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Gene Therapy Market

TechSci Research Analysts in Conversation with:

Ibrahim Malki

(Cell and Gene Therapy Associate)

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Cell and Gene Therapy Associate

Can you briefly describe your background and experience with gene therapy?

I have worked for 2 years as a cell and gene therapy manufacturing associate. My job was to assist in the production of blood derived medicine after it goes commercial or very late phase clinical. Outside of my industry experience, I have a BA in Biology and one thing I studied a lot was CRISPR.

How has your career evolved within the field of gene therapy, and what specific areas do you focus on?

On a personal level, I'm still relatively new to the industry. I have worked in CAR-T for a year and a half and I worked at a CDMO for 8 months, particularly focusing on LVV. On a broader scale, biomanufacturing has changed as an industry. Technology has improved significantly over the years, especially post-COVID.

The use of software to streamline production and regulatory compliance is one of the few positives to emerge from the pandemic. One of the most useful softwares I've noticed is eMES, a system that digitizes process batch records to ensure drug product traceability, real time monitoring, and ease of data collection for continuous improvement. I have observed the companies I have worked for go through transitions involving these technological advancements.

In your opinion, how has gene therapy evolved in the past few years?

Within the past few years, there has been heightened interest and scrutiny in the cell and gene therapy industry. Even though the COVID vaccine is not a gene therapy, it has been strongly associated with the industry and for understandable reasons. It was derived from a gene therapy research program that utilized mRNA technology.

Now there is more skepticism around biopharmaceutical companies because of the governmental response to COVID and the involvement of biopharma via the political revolving door.

Furthermore, there has also been more interest because people realize the potential these technologies have. This heightened scrutiny has forced bio-

pharma companies to adopt new methods to increase transparency such as eMES. Also, the increased interest has brought about more funding, so it's the perfect storm.

What are the most significant breakthroughs you've witnessed in gene therapy to date?

I helped support the first commercial patient for Lyfgenia, the first lentiviral treatment for sickle cell. I helped with the implementation of eMES for Abecma at BMS and I aided the company during their most significant production ramp ups. The implementation of eMES at a large biopharmaceutical company is an important milestone toward achieving widespread adoption. Additionally, multiple successful production ramps indicate both strong demand for the product and success in its commercial application, further contributing to its broader adoption.

How do you see the current clinical landscape for gene therapy (key diseases being targeted, technology used)?

Cell and gene therapy is trending towards ubiquity. Despite early success proving that CGT is useful, the focus was on rare genetic disorders because the patient population is smaller and the need for treatment was critical. Now that CGT has proven successful on a commercial level for rare disorders, the next step is targeting more common diseases. One of the most promising indications of this, in my opinion, is clinical trials for Type I diabetes. As for the technology, there are 3 that I can speak to. First is CRISPR/Cas9. This technology was fundamental for rapid covid testing and shows promise in many ways despite serious concerns about side effects and ethicality. The others are CAR-T and LVV, they are revolutionary methods for modifications of immune cells rather than genetic code.

What are the key scientific challenges that gene therapy faces today (e.g., delivery methods, safety concerns)?

Concerns about side effects and ethicality are still a serious consideration. However, an underrated issue is logistics, in my opinion. Particularly, there needs to be more communication to achieve a more seamless transition from clinical to commercial. This is especially crucial since changing a process takes so much time due to the strict regulatory requirements.

Additionally, if logistic concerns are addressed, concerns about side effects and ethicality will largely be addressed by proxy.

Can you share insights into the most promising gene therapy techniques (e.g., CRISPR-Cas9, viral/non-viral vectors)?

One thing that I think is important about CRISPR-Cas9 is the introduction of base and prime editing. One of the biggest concerns with CRISPR is unintended mutations as side effects due to imprecision. These advancements allow for more precise gene editing which can open doors to many applications in the future. Another thing is CAR-T doesn't get enough recognition. Theoretically, CAR-T therapy can be applied to solid tumors. There has been some success but there are still a lot of work to be done.

What advancements in delivery mechanisms (viral vectors, non-viral vectors, etc.) show the most promise?

This is a difficult question to answer because all of these innovations are connected in terms of their scientific foundation and underlying principles. Also I believe the question isn't whether they are useful because many have proven to be, the question is in what specific diseases can they be used for. What's the most surprising is many have proven successful even in the long term. Some CAR-T therapies have patients that are healthy after many years. I'm surprised that hybrid systems, particularly those combining viral and nonviral methods, aren't discussed more often. They not only hold great promise but also help mitigate risks, making them a valuable area of exploration.

What are the most common hurdles encountered in gene therapy clinical trials, and how are they being addressed?

