# The Challenges of Gene Therapy

## Establishing Trust

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For any emerging biotech company with a novel platform technology, establishing trust in that platform is essential to building momentum and long-term success. Trust must be established with multiple stakeholders, including potential licensing partners, investors, regulators, clinicians and, foremost, with patients.

In the gene therapy and genome editing space, these concerns are heightened by the unprecedented manipulation of the body's basic building blocks, where failures of past programs effectively delayed progress for decades. Building a meticulous plan to establish evidence of safety and of clinical utility in a stepwise manner is thus of heightened concern for companies advancing technologies into this arena.

As companies develop and expand their pipeline programs, they must often consider the tradeoffs between pursuing low-impact / low-risk programs with commensurately moderate returns on investment against high-impact, high-reward programs with considerable technical risks that accompany it. The ramifications of those decisions affect the ability to attract partners and investors. While there are notable benefits to pursuing low-risk programs, such as proving the technical capabilities of a technology while de-risking any early return on the investment, those benefits must be weighed against the potentially higher impact that a truly differentiating, disruptive gene therapy or genome editing program could have for patients, and by extension for investors and partners.

Crafting a gene therapy or genome editing portfolio strategy isn't an "either/or" situation, and there is no single best program. Instead, companies must consider their own technical differentiation as well as their investors' appetites for risk and the commercial viability of their programs. Ideally, they strike a balance between risk undertaken and contributions to advancing the science as well as downstream returns.

## Introduction

Since gene therapy began to transition from the realm of theory to the realm of possibility in the 1990s, perceptions of its potential have pendulumed back and forth between great excitement for "magic bullet" cures and trepidation as therapies evolved and experienced setbacks. While not unusual in an innovative field, the widely changing opinions contributed for a long time to a perception of outsized risk among investors, potential partners, and physicians and patients participating in clinical trials. Given that backdrop, progress in recent years has been remarkable. As gene therapies and genome editing products begin to enter the market, innovator companies who are able to establish trust in the efficacy and safety of their platform technologies will be positioned to lead the field.

## The State of Gene Therapy Today

Gene therapy is hitting an inflection point. Globally, four gene therapy products have received regulatory approval. The EU has approved Glybera, Imlygic® and Strimvelis™. In August 2017, Kymriah™ (tisagenlecleucel) became the first gene therapy approved in the US. Kymriah, a cell based gene therapy, treats acute lymphoblastic leukemia, a rare, aggressive hematologic cancer. Kymriah's efficacy benefit was unprecedented, demonstrating 83% complete response despite being studied in a heavily previously treated population. Additionally, Luxturna™ (voretigene neparvovec) by Spark Therapeutics, received FDA priority review for patients experiencing inherited retinal disease linked to RPE65 mutations and is poised to become the first FDA-approved in vivo gene therapy. In Phase 3, 93% of patients achieved a gain of visual function and earlier studies suggest durability of over three years in a condition with progressive vision loss. These therapies deliver substantial clinical benefits, for diseases that had lacked compelling therapeutic options.

A flurry of additional approvals is expected over the next several years, and earlier stage clinical trials are underway throughout the world. As of September 18, 2017, ClinicalTrials.gov listed 2,825 gene therapy studies, of which 1,098 were active, enrolling by invitation, or recruiting.

These therapies have the potential to address previously intractable diseases and substantially alter the face of medicine in the coming decades. While most in the space shy away from the term "curative," gene therapies have the potential to confer unprecedented durable clinical benefit for patients previously lacking treatment options.

## Risks vs Rewards

Despite the progress made in recent years, significant challenges endure, many of which involve the technical challenges unique to the underlying technologies. Will the levels of knockdown or protein expression deliver clinically meaningful benefit? What will be the durability of benefit? What will be the true specificity of genome editing technologies as they enter the clinic? Independent of the underlying modality, what types of long-term safety risks exist? Each of these uncertainties directly contributes to the risk-benefit of developing novel gene therapies.

Gene therapy and genome editing – which introduces new genes extrachromosomally or modifies a patient's DNA – are set apart from other therapies for the simple reason that once administered, the effects are presumed durable, and potentially permanent. That presumed permanence means that gene therapy or genome editing holds curative potential for many conditions. "Presumed" is the operative word. At approval, there is anticipated to be a paucity of long-term data documenting the duration of benefit for gene therapy. No one knows how long those added or modified genes will remain effective, making it difficult to truly predict the value of these therapies to patients, and in turn to payers (See Payers are Watching).

Additionally, off-target effects are also anticipated to remain poorly understood in the near-term given that genomic integration of gene therapy or off-target editing may go undetected for decades. There then remains the concern that, even at the time of regulatory approval and launch, these treatments may trigger unforeseen complications

## Payers are Watching

Payers are watching the evolution of gene therapy carefully, weighing the costs and benefits against those of current treatments. In 2012, Glybera® became the first gene therapy approved in the EU. Developed by UniQure and marketed by Chiesi, this one-time treatment for lipoprotein lipase deficiency (LPLD) came with a million dollar price tag that quickly labeled it as the "most expensive" therapy, but was arguably comparable to that of prolonged use of typical orphan drugs. Although LPLD affects only about 200 people in all of Europe, payers perceived the price to be unsustainable. UniCure does not plan to renew Glybera's marketing authorization, after treating only one patient commercially in the past five years.

