ISSCR 2013: Back to Bean Town

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ISSCR 2013: Back to Bean Town

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The International Society for Stem Cell Research 11th Annual Meeting was held in Boston in June 2013, bringing together just over 4000 attendees. An emphasis on therapeutic applications in many talks reflected the maturation of the stem cell field from its origins in basic science to one that is beginning to show therapeutic promise.

This year’s International Society for Stem Cell Research (ISSCR) Annual Meeting returned to Boston, where the organization was founded 11 years ago. Remarkably, the number of ISSCR members has grown 20-fold, from 200 to 4000, over the years, reflecting the increasing interest in stem cell research. The fact that this report appears in the ISSCR’s new journal provides further documentation of the expansion of the stem cell field and, with it, the growth of the society. Just over 4000 attendees from around the world gathered in Boston to celebrate the ISSCR’s anniversary and to share their exciting results with the scientific community. This year, particular emphasis was given to presentations discussing therapeutic applications, exemplifying the maturation of the stem cell field from its origins in basic science to one that is beginning to show therapeutic promise.

**Pluripotency and Epigenetic Gene Regulation**

James Thomson (Morgridge Institute for Research, USA) received this year’s McEwen Award for Innovation for his seminal contributions to human pluripotent stem cell research. The award was introduced by Shinya Yamanaka, ISSCR President (2012–2013) and presented by Cheryl and Rob McEwen, the founding contributors of this prestigious ISSCR award (Figure 1). Thomson shared his personal perspective on the derivation of the first human embryonic stem cell (ESC) lines in 1998 with a discussion of the scientific, legal, and political challenges the field of human pluripotent stem cell research was facing until the derivation of the first human induced pluripotent stem cells (iPSCs) in 2007 by Yamanaka’s and his laboratories.

Edith Heard (INSERM, Institut Curie, France) discussed recent data from her laboratory interrogating an unexpected link between X chromosome inactivation and early development. Female mouse ESC lines carry two active X chromosomes. By comparing female and male ESC lines, Heard noticed that pluripotency-related genes (e.g., Nanog, Esrrb) are expressed more abundantly in female than in male ESCs. Moreover, female ESCs exhibited a delay in exiting pluripotency compared to male ESCs when stimulated with FGF and ACTIVIN A. Mechanistically, Heard’s lab could show that female ESCs inhibited the differentiation-promoting mitogen-activated protein kinase (MAPK) signaling pathway more efficiently than male ESCs. This, in turn, led to a reduction in the expression of the de novo methyltransferases DNMT3A/B and thus inefficient methylation silencing of pluripotency genes. While the X-linked gene(s) responsible for decreased MAPK signaling and global hypomethylation remain elusive, this study provided a compelling mechanism by which X chromosome inactivation is tightly linked with developmental progression.

Richard Young (Whitehead Institute, USA) summarized work from his laboratory, which identified enhancer elements that are densely occupied by Mediator coactivator and cell type-specific master transcription factors (Whyte et al., 2013). These so-called “super enhancers” are transcriptionally more active and more sensitive to perturbation than regular enhancers. They are typically found around loci that specify cell identity, e.g., Esrrb and Klf4 in ESCs or MyoD in muscle cells. Of note is Young’s laboratory’s finding that cancer cells often utilize super enhancers to corrupt cell identity. An example is the immunoglobulin enhancer that is fused to the MYC gene in multiple myeloma. Given that the transcriptional cofactor BET-bromodomain (BRD)-4 is also enriched at super-enhancers, treatment of myeloma cells with the BRD inhibitor, JQ1, resulted in selective decommissioning of this and other oncogenic enhancers. These findings provide an exciting possible strategy to target oncogenes without perturbing normal cellular function (Lovén et al., 2013).

