Technology Intelligence and IP Research

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GENE THERAPY

Advanced Treatments for a New Era

Thematic Report By

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Executive Summary

Considerable research has been conducted in genomics in the past two decades. Extensive research in the gene therapy domain began in 2001, when two separate versions of human genome sequences were published. These drafts contained 30,000 genes, which were used to decipher gene function, gene abnormality, and malignant alternations at the gene levels.

James Watson was quoted as stating, "We used to think that our fate was in our stars, but now we know, in large measures, our fate is in our genes." Genes are the functional unit of heredity. When altered, the proteins that they encode are unable to carry out their normal functions. Gene therapy (the use of genes as medicine) is basically used to correct defective genes.

Gene therapy involves inserting/deleting/correcting genetic material into human cells to fight or prevent diseases. It is a promising tool not only for cancer but for several other diseases, such as Parkinson's, HIV, severe combined immuno-deficiencies and hemophilia, to name a few.

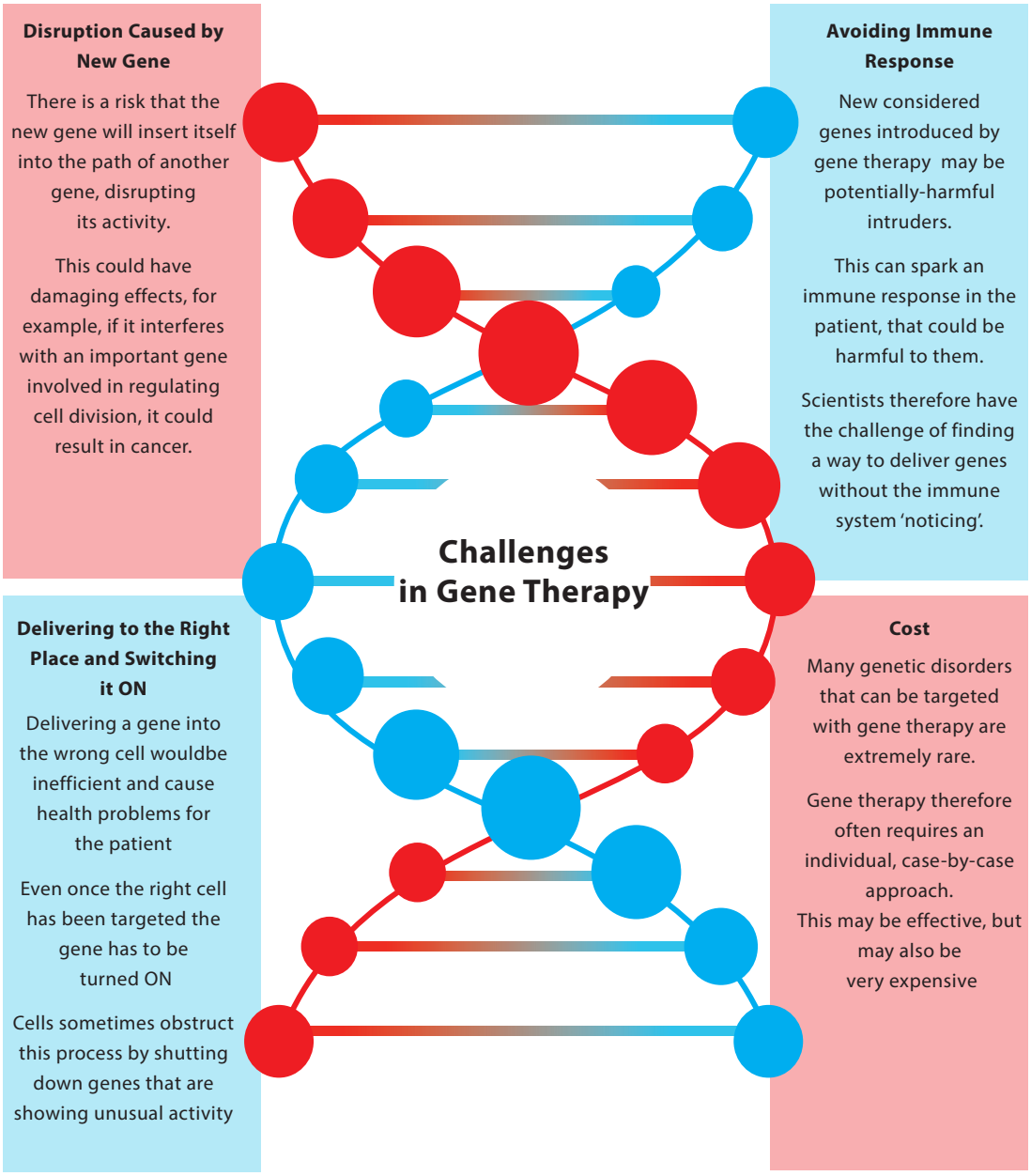
Gene therapy initially encountered a lot of problems as people considered it unethical to use humans as subjects for clinical trials. However, as time passed, gene therapy has proved to be a useful tool to cure several forms of disease.

