Gene Therapy:
Moving Toward Commercialization

Insight Pharma Reports’ Gene Therapy: Moving Toward Commercialization, outlines the progress of the gene therapy field since its inception in the 1970s, with a special focus on clinical-stage gene therapy programs that are aimed at commercialization, and the companies that are carrying out these programs. A major theme of this report is whether gene therapy can attain commercial success by the early-to-mid 2020s, which types of gene therapy programs have the greatest likelihood of success, and what hurdles might stand in the way of clinical and commercial success of leading gene therapy programs.

In accord with the focus of this report, we have been asking:
• Whether gene therapy can attain commercial success by the early-to-mid 2020s,
• Which types of gene therapy programs have the greatest likelihood of success,
• What hurdles might stand in the way of clinical and commercial success of leading gene therapy programs.

In addition to chapters that focus on various areas of commercial gene therapy, this report includes:
• An expert interview with Sam Wadsworth, Ph.D., the Chief Scientific Officer of Dimension Therapeutics and former Head of Gene Therapy R&D at Genzyme.
• Survey data from 88 researchers involved in gene therapy
• Companies profiled: uniQure, Voyager Therapeutics, Oxford BioMedica, GeneQuine Therapeutics, Celladon Corporation, and bluebird

Topics covered:
• Development of improved vectors (integrating and non-integrating vectors)
• Gene therapy for ophthalmological diseases
• Gene therapy for other rare diseases
• Clinical-stage gene therapies for selected rare diseases other than hemophilias
• Gene therapy for more common diseases
• Companies whose central technology platform involves ex vivo gene therapy
• CAR T-cell immunotherapy as an area of ex vivo gene therapy
• Gene editing technology
• Outlook for gene therapy
• Market outlook for eight gene therapy products
Executive Summary

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In addition to chapters that focus on various areas of commercial gene therapy, this report includes:

- An expert interview with Sam Wadsworth, Ph.D., the Chief Scientific Officer of Dimension Therapeutics and former Head of Gene Therapy R&D at Genzyme. This interview is appended to Chapter 5.
- A survey on gene therapy, which was conducted by Insight Pharma Reports in conjunction with this report, and is discussed in Chapter 9.

Chapter 1 discusses the history of gene therapy, including early FDA-approved human studies of gene therapy in academic and government laboratories in the 1990s. These were based on studies in the 1970s and 1980s, in which researchers applied such technologies as recombinant DNA and development of viral vectors for transfer of genes to cells and animals to the study and development of gene therapies.

Chapter 2 focuses on development of improved vectors, which are designed to circumvent the problems seen in early clinical gene therapy studies. These vectors are of two general types—integrating and non-integrating vectors. Integrating vectors insert themselves into the DNA of the host genome. The advantage of using integrating vectors is that when host cells replicate their chromosomal DNA and divide, they replicate the vector DNA (including inserted therapeutic transgenes) as well. In contrast, non-integrating vectors used in gene therapy would be lost as the result of any cellular proliferation. Thus non-integrating vectors should be used in tissues in which cell division does not occur.

Chapter 3 focuses on one company, uniQure (Amsterdam, the Netherlands). The reason for this is that uniQure is the first company to commercialize a gene therapy. This therapy is Glybera (alipogene tiparvovec), which is a treatment for the ultra-rare genetic disease lipoprotein lipase deficiency (LPLD). As of now, it is the only gene therapy product to have received regulatory approval in a regulated market.
Chapter 4 focuses on gene therapy for ophthalmological diseases. Retinal diseases constitute an attractive target for gene therapy. Researchers can target the retina easily via intravitreal injection or subretinal injection. The retina is also an immunoprivileged site. The existence of a contralateral control—the other, untreated eye—also provides an advantage in targeting the eye. There are also non-invasive methods that may be used to monitor therapeutic effects. The small size and compartmentalization of the eye also constitute advantages for gene therapy (especially when compared to targeting much larger organs or tissues such as the skeletal musculature, the liver, or the heart). There is also the issue of medical need, since blindness severely reduces the quality of life.

Chapter 5 focuses on gene therapy for other rare diseases. The first section of this chapter discusses clinical-stage gene therapies for hemophilias. Hemophilias are important genetically determined bleeding disorders, which include hemophilia A and B. Both are X-linked recessive disorders, and thus affect mainly males. Hemophilia A involves a deficiency in factor VIII (FVIII), and hemophilia B involves a deficiency in factor IX (FIX). Both of these are clotting factors that are made in the liver.