Timm Schroeder (Swiss Federal Institute of Technology, Switzerland) presented his laboratory’s approach to studying pluripotent and multipotent stem cell decisions by utilizing long-term single cell imaging strategies. Dubbed “TTT” for “Timm’s Tracking Tool,” Schroeder has generated imaging and software capabilities to track individual stem and progenitor cells carrying fluorescent reporter alleles that indicate distinct lineage decisions. He used this system to revisit the old dogma that hematopoietic progenitors...
commit to either the granulocyte/myeloid (GM) or mega-karyocyte/erythroid (MegE) lineages by coexpressing specifying transcription factors of both lineages (e.g., PU.1 for GM lineage and GATA-1 for MegE lineage) until one factor “wins,” shifting the balance toward one lineage in a stochastic manner. In contrast to this model, Schroeder’s laboratory found that very few progenitors ever coexpress both lineage markers but instead directly upregulate either PU.1 during GM differentiation or GATA-1 during MegE differentiation. His laboratory also exemplified the use of single cell imaging with reporters to study monoallelic versus biallelic expression of pluripotency genes. For example, Schroeder could show by tracking ESCs expressing two different colors from each of the endogenous Nanog loci that NANOG is, in fact, primarily expressed from both alleles at a given time (Filipczyk et al., 2013).

Ian Chambers (University of Edinburgh, UK) summarized recent work from his laboratory on the role of OCT4 expression levels on the heterogeneity of ESCs. His laboratory made the surprising observation that Oct4 heterozygous mutant ESCs are more refractory to differentiation cues and exhibit more homogenous NANOG expression compared to wild-type cells (Kawacki-Neisius et al., 2013). This heterogeneity was linked to refractoriness to FGF signaling, which normally stimulates differentiation, as well as hyper-responsiveness to LIF and increased expression of Wnt ligands. Despite a lower level of expression, in Oct4 +/− cells, OCT4 protein showed higher occupancy at the chromatin of targets that reinforce pluripotency, such as Esrrb and Wnt6, providing a possible explanation for the observed phenotype.

Josef Penninger (Institute of Molecular Biotechnology, Austria) demonstrated the usefulness of haploid mouse ESC lines to perform saturated genetic screens at low cost and with high efficiency. By using loxP-flanked viral vectors, his laboratory can screen 50–100 million mutations in one experiment. Cre-mediated removal of the gene trap virus allows testing for specificity of the obtained phenotype. Using several examples, Penninger presented the successful identification of molecules whose disruption conferred resistance to ricin-induced cell death and might thus provide potential “antidotes.” Moreover, he showed that Notch1 expression is essential for blood vessel sprouting from embryoid bodies derived from haploid ESCs, exemplifying the utility of this approach to study mechanisms of cellular differentiation. His institute in Vienna is now gearing up to generate a library of haploid ESC cloned carrying mutations in essentially all genes for academic distribution.

**Coaxing Pluripotent Cells into Mature Cells**

Several plenary talks discussed efforts to drive differentiation of pluripotent cells toward therapeutically relevant, mature cell types. For example, Douglas Melton (Harvard University, USA) gave an update on his laboratory’s approach to coax human ESCs and iPSCs into insulin-producing cells by recapitulating normal stages of development. This strategy allowed his lab to generate populations of insulin-producing cells within only 3 weeks. However, a major challenge is that these in vitro-derived cells are not mature, glucose-sensing β cells. His laboratory is taking three approaches to solve this problem: (1) coculture of differentiating cells with endothelial cells, which are important for β cell maturation in vivo—this strategy...
indeed supported maturation of β cells in vitro; (2) transcriptional comparison of in vitro-derived and in vivo-matured β cells to identify candidate genes that promote maturation; and (3) combinatorial chemical screening for compounds that enhance glucose-dependent insulin secretion. Melton presented a combination of four compounds that significantly enhanced glucose responsiveness of in vitro-derived β cells upon transplantation into SCID mice.

Kenneth Zaret’s (University of Pennsylvania, USA) approach to this question is to study the dynamic changes of epigenetic modifications during the embryonic development of β cells, with the goal to identify responsible enzymes and then small molecules that could promote β cell formation for stem cell differentiation studies. His laboratory identified repressive H3K27 methylation domains in undifferentiated β cell progenitors that map over β cell genes. Accordingly, his group showed that genetic loss of the catalyzing enzyme EZH2 in the developing pancreas or adding chemical inhibitors of EZH2 to early pancreatic explants resulted in an increased number of β cell progenitors in vivo and in vitro, respectively. Zaret also discussed his recent work on the immediate response of somatic cells to reprogramming factor expression (Soufi et al., 2012). This study discovered that OCT4, SOX2, and KLF4 function as “pioneer factors” by facilitating chromatin access to target genes. Moreover, his laboratory identified broad genomic regions, marked by H3K9 methylation, that remain refractory to transcription factor binding during the initial phase of reprogramming but are ultimately bound in the minority of cells that become reprogrammed. These genomic regions include a number of core pluripotency genes such as SOX2 and ESRRB, and their initial lack of activation thus appears to provide a bottleneck for efficient and fast reprogramming.

