Opportunities and challenges in cell and gene therapy development

Q&A with Dr. Ger Brophy, Executive Vice President, Biopharma Production, Avantor

One of the most revolutionary trends driving the biopharmaceutical sector is cell and gene therapy. At its most basic definition, gene therapy (also called human gene transfer) is the therapeutic delivery of nucleic acid into a patient's cells as a drug to treat disease. According to documentation published in The Journal of Gene Medicine, as of November 2017 nearly 2,600 gene therapy clinical trials have been undertaken in 38 countries around the world.

We interviewed Dr. Ger Brophy, Executive Vice President, Biopharma Production at Avantor, to get his perspective on this exciting segment of the bioprocessing industry. He is especially eager to work with innovative leaders, scientists and researchers in the industry who are seeking to explore and expand the potential for gene therapy.

There is a great deal of attention around a select number of approved cell and gene therapies for relatively small patient groups. Can you describe the most exciting benefits arising from these therapies?

I think it is a very exciting space, and we're seeing the number of trials grow. It's probably most exciting because of the technology's ability to impact patients' lives.

Yes, the numbers of patients are relatively small at this point in time, but that's to be expected. Many biopharma researchers and manufacturers started with smaller defined patient populations, and in particular those with pediatric relapse refractory acute lymphoblastic leukemia. That's partly because they wanted to deal with small populations that they understood well and, in many cases, that didn't really have many other options for treatments.

We're seeing these companies moving on now to larger populations — starting with leukemia, now lymphomas. From our perspective, a key goal would be finding a treatment for is multiple myeloma. If those patients begin to see benefits from cell and gene therapies, I think the excitement will feel justified.

Scalability and manufacturability — that's the next question we will all be looking at. Can we manufacture cell and gene therapies at scale? If we can manufacture these treatments at scale, can we do so safely?

What are the real game-changers driving the progress with cell and gene therapy?

For the first time, people are talking about curing these dreadful diseases. We're seeing the patient's own immune system used to fight cancer. Many of the first patients treated for acute lymphoblastic leukemia, are thriving — four to six years later.

The game-changer here is that you are using the body's own systems, either from a cellular immune system or from the ability to repair and replace defective or missing genes. CAR-T cell therapy is arguably among the most personalized medicine one can consider. The patient's own T cells are extracted, modified, activated, expanded, purified and returned to that patient.

The promise of personalized medicine has been growing for a long time. We're actually beginning to see real, tangible effects from the molecular knowledge now that we have an understanding of how the disease develops and how the patient responds to it.

Tell us about the industry — what kind of companies are working today in cell and gene therapy, and do you think this will change?

Many of the early movers in cell and gene therapy were small biotech startups. In some cases, these treatments were supported by major hospital centers. Increasingly, we've all seen a greater interest by the major biopharma industry. Novartis was probably the biggest; it started the earliest, and was successful in getting approval for Kymriah. But in the last year, we've seen Kite being acquired by Gilead, Juno being acquired by Celgene, and other companies in China driving major strategic partnerships with major biopharma companies.

As companies of this size get involved, we expect they will leverage their increased breadth and depth to develop new labels, develop new trials, and find ways to manufacture these therapies at scale.

