Accelerating the Future of Medicine with Gene and Cell Therapy

What Comes Next

WORLD MEDICAL INNOVATION FORUM

gene and cell therapy

Mass General Brigham

With a handful of approvals and a triple digit pipeline, gene and cell therapies (GCT) are on the cusp of ushering in a transformation in therapeutics reminiscent to where we were with antibodies 25 years ago. Recent successes of GCTs in treating hematological malignancies and certain monogenic disorders have demonstrated the curative potential of a therapeutic modality that addresses the genetic root of disease. The field is developing rapidly, and powerful technologies, including innovations in gene editing and delivery, have enabled researchers to tap into a broader range of indications. This is reflected in the GCT pipeline, with clinical programs in development spanning beyond rare disease to include more common burdens, such as cardiovascular disease and type 1 diabetes. As a result, the potential impact of GCT is immense.

To shed light on the direction of this dynamic and fast-moving field, we spoke with nearly two dozen GCT leaders, spanning the academic, biopharma, and life science investor communities. What we heard was a mix of great optimism on the power and versatility of GCT along with realism on the tremendous complexity to bring these therapies to patients. From validation of vector technology to scaling of manufacturing, from regulatory frameworks to reimbursement schemes, our aim in this summary is to highlight key issues and opportunities brought up by GCT leaders as a starting point for discussions at the upcoming World Medical Innovation Forum and beyond.

> Autologous hematopoietic stem cell gene therapy has emerged as a promising approach. Across the companies in this space, it has been used in 10 or 11 diseases and resulted in a durable, potent effect.
> **CEO, cell therapy company**

Gene therapies

There are a number of gene therapy modalities with a range of tools – understanding which modality may dominate in the future

In understanding the future of GCT, one of the first distinctions is between gene augmentation (frequently referred to as gene transfer), whereby a new fragment of genetic code is added, and gene editing, whereby existing genetic information is modified. Of note is that gene editing still involves some form of gene transfer techniques because it often relies, for instance, on guide RNA fragments or encapsulated payloads. And finally there is durable gene silencing in which shRNA-based techniques play a prominent role.

While all agree that gene editing is less mature than gene augmentation, there is divergence among experts on which modality will dominate in the long-term. The advantage of gene editing is that it achieves a high degree of localization in the genome, whereas gene augmentation is more random. Supporters of gene editing extoll the ability to manipulate control of elements of the genome, while proponents of gene augmentation feel more comfortable with a clear first order effect on expression based on the addition of a new gene to the cellular milieu.

Enhanced delivery and manufacturing are highlighted as key to accelerating near term progress and scalability

The most immediate challenges for ongoing gene therapy programs are related to vector delivery and consistent, efficient manufacturing (which is also a challenge for cell therapies). Vector delivery faces twin issues of tissue/cellular targeting specificity as well as immune reactivity and safety. And because both are highly dependent on the details of the makeup of the vector in subtle ways this presents a significant challenge to quality in manufacturing processes already burdened by poor yields.

There is significant fragmentation in the field as dozens of PIs and small companies explore approaches to those vector and manufacturing issues. On the positive side, this allows for diversity of ideas and innovative approaches, on the flip side, many are reinventing the same things and stumbling down the same blind alleys. Some GCT leaders feel that a significant investment in delivery and manufacturing technology is merited, potentially under a shared umbrella. These are now beginning to occur under a number of settings: at the academic level (e.g. UPenn Gene Therapy Program), at the non-profit level (Odylia Therapeutics), in public-private partnership (NCATS/FDA Bespoke Gene Therapy Consortium), in CMO (launch of Resilience with $800M of capital), and in large pharma (Novartis/Novartis Gene Therapies, formerly AveXis, gene therapy platform).