Ludovic Vallier (Cambridge Stem Cell Institute, UK) compared human iPSCs derived from different individuals and cell types using distinct reprogramming methods to assess the degree of variation introduced by cell of origin, genetic background, and iPSC derivation strategy. Two important conclusions emerged from this analysis. First, interindividual genetic differences had by far the strongest impact on differentiation potential whereas cell type of origin and reprogramming method contributed much less. Second, variability in differentiation potential can be abrogated by deriving endodermal progenitor cell lines prior to derivation of a more terminally differentiated state. The latter point was also made by Oliver Bruestle (University of Bonn Medical Center, Germany), who emphasized the advantage of first deriving neural progenitor cell lines from iPSCs before coaxing them into neuronal or glial cell fates for comparative studies. Vallier also presented ongoing efforts by the UK-based initiative HipSci (http://www.hipsci.org) to derive large numbers (~500) of control and patient-derived iPSC lines with the goal to detect the impact of genetic variation on disease and cellular phenotype.

George Daley’s laboratory (Boston Children’s Hospital, USA) is taking steps to derive hematopoietic stem cells (HSCs) from pluripotent and other cellular sources. He summarized recent work on transcriptional analyses of different stages of HSC development, which identified NOTCH signaling as a limiting component in culture-derived HSC-like cells (McKinney-Freeman et al., 2012). Given that blood cells are exposed to certain shear forces in vivo, Daley’s laboratory utilized microfluidics technology to mimic the effect of blood flow on in vitro-derived cells. This strategy indeed activated Notch signaling and enhanced formation of more definitive hematopoietic cell fates. A major limitation in the HSC field is that HSC-like cells derived from pluripotent cells fail to engraft long term upon transplantation. In an attempt to resolve this shortcoming, Daley’s group has devised a screening approach to identify transcription factors that can revert hematopoietic progenitors into authentic, transplantable HSCs (Doulatch et al., 2013). Overexpression of ERG, HOXA9, and RORA in short-term progenitors was indeed sufficient to produce cells that engrafted for several weeks, reconstituted the myeloid and lymphoid lineages, and gave rise to red blood cells expressing adult β-globin.

Benoit Bruneau (Gladstone Institute of Cardiovascular Disease, USA) summarized work on the epigenetic and transcriptional analyses of pluripotent cells undergoing step-wise differentiation into cardiomyocytes via mesodermal and cardiac progenitor intermediates (Wamstad et al., 2012). This analysis provided a chromatin landscape of enhancers that become sequentially activated and predict binding of other regulatory transcription factors based on motif analysis. In follow-up experiments, Bruneau’s laboratory discovered that the SWI/SNF component BRG1 is responsible for establishing these enhancers. BRG1 was shown to co-occupy H3K27-acetylated mesoderm enhancers, and its genetic deletion at the mesoderm progenitor stage abrogated the formation of cardiomyocytes due to inefficient activation of mesodermal genes and ectopic expression of other lineage markers. Interestingly, BRG1’s role in suppressing alternative cell fates during cardiac mesoderm induction was proposed to involve modulation of Polycomb activity, but not binding, at target genes.

Reprogramming and Transdifferentiation
The reprogramming of somatic cells into iPSCs is notoriously inefficient and the underlying mechanisms are incompletely understood. Jacob Hanna (Weizmann Institute, Israel) presented intriguing data, which suggested
that the commonly used transcription factors OCT4, SOX2, KLF4, and c-MYC normally fail to efficiently reprogram somatic cells because of their aberrant recruitment of the repressor molecule MBD3 to target genes. This mechanism was suggested to prevent the ability of most cells to become iPSCs. Consistent with this model, depletion of Mbd3 from mouse or human fibroblasts increased the efficiency of iPSC induction from a few percent up to nearly 100% (Rais et al., 2013). Hanna’s data further documented that all Mbd3-depleted cells undergo reprogramming into iPSCs within 8 days in an apparently deterministic manner. Similarly, loss of Mbd3 enhanced the normally inefficient “spontaneous” reprogramming of unipotent primordial germ cells into pluripotent embryonic germ cells and that of epiblast stem cells into ESCs from 5%–10% up to 90%–100%.

