# Stem Cell Research—The Promise and Current Progress

BY DAVID FENSTERMACHER, *MEMBER IEEE*

Stem cell research began more than twenty-five years ago with the isolation of pluripotent mouse stem cells from teratocarcinomas. Since the first isolation of mouse stem cells, many scientific and technological advances have arisen which are the genesis of new forms of biomedical research. One advance, the isolation of human embryonic stem cells from the inner cell mass of blastocyst stage embryos by Thomson and colleagues in 1998, has polarized communities to proclaim the huge potentials and monstrous consequences of these technologies. Both inside and outside the scientific community, stem cell research is mired in controversy through the input of numerous advocates and critics such that the true potential of the technology is lost in moral, ethical and social discussions. Putting non-scientific issues aside, stem cell technology is pushing the envelope of scientific discovery with a future that may be a foundation for biomolecular medicine.

## I. WHAT ARE THEY?

Stem cells are undifferentiated cells that are the precursors for other cell types. Stem cells can be isolated from embryos or from adult-derived stem cells that are isolated from specific organs such as bone marrow, liver or skeletal muscle. Embryonic stem cells (ESC) are pluripotent, meaning they can differentiate into all three embryonic germ layers, the mesoderm, the ectoderm and the endoderm. These germ layers differentiate to form all the tissues in the developing fetus during embryonic development. Adult-derived, or somatic stem cells exist in many forms: the pluripotent epiblast-like stem cells (ELSC); germ layer lineage stem cells that are committed to form only one of the embryonic germ layers; and progenitor cells that are more differentiated and characterized as multipotent to unipotent. Somatic stem cells are present in tissues to replenish those tissues throughout life. Today, stem cells are being isolated from embryos and numerous tissues to determine the potential medical breakthroughs that each type may harness.

## II. OF MOUSE AND MAN

The isolation and genetic manipulation of mouse stem cells has created technologies known as transgenics that allow researchers to mimic human disease in mice through the use of homologous recombination in embryonic stem cells. But anatomical and immunological differences between humans and mice have, at least for some disease models, proven less than ideal. As an example, transgenic mice created to mimic cystic fibrosis disease demonstrated the intestinal and gallbladder pathologies similar to the human while only minor lung disease was revealed, which is the main cause of human death. To overcome the limitations of mouse models, stem cell technologies may provide an answer. The fact that stem cells have

Digital Object Identifier: 10.1109/JPROC.2007.888375

the ability to differentiate in vitro into adult somatic cell types and that live differentiated cells can be separated with technologies such as flow cytometry, genetic manipulation of human stem cells has the potential to usher in a new age mimicking human disease in the laboratory without the need to maintain large colonies of research animals.

## III. APPLICATION: MIMIC DISEASE OF PATIENT

The practical applications for biomedical research to mimic human disease in human cells are profound. Creating disease models in human cells would allow for the screening of large number of drugs to be analyzed quickly for the specific disease to determine cytotoxicity and efficacy. This technology has already been utilized to develop a drug-screening assay for Alzheimer's disease. But, a single genetic disease can be caused by a number of individual mutations in a specific gene and, depending on the mutations inherited by a specific patient, the disease characteristics and responses to therapy may vary greatly. Also, a single genetic disease can affect many tissues and the phenotype may differ in each tissue type. The combination of nuclear transfer technologies, the use of adult somatic cell nuclei to be placed into an enucleated embryonic stem cell, and stem cell differentiation would allow cell lines to be developed that mimic the disease of a specific patient in the tissue type of choice. This would be a breakthrough that would parallel many of the efforts to develop personalized medicine methodologies with the use of genomics and proteomics technologies through the creation of a platform to quickly study the biological consequences of new treatments prior to administering to the patient.

## IV. CELLULAR THERAPY POTENTIAL

Another potential of stem cells, and the most hyped, is cellular therapy. Numerous reports have been published demonstrating the potential utility of stem cells: the creation of new insulin producing cells in the pancreas for diabetes mellitus; the regeneration of cardiac muscle following myocardial infarctions; the production of motor neurons for treating spinal cord injuries and, the generation of new dopaminergic neurons to treat Parkinson's disease. To date, most of these breakthroughs have been demonstrated only in rodent models although some phase one and phase two clinical trials are ongoing to help determine the usefulness of cellular therapy. The potential for cellular therapy is staggering with other reports suggesting potential therapies for strokes, lupus, neurological diseases, kidney disease, vision diseases and many others. Still other reports suggest the utility of stem cells in the manufacturing of organ, tendon and ligament replacements.

## V. TECHNICAL & SOCIAL LIMITATIONS

Although the potential of stem cell technology is truly incredible, as with new biomedical breakthroughs, there are technical and social limitations that must be overcome before stem cells will be routinely used for patient care. The maintenance of ESCs in culture have required feeder layers, usually isolated from mice, to prevent the cells from differentiating from a pluripotent to a multipotent state. Techniques have been developed to separate the feeder cells from the human cells but the possibility of contamination remains a serious issue. Mouse cell contamination has significantly reduced the viable number of publicly available ESC lines usable for biomedical research. Recent reports have described culturing techniques for ESC lines that do not require feeder layers or that use human feeder layers to overcome this barrier. Although somatic stem cells, such as the ELSCs, do not spontaneously differentiate in conditions that ESCs would differentiate, somatic cells can only be maintained in culture for a limited number of cellular divisions thereby limiting the number of therapeutic cells that can be generated. ESCs do not have this limitation and can be grown indefinitely.

Other issues that may limit the use of stem cells are genetic instability, uncontrolled proliferation of stem cells (e.g. the formation of cancerous tumors), rejection of stem cells due to immune responses, the lack of human genetic manipulation methodologies and cell lines that meet good manufacturing protocols (GMP) required by the FDA and other regulatory bodies for therapeutic agents. And, as research labs develop new cell lines, there will be a need to characterize and compare cells lines to understand the biological subtleties that may result in severe consequences for the patient.

## VI. REALIZING THE PROMISE

Researchers around the world are currently addressing these technological challenges but they still remain a huge barrier to realizing the promise of stem cell technology. One advance, the creation of the United Kingdom Stem Cell Bank, requires rigorous regulations for the procurement and use of stem cell lines representing the beginning of the quality controls required for use of stem cells in human therapy. In addition, the social and legal limitations of the development of stem cell technologies are negatively impacting the quality of the research being performed and the number of researchers that are able to devote time and effort to develop these technologies.

Luckily, the potential of stem cell technologies are so great that the necessary research will continue despite unscientific challenges and the promise of stem cell-based disease modeling, drug discovery and cellular therapeutics should be realized in the not to distant future. ■