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Gene Therapy/Editing Series 1: A Brief Introduction To Gene Therapy

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Summary

This is the first article in a series on gene therapy/editing which was first published on the Marketplace premium service last week.

The next article in the premium service will discuss the various delivery systems for gene therapy/editing.

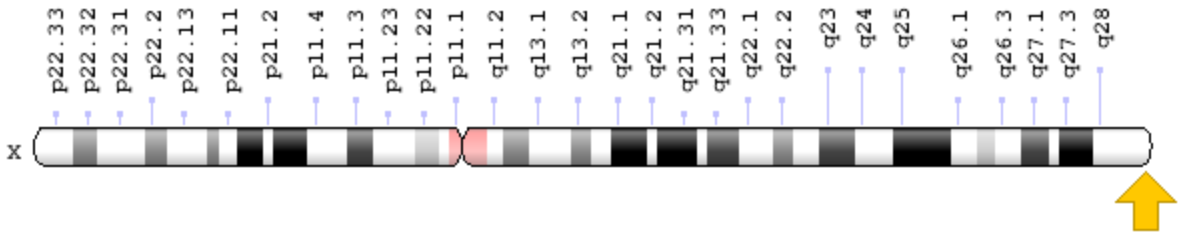
After discussing the basics like delivery systems, manufacturing processes, etc., the series in the premium service will focus on landscape of gene therapy/editing in different genetic diseases.

This will be followed by discussion of individual gene therapy/editing companies, their SWOT analysis, many of which already belong to the premium service portfolio.

The recent approval of various gene therapies, for example, Luxturna and Zolgesma and high premium acquisitions of gene therapy companies have shifted the investor focus to this rapidly growing biotechnology field. In this series of review articles, I will review the gene therapy and gene editing

field, starting first with the basics, including a brief overview of the history of the field and then moving on to some technical aspects, for example, the manufacturing, different methods of delivery, and then moving on to discussing the competitive landscape covering one genetic disease in each article.

Let's first define what is a gene? A gene is a sequence of nucleotides in DNA that encodes the synthesis of a gene product, which is usually a protein.

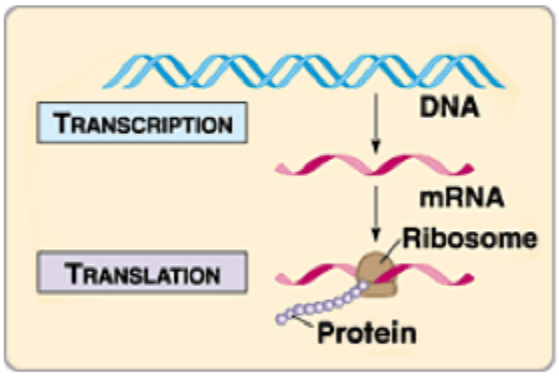


(F8 gene, mutations in the gene cause Hemophilia A)

Usually, the code (in the form of a specific arrangement of nucleotides or base pairs contained in the gene is used to form mRNA (called transcription) which acts as a messenger to take the code to the target organ of the body. The information stored in the mRNA is then used to encode and synthesize the target protein (called translation) which then performs its intended function in the body.