Chapter 6 focuses on gene therapy for more common diseases. The great majority of preclinical and clinical gene therapy programs are directed toward treatment of rare diseases. A key question in the gene therapy field is whether gene therapy is applicable (both in terms of technical feasibility and in terms of commercialization strategies) to more common diseases.

Chapter 6 focuses on the efforts of four companies—Voyager Therapeutics, Oxford BioMedica, GeneQuine Therapeutics, and Celladon Corporation—to develop gene therapies for common human diseases. It illustrates both the promise and the difficulties of developing gene therapies for such diseases.

Chapter 7 focuses on companies whose central technology platform involves ex vivo gene therapy. Several ex vivo gene therapies discussed in this report are based on studies with retroviral vectors from the earliest days of gene therapy research. In contrast, development of the therapies discussed in Chapter 7 has been initiated much more recently.

The first section of Chapter 7 focuses on bluebird bio (Cambridge, MA). bluebird is a publicly-traded clinical stage biotechnology company that is developing and commercializing gene therapies designed to be one-time treatments for severe genetic and rare diseases and cancer. The company’s technology platforms encompass gene therapy for rare diseases, cancer immunotherapy, and gene editing.

The second section of Chapter 7 focuses on CAR T-cell immunotherapy as an area of ex vivo gene therapy. A full discussion of CAR T-cell therapy, especially a discussion of the technical aspects of this field, belongs in a report on cancer immunotherapy. As such, it is beyond the scope of this gene therapy report. For such a full exposition of CAR T-cell therapy (and of other aspects of cancer immunotherapy), see our September 2014
Chapter 8 focuses on gene editing technology. In recent years, a growing number of researchers have been seeking to develop gene therapies that work via “gene editing”—directly changing DNA sequences of deleterious genes in a patient’s genome into functional sequences. Gene editing, which is in its early stages, is considered “next generation” gene therapy.

**Outlook for gene therapy**

In accord with the focus of this report—which we have entitled “Gene Therapy: Moving Toward Commercialization”—we have been asking:

- Whether gene therapy can attain commercial success by the early-to-mid 2020s,
- Which types of gene therapy programs have the greatest likelihood of success,
- What hurdles might stand in the way of clinical and commercial success of leading gene therapy programs.

In Chapter 9, we list eight gene therapy products that in the opinion of leading researchers and corporate leaders in the field have the greatest prospect for reaching the market before 2020. One product (uniQure/Chiesi’s Glybera) has been approved in Europe, another (GSK/TIGET’s GSK2696273) is in preregistration in Europe, and the others are in or nearing pivotal clinical trials. We therefore conclude the answer to the question as to whether gene therapy can attain at least some degree of near term commercial success is yes.

Of the eight therapies highlighted in Chapter 9, six are ex vivo gene therapies, which suggests that the ex vivo strategy (exemplified by bluebird bio) is a potentially successful one for moving gene therapies toward registration and marketing in the near term. Three of these ex vivo gene therapies are CAR T-cell cancer therapies that target CD19.

All of the eight therapies are for rare diseases. However, several of the diseases addressed by these therapies are for some of the more common rare diseases, especially beta-thalassemia and sickle cell disease. Thus the concern that gene therapy will only be applicable to ultra-rare diseases such as lipoprotein lipase deficiency (LPLD) is likely to be unfounded. However the prospect for gene therapies for common diseases has not yet been realized.

In terms of expected revenues for gene therapy products reaching the market in the near term, there is a great deal of uncertainty. However, at least some analysts project sales of Lenti-D of around $250 million and of LentiGlobin of around $4 billion. As for the CAR T-cell therapies, one analyst projects peak sales of around $1.7 billion for Kite’s KTE-C19. Other CAR T-cell therapies may achieve comparable results, depending on competition and payer acceptance of the therapies and their prices. These projections suggest that near-term gene therapies may attain commercial success.
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About Insight Pharma Reports

CHI’s Insight Pharma Reports are written by experts who collaborate with CHI to provide a series of reports that evaluate the salient trends in pharmaceutical technology, business, and therapy markets.

Insight Pharma Reports are used by senior decision makers at life sciences companies to keep abreast of the latest advances in pharmaceutical R&D, their potential applications and business impacts. Our clients include the top 50 pharmaceutical companies, top 100 biotechnology companies, and top 100 vendors of life science products and services. Typical purchasers are managers, directors, and VPs in business development, discovery research, clinical development, strategic planning, portfolio management, new product planning, and marketing.

