CELL AND GENE

FROM the Medicine Maker

Presenting our special supplement to celebrate the fast-growing field of cell and gene therapies

Planes, Trains, and Autologous Therapies
The need for coordinated action to tackle challenges in cold-chain systems

Afraid of Banality, Driven by Beauty
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THE FUTURE AWAKENS

The new dawn for gene-edited medicines brings both optimism and caution

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CRISPR: A Modern Day Superpower?

The more we learn about gene editing, the greater the possibilities

One hot topic right now in gene therapy is CRISPR genome editing, which is being hailed as "the ultimate therapy," along with other mesmerizing superlatives. A number of pharma companies, including Beam Therapeutics, Editas Medicine, Caribou Biosciences, Vertex, and CRISPR Therapeutics, are pursuing further developments in the field. We saw the world's first approval of a CRISPR gene edited therapy in November 2023. There are also dozens of new research papers and announcements on the topic emerging every week that could affect gene therapies and other types of treatment modalities.

One example: researchers at Duke University have adapted CRISPR technologies for high-throughput screening of gene function in human immune cells, discovering that a single gene (BATF3) can be used to reprogram the network of thousands of genes in T-cells, enhancing their ability to attack and kill cancer cells. (I'm reminded of scientists augmenting Steve Rogers' ability to fight bad guys from all over the universe; hence the title.) "Master Regulator" and "Dark Genome" – these are not the members of a league of post apocalyptic supervillains, but terms coined by Duke when reporting on the work of its researchers (1). BATF3 overexpression, the researchers found, augmented the T-cells to the point that they were able to counter the phenotypic and epigenetic signatures of exhaustion in both in vitro and in vivo tumor models (2).

Another example: at Aarhus University, Denmark, a study led by Maja Ludwigsen shows the promise of a treatment method for cancers caused by an error in cell division that creates a fusion of different genes (3). Using CRISPR/Cas9, Ludwigsen's team has developed a gene therapy that can stop cell division in a subtype of acute myeloid leukemia.

According to McGovern Institute investigators at MIT, several species, ranging from eukaryotes to snails, possess a genome editing superpower of their own. Researchers observed how microscopic plants, single-cell creatures, and selected mollusc species (from clams and mussels to Japanese mud snails) can make programmable DNA-cutting enzymes called Fanzors. These RNA-guided enzymes can be programmed to cut DNA at specific sites, much like the bacterial enzymes that power CRISPR (4). These, the team proposes, could also be developed for biotechnological applications in human genome editing.

Gene editing is a broad, dynamic, and exciting field, which is why we assembled a team of experts to discuss the topic in detail. You will find this on page six.

Rob Coker
Deputy Editor, The Medicine Maker

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Planes, Trains, and Autologous Therapies

The potential of the cell and gene therapies sector depends – partially – on the expertise of the transport and logistics partners that complement it

By Sumukhi Sreevatsan, General Manager at IMAPAC

The biopharma industry has seen exponential progress in the science of cell and gene therapy in recent years. Through my own work, the accounts of our clients, and across the newspapers, I have seen more and more stories about lives changed and individuals cured by revolutionary therapies that would not have been possible 20 years ago. In 2023, a 19-month-old child became the first person in the UK to have her life saved by the gene-based therapy, Libmeldy. In 2019, a UK-based 11-year-old was the first child to receive CAR-T cell therapy that has been proven to fight against leukemia.

Conditions and diseases previously believed to be terminal are now being overcome by the great advances made in cell and gene therapies. As the field progresses, however, the biopharmaceutical industry will need to keep pace with its development in all aspects of manufacturing, distribution, logistics, and administration. Key to seeing cell and gene reach their full potential will be the advancement of cold chain systems.

In my view, the sensitive nature of cell and gene material has constrained both research and treatments. Though cold chain systems have been well established in the dissemination of pharmaceutical and biologic products, their application for cell and gene remains in the early stages.

Cell and gene material is highly susceptible to metabolic decline. When left for a protracted period of time at unsuitable temperatures, the quality of the material declines irreparably and the product ceases to be usable. This problem is particularly true in the case of cell material. Genes are inherently more stable and can therefore be transported with much the same systems as conventional pharmaceuticals and biologicals, but cells require much lower temperatures to retain their treatment value over periods of distribution. By storing and transporting this cell material at cryogenic temperatures, the product can remain, almost indefinitely, in a metabolically inactive state, and thereby invulnerable to any related decline.

The importance of cold chain systems to cell and gene therapies ramps up with the increasingly widespread distribution of the therapies. Cell and gene material has the power to endure over short periods of time without the need for significant temperature reduction. In such short-term cases, products can be refrigerated before use in treatment or research. As cell and gene therapy expands, however, and as demand for products becomes more widespread globally, the biopharmaceutical sector will need to bolster existing channels and build new means of transporting material across vast distances – from the manufacturing lab to the hospital.

We must strive to deliver cell and gene products as widely as possible. Without sufficient cold chain systems in place, these therapies are reliant on a "just-in-time" method of delivery – meaning that cell and gene material needs to reach the intended patient within a strict time frame. For the biopharmaceutical clients that I work with, this limitation means that the manufacturing of products is tightly bound to the schedule for their administration. If that schedule changes – because the treatment is canceled or postponed by the hospital, for example – the cell or gene material will no longer reach the patient within the necessary timeframe, and the product must be discarded.

From speaking with our biopharmaceutical clients and reading reports on the sector's progress, it has become increasingly clear to me that the industry needs coordinated efforts and investment into developing a more robust cold chain system for cell and gene therapies. Fortunately, progress is being made. In fact, the cell and gene therapy supply chain and logistics market is expected by InsightAce Analytic to be worth $3.12 billion by 2031 – but this promising trajectory of funding and production will need to continue.

Cell and gene therapies bring with them great promise but also, like many medical innovations, some grand challenges. Addressing the sector's logistical challenges is fundamental to the future of the field; we must work together, if we are to take the next big step forward in realizing this great promise across the globe.

