New Technology Commercialization Opportunities and Challenges – Gene Therapy

by groupH

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WHAT IS IT?

- Gene therapy is a technique that modifies a person's genes to treat or cure disease; gene therapy can replace, inactivate, or introduce a gene
- There are two broad categories of gene therapies, those that are delivered via a viral vector and those that are delivered without a viral vector

Viral vector-based gene therapies

- **AAV-based gene therapy** is an approach to deliver a therapeutic gene into a patient by packing the transgene inside of an adeno-associated viral (AAV) capsid, using the viral capsid as a targeting system to find and deliver the gene to the appropriate tissue type; multiple AAV-based gene therapies have been approved in the US and EU
- **Lentiviral gene therapy** is similar to AAV-based gene therapy but uses a retrovirus to deliver the transgene by integrating into the patient's genome. Recently, lentiviral approaches that do not integrate are also being attempted in clinical trials

Non-viral vector-based gene therapies

- **Gene editing** is an approach to gene therapy that directly modifies the patient's genome, either by correcting a disease-causing mutation or by inactivating a disease-causing gene. Gene editing is at an early stage, and no gene editing approaches have been approved to date in the US or EU. Genome editing is typically performed with DNA editing systems such as CRISPR-Cas9, zinc finger nucleases (ZFNs), and transcription activator-like effector nucleases (TALENs)

COMMERCIALIZATION OPPORTUNITIES

General

- Gene therapy is especially well-suited to addressing diseases where a single gene is known to be the causative agent
- The gene therapy approach provides the ability to address previously undruggable targets, bringing new therapeutic options for difficult-to-treat diseases (for example, Spark's Luxturna for Leber congenital amaurosis and Novartis' Zolgensma for spinal muscular atrophy)

- To date, gene therapy has been applied to monogenic disorders with extremely high unmet need; these inherited conditions can disproportionally impact pediatric populations, meaning this first wave of marketed gene therapies have brought life-changing benefit
- Gene therapies can bring a step-change in therapeutic profile over traditional alternatives:
    - Gene therapy has the potential to deliver durable (multi-year) efficacy from a single treatment because the genetic payloads are generally long-lived, enabling favorable systems economics that justify high pricing
    - Gene therapy can bring convenient one-time dosing in diseases that are managed chronically by the current standard of care, bringing convenience to patients and caregivers
    - Gene therapies have the built-in advantage of 100% therapy adherence; poor adherence to chronic therapy ultimately hurts treatment outcomes
- Successful launches of Luxturna, Zolgensma, and others have increased confidence in gene therapy, and have paved regulatory and reimbursement pathways, thereby lowering the risk for future therapies
- Once developed, gene therapy platforms are applicable to many diseases across multiple therapy areas, providing learning synergies for developers; furthermore, there are time-saving efficiencies for manufactures applying their platform across several diseases

Viral vector technology progress

- The advent of AAV vectors has brought many advantages to the field: (1) wildtype AAVs are non-pathogenic and therefore bring a good side-effect profile, (2) recombinant AAV vectors do not typically integrate into the host genome and so do not bring a risk of oncogenesis, and (3) AAV serotypes have the ability to infect different tissue types such as muscle, liver, kidney, lung, heart, eye and the CNS (tropisms). For these reasons, AAV vectors are preferred for *in vivo* treatments and are the dominant gene therapy platform
- In contrast, lentiviruses integrate their payload into the host genome. This brings an oncogenesis risk but prevents the dilution of genetic material over time due to cell division which greatly increases persistence. For these reasons, lentiviruses are preferred for *ex vivo* gene-modification, such as manufacturing CAR-T cell therapies (described separately here), and bluebird bio's Lentiglobin in development for β-thalassemia and sickle cell disease
- The next gene therapy technologies are hoping to bring a number of benefits:
    - New AAV capsids with new and/or improved tissue tropisms that will enable gene therapies to target new tissues and therefore treat new diseases and/or target tissues more specificity with fewer off-target tissue activity
    - Approaches to reduce AAV immunogenicity that aim to increase the eligible patient population and enable repeat dosing

    - Lentiviral vectors that do not integrate into the host genome and therefore eliminate the oncogenic risk

