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Stem Cell Biology

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Supplement Aims and Scope

This supplement is intended to focus on stem cell biology. Stem cell properties, stem cell biology and therapeutic approaches are included within the supplement's scope.

Biomarker Insights aims to provide researchers working in this complex, quickly developing field with online, open access to highly relevant scholarly articles by leading international researchers. In a field where the literature is ever-expanding, researchers increasingly need access to up-to-date, high quality scholarly articles on areas of specific contemporary interest. This supplement aims to address this by presenting high-quality articles that allow readers to distinguish the signal from the noise. The editor in chief hopes that through this effort, practitioners and researchers will be aided in finding answers to some of the most complex and pressing issues of our time.

Articles should focus on stem cell biology and may include the following topics:

- Stem cell properties
  Types, including hematopoietic stem cells, embryonic stem cells, mesenchymal stem cells and induced pluripotent stem cells, plasticity and immunophenotype.
- Stem cell biology
  Microenvironment niches, including bone marrow and fetal liver, gene regulation including that of transcription factors, non-coding RNAs and epigenetics and cell development.
- Therapeutic approaches
  Sources of stem cells for therapy, autologous and allogeneic stem cell transplantation, uses in cancer and other situations including the skin and nerves, diseases.

The concept of a stem cell was first proposed by the German biologist Ernst Haeckel to describe how multicellular organisms are derived from a unicellular organism[1]. In the almost 150 years that have passed since Haeckel's initial proposal, the works of McCulloch and Till[2], Evans and Kauffman[3], Martin[4], Thompson[5], Takahashi and Yamanaka[6,7], and many others too numerous to list here, have significantly advanced the scientific and clinical applications of stem cells. As such, stem cells have transformed the manner in which scientists study human development and (hopefully) in the near future treat human disease. In this supplement, we present a series of articles that highlight the recent advances in the use of stem cells in disease modeling, drug discover, and regenerative medicine applications. These articles are organized into five subsections, which are previewed here.

Stem cells and the heart: Embracing opportunities and overcoming obstacles (Guest Editor: Dr. Stuart Campbell, Yale University). Cardiac research continues to be profoundly impacted by stem cell technology, especially with the development of methods that can transform cells from skin biopsies or blood samples into functioning cardiomyocytes. Such cells are finding use in regeneration and repair of the myocardium (reviewed by Jacot), basic research into cardiac developmental biology (reviewed by Rupert and Coulombe), and modeling of diseases in specific patients (reviewed by Schwan and Campbell). However, before these applications can reach their full potential, major obstacles must be overcome. Methods are needed that can increase the quantity and purity of cardiomyocytes produced from stem cells in order to make regenerative therapies realistic.

In their article, Batalov and Feinberg survey current techniques for differentiating cardiomyocytes from pluripotent stem cells, and report on technologies that are improving efficiency and throughput. Even as efforts to improve differentiation intensify, many questions remain about how to define success. Schwan and Campbell argue that successful differentiation should be gauged by measuring the physiological function of stem cell-derived cardiomyocytes. Clearer definitions of success coupled with a multitude of technologies that can guide differentiation should accelerate progress toward the routine use of stem cells for cardiac research, diagnosis, and therapy.

Stem cells and kidney disease (Guest Editor: Dr. Albert Lam, Brigham and Women's Hospital in Boston). Chronic kidney disease (CKD) is a major global health problem that affects approximately 1 in 8 adults in the United States. The limited options available to treat patients with CKD and end-stage renal disease (ESRD), namely dialysis and kidney transplantation, highlight the urgent need for novel therapeutic strategies for patients with these conditions. In this special section on stem cell-based approaches for studying and treating kidney diseases, the most recent developments in stem cell and developmental biology and bioengineering are reviewed. In addition, the utility of *in vivo* and *in vitro* biomarkers in the identification, characterization, and derivation of stem cell and progenitor cell populations relevant to kidney development and regeneration are discussed. In the concise review entitled "Stem Cells/Progenitors in the Kidney", Valerius focuses on the multipotent progenitor cell populations in both the developing and adult kidneys that are crucial for the proper formation of nephrons, the individual functioning units of the kidney, as well as the repair of damaged nephrons after injury. This review highlights the methodologies used to identify these progenitor cells and their molecular regulation. Current approaches to reproducing and expanding these progenitors *in vitro* for regenerative applications are discussed in subsequent reviews in this section.

Stem cell-based models of human disease (Guest Editor: Dr. Jean J. Kim, Baylor College of Medicine). A mini-review by Kim summarizes important advances in modeling cancer with induced pluripotent stem cells (iPSCs), with special emphasis on potential biomedical applications of iPSCs and their derivatives. In spite of significant interest in generating iPSCs from cancer cells to study the mechanisms of tumorigenesis and the positive role of oncogenes in enhancing the reprogramming process itself, reprogramming human primary cancer cells has proven to be paradoxically inefficient compared to non-cancerous tissues (coined the 'Reprogramming Paradox'), perhaps due to a combination of biological and technical limitations. Reports of successful reprogramming from various cancer cell lines and primary cancer cells are aptly summarized. Another review in this section by Brennand focuses on applications of iPSCs in the study of human neuropsychiatric disorders, where primary cell sources are limited and animal models often inadequate. With continued efforts in the field, human iPSCs are likely to offer new avenues to modeling human diseases, novel drug development, and cell-based therapies.