The 2013 recipient of the ISSCR-University of Pittsburgh Outstanding Young Investigator Award (Figure 2) Marius Wernig (Stanford University, USA) presented a road map of his laboratory’s work reviewing the strategies they exploited to transdifferentiate murine and human fibroblasts into functional neurons. Wernig had previously shown that a combination of three transcriptional factors was sufficient to convert fibroblasts into neurons. In recent experiments, Wernig has discovered that one of the transdifferentiation factors, ASCL1, functions as a pioneer factor that can bind to nucleosomal DNA at its cognate targets in the fibroblast chromatin (Wapinski et al., 2013). Moreover, it recruits BRN2, another reprogramming factor, to many of its target sites. Genome-wide chromatin analysis revealed that ASCL1 target sites are enriched in a novel trivalent histone configuration consisting of H3K4 monomethylation, H3K27 acetylation, and H3K9 trimethylation, which can predict the permissiveness of induced neuron reprogramming among different cell types.

Disease Modeling and Cell Therapy
After great coverage on the basic biology of stem cell regulation and potency, the focus of the meeting transitioned to questions addressing the utilization of stem cells for modeling and treating disease.

Lawrence Goldstein (University of California, San Diego, USA) presented his laboratory’s progress in deciphering the mechanisms of Alzheimer’s disease using iPSCs as a model. A hallmark of Alzheimer’s disease is the formation of plaques containing amyloid-beta protein as their major constituent. Previous work from the laboratory has shown that patient iPSC-derived neurons recapitulate phenotypic aspects of the disease in vitro, such as increased levels of amyloid-beta and hyperphosphorylated TAU protein (Israel et al., 2012). Based on this in vitro system, Goldstein’s laboratory has uncovered one mechanism by which an Alzheimer’s disease risk allele, SORL1, affects an increase in amyloid-beta levels and has developed an assay that allows identification of protective alleles.

Bruestle also summarized his laboratory’s efforts in modeling Alzheimer’s disease and polyglutamine disorders using pluripotent stem cells (PSCs). The team expressed a pseudo-hyperphosphorylated variant of the TAU protein in PSC-derived neurons. They found that this leads to defects in axonal transport of mitochondria resulting in axonal pathology and a slow neurodegeneration when the cells were cultured under non-redox-protected conditions (Mertens et al., 2013). In another line of experiments, the group demonstrated that neurons derived from Alzheimer’s disease iPSCs can be used to assess the efficacy of pharmaceutical compounds modulating amyloid precursor protein processing. As a prelude to exploiting direct neuronal conversion for disease modeling, they used small molecules to boost human fibroblast-to-neuron conversion to yields exceeding 150%.

Kristin Baldwin (Scripps Research Institute, USA) is investigating the genetic integrity of adult postmitotic neurons through reprogramming by somatic cell nuclear transfer (SCNT). Her laboratory derived ESC lines produced from seven active adult postmitotic neurons from the olfactory bulb (mitral and tufted neurons) through SCNT in mouse. Three of the resultant nuclear transfer (NT)-ESC lines gave rise to entirely stem cell-derived mice using tetraploid embryo complementation, whereas three other tested lines did not, documenting that the genome of at least some of these neurons is genetically fully pluripotent. Extensive genome-wide sequencing analyses of three NT-ESC lines derived from the same 4.5-month-old donor animal (one line was capable of producing viable mice and the other...
two were not) revealed that they carried multiple classes of genomic mutation, including rare and complex structural variants that appeared to be specific to the individual neuron (not expressed in any other tissues) and a considerable number of point mutations and “indels.” Each neuron carried a unique set of mutations, and no shared mutations were observed. Together, this suggests that many of these mutations may have occurred in the nondividing postmitotic stage of each neuron. However, these aberrations did not correlate with the cells’ ability to generate mice. The functional consequence of these abnormalities remains to be elucidated.