Economic viability currently limits many applications for which gene therapy is a good fit

Ultra-rare genetic diseases are too small to be economically viable with a traditional development process, although in aggregate these diseases represent a large unmet need. What is needed is a "razor-razorblade" model that allows for streamlined creation of tailored payloads, something that the Bespoke Gene Therapy Consortium is trying to address as a public-private partnership bringing together the NCATS-NIH, the FDA, and a number of industry stakeholders.

> With new tools like base editing, we are able to make a single base change. It is a lot more elegant, and it opens up the opportunity to treat diseases resulting from point mutations.
>
> **CEO, gene editing company**

There is a balance between safety and innovation

The memory of Jesse Gelsinger's death in 1999 from an adverse reaction to a gene therapy trial remains vivid for stakeholders, and there is a high level of awareness of the impact it had on the overall gene therapy field in the early 2000s. However, with several products on the market, there is a sense that the growing maturity of the field makes a setback of a similar magnitude unlikely. All stakeholders we talked to felt that the current US regulatory environment is near the right balance between promoting safety and enabling innovation.

However, there were divergences between stakeholders on their view of how mature gene therapy is and how well the risks are understood. An area of concern is that titrating up the dose seems to be the default to get to therapeutic activity, which increases the risk for adverse events, when a potential alternative approach of working to improve delivery efficiency could be safer. Another sentiment that was occasionally expressed is that we are early in the experience curve, such that the benefit-risk ratio is most tolerable in diseases with severe consequences and high unmet need. Less severe diseases or those with reasonable existing treatments would be more suitable to be pursued once the safety of gene therapies is better characterized.

Cell therapies

An expanding pool of applications leveraging the hematopoietic system, slower progress elsewhere

So far, the main successes in cell-based therapies have heavily leveraged the hematopoietic system, with modified T-cells (CAR-T) enjoying multiple recent approvals. According to GCT leaders, this will continue for several reasons: the level of understanding of the biology is higher on the back of several decades of work on HIV and hematologic cancers, but also because hematopoietic cells can have effect in a "de-localized" manner, or self-home to the right environment. This leads to a broad range of potential applications down the road from replacing a missing enzyme in congenital disease to addressing certain CNS degenerative processes exploiting the crosstalk between the hematological system and the microglia.

Further down the road, but still near term, the main opportunity that comes up in discussions is the correction of systemic endocrine deficiencies, principally diabetes. There too, localization is less of an issue, though clearly encapsulation for immuno-protection of the implant is a major concern.

Blank cell technology remains elusive

A key area of debate and divergence is the applicability of allogeneic vs. autologous cell-based approaches. From a process and manufacturing perspective there is clearly a huge advantage to a standardized allogeneic product. However, most of the experts we talked to feel that except for very specific applications, the technology is not mature: we simply do not have the ability to maintain a "blank cell" that would be non-immunogenic, expandable, and customizable, and that capability is still far in the future.

One area where we heard speculation and interest is the potential for convergence of gene and cell therapy through actual in-vivo reprogramming of cells through a dedifferentiation/redifferentiation process akin to what is currently done ex-vivo with induced pluripotent stem cells or iPSCs. Clearly, many technical challenges will need to be resolved before this be done in the clinic, but several leaders we talked to felt that this may represent the long-term end game of the techniques being developed today.

There are bottlenecks for near term progress and scalability…

There is a lack of understanding and clarity on what are critical factors of efficacy and safety. A modified cell embodies a large number of variable characteristics, and the painstaking work of figuring out which are determinative for safety and efficacy is incomplete. This has knock-on effects on CMC, because there is no clear evidence on which features quality control should focus on as most relevant. This results in considerable back and forth between industry and regulators as each side tries to figure out what is good enough in a field where perfect reproducibility is an illusory goal.

…as well as long standing issues that will take time to resolve

It has proven very difficult to develop cell therapies that address specific spatial and structural organ dysfunction. Delivery to the precise location of the right type of cell is a challenge. In addition, this is not a feasible approach once an organ is severely damaged, at which time the right answer would be implantation of a replacement organ, either in the form of a transplant, or a newly grown organ -- the latter would require further progress from our current limited ability to work with organoids.

