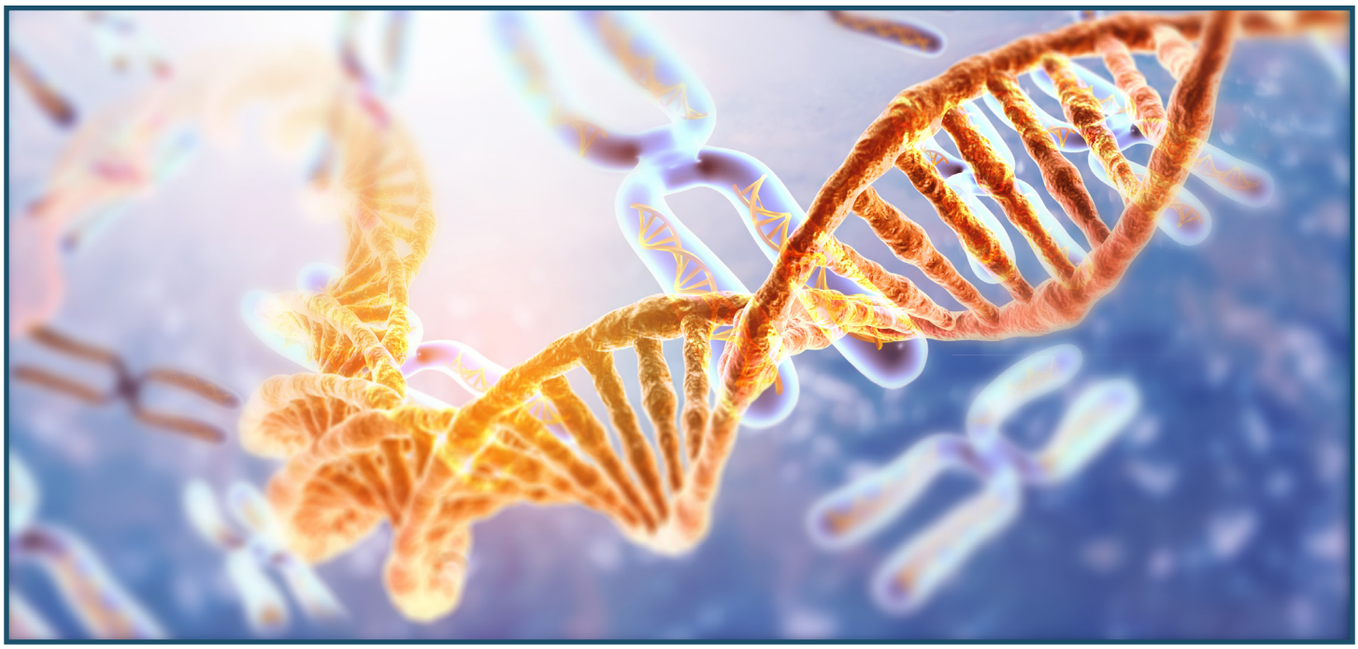

Cell & Gene Therapy: Implications on Drug Development

What is Cell & Gene Therapy?

Genes are defined by the NIH as the "basic physical and functional unit of heredity." We receive these valuable sequences of DNA from our parents, however genes go far beyond inheritance. Genes are code for the creation of all proteins in living organisms and serve as the metaphorical instructional manual for our body's proteins.

This set of instructions lays the groundwork for the colloquial building blocks of life: cells. Missing sections or pages in this instruction manual, known as genetic mutations, may cause serious dysfunctions at the genetic or cellular level. These dysfunctions, if severe enough, can manifest as syndromes or diseases. Traditional small molecule therapies often fall short in treating these types of dysfunctions. Cell and gene therapies, however, offer promise for untreated syndromes or diseases caused by genetic mutations.

Cell and gene therapies have the potential to lay the foundation for the next big paradigm shift in drug development. Similar to the way that monoclonal antibody treatments completely altered the treatment options in some therapeutic areas, cellular and gene therapies offer the promise of treating, and, in some cases, potentially curing diseases that have no current standard of care or where only symptomatic treatment was traditionally available.

Differences Between Cell and Gene Therapy

According to Keith Wonnacott, PhD, former Chief of Cellular Therapies Branch of CBER, somatic cell therapy can be defined as "autologous, allogeneic, or xenogeneic cells that have been propagated, expanded, selected, pharmacologically treated, or otherwise altered in biological characteristics ex vivo to be administered to humans and applicable to the prevention, treatment, cure, diagnosis or mitigation of disease or injuries." In other words, cellular therapy is the use of intact cells, from either the patient or an outside source, to treat a disease.

While the goals of cellular and gene therapies are the same, the way in which these treatments exert pharmacological effects is different. The FDA defines gene therapy as a treatment that "seeks to modify or manipulate the expression of a gene or to alter the biological properties of living cells for therapeutic use."

