## Genome Editing

Improvements of genome editing tools are revolutionizing the ability of researchers to make precision changes in the genomes of stem cells from humans, facilitating the fast and cost-effective production of genetically engineered animals (e.g., mouse and rat) and human cells. The clustered regularly interspaced short palindromic repeats (CRISPR) pathway was first discovered in bacteria, in which it provides an immunologic memory of previous viral infection.

Along with CRISPR-associated protein 9 (Cas9) and guide RNA (gRNA), this relatively simple prokaryotic system has been shown to function as an efficient site-specific nuclease with low off-targeting effects at recognition sequences in mammalian cells. From dermal fibroblasts of an affected organism or patient, for example, we can generate induced pluripotent stem cells (iPSCs) used for the differentiation of iPSC-derived cardiomyocytes or skeletal muscle, or both. Correction of the mutation involves a co-targeting strategy in which a selection cassette capable of the zinc finger–stimulated homologous recombination is targeted to the affected locus at the same time as the mutation is corrected. The CRISPR system is increasingly being used to target a variety of mammalian loci of stem cells and functionality of this targeting vector containing an excisable piggyback construct, allowing the stem cells to be gene corrected "without a trace."

## Pharmacogenetics

The future of pharmacogenetics is to know all the factors that influence adverse drug effects. In this way, the premature abandonment of special drug classes can be avoided in favor of rational drug design and therapy.

Many hurdles must be overcome for pharmacogenetics to become more widespread and to be integrated into medical practice. Current approaches of trial and error in medical practice are well engrained, but the allure of blockbuster drugs produced by the pharmaceutical industry warrants a new model for approaching individualized doses. Training for physicians in molecular biology and genetics should complement clinical pharmacogenomic studies that determine efficacy in an era of evidence-based medicine. Pharmacogenetic polymorphisms, unlike other clinical variables such as renal function, need only a single test, ideally performed for newborns.

Polygenic models of therapeutic optimization still face hurdles that reduce the chances for abuse of genetic information and additional costs. However, SNP haplotyping has the potential to identify genetically similar subgroups of the population and to randomize therapies based on more robust genetic markers. On a population level, genomic variability is much greater within than among distinct racial and ethnic groups.

Therapeutic efficacy and host toxicity are influenced by the patient's specific disease, age, renal function, nutritional status, and other comorbid factors. New challenges will be posed for the selection of drug therapy for patients with cancer, hypertension, and diabetes. Treatment of multisystem disorders (e.g., metabolic syndrome) may be derived from novel therapeutics based on individual, interacting, and complementary molecular pathways.

## Regenerative Medicine

Regenerative medicine entails the uses of novel applications and approaches to repair damaged cells or tissues with the anticipated full restoration of normal function. By harnessing the compendium of biologics, drugs, medical devices, and cell-based therapies, this emerging field represents the convergence of multiple disciplines that integrate tissue engineering, stem cell biology, biomaterials, and gene therapy. Over 50 years, the transplantation of solid organs such as corneas, hearts, lungs, kidneys, and living-donor livers has become a well-established medical-surgical intervention, but the limited availability of organs restricts widespread applications. Tissue-engineered grafts for skin replacement of wounds after burns and diabetic foot ulcers are the antecedent strategies for the use of a patient's own cells, grown outside the body, to ultimately replace a bladder or vascular grafts used for bypass surgery.

A new era of regenerative biology has emerged with the discoveries by James Thompson that human embryonic stem cells can be cultured in a Petri dish and by Shinya Yamanaka that adult mammalian cells can be reprogrammed to become iPSCs. The iPSCs share the common features of somatic cell reprogramming but with the aid of one to four transcription factors. Embryonic stem (ES) cells share common features of clonagenicity, self-renewal, and multipotentiality, a prerequisite for differentiation into diverse cell lineages of multicellular adult organism. Technical and ethical concerns propelled the search for new sources, including the isolation of ES cells from a single blastomere, which circumvents destruction of the embryo, and the use of postimplantation embryos as ES cell donors. Somatic cell nuclear transplantation (SCNT) or nuclear transfer is a technique for successful cloning and reprogramming of adult animal cell nuclei from healthy oocyte host cells. SCNT provides a source of stem cells tailored to the donor organism and promises to accelerate the pace for human use. Because stem and precursor cells can be obtained from a variety of sources (e.g., embryos, adult tissues), their manipulation and transplantation in animal models and pilot human studies are increasingly providing alternative and complementary strategies to solid organ transplantation, thereby expanding the platform for regenerative medicine.

Previous dogmas that postmitotic, terminally differentiated organs are devoid of regenerative capacity have been overturned by evidence for cellular plasticity and low-level regeneration of adult solid organs throughout adult life. Age, gender, disease status, and other risk factors influence cellular regenerative plasticity, proliferation, and cellular functions.

Can progenitor cells derived from bone marrow or circulating blood be administered safely and efficaciously? Clinical and translational scientists are actively pursuing clinical trials to address whether stem cell therapy has efficacy for the victims of stroke, heart attack, and spinal cord injury. Given the large investments from federal, state, and private agencies, there have been concerns raised about the claims of stem cell therapy to engender false hopes. Notwithstanding, stem cell transplantation of bone marrow has become the standard of care for several blood dyscrasias, and new combinatorial strategies are in clinical trials. Beyond the questions of feasibility related to benefits from