In this report, we'll cover the challenges associated with gene therapy, various modes of administration of gene based therapies, expected future of gene therapy, companies that are investing heavily in gene therapy research, as well as FDA approved gene-based drugs that are currently available in the market or undergoing clinical trials.

Challenges Associated with Developing Genetic Treatments

Dealing with diseases at a genetic level is not easy. While gene therapy isn't a new field, it has witnessed very limited success despite over half a century research and development.

Researchers are constantly working on overcoming several challenges being faced by gene therapy.



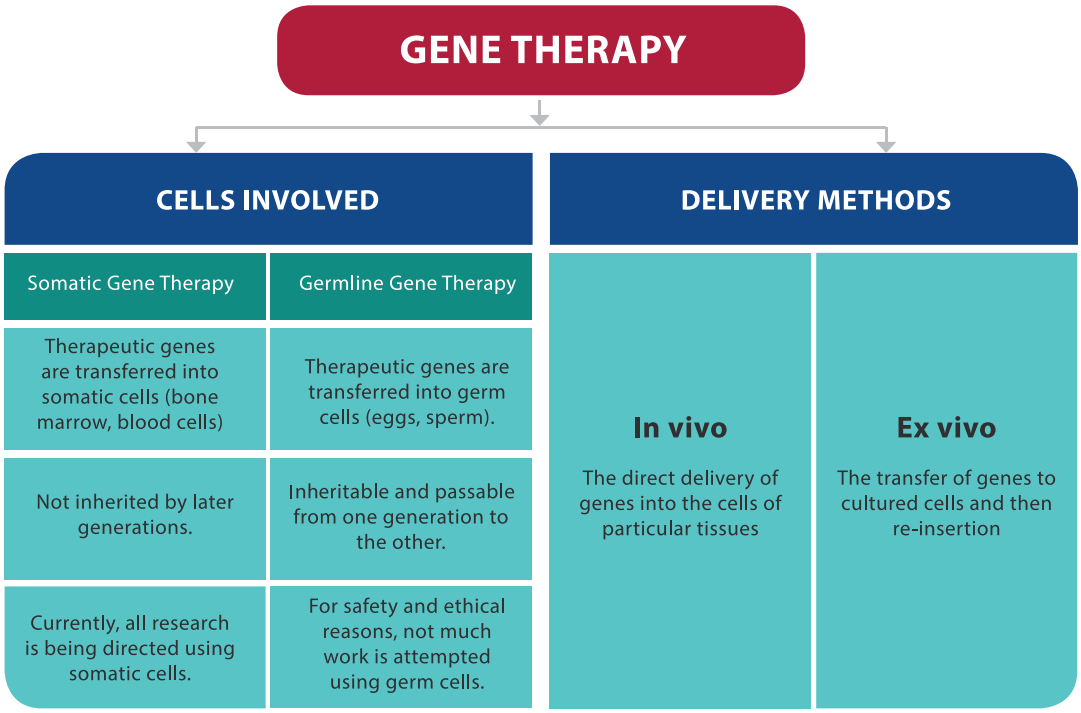
Source : Aranca Analysis

Administering Gene Therapy

Gene therapy may be defined as the introduction of genetic material into defective cells for a therapeutic purpose.