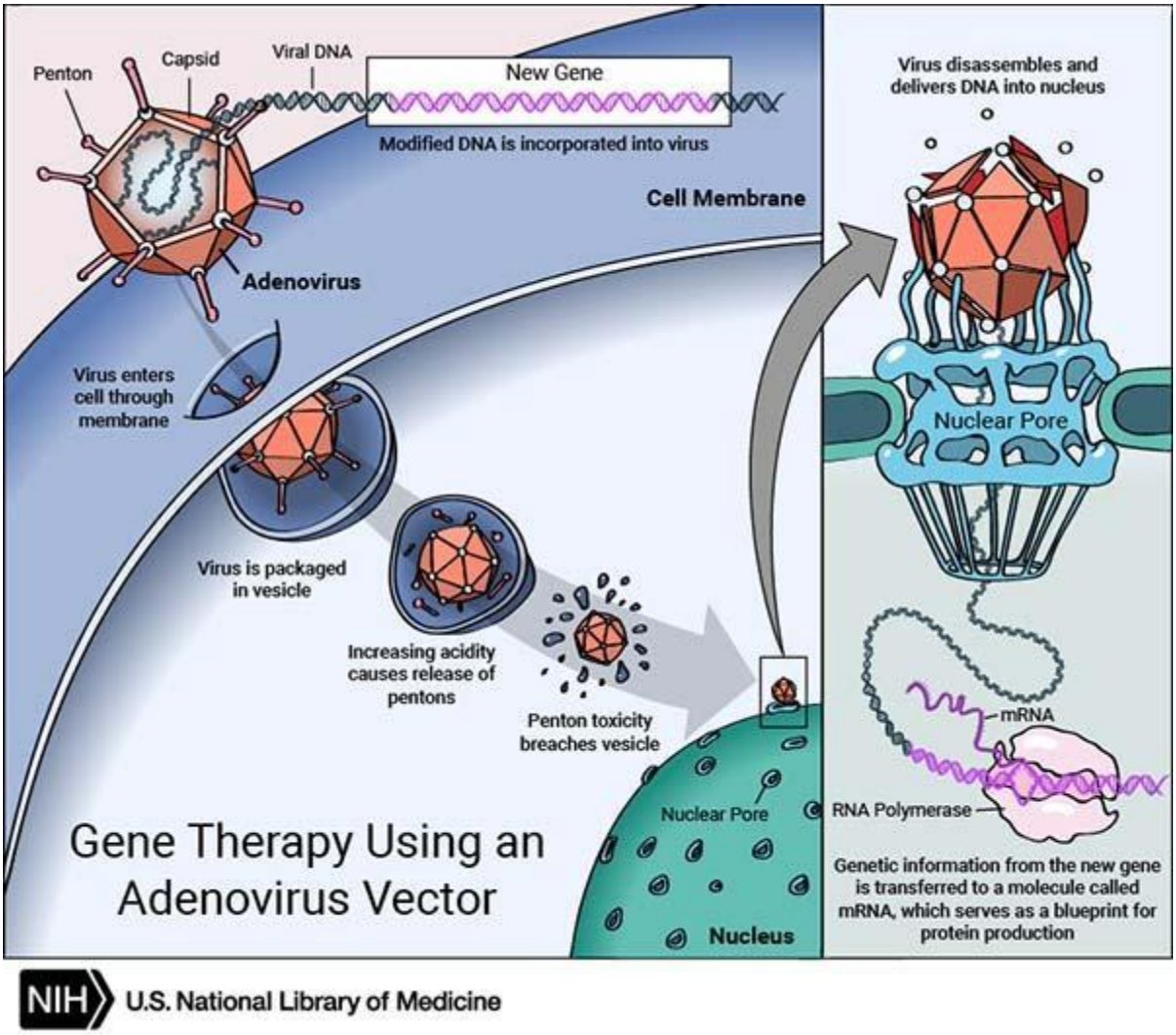
Transcription & transcription: overview

- *Transcription*
  - DNA → mRNA
  - Synthesis of mRNA from DNA
- *Translation*
  - Converting genetic information into proteins
  - mRNA is code for proteins synthesized at ribosome



(Steps involved in synthesizing a protein from the code in a gene)

An estimated number of protein-coding genes in the human body is approximately 20,000 to 25,000, which has been revised down from the initial prediction of 100,000 genes. Each gene contains a number of base pairs, the number of which is estimated to range from about 50 million to 300 million in the human body. In general, a gene therapy can be broadly defined as delivering in a new gene into the cells to compensate for a defective gene. In gene therapy, a newly delivered gene can perform different functions; for example, it can either replace the defective gene or it can silence an abnormal gene.



(An example of a gene therapy using an adenoviral vector to deliver the normal gene)

While I will discuss the various steps and delivery systems in gene therapy in detail later, viruses like lentiviruses and adenovirus are most commonly used as vectors in gene therapy. It was as early as 1950s that scientists first discovered that a virus can be used to inject the DNA in the cells of the host. In 1970s, various experiments started to use viruses as delivery systems for genes in the human body. In 1971, Merril, *et al* conducted a scientific experiment showing that DNA could be injected into the human cells to fix a biological problem in the cells. This group of scientists extracted the cells from patients suffering from a disease called Galactosemia. It is important to

note that this first gene therapy experiment involves the manipulation of genes *ex vivo,* that is in cells growing in a petri dish outside the body in a lab, which is easier to perform than manipulating the genes inside the human body, called *in vivo* approach. In 1972, a famous article in the prestigious journal Science by authors Friedman and Roblin first proposed that the gene therapy may ameliorate some human genetic diseases in the future. During the 1980s, various scientists like Martin Cline and French Anderson conducted experiments on using viruses as delivery vehicles for DNA in human or mouse cells. The first human trials of gene therapy started in the late 1980s and the results were reported in early 1990s. One of the first reported clinical studies in humans involved *ex vivo* modification of white blood cells taken from patients with advanced melanoma, using a retroviral vector to insert a gene coding for interleurkin-2 and injecting the genetically altered cells back into the patients. During the 1990s, French Anderson reported a successful clinical trial where a retroviral vector was used to transfer a gene encoding for adenosine deaminase, ADA in children with severe combined immunodeficiency, SCID. During the 1990s, most of the work in gene therapy continued in the therapeutic area of ADA-SCID.