The VLP Promise

Here's why virus-like particles could open a new chapter in combating disease

By Nicholas (Nik) Barbet, Head of Operations at Vector BioPharma AG

Virus-like particles (VLPs) leverage the advantages of both viral and nonviral delivery systems and have the potential to revolutionize the field of cell and gene therapy. But how do they compare with other delivery systems. And what does the future look like?

The advances made in the field of genomic medicine over the last decade have been truly astounding. Novel gene editing techniques (for example, base, prime and epigenome editing), more sophisticated approaches for gene writing and replacement, tools for reprogramming T cells and the tumor microenvironment are all propelling the sector forward. I'd love to be able to say that we can fully harness the power of these technologies to create new medicines across the full spectrum of human disease, but sadly this is not yet the case. Existing gene delivery vehicles employed to deliver these exciting new technologies in vivo either lack tissue specificity or are difficult to reprogram, have limitations in cargo capacity, and can lead to other issues, such as immunogenicity or genotoxicity.

Recent years have seen growing interest in employing non-viral technologies as delivery vesicles – primarily due to the success of mRNA COVID-19 vaccines (1). Specifically, LNPs have a couple of advantageous properties over viral delivery vehicles: namely, relatively low immunogenicity and cytotoxicity, and the ability to deliver different types of payload (for example, RNA, proteins, and, to a limited extent, DNA). The primary limitation? It can be challenging to achieve sufficient payload delivery to the cells or tissues of interest with LNPs. Despite efforts to retarget, LNPs naturally gravitate to absorption by the liver and thus delivery of extrahepatic payloads is problematic. As such, LNPs are not well suited for delivering DNA payloads. Finally, non-viral systems are characterized by transient persistence in the circulation, resulting in challenges in delivering payloads (such as DNA) that are needed for a longer time to achieve a therapeutic effect.

Among the various viral delivery systems explored for gene therapy, adenovirus and adeno-associated virus (AAV) are the most extensively studied vectors (2). Engineered AAV vectors have been modified to eliminate non-essential viral genes, such as the cap and rep genes, rendering them unable to replicate. Despite these favorable features, as genomic medicine technologies become increasingly complex, the limited cargo capacity of AAVs (4.7 kb) poses a significant challenge. Moreover, AAVs are poorly compatible with precise, cell epitope-specific retargeting and repeated dosing. They also need to be delivered at high doses leading to concerns about genotoxicity; AAV genomes can integrate into host DNA at a rate of up to 1 percent.

In contrast to AAVs, engineered adenovirus vectors exhibit broad tropism profiles, high transduction efficiency, and packaging capacity. They have also not been found to integrate into the host genome, ensuring a lower genotoxicity risk. However, the major challenges in adenovirus vector development arise from a widely pre-existing viral immunity among the general population, robust innate immune responses to its capsid proteins, and strong adaptive immune responses to synthesized viral and transgene products.

In my view, answers to this "grand challenge" of gene delivery are thankfully just around the corner. The development of virus-like particles (VLPs), which efficiently overcome cargo packaging, safety, and localization issues, hold significant promise for gene therapy. Specifically, there is a reignited interest in VLPs based on "gutless" non-replicative high-capacity engineered adenovirus vectors (HCAdVs) that lack all viral genes except for the capsid packaging signal (2). Addressing immunogenicity concerns associated with the capsid, any remaining virus-based components can be engineered and shielded from the immune system, providing a safe and stable delivery system that is uniquely equipped to carry complex gene cassettes because of a large genome packaging capacity of 36 kb (3, 4). For example, a shielded, retargeted adenovirus-based platform, harnessing the capabilities of HCAdVs, has been combined with exogenous, high-avidity adapter proteins to shield the particle from immune surveillance without affecting the infectivity of the VLP (3-5). Such VLPs can also be easily reprogrammed to target a tissue or cell of choice, where the large payload can be delivered at high efficiency thanks to the innate ability of the adenovirus capsid proteins to facilitate cellular transport and delivery of cargo into the nucleus (5).

The combination of large payload, exquisite retargeting, and immune "stealth" makes such platforms a very promising vehicle for in vivo delivery of sophisticated genomic medicine technologies. I'm hopeful that this will unlock the true potential of the advances we have witnessed in recent years, enabling us, for example, to reprogram the tumor microenvironment and deliver biological medicines to the site of action, or to reprogram human T cells in vivo. In the latter case, issues of supply chain and cost considerations can be effectively circumvented, permitting access to these medical advances for patients around the world.

References available online at tmm.txp.to/virus-like-particles

The Future AWAKENS

Experts in the cell and gene therapy space are excited about things to come. And why shouldn't they be? After all, these are the pioneers of a burgeoning field of medicine. With so few generations of expertise before them to call upon, their legacy in medical circles has been founded on a base of wonder – but is wonder a strong enough foundation upon which to establish an institution with the potential to eradicate disease? Here, we share views from various experts across the industry on why the sector is so exciting, and why caution is more important than glory.

MATTHIAS BOZZA
– Director of Gene Regulation at Vector Biopharma

"The possibility of reverting genetic errors using nuclease-free systems, such as base or epigenetic editors, is of great interest because of their high safety profile. These editors possess the unique ability to precisely and reliably elicit single base edits in the genome; genetic disorders that can be cured by fixing one nucleic acid will be the ones that benefit the most."

MICHELLE FRASER
– Head of Cell and Gene Therapy at Revvity

"As the field progresses, we are starting to see a shift from autologous cell therapies to allogeneic cell therapies, which offer the benefits of scaled up manufacturing, off the shelf therapies, and reduced costs. There is also a move from academic research and product development towards industry taking the lead. The benefit of having industry engagement is that they bring the systems and processes to develop, manufacture and deliver cell and gene therapies globally.

"I am also excited by newer generation editing systems, such as base editing, that offer more controlled gene editing, which can make cell and gene therapies safer and more effective. The development editing systems also underpins the groundswell of innovation around alternate Cas enzymes, including i) different effector molecules that can be deployed alongside cytosine and adenosine base editors, ii) the ability to multiplex gene knockouts in a single reaction to make therapies more efficient, and iii) the potential to simultaneously knock-in genes, such as a CAR, to create a CAR-T therapy to treat cancer."

