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The 2nd International Collaborative Symposium on Stem Cell Research

The 2nd International Collaborative Symposium on Stem Cell Research, Seoul, Korea, 18–19 September 2008

The Second Biennial International Collaborative Symposium on Stem Cell Research, held in Seoul, Korea, on 18–19 September 2008, showcased talks by a roster of established and emerging leaders in stem cell biology, and demonstrated how far and fast the field has moved in the last 2 years.

The first day of the conference highlighted a range of new topics, including: induced pluripotent stem (iPS) cells; epigenetic reprogramming of stem cells *in vivo* in early embryos versus reprogramming observed in embryonic stem (ES) cells *in vitro*; evidence for cancer stem cells in a mouse model of brain tumor; small molecule approaches to stem cell differentiation; and the derivation of red blood cells from human ES cells, an important advance in the field of blood banking. Presentations on the morning of the second day focused on the derivation and transplantation of neural progenitor cells, particularly in the context of treatment for neurodegenerative disorders. In the afternoon, applications of a variety of 'adult' stem cells including amnion- and amniotic fluid-derived stem cells, as well as progenitor cells from adipose tissue and vasculature, were discussed.

Pluripotency, a defining property of ES cells, is a two-edged sword in its potential utility in new cell-based therapies. On the one hand, being pluripotent means that stem cells have the potential to differentiate into all the tissues of an organism, and it is this prospect that has triggered worldwide interest in the field. On the other hand, the definitive test of pluripotency is the formation of teratomas *in vivo*; the threat of tumor formation by undifferentiated human ES cells still represents the strongest argument against their use in cell-replacement therapy. In addition, there are serious ethical concerns about the destruction of human embryos to generate human ES cell lines. iPS cells are an exciting possible alternative to ES cells that bypass these ethical concerns because they are produced by reprogramming somatic cells into an ES cell-like state with the introduction of transcriptional factors and small molecules. Kwang-Soo Kim (Harvard University, MA, USA) described methods to drive rat neural precursor

and fibroblast cells into iPS cells, which are then capable of differentiating into many cell lineages, including into dopamine neurons. As pointed out by In-Hyun Park (Harvard University), the ability to produce iPS cells now makes it possible to derive a wide variety of disease-specific stem cells. These cells in turn will allow investigators to study disease mechanisms and to design novel assays for functional, toxicological and/or small-molecule screening. Dong-Wook Kim (Yonsei University, Korea) explained how small-molecule kinase inhibitors can be used to derive functional dopamine neurons from ES as well as from iPS cells.

Several investigators, including Kyuson Yun (The Jackson Laboratory, ME, USA), Martin Pera (University of Southern California, CA, USA) and Alexander Storch (Dresden University of Technology, Germany), described how they harnessed the power of genomics and epigenomics to characterize different populations of stem cells. Dr Pera cautioned that genomic analysis of mass stem cell cultures may introduce significant errors owing to the inherent heterogeneity of such cultures since significant intercellular variation exists in genomic expression patterns within even a single clump of ES cells. Dr Yun exploited this variation to characterize cancer stem cells using FACS analysis. She discovered characteristic genomic expression signatures of staged gliomas in the significantly enriched 'side' populations that are distinguished by dye exclusion. Dr Storch used genomics and novel bioinformatics analyses to identify HIF1 α as a key regulator of hypoxia-mediated control of dopamine neurons, as evidenced by conditional knockout mice analysis.

Philippe Collas (University of Oslo, Norway) and Yong-Mahn Han (KAIST, Korea) showed that genes that are 'off' may actually be as or

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more important than those that are 'on' in stem cell reprogramming. Dr Collas noted that methylation is present in progenitor cells and that strong methylation may be responsible for lineage restriction during stem cell differentiation. Dr Han identified striking changes in epigenetic methylation patterns in cloned bovine embryos and suggested that these patterns may explain the severe and often lethal side effects of ovine as well as bovine cloning.

Several ingenious approaches to inducing or manipulating stemness in different cell populations were presented. Soo-Kyung Kang (Seoul National University, Korea) proposed that the inhibition of reactive oxygen species in response to hypoxia as well as the presence of a novel small molecule are key prerequisites for dedifferentiation of adipose stem cells into more primitive stem cells with more potent regenerative function. This was consistent with Dr Storch's results showing that hypoxia and HIF1 α can induce the derivation of neural cells from mesenchymal stem cells.

Mahendra Rao (Invitrogen, USA) described an elegant vector expression system that can be used to express several differentiation factors simultaneously with relatively high efficiency, resulting in the efficient derivation of iPS cells.

A timely discussion on the need for team building to bring stem cell therapies from the laboratory to the clinic was provided by Arlene Chiu (City of Hope Medical Center, CA, USA). Basic scientists, translational investigators, clinicians and biotech enterprises tend to operate in separate silos. 'Siloing' of funding for each investigative group exacerbates this segregation of research. To accelerate the process, funding agencies are beginning to promote and fund research team projects that require dynamic collaboration between these different groups of investigators. The goal is to ensure seamless transitions between basic discovery, therapy development, manufacturing, clinical trials and clinical practice. Although ideal teams are rare, similar collaborative approaches in genome sequencing and genomics have produced spectacular results that have benefited the whole scientific community.

Shin-Ichi Nishikawa (Rikagaku Kenkyusho, Japan) presented elegant genetic analyses using tamoxifen-inducible Cre-mediated genetic approaches, which revealed that all hematopoietic stem cells are derived from E7.5 Runx1⁺ cells in the yolk sac. This emphasized that this type of actual differentiation process will eventually allow us to generate an unlimited number of definitive hematopoietic stem cells from ESC or iPS cells for clinical application.

