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Fast-Tracking Cell Therapy Manufacturing across Borders

The idea of a borderless world can suggest vulnerability—or the benefits of freely sharing ideas and, ultimately, creating and sustaining globe-spanning cell therapy supply chains

By **Josh P. Roberts**
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The Cell Therapy Manufacturing Asia 2020 conference was held in Kyoto in February, not long before the coronavirus epidemic led to the cancellation of many such gatherings around the globe. Attendance was diminished, and many attendees resorted to teleconferencing. Still, the event provided presenters and attendees an opportunity to share perspectives on a wide swath of topics, from scale-up and process analytics to regulatory navigation. Several representative presentations—some of which were delivered on site, and some of which were live streamed from elsewhere—are summarized in the text that follows.

Vertical scale-up

Cell therapy production for many preclinical studies and some early-stage clinical studies can be accomplished in two-dimensional planar flasks or spinner flasks. Nonetheless, if commercial success is to be achieved, said Brian Lee, PhD, president of PBS Biotech, the producer must scale up manufacturing while maintaining the quality of the product as well as the cell growth. “Single-use bioreactors, he added, “are considered a much more cost-effective and scalable manufacturing platform for cell therapy products.”

Anchorage-dependent human stem cells cannot grow freely as single cells in the suspension cultures typically used for *Escherichia coli* or adapted Chinese hamster ovary (CHO) cells. Instead, they are grown on microcarrier beads or as cell aggregates while suspended in a bioreactor. Unfortunately, a traditional horizontal, stirred-type bioreactor can pose problems. “As the vessel size increases,” Lee noted, “the fluid dynamic characteristics are difficult to scale up while maintaining the conditions at the small scale.”

He asserted that the geometry and mixing mechanism of PBS Biotech's Vertical Wheel™ bioreactor system is "completely different," providing homogeneous mixing and uniform particle suspension in a very low sheer stress environment for cells. The same mixing parameters developed in a 100-mL working volume can be applied to larger-scale vessels to give a similar fluid dynamic microenvironment.

Lee shared data selected from PBS Biotech customers that had used 0.1-L (and above) bioreactors. The company has more than 100 such customers. Although they used different cell types, cell lines, media, and processes, their data, Lee asserted, "demonstrate the difference in the biological performance purely based on the bioreactor fluid dynamic function."

Consistency of scale-up results has been shown at up to 50 L in an 80-L bioreactor, with plans for up to 400- or 500-L vertical bioreactors—sufficient for large-scale commercial manufacturing.

Industrialized MSC supply chain

But does a company even have to source its own stem cells and maintain its own banks? Mayasari Lim, PhD, bioprocessing specialist at RoosterBio, argued that it may be better to industrialize this part of the supply chain "so that these companies in the cell and gene therapy space can really start focusing on developing their final products."

Mesenchymal stem cells (MSCs) are adult stem cells that can be used in a variety of ways, for example, as pluripotent or differentiated cells; as engineered tissue, possibly genetically modified for gene therapy; or even as factories for producing extracellular vesicles (EVs).

Providing off-the-shelf cellular starting material—MSCs and optimized bioprocess media—supports RoosterBio's "mission to fuel the rapid commercialization of scalable regenerative cures," she said. The growth medium is formulated so that it doesn't have to be changed every two or three days—typical in the stem cell field—which is labor intensive and costly. Instead, a nutrient supplement is added to the continuing culture for a fed-batch protocol. For harvesting EVs, RoosterCollect-EV medium is formulated with a low particle count for minimal background.

RoosterBio aims to help companies significantly shorten their clinical development timelines. "They are able to reference our master files that are already with the U.S. Food and Drug Administration," noted Lim. "That reduces the regulatory burden and the cost. By providing them all the cells, all the media, all

the starting materials, and by supporting them for their IND filing, we can help them develop the target product that they're going after."

Does potency predict efficacy?

Rohto Pharmaceutical, best known for its over-the-counter pharmaceuticals and cosmetics, is moving into the field of regenerative medicine. It is conducting Phase I/II studies in Japan using allogeneic MSCs as therapeutics for indications such as liver cirrhosis.

It can be frustrating not to know, while developing a cell therapy, if the process will yield the hoped-for product for release. "Potency tests need to predict clinical efficacies," said Hidenori Nonaka, group leader of Rohto's division of regenerative medicine. The potency test should be based on the mode of action. However, whether potency tests will accurately predict clinical efficacies may not be discovered until the late clinical stage or later.

"We know there are some parameters that can differ from one lot to another," he continued. "But we are not sure these differences are really critical to having an effect in the patient. The challenge is, we don't know much about the mode of action, which remains to be understood." This should become clearer as data comes in from the clinical trials.

Rohto is looking at several different assays that can be performed on the intermediate and final products (cells) or disposed material (such as supernatant) along the way, to help find critical quality attributes that will correlate with a successful product. The company is focusing on potency tests for matters such as immunomodulatory function, differentiation capability, and senescence of the MSCs as part of a matrix of complementary measures.