- Targeting new tissues and reducing immunogenicity are important ways for gene therapies to open up new opportunities, bring the ability to treat new diseases, reach a larger proportion of patients, enable re-dosing, and thereby differentiate themselves from other gene therapies

Expanding beyond rare diseases

- While we expect the development of gene therapies in rare diseases to continue (such as hemophilia, lysosomal storage disorders, metabolic disorders like PKU, ophthalmic disorders like Leber's hereditary optic neuropathy and retinitis pigmentosa, and musculoskeletal disorders like muscular dystrophy), the next wave will expand into 'rare-adjacent' diseases (such as β-thalassemia and sickle cell disease) and into 'non-rare' diseases (such as wet AMD, diabetic retinopathy, osteoarthritis, and Parkinson's disease). There is great potential for gene therapy in indications where (1) there are few effective treatments and/or (2) the current SoC is already premium-priced and the administration is inconvenient and/or resource intensive (i.e., where long duration of action would be beneficial)

Gene editing

- In contrast to gene therapy, gene editing directly changes an individual's DNA. Gene editing tools can be used to correct a disease-causing mutation or inactivate a disease-causing gene, and also have the potential to alter gene expression regulation and epigenetic modifications
- Therefore, the breadth of diseases that can be treated with gene editing is far broader than with gene therapy
- Gene editing brings the promise of treating, curing, and potentially even preventing genetic diseases
- Numerous gene editing platforms are in early-stage development[1]: (1) CRISPR–Cas9 systems are the simplest and expected to drive the expansion of the gene-editing pipeline, (2) zinc-finger nucleases (ZFNs), pioneered by Sangamo, were the first gene editors to enter the clinic and bring improved targeting precision, (3) Cellectis is using transcription activator-like effector nucleases (TALENs), (4) Precision Biosciences is working with a gene-editing meganuclease platform, and (5) bluebird bio is advancing with megaTALs, a hybrid of the TALEN and meganuclease machinery
- *Ex vivo* applications (such as β-thalassemia and sickle cell disease and allogeneic CAR-Ts for oncology), where off-target cell editing is inherently limited, are likely to be first, followed by *in vivo* therapies for rare diseases and infection (such as HBV and HIV)

COMMERCIALIZATION CHALLENGES

General

- AAV-based approaches suffer from several drawbacks that are intrinsic to the approach:
    - Firstly, the AAV episomes that carry the transgene are not replicated and can be diluted over time by cell turnover, decreasing durability and preventing the gene therapy promise of a long-term 'cure' from being achieved
    - A limited amount of DNA can fit into the AAV capsid (~5,000bp), which confines potential applications to short genes or genes that can tolerate truncation, ultimately restricting the types of diseases that can be treated
    - Between 30% and 70% of patients may have pre-existing neutralizing antibodies (depending on AAV serotype)[2]. For example, before treatment with Zolgensma, patients receive an AAV9 antibody test which may make them ineligible of therapy if titers are too high. These pre-existing neutralizing antibodies can significantly reduce the revenue potential and limit the business case for new opportunities
    - Furthermore, anti-AAV neutralizing antibodies can develop after dosing, meaning that a gene therapy cannot be re-administered
    - The range of tissue tropisms of different AAV serotypes is limited, meaning that the range of diseases that can be tackled is also limited. Furthermore, AAV vectors display tropism to more than one cell type, which risks off-target delivery to incorrect cell types. This may cause adverse events to arise, as well as prompt scrutiny from physicians and regulators if the therapy is delivered systemically rather than locally
- Given that gene therapies are dosed once, they can be disruptive to a provider's economics, including loss of repeat administration fees for chronic therapies and less frequent touchpoints with patients, which may disincentivize prescribing
- Long trials are needed to validate claims of multi-year durability and safety to regulators and payers, leading to a commercial trade-off for manufacturers between time to market vs. robust evidence
    - Regulatory bodies are closely scrutinizing durability claims (for example, BioMarin's ValRox received an FDA complete response letter because Factor VIII levels declined after 12-18 months in some patients, prompting the FDA to request 2 full years of data for each patient)
    - Payers expect the data package to reflect claims about durability, and will likely require multi-year follow-up data, depending on the indication and value proposition