While gene therapy holds great potential as an effective means for selective targeting and treatment of disease, the field has seen relatively slow progress in the development of effective clinical protocols.

Although identifying genetic factors that cause a physiological defect is pretty straightforward, successful targeted correction techniques are proving continually elusive. Creating an ideal delivery vector to target diseased — and only diseased — tissue has proved difficult for those researchers toiling away tirelessly in their search for the safe treatments of tomorrow.



Viral Vectors

These are virus-based vectors. Examples include the retrovirus vector, adeno virus vector system, adeno associated virus vector, and herpes simplex virus. Extensive research is being conducted on the various viral vectors used in gene delivery. Here's a snapshot depicting some of the research being conducted on various viral vectors.

Viral Vector	Type	Advantages	Disadvantages
Retrovirus	Integrates with host chromatin	Effective over long periods Effective transfection ex vivo Low immune response in host	Small insert size Effective transfection in vivo Safety concerns
Lentivirus	Integrates with host chromatin	New generations self-inactivate for safety purposes Transfects proliferating, non-proliferating host	Small insert size Safety concerns, immuno-deficiency origin Needs active transport in the cell
Adeno-Associated Virus	Integrates with host chromatin	Good length of expression in vivo Effective transfection ex vivo Low immune response in host	Safety problems owing to potential insertional mutagenesis Small insert size Technologically challenging
Adeno Virus	Extrachromosomal DNA	Highly efficient transfection in vivo/ex vivo Transfects proliferating, non-proliferating host	Repeat treatments ineffective due to strong immune response Small insert size Technologically challenging
Herpes Simplex Virus	Extrachromosomal DNA	Good length of expression in vivo Safe for use in immune-compromised patients Large insert size up to 30kb Effective on various cell types	Difficult to produce in large quantities

Non-viral Vectors

Examples of non-viral vector systems include pure DNA constructs, lipoplexes, DNA molecular conjugates, and human artificial chromosomes. Owing to the following advantages, non-viral vectors have gained significant importance in the past few years:

1. Less immunotoxic
2. Risk-free repeat administration
3. Relative ease of large-scale production

A major disadvantage is that the corrected gene needs to be unloaded into the target cell, and the vector has to be made to reach the required treatment site.

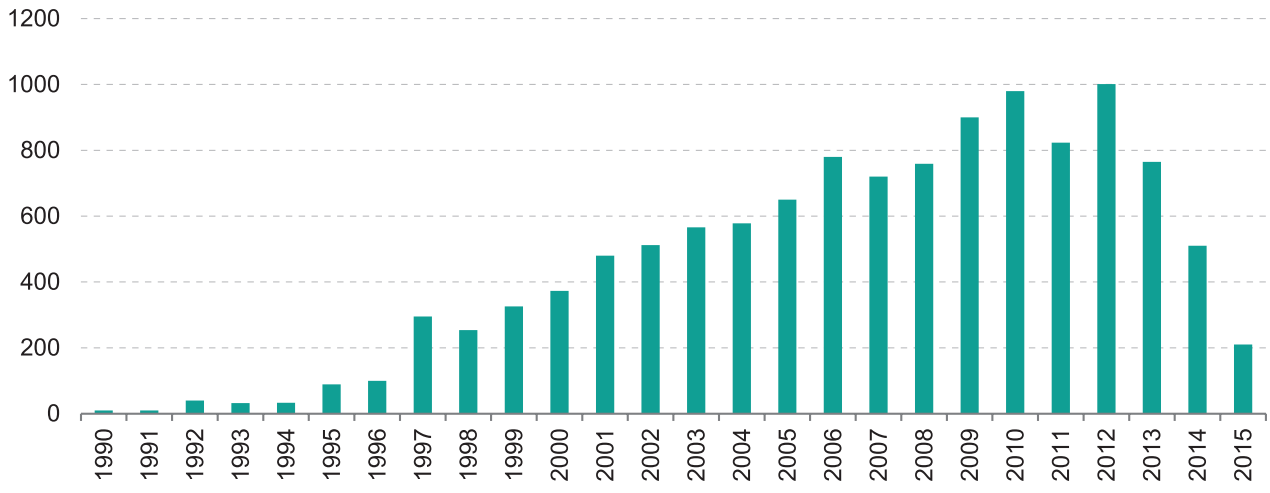
Possible Strategies to Improve Current Viral/Non-viral Vector Systems