Insight Pharma Reports offer:

• Current Information and analysis of R&D technologies, therapeutic markets, and critical business issues.
• Analysis of the probability of success for various applications of each technology.
• Expert insight based on interviews with key personnel in companies at the forefront of technological advances who share their views on their technology’s current status, applications, future direction, and market environment.
The idea of gene therapy has been around at least since the early 1970s. In a 1972 article, Theodore Friedmann and Richard Roblin advanced the concept of treating genetic diseases by replacing defective endogenous DNA with exogenous non-defective DNA. These authors—as well as other researchers up to the present day—have viewed genetically caused diseases that cannot be well managed by such treatments as dietary or drug therapy as potential candidates for gene therapy.

For example, the causative mutation of sickle cell disease (SCD) (also known as sickle cell anemia) was identified in 1957 by Vernon M. Ingram, Ph.D. of MIT, long before the era of genomics. Dr. Ingram showed that a glutamic acid to valine mutation at position 6 of the β-chain of hemoglobin was the sole abnormality in SCD. For this discovery, Dr. Ingram has been called “The Father of Molecular Medicine”. Dr. Ingram’s work was made possible by a 1949 study by Linus Pauling and his colleagues, which showed that SCD hemoglobin had a different electrophoretic mobility than normal hemoglobin. Thus the sickle cell trait was likely to be due to a mutation in the β-hemoglobin gene that changed its amino acid composition, as confirmed by Dr. Ingram.

However, to this day, although SCD (which occurs in individuals who are homozygous for the sickle-cell mutation) can be managed by various treatments (such as hydroxyurea and blood transfusions and bone marrow transplants) that can result in survival into one’s fifties, there is no mechanism-based therapy for this disease. Thus the identification of the causative mutation of SCD has not led to any treatments.

The reason for this is that the mutation that causes this disease affects an intracellular protein, hemoglobin, which is neither a receptor nor an enzyme. Unlike secreted proteins such as insulin, it is not possible to develop protein drugs to replace missing or defective hemoglobin. It is also not possible to replace the missing function of normal hemoglobin by treatment with a small molecule drug.

Such diseases, in which the function of an essential intracellular protein is defective or missing, have often been cited as candidates for gene therapy. Most of the genetic diseases cited as potential candidates for gene therapy in Drs. Friedmann and Roblin’s 1972 paper would be classified as “rare diseases”. However, as noted by these authors, when taken as a group, the aggregate number of patients affected by “rare genetic diseases” was quite significant, and was “becoming an increasingly visible and
significant medical problem, at least in developing countries”.

This is even more so today. For example, the website of the National Organization for Rare Disorders (NORD) states (in the U.S. context) that a “rare disease” is one that affects fewer than 200,000 Americans. There are nearly 7,000 rare diseases that affect nearly 30 million Americans. Although the numbers of people affected by any one rare disease is small, the aggregate number of people affected by rare diseases is quite large.

Nevertheless, in 1972 such technologies as recombinant DNA and DNA sequencing were in their earliest stages. So Drs. Friedmann and Roblin concluded that it was premature to begin gene therapy studies in humans because of lack of basic knowledge of genetic regulation and of genetic diseases, and also for ethical reasons. They did, however, propose that studies in cell cultures and in animal models aimed at development of gene therapies be undertaken. Such studies – as well as abortive gene therapy studies in humans – had already begun as of 1972.

Early gene therapy studies in academic and government laboratories

In the 1970s and 1980s, researchers applied such technologies as recombinant DNA and development of viral vectors for transfer of genes to cells and animals to the study and development of gene therapies. In the 1990s, several research groups conducted FDA-approved human studies of gene therapies, based on this technological development and increased knowledge of genetic diseases. These highly experimental studies took place in academic and government laboratories.

For example, in 1990, the first approved U.S. gene therapy trial was conducted at the National Institutes of Health (NIH), led by William French Anderson, M.D. The results of this study as of four years after treatment were reported in a 1995 publication in Science.

Two young children were treated for severe combined immunodeficiency (SCID) due to genetic defects in the gene for adenosine deaminase (ADA). This disease can be successfully cured via marrow transplantation from a lymphocyte antigen-matched ADA+ sibling, in order to provide immunocompetent ADA+ immune cells. However, if children with ADA-SCID do not have such a donor, this is not possible. Enzyme replacement with bovine ADA conjugated to polyethylene glycol can provide noncurative, but lifesaving treatment. The children treated by Dr. Anderson and his colleagues did not have the appropriate donors, and did not do well with enzyme replacement therapy.