CHELSEA PRATT
– Biopharma Segment Marketing Manager at Bio-Rad Laboratories

"The introduction of in vivo gene editing techniques, such as CRISPR-Cas9, has propelled the field forward, providing exceptional precision in addressing rare genetic conditions. We've also seen the approval of a new type of therapy with Sarepta Therapeutics' SRP-9001 gene therapy for Duchenne muscular dystrophy, a genetic neuromuscular disease that affects 1 in 3,500 to 5,000 males born worldwide.

"However, a significant hurdle faced by these treatments is the limited number of patients available for clinical trials in a given rare disease. Recognizing this challenge, different regulatory agencies are engaged in collaborative discussions to harmonize clinical trial requirements."

ANGELA OSBORNE
– CEO and Founder at eXmoor Pharma

"Since I started in this field, people have said things like "autologous therapies aren't going to last; allogeneic is the future," or "viral vectors won't last; our focus will shift towards non-viral deliveries." I believe there is a space for everything – but it will be indication dependent.

"The biggest opportunity in the field is moving towards the mass market. Moving from monogenetic diseases and orphan drugs, to major diseases, such as Parkinson's disease, liver disease, heart disease, will become our collective focus. Solving these issues will be dependent on robust processes – whether it's a scale out or scale up, it's about getting your development focus right."

VERED CAPLAN
– CEO at Orgenesis

"When people ask me about cell and gene therapy, I can't help but say, "You don't know what is coming!" We are literally learning how to reprogram advanced cellular function, and I couldn't be more excited. To enable growth in this industry, we need to standardize and converge. We don't have to invent the wheel per say; perhaps there are basics we can adapt from other industries.

"I'm particularly interested in the development of autologous therapies. The moment we pull together our knowledge on how to effectively use these processes, is the moment we will take off as an industry."

STACEY TREICHLER
– Director, Head of Marketing & Strategy of BioModalities at Catalent

"High levels of investment in the field have led to an increase in the number of novel cell types and proprietary technologies entering the clinic. Autologous therapies are currently the most numerous, but there is a trend towards a greater number of clinical trials being initiated for allogeneic therapies. It is all very exciting, but companies need to find a way to make these breakthrough therapies affordable to all."

FABIAN GERLINGHAUS
– Co-founder and CEO, Cellares

"As cell therapies move up the treatment paradigm, and cell-based therapeutics are eventually approved to treat a range of cancers, the spotlight will turn (again) to manufacturing capacity. At Cellares, our belief is that high-throughput, end-to-end automation is set to revolutionize cell therapy manufacturing, allowing us to deliver more doses, at lower cost to meet the demand. It's a truly exciting time for our industry!"

PHIL VANEK
– CTO at GammaBioscience; Industrial Committee Member and Business Development and Finance Committee Member at ISCT

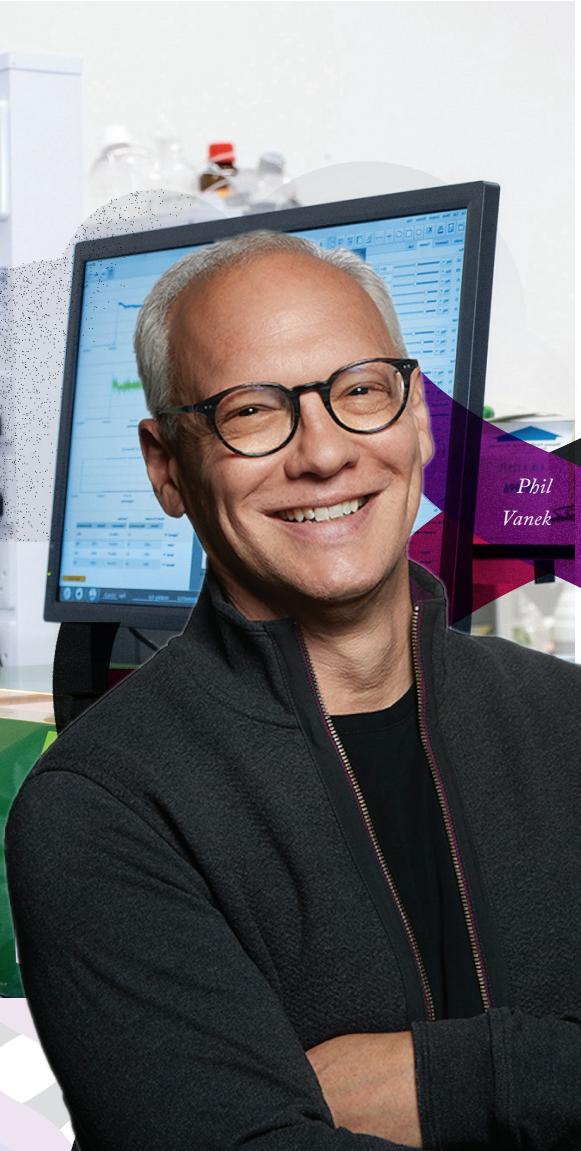
"There is a growing focus towards pluripotent stem cells and their ability to drive allogeneic therapies, while continuing to solve the cost of manufacturing for autologous therapies. As an industry, there is room for both autologous and allogeneic therapies for different indications and for different acuteness of therapy. I can foresee the evolution of technologies to be better suited towards the indications of what the industry needs right now. Certainly, with gene therapy, the argument is whether we can ever get beyond the virus gene delivery platform, and look at direct LNP delivery into cells in a targeted fashion – these are areas for rich discussion over the coming weeks, months, and years."

The future is compelling, exciting, and constantly changing – it will be what we make it. The thing that will not change, however, is the human nature within the hands wielding the technology. What will make cell and gene therapeutics successful for generations hence, will be the wisdom gained from learning more about it now. The sun doesn't rise each day like a missile launched. It's a gradual process to be marvelled and wondered at. And if we truly are at the breaking of a new dawn for advanced therapeutics, the world will need time to wake up and adjust.