Biomaterials in stem-cell based therapies (Guest Editor: Mehdi Nikkhah, Arizona State University). Stem cell-based therapies have attracted significant attention toward regeneration of various organs and tissues. The review article by Lee et al. provides a comprehensive overview on the use of synthetic biomaterials to regulate stem cell behavior for specific applications in regenerative medicine. The article primarily discusses the native microenvironment, termed the niche, and the role of biophysical and biochemical cues, which influence stem cell functions from migration to self-renewal and differentiation. The authors have presented the recent attempts in the synthesis of biomimetic materials, as delivery vehicles in cell-based therapies and neo-tissue formation. Specific properties of the previously developed synthetic matrices including immobilized growth factors, surface chemistry (ie, peptides and proteins) and topography (ie, pillar, grooves and ridges) have been outlined in detail as the key parameters guiding stem cell-substrate interactions. This article finally discusses the future directions toward the design of novel biomaterials to control stem cell microenvironment for potential translation into clinical practice.

Cell-based regenerative strategies for neural injury and disease (Guest Editor: Sarah Stabenfeldt, Arizona State University). In this section, a collection of articles nicely frames the recent advances in and cutting-edge approaches for regeneration of neural injury and/or disease. Specifically, Seidlits et al. presents a thorough review on gene delivery developments over the past decade specifically for spinal cord injury. This elegant review not only highlights improvements in delivery strategies, but also potential gene targets aimed at mitigating immunological issues while promoting neural regeneration. Complementary to the Seidlits review, Stabenfeldt et al. delve into approaches to harness endogenous repair/regeneration response after brain injury. This review highlights injury-related chemokines and their impact on resident neural stem cells and summarizes how these known biological factors may be exploited for stem cell- and drug delivery-based therapies. Finally, Willerth and colleagues present a method to achieve robust dopaminergic neuron differentiation from human induced pluripotent stem cells using xenogenic-free culture conditions. Collectively this series of articles provides unique perspective into the historical and most recent advances in cell-based regenerative strategies for neural injury and/or disease.

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Lead Guest Editor **Dr David Brafman**

Dr David Brafman is an Assistant Professor in the School of Biological and Health Systems Engineering at Arizona State University. Prior to joining ASU, Dr. Brafman was the Kaehr Stem Cell Young Investigator at the Sanford Consortium for Regenerative Medicine at the University of California-San Diego. Dr. Brafman received his B.S. in Bioengineering from the University of California-Berkeley and his Ph.D. and M.B.A. from the University of California-San Diego. Dr. Brafman's laboratory uses an interdisciplinary approach that combines various aspects of developmental biology, genetic engineering, and bioinformatics to investigate the chemical, biological, and physical stimuli that govern human pluripotent stem cell fate. Dr. Brafman's laboratory uses these approaches to elucidate the mechanisms and design targeted therapies related to three disease areas–idiopathic pulmonary fibrosis, heart failure, and Alzheimer's disease. Dr. Brafman's work has been featured in journals such as *Biomaterials*, *Cell Death and Differentiation*, *Stem Cell Reports*, *and Stem Cells and Development*. Dr. Brafman's research has been funded by the Arizona Alzheimer's Consortium, California Institute of Regenerative Medicine, National Science Foundation, and University of California Biotechnology and Research Program.

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Guest Editors

STUART CAMPBELL

Dr. Stuart Campbell is an assistant professor in the Department of Biomedical Engineering at Yale University. His research focuses on cardiac muscle biomechanics, with a special emphasis on inherited cardiomyopathies. These disorders are driven by complex multiscale phenomena that Dr. Campbell's laboratory is working to understand using a combination of computational and experimental approaches. His work has appeared in *Biophysical Journal*, the *Journal of Clinical Investigation, Proceedings of the National Academy of Sciences*, and other journals.