The researchers treated them by isolating T cells from their blood, inducing the T cells to proliferate in vitro, and transducing the T cells with a retroviral vector carrying a wild type ADA gene. The vector (as is typical of retroviruses) integrated into the DNA of the T cells; this integration required proliferation of the T cells. The vector transduced T cells were expanded in culture, and reinfused into the patients after 9-12 days.

Gene therapy infusions continued over a two-year period for both patients, and were then stopped. However, ADA expression, the presence of integrated vector in patient T cells, and clinical benefits continued over at least a four-year period. The researchers concluded that the initial trial demonstrated the potential efficacy of using gene-corrected autologous cells for treatment of children with ADA-SCID. They therefore enrolled 11 additional children in gene therapy studies, using different retroviral vector designs and different target cell populations.

Beginning in 1992, a European group working in Milan, London, and Paris used gene therapy to treat children with severe combined immunodeficiency–X1 (SCID-X1) (also known as “bubble boy disease”). SCID-X1 is an X-linked inherited disorder that results in an early block in T and natural killer (NK) lymphocyte differentiation. This is caused by mutations of the gene encoding the γc cytokine receptor subunit of interleukin-2, -4, -7, -9, and -15 receptors. These receptors participate...
As was discussed in Chapter 1, issues with viral vectors caused many of the problems with early clinical studies of gene therapy—including several tragic deaths and the development of leukemia in several patients who received gene therapies. Researchers had a limited knowledge of the biology of viral vectors, and their interactions with host cells, tissues, and physiological systems. Thus the development of improved vectors, and improved understanding of how these vectors interact with host physiology (especially in the diseases that are targets for gene therapies), have been cited as critical for the development of safe and effective gene therapies.

This chapter focuses on the development of vectors for gene therapy, especially improved vectors designed to circumvent the problems seen in early clinical gene therapy studies.

**Retroviral vectors**

**Gammaretroviral vectors**

Viral vectors for gene therapy may be divided into two classes: integrating vectors and non-integrating vectors. Integrating vectors insert themselves into the DNA of the host genome. The advantage of using integrating vectors is that when host cells replicate their chromosomal DNA and divide, they replicate the vector DNA as well. Thus any gene product that is expressed by the vector DNA continues to be expressed in new cells that arise via cellular proliferation. In contrast, non-integrating vectors used in gene therapy would be lost as the result of any cellular proliferation. Thus non-integrating vectors should be used in tissues in which cell division does not occur. Fortunately, cells in many tissues in mature individuals do not appear to undergo division, and may thus be good targets for gene therapy involving non-integrating vectors.

An important disadvantage of using an integrating vector—which was seen in some early gene therapy studies—is that the vector DNA may insert itself into or near cancer-promoting genes and activate them. As discussed in Chapter 1, the retrovirus-based vector used in clinical
studies aimed at correction of SCID-X1 inserted itself—in two cases—into the LMO2 oncogene, which is associated with childhood leukemia. This resulted in activation of the oncogene, which was thought to be the trigger for the development of leukemia.

The initial clinical studies in ADA-SCID and SCID-X1 discussed in Chapter 1 used vectors based on gammaretroviruses. Gammaretroviruses are members of a genus of retroviruses that includes murine leukemia viruses (i.e., retroviruses that infect mouse cells and can cause leukemia in certain laboratory mouse strains). The gammaretrovirus that was used in early gene therapy studies was based on Moloney murine leukemia virus (Mo-MuLV).

Retroviruses are RNA viruses that, after infection of host cells, are reverse transcribed into DNA by the reverse transcriptase enzyme that is encoded in the viral genome. The resulting DNA genome, known as a provirus, is integrated into the chromosomal DNA of the host.

Gammaretroviral genomes are considered “simple” retroviral genomes because they contain few genes as compared to more complex retroviral genomes. The structure of a gammaretroviral DNA (integrated into a host genome, and oriented from the 5′ to the 3′ direction) is shown in Figure 2-1. The three genes encoded by the virus are—in order—gag, pol, and env. Gag (“group specific antigen”) encodes the structural genes of the packaged viral capsid. Pol (“polymerase”) encodes reverse transcriptase, as well as the viral integrase, the enzyme responsible for the integration of the provirus into the host genome. Env (“envelope”) encodes the viral envelope glycoprotein that covers the surface of the packaged virus, and is necessary for entry of the virus into the cell. At the 5′ and 3′ ends of the inserted DNA genome are the 5′ and 3′ long terminal repeats (LTRs), which comprise important regulatory sequences.

