# ...But Is It Gene Therapy?

## Debating a (Controversial) Definition

By Daniel Kavanagh, PhD

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***On August 29, 2017 the Food and Drug Administration (FDA) announced the approval of Kymriah™ (tisagenlecleucel, Novartis Pharmaceuticals) for certain forms of acute lymphoblastic leukemia (ALL). Several weeks later, the FDA issued an approval for YescartaT™ (axicabtagene ciloleucel, Gilead Sciences) for certain types of large B cell lymphoma. Kymriah was the first CAR-T therapy to receive FDA approval, and according to an FDA press release[1], was also the first "gene therapy" to receive such approval. The news was greeted with widespread enthusiasm, and also quickly became the occasion of significant debate about whether it is correct to refer to Kymriah and Yescarta as "gene therapy." At around the same time, an FDA committee recommended approval for LuxturnaTM (voretigene neparvovec, Spark Therapeutics) for a form of inherited retinal disease. Unlike the CAR-T therapies, Luxturna can be unambiguously classified as bona fide "gene therapy." This paper looks at the various definitions of gene therapy used by scientific and regulatory organizations, and why the use of this term generates both confusion and passionate opinions.***

While the term "gene therapy" has been used in medical and scientific discussions for decades, there actually is no universally accepted definition of *"gene therapy".* There is every reason to expect that the accepted usage of the term will evolve over time, and that it will be used differently by technical specialists as compared to the general public.

According to the Oxford English Dictionary[2] , gene therapy is "The introduction of normal genes into cells in place of missing or defective ones *in order to correct genetic disorders,"* This is a narrow and specific definition of the term, approaching the definition favored by a large percentage of molecular biologists. Notably, chimeric antigen receptor T- cell (CAR-T) therapies—which involve the genetic manipulation of receptors on immune cells so that the immune system recognizes and attacks cancer cells —are not intended to treat genetic disorders. Many molecular biologists and gene therapy scientists do not consider CAR-T treatments to be gene therapy.

The basic concept of CAR-T therapy is that normal white blood cells known as T cells are removed from the patient; the T cells are then subjected to a gene transfer procedure whereby they are given an artificial gene—comprised of a recombinant DNA sequence—encoding a receptor protein that directs the T cells to attack cancer cells; the T cells are then re-infused into the patient and, if all goes well, immediately get to work eliminating the cancer. Clearly, CAR-T therapy is an example of genetic engineering and is produced by gene transfer. However it does not involve delivery of a normally functioning gene. Furthermore, it is not intended to treat an inherited genetic disease or disorder (such as hemophilia or cystic fibrosis). For these reasons, CAR-T does not meet a narrow, technical definition of "gene therapy".

On the other hand, from commercial, technological, and public-welfare viewpoints, the narrow technical definition may not be the most important one. The FDA Center for Biologics Evaluation and Research (CBER) website includes different definitions of gene therapy in


different places, including 1) "Gene Therapy is a medical intervention based on modification of the genetic material of living cells;"[3] and 2) "Human gene therapy refers to products that introduce genetic material into a person's DNA to replace faulty or missing genetic material, thus treating a disease or abnormal medical condition."[4] According to the broader definition (1), CAR-T therapy clearly is a form of gene therapy. According the narrower definition (2), however, CAR-T therapy would not be gene therapy, as it does not involve replacement of faulty genetic material.

Notably, the FDA does not consider talimogene laherparepvec (Imlygic®) to be gene therapy. Imlygic is a tumor-killing virus genetically modified to express a human immune signaling gene, stimulating an immune response against tumor cells. According to a recent report, an FDA spokesman stated, "…although Imlygic has been genetically modified, Imlygic's primary biological activity is attributable to the oncolytic virus, not the genetic modification," whereas "the function of the CAR-T cell product depends on the genetic material transferred to the patient's cells. Therefore, the agency considers CAR-T cells to be a type of cell-based gene therapy."[5] Thus a practical working definition of gene therapy seems to take into account the degree to which a genetic modification contributes to therapeutic efficacy.

In the context of the FDA mission to protect the public health by ensuring the safety, efficacy, and security of drugs, biological products, and medical devices, there may be little value in drawing distinctions among the many new kinds of genetically modified products under development.

Other governmental and scientific bodies use closely-related terms to define regulated technologies. The *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules* use the term "human

gene transfer" (HGT), whereas the European Medicines Agency (EMA) uses the regulatory category of "gene therapy medicinal products" (GTMPs). In each case, there are specific technical considerations that apply to the oversight of research and medical interventions with agents in these categories. Notably Kymriah and Imlygic each qualify as both HGT products (NIH definition) and GTMP (EMA definition), whereas only Kymriah is considered "gene therapy" by the FDA.

Days before the FDA issued final marketing approval for Yescarta, an FDA advisory committee recommended approval for another new molecular therapy: Luxturna. Luxturna is intended to treat an inherited form of blindness, known as retinitis pigmentosa, which is caused by a mutant form of a gene—RPE65—that is required for vision. Luxturna is composed of a geneticially engineerd virus that delivers a functional form of the RPE65 gene to cells of the retina. Thus retinitis pigmentosa is an inherited disease caused by a genetic defect, and Luxturna is a therapy designed to correct the disease by introduction of a normal gene into affected cells. Luxturna satisfies even the most stringent criteria for a true "gene therapy." It is likely that many scientists will consider Luxturna to be the first gene therapy approved by the FDA.

An additional twist to the way that different investigators apply the term "gene therapy" relates to molecular techniques that are capable of re-writing, or "editing" a subject's chromosomal DNA in targeted cells. Gene editing technology, including approaches using CRISPR, TALEN, and Zinc Fingers, differs from gene therapy techniques like Luxturna in that while Luxturna delivers a DNA sequence representing a functional gene to a target cell, it does not alter or correct the original defective DNA in the chromosome of the cell. Gene editing, and the closely related genome editing technologies, are designed to re-write the chromosomal DNA of the target cell to create an edited DNA sequence. Many investigators in this area draw a distinction between "therapeutic gene editing" and "gene therapy." Whether this distinction becomes significant in common parlance remains to be seen.

As diverse new technologies—gene editing with CRISPR, molecular vaccines, engineered stem cells—are brought to the clinic, the definition of gene therapy is likely to become even more convoluted. We can certainly imagine a medical future where molecular interventions are so routine that there is no need to distinguish between gene therapy and other medical therapies. Until then, the debates will continue.

## References


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