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ALBERT Q. LAM

Dr. Albert Q. Lam is an Associate Physician in the Division of Renal Medicine at Brigham and Women's Hospital in Boston, Massachusetts, and an Instructor in Medicine at Harvard Medical School. After earning his M.D. from the Northwestern University Feinberg School of Medicine, he completed his residency training in internal medicine at Northwestern Memorial Hospital in Chicago, Illinois, followed by a nephrology fellowship at the joint program between Brigham and Women's Hospital and Massachusetts General Hospital. Dr. Lam's research interests as a basic scientist focus on the application of human pluripotent stem cells in modeling and treating human kidney disease ("disease in a dish"), with the ultimate aim of developing strategies to differentiate human embryonic stem cells and human induced pluripotent stem cells into cells of the kidney lineage for kidney regeneration. He is an Affiliated Faculty member of the Harvard Stem Cell Institute. Dr. Lam was awarded a BD Biosciences Stem Cell Research Grant Award in 2013. He has published in such journals as the *Journal of the American Society of Nephrology, American Journal of Kidney Disease, and Molecular and Cellular Biology*. Dr. Lam's clinical interests are in onco-nephrology, a growing subspecialty within the field of nephrology focusing on the diagnosis and management of kidney complications in patients with cancer. He is particularly interested in the development of kidney disease in patients who have undergone hematopoietic stem cell transplantation. He is a member of the American Society of Nephrology Onco-Nephrology Forum.

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Dr. Jean J. Kim is currently an Assistant Professor in the Department of Molecular and Cellular Biology at Baylor College of Medicine (BCM). She has over 19 years of experience in basic biomedical research, and in the last 8 years has been focusing on human pluripotent stem cell research. She received a Ph.D. in Neuroscience from Yale University and trained as a postdoctoral fellow in Dr. Anirvan Ghosh's laboratory at the University of California San Diego (UCSD). She received a Postdoctoral Fellowship from the California Institute for Regenerative Medicine (CIRM) to study the differentiation of human pluripotent stem cells into neural lineages. In 2009, she won a Stem Cell Research Center Research Award sponsored by Yonsei University at the Association of Korean Neuroscientists Annual Symposium (Chicago, IL). She worked in Dr. Alysson Muotri's group as an Assistant Project Scientist at UCSD and developed iPSC-based models of neurodevelopmental disorders. In 2014, she was recruited to BCM's Stem Cells and Regenerative Medicine Center (headed by Dr. Margaret "Peggy" Goodell), and she also serves as Director for the Human Stem Cell Core facility, which provides hands-on training and research support for not only BCM but also the various institutions at the Texas Medical Center and beyond. Her core facility is a member of Stem Cell COREdinates, a national consortium of more than 20 human pluripotent stem cell-focused core facilities. Her research has been featured in journals such as *Neuron*, *PNAS*, and *Journal of Neuroscience*.

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Dr. Mehdi Nikkhah is an Assistant Professor of biomedical engineering at the School of Biological and Health Systems Engineering, Arizona State University. His laboratory is currently focused on the integration of innovative biomaterial and microscale technologies to create biomimetic model tissue constructs for regenerative medicine and disease modeling applications. Dr. Nikkhah has published more than 30 journal articles, 5 book chapters and 50 peer-reviewed conference papers and holds 5 patent/invention disclosure applications. His work has been published in reputable journals such as *Advanced Materials*, *Scientific Reports*, *Biomaterials*, *Lab on a Chip*, *and Advanced Functional Materials*, which has been cited more than 950 times with H-index of 17. He has also presented several invited talks in national and international conferences. Dr. Nikkhah has received numerous prestigious awards and recognitions during his career including: 2014 Fellow Award from Cellular and Molecular Bio-engineering Division of Biomedical Engineering Society (BMES), 2013 National Institute of Health (NIH) Ruth L. Kirschstein National Research Service Awards for Individual Postdoctoral Fellows, 2011 "Outstanding Ph.D. Dissertation in Engineering, Science and Mathematics" at Virginia Tech. He is a member of American Society of Mechanical Engineering (ASME) and Biomedical Engineering Society (BMES). Dr. Nikkhah completed his postdoctoral fellowship training at Harvard Medical School and Brigham and Women's Hospital where he was also affiliated with Harvard-MIT Division of Health Sciences and Technology (HST). He received his B.S. in mechanical engineering and the M.S. degree in biomedical engineering from Tehran Polytechnic University. He received second M.S. degree in mechanical engineering from Villanova University and Ph.D. degree in mechanical engineering from Virginia Tech. Dr. Nikkhah's research has been funded by National Science Foundation.

SARAH STABENFELDT

Dr. Sarah Stabenfeldt received her B.S. in Biomedical Engineering from Saint Louis University and her Ph.D. in Bioengineering from Georgia Institute of Technology. She was awarded an NIH NRSA pre-doctoral fellowship for her doctoral thesis research on developing neural tissue engineering therapies for traumatic brain injury. As a NIH post-doctoral fellow at Emory University School of Medicine and Georgia Tech, she investigated fibrin-derived peptide-protein binding interactions, designing fibrin-based wound healing therapeutics. She joined Arizona State University's School of Biological and Health Systems Engineering as an Assistant Professor in 2011 and leads her research team in developing regenerative medicine strategies for acute neural injury. Since joining ASU, Sarah has been awarded the Arizona Biomedical Research Consortium Early Stage Investigator Award, the NIH Director's New Innovator Award, and NSF CAREER Award. Publications include *Blood*, *Nature Materials*, *Biomaterials*, *Tissue Engineering*, *and Journal of Biomedical Materials*.

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