One of the biggest hurdles is red tape. As important as regulatory standards are for ensuring efficacy and ethicality, they can act as a bottleneck for addressing breakthroughs whether they are completely new drugs or improving an existing process.

Legislatively, existing laws have been applied to CGTs and new laws have been implemented. Examples of these are the FDA's fast track designation, Regenerative Medicine Advanced Therapy (RMAT) designation, and Real-Time Oncology Review (RTOR).

How do you perceive the safety profile of current gene therapies? What are the main safety concerns?

I would describe the safety profile of current gene therapies as positively dynamic, meaning they are constantly getting better. The simplest way to explain all of the safety concerns is adverse effects, specifically immune responses and off-target genetic modifications.

What strategies are being employed to enhance the efficacy and reduce off-target effects?

So one I've already mentioned would be hybrid systems, specifically ones with a non-viral component. Hybrid systems mitigate risk because they selectively utilize the positives of different therapies and when used in conjunction can mitigate the risk of each one while enhancing their efficacy.

Non-viral therapies are great because they are safe (less likely to cause an immune response or adverse genetic effects). But they aren't as effective as viral therapies. One that hasn't been discussed is transient delivery methods. This means using therapies don't cause permanent genetic modifications and instead cause a short-term change in a patient's gene expression.

Can you explain the importance of long-term follow-up in assessing the efficacy of gene therapies?

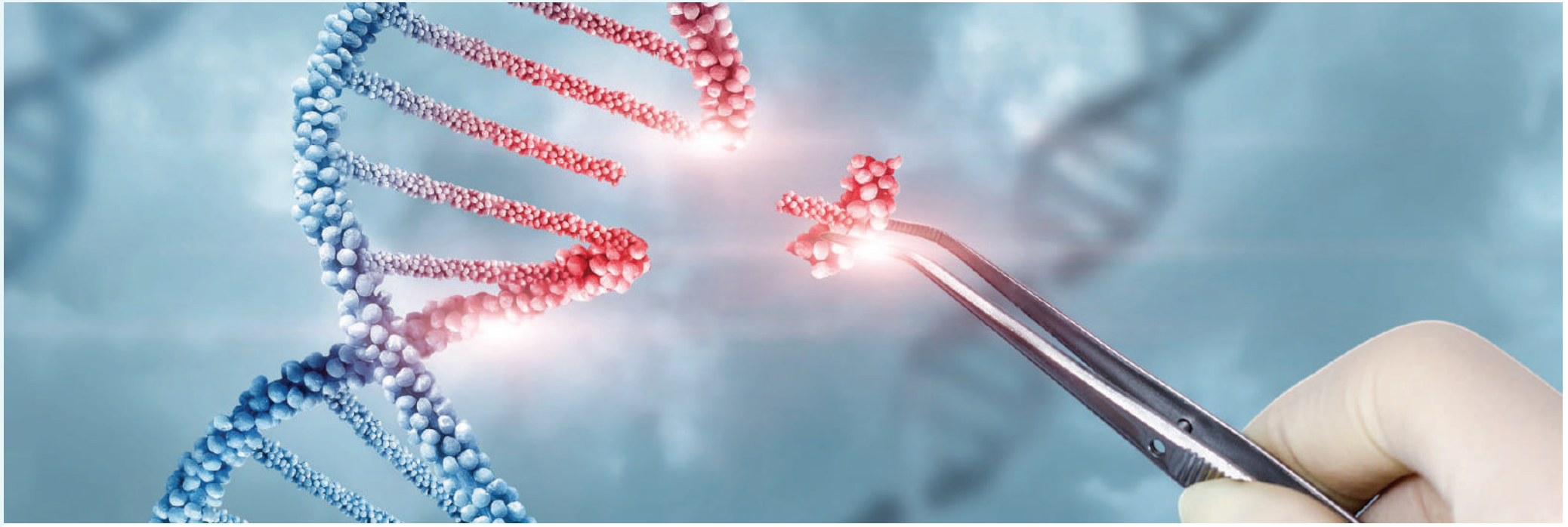
Besides the obvious importance of long-term outcomes in medicine, it is especially important to CGTs because modifications to a person's cells or genome can lead to catastrophic health outcomes later in life. Giving a treatment that could only shortly extend a person's lifespan and potentially cause them far more suffering is the biggest drawback. Which is why long term follow-ups are crucial to this type of treatment.

What are the major ethical concerns surrounding gene therapy, especially regarding germline editing?

Besides the concerns that have been around about the use of stem cells in general (namely fetal rights and adverse effects), there is the unique concern of affecting future people. People obviously have no control over their parents' genes but the deliberate manipulation of people's genes raises the question of whether we are overstepping natural boundaries. Furthermore there is also the concern of using this technology to develop dystopian phenomena like super-soldiers, designer children, etc.