- Traditional reimbursement models are not conducive to large upfront payments necessary for single-administration therapies that provide long-term benefit
- Early gene therapies (1990s) had troubling safety issues such as leukemia that are well-known among physicians. To this day, many physicians are hesitant to be the first among their peers to prescribe gene therapies out of an abundance of caution
- Manufacturing AAV therapies can be daunting: generating stable cell lines is time consuming, technically challenging, expensive, and complicated, and provides multiple avenues for failure

Gene editing

- Gene editing technology is still in its infancy, and there are conflicting reports on off-target mutations that could stall commercial viability for the class, directly undermining gene editing's promise of high specificity. Advances in these platforms need to reduce off-target edits without reducing on-target editing performance
- Questions remain about the immunogenicity of different editing technologies, especially CRISPR-Cas9 systems since they are derived from bacteria[1]
- Also, the long-term effects of gene editing are unknown[1]

Expanding beyond rare diseases

- As gene therapies move from ultra-rare indications to larger indications and therapeutic areas with more diverse competition, they will likely face increased scrutiny from payers who may be strained by increased budget impact. 2019 analysis found that the high upfront reimbursement for these products means that the total costs could exceed what the healthcare system can manage[3]
- Also, payer experience with gene therapies is currently variable – payers at smaller plans may not yet have had a patient with a rare disease requiring gene therapy. Broader payer education will be necessary as the use of gene therapy expands
- Building manufacturing capacity for the significantly higher number of patients in 'non-rare' diseases will require considerable investment and risk

Impact of COVID-19

- In general, the use of gene therapies has been far less disrupted by COVID-19 than use of CAR-T therapies, since the treatment process is far less complex
- However, COVID-19 has increased competition for staff and resources at several levels:

- Many of the raw materials used to manufacture adenovirus-based COVID-19 vaccines (such as AstraZeneca's and Johnson & Johnson's) are the same as those used to manufacture gene therapies[4]
- Regulators and HTA committees are expected to be under resourced – stretched further while looking at COVID vaccines, convalescent plasms, etc[4]
- Gene therapy manufacturers have seen CMC inspections and BLA submission reviews delayed[4]

WHAT TO GET RIGHT

Route of administration and ecosystem

- The route of administration is closely tied to the target tissue, as is the choice of AAV serotype. Some gene therapies are given systemically and the AAV tropism targets the desired tissue (for example, Novartis' Zolgensma uses an IV-administered AAV9 vector that delivers the SMN gene to motor neuron cells). Others are administered locally to the intended tissue (for example, Spark's Luxturna is given as a surgical injection beneath the retina of each eye)
  - The eye is a popular target for gene therapies for several reasons: (1) it has limited immune surveillance meaning a reduced risk of antibody neutralization, (2) compartmentalization that significantly reduces the systemic spread of the locally-delivered gene therapy product therefore minimizing off-target tissue effects, and (3) it can be injected directly
  - However, given the number of gene therapies in development for eye / ophthalmic disorders, it is critical to think beyond the gene therapy product itself and focus also on building a broader treatment ecosystem. Administration of gene therapies can be difficult and fraught with technical challenges, and consequently only a small handful of physicians are certified to administer, which can create capacity constraints on delivering the therapy to patients in a timely manner. It is important to weigh trade-offs between broader roll-out to more centers to increase capacity, and the drawbacks of increasing investment in physician education even though there will be an eventual churn through the eligible population

Demonstrating manufacturing consistency

- Manufacturing gene therapies is challenging. The FDA is becoming stricter about manufacturing and is requiring additional data regarding manufacturing to ensure consistent scale-up from clinical to commercial manufacturing (for example, the FDA requested an analytical comparability strategy for bluebird bio's lentiviral Zynteglo and demonstration of manufacturing product from healthy donors, and issued a complete response letter for BioMarin's AAV ValRox due to concern over manufacturing consistency for scale-up between Phase 1/2 and Phase 3 studies)