Despite reasonably successful clinical results, the field of gene therapy suffered a serious setback in 1999. Jesse Gelsinger, an 18-year-old patient with a disease called ornithine transcarbamylase, OTC deficiency, which results due to a missing gene coding OTC died 4 days after receiving the gene therapy in a clinical trial conducted by the University of Pennsylvania due to massive immune response resulting in multi-organ failure. As a result, FDA put a suspension on various gene therapy clinical trials.

The New York Times Magazine

The Biotech Death of Jesse Gelsinger

By Sheryl Gay Stolberg

Nov. 28, 1999

The field of gene therapy was then suspended for almost a decade. Glybera, a gene therapy was approved in Europe for reading a genetic disease, lipoprotein lipase deficiency in 2012. However, Glybera was a commercial failure after insurers in Europe were reluctant to pay for its expensive $1 million per patient tag. Finally, uniQure (QURE) the company that developed Glybera discontinued it.

Another commercial gene therapy failure was Strimvelis, a stem cell gene therapy to treat ADA-SCID. Despite its price being lower than Glybera ($665,000 per year), the therapy was not commercially successful in Europe and was sold by GlaxoSmithKline (GSK) to Orchard Therapeutics (ORTX) in 2018. In the US, the first approved gene therapy was Kymriah, an

autologous CAR-T therapy to treat autologous lymphoblastic leukemia (ALL), which was developed by Novartis (NYSE:NVS).


The New York Times

F.D.A. Approves First Gene-Altering Leukemia Treatment, Costing $475,000

After Kymriah, another autologous CAR-T therapy, Yeskarta (by Kite Pharmaceuticals) was approved by FDA to treat adult diffuse large B-cell lymphoma. Kite was later acquired by Gilead (NASDAQ:GILD). The first *in vivo* gene therapy approval in the US was Luxturna, an AAV gene therapy for patients with RPE 65 mutation-associated retinal dystrophy, which was developed by Spark Therapeutics which also was later acquired. Luxturna was another major milestone in the history of gene therapy as it resulted in a miraculous effect of restoring vision to children who were blind since birth. Recently, bluebird bio's (BLUE) gene therapy for transfusion-dependent beta-thalassemia was approved in Europe.