How do you view the regulatory landscape for gene therapy across different regions (US, EU, Asia)?

Despite the significant differences in the priorities and protocols of these various regulatory bodies, I think the most important trend about the regulatory landscape as a whole is harmonization. There is a big need for nations to work together on CGTs. Something that I think has changed the landscape is Project Orbis because it is demonstrated that collaboration is effective rather than daunting.



Do you think current regulatory frameworks are sufficient to address the unique challenges of gene therapy, or are changes needed?

I think the current regulatory frameworks are handling the challenges of gene therapy well, but there was always room for improvement. It's easy to point out what outcomes need to be changed such as the aforementioned problem of balancing compliance and creativity. But I wouldn't be able to point out the specifics because if I could, I would be a rich man.

What are the biggest challenges in bringing gene therapies to market (cost, scalability, regulatory hurdles)?

Besides everything discussed, one thing that is often overlooked is the workforce. Hypothetically if none of those things were an issue (cost, scalability, regulatory hurdles), there is still the problem of skilled labor. As of now, entry level certifications for biopharma (let alone CGTs in particular) are rare and there is no industry standardization like with other licensed healthcare professionals.

Furthermore, because nothing out there is standardized and therefore there is no "near guarantee" of getting a job if one has a background in biopharma. This has a bottom up effect. People entering college will be reluctant to consider this field (if they even know about it), people that are working on or have a biotech degree will struggle to find work, and people with relevant experience would struggle to get in. Even if you have secured a job, the lack of standardization means people in the industry will take longer on average to achieve a certain competency.

How do you foresee the pricing and reimbursement challenges for gene therapies being addressed?

I know how it's being done now but I wouldn't know how it would

be in the future. The reason for this is based in the same logic as my answer for how regulatory bodies need changes: it's easy to say what needs to be done but figuring out how to do it is where the experienced folks would be making a living. Now, what is being done is payment plans contingent on patient outcomes and I based on what I know, I consider this is an adequate system.

How can gene therapy treatments be made more accessible to patients, considering the high costs?

I would imagine government funding legislation drafted with scientific professionals to craft criteria for patients to receive the treatments would be the best approach.

What advancements in gene therapy do you expect to see in the next 5-10 years?

The only advancement that I can speak to would be about CAR-T, as I have industry experience and learned about it on my own. As I mentioned before, theoretically it can be used to treat solid tumors. This is significant because then CAR-T can be used to treat a wider variety of more common diseases such as lung cancer, ovarian cancer, breast cancer, and brain cancer.

Which diseases or conditions do you think will benefit most from gene therapy in the future?

Depending on how far in the future, I think a pragmatically optimistic answer is all of them, though it's too soon to tell for that. Monogenetic disorders are most likely the easiest to address in the near future since they involve a single gene, making them simpler to target with current techniques.

How can the field of gene therapy benefit from collaborations between academia, industry, and regulators?

I think what I mentioned before about standardized certifications and adequate training would apply here. If institutions worked together to create solid pathways to success for individuals, we would see changes on a very large scale. This is because of a bottom-up effect wherein individuals have adequate incentives for their hard work and therefore, more people put in more effort to push for better outcomes.

Are there emerging trends or technologies (such as AI, machine learning, precision medicine) that you believe will accelerate gene therapy research and development?

Interestingly enough, I wrote a LinkedIn post about this topic recently. NVIDIA recently implemented a program called NVIDIA Inference Microservices (NIM). This is described as “an AI in a box”. There is great potential for AI to streamline and accelerate drug discovery. I believe this is important because one of the greatest barriers to innovation is financial burden.

AI could streamline biomarker identification for drug efficacy, reducing the need for costly methods like mass spectrometry, ELISA, and PCR, thus freeing resources for further innovation. Furthermore, this program gives smaller companies access to this innovative technology. This means that if the technology proves successful, the market can be filled with more innovative medicine and procedures.

How are patient perspectives being incorporated into the development of gene therapies?

The only way that I knew of is patient advocacy groups. They sort of play as a mediator. They educate patients about treatments and educate biopharma companies about patient concerns. They have also been involved legislatively. For example, the 2018 Right to Try bill allowed terminally ill patients to access experimental treatments that have passed Phase I clinical trials that don’t have FDA approval.

What role do you see patient advocacy groups playing in advancing gene therapy research?

Ironically I inadvertently answered part of this question in the previous question. But to build on it, patient advocacy groups raise awareness for genetic disorders, which helps to draw the attention of generous patrons. Furthermore, they also provide financial support for gene therapy research through fundraising or government grants.

What advice would you give to early-stage researchers or companies entering the gene therapy space?

