Roundtable Session 1 – Table 7 – Non-Viral Delivery Options for Cell-based Gene Therapy Products

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Abstract:

The field of cell-based gene therapies has seen a dramatic surge since the first landmark approval in 2017. This new therapeutic approach has been life-changing for thousands of patients worldwide. While viral vectors are the current workhorse for these ex-vivo therapies, they have some limitations, such as restricted cargo size, immunogenicity, oncogenic potential, and high production costs.

Two gene therapies were approved by the FDA for the same disease on the same day last December. One (Lyfgenia) utilizes a lentivirus vector; the other (Casgevy), leverages CRISPR, a non-viral option. Both therapies appear to have similar efficacy in clinical trials.

Our roundtable discussion will delve into these exciting advancements and address key challenges:

Discussion Questions:

1. **Unique Manufacturing Challenges for CRISPR:** What specific hurdles do CRISPR-based therapies face in CMC development and product production?
2. **Tackling CRISPR therapy Manufacturing Challenges**: What strategies can we employ to overcome these challenges?
3. **Scaling Out Production**: How can we rapidly ramp up CRISPR production capacity to ensure enough therapy reaches patients who need it?
4. **Beyond CRISPR**: Which alternative non-viral delivery technology holds the most promise in further overcoming the limitations of viral vectors?
5. **Challenges of Beyond CRISPR**: What is the most significant CMC hurdle for this promising non-viral delivery technology?

Notes:

1. **Unique Manufacturing Challenges for CRISPR**

Compared to viral vector-based therapies, CRISPR is a less proven technology for ex-vivo therapies. There are higher risks of off-target gene editing leading to unknown effects.

Although CRISPR allows for a more complicated editing, the development challenges are higher. Even a small variability in components like Master Cell Lines can lead to a significant impact on the functionality. Thus, validating different aspects of a CRISPR based therapy is challenging.

With CRISPR, we also need to find a suitable delivery vehicle, whereas viral vector such as lentivirus (LVV) is more straightforward. CRISPR therapies requires a guide, template, delivery vehicle like LNP, etc. leading to complex and expensive development.

CRISPR needs to have a well characterized guide (gRNA), which needs a lot of bioinformatics work for mapping purpose, as well as complex chemical & biological assays to support the analytics.

2. Tackling CRISPR therapy Manufacturing Challenges

It is important to think about what elements of the overall CRISPR therapy can be platform, for example guide RNA. Although this means higher investment upfront for optimizing the process and developing the methods to fully characterize, thinking is that for a synthetic molecule like guide RNA it can be widely applicable once its established. It can aid in creating value by developing multiple products with different targets by using the platform technology and just changing the target sequence.

It is also crucial to mitigate off-target editing risks by having appropriate analytical tools early in the development and identify the right strategy.

3. Scaling Out Production

With autologous therapies such as Exa-Cel where each patient has its own lot of manufacturing causes challenges with scaling it out. It cannot be just scaled-up. One must scope out the key strategies to increase production. A couple of solutions are to a) develop an allogeneic therapy and b) shorten the overall process time by use of automation in the manufacturing process.

For example, BMS manufactures approximately 5000-7000 doses of their CAR-T therapy. Their initial manufacturing process was ~18 days and with use of more automation they reduced it to ~16 days. That said, is that considered meaningful? It must have been a lot of optimization effort to shorten the manufacturing time by 2 days and it will have also required comparability studies to support the change. At the end of the day, the sponsor must have had good rationale for the changes with expected benefits. A lot of times, multiple small incremental changes over the lifecycle of the product can lead to substantial improvement.

4. Beyond CRISPR

When it comes to alternative non-viral delivery technologies, lot of the products in clinical trials are Lipid Nanoparticles (LNPs) based.

LNPs are already clinically validated for delivery to liver. See Alnylam's ONPATTRO – an approved LNP based infusion for the treatment of polyneuropathy caused by an illness called hereditary ATTR amyloidosis.

This makes LNPs a reasonable strategy to use for delivery of CRISPR based therapies in liver focused diseases. So, from a systemic administration point of view, technologies for delivering LNP based cargos in the liver are certainly progressing. However, the challenge will be for targets outside liver tissues. Some companies are also exploring delivering T-cells in-vivo using LNPs, however even with those, targeting extra-hepatic tissues will remain a challenge.

Other non-viral delivery options include polymeric delivery systems but there is limited knowledge in this space, especially for delivery of RNA based cargo. There is also research around using Electroporation with CAR-T type therapy, but the panel thinks it would be a GMP nightmare.

With all that, there is a consensus from the panel that LNPs are the most promising non-viral delivery technology.

5. Challenges of Beyond CRISPR

One of the challenges is in the Intellectual Property (IP) space. So, there is not a lot of freedom of operations. IP and proprietary restrictions also lead to increase cost.

These therapies also use novel excipients that leads to safety concerns. Each company will have to show toxicological data because of slight differences.

On top of that, these novel excipients are required by regulatory agencies to be filed at the level of a Drug Substance, which points to the current challenge in the industry with respect to the classification of these components. For example, lipids used in the LNP based products are not starting materials but are part of Drug Product, in the chemical form of delivery. For the COVID vaccine, Moderna classified two of the novel lipids as starting materials, while commercially available lipids DSPC & Cholesterol were classified as excipients. Irrespective of the classification, all components need to be well characterized and relevant information needs to be part of regulatory submissions.

There are also general challenges associated with CRISPR, regardless of the mode of delivery. While the patient perception is favorable for CRISPR being more transformative, the long-term effects are unknown. For in-vivo therapies, how can germ-line transmission be prevented. It is important to perform non-clinical assessments and risk analysis based on the target tissue, biodistribution and product understanding with supporting characterization studies. All of that should be submitted as a comprehensive package for safety assessment.

Another challenge for CRISPR is keeping up with the CMC development against accelerated clinical timelines. Risk-benefit evaluation should be done by establishing safety profile and indication for a strong unmet need. Developers should emphasize for thorough consultations, regulatory compliance and navigating the industry successfully.

Summary

In summary, non-viral delivery options such as LNPs have several benefits, but it comes with its own set of challenges. On one hand, these processes are easier to scale up compared to viral vector-based processes and the manufacturing times are also much shorter. While on the other hand, there are more components required for manufacturing and it gets more nuanced based on the complexity of the cargos.

Even with the higher development costs due to complex manufacturing and IP restrictions, the actual COGs in the commercial space may be potentially cheaper. Ultimately, the companies need to have a robust process and control strategy.

Viral vector therapies such as LVV cannot be used for in-vivo delivery. For in-vivo therapies, non-viral options such as LNPs are favorable. However, more consideration is needed for use of LNPs for ex-vivo therapies as well as enabling extra-hepatic delivery.

The CGTP industry should continue discussions on platform approaches, strategies to mitigate off-target editing risks as well as other promising non-viral technologies beyond CRISPR.