A number of important talks focused on neurodegenerative diseases including Parkinson's disease and Huntington's chorea. Patrik Brundin (University of Lund, Sweden) reviewed clinical trials where patients with Parkinson's disease received transplants of fetal neural tissue. He cautioned that while clinical response in some patients has been highly salutary, with some patients surviving more than 10 years, others experienced transitory effects or even significant adverse side effects, including the development of involuntary movements or dyskinesias. Dr Brundin reminded the audience that the fetal cell populations used in these trials were highly heterogeneous and suggested that development of a safe and reproducible supply of ES- or iPS-derived dopaminergic cells will be necessary for successful large-scale clinical trials. The challenge is to devise relatively simple, safe and effective stem cell preparations using Good Manufacturing Practices (GMP). Another key issue regarding therapeutic surgical approaches was raised by Ivar Mendez (Dalhousie Medical School, Canada), who presented new methodology – the Halifax neurosurgical protocol – for precisely implanting fetal cells into the brain of Parkinson's patients. Using virtual reality to plan and execute the complex surgery, he employs a specially designed cannula with dual side ports that markedly improves cell delivery. Using such a precise and reproducible protocol will be extremely important in designing future clinical trials to compare the efficacy of human ES or iPS cell therapy with fetal cell therapy. In addition, there was discussion regarding conflicting observations of Lewy body formation from fetal cell transplantation more than 10 years ago in postmortem tissues.

The discussion of other nontraditional sources and applications of neural stem cells was interesting and informative, and provided alternatives to ES cell-based therapies. Neural progenitor cells (NPCs) derived from the human fetal nervous system were posited as a reliable source of tissue-specific precursors by Johannes Schwarz (Leipzig University, Germany). Also, he described how medium spiny GABAergic projection neurons can be derived from the striatum under the control of the transcriptional factor Foxp2. When he generated mice with humanized Foxp2, this produced a gain-of-function effect on neurite outgrowth, plasticity and synaptic connections. Sang-Hun Lee (Hanyang University, Korea) described driving NPC differentiation by using the transcription factors *Mash1* or *Ngn2*, which dramatically enhanced donor cell survival and hence resulted in larger grafts following transplantation in mice.

Papers on stem cells derived from the amnion or from amniotic fluid were presented by Stephen Strom (University of Pittsburgh, PA, USA) and David Warburton (University of Southern California, USA), respectively, who described how these novel classes of cells can contribute to the amelioration of heart and liver failure and the treatment of lung injury. Since both types of stem cells are derived from discarded fetal tissues, they do not face the same ethical challenges as ES cells. They are also being banked under GMP conditions, requiring little manipulation, and therefore are likely to face fewer problems in getting US FDA approval.

Gou Young Koh (KAIST, Korea) reported on the repopulation of the hematopoietic system using hematopoietic stem cells residing in adipose tissue. Interestingly, these stem cells were also capable of generating functional vessels. Blood vessels were produced in Matrigel™ cultures using VEGF and Angiopoietin1 as driver molecules, and lymphatic vessels with transcription factor Prox1 as the driver. Therapeutic applications of vascular angiogenic progenitor cells (VAPCs) derived from human ES cells were discussed by Hyung-Min Chung (Pochon CHA University, Korea). Noting that VPACs secrete angiogenic factors, Dr Chung demonstrated that these cells could revascularize the ischemic rat hind limb. Hypoxia was deemed a major factor in promoting the differentiation of VAPCs from human ES cells. Il-Hoan Oh (The Catholic University, Korea) stressed the importance of the microenvironment and crosstalk between Wnt and Notch signals for hematopoietic stem cell regeneration.

While advocating strongly for more stem cell research in the urologic system, Chester Koh (University of Southern California) presented data suggesting that the derivation of bladder epithelium and smooth muscle from stem cell populations will soon become available for clinical use.

Dan Kaufman (University of Minnesota, MN, USA) not only demonstrated that NK T cells could be derived from human ES cells, but caused a wave of excitement by showing that these NK cells are extremely effective at obliterating a variety of solid tumors, including subcutaneously injected primary tumors, metastases and micrometastases. This approach opens the possibility of applying human ES cell-based T cells as a highly effective immunotherapy for solid cancers, most of which continue to have a dismal prognosis with currently available therapies.

Lastly, significant improvements in stem cell derivation and banking technology were

discussed by a number of speakers. Dong Ryul Lee (Pochon CHA University, Korea) described how mechanical isolation, the use of human feeders and culture media free of animal-derived products are now used by his team to derive and to bank new lines of human ES cells. Young Chung (Advanced Cell Technology, MA, USA) described improved methods for generating human ES cells from single blastomeres in a move towards technology for derivation of new cell lines that avoids the destruction of human embryos. Yukio Nakamura (RIKEN, Japan) presented results suggesting that stem cell banking could lead to the establishment of critical numbers of human hematopoietic erythroblast cell lines for the production and banking of red blood cells. This line of research is highly significant because it addresses directly the current shortage of clean, Rh-negative, group O blood universally accepted and needed for transfusions throughout the world. The problems of scalability will need to be overcome for this approach to become practical.

The rapid pace of progress in stem cell technology raises the possibility that useful therapeutic applications will be forthcoming within a decade. Some applications are likely to be based on research and products derived from the use of human ES cells. Ethical concerns regarding these cells may be removed with advances that enable the extraction of stem cells without causing the destruction of donor embryos. Such technology will allow for the safe generation of viable stem cell banks. Alternative sources of human stem cells, including iPS cells, adipose and vascular tissue, and discarded materials such as amniotic fluid and amnion, are also emerging as viable and even sometimes preferable alternatives to human ES cells. The future for stem cell research in Korea and around the world continues to be bright. It is clear from this symposium that the field will benefit tremendously from international collaboration and the fruits of such synergy will be applications that ultimately benefit all humankind.

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