While Glybera faced a plethora of challenges, including tenuous clinical benefit, its struggles to achieve reimbursement highlights that our reimbursement systems are poorly equipped to attribute value to and pay for one-time, durable therapies. While pay-for-performance models are gaining traction, as seen with Strimvelis and Kymriah, these typically are designed to assess early response to therapy rather than durable benefit. Consequently, in the absence of long-term data, payers are exposed to considerable risk and reluctant to truly account for the central value proposition of gene therapies today – long-term clinical benefit.

Solving the reimbursement question is one of the most challenging hurdles that must be overcome before gene therapy can gain widespread adoption and commercial viability, particularly for exceptionally rare conditions. Recognition broadly exists that our current framework disincentives investment in potential cures, and considerable dialogue is ongoing across the industry to explore innovative payment models or policy solutions that might distribute risk and enable access to curative treatments.

Source: ClearView Healthcare Partners

in the distant future. This risk suggests that early gene therapies targeting pediatric indications should face disproportionately high scrutiny, particularly if they target established, efficacious conventional therapies.

Biotech companies, therefore, must innovate with these additional concerns in mind. When pursuing gene therapies, they must think not only about the clinical feasibility and commercial viability of their products, but also about whether the risks and rewards are justifiable, not only to patients and payers, but also to partners and investors. Importantly, with each program and each study, we will enrich our shared understanding of these technologies, which in turn changes the risk-reward equation and unlocks additional applications.

## "New" Doesn't Mean "Best"

Just as there's no single best pipeline portfolio strategy, there's also no single best technological approach. Early gene therapy products are often developed as in vivo, in which a DNA vector is delivered to patient cells through direct administration, while early genome editing products have been developed as ex vivo, wherein cells are modified outside a patient's body before re-introduction. Furthermore, there are a variety of genome editing technology platforms available (including zinc finger nucleases, TALENs, and the CRISPR/Cas9 system, among others), each offering alternate ways to modify a patient's genome and each with different levels of clinical and scientific validation.

Each approach has its relative merits but, despite bursts of media hype, no single platform has emerged as the clear winner. Until one gains repeated clinical validation, it will be impossible to determine which approach is most efficient and effective for developers, for investors, or most of all, for patients.

As with most biotechs, gene therapy and genome editing companies have formed around technologies, which create a platform-driven incentive structure. As companies develop young, exciting, but relatively invalidated technologies, they face the challenge of introducing a potentially disruptive technology to a highly regulated industry. They need to capture momentum and investment, but to do so they need early successes – they need to validate their platform – and often seek to do so by minimizing technical risk outside the platform itself.

For companies, this predilection to innovate around a specific technology platform transforms portfolio decisions from a clinical decision based predominantly on unmet need to a technology decision in search of proof of concept. To minimize this constraint, companies trying to validate their platforms may consider diversifying their pipelines. Diversifying enables companies to broaden their therapeutic targets, to derisk their platform technology and, in so doing, develop the "multiple shots on goal" approach that many investors find most compelling.

On the investor side, there is a tendency to pool around the latest technology. What's new, however, may not be what's best - and it's unlikely that any platform technology could achieve clinical validation in the same timeframe as initial investor hype. This creates a "flavor of the month" approach that may prove deleterious to the field. While it spurs tremendous interest among researchers and in the media, it often prioritizes a rapid march to the clinic over the validation and maturation of the technology. Ultimately, clinical success will be the barometer against which these platforms are judged, and with that lens in mind, companies would be wise to ensure their technologies are robust.

There's another danger of flocking to trendy technology. If companies follow investors' dollars and gravitate to new, high-risk technologies too soon, before those technologies develop a

foundation of evidence, they may, in essence bet their patients' welfare and the company itself on very high-risk technologies. Any major, public setbacks or failures that may ensue can severely erode stakeholder trust more broadly in the field.

## Where to Go Next?

Risk-mitigation has been a key determinant of the first generation of diseases targeted, as many of the most advanced clinical programs target monogenetic diseases with established protein replacement therapies. For these indications, which genes to replace and how to measure the benefits of the therapy are well-established. These programs focus on using precedence to minimize developmental uncertainty and incrementally improve care for patients.

Low-risk development programs that build on established knowledge go a long way toward fostering trust by showing that a gene therapy or genome editing technology is safe and efficacious in conditions in which there is less ambiguity. Such low-risk programs help companies gain stakeholders' trust early in development, which generally improves their funding outlook. Eventually, low-risk programs minimize regulatory and technical uncertainty and by extension offer an earlier return on investment for investors. These programs may bolster startup gene therapy companies' chances of achieving validation by accelerating development and demonstrating clinical proof of concept.

