Mastering the genetic reprogramming of cells

The recent completion of the Human Genome Project has proven to be an extraordinary basic science achievement with respect to human health and disease. If the work by Watson and Crick introduced the alphabet of our genome, the ability to sequence our DNA provided scientists and physicians with the necessary tools to study its syntax and grammar. However, once the dust settled, our optimism surrounding genetic sequencing was supplanted by the realization that even with these tools we remain illiterate in the language of our genome, incapable of understanding even its most rudimentary messages.

I believe that the human genome remains our most significant frontier yet to explore in the basic sciences because it holds the fundamental axioms from which all physiology and pathophysiology of human health is derived. Thus, in an effort to attack human health and disease at its core, I believe the most important fundamental mystery in biology that would yield the greatest dividends for human health is mastering the genetic reprogramming of cells. Reprogramming the gene expression profile of cells would not only allow us to control the fate of undifferentiated cells, but also to navigate cellular lineage conversion from one mature cell type to another. By commanding these properties of the human genome, basic science research would help catalyze our ability to overcome what I consider the most significant challenges to human health moving forward.

The first challenge will be the need to manage chronic illnesses. Science, medicine, and technology have revolutionized our treatment of acute and congenital diseases, but in the process, have transformed these conditions into chronic illnesses. For example, fifty years ago only 25% of infants with congenital heart disease would survive beyond the first year of life (Warnes 2005). These grim statistics provided the impetus needed to restructure the field, separating pediatric and adult cardiovascular practitioners. Together, pediatric cardiac surgeons and pediatric cardiologists worked to improve diagnostics, surgical interventions, and post-operative management of this patient population such that it is now estimated that 95% of patients with congenital heart disease will live into adulthood (Warnes 2005). In the wake of this resounding success within the field of pediatric cardiovascular medicine, a new population of

roughly 800,000 adults with congenital heart disease was born (Warnes 2005). This has shifted the burden of congenital heart disease onto the field of adult cardiovascular medicine, which is now charged with the task of managing these patients for the remainder of their lives. This narrative is not unique to congenital heart disease. Efforts to obviate many acute and congenital illnesses have transformed these conditions into chronic illnesses that not only require a lifelong commitment from the patient and the physician, but also reflect an extraordinary burden on the resources available in the field.

The second significant challenge will be to manage diseases associated with pathologic aging. Because of the widespread dissemination of vaccines, antibiotics, and other advancements made to combat infectious diseases, many populations around the world are living longer. As these aging populations outlive their reproductive peak, they are acquiring a myriad of diseases associated with the pathologic aging process such as Alzheimer's disease, macular degeneration, and many forms of somatic cancers. These diseases are physiologically diverse, with nearly every system of the body susceptible to illness, and are expanding at exorbitant rates. For example, in 2006 it was estimated that 26.6 million people were living with Alzheimer's disease worldwide (Rocca 2011). This prevalence is projected to quadruple by 2050, so that 1 in 85 persons will be living with the disease (Rocca 2011). In addition to their physiologic diversity and rapidly expanding global prevalence, these diseases are particularly challenging to treat medically because they are nascent in the history of human health, and thus their clinical course remain unchartered territory in medicine.

Basic science initiatives in the integrative field of regenerative medicine have already begun to address these challenges. Specifically, regenerative strategies are poised to revolutionize the care of patients suffering from chronic and age-related illnesses by the promise of enabling a permissive cellular environment for endogenous repair or growth, replacing dysmorphic tissue with a living and growing replacement, or regenerating diseased tissues and organs to restore function. While on the surface these techniques appear varied in their approach, at their core, each of these strategies is united by the common need to manipulate the cellular genome — a prerequisite in the process of manufacturing personalized cells with such desired regenerative potential. Although strides to address these challenges have been made in the field of stem cell

biology, we remain limited by the accessibility and viability of these cells. In order for personalized regenerative therapies to succeed on a global scale, we need to discover a repeatable, efficient, and reliable method to transform, culture, and mobilize easily retrievable cell populations into these regenerative target cells. I believe the pillar for the success of regenerative medicine therapies lies in the ability to command the genetic reprogramming potential of every cell. This basic science achievement would give us the ability to seamlessly transition within and between cell lineages in order to develop personalized models of disease pathogenesis, streamline drug discovery, and therapeutically alter or reverse the fundamental mechanisms underlying human disease.

Basic science research serves as the cornerstone of our understanding of human health and disease. It provides the intellectual capital necessary to expand current knowledge, serves as the catalyst for translational therapies, and is the fulcrum upon which paradigm shifts are made. I believe that future advancements in genetic reprogramming will be the most significant basic science contributions to regenerative medicine, a field that will be at the forefront of human health moving forward, transforming current palliative standards of care into effective and curative treatments.