Here's a list of likely strategies that can be employed to improve current vector systems:

1. Making the systems correctly target the defective cell
2. Rendering them capable of transcription
3. Making the systems efficiently penetrate the cell membrane barrier
4. Making them appropriate bio distribution vectors
5. Improving their circulation time in the body
6. Making the systems efficiently interact with the serum component's therapeutic material so the therapeutic material is not lost
7. Ensuring that the systems do not react with the immune system and macrophages
8. Rendering them capable to interact with a defective cell surface
9. Making the systems competent to escape degradation by nucleases
10. Maintaining the correct gene expression over a longer time

Patent filing in gene therapy has picked up in the last decade, primarily due to unmet requirements in life-threatening diseases.

Patent Filing Trend in the Domain of "Delivery Vehicles Used in Gene Therapy"



Source : Aranca Analysis

Note: The data post 2012 is not reliable, as the patents that are filed in this period are yet to be published.

Gene Therapy Considered a Path-changing Treatment for the Coming Era

Gene therapy has transitioned from the conceptual, technology-driven, laboratory research, to clinical trial stages for a wide variety of diseases. In addition to curing several genetic disorders, such as Hemophilia, Chronic Granulomatous Disorder (CGD) and Severe Combined Immune Deficiency (ADA-SCID), it is also being tested to cure acquired diseases acquired diseases such as cancer, neurodegenerative diseases, influenza and hepatitis, to name a few.

Gene therapy is not limited to any particular disease. It is also proving to be a promising treatment for rare diseases such as X-linked adrenoleukodystrophy.

This therapy has proved effective in research conducted for the following diseases:

Fat Metabolism Disorder

Gene therapy is used to correct rare genetic diseases caused due to lipoprotein lipase deficiency (LPLD). This deficiency leads to fat molecules clogging the blood stream. An adeno-associated virus vector is used to deliver the corrected copy of the LPL to the muscle cells. This corrected copy prevents the excess accumulation of fat in the blood by breaking down the fat molecules. In 2012, the European Union approved Glybera, the first viral gene therapy treatment for LPLD, manufactured by UniQure. Glybera is likely to be approved for the American market by 2018.

Adenosine Deaminase (ADA) Deficiency

Gene therapy has successfully been used to treat another inherited immune disorder: ADA deficiency. More importantly, none of the patients undergoing this treatment developed any other disorder. The retroviral vector is used in multiple small trials to deliver the functional copy of the ADA gene. Primarily, all the patients involved in these trials did not require any injection of ADA enzyme as their immune functions had immensely improved.

Severe Combined Immune Deficiency (SCID)

A lot of documented work is already available regarding treating this immunodeficiency with gene therapy; however, clinical trials have not shown promising results. The viral vectors used during the trials triggered leukaemia in patients. Since then, the focus of the research and trials has been on preparing new vectors that are safe and do not cause cancer.

Hemophilia

Patients with haemophilia suffer excessive blood loss as the blood clotting protein (Factor IX) is absent. Researchers have successfully inserted the missing gene in the liver cells using an adeno-associated viral vector. After undergoing this treatment, patients experienced less bleeding as their body was able to create some of the Factor IX protein.

Cystic Fibrosis (CF)

CF is a chronic lung disease caused due to a faulty CFTR gene. Genes are injected into cells using a virus. Recent studies also include testing the cationic liposome (a fatty container) to deliver DNA to the faulty CFTR gene, thus making the use of the non-viral gene carrier more successful. Phase II trials using this therapy were published in early 2015, which promised a novel therapeutic approach to CF.

