CASE STUDY: BRIDGING THE CELL AND GENE THERAPY TECHNOLOGY GAP

Dave Backer, Chief Commercial Officer at Oxford Biomedica

SITUATION

The range of viral vectors used in the production of gene therapies are quite different. The most common, AAV, is a capsid-based virus, which makes it hard to kill but also hard to purify out, and it can be a contaminant. The other viruses, lentivirus, retrovirus etc, are not capsids, but they have an envelope around the virion, which makes the product more labile and therefore easier to kill and to purify away, but it's also a lot harder to make a lot of that product.

ABOUT

Dave Backer has been in the cell and gene therapy (CGT) industry for over 20 years, giving him a long-term view of the differences and similarities of manufacturing CGTs vs monoclonal antibodies (MAbs) and how that plays out in terms of tech transfer and scale-up.

In this case study, Dave discusses the technology needs of viral vector manufacturing.

CHALLENGES

One of the companies we were working with closely was able to create, upstream, high volumes of lentiviral product but on the downstream side the recovery rates were dire across a couple of unit operations but the one we focused on was the final sterilising filter. In theory, the lentivirus is smaller than the 0.2-micron sterilising filter should be able to go through, but the recoveries were sometimes as low as 10%. The fundamental problem with the final filters is that they are made for different types of products, not viral vectors. This occurs throughout advanced therapy development, particularly gene therapies and mRNAs, not as much in cell therapy where equipment, buffers and raw materials are used that were designed for something else initially. There are some options when it comes to final filters – PDS, cellulose acetate, nylon – and several ways they can be applied but some companies get to a point where they decide they're not going to put a sterilising filter in and run the downstream process but do it aseptically.

The challenge of borrowing process technologies from the monoclonal world is that this industry has spent many years solidifying to a single process, so it's the variability of processes in CGT that are not allowing the crossover of technology.

SOLUTIONS

The company we were working with did not want to take the aseptic approach, they wanted a sterilising filter, so we started talking to different tools suppliers and while we were met with interest, as they were seeing growth in CGT, we were also in competition with a bigger biologics market, and when covid hit it just exacerbated the situation.

This is a case study that does not have a happy ending. The vendor partner that we started working with became subsumed with other activities and while we're hoping that development will continue with the filter product, for the clinical trials at hand we had to stay with the incumbent process and do repeated batches to get enough product. The lentivirus itself was a raw material for an autologous oncology CAR product so being able to go ahead with the process was an acceptable near-term result.

The work done throughout this project was not in vain as there are opportunities to continue development as and when the project reaches commercial-scale or for the next compound in the company's pipeline.

Outlook

However, it's not a particularly satisfying result and developers are still completely dependent on both supply chains and the interest of the vendors. In terms of cell therapies, vendors are starting to make products that are specifically designed for that technology but for viral vectors, there is still a significant gap to bridge.

The CGT market has expanded significantly in the last decade and the talent is primarily coming from biologics and from MAbs. This is bringing larger scale and commercial experiences with a quality standpoint into the CGT space. For years, technology has been at pilot scale for most indications, right now because of the productivity seen in the primary vector – lentivirus and AAV – the indications that can be treated are limited to rare diseases, so a 10x improvement is needed in upstream and downstream technologies so that expected batches can treat an indication that's not a rare disease. For the most part, the technology is not there and the success of the industry is dependent on moving upscale.

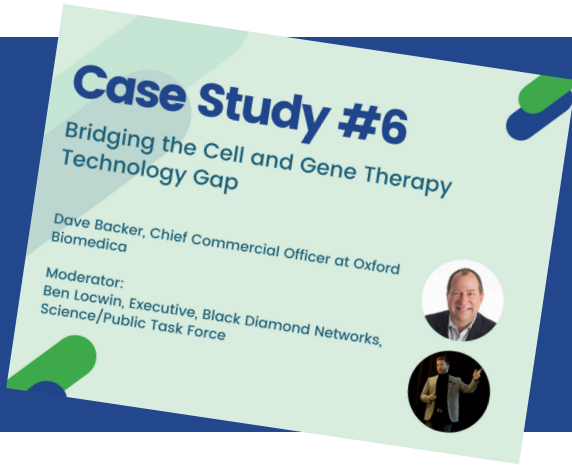
LESSONS

It's crucial to have an internal process group that's taking into consideration the whole process, as the reality was the formulation buffer and several unit operations that occurred before you get to the filter were important and it was the internal team discovering that. The filter team were just looking at feed supply really.

This case study was presented at a recent virtual event 'Pharma Shifts to Biologics', which included six in depth case studies and networking sessions.

Details of future events can be found here.

You can watch Mark's case study in full and on demand here



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