4th Annual

Next Generation Gene Therapy Vectors

June 12-14, 2024 | Boston, MA

An Interview with Lonza

AN EXCLUSIVE INTERVIEW WITH:

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Dr. Lisa Prendergast leads innovation for Lonza's Licensing Business Unit, supporting the growth of expression system platforms which are available through 'Lonza in Your Lab®' programs. She is an expert in Molecular Technologies, including vector-based gene expression systems and sequence-based technologies supporting the development of complex biologicals.

Ahead of the 4th Next Generation Gene Therapy Vectors Summit (June 12-14, Boston), we sat down with Lisa to discuss key trends in viral vector production, platform approaches, and the latest research with extracellular vesicle delivery.

For adeno-associated virus (AAV) and lentiviral vector (LV) production, there remains an ongoing debate around whether to rely on transient transfection or stable producer cell lines. Could you tell us a bit more about the difference in methods and when a drug developer might want to choose one over the other?

Right now, the most common method in viral vector production is transient transfection, where plasmid DNA encoding viral genes is transfected into cells, leading to high-level expression of the desired virus, over a short time frame – usually 48-72 hours. This method is fast to implement, flexible for process development, and suitable for early-stage production. Usually, cells used for expression are in suspension, unlike older manual methods that were open and adherent.

Industry has moved towards closed systems using bioreactors, which has made production more consistent, robust, and scalable. It's become the go-to standard in our industry.

We have also seen engineering approaches focused on improving the plasmids used for transient viral production which can improve titre and product quality characteristics.

Even with these improvements, we still face hurdles like limited plasmid availability, scalability issues, and high production costs.

Looking ahead, stable producer cell Lines look really promising for improving quality and reducing the over cost of new gene therapy drugs. This approach involves integrating the genes needed for production directly into a single stable cell line. Not only does this cut down on costs, but it also makes the whole supply chain more reliable and offers a scalable solution that maintains high quality.

Drug developers might choose transient transfection for rapid process development and early-stage production due to its flexibility and ease of use. Ultimately, stable producer cell lines would be preferable for large-scale, consistent manufacturing needed in late-stage clinical trials and commercialization. The size of the target therapeutic population will also impact the choice of approach to use. The fact that the industry is pushing towards these Stable Producer Cell Lines shows the importance of the need to standardize viral vector manufacturing.

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A hot topic right now is in developing platform approaches for clinical- and commercial-stage viral vector production. What are the considerations for taking a platform approach or using customised processes?

The main considerations for using a platform or a customised process depend really on the properties of the therapeutic, and these are not necessarily mutually exclusive options. . Different serotypes, both native and engineered, will express at different levels and the transgene sequence the capsid carries will also impact expression levels, and ratios of full to empty capsids.

Using an established platform approach involves using standardized processes, equipment, and methodologies, including in some cases cell lines and plasmids. The emphasis with this approach is around process optimization, scalability, and most importantly consistency.

Customized processes may be necessary for addressing specific vector characteristics or unique therapeutic needs. This approach allows for tailoring of production methods to specific vector types, for example engineered capsids, or individual product requirements, such as a specific ratio of full to empty. This approach offers flexibility

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to address unique challenges but may require more resources and time for process development and optimization.

As Lonza's subject matter expert for exosomes, your talk at the Next Generation Gene Therapy Vectors Summit in June will touch upon your work exploiting them as natural nanocarriers for delivering a range of cargo. Could you tell us a bit more about the latest research with exosome-mediated drug delivery?

Extracellular vesicles (EVs) such as exosomes show tremendous promise as vehicles for drug delivery, boasting several advantages such as their ability to carry diverse cargo, their innate immune 'silence' and low risk of toxicity. EVs can also be re-dosed, which is a limitation of other modalities including AAVs due to immunity. Research and development, spearheaded by companies like Codiak, have driven the development of engineering technologies that enable the creation of customized engineered exosomes or EVs. Engineering approaches offer the flexibility to tailor specific properties of the EV and importantly load or carry targeted payloads.

At Lonza, we are proud to introduce this technology to the wider EV community through the launch of the Xcite EV platform. This platform enables generation of engineered EVs. engEx exploits 2 proteins which are endogenously associated with exosomes, PTGFRN and BASP-1 to load cargo to the surface, or into the lumen of exosomes. The loading is achieved through the use of plasmids engineered to make the linking and loading technologies easily available.

A significant advantage of this technology is its clinical validation through successful Phase 1 trials of Codiak's three clinical assets: exoSTING, exoASO-STAT6, and Exo-IL-12. These therapeutic examples showcase the platform's versatility in transporting small molecules (STING agonists), proteins (IL-12), and nucleic acids (ASOs). Our aim is to leverage this technology to support new EV-based drug programs in the field.

A key focus area of the meeting this year will be in optimising vector selection and design with scalable and efficient manufacturing in mind. What advice would you give to early-stage drug developers looking to equip themselves with delivery platforms that will manufacture at scale downstream?

Two factors with a substantial impact from the start of the development process are scalability and quality.

For those embarking on the gene therapy development journey, my advice would be to consider scalability from the outset and evaluate whether your chosen approach aligns with a pathway to commercial manufacturing. For instance, starting with an adherent process for generating initial material may necessitate transitioning to a suspension process later for scaling up during IND enabling or clinical studies.

Partnering with a CDMO can be highly beneficial, as it allows developers to leverage established, validated platforms that have generated commercial products. It also allows you to select a versatile platform capable of accommodating various therapies, which ultimately saves time and cost in the long run.

Early emphasis on quality and consistency is critical. It's essential to establish processes that yield dependable results and meet regulatory standards as you progress towards larger-scale manufacturing. Investing time in robust process development upfront pays dividends later by facilitating smoother scaling up and navigating regulatory requirements more effectively.

And finally, why are you excited to take part in the Next Generation Gene Therapy Vectors Summit this year?

The exceptional program is what drives my interest! This year, in particular, there are several highly innovative approaches from developers aimed at addressing challenges in the therapeutic implementation of gene therapies—such as targeting and toxicity—as well as a strong focus on payload design. It's also a fantastic opportunity for engaging discussions over the course of a few days.

Join **Lisa**, the rest of the Lonza team, and 70+ vector development experts at the **4th Next Generation Gene Therapy Vectors Summit** in Boston, June 12-14, 2024.

DOWNLOAD YOUR COPY OF THE FULL PROGRAM HERE