The advent of Gene Therapy could disrupt the healthcare industry as we know it, redefining the traditional avenues that pharmaceuticals and biotechnology make profits. To help understand this potential seismic shift to the current healthcare landscape, Mellon’s Amanda Birdsey-Benson explores the science behind what’s changing, why it’s important, and how we are identifying companies poised for the future.

Over the past five years, biopharma’s approach to disease treatment has changed dramatically. Historically, biopharma has focused on the development of oral small molecules to alter the activity of malfunctioning proteins, or engineering recombinant replacement proteins to supplement ineffective or inactive proteins. Typically, these types of therapies are taken chronically for the lifetime of the patient and can offer some disease modification; they are not curative. Nonetheless, they have resulted in a very lucrative business model, where patients become repeat customers. Now, in the post Human Genome era, scientific advances have enabled us to develop techniques to target the root cause of disease—the genes that encode for these malfunctioning proteins. Collectively, we refer to these therapies as Gene Therapy (GTx). This technology is far more precise and powerful and, in some cases, it can offer close to curative treatments in a single dose.

While there has only been a few GTx approved by the US Food and Drug Administration (FDA) to date, the research into such therapies has rapidly expanded, as exemplified by the Investigational New Drug (IND) applications that are filed to test therapies in clinical trials. Thus far, most of these therapies target orphan monogenic diseases (diseases caused by a defect in a single gene). However, we believe that GTx will ultimately be used to treat far more prevalent conditions like heart failure, diabetes and even Alzheimer’s. The rapidly expanding addressable market, cutting-edge scientific techniques, and remarkable healthcare benefits GTx can provide make it a theme that is incredibly ripe with investment opportunities.

New Gene Therapy Product IND Submissions (1990-2018)

We define Gene Therapy (GTx) as any treatment that changes the genetic profile of an individual with the purpose of treating a disease. In this series, we will first discuss approved GTxs, the various methods used to employ them, and their associated risks. We will eventually move towards the promising, but higher-risk Gene Editing technology on the horizon and discuss what scientific, regulatory and reimbursement hurdles need to be overcome to successfully commercialize GTxs.

Every individual has a unique genetic blueprint in the form of DNA. DNA represents the master list of instructions for every cell in the body. These instructions are in blocks of genes, which transcribe individually into short messages called messenger RNA (mRNA). In turn, the mRNA is “read” by the cellular ribosome to produce proteins—the final output of DNA and the master controller of all cellular function.

In most cases, the differences between individuals’ DNA simply lead to our unique hair color, height, or nose shape. However, if there is an error (mutation) in the DNA in a more critical gene—for example, in the gene that encodes for the survival of motor neuron (SMN1)—there can be disastrous consequences.

Children that have inherited two mutated copies of SMN1 from their parents do not produce enough SMN protein and develop a condition called Spinal Muscular Atrophy (SMA). These children suffer from progressive muscular atrophy and rarely live to see their second birthday. This type of disease is referred to as a monogenic disease because it affects only one gene: the SMN1 gene. One of the first forays into GTx was a so-called exon skipping approach, which has dramatically improved the lives of individuals impacted by SMA.

Here is how Gene Therapy works in the case of Spinal Muscular Atrophy:

All humans have a similar gene to SMN1 called SMN2. The mRNA of SMN2 is usually cut to be shorter than the SMN1, and therefore does not work as well. However, there is a drug that uses a short complimentary (antisense) sequence of mRNA to prevent the SMN2 mRNA from being cut too early, essentially forcing the cell to make a longer, more functional SMN2 protein. Children treated with this drug have shown dramatic improvements and are reaching milestones such as sitting, walking and talking that never would have occurred without the ability to increase SMN2 protein function.

While exon skipping has demonstrated remarkable capabilities, the antisense sequences of mRNA delivered are short-lived. The aforementioned drug requires children be dosed through a cumbersome spinal injection every few months to maintain the benefit. Luckily, as the science has advanced, so have the treatment options.

