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Stem Cells in Translation: Impression of the ISSCR Regional Meeting in Florence

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The International Society for Stem Cell Research hosted an exciting meeting on stem cell-based translational medicine in Florence, Italy in September 2013. This report gives an overview of recent advances and breakthroughs presented at the meeting.

Florence, the cradle of the 14th–17th century European Renaissance (French for re-birth), aptly hosted the International Society for Stem Cell Research (ISSCR) Regional Forum on "Stem Cells in Translation" in September 2013. Over 300 delegates from 36 countries gathered at the 19th century Villa Vittoria (see Figure 1 for impressions from the conference) to share their recent findings on potential clinical applications of stem cells. There is great hope that stem cells will find multiple applications in regenerative medicine, perhaps the most obvious being the replacement of damaged or lost tissue. Cell replacement, however, may not be the only translational route: in vitro modeling of human development and disease, drug screening platforms, or the delivery of therapeutic molecules in vivo were all aspects of translation covered in the meeting. The meeting would not have been complete without some cautionary notes; specifically, teratoma risk using pluripotent stem cells or the propensity of adult stem cells to undergo malignant transformation, as observed in some experimental tumors and in patients receiving gene-modified hematopoietic stem cells.

Co-organizer Michele De Luca (University of Modena and Reggio Emilia, Italy) opened the meeting with a passionate appeal for rigorous standards in the introduction of stem cells into the clinic and discussed the potential damage to the field irresponsible use of unproven therapies could bring. In his presentation, De Luca gave an example of what this can mean: the Italian Stamina Foundation has engaged in treating patients with autologous mesenchymal stem cell-like cells, which he described as "based on flawed and fraudulent preclinical tests" (see also Abbot, 2013). He called for stem cell researchers to actively seek dialog with decision makers in politics and regulatory agencies, as well as with the general public, to avoid misrepresentation of treatments under the label of stem cell therapy. The ISSCR has addressed this issue at length in their "Guidelines for the Clinical Translation of Stem Cells" for researchers (http://www.isscr.org/docs/guidelines/isscrglclinicaltrans.pdf) and patient-directed website "A Closer Look at Stem Cell Treatments" (http://www.closerlookatstemcells.org/).

Stem Cells and Regenerative Medicine

Hope in the future rise of stem cell-based therapies was fueled during this meeting by a series of reports on the successful application of stem cells to regenerate lost or damaged tissues in both preclinical models and in patients. Tissue-specific stem cells are already showing efficacy in the clinic, the best known example being allogeneic hematopoietic stem cell (HSC) transplantation to reconstitute functional hematopoiesis in patients. Bobby Gaspar (UCL Institute of Child Health, UK) and Alain Fischer (CHU Necker INSERM U768, France) took HSC therapy one step further and combined autologous HSC transplantation with gene therapy to treat primary immunodeficiencies. At the meeting, Gaspar and Fischer summarized the follow-up of these studies, showing considerable success in long-term reconstitution of a functional immune system in patients with severe combined immunodeficiency (SCID). In the same session, Luigi Naldini (San Raffaele Scientific Institute, Italy) presented results from pilot studies in patients suffering from metachromatic leukodystrophy and Wiskott-Aldrich syndrome and showed successful gene correction and a clinical benefit in these patients. Another example of successful clinical application of adult stem cells was presented by Graziella Pellegrini (University of Modena and Reggio Emilia, Italy), who together with Michele De Luca developed a limbal stem cells transplantation regime to restore damaged corneal epithelium in patients with ocular burns. These and other examples of clinical applications of adult stem cells presented at the meeting are summarized in Table 1.

Many presentations followed that focused on promising preclinical studies for potential stem cell therapies, which, taken together, suggested that clinical translation may expect significant growth within the coming years. Notably, therapies based on pluripotent stem cells are catching up with adult stem cells: Lorenz Studer (Sloan-Kettering Institute for Cancer Research, USA), for example, who has carried out research on the derivation of dopaminergic neurons from pluripotent stem cells for more than a decade, revealed his plans for the first clinical trials to treat Parkinson's Disease in the coming years.

Figure 1. Impressions from the ISSCR Regional Meeting in Florence, Italy, in September 2013

Other clinically relevant cell types being generated through expansion and differentiation of stem cells in vitro, through stimulation of endogenous progenitors in situ, or through direct reprogramming included vascular endothelial cells, retinal pigment epithelium, hepatocytes and oligodendrocytes (see Table 1 for a complete list).

Major hurdles for bringing induced pluripotent stem cells (iPSCs) to the clinic (which also applies to some other types of stem cells) were discussed by George Daley (Boston Children's Hospital, USA): (1) efficient iPSC derivation under GMP conditions, (2) safe methods for genetic modification, (3) efficient differentiation and maturation of cells, and (4) scaling up production to clinically relevant cell numbers. Daley announced the introduction of a new cell type classifier, Cell Net, which is an online platform trained on gene expression data from murine and human cell types. This platform will allow researchers to discover gene regulatory networks within the gene expression data from cells generated in their lab and to compare their in vitro engineered cells with their in vivo counterparts, with the aim of validating the identity of the cell types formed and enhancing the efficiency of directed differentiation and direct reprogramming experiments.

Cancer and Stem Cells

Accumulating evidence suggests an intimate link between stem cells and cancer, although this is still controversial. The cancer stem cell model suggests that cellular hierarchies, much resembling hierarchies in normal tissues, are active even in malignant tumors, whereby tumor growth is fueled by a subset of continuously dividing and differentiating cancer stem cells. Furthermore, it has been suggested that cancer stem cells may arise from malignant transformation of normal tissue stem cells.