A key question in cell therapy for oncology is how to tackle solid tumors. Some companies are doing this well by using a TCR approach rather than a CAR-T approach.
Managing Director at leading VC

Common themes in gene and cell therapy

Although the modalities have distinct features, we heard several recurring themes that apply to both gene and cell therapy in how they stretch the classic drug R&D paradigm as well as present issues for reimbursement:

The GCT translational valley is especially wide

Relative to small molecule drugs or even traditional biologics, there is greater complexity in developing gene and cell therapies. There are many potential choices and tradeoffs in process decisions that are not optimized yet, and as a result, progress is highly dependent on a body of experience accumulated in the laboratory and in the clinic. Several sector leaders highlighted that there are structural impediments that slow this learning process.

One is the gap between academia and industry: like other therapeutic approaches, GCT technologies are often licensed out at a very early stage, but lack of continued tight connectivity with the originating PI who has the most experience with the technology can have a disproportionate impact on the ability to overcome inevitable development challenges. Sometimes, the PI follows the technology into industry, and that has been the case in some of the greatest success stories of the field. But often it is difficult for the PI to bridge that gap -- because they are committed to staying in academia and there are barriers (minimizing conflicts of interest, IP concerns) to their level of involvement with a private entity. Proposed solutions include better collaboration models between industry and academia; or alternatively, academia incubating assets to a further stage of maturity (e.g. first in humans (FIH) as was done by Penn for Kymriah).

Another impediment is that experiential know-how is a core competitive advantage in this field and an obstacle to publication of methodological findings by industry. As one of our interviewees told us, there is a lot of important empirical knowledge that they learn through informal discussions at conferences. Suggestions for improvement included greater pre-commercial (NIH) funding for technology development, or a role by the FDA in publicizing summary aggregate findings of the various signals they are observing in the industry. But there is also recognition that this circumstance may be an inevitable temporary by-product of the nature of the technology.

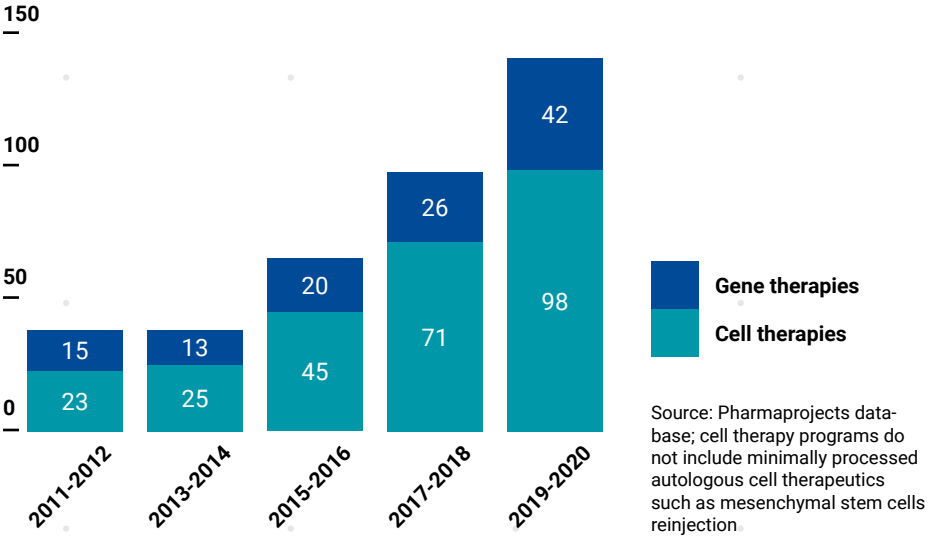
GCT could be accelerated with a fit-for-purpose regulatory framework

With some exceptions, GCT leaders we talked to believe that these therapies would benefit from a different regulatory framework from typical biologics. Two main elements drive this thinking. One is the potential for a high level of modularity of the therapeutics and manufacturing processes -- encapsulation, vectors, payloads, where certain standardized components would be validated and reusable with a limited regulatory burden. The second, which is especially applicable to autologous cell therapy, is that anchoring to a fully deterministic step process is sometimes impractical for an individualized therapeutic.