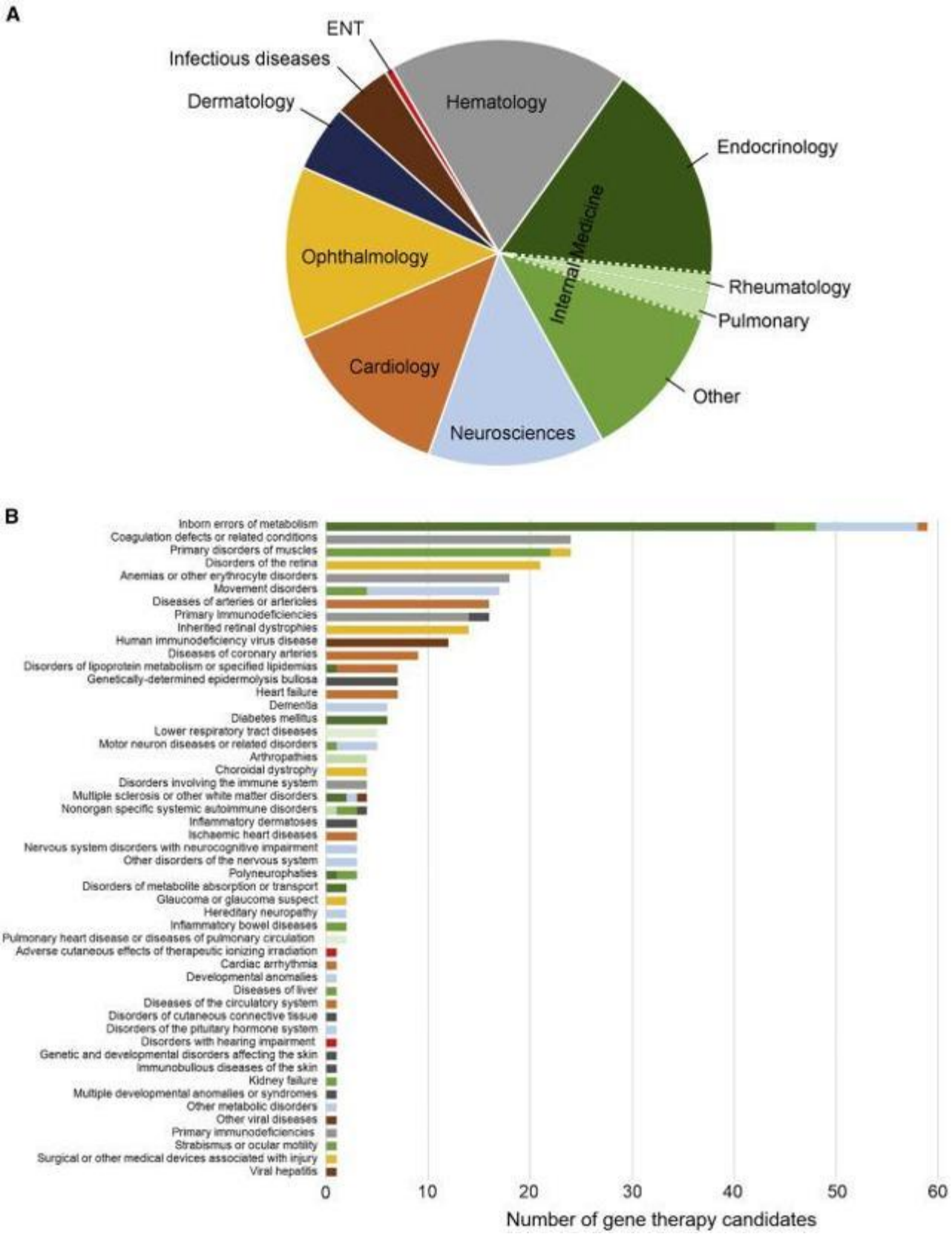

Technology

Bluebird Bio's First Gene Therapy Wins Approval in Europe

By James Paton

June 3, 2019, 12:44 PM EDT *Updated on June 3, 2019, 1:56 PM EDT*

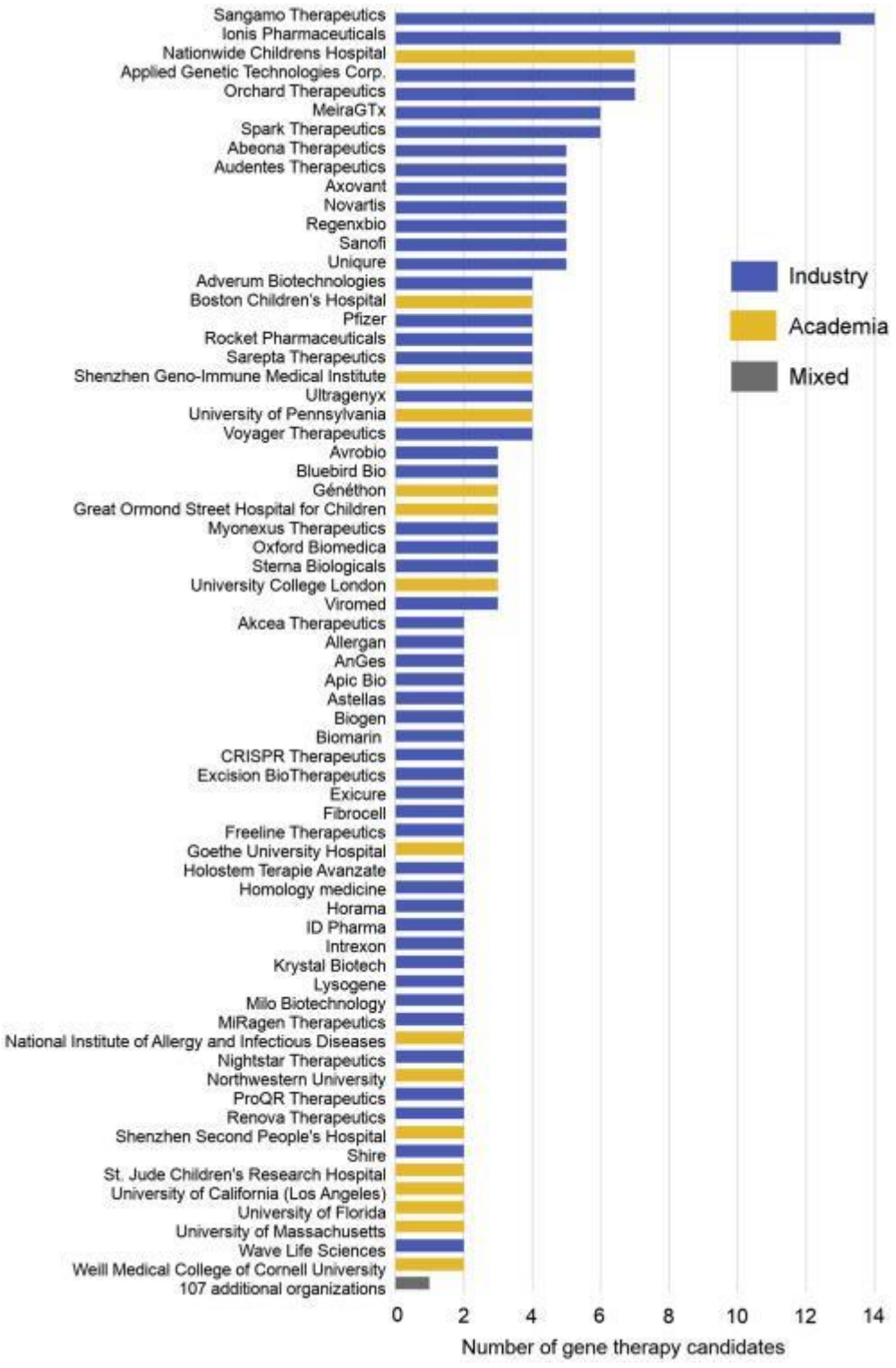
The developmental landscape of gene therapies can be summarized in some excellent figures from the journal Molecular Therapy published by the American Society of Gene and Cell Therapy (ASGCT). A group of researchers reviewed the medical literature and identified 336 gene therapies being developed for 138 different clinical indications covering 165 genetic targets excluding oncology. The researchers found that 74% of these 336 gene therapies were concentrated in five medical specialties, that is, hematology, endocrinology, neurosciences, cardiology, and ophthalmology. When classifying by different disease families, inborn errors of metabolism was the disease category with a majority of ongoing gene therapy trials.