Angela Osbourne

Fabian Gerlinghaus

Chelsea Pratt



Phil Vanek

Vered Caplan

A NEW HOPE FOR CRISPR TECHNOLOGY

A roundtable discussion about the hype and true potential of genome editing

Someone's famous uncle once said, "With great power comes great responsibility." Genome editing is an incredibly powerful technique with huge promise and potential for medicine, as well as many other fields including agriculture and the environment. But those wielding the power must cut through the hype, evaluate the potential, and use it wisely. Here, we talk to a selection of experts using genome editing and CRISPR/Cas9 for drug development purposes to get their views on the field.

"A new genetic revolution."
"The ultimate therapy."

These are just two of the tantalizing phrases used by our panel when describing the technology and what it could accomplish…

Why are you so excited about the potential of gene editing?

LDJ: CRISPR/cas9 is a captivating technology. In 2019, the first American patient treated with CRISPR technology for sickle cell disease achieved disease-free status. This technology's potential also extends beyond medicine; it has the power to address food crises, improve agriculture, aid drug development and pathogen detection, and offer solutions to climate change. CRISPR technology has made re-writing the code of life easy, accurate, and accessible, fueling a new genetic revolution.

TC: It is such an exciting area. Changing a fundamental aspect of biology and permanently correcting genetic messages with a level of elegance that was previously unthinkable. If diseases were created by nature, then now we have the ability to challenge them using tools presented to us by Mother Nature herself. Gene editing could be the ultimate therapy for targets that have previously been undruggable.

RH: For me, it's about opening the door to what I think of as the third leg of the stool in the world of drug development. Today, that stool is a bit rickety with just two legs: small molecules and antibody/protein therapies. I believe the third leg is genetic medicine. Genome editing is important because if we can manipulate the genome, either ex vivo or in vivo in a variety of contexts, then we will be able to help so many different kinds of patients with different diseases.

ER: Ever since the completion of the human genome project, and in the years following, the scientific community has accumulated a massive amount of sequence data. What was initially lacking was the ability to actually manipulate that information in cells. Gene editing is the tool that allows us to utilize that information in the context of a living system to better understand pathways and how those sequences interact and are controlled. An analogy I like to make is to consider the genome a database of information; the cellular machinery is the software that runs the programs; and gene editing is a programming language we can use to manipulate the data and run programs. The introduction of CRISPR has also been a revolutionary step in making genome editing applications available to everyone, no matter what organism they may be working with.

How do we separate the hype from the reality?

LDJ: It is essential to approach CRISPR technology with critical thinking and a balanced perspective. While acknowledging its incredible potential as a powerful gene editing tool, it is equally important to recognize that the field is still in the early stages of development and faces significant challenges. Researchers worldwide are working to overcome these obstacles, and though wide-scale implementation of CRISPR applications, particularly in clinical settings, may take time, the technology continues to demonstrate hope.

TC: The hype and excitement will help to fuel interest and further research in the field. However, we are not yet at the epicentre of precision genome engineering for most cells in the body, so while there is hype, we need to be careful about what is truly attainable with today's technology and what is not. We still cannot get to every part of the body, even with existing delivery technologies for in vivo genome engineering. Most of the focus to date has been on the liver. How do we target the lung? Or neurons? Or even the skin? We can't do this regularly just yet. If a delivery technology emerges that is capable of reaching every part of the body, without tissue off-target effects, then we will have a real victory. Additionally, most cells in our body do not divide. Today's standard CRISPR/Cas platform is not very good in the precision engineering of those cells. That needs to be resolved as well, if the potential of this technology is to be fully harnessed.

The negative side of the hype is that there are some people out there who believe we're going to make CRISPR babies every day. If you want to change the world, you need to be cautious. We need to work very closely with regulatory authorities about what is possible and what is not, as well as to understand what the implications are when we're working with humans rather than mice.

RH: We can all be guilty sometimes of creating hype. Scientists have pointed out that there are around 7000 monogenic genetic diseases. Wouldn't it be great if you could

Rachel Haurwitz

Tirtha Chakraborty

Linda De Jesus

Eric Rhodes

MEET THE EXPERTS

Rachel Haurwitz – *CEO at Caribou Biosciences*
Tirtha Chakraborty – *Chief Scientific Officer, Vor Biopharma*
Linda De Jesus – *Vice President and General Manager, Global Head of Commercial at Integrated DNA Technologies (IDT)*
Eric Rhodes – *CEO at ERS Genomics*

use CRISPR to address each of them? While certainly true at the 50,000 foot view level, I think the practical reality of how you do that becomes complex quickly. Sickle cell disease is a classic example where one mutation is shared across all patients, which opens the door to one genome editing strategy that could potentially serve the entire patient population.

In diseases like cystic fibrosis or muscular dystrophy, patients have different mutations that may require a multiplicity of different kinds of genetic medicines. And that's just the tip of the iceberg. There is definitely a lot of potential, but we have a lot of work to do.

However, I always get worried when I talk to friends who are not in the biotech world and who base their reading on mainstream news; some of them have come to the conclusion that you can CRISPR any gene in any cell at any time. That is not reality – nor will it be anytime soon. We have to be very cautious about the kinds of promises we make to patients and to our communities about what is actually possible today, what we hope will be possible tomorrow, and what some futuristic landscape might look like.

The reality today is that there is a fairly short list of cell types, either outside the body or inside of the body, that we can edit with high fidelity in a way that could lead to near-term clinical translation. However, there's a lot of work happening that will open the door to additional tissues and cell types in the not too distant future.

ER: The hope has always been that once a genetic mutation leading to disease was known, genome editing might be applied to repair the mutation and lead to a cure. But from a therapeutic reality perspective, this is not as easy as it sounds. The main challenge for gene editing remains the matter of delivery. If the mutation requires only a small portion of cells to be targeted for delivery and editing, there is a good chance that gene editing can play a role, but with most diseases this is often not the case. I frequently receive letters from desperate parents whose child has been diagnosed with a disease associated with a genetic mutation asking if CRISPR can be deployed to help their child, but often the situation would call for editing of virtually all the cells in the body and this just isn't possible at this time.

What are the biggest challenges facing this area of the industry?