Shoukhrat Mitalipov’s laboratory (Oregon Health and Science University, USA) is studying nuclear transfer in primates, recently using this technique to replace one animal’s defective mitochondrial DNA in an oocyte with that from a nonaffected animal. In further studies, Mitalipov succeeded in human SCNT and in deriving first, SCNT blasts-cysts and then human NT-ESCs, which remained one of the major barriers in the cloning field (Tachibana et al., 2013). Optimization of oocyte/donor cell synchronization and subsequent activation were key for successful NT-ESC derivation. This allowed him to compare transcriptional, epigenetic, and genomic differences between human pluripotent stem cell lines derived by SCNT, iPSC technology, or in vitro fertilization. A preliminary analysis found differences between the approaches at the level of genetic stability. For example, iPSCs appeared to have a 3-fold increase in the number of copy-number variations compared with NT-ESC lines. Global methylation analysis suggested that NT-ESCs more closely resemble genuine in vitro fertilization-derived ESCs than iPSCs.

Alessandra Biffi (Ospedale San Raffaele, Italy) discussed her recent work on metachromatic leukodystrophy, a demyelinating lysosomal storage disorder caused by mutation in the arylsulfatase A (ARSA) gene, which is normally produced by microglia. HSCs from presymptomatic patients were infected with third generation ARSA-encoding lentivirus. After HSC correction, patients showed evidence of therapeutic benefit for many months beyond the predicted disease onset (Biffi et al., 2013). Moreover, vector integration into HSCs revealed stable engraftment, sustained polyclonal contribution, and normal behavior. These data provide compelling evidence for the successful treatment of human malignancies with genetically engineered stem cells.

Charles Murry (University of Washington, USA) discussed his recent work using human ESCs to improve cardiac recovery after infarction in nonhuman primates. Cardiomyocytes derived from human ESCs were injected into the left ventricle of nonhuman primates that had undergone an experimentally induced infarct (2% of the left ventricle) and led to a significant improvement of cardiac repair based on morphological and functional indicators. These findings provide proof-of-principle that human ESCs can be used to augment repair of terminally differentiated tissue in nonhuman primates.

**Tissue-specific Stem Cells**

Many excellent talks at ISSCR 2013 focused on tissue-specific adult stem cells in the skin, blood, brain, and muscle. Elaine Fuchs (Rockefeller University, USA) presented the Anne McLaren Memorial Lecture and provided an overview of skin biology, discussing epidermal stem cells in vitro, skin grafts, squamous carcinoma, and regulation of hair follicle stem cells. Over the past few years, the Fuchs laboratory has uncovered a network of epigenetic and genetic regulators of stem cell fate. More recently, they have investigated apoptosis as a homeostatic regulator of stem cell number. Fuchs presented a recent collaboration with Hermann Steller’s laboratory using a conditional knockout of ARTS (inhibitor of the antiapoptotic factor XIAP) in hair follicle stem cells (Fuchs et al., 2013). Loss of this apoptosis inhibitor led to increased survival and a 2-fold increase in the number of stem cells. Moreover, wound repair and hair regrowth was accelerated after ARTS deletion. Importantly, when XIAP was deleted in the ARTS mutant background, stem cell number and wound response was restored to normal. This demonstrates the balance between anti- and proapoptotic regulators in achieving stem cell homeostasis.

Next, Fuchs discussed the signaling transduction between extracellular morphogens and the microtubule cytoskeleton, necessary for cell polarity of proliferating stem cells in the hair follicle. It is known that WNT is a potent regulator of polarity and cell fate in stem cells from different niches. Fuchs demonstrated that a downstream target of this apoptosis inhibitor led to increased survival and a 2-fold increase in the number of stem cells. Moreover, wound repair and hair regrowth was accelerated after ARTS deletion. Importantly, when XIAP was deleted in the ARTS mutant background, stem cell number and wound response was restored to normal. This demonstrates the balance between anti- and proapoptotic regulators in achieving stem cell homeostasis.

