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Editorial

Gene Therapy Comes of Age

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Gene therapy has made remarkable recent strides, particularly in contrast to the initial problems two decades ago. Since we first understood the role of genes in human disease, gene therapy became the holy grail of clinical medicine. The alleles that caused disease might someday be replaced with alleles that could cure disease. Gene therapy was first described in the medical literature half a century ago but the first successful human trials have taken additional decades of effort and frustration.

Twenty years ago, Jesse Gelsinger was the tragic victim of an effort to use gene therapy to cure ornithine transcarbamylase deficiency, resulting in an overwhelming immune response, secondary organ failure, and death. Many of us remember the fatal outcome, but there are critical lessons to remember as well.

That initial fatality stalled subsequent human trials, within the US and globally. The FDA concluded that the problem was not gene therapy per se, but poor attention to exclusion criteria, failure to report previous side effects, and inadequate informed consent procedures. The crucial point was not that gene therapy could be dangerous, but that gene therapy requires careful use. This point is equally true of most effective interventions that work at fundamental cellular levels and must therefore be used judiciously. Whenever there is potential for effective intervention, there are also potential risks that need to be carefully considered and prudently avoided.

In the past two decades, gene therapy has gradually climbed back toward clinical success, but even that success has come with pitfalls. The first gene therapy in the world to be licensed barely squeaked through EMA acceptance in 2012, and was then withdrawn from the market in 2017,

not for safety, but for economic reasons. The case is complex, but the very questions that plague this first release (efficacy, safety, appropriate clinical targets, and cost, for example) are the same questions that remain key questions for other current gene therapies and their prospects for curing human disease.

Despite these questions, there has increasing success using gene therapy. Several therapies are already in the regulatory pipeline or progressing to human trials. Despite the historical problems, these successes have charmed the media and brought hope to patients. There are at least five different approaches to gene therapy in current trials, each with different clinical applications. The potential applications depend on the pathology, the organs involved, and current technical limitations. Some are appropriate to specific genetic diseases, some to certain cancers, some to infectious disease, and some to age-related (i.e., epigenetic) disease.

The first approach, in vivo gene replacement, might be ironically termed "traditional" gene therapy. It delivers a normal allele in vivo to many or all affected cells, to alleviate the effects of an abnormal allele. Such approaches are typically aimed at children with genetic disease, such as the recent successful demonstration of gene therapy to treat spinal muscular atropy (SMA), a disease that paralyzes and kills affected children. The details were published in the NEJM in November of 2017, and involved the use of an adeno-associated virus to deliver a human gene to children. The potential uses for this approach include a recent success in treating hemophilia B, and encompass most genetic diseases.

The second approach, in vivo gene editing, is exemplified by its recent use in treating Hunter's syndrome, a fatal genetic disease that results in an inability to break down mucopolysaccharides. Rather than delivering a normal allele via gene therapy, zinc-fingers were delivered, which recognized the abnormal allele and edited the DNA sequence to create the normal allele. In this case, the patient's own DNA was literally "rewritten" directly in the cells of the patient's body.

The third approach, ex vivo gene editing, was employed in a recent trial, also published in NEJM, that removed donor cells, then was edited the genes to correct a fatal genetic disease called adrenoleukodystrophy (ALD) that destroys the myelin sheath around neurons. The edited cells, once returned to the patient's body, produce the normal molecule and thereby improve the patient's health. Similar ex vivo approaches have been used in CAR-T trials in patients with refractory cancer. In this case, the patient's T cells are removed and edited to ensure that they recognize cancer-related antigens, then reinfused into the patient's body. This approach is especially promising for refractory leukemias and lymphomas, but may also be applicable to liver cancer, multiple myeloma, neuroblastoma, pancreatic cancer, ovarian cancer, mesothelioma, and other cancers.

The fourth approach, in vitro phage editing, is distinctly different in that the genetic editing is not done to human cells, but to bacteriophages that are then used to attack the bacteria that cause infections. This approach could target new or newly-resistant bacteria rapidly and effectively. It would allow us to end-run the current problems with antibiotic resistance, permitting precise attacks on pathologic bacteria and rapidly responding to genetic changes that result in resistance. Tailored phages would kill bacteria, while ignoring human cells and offering fewer side effects.

The fifth approach, in vivo gene therapy to reset aging cells, offers the most extraordinary potential in geriatric medicine. This approach uses viral vectors to deliver an active human telomerase gene to transiently reset gene expression in aging cells, restoring normal young cell

function and reversing age-related pathology. Telomerase therapy has proven effective in human cells, in human tissues, and in animal studies. Human trials are now planned for 2018, with Alzehimer's disease as the initial clinical target, but with potential for vascular aging, osteoarthritis, osteoporosis, and a host of other age-related diseases.

Despite a rocky beginning, gene therapy trials are demonstrating unprecedented clinical success and promise to enable therapy (and cures) for diseases that have never been previously treatable, including age-related disease. The remaining practical issues include efficacy, the possible need for repeat therapy, and – most critically – the issue of cost. Regardless of these issues, the reality is remarkable. As the FDA Commissioner said, gene therapy is "no longer the stuff of science fiction."