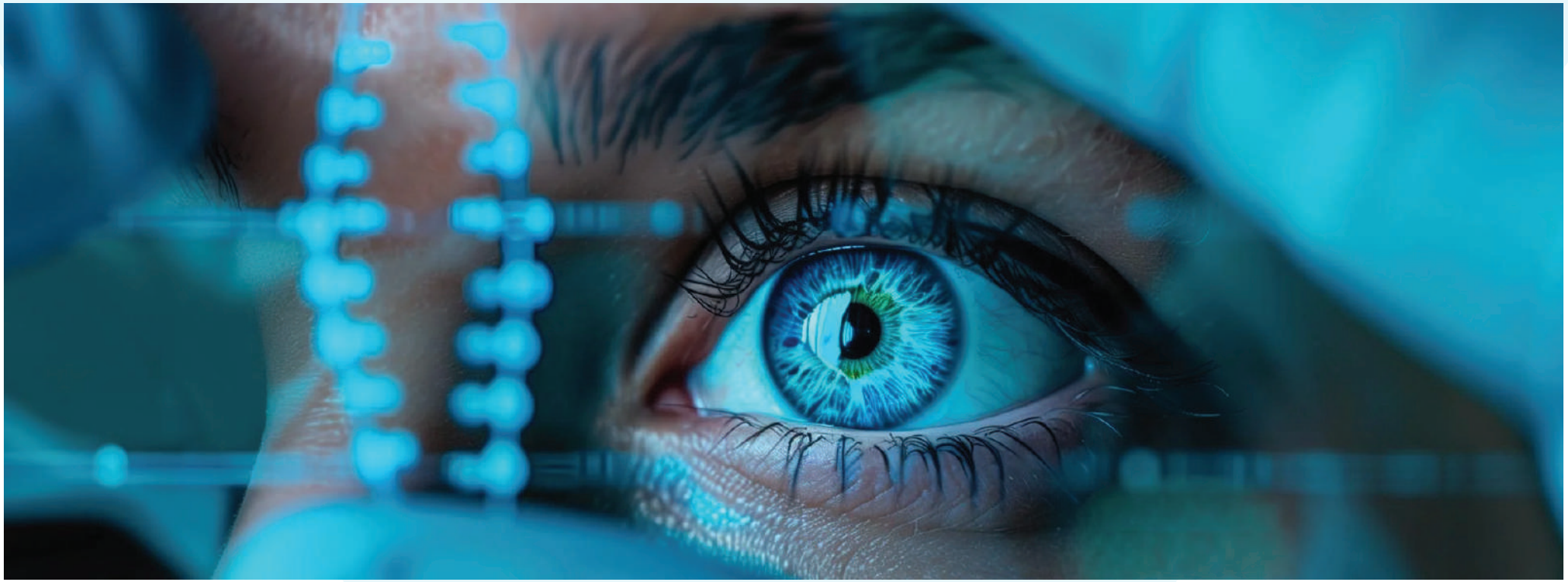
Communication with people experienced in commercial production is the key to long term success, especially for developing companies. Interdepartmental communication is more important in biopharma than any other industry because of all the regulatory hurdles that make continuous improvement financially and temporally burdensome in the most Herculean fashion.

Getting things as close to perfect the first time around counts for a lot. It can mean the difference between success and stagnation.

What are the critical success factors for a gene therapy program, in your experience?

One of the most overlooked factors is delegation. CMOs, CDMOs, CROs, and similar life sciences outsourcing organizations are critical to success. CGTs are expensive and therefore require significant cash flow to be sustained.

Organizations like this increase the chances of a company scaling up in a timely manner, which increases their financial viability. Furthermore, these companies help with the other factors like patient recruitment strategies, quality, compliance, clinical trial design, technology, innovation, etc.



What is your personal vision for the future of gene therapy? What should the next big focus be?

My personal vision for the future of gene therapy involves the financially viable ubiquity of industry standard certifications and the use of CGTs in enhancing the quality of life for the average person. For example being able to use CGTs to develop personalized exercise and nutrition plans based on a person's genetic makeup.

I think the next big focus should be validating more advanced delivery systems to reduce side effects and increase efficacy.

Is there anything else you believe is important for the broader scientific or medical community to understand about gene therapy?

Unfortunately, CGTs are a double edged sword. They demonstrate both danger and promise, making it especially important to allocate resources toward shaping public perception. Misinformation could hinder their acceptance and impede progress.

What do you think will be the single biggest challenge and opportunity for the future of gene therapy?

The greatest challenge and opportunity lies in developing or enhancing drug delivery systems that are both efficient and cost-effective, all while maintaining the highest levels of efficacy. This might fall under idealism now, but if the field keeps advancing like it has been doing, it might become a reality.

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