LDJ: There are several crucial questions in the field that scientists are actively addressing. These include concerns about off-target effects, where unintended editing occurs in regions of the genome similar to the target region. Additionally, efficiently delivering CRISPR reagents in a cell type- and tissue-specific manner remains challenging. Evaluating the long-term effects and ensuring the safety of CRISPR-based therapies are also essential. Comprehensive long-term studies, both preclinical and clinical, are necessary to assess gene editing stability, potential immune responses, and any unintended consequences resulting from genome alterations.

RH: Not every underlying technology is going to be the best fit for every disease. For any given disease, we have the responsibility to figure out what is the best collection of technologies needed that could develop the right therapy.

At Caribou, we have been focused on off-the shelf cell therapies for oncology, and use our genome editing capabilities to do what we call "armoring" to enhance the cells and make sure they have sufficient antitumor activity, which is needed to rival that of today's approved autologous CAR T therapies.

We believe that off-the-shelf has to be the answer if we want to deliver these kinds of therapies to increasingly broad patient populations. But it's not as easy as taking a healthy T cell from a healthy donor and adding a CAR, which would be foreign to the patient's immune system and thus rejected. We have to enhance, or armor, the cells to bridge the gap.

ER: I think concerns remain around safety and which version of genome editing might be the safest to use in each clinical situation. Base editing and prime editing are both seen as potentially safer versions of CRISPR, but both have limitations that don't make them as broadly applicable as the more traditional CRISPR/Cas9.

I also believe that further discussion on the ethical concerns of genome editing must be clearly a priority. Making gene editing therapies affordable and broadly available will also be a challenge for the industry in the coming years. For my company, our goal over the next decade is to expand the use of CRISPR/Cas9. We want more companies using CRISPR/Cas9 globally and realizing its great potential.

TC: I would point to the quality of scientists as a challenge. There is not a lot of expertise in this area since the field is so new – particularly in manufacturing. High science cannot be limited to just research departments; we need people who will ask manufacturing, regulatory, and quality questions too. In many areas of drug development, there are pre-existing templates, but for genetic medicines, the lack of familiarity amongst people trained in a much more templated, traditional environment, and believing that the previously tried and tested template is going to work each time, could be a recipe for disaster. We need education across the board. We need to educate and inform patients too so they can understand the reality of these therapeutics, and to alleviate their concerns.

Read an extended version of this discussion at https://bit.ly/3FXlFU4

CRISPR WITH CAUTION

Deputy editor Rob Coker recalls his trip to the labs of Vilnius-based biotech start-up Caszyme, where he spoke with CEO Monika Paule about the potential of genome editing

Vilnius-based biotech company Caszyme specializes in the development and application of CRISPR-Cas technology. Applications that use CRISPR-Cas technology (new diagnostic tools, therapies, reagents, and others) require Cas proteins with various characteristics, which Caszyme identifies, characterizes, and develops based on the individual needs of a project.

In May 2023, I enjoyed traveling to the Lithuanian capital to see for myself the lab space in which all this potential is generated. Co-founded by 2018 Kavli Prize laureate Virginijus Šikšnys, Caszyme is located in the life science campus of Vilnius University. There, I met co-founder and CEO Monika Paule, who shared her excitement about the potential of the company, the technology, and the field.

"Prior to discovery of this technology, there were no tools that would allow us to edit the genomes of cells or organisms so precisely and simply," Paule said. "Now, even more than a decade since the technology was discovered, CRISPR-Cas continues to display its versatility. It's a fascinating field of ongoing research and innovation."

CRISPR-Cas and its potential has generated a great deal of hype but also driven clear scientific progress. Researchers have developed enhancements and variations of CRISPR-Cas technology, including base editing, prime editing, and epigenome editing, which have all helped to expand the possible applications. However, some people are still confused about the true reality of the technology. That said, many expect FDA approval of the first CRISPR-Cas drug soon (with the UK's MHRA approving the world's first CRISPR medicine in November 2023).

Paule believes that (mis)understanding CRISPR-Cas technology relates to a unique set of challenges. "It is necessary to stay up-to-date with the latest research and scientific discussions surrounding gene editing. This can be achieved by following reputable scientific journals, attending conferences, and engaging with experts in the field. By actively seeking reliable sources and evaluating the credibility of the information encountered, a more accurate understanding of the current state and potential of CRISPR-Cas technology can be made."

Safety and ethics

CRISPR technology is still new, and any major safety issues could cause serious setbacks for the field as a whole. Ensuring the accuracy and safety of gene editing in different contexts remains crucial. I asked Paule what the biggest questions were as far as the long-term effects of CRISPR gene editing in humans is concerned. "Safety is essential for the widespread clinical application of the technology in the human therapeutics field," she said. "Also, I believe that we must find more efficient ways to deliver gene editing tools to different cell types and tissues, and to identify solutions that lower off-target effects."

The social perception and acceptance of CRISPR is another obstacle, however, to which Paule added, "To address public concerns, we must provide accurate information, engage in meaningful dialogue about the benefits, risks, and ethical considerations, while developing appropriate regulatory frameworks and oversight mechanisms for CRISPR gene editing technologies. Ensuring responsible use, addressing safety concerns, and balancing innovation with ethical considerations requires robust and adaptive regulations that could keep pace with scientific advancements."

As the technology increasingly faces regulatory approval, safety and efficacy of CRISPR-based therapies will be validated, which should help generate public awareness and trust. But ethical considerations cannot remain unaddressed… "One of the applications in which ethical questions emerge is evaluating the use of gene editing to resurrect extinct species or their traits, weighing the benefits against potential risks to ecosystems, and the moral implications of altering – even reversing – natural processes," Paule concluded. "But these ethical considerations can be addressed through the development of novel, more precise editing tools and by careful deliberation and open conversation between businesses, government, and regulatory institutions that would guide the ethical and responsible use of CRISPR technology."

Nevertheless, and as Paule confirmed, research will continue in Lithuania – and around the globe – with various stakeholders seeking to optimize current approaches to ensure the effective and precise delivery of CRISPR gene editing tools for a wide range of applications.