In his opening lecture, John Dick (University Health Network, Canada) followed up on the debate on the origin of cellular heterogeneity within tumors and whether it results from the activity of cancer stem cells or from clonal

Table 1. Applications of Stem Cells in Translational Medicine Presented at This Meeting

Presenter	Cells (Re) Generated	Method and Starting Cell Population	Status	Related Publication
Direct Reprogramming				
Shahin Rafii	Vascular endothelial cells	Overexpression of transcription factors in amniotic cells, TGFβ-inhibition	Preclinical	(Ginsberg et al., 2012)
Activation of Endogenous Progenitors				
Robin Franklin	Oligodendrocytes	Stimulation of oligodendrocyte progenitors with systemic factors, pharmacological compounds	Preclinical	(Ruckh et al., 2012; Yuen et al., 2013)
Mauro Giacca	Cardiomyocytes	Stimulation of cardiomyocyte proliferation by in vivo expression of secreted proteins, miRNAs	Preclinical	(Eulalio et al., 2012)
Stuart Forbes	Hepatocytes	Stimulation of hepatocyte progenitor cell proliferation/differentiation by macrophage infusion	Preclinical	(Bird et al., 2013; Boulter et al., 2012)
Regeneration from Adult/Tissue-Specific Stem Cells				
Hans Clevers	Hepatocytes	Organoid culture/ expansion and transplantation of liver stem cells	Preclinical	(Huch et al., 2013)
Graziella Pellegrini	Corneal epithelium	Culture/expansion and transplantation of autologous limbal stem cells in patients with ocular burns	Clinical	(Pellegrini et al., 2013; Rama et al., 2010)
Paolo Macchiarini	Tracheal epithelium	Transplantation of bioartificial trachea seeded with autologous bone-marrow mononuclear cells in patient with tracheal cancer	Clinical	(Jungebluth et al., 2011)
Giulio Cossu	Skeletal muscle	Transplantation of HLA-matched mesangioblasts via artery infusion in patients with Duchenne muscular dystrophy	Clinical	
Bobby Gaspar	Immune system	Infusion of gene-modified autologous HSCs in patients with ADA-SCID and SCID-X1	Clinical	(Gaspar et al., 2011a; Gaspar et al., 2011b)
Alain Fischer	Immune system	Infusion of gene-modified autologous HSCs in patients with SCID-X1	Clinical	(Hacein-Bey-Abina et al., 2010)
Luigi Naldini	Blood system	Infusion of gene-modified autologous HSCs in patients with Wiskott-Aldrich syndrome	Clinical	(Aiuti et al., 2013)
Luigi Naldini	Immune system	Infusion of gene-modified autologous HSCs in patients with metachromatic leukodystrophy	Clinical	(Biffi et al., 2013)
Sally Temple	Retinal pigment epithelium (RPE)	Subretinal transplantation of RPE generated from autologous/allogeneic RPE stem cells	Preclinical	(Salero et al., 2012)
Regeneration from Pluripotent Stem Cells				
Lorenz Studer	Dopaminergic (DA) neurons	Directed differentiation of ESCs to DA neurons via floorplate intermediate	Preclinical	(Ganat et al., 2012; Kriks et al., 2011)
Yoshiki Sasai	Neural retina	Self-organization of ESCs in vitro, enhanced thorough Notch inhibition	Preclinical	(Nakano et al., 2012)
Gordon Keller	Hepatocytes	Directed differentiation of ESCs, maturation with aggregation and cAMP	Preclinical	(Ogawa et al., 2013)
Gordon Keller	Definitive hematopoietic progenitors	Directed differentiation of ESCs	Preclinical	(Kennedy et al., 2012)

evolution. Dick suggested that in human leukemias, both might synergize to drive disease progression. Thus, a subset of leukemia stem cells (LSCs) would with time acquire mutations, which lead to accelerated proliferation and decreased apoptosis/chemosensitivity. Notably, the LSC gene expression signature is highly correlated with the expression signature of normal HSCs, suggesting that HSCs are the cell or origin of some leukemias, and that HSC signature genes might be promising therapeutic targets (Eppert et al., 2011). Hans Clevers (Hubrecht Institute, Netherlands) reported that tissue-specific stem cells expressing the WNT target LGR5 can be found in many adult tissues, including colon, small intestine, liver, stomach, and hair follicles. Recent evidence from Clevers' lab suggests that LGR5+ stem cells are the target cell of oncogenic transformation in intestinal carcinomas. Likewise, a cellular hierarchy was observed in these tumors, lending further evidence to the cancer stem cell concept (Schepers et al., 2012).

It is commonly known that undifferentiated pluripotent stem cells can give rise to tumors, so-called teratomas, and that undifferentiated stem cells need to be eliminated before grafting to avoid tumor formation. Even tissue-specific stem cells can acquire tumorigenic properties under certain circumstances, as evidenced in some early gene therapy trials in which insertional mutagenesis in transplanted HSCs caused leukemias in patients (Hacein-Bey-Abina et al., 2008; Howe et al., 2008). Although this observation warrants caution for gene and cell therapy strategies, enhanced safety features in vectors used to deliver the gene therapy constructs, such as the self-inactivating lentiviral vectors presented by Christopher Baum (Hannover Medical School, Germany), and improved transduction protocols will minimize the leukemic risk in future patients. Thus, plasticity and self-renewal of stem cells, and susceptibility to malignant transformation, may be two sides of the same coin and need to be properly balanced and controlled when using stem cells in a clinical setting.

Conclusions

Stem cell-based preclinical studies and clinical applications are clearly on the rise, and important breakthroughs in clinical use of stem cells have been achieved with more to be expected in the near future. As the field advances at an ever-growing pace, researchers, clinicians, patients, and regulatory authorities need to be aware of associated risks and commit to rigorous preclinical and clinical investigation to maximize safety and the clinical utility of treatments.

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