A
ENT
Infectious diseases
Dermatology
Hematology
Endocrinology
Internal Medicine
Ophthalmology
Rheumatology
Pulmonary
Cardiology
Other
Neurosciences
B
Inborn errors of metabolism
Coagulation defects or related conditions
Primary disorders of muscles
Disorders of the retina
Anemias or other erythrocyte disorders
Movement disorders
Diseases of arteries or arterioles
Primary immunodeficiencies
Inherited retinal dystrophies
Human immunodeficiency virus disease
Diseases of coronary arteries
Disorders of lipoprotein metabolism or specified lipidemias
Genetically-determined epidermolysis bullosa
Heart failure
Dementia
Diabetes mellitus
Lower respiratory tract diseases
Motor neuron diseases or related disorders
Arthropathies
Choroidal dystrophy
Disorders involving the immune system
Multiple sclerosis or other white matter disorders
Nonorgan specific systemic autoimmune disorders
Inflammatory dermatoses
Ischaemic heart diseases
Nervous system disorders with neurocognitive impairment
Other disorders of the nervous system
Polyneuropathies
Disorders of metabolite absorption or transport
Glaucoma or glaucoma suspect
Hereditary neuropathy
Inflammatory bowel diseases
Pulmonary heart disease or diseases of pulmonary circulation
Adverse cutaneous effects of therapeutic ionizing irradiation
Cardiac arrhythmia
Developmental anomalies
Diseases of liver
Diseases of the circulatory system
Disorders of cutaneous connective tissue
Disorders of the pituitary hormone system
Disorders with hearing impairment
Genetic and developmental disorders affecting the skin
Immunobullous diseases of the skin
Kidney failure
Multiple developmental anomalies or syndromes
Other metabolic disorders
Other viral diseases
Primary immunodeficiencies
Strabismus or ocular motility
Surgical or other medical devices associated with injury
Viral hepatitis
0
10
20
30
40
50
60
Number of gene therapy candidates

(Landscape of gene therapy programs by organ system and disease area, source: Mol. Therapy)

When looking at specific clinical indications, Duchenne muscular dystrophy (DMD) was the clinical indication with the highest number of gene therapies being developed (15). HIV gene therapies (12 gene therapy programs) and hemophilia (11 gene therapy programs) took the second and third place respectively.

In terms of the number of gene therapy/editing programs being developed by a particular company or organization, Sangamo Therapeutics (SGMO) took the top spot (see the figure below).



(Landscape of gene therapy programs by company/organization, source: Mol. Therapy)

In conclusion, gene therapy has recovered from its earlier setbacks to emerge as one of the most innovative areas in biotechnology. In this first article of the series, I have provided a brief background about gene therapy, its history, and a broad top-down landscape. In the next article in the premium service, I will discuss various delivery systems for gene therapy.

A free two-week trial for the premium Marketplace service is open for another week only. Only 25 more spots left.