Producing quality content requires considerable time and resources.

This supplement would not have been possible without the support of our sponsors.

In recent years, new technologies have emerged to improve human living conditions. Two popular examples are cell therapy, where cells are enriched or modified before being introduced to the patient, and gene therapy, where genes are introduced, replaced, or altered within the body. Consolidated as cell and gene therapies, both are projected to revolutionize the treatment of genetic or acquired diseases, such as cancer.

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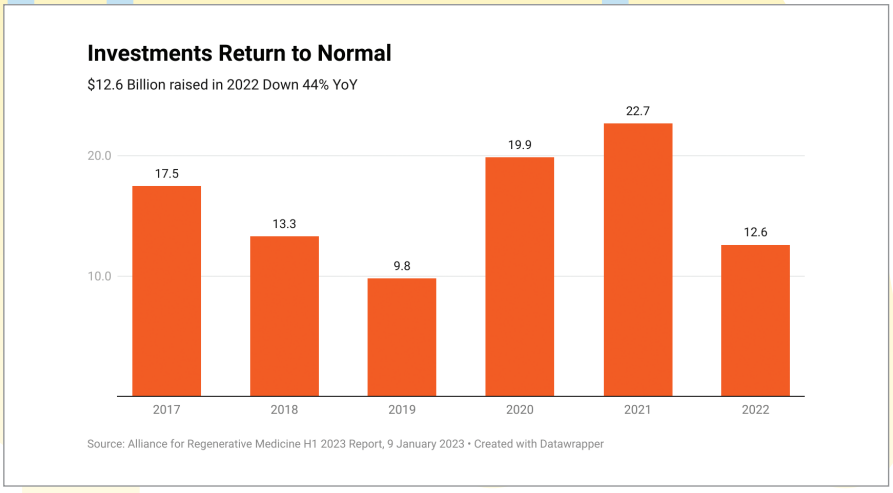
Weathering the Storm: Cell and Gene's Economic Downturn



An early wave of investor enthusiasm followed by an economic crisis has landed our field in a sea of trouble – so how can we swim to shore?

By James Wilson, Professor of Medicine and Pediatrics, Perelman School of Medicine, University of Pennsylvania, and Anshul Mangal, President, Project Farma

The biotech industry enjoyed years of prosperity in which capital was easily accessible and saw record-setting investments, most notably from 2020 through 2021. During that time, technology, research, and drug development – specifically for cell and gene therapies – flourished to reach incredible heights, offering new hope to patients suffering from rare diseases. Substantial investments in programs led to first-of-their-kind product approvals for regenerative medicines and enabled researchers to dramatically advance therapies for small patient populations living with unmet medical needs.

Following record-setting milestones in fundraising over the past two years, the advanced therapy investment landscape is experiencing a natural correction and has returned to pre-pandemic numbers (2018 and 2019). In the face of a market downturn, company leaders must save capital and make difficult decisions and consider mitigating measures, such as forced layoffs and the pausing of critical product programs, which ultimately put industry progress at risk. Divesting from bad assets, such as unnecessary manufacturing facilities, can also help stretch capital.

When it is difficult to raise capital, more financially rewarding programs are prioritized. Programs serving smaller patient populations are often viewed as less attractive from a commercial standpoint and may be sidelined, regardless of their likelihood of success. However, this does not mean the end for these programs. The leaders of the advanced medicines industry and champions of patients with rare diseases are dedicated to ensuring these programs weather the storm and ultimately succeed.

The state of the landscape

When discussing the current financial landscape, it is crucial to consider what is happening within the industry and the larger macroeconomic environment. As the economic downturn looms, we are seeing a delay in public offerings, layoffs, and lowered valuations as companies attempt to stretch their dollars. With the rising prices of capital, materials, and extended supply chain timelines driving costs up further, many critical programs are now at risk.

Though it is certainly more difficult to raise money today than in the past two years, there are still exciting developments in the cell and gene therapy industry. According to the Alliance for Regenerative Medicine (ARM) Report in 2023 (1), 2,220 trials were ongoing at the start of 2023 – 254 of those currently active were initiated in 2022. With 202 of these trials reportedly in phase III, there are still an impressive number of therapies in the approval pipeline. Despite the decline in investment dollars and clinical trial numbers, we have still seen exciting new approvals in 2023.

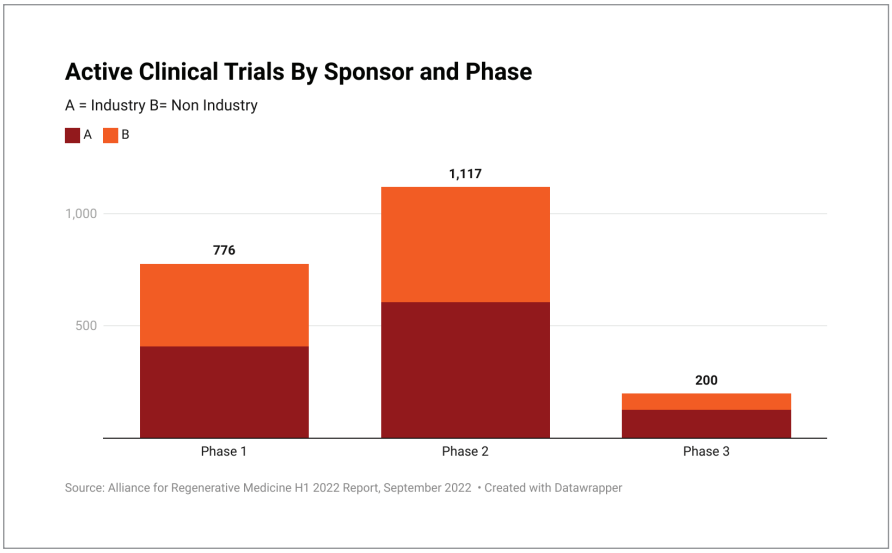
The advanced therapy industry continues to see success, but there is no denying that the market has contracted. Both companies and investors will be forced to act with purpose moving forward, employing strategies that make existing capital work harder and more efficiently.