A rigorous framework appropriate to produce a monoclonal antibody will have to be stretched to be applied to a CAR-T process. So far, the regulators have been climbing the experience curve along with the industry, but there will come a time when an updated regulatory approach based on first principles of safety and efficacy, but specifically tailored for GCT will be optimal.

Rapid acceleration in cell and gene therapy activity in the last five years

of new programs entering clinical development in the US in each time period



Source: Pharmaprojects database; cell therapy programs do not include minimally processed autologous cell therapeutics such as mesenchymal stem cells reinjection

Sector leaders have a range of perspectives on reimbursement

At one end, there is a view that the argument is clear: a one-time cost for a curative therapy should be recognized as a good value, even while nominal prices appear higher. On that side, the assessment is that GCT will be a relatively small fraction of total health spending for the foreseeable future and that current systems are adequate to manage that with limited adjustments.

At the other end of the range, we find a concern that the reimbursement system was not built for one-time drug treatments, and that standard incentives and mechanisms could be stretched to the breaking point for patients, providers, and payers. In addition, there is awareness that public opinion as well public policy could affect the industry. This is driving an enduring interest in outcomes-based contracting that provides a stronger link to multi-year value, even though there is broad recognition that these mechanisms are hard to design and implement. It may end up that ex-US countries that have less fragmentation from a payer and/or EHR standpoint may be suited for piloting such models, as has been done with CAR-T therapies in Europe.

We have an unprecedented opportunity to transform medicine

With robust investment propelling the sector, a rapid maturation in both delivery technology as well manufacturing processes can be expected. At the same time, regulatory frameworks will evolve to be better aligned with GCT and this will open the doors to razor/razorblade models, in which platform components can be recycled between indications, and in particular for rare diseases which otherwise would not be commercially viable. Looking even further ahead, the dual approaches of gene and cell therapies may finally merge with actual in-vivo cell reprogramming approaches, either with gene editing or gene silencing.

The technical body of work required to move GCT from a quasi-cottage industry to a standardized industrial architecture is vast, and the risk that it is slowed by a pattern of many sub-scale duplications is real. It is the ambition of the World Medical Innovation Forum to accelerate the future by bringing together the GCT community in thinking about and advancing these issues.

> Cell therapy's applications in regenerative medicine will be in treating endocrine deficiencies, where the cells act as a biomanufacturing system to secrete a product while responding to their environment.
> **Managing Director at leading VC**

About the World Medical Innovation Forum

Mass General Brigham is pleased to present the World Medical Innovation Forum (WMIF) virtual event Wednesday, May 19 – Friday, May 21. This interactive web event features expert discussions of gene and cell therapy (GCT) and its potential to change the future of medicine through its disease-treating and potentially curative properties. The agenda features 150+ executive speakers from the healthcare industry, venture, start-ups, life sciences manufacturing, consumer health and the front lines of care, including many Harvard Medical School-affiliated researchers and clinicians. The annual in-person Forum will resume live in Boston in 2022.

The World Medical Innovation Forum is presented by Mass General Brigham Innovation, the global business development unit supporting the research requirements of 7,200 Harvard Medical School faculty and research hospitals including Massachusetts General, Brigham and Women's, Massachusetts Eye and Ear, Spaulding Rehab and McLean Hospital. Follow us on Twitter: twitter.com/@MGBInnovation

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Today, the promise of GCT seems limitless. As we discover the underlying genetic cause of more and more human diseases, the horizon keeps expanding.

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