SMART SCALE-UP: EXPANDING VIRAL VECTORS WITH MICROCARRIER BEAD TECHNOLOGY

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As health professionals administer the Pfizer-BioNTech and Moderna mRNA-based COVID-19 vaccines, other companies are working to develop viral vector-based vaccines to combat coronavirus and other viral diseases. Viral vectors require cells to grow, but certain viral vectors can only be produced on adherent cell cultures, while others can also be produced on suspension cell cultures. Vaccine manufacturers often encounter significant challenges in scaling up the adherent cell cultures used for these treatments, and novel technologies are needed to facilitate safe, rapid production.

Microcarrier bead technology is a relatively new, but proven, technology for imprinting adherent cells onto carriers, which can then be grown in SUT reactors and scaled up for clinical and commercial production volumes. When combined with complementary cell lines, such as Vero, microcarrier beads can help companies make better use of the equipment and systems they already have in place for suspension cell technology.

Some companies may lack the analytical capabilities to characterize cell lines that will replicate target viruses well enough to yield titers sufficient for high-volume production, or lack qualified cells. Relying on a CDMO can help to accelerate early-phase development and reduce costs, but companies must ensure their partner has the process understanding necessary to apply this technology and these cell types specifically to their project.

HOW MICROCARRIER BEADS MAKE OLD EQUIPMENT NEW AGAIN

Viral vector manufacturers know well the limitations of scaling up viral vectors from adherent cell cultures in two-dimensional models like cell stacks. Until recently, common scale-up equipment like stir-tank bioreactors could only be used in suspension cell applications, making cell culture expansion for most vectors a difficult and time-consuming process. Each stack must be precisely manipulated to ensure proper seeding across each layer. When working with a high number of cell stacks, a larger footprint for equipment is required in order to move, manipulate, and incubate the cell stacks. Additional materials (tubing manifolds) or equipment (biosafety cabinets) are required to ensure sterility throughout their lifecycle.

Microcarrier beads, however, provide an ideal surface for adherent cells to attach and grow. Once attached to the beads, cells can be suspended in solutions that are compatible with stir-tank reactors, allowing for rapid replication and scale-up. Cells grown in suspension – such as CHO or HEK – achieve much higher concentrations of cells per milliliter. So, manufacturers can expand viral cell cultures from 50 ml up to 50 L, and with the right systems in place, a developer or CDMO using microcarrier beads can achieve viral vector manufacturing yields up to 200 L much more efficiently than with cell stacks.

Microcarrier bead technology allows developers to grow adherent cell cultures at similar densities in steel or single-use bioreactors. The technology actually favors SUT systems, and SUT reduces cleaning validation and eliminates the potential for product carryover, which can further reduce the equipment footprint of a manufacturing operation while generating proportionately higher yields for the space consumed.

Cell monitoring and control are easier, too. With cell stacks, manufacturers must pull representative samples from one or two stacks, and imaging can be difficult, especially with larger stacks like CS40s. If they do not have a large enough microscope or low enough bed, sometimes a handheld microscope can be used, but it still takes a great deal of time and effort to obtain a good image and determine progress. Cells growing on microbeads in a bioreactor make for simpler monitoring of daily cell counts, bonding, and growth. Developers can quickly control pH levels, sparge with oxygen, adjust suspensions and easily perform a media exchange if needed, check metabolites, and feed the cells. This degree of control is not possible with cell stacks – for example, pH is usually controlled indirectly, as a function of the CO_2 concentration in the incubator – and any imbalance in the chemistry of the cell stacks will stop cell growth.

A CDMO that understands how this technology works can tailor a process for efficiently scaling up viral vector-based vaccines in any lab, using traditional equipment or SUT systems. However, the technology – which has become more widely available in the industry – is only part of the equation. The more complicated factor to contend with is cell line selection.

THE RIGHT CELL LINE FOR THE JOB

Manufacturers familiar with microcarrier bead technology may already have incorporated it into the process they have developed in their R&D labs. When they approach a CDMO for help with scaling up to Phase 3 or other GMP production, it usually is a safe, compliant cell line they need. Early-stage and start-up companies often develop processes using cell lines from uncontrolled sources, which are unsuitable for GMP work. Microcarrier bead technology is compatible with many different adherent cell lines, including MRC-5, BHK-21, MDCK, and Vero.

Vero cells have been widely used in the industry to produce inactivated virus and especially live-virus vaccines, due in large part to their susceptibility to a broad range of viruses and their well-acknowledged and well-regarded safety profile. Vero cells may not always be permissive for all viral vectors of interest and grow them to higher titers, but the panel of viruses that replicate in Vero cells is broad. A number of COVID-19-targeted products have been made using the Vero cell line, and it offers great potential for multiple viral vectors to introduce genes of interest into patients. For

example, one vaccine against COVID that uses Vero cells is PiCoVacc, an inactivated coronavirus. COVID-targeting genes also could be intro duced through the Vero cell line using the measles virus. And similar applications are being considered to produce vaccines for diseases like influenza.[1]

Various manufacturers have intensively characterized Vero cells, in terms of adventitious agents, including tumorigenicity studies and robust qualification of all raw materials. The line also has been adapted to work in serum-free conditions – which eliminates potential concerns about transmissible spongiform encephalopathy components – while still yielding a good rate of viral replication.

THE RIGHT TECHNOLOGY, THE RIGHT CELLS, THE RIGHT PARTNER

The team at IDT Biologika's Rockville, Maryland site has developed its own Vero cell line based on one obtained from the WHO, adapted to serum-free conditions and characterized according to current regulatory standards. This proprietary cell line is available for client projects, free of any licensing fees, along with IDT Biologika's expertise in combining Vero cells with microcarrier bead technology.

Located in Rockville's biotechnology corridor, IDT Biologika's U.S. site specializes in Phase 1 and Phase 2 clinical production and process development. With dedicated suites for process and assay development, quality control, GMP and non-GMP manufacturing, and quality assurance, our flexible and agile site can handle multiple projects at once. Our German location, which has a larger capacity and is FDA, EMA, and ANVISA approved, can provide clients with the necessary support for Phase 3 and commercial production. IDT Biologika can take viral vector products from development all the way to commercial production and can expertly facilitate project transfer between our clinical and commercial sites.

1. https://www.raps.org/news-and-articles/news-articles/2020/3/covid-19-vaccine-tracker

ABOUT THE COMPANY

IDT Biologika is an international leader in contract development and manufacture of vaccines, viral vectors, and biologics. IDT Biologika is a full-service CDMO providing end-to-end services for viral vaccines and viral vectors and have supported clients in developing and manufacturing some of the leading human vaccines in use today against infectious diseases and viruses around the world, including COVID vaccines.

IDT Biologika offers biologics development and manufacturing to support clinical to commercial scale drug substance and drug product manufacturing capabilities in Europe (Germany) and North America (Rockville, Maryland). These locations support our fully integrated services and are cGMP and up to BLS2-compliant, with approvals from the FDA, EMA, and ANVISA.