Thinking big: the need for innovation in the production of lentivirus-based cell and gene therapies

ROUNDTABLE ROUND-UP

In a recent Expert Roundtable discussion, we spoke to five experts about strategies for scale up of lentivirus-based cell and gene therapies. Here, we sum up some of their key thoughts.

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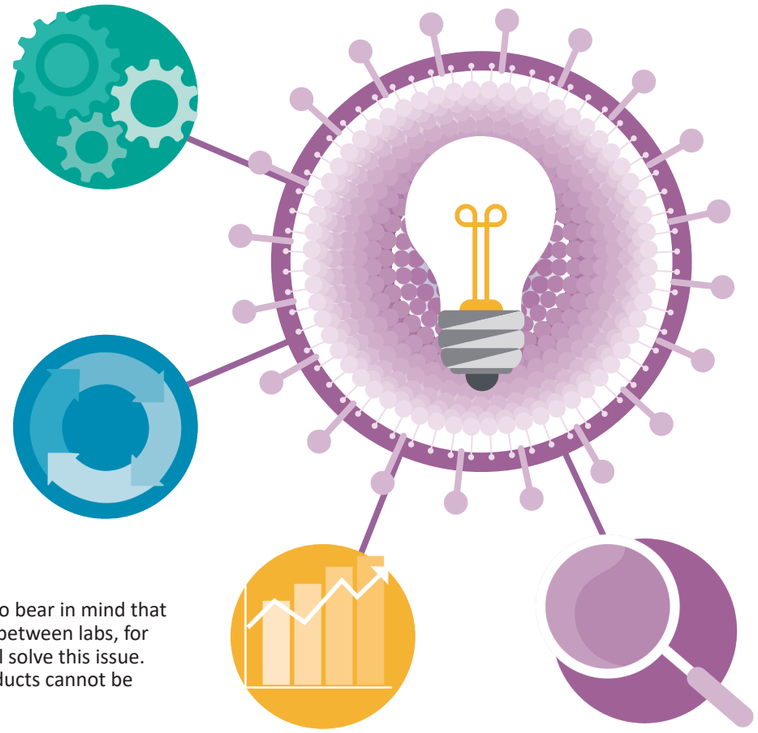
EVOLUTION OF LV-BASED CELL AND GENE THERAPY MANUFACTURING:

"The field has made good progress in the last few years, moving from an idea of clinical demand to things that will enable commercial demand. There has been a lot of focus on what technologies are scalable, and how to make sure we can meet the demand of a commercial product. CAR T programs and *ex vivo* uses of lentiviral vectors (LVs) to make cellular therapies have come to the forefront, and with this great progress people are now excited about the commercial possibilities of these products."

John Moscariello, *Bristol Myers Squibb*



PROCESS DEVELOPMENT CONSIDERATIONS FOR ENSURING A COMPARABLE TITER AND DRUG PRODUCT:

"Looking at process development, the most important aspect is quality by design – quite early during process development ranges for different process elements such as pH, cell density and so on should be statistically defined. With biological processes there is always some variation in productivity and impurity levels. It's important to bear in mind that LV titer is dependent on cell line, and titers cannot be directly compared between labs, for example. Reference standards should be available quite soon, and we will solve this issue. But without reliable analytical tools, comparability of titers and drug products cannot be ensured."

Hanna Leinonen, *Kuopio Center for Gene and Cell Therapy*

"We are in a relatively new part of the biotech industry, and robust, established and even compendial analytical methods are still a long way away. Measurement is a problem. Looking at titer and genome copy is important. The dialogue we've had with agencies in our jurisdictional scope are always about patient safety – what is it that makes the vectors efficacious? Reproducible and consistent transduction results in T cells. This is the biggest analytical space that we're dealing with. Out of every lot of vector generated, how is it comparing to the ones that came before, and how are things changing? In the end, what is going to sell everything you do is demonstrating safety."

Will Junker, *Kite Pharma*

THE BEST TIME TO BEGIN BUILDING YOUR ANALYTICAL ASSAYS:

"Start developing your analytical strategy as soon as possible. You will need the analytical titer and infectious titer during your development – this will help you ensure the constructs you are making are producing enough titer. You also need to make sure the titer is functional on your target cells – we always recommend doing this before you get too far into the process. You also need assays for residuals: your host cell DNA, plasmid DNA, host cell protein, everything you want to clear through your purification process. Overall, this will help you characterize and understand your manufacturing as you move through the process."

Scott Cross, *Dark Horse Consulting*

WHERE INNOVATION IS STILL NEEDED TO IMPROVE THE COST EFFECTIVENESS AND SCALABILITY:

"When considering cost, primarily what we're looking to do is increase the yield of the process, both at large and smaller scale. It fundamentally comes down to cost per dose for the patient. I don't see one huge improvement to the current transient transfection process that will solve our problems. It will be lots of small increases across the whole process that add up to make a significant difference. One area that hasn't received a lot of attention in the past is the vector constructs themselves. We're largely still using vector plasmids and genome constructs that are 10-15 years old and haven't changed much. Something we're doing is taking a deeper dive into these sequences to see if we can improve the overall efficiency of the process."

Lee Davies, *Oxford Biomedica*

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