The current environment in advanced therapies was brought about by a combination of industry-specific factors, such as investments from inexperienced players and talent gaps, as well as macroeconomic factors, such as the public market and supply chain issues resulting from the pandemic.

Following a seemingly endless flow of capital into advanced therapy and a series of product successes in 2020 and 2021, an irrational exuberance gripped investors. New players flooded the field, and companies were quickly spun out and scaled prematurely. During this boom it became extremely easy to make decisions that should have taken more time and consideration, and that allowed for rapid and unchecked progress for countless programs across the industry. Thanks to a plethora of emerging technologies and large infusions of capital from investors new to the industry, it became difficult to identify the "best-in-class" products. Now we are seeing a major wave of redundancies, and the industry will continue to suffer without solutions.

Focusing on patients

In fact, recent news has shown that as more clinical data is published and mergers and



acquisitions are occurring, we are now seeing who is emerging victorious in this sector. In this case, consolidation is not a negative thing – it's an essential process that funnels and allocates investments that enable the advance of the best possible treatments towards patients.

Constructing a strong portfolio means thoughtfully defining and differentiating products and considering how new products could make a meaningful impact. In this process, we need to ask ourselves, "What is the actual innovation?" Being clear on this issue helps developers focus on their main mission and prioritize the best products in their portfolio. This may lead companies to modify their organizational structures by deciding what aspects to keep in house, while moving to outsource everything else. Leveraging other industry experts whenever possible may also protect companies' resources from being allocated to ventures that do not move the needle; for example, patient advocacy groups are a hugely underutilized resource for drug developers and investors. These groups are dedicated to advancing treatments for patient populations and are host to untapped knowledge that can provide solutions to problems that may lead to failure. Leveraging their expertise, resources, and data to drive decision making helps bridge a wide gap in the drug development process and can only increase chances of success. Moving forward, the industry must foster a collaborative ecosystem by engaging developers, patient advocates, regulatory bodies, and investors to tackle problems and move the industry forward.

A clear path

Programs appearing across different companies without a clear path for product development ultimately lead to inefficient use of capital. Rare diseases are a strong investment, but without a direct route to develop and deliver products, the mission's overall chance of success is low. Rethinking commercialization to use platform models and pool assets will allow for diversification, decreased risk, and access to a broader range of patients.

The likelihood of product success increases when goals are defined on patients' terms, rather than on public offerings and short-term paper value. Cell and gene's road to economic recovery will not be straightforward – setbacks will inevitably occur – but, if the industry centers all goals around delivering life-saving therapies to the patients who need them, there is good reason to remain optimistic.

Reference

1. *Alliance for Regenerative Medicine, "Cell & Gene State of the Industry Briefing," (2023). Available at https://alliancerm.org/arm-event/sotibriefing/*

Between Two Worlds: Doing Business as a Cell and Gene Academic

The pharmaceutical industry depends on academia, but that relationship – and its points of interchange – could be improved

By Stuart Curbishley, Head of Business and Project Development – Advanced Therapies, University of Birmingham, UK

Medicine making for cell and gene therapy is a tripod; its three legs are academia, business, and the state. Pull out one leg and it falls. Without university laboratories, we would not have a single therapy for the market. And without state support through institutions such as the UK's Cell and Gene Therapy Catapult, cell and gene companies would not perform at their best. For the foreseeable future, we can expect these things to remain true.

However, I do think that, if funding worked differently, the academic leg could stand on its own for longer. The problem is that academics simply cannot set out to raise, say, £150 million to fund the commercialization of a therapy. This is where the private sector steps in, turning the pure science of academia into viable IP.

Conversely, I seriously doubt that the private sector leg could ever stand entirely on its own. Although certain big pharma companies have set up cell therapy development teams, I expect that these companies are far more likely to release new iterations of existing products than truly novel therapeutics. This is where business needs academia.

I believe that we would be able to advance

the field far more quickly if we could establish a way to distribute industry's financial resources to academic programs earlier. If we could lead big pharma to fund the bakery, rather than buy the bread, we would shave years off the development process.

Though I would not claim to have all the answers to what is certainly a very difficult and inflexible problem, I would insist that new and better bridges be built between pharma and academia. You don't need to take it on faith. I'm living proof.

This is my journey…

In 1999, I launched my academic career with a Master's research degree at the University of Birmingham, UK. I stayed on to undertake a PhD on how chemokines drive inflammation and inflammatory liver disease. After completing that, I stayed on again, this time in a postdoctoral position researching monocyte myeloid cell biology with a view to developing dendritic cells as a primary liver cancer therapy. It was at this job that I first worked on a cell therapy program. It eventually led to my first involvement with a cell therapy trial, treating end-stage liver cancer with a dendritic cell vaccine. That trial reached its target and closed during the COVID-19 pandemic, ultimately yielding positive results.

Across the last half-decade, I have taken over running GMP activity for the University of Birmingham as a whole. We've grown from a small, self-enclosed facility to one with a variety of academic and commercial partners. Today, we manufacture a wide range of cell types and run a wide range of GMP services for the university.

Adding commercial viability to academic centers could transform the offer to early-stage startups. This is where academic CDMOs tend to falter; they are simply not designed with commercial questions such as speed and contracting in mind. Juxtaposition with appropriate commercial partners could smoothly speed the transition of academic programs to the world of privately financed cell therapy trials.

As a sector, academic CDMOs need to show a way out for people stuck in the rut of trying to build a therapy entirely on grant funding. After all, the moves that win you a grant are usually not the moves that will help you set up a robust, sustainable business. We need to spare these people from an imperative to regularly reinvent the wheel just to keep moving forward.

… and this is my bridge

In the case of my own company's transition to the market, I don't expect a massive change in our basic function – a CDMO with a strong focus on development. We will continue to work with commercial partners and focus on how they can complement our academic program. There are partial precedents for this here in the UK, where we have seen people take academic programs into our government-funded Cell and Gene Therapy Catapult and go on to raise impressive capital investments. However, in many instances, there is a lack of preparation and a lack of understanding of what is needed to commercialize. Often, the company's processes require expensive development that comes far too late, after the company has already moved into rented manufacturing space.

