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Stem Cell Themes: Promises and Challenges

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We, as guest editors of the *Journal of Biomolecular Screening* (JBS), are pleased to bring you this special issue focused on the use of stem cells for drug discovery. This is an exciting, fast-moving, and cutting-edge field encompassing elements of promise together with challenge. Recently, traditional high-throughput screening (HTS) technology has been adapted to enable and complement drug discovery applications of stem cell research. Herein, we have selected a number of key papers that represent advancements in the production and use of stem cells for drug discovery and furthering our understanding of disease.

Generally, embryonic stem cells (ESCs) are pluripotent and therefore can offer an unlimited source of homogeneous-specific cells that can be differentiated into any cell type in the body. ESCs play a critical role during development and are tightly associated with repair mechanisms required to maintain homeostasis. Adult stem cells are also considered undifferentiated cells. They can be located in tissues that renew themselves with limited drug discovery applications due to their more restricted ability to differentiate into multiple cell types. The primary roles of adult stem cells are to maintain and repair the tissues in which they are found. Stem cells are powerful reagents because they can serve as a source of "physiologically relevant" cells for understanding the etiology of certain diseases. They have the possibility to serve as new tools to probe complex pathways in disease and healthy states. By understanding the genetic and molecular controls of the differentiation and disease process, stem cells will help uncover how diseases arise. This is the promise for biology that the stem cell field can offer to identify novel targets for the drug screening field.

For drug discovery, stem cell use also shows great potential. Stem cells can be used as cell therapies providing new sources of cells for forming healthy tissue. In 2006, Shinya Yamanaka, MD, PhD, of the Gladstone Institutes in San Francisco, California, created iPS (induced pluripotent stem) cells by viral transduction with four transcription factors to somatic cells to generate embryonic stem (ES)–like cells.[1–4] These findings opened new doors in drug discovery stem cell research, specifically using HTS technology to replace transcription factors to avoid genome alteration due to viral transduction. Either ES cells or iPS cells can serve as a source of cells for drug discovery. The iPS cells have the advantage of being established from a variety of patients, multiple patients with the same disease, and across multiple diseases.

Although much promise is evident in the stem cell field, there are of course, many challenges. Establishing the best methods and conditions for working with ES or iPS cells that provide consistent and reproducible results is essential to the successful use of stem cells for drug discovery. It is important to determine the conditions that most closely mimic the in vivo state. Many of the challenges involve unknown variables and highlight why a special issue of JBS devoted to stem cell applications is warranted at this time.

The use of stem cells for health care is not a novel concept, as bone marrow transplants have been around for more than 40 years. What is new is the application of stem cells in many different areas, ranging from preclinical toxicology screens to small-molecule drug discovery screenings and potential cell therapy applications. They have provided access to sources of patient samples containing the complexity of genetic backgrounds and providing new models of disease.

An excellent reflection of the heightened interest in the utility of stem cells for health care is the fact that over 1700 clinical trials are listed when *stem cells* is used as a keyword in www.clinicaltrials.gov (a database that provides clinical trials information to the general public about ongoing clinical research studies). The results from these ongoing clinical trials will have a huge impact in the field of stem cells. The boundaries for identifying new uses for stem cells are likely to continue to reach into many new areas.

This special issue of JBS includes papers on a wide variety of aspects of stem cell research (authors listed below). These include methods on how to grow stem cells, a seemingly simple concept. However, stem cells require many key factors to grow in a consistent state. Propagation can either be as spheres or as adherent cells (Mavromatis et al.,[5] Foong et al.,[6] and Vega et al.[7]). This type of characterization is important for the use of stem cells in HTS. The use of circulating stem cells to determine risk factors for cardiovascular disease is explored in Mavromatis et al.[8] Application of tools such as automated patch clamp for measuring electrical channel activity is vital to characterizing neuronal function, disease state, and cytotoxicity and is described in the Application Note (Haythornthwaite et al.[9]). This paper offers data to support the use of iPS differentiated neurons as an alternative to primary neurons isolated directly from animals. Methods for stem cell differentiation are described in another group of papers (Kowalski et al.,[10] Pai et al.,[11] and Shinozawa et al.[12]). Adapting differentiation conditions to be amenable to automation has been a challenge. The area of differentiation has an impact for stem cells as a screening platform as well as to use stem cells as models of disease. Using differentiated stem cells to create more physiological models through bioengineering is reviewed (Adams et al.[13]). Once reliable and robust assays are established, HTS can be carried out as described in another group of papers (Carmody et al.,[14] Swaroop et al.,[15] Dykhuizen et al.,[16] Yoo et al.,[17] Zhao et al.,[18] and Mathews et al.[19]). The results from HTS will be followed with much interest to see if these new disease models are indeed more predictive of human disease and the resulting molecules from these screens can also serve as probes to uncover complex biology.

The papers featured in this special issue represent early work in a rapidly expanding field with the use of stem cells for drug discovery. It is anticipated that they will ultimately contribute to our understanding of the usefulness of stem cells not only for therapeutics but also to identify chemical tools to understand the biology in healthy and disease states.

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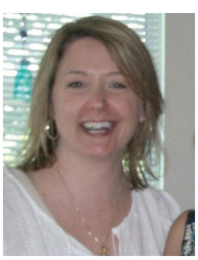

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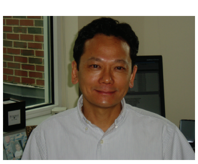

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