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In essence, cellular therapy uses actual cells as the therapy, whereas gene therapy alters the genetic material of a patient in order for the patient to begin producing healthy cells, themselves. Although cellular and genetic treatments work differently at the biological level, they are both regulated by the Center for Biologics Evaluation and Research (CBER) and the Office of Tissues and Advanced Therapies (OTAT). The FDA has compiled a list of all FDA-approved cellular and gene therapies. Some examples of cell and gene therapies are described below.

Examples of Cell Therapies

While the history of cellular therapies began with the human hematopoietic progenitor cell (HPC) cord blood treatments, a truly groundbreaking achievement in cellular therapy was the invention of chimeric antigen receptor T-cell (CAR-T) immunotherapy.

CAR-T therapy involves multiple steps, the first of which is harvesting a patient's own cells T-cells. The cells are then genetically altered via a viral vector transgene, which encodes various chimeric antigen receptors (CAR) relevant to the disease of interest. The modified cells are then re-infused into the patient (known as an autologous transplant), where the CAR-T cells eliminate cells expressing the targeted antigen. A couple of examples of CAR-T therapies are listed below:

Kymriah

Description: Kymriah is a CD19-directed CAR-T therapy used for the treatment of specific leukemias and lymphomas (listed below) that is administered via an intravenous (IV) infusion.

Manufacturer: Novartis

Year of Approval: 2017

Indications: 1. Patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse. 2. Adult patients with relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma.

Yescarta

Description: Yescarta is a CD19-directed CAR-T therapy used for the treatment of specific B-cell lymphomas (listed below) that is administered via an intravenous (IV) infusion.

Manufacturer: Kite Pharma

Year of Approval: October 2017

Indications: Treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

Examples of Gene Therapies

Gene therapy involves the use of genetic material to alter the way proteins are expressed in order to mitigate or cure disease. The FDA lays out 3 potential mechanisms of gene therapy, which are highlighted below:

1. Replacing a disease-causing gene with a healthy copy of the gene
2. Inactivating a disease-causing gene that is not functioning properly
3. Introducing a new or modified gene into the body to help treat a disease

Various gene therapy modalities are available, and include the use of plasmid DNA, viral vectors (like lentiviral and adenoviruses), bacterial vectors, human gene-editing technology (like CRISPR-Cas9), and patient-derived cellular gene therapy products (like CAR-T therapies). The only two direct-acting FDA-approved gene therapies are below:

Zolgensma

Description: Zolgensma is recombinant AAV9-based gene therapy designed to deliver a copy of the gene encoding the human survival motor neuron (SMN) protein for the treatment of spinal muscular atrophy (SMA) that is administered via IV infusion.

Manufacturer: AveXis

Year of Approval: 2019

Indications: Treatment of pediatric patients less than 2 years of age with SMA with bi-allelic mutations in the survival motor neuron 1 (SMN1) gene.

Luxturna

Description: Luxturna is an AAV gene therapy for subretinal injection. Luxturna delivers a normal gene encoding the human retinal pigment epithelial 65 kDa protein (RPE65) to cells of the retina in persons with reduced or absent levels of biologically active RPE65.

Manufacturer: Spark Therapeutics

Year of Approval: December 2017

Indications: Treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy. Patients must have viable retinal cells as determined by the treating physician(s).

Implications on Drug Development

As previously stated, cellular and gene therapies may usher in a new paradigm for drug development. While the development of these therapies is novel territory for both sponsors and the FDA, as medical knowledge continues to expand in this area, the FDA has a better understanding on how to regulate and guide the development pathway for these types of treatments.

The FDA has a repository of cellular and gene therapy guidances to guide the development of such treatments. Prior to 2000, there was only one available guidance for human somatic cell and gene therapy. Over the past 20 years, a multitude of guidances have been released by the agency, with 7 draft guidances being released in 2020 alone.

Despite the newly released draft guidances and hundreds of open cellular and gene therapy INDs, there has been a relatively small number of candidates that have been granted market approval by the FDA. The disparity between the number of investigational candidates and the number of approvals in the cellular and gene therapy space highlights the need for expert opinion and quantitative methodologies for determining the proper dose of cellular and gene therapy products.

Novel quantitative methods, such as quantitative systems pharmacology and exposure-response relationship analyses, in combination with traditional population pharmacokinetic analyses, can provide guidance on dosing strategies to mitigate adverse events, while maximizing efficacy. These types of analyses, in combination with expert opinion in the field, can be the difference between a failed candidate and market approval.

Conclusions

Cell and gene therapies both use the body's own cells and genetic information to fight diseases but do so in different ways. Cellular therapy uses actual cells as the therapy, whereas gene therapy alters the genetic material of a patient. Both types of therapies offer huge promise to treating and curing diseases that until recently had no treatment options.

While any drug development program can face pitfalls and uncertainties, developing cellular and gene therapies often present unique challenges above and beyond those encountered for small molecule drugs.

Nuventra's senior consultants and scientists have extensive experience in developing cellular and gene therapies. Whatever your drug development need — contact us to learn how Nuventra can help maximize your success.

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