High-impact programs, in contrast, hold the promise of delivering therapeutics that provide significant differentiation. Substantial improvements in clinical care may be possible when companies bring to bear the full potential of genome editing against demanding areas of unmet medical need. These programs may truly transform outcomes for patients, tackling unmet needs that may be heretofore unsolved, helping showcase the transformative potential of genomic medicine. But, high-impact typically also means high-risk. Technical and regulatory risks are elevated, and setbacks for programs at this level aren't uncommon. Challenges may be amplified in ways that erode investor confidence and hamper further developmental opportunities. Those that succeed, however, have the potential to generate disproportionate returns on investment.

As gene therapy companies and technologies mature, they must strike a balance between minimizing risk by focusing on modest

**Therapeutic Modalities**

| THERAPY MODALITY | *In-Vivo* Gene Therapy | *Ex-Vivo* Genome Editing | *In-Vivo* Genome Editing |
|---|---|---|---|
| DESCRIPTION | *DNA directly into patient cells but not into the genome* | *DNA manipulated externally and placed into the genome* | *DNA directly into patient cells and their genome* |
| EXAMPLES | uniQure's Glybera approved in the EU for familial lipoprotein lipase deficiency | Novartis' Kymriah approved in U.S. for acute lymphoblastic leukemia | Sangamo's SB-FIX/SB-318/SB-913 enrolling first-in-human trials in the U.S. for hemophilia B and Mucopolysaccharidosis Type II (MPS II) respectively |
| | Spark's Luxturna in U.S. pre-registration for RPE65 inherited retinal disease | GSK's Strimvelis approved in EU for ADA-SCID | |

Source: ClearView Healthcare Partners

improvements and likely returns versus maximizing impact through moon shot programs with high risk and compelling rewards. They must weigh their portfolio decisions carefully. Ideally, they will select a mix of programs and targets that not only are technically feasible but that also have the potential for an attractive return on investment.

## Development Challenges and Implications

Hybrid development strategies can blend the best of both high- and low-impact approaches, to create a stronger, more resilient value proposition to investors. Balancing their pipeline portfolio between higher-impact and lower-risk approaches can generate near-term returns and build trust with potential partners and investors as well as with physicians and patients who may participate in clinical trials.

Before designing your approach, consider these questions:

- What are our priorities as we build our product pipeline?
- What's the appropriate balance between investing in low-risk/modest-reward programs versus those with high-impact/high-risk?
- What is the appropriate balance between using the existing technology as-is to advance a pipeline versus re-investing in advancing the technology further?
- How can we build sustainable businesses through a balanced portfolio?
- What roles will biotech and pharma partners play in therapeutic development, regardless whether the platform advances?
- How do these questions change as the company gains stakeholder trust and begins to create value?

There's no industry-standard framework to address these questions. Individual companies must consider the broad options and implications themselves before beginning or advancing a gene therapy development program.

The therapeutic platforms that are advancing toward the market are creating a scientific renaissance, with the potential to bring disruptive, transformative change to how diseases are prevented, treated, and even cured. Accepting and understanding those changes, however, takes time.

The ideal portfolio, therefore, may be crafted in a way that supports scientific advances while also ensuring an attractive return for investors. As their underlying technologies mature and advance, companies will find themselves faced with ever-changing calculus in pipeline optimization. Companies that best balance risk, validation, and commercial opportunity over time may best attract forward-thinking investors and partners focused on truly transforming medicine through gene therapy and genome editing.

## What Now?

Success for any transformative technology rarely occurs overnight. Gene therapy has moved past the setbacks that beleaguered early programs and past the "fancy toy" connotations and "magic bullet" dreams of prior years, yet its immediate future remains clouded.

There are significant risks – not all of which are understood – and numerous stakeholders to be considered before commercially viable genomic therapies become mainstream. None-the-less, potential partners and investors are beginning to see gene therapy as a viable solution at the forefront of a novel realm of medicine that is

becoming a commercial reality. It is poised to become a part of mainstream medicine sooner, rather than later.

That leaves gene therapy developers with a conundrum: continue to perfect low-risk therapies that minimize uncertainty and maximize the chances of success, or advance platforms and pursue therapies that present high technical risk, but that offer game-changing, paradigm-shifting potential.

As gene therapy companies mature, they have the opportunity to do both, balancing their portfolios to generate modest returns on investment today, while pursuing less-understood science that offers the possibility of significant returns from more disruptive programs in the future. Balancing these alternatives enables stepwise building of knowledge and trust, and earning trust is a continual process.

## About ClearView Healthcare Partners

**Founded in 2007, ClearView Healthcare Partners is a global strategy consulting firm serving the life science sector.** The firm combines international industry knowledge and deep scientific expertise across a range of therapeutic areas with an extensive network of external stakeholders to deliver practical and actionable recommendations to our clients' most complex challenges. The firm's projects include cross-functional support at the corporate, franchise, and product levels for pharmaceutical, biotech, medical device, and diagnostics companies worldwide.

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