In particular, the 5′ LTR includes the viral promoter, which enables transcription of the viral genome. The 3′ LTR includes a polyadenylation site, which enables the addition of a polyA tail to the transcribed messenger RNA (mRNA) transcript, which is important for the stability of the mRNA. The genome also includes a packaging signal (ψ), which is necessary for packaging of viral RNA into a virion.

For creating a gene therapy vector, a desired gene to be expressed in the host genome is inserted into the retroviral genome, replacing the viral genes. In order to produce viral particles that contain the vector, researchers must create “packaging cells” that contain a provirus that expresses the three retroviral genes, but cannot be packaged into virions. The packaging cells are then coinfected with the vector.

In a simple version of a packaging cell, illustrated in Figure 2-1,
CHAPTER 5: Gene Therapy for Other Rare Diseases

Hemophilia and gene therapy

As we discussed in Chapter 4, ophthalmological diseases (including several rare genetic diseases and AMD) constitute a major target for companies working to discover, develop and commercialize gene therapies. However, gene therapies for rare and more common diseases that affect organs and tissues other than the eyes have also been emerging from academic and government laboratories to commercial companies. This chapter will focus on gene therapies for rare non-ophthalmological diseases, and Chapter 6 will focus on gene therapies for more common non-ophthalmological diseases.

Among gene therapies for rare diseases that affect organ systems outside the eyes, an important focus for near-term commercial development is hemophilia. Hemophilias represent a type of bleeding disorder. Bleeding disorders are a group of conditions that involve the inability to form a proper blood clot. \(^{114}\) They result in extended bleeding after injury, surgery, trauma or menstruation. Difficulties in clotting can be caused by defects or deficiencies in blood platelets and/or in clotting proteins, which are also called clotting factors. There are 13 human clotting factors. If any of these proteins is defective or deficient, a mild, moderate or severe bleeding disorder can result.

Hemophilias are genetically determined bleeding disorders, as is von Willebrand disease (VWD). VWD is a genetic disorder caused by deficiencies or defects in von Willebrand factor (VWF), which is a clotting protein. VWD, an autosomal recessive trait, is the most common bleeding disorder, which affects up to one percent of the U.S. population. VWD is currently treated with a variety of biologic and pharmaceutical agents. Gene therapy for VWD is being investigated by academic laboratories; these studies are early-stage. \(^{115}\) There are also ultra-rare genetically determined bleeding disorders that involve deficiencies in other clotting factors.

Hemophilias include hemophilia A and B. \(^{114}\) Both are X-linked recessive disorders, and thus affect mainly males. Hemophilia A involves a deficiency in factor VIII (FVIII), and hemophilia B involves a deficiency in factor IX (FIX). Both of these are clotting factors that are made in the liver.

According to the U.S. Centers for Disease Control and Prevention, hemophilia occurs in approximately one in 5,000 live births, and there are approximately 20,000 people with hemophilia in the United States, representing all races and ethnic groups. Hemophilia A is four times as common as hemophilia B, and more than half of patients with hemophilia A have severe hemophilia.
Survey on Gene Therapy

(n=88)

Please classify your organization

- Top 20 pharma: 14.3%
- Mid-size pharma: 7.7%
- Small biopharmaceutical company: 9.1%
- Research products company: 4.4%
- Diagnostics company: 7.7%
- Academic lab or center: 34.4%
- Government or NGO research center: 5.2%
- Contract research organization (CRO), contract manufacturing organization (CMO), etc.: 6.1%
- Other: 11.0%

Do you work in any aspect of discovery and development of gene therapies or of research products or enabling technologies (e.g., vectors, CRISPR/Cas9, TALENS) to be used to design gene therapy?

- Yes: 32.5%
- No: 67.5%

For which types of disease(s) are your efforts directed to?

- Blood diseases (e.g., hemophilia): 18.3%
- Neurological diseases (e.g., Parkinson's disease, motor neuron disease, Huntington's disease): 16.7%
- Cancer (e.g., CAR-T adoptive immunotherapy for cancer): 5.0%
- Other rare diseases: 68.3%
- Heart failure: 8.3%
- Osteoarthritis: 3.3%
- Other: 15.0%

Which aspect of gene therapy do you work on?

- Discovery and/or development of gene therapies: 56.3%
- Enabling technologies: 43.7%