Paul Frenette (Albert Einstein College of Medicine, USA) and Charles Lin (Massachusetts General Hospital, USA) discussed their efforts to track stem cells and define their niches. Frenette used Nestin-GFP reporter mice to distinguish two distinct vascular niches, demonstrating arteriolar stromal niche cells as RESTINGh and sinusoidal stromal niche cells as RESTINGlow (Kunisaki et al., 2013). During normal homeostasis, quiescent HSCs, in contrast to active HSCs, were more often localized to RESTINGh arterioles. Various perturbations were used to drive HSCs into cycle and led to a redistribution of active HSCs away from the arterioles. Those HSCs that remained quiescent remained in close proximity to the arterioles. Using a computational
In the embryo, a large fraction of the adult NSC pool. This elegant work presents at E12.5. In addition, cycling cells at E15.5 form a progenitor at E13.5–E15.5 and that a common progenitor may be NSCs. His work demonstrates that precursors of adult SVZ using a retrovirus barcode library and other lineage-tracing methods to identify the embryonic origin of adult SVZ versus a nonneurogenic region, the cortex, Doetsch identified a series of marker combinations that can be used to distinguish between quiescent and activated NSCs. Based on the expression of these markers, it was shown that activated NSCs are preferentially located next to blood vessels, interestingly at sites that lack astrocyte end-foot coverage, suggesting that both direct contact-mediated and diffusible signals from the vasculature are important in this niche. In addition, signals from the blood directly access the SVZ. To better understand the differences between the vasculature of the SVZ versus a nonneurogenic region, the cortex, Doetsch has established cocultures of NSCs with pericytes, endothelial cells, or cerebrospinal fluid-enriched media. This work is beginning to unravel the specific growth factors and their cellular sources that differentially target quiescent and activated NSCs.

Luis Fuentealba (University of California, San Francisco, USA; Alvarez-Buylla laboratory) presented his recent work using a retrovirus barcode library and other lineage-tracing methods to identify the embryonic origin of adult SVZ NSCs. His work demonstrates that precursors of adult NSCs are separate from the other embryonic progenitors at E13.5–E15.5 and that a common progenitor may be present at E12.5. In addition, cycling cells at E15.5 form a large fraction of the adult NSC pool. This elegant work demonstrates the ability to track early forming adult cells in the embryo.

Turning to the skeletal muscle, Helen Blau (Stanford University School of Medicine, USA) described a bioengineered niche developed in her laboratory a few years ago and the group’s continued work to identify strategies that augment stem cell function during aging (Lutolf and Blau, 2009). Blau showed that aged muscle stem cells (MuSCs) have a significant, intrinsic defect in self-renewal capacity and regenerative function compared to young MuSCs, when transplanted into irradiated injured muscles. Analysis of signaling cascades illustrated that elevated p38 mitogen-activated protein kinase (MAPK) activity was driving the loss of self-renewal in MuSCs. In combination with the bioengineered niche, an inhibitor of p38 MAPK activity increased stem cell engraftment, self-renewal, and regeneration through serial rounds of transplantation, thus demonstrating a rejuvenation of the population of stem cells. Importantly, the contractile force of the new muscle in transplant recipients of aged MuSCs was also greatly improved when donor cells were treated with the p38 MAPK inhibitor. These data highlight the synergistic interaction of biophysical and biochemical cues in rejuvenating and restoring the function of a MuSC population lost during aging.

Robert Signer (University of Texas Southwestern Medical Center; Sean Morrison’s laboratory) presented a novel approach to study the rate of protein synthesis of HSCs and their progeny in vivo. Previous methods to calculate global protein synthesis rates have relied on population-based averaging in vitro. Using a FACS-based readout, Signer reported that HSCs synthesize nascent proteins at a slower rate than lineage-restricted progenitors, irrespective of whether the HSCs are quiescent or undergoing self-renewing divisions. Moreover, genetic strategies that increase or decrease protein synthesis impaired HSC function. This approach raises the possibility that the longevity of some long-lived cells depends upon a low rate of protein synthesis. This will undoubtedly be informative for the analysis of protein synthesis in other stem cell compartments.

This year’s annual meeting concluded with a keynote lecture delivered by Eric Lander (Broad Institute of MIT and Harvard University, USA). With his fascinating and energetic look at some of the secrets that have been uncovered about the human genome, Lander addressed several issues that have direct implications on research using stem cells, particularly with regard to the causes of a variety of human diseases. Through the systematic mapping of genetic variants, more than 2000 loci have been implicated in more than 250 common diseases including age-related macular degeneration and cancer. The lessons learned and shared by Lander and all of the presenters this year in Boston will continue to shape the fast-paced field of stem cell research, the effects of which will be
on display at the ISSCR’s 12th Annual Meeting in Vancouver in 2014.

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