Gene Therapy Research Update – In Celebration of DNA Day

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DNA Day was established on April 25, 2003 to commemorate publication of the structure of DNA in *Nature* by James Watson, Francis Crick, Maurice Wilkins, Rosalind Franklin and colleagues on that same day in 1953. It was also intended to celebrate completion of the Human Genome Project, which was in its final stages at the time.

DNA is an intricate molecule coding for all the functions that make us who we are. Even the slightest change in its base pair sequence can result in a genetic disease. Human gene transfer, or “gene therapy” as it has become more popularly known, is a powerful tool which has the potential to reverse the effects of deleterious changes to a patient’s DNA.

Gene therapy describes the therapeutic delivery of DNA, RNA, or synthetic nucleic acids into a patient's cells to treat disease. Once in place, these molecules can be expressed as proteins, interfere with the expression of proteins, or possibly even correct genetic mutations. The most common form of gene therapy involves using DNA that encodes a functional, therapeutic gene to replace a mutated gene. In gene therapy, the nucleic acid molecule is packaged within a "vector," which is used to transport the molecule inside cells within the body. Potential vectors include common viruses such as adenoviruses and retroviruses.

Gene therapy was first conceptualized in a 1972 article in *Science* magazine, entitled “Gene Therapy for Human Genetic Disease” by Theodore Friedmann and Richard Roblin. Acknowledging the lack of full understanding of the long-term effects of gene therapy, the authors urged caution before commencing gene therapy studies in humans, and proposed that “a sustained effort be made to formulate a complete set of ethico-scientific criteria to guide the development and clinical application of gene therapy techniques.”

The first FDA-approved gene therapy experiment in the United States occurred in 1990, when four-year-old Ashanti DeSilva was treated for a genetic defect that left her with ADA-SCID, a severe immune system deficiency. The effects of the therapy were temporary, but successful. Since then, close to 2,000 clinical trials have been conducted using a number of techniques for gene therapy.

Although early clinical failures, including the death of Jesse Gelsinger in 1999, led many to dismiss gene therapy as an over-hyped strategy, clinical successes since 2006 have bolstered new optimism in this approach. Recent achievements include the successful treatment of patients with the retinal disease Leber's congenital amaurosis, X-linked SCID, ADA-SCID,
adrenoleukodystrophy, chronic lymphocytic leukemia, acute lymphocytic leukemia, multiple myeloma, hemophilia, and Parkinson's disease. These clinical successes led to the publication of several articles in scientific and popular publications calling for continued investment in the field. Between April of 2013 and April 2014, U.S. companies responded, investing more than $600 million in gene therapy.

The first commercial gene therapy, Gendicine, was approved in China in 2003 for the treatment of a specific cancer: head and neck squamous cell carcinoma. In 2012, Glybera, a treatment for lipoprotein lipase deficiency – a rare inherited disorder which causes severe inflammation of the pancreas – became the first gene therapy treatment approved by the European Commission for clinical use in Europe and the United Kingdom. To date, no gene therapy has been approved in the U.S., although at the time of this writing, there are 144 clinical trials for gene therapies in various stages of clinical development for the treatment of cancer, and ocular and cardiovascular disorders. As an example already in 2015, LentiGlobin BB305, a gene therapy undergoing clinical trials for the treatment of beta thalassemia gained FDA "breakthrough" status after several patients were able to forgo the frequent blood transfusions usually required to treat the disease. Animal tests for antibodies to ebola, malaria, influenza and hepatitis are also underway.

To ensure that gene therapy research in human subjects is conducted safely and ethically, if NIH funding is involved, each study protocol must be approved by an Institutional Biosafety Committee (IBC) and an Institutional Review Board (IRB). Gene therapy research differs significantly from other clinical research because a risk assessment of the protocol needs to weigh potential biosafety issues pertaining to the creation of novel biological material in addition to evaluating the safeguards for trial participants. IBCs must also consider issues such as potential side effects, viral shedding, and the changing regulatory environment as part of their research review. WIRB-Copernicus Group has evaluated more than 150 human gene transfer protocols to date – more than any U.S. organization outside of the Food and Drug Administration and the National Institutes of Health. Gene therapy represents an especially exciting area of research because it holds the potential to deliver a treatment that is as unique as the patient receiving it. This approach can deliver an intact gene sequence to replace a mutated copy, thus negating the impact of a rare genetic disease, or transport a tailored response to arrest the development of a specific tumor. Please join us as we celebrate DNA Day, lauding the creativity of that remarkable molecule and the potential of this powerful new therapy.