch meeting with **Dr. Marius Wernig**, one of the leaders in direct cellular reprogramming field, and some other passionate young scientists. Dr. Wernig introduced some of the recent progress in his lab: 1) Ascl1 alone is sufficient to generate fully functional neurons; 2) Ascl1 binds its physiological sites and rapidly induces global chromatin changes in fibroblasts; 3) interestingly, Ascl1 and MyoD share many binding sites in fibroblasts which results in the induction of muscle-like cells during iN generation. Apart from the scientific discussion, Dr. Wernig also shared his own personal experience regarding career development with us, suggesting that determination and patience are the keys to make successes in science.

In addition, the social events organized by ISSCR and GSCN undoubtedly filled the breaks of the meeting with relaxation and joy, for example the "junior investigator networking social night" and the "GSCN WunderBar Evening".

All in all, the ISSCR 2016 annual meeting in San Francisco was a great success for me. I enjoyed the open-minded atmosphere, exchanged ideas with scientists from all over the world, engaged and networked with some of them for potential collaborations, which are extremely beneficial for my own scientific career. Therefore, I would like to thank the GSCN again for funding me for this wonderful conference.

Sincerely,

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ISSCR 2016 Annual Meeting – Short Report

Manuela Völkner, German Center for Neurodegenerative Diseases (DZNE), Dresden

The ISSCR is the largest stem cell and regenerative medicine community worldwide and brings together leading research in the field. Supported by a travel award from the GSCN working group “Stem cells in disease modeling and drug development”, I attended the ISSCR 2016 Annual Meeting in San Francisco.

At the meeting a number of new insights into basic stem cell biology were presented. For example, Pier Paolo Pandolfi presented data on the importance of circular RNA species in gene regulation, Fiona Watt on the effect of the ECM stiffness and composition on stem cell behavior and Marius Wernig showed new insights into the dynamics of the process of chromatin remodeling in cell reprogramming. In the future, a better understanding of the these basic processes in the regulation of stem cell behavior will also help to decipher disease mechanisms and develop new treatments.

Christine Mummery highlighted some of the challenges the field of stem cell-derived disease modeling is facing, like the question of proper controls, immaturity of generated cell types, variability of cultures and dell types generated. Thereby she highlighted the need for a further standardization like the use of isogenic lines or fully defined culture conditions, as well as the need to advance the current models further to model aging in culture and processes requiring interaction of several cell types. The latter, is a challenge, which may be solved in the future by improving the current organoid models that already exist for several types of tissue.
In this regard, James Wells presented a new protocol to generate fundus-like stomach organoids from human iPSC for the first time. This will enable modeling the involvement of Helicobacter pylori in the formation of peptic ulcer and gastric cancer in the future.
In the field of neurodegenerative disease modeling e.g. Justin Ichida presented new data on the involvement of endosomal trafficking defects of motor neurons in ALS and frontotemporal dementia. In their models promotion of endosomal trafficking by activators could rescue motor neurons from degeneration. Further, Steven Finkebeiner presented data on Huntingtons disease modeling and the involvement of autophagy deregulation. They developed small molecule autophagy activators, which could protect patient iPSC-derived neurons from degeneration. As many neurodegenerative diseases show deregulated autophagy pathway, these activators may also be effective to prevent neuronal degeneration in other diseases. Further, the Finkebeiner group also developed a new algorithm to analyze disease relevant phenotypes in culture in high throughput, which can also be applied for other neural disease models. Further, such high throughput and high content phenotype analysis may offer enough power to also look at sporadic forms of neurodegenerative diseases. Currently this is not possible, but the majority of patients e.g. in Alzheimers or Parkinsons disease is affected by sporadic rather than genetic forms.

More personally, I benefited mostly from the poster sessions and all the advice I received there. In the field of retina research that I am working in, many groups presented novel data on improved differentiation of retinal cells from PSCs during the poster session. Thus, I gained a lot of advice on how to potentially improve our differentiation protocols for human PSC. Further, I presented my data on an induced reactive gliosis model in mESC derived retina organoids. I received advice on how to

further characterize and improve the model we generated and how to best try to proceed to do a similar model in human retina organoids. I also received suggestions on how we could use our mESC retina organoid model to test drugs for retinal degeneration phenotypes. In addition, several people where also interested in our differentiation protocol and we are now in contact also for some potential collaborations.

In summary, at the ISSCR 2016 Annual Meeting in San Francisco many groups presented data showing significant progress in the field of stem cells in disease modeling and drug development. However, challenges that are still remaining to achieve faithful disease models especially for sporadic and aging associated diseases were also highlighted at the conference. These challenges need to be solved by future research and different groups also already presented some improved protocols and screening strategies they are testing, which may provide potential solutions to some of these problems in the future.

Report

GSCN Travel Award – ISSCR San Francisco 2016

Working Group "Somatic stem cells and development"

Stefan Weiß

The Annual Meeting of the International Society for Stem Cell Research (ISSCR) in San Francisco was one of the world leading and largest international conferences for Stem Cell Research with over 4000 scientists participating. As a member of the German Stem Cell Network (GSCN), I was selected for the GSCN Travel Award to actively contribute to this event with a poster presentation entitled "Identification of a new neuronal lineage specifier, Glypican 4, using high-content imaging of stem cell-derived neurons". As the annual meeting of the biggest society for Stem Cell Research, several outstanding leaders of the stem cell field presented their newest discoveries. One of my personal highlights was the presentation by Prof. Jaenisch from the MIT / Whitehead Institute, USA. His group tries to establish human-mouse chimeras to model developmental diseases. Prof. Jaenisch reported that human ESC-derived neural crest cells can integrate and migrate in the developing mouse embryo although the contribution rate is still very limited (<0.1%). Therefore, possible reasons for these limitations were discussed (differences between host and donor in cell cycle state, differentiation status and possible immune rejections) as well as strategies to overcome them (the use of immune deficient host mice, better matching of differentiation stages). Especially interesting regarding my own research was the talk of Prof. Anderson about epithelial-mesenchymal-transition (EMT) in gastrulating mouse embryos. After her presentation, I discussed with her my own research results of anterior forebrain defects in the early mouse development and gained important feedback for future experiments (e.g. the use of special reporter mouse lines). The possibilities to interact personally with academic experts from the field as well as to discuss future career options with members from industry were my main goals for this conference. In each single aspect, my expectations were strongly fulfilled: During my poster presentation I discussed in high detail my results with a glycobiology expert from Japan, Prof. Nishihara, who gave me vital and fruitful feedback on my stem cell differentiation results and who might become a collaborator in the future. One of the nicest and most relevant experiences apart from the conference itself was the WunderBar get together of the GSCN at a local microbrewery organized by Daniel Besser. The relaxing location with tapas and home-made beer created a perfect atmosphere to meet representatives of academia and industry. Thereby, I could discuss possible job opportunities in the field of stem cell research and strengthened my existing international network of stem cell scientists. Taken together, I am grateful to have been able to join the ISSCR Meeting in San Francisco. My future career was not only strongly supported by GSCN Travel Award itself; also the GSCN networking event represented a very important step to elaborate my future opportunities.