Another method of GTx delivers entire genes using viruses as cargo transporters (Gene Transfer). Viruses have an outer shell called a capsid that protects the viral DNA or RNA. While we typically think of viruses as cellular invaders that can be harmful, by taking out the viral genes and replacing it with a gene of interest we can harness their capabilities for the purposes of treating disease.
Another treatment uses an adeno-associated virus (AAV) that has been manipulated to carry the SMN1 gene inside of it. The virus docks onto the cells of the spinal cord and effectively delivers a corrected version of the SMN1 gene to the cell. The corrected gene, referred to as a transgene, sits within the nucleus alongside the individual’s DNA. Since the motor neurons impacted in SMA rarely divide, the transgene provides long-term SMN protein production. In fact, it has been shown that the clinical benefits persist four years after a single IV.

Gene Transfer is remarkably flexible. The next FDA approved gene transfer product will likely be for the treatment of Hemophilia. Typically, severe Hemophilia A patients are dosed with intravenous Factor 8 several times a week to prevent possible lethal bleeding episodes. Routine Factor 8 administration can cost hundreds of thousands of dollars a year. With the GTx approach, patients who receive a single AAV-factor VIII dose, can reliably be free from needing any further Factor 8 for years, which can dramatically improve a patient’s quality of life.

While remarkably efficacious and able to offer dramatic improvements to patient quality of life, GTx is not cheap. The gene transfer drug discussed above costs $2.15M per patient. To date, we do not know how long these therapies will offer benefits to patients. In some cases, like Hemophilia, a pricey one-time therapy can be justified because it negates the need for prophylactic factor VIII therapy. For SMA1 treatment, we are relying on the simple fact that we are saving lives and time in the NICU to justify a hefty price tag. We explore this question further, as well as ways it is changing business models, in our next article.
Amanda Birdsey-Benson, PhD  
Director, Senior Research Analyst

Amanda is a senior research analyst responsible for research across capitalizations in the Biotechnology industry. In this role, she provides stock recommendations and insights for both developed international and domestic strategies.

Prior to joining the firm, Amanda spent four years as a senior research analyst at Tekla Capital Management where she was responsible for biotechnology and pharmaceuticals, including specialty pharma segments. Prior to that, she worked as an analyst at R.A. Capital focused on health care. Amanda began her career in academics, devoting over 10 years to biology and biochemistry research.

Amanda earned her BS in Biology from the University of Connecticut and her Ph.D. in Biochemistry from Dartmouth College. She later worked as a postdoctoral fellow at MIT McGovern Institute for Brain Research.
Disclosure

Mellon Investments Corporation (“Mellon”) is a registered investment advisor and subsidiary of The Bank of New York Mellon Corporation (“BNY Mellon”). Any statements of opinion constitute only current opinions of Mellon, which are subject to change and which Mellon does not undertake to update. This publication or any portion thereof may not be copied or distributed without prior written approval from the firm. Statements are correct as of the date of the material only. This document may not be used for the purpose of an offer or solicitation in any jurisdiction or in any circumstances in which such offer or solicitation is unlawful or not authorized. The information in this publication is for general information only and is not intended to provide specific investment advice or recommendations for any purchase or sale of any specific security. Some information contained herein has been obtained from third party sources that are believed to be reliable, but the information has not been independently verified by Mellon. Mellon makes no representations as to the accuracy or the completeness of such information. No investment strategy or risk management technique can guarantee returns or eliminate risk in any market environment and past performance is no indication of future performance. The indices referred to herein are used for comparative and informational purposes only and have been selected because they are generally considered to be representative of certain markets. Comparisons to indices as benchmarks have limitations because indices have volatility and other material characteristics that may differ from the portfolio, investment or hedge to which they are compared. The providers of the indices referred to herein are not affiliated with Mellon, do not endorse, sponsor, sell or promote the investment strategies or products mentioned herein and they make no representation regarding the advisability of investing in the products and strategies described herein. Please see mellon.com for important index licensing information.

For more market perspectives and insights from our teams, please visit www.mellon.com.