β-thalassemia

Clinical trials on gene therapy for β-thalassemia (the faulty beta-globin gene, which codes for an oxygen-carrying protein in RBC) can be tracked back to 2007. Blood stem cells were taken from the patient's bone marrow and a retrovirus was used to transfer a working copy of the faulty gene. The modified stem cells were re-injected into the body to supply functional red blood cells. This treatment, once conducted, lasted over seven years, even if the patient did not undergo blood transfusion during this time.

Hereditary Blindness

Currently, gene therapy is being tested to treat the degenerative form of inherited blindness, where patients lose the light-sensing cells in their eyes with time. Experimental data suggests that the animal models of a mouse, rat and dog show slow or even reverse vision loss using gene therapy.

The most important advantage associated with gene therapy for eye disorders is that AAV (adeno-associated virus) cannot shift from the eye to other body parts and hence does not cause an immune reaction.

In one of the trials, gene therapy was used to improve the vision of a patient with a degenerative blindness named Leber Congenital Amaurosis (LCA). However, although their vision improved, the retina kept degenerating with time.

Another trial reported that the vision of six of nine patients who suffered from degenerative blindness (choroideremia) had improved when the corrected form of REP1 was delivered to them using a viral vector.

Parkinson's Disease

Patients with Parkinson's disease lose the ability to control their movement as their brain cells stop producing the dopamine molecule used for signaling. A small group of patients showed improved muscle control when a small area of their brain was treated with a retroviral vector that contained dopamine-producing genes.

Top Players in Gene Therapy

A majority of the big pharmaceutical and biotech companies are actively researching the various aspects of gene therapy. A lot of research is also being conducted by universities. Players with high patenting activity include:

Source : Aranca Analysis

Despite the high number of patents being filed, very few gene therapy products have been commercialized, and some are in the clinical trial stage. A few examples are listed below:

FDA Approval Status for Key Gene Therapy Players

Company/Institution	Collaborator	Disease Targeted	Status
Amgen	--	Metastatic melanoma	Late-stage human trials
Advantagene	--	Prostate cancer	Expected to complete last stage clinical trials in September 2015
UniQure	--	Fat metabolism disorder	Approved for sales in Europe
Bluebird Bio	--	Neurodegenerative disease	Mid- and late-combination trials completed in 2013
Glybera Europe	--	LPDL	EU commercial plan launched for 2015
Glybera US	--	LPDL	IND filing initiated in 2014
AnGesMG	--	Artery failure in limbs	To commence late-stage global testing
Children's Hospital of Philadelphia	--	Hereditary blindness	Human trials ended in April 2015
Human Stem Cell Institute	Neovasculogen	Critical limb ischemia	Marketing in Russia since 7 December 2011

Source : Aranca Analysis

The Future of Gene Therapy

According to consulting firm Global Data, "The total number of deals in the global gene therapy market more than doubled from 16 in 2013 to 36 in 2014, with their combined value rising spectacularly from $122.8 million to $4.9 billion over the same period, representing a forty-fold increase."

The focus areas for gene therapy include:

1. The genetic manipulation of viral vectors for efficient delivery
2. New viral vectors for delivery
3. Various routes of administration, and the dosage range for new diseases
4. New approaches of gene therapy such as Spliceosome-mediated RNA Trans-splicing (SMaRT), hybrid vectors, gene splicing using ribozymes, triple helix forming oligonucleotides, antisense, zinc finger nucleases and nano-robotics are also picking up

Documented data shows that gene therapy involves substantially low mergers and acquisitions; this is due to the technology being highly experimental and the majority products being in the early stage of clinical development. A few famous mergers and acquisitions include:

1. The acquisition of CFR Pharmaceuticals by Abbott Laboratories to develop gene therapy for chronic pain and alcoholism
2. The licensing agreement with UniQure and Bristol-Myers Squibb to develop UniQure's phase I candidate for congestive heart failure; this deal is forecast to have the greatest financial impact in the current fiscal year
3. Voyager Therapeutics signed a multi-million dollar agreement with Genzyme to develop three phase I programs to develop therapies for central nervous system disorders

Aranca considers gene therapy a promising technology of the present times. The future of gene therapy is expected to revolutionize the medical world.

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