Foreword

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It is only about 75 years ago that Joachim Hämmerling demonstrated by nuclear transfer between two species of Acetabularia, a unicellular green alga, the importance of the nucleus in conferring genetic information. In brief, Hämmerling showed that the nucleus contains all of the information necessary to control the morphology of the cell. He surgically transferred the nucleus from the base of *Acetabularia crenulata* which has a crenulated cap to the base of *A. mediterranea*, which has a smooth cap, and showed that the transferred nucleus conferred a smooth morphology to the newly formed cap that had previously displayed a wrinkled phenotype. Since Acetabularia is a single cell organism, Hämmerling's experiment did not address the question of whether nuclei of multicellular organisms, particularly those comprised of multiple cell types, had similar capabilities. Approximately 20 years after Hämmerling's insightful experiments, Sir John Gurdon showed that he was able to produce a completely differentiated organism by transplanting a nucleus from an intestinal epithelial cell of a tadpole into the enucleated egg from the South African clawed toad, *Xenopus laevis*. Although this experiment demonstrated the plasticity of nuclei from vertebrate cells, it did not distinguish whether the nucleus that gave rise to a complete organism was the consequence of reprogramming of a fully differentiated gut epithelial cell or whether it arose from an undifferentiated 'stem' cell. Almost a quarter of a century later, the isolation of mouse embryonic stem (ES) cells gave impetus to the concept of nuclear pluripotency beyond the capabilities of germ cells. Gail Martin and Martin Evans independently demonstrated the capacity of ES cells derived from the inner cell mass of embryonic blastocysts to differentiate into multiple differentiated cell lineages. It was not until 1997 that Gurdon's transformational experiment with nuclear transplantation of somatic nuclei into a Xenopus egg that Ian Wilmut achieved the same outcome in a mammal and produced Dolly the sheep by somatic cell nuclear transfer. The demonstration that somatic cell nuclei can be reprogrammed to ES cell status by simply expressing four transcription factors was finally realized in experiments performed Shinya Yamanaka, who shared the Nobel prize with John Gurdon, in 2012. These cells, designated as induced pluripotent stem (iPS) cells, are able to give rise to cell types of all differentiated lineages and together with ES cells represent the future hope for new, effective regenerative and therapeutic approaches to the management and treatment of disease.

This abbreviated journey through the history of nuclear plasticity and differentiation potential forms the foundation of the articles that appear in this special issue. Although the articles cover a wide range of ideas, disease states, regulation of differentiation and utility of ES and iPS technologies in toxicity assays, they all underscore the power of these pluripotent cells as new tools in understanding the underlying causes of disease states from neurodegenerative diseases to cancer. In the first article, Lourdes Serrano and her colleagues review how epigenetics, and global chromatin architecture, including the spatial organization of chromosome territories and subdomains may define pluripotency and the differentiation of mouse and human ES cells. The following contribution from Ales Hampl and his laboratory examines how human ES cells regulate their cell cycle, its importance in maintaining pluripotency and how its properties change with long-term culture. Peter Hornsby and his associates describe the use of IPS cells from the marmoset, a New World monkey, to develop an iterative approach with multiple factors to optimize differentiation into a neurectoderm lineage. The ability to optimize the process of directing differentiation into a desired lineage is one of the keys to the therapeutic utilization of pluripotent stem cells. The next article by Paul Hasty and colleagues describes how some of the unique advantages of mouse ES cells can be exploited to better understand how various genotoxins can cause DNA damage and how that damage is repaired. By this manner, they devised a strategy for rapidly screening chemicals in the environment that are potentially damaging as well as for the adverse genotoxic effects of therapeutics used for disease treatment and prevention.

As ES cells or iPS cells develop, they retain the potential for self renewal but become restricted in their capacity to differentiate into different lineages. These lineage-restricted

'adult stem cells' are the subject of intense investigation for their potential therapeutic application. Neal Weintraub and his colleagues describe the isolation and expansion of multipotent, but lineage restricted, cardiac adult stem cells that participate in postnatal cardiac renewal or repair. These cells have been administered therapeutically as autologous cells in the context of patients with ischemic cardiomyopathy. Results have been encouraging and portend a potential change in our approach to treating end-stage heart failure.

In addition to possible stem cell-mediated treatment of heart disease, there is new hope for similar strategies for neurodegenerative diseases. Ataxia telangiectasia (A-T) is an autosomal recessive neurodegenerative syndrome that is hereditary and that also predisposes to cancer. To address the role of A-T in the maintenance of neural integrity and why its absence produces such serious neurological consequences, Claudio Delia and his associates have generated human iPS cells from fibroblasts of A-T patients and have induced them to differentiate into neural precursor cells that can give rise to neurons with GABAergic and electrophysiological function to better understand the underlying causes of the disease with the hope of developing new therapeutic approaches. In a related article, Kevin Ess more broadly reviews the current status of generating iPS cells from patients with neurological and neurodegenerative diseases and the hopes and challenges that the field faces before regenerative therapies with patient-derived IPS cells will become a reality.

Cancer is yet another disease for which some form of stem cell therapy may become applicable. Eric So and Bon Ham Yip review molecular features of aberrant reprogramming of normal hematopoietic progenitor/stem cells into leukemic stem cells, focusing on the mixed lineage leukemia gene (*MLL*). Aberrations such as MLL fusions, MLL amplification or intragenic deletions have a deterministic effect on the oncogenic outcome on malignant hematopoiesis. It is now accepted that within the body there are niches in which adult stem cells reside. Similarly, tumors contain cells with similar characteristics. They harbor 'tumor initiating cells' or 'cancer stem cells' that are self-renewing and have the capability to populate or repopulate a tumor after resection or therapy. Susan Kasper and her colleagues discuss the role of the CD44 transmembrane glycoprotein as an important component of the stem cell niche, including the role of the CD44 variants in cell–matrix interactions and in 'cancer stem cell' maintenance and survival in (pre)metastatic niches.

The goal of this themed issue has been to provide a broad view of the many ways that ES cells, iPS cells, and adult stem cells may be exploited or manipulated to improve human health and well being. Many of the clinical goals are truly aspirational, but their realization may be within reach. What is very clear, however, is that an enormous amount of work remains to be done to better understand the biology of these extraordinary cell types before their regenerative and therapeutic can be confidently and safely utilized.