Rare disease commercialization model

- For the time being, gene therapy developers need to be optimized for rare disease product commercialization (~80% of the 7,000 known rare diseases have a genetic basis) since rare disease product development entails unique requirements:
    - Gene therapy developers need to work closely with leading rare disease treatment centers since knowledge about these diseases is highly concentrated in only a handful of centers. Drug developers should seek input from therapeutic area experts early in the clinical development planning process to ensure they are using trial design attributes, such as endpoints, that are meaningful to the handful of clinician experts who will be running the trials
    - It is very important to align across internal functional teams on how to properly engage the very small number experts for a rare disease, since it is easy for multiple teams to unknowingly engage experts simultaneously, potentially and unnecessarily over-burdening them. Expert engagement approach and messages should be highly coordinated and resulting insights should be additive rather than duplicative
    - Developers need to have early and frequent interfaces with patient advocacy groups by including these groups on their advisory panels to help drive initiatives such as the development of patient registries and enrolment in clinical trials to speed-up development timelines
    - New rare disease therapeutics will need to be supported by a range of added value services and solutions which will support the performance of the brand, whether that be by enabling earlier diagnosis and intervention, increasing access to treatment, easing the financial burden, supporting adherence or helping to overcome some other barrier that currently limits outcomes
    - Several manufacturers provide resources to support registries focused on rare disease and gain the ability to mine the data for insights over long periods of time; working alongside medical colleagues to support existing patient registries (or perhaps looking to begin a new registry if required) can be key to finding a way to quantify the market dynamics of a rare disease

Speed to market

- Being early to market is critical – since most gene therapies bring multi-year efficacy and target rare diseases with inherently small patient populations, it is possible for a competitor therapy to quickly churn through the available prevalent patient population. This creates a 'winner-takes-all' dynamic, in which the first product treats the currently available patients, with subsequent therapies treating only a share of newly diagnosed patients. Thus, later entrants may find there is little commercial potential remaining

Pricing and reimbursement

- While payers may have been initially more accepting of lower quality evidence for new products in rare diseases (driven by the high unmet for new therapies and small number of patients available for trials), the high price points for recently approved gene therapies has meant that evidence generation remains key (see groupH's post on EU Payer Opinion on Assessing Value in Rare Diseases). Duration of effect, pricing of alternative treatments (where available) and cost offsets from lower healthcare utilization from improved outcomes and/or less frequent administration all need to be adequately quantified.
- Developers need to initiate dialogue with payers early in development to drive successful HTA assessment in EU and pricing in US since payers often have unique needs compared to providers and regulators. For example, elements of the data package such as endpoints that are important to payers are often different than those valued by providers or regulators, and these elements need to be built into the pivotal study design in order to support payer's clinical and economic value proposition
- Novel reimbursement models need to be considered, especially as more therapies are approved for larger indications, to ease the burden of payment and ensure access and reimbursement is granted. Risk-sharing and capped annuity approaches have been considered, but come with implementation challenges in many markets (see groupH's paper on The Payers' Perspective on Gene Therapies)

WHAT CAN GROUPH OFFER?

groupH has conducted…

- Indication landscaping (inc. market access) for rare genetic disorders in US, EU5 + Canada
- Numerous opportunity assessments for gene therapies in US and Europe including epidemiology, market landscape, commercial forecasting, pipeline and competitor analysis, and market access

- Market access landscape assessment for gene therapy to understand payer perspectives on transplant safety, efficacy, and payment logistics, how payers can better interact with manufacturers, payer perceptions for care delivery network structure, and payer expectations for evidence generation, and to elucidate payer expectations for payment and engagement in MEAs
- Opportunity and market access strategy (US and EU4) for a gene therapy for rare ophthalmic disease, including patient focus groups, physician interviews and payer Advisory Board
- Strategic competitor role-play workshop to understand how competitor activity could shape the future treatment landscape, and characterize future patient segments and remaining unmet needs
- Scenario planning workshops to understand the implications of different possible future rare neurology disease markets to the clinical development plan and TPP for our client's early-stage products

groupH can conduct…

- Technology scans of next-gen gene therapy technologies (AAV, lentiviral, genome editing, novel vectors)
- Early TPP testing and development to optimize product positioning in the treatment landscape, refine value proposition, identify any commercial challenges or barriers to prescribing, and inform clinical strategy
- Robust opportunity assessments and forecasts incorporating physicians', patients' and payers' views
- Gene therapy pricing and reimbursement research to understand the payer landscape, characterize the value proposition, understand the payer value elements in the TPP, assess the evidence generation against payers' needs and understand the implications of any gaps, understand the price potential and rationale and any potential access restrictions for given price points, and identify any potential market access hurdles and develop potential approaches to overcome these hurdles

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