Sensible commercial partnerships should help ease such transitions. We need to leverage the proximity of academic CDMOs to patient treatment centers and their populations of key opinion leaders at centers of clinical excellence. Our goal should be to work closely with early-stage therapy developers to get the product and the process right first time.

Skeptics may ask: doesn't coupling with commercial partners introduce new problems, swapping the games of academia for the games of business? These are valid concerns, but all I can say in response is that, if we are careful in our establishment of key partnerships, we can still make a difference for patients. In business, of course, we have to deliver a return on investment – but the right market exists and is receptive, as we can see from the sector's ongoing acceleration. In my university role, I am expected to make my current facility break even, but I am not being pushed to make returns to shareholders. Developing a commercial strategy would mark a change in my work, but I don't see it as a major challenge.

Centers with no center

One of the factors we need to consider is scale. Academic CDMOs must take advantage of economies of scale to become profitable because there are huge costs involved in running a GMP facility. If we can create a network of academic centers with the right industry partnerships, the initial cost of setting up this cooperative enterprise will pay for itself down the line. For example, you can achieve a certain degree of leadership and quality oversight remotely – so these elements can be dispersed across your network, rather than replicated at every node. Therefore, the larger your network is, the more you can dilute these aspects of your running costs.

A dispersed network is also well suited to delivering autologous therapies to patients because it helps avoid the current situation. Right now, we ship materials thousands of miles to factories in the middle of nowhere only to then ship them back again. This is a bad economic practice, bad environmental practice, and adds an unnecessary high risk to your process.

To sum up…

Companies like mine must play a significant role in providing GMP manufacturing for cell and gene therapy clinical development post-grant-funding. We want to provide a bridge in manufacturing provision for smaller institutions who wish to develop cell and gene therapies, but do not have either the resources or the need to engage a large CDMO. This will enable more cell and gene therapies from a wider group of specialist organizations to progress to the clinic and potentially reach an even wider group of patients than may currently benefit from therapies in development.

Afraid of Banality, Driven by Beauty

Sitting Down With … Tirtha Chakraborty,
Chief Scientific Officer at Vor Bio.

Did you always want to be a scientist?
I was born and brought up in India and most of my early science lessons came from my father – a veterinarian turned scientist. He introduced me to a laboratory where he performed cell culture for vaccine research. It became as much a part of my upbringing as dinner table conversations. Personally, I am terrified of banality – day-to-day repetition. I like change and, for me, science and the arts are two extremely dynamic areas that naturally complement each other.

How do you combine art and science?
Art was also a very big part of my upbringing. Art and science are, for me, the two most beautiful things – although I will include sports as a close third! There is a pattern – you need to recognize the beauty in the pattern and strive for perfection. A "good enough" mentality is not going to solve the big problems. I'm fortunate to have extraordinary team members who subscribe to the same philosophy of seeing beauty in science. Science is an art in its own sense.

How does the artist in you manifest today?
I painted for many years when growing up, but now photography is my primary inspiration. I think photography is a powerful combination of both science and art; you need to understand the science of light, as well as the mechanics of your equipment. For me, science is the same as photography – visual intonations influence the way I do science. I don't like ugly science. There's a lot of it – and some of it even works – but I'm not going to work in an environment where that becomes the norm.

What big scientific moments have excited you recently?
At the risk of sounding a little obvious, the CAR T field is a great success story, but I also think its early success is a bit of an issue for cell and gene therapy because it has reached the point of "good enough." It sometimes feels like people don't want to change a lot in that field now, and there is a reluctance to understand the fundamentals of what drives both safety and efficacy for these living drugs. This highlights one of the internal struggles in a profession where we encourage the industry to try and push the boundaries.

An area I'm excited about is gene engineering. I was very fortunate to be part of the team that led hematopoietic stem cell transplants based on gene engineering all the way from discovery to the clinic. Hematopoietic stem cell engineering is one of the most difficult things in science. To genome engineer cells and cure sickle cell or beta thalassemia patients – which has been done at a previous company I worked for, CRISPR Therapeutics – is science fiction that became science fact.

In what areas could we see breakthroughs in the future?
Whenever we talk about cell and gene therapy, the three most important things are delivery, delivery, and delivery. Ex vivo gene therapy is getting pretty crowded – again thanks to everyone rushing to make another CAR T product. Intellia had an extraordinary breakthrough in liver-directed gene editing, but the delivery problems of being able to use it exactly where it is needed in vivo are not yet solved. The whole CRISPR field exploded because of the excitement around precision genome engineering. If the potential in this area can be realized, it will be a game changer, but I think the key is devising the right delivery technology for each application.

Most of our cells in the body never divide. Because of that, the genome repairing mechanism allows for only imprecise genetic changes. That is what first-generation genome editing technology focused on. Technologically and scientifically speaking, the biggest frontier we need to tackle is where we can make precise genomic changes in non-dividing cells of the body. That will open an entire new universe of therapeutics. With base and prime editing, I think we can get there, but it is not going to be easy. Alternatively, if we want to make precise genetic changes, we need cells that can divide to allow alternate repairing mechanisms to kick in.

What is Vor Bio's current area of focus?
We are focused on the treatment of hematopoietic diseases, starting with hematopoietic malignancies such as acute myeloid leukemia, and are making next-generation hematopoietic transplants that are shielded from targeted therapy. We hope these products could become the standard of care in the near future. For this application, we are genome engineering hematopoietic stem and progenitor cells. Creating a stem cell transplant that provides universal protection from targeted therapy may open all kinds of treatment opportunities, and radically change outcomes for patients.

What should be the priorities of the advanced medicine space?
Education across the board. Advanced medicines like cell and gene therapies are still in their infancy, and it is vital to appreciate how radically different these drugs and the requirements during drug development are in comparison to decades of the existing paradigm. Drug development in advanced medicines has no template. We are the ones creating the template. The quality of science and the quality of scientists who need to drive these priorities are very different now from what they were 20 years ago, so the industry needs to focus on hiring the best brains in the world rather than letting the best brains go into only academia!

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