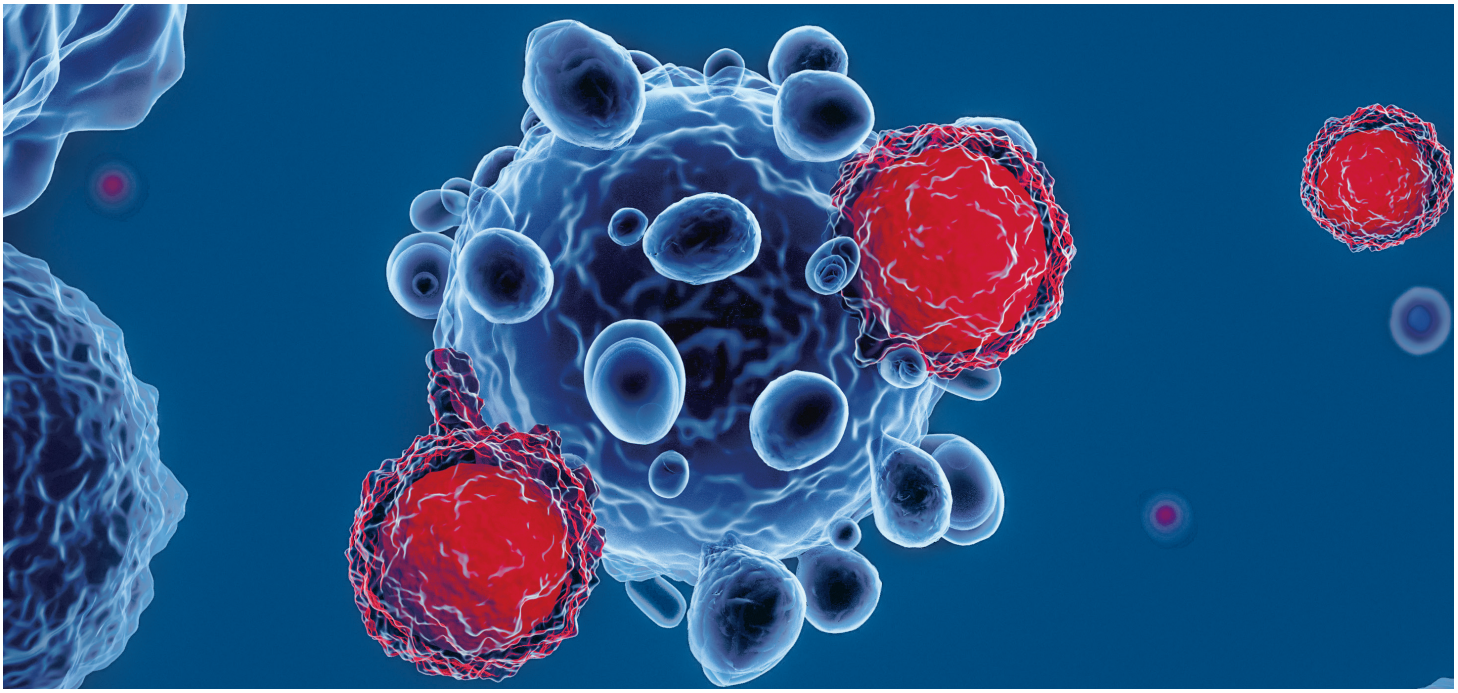
What are the critical challenges for companies working or going into this field?

Scalability and manufacturability — that's the next question we will all be looking at. Can we manufacture cell and gene therapies at scale? If we can manufacture these treatments at scale, can we do so safely? Can we do so at a reasonable cost so that the populations affected by these diseases can access treatments?

The issue is process standardization. When you're talking about a cell therapy, the single biggest point of variability is the patient's own cells. And by its very nature, this is individual to the patient, and individual to the health of the patient at the time of leukapheresis.

Variables and failure modes have to be taken out of the process. We can standardize, close systems so that they're not exposed to failure modes, miniaturize these systems — all this can help. We can improve technologies, like sterile fluid transfer, if we can use excipient technology to further stabilize and use analytical technology to understand what will make a successful or less successful therapy. We can increase the efficacy, decrease the risk and decrease the cost.

This is where Avantor can help, since we supply cell-culture components, production chemicals and single-use technologies that aid in these processes. I think our knowledge – of cell culture, of technology development, sterile fluid transfer, fill and finish and excipients and the technology surrounding those – will be valuable and applicable to helping make these technologies available at scale.



How can companies react to those challenges? What are the tools or solutions they are looking for?

We need to better analyze and understand the variability that comes from the research data, even at the early stages of these trials, and use it to correlate to both clinical and process outcomes. Taking out manual steps as early as possible is going to be important, as well as creating closed systems using sterile fluid transfer technologies.

We need solutions around side effects, which is one of the most significant challenges. As we understand how to provide a more efficacious dose, perhaps using less cells, some of the side effects of these drug therapies may be improved.

And we must find scalable ways to address costs, which are far too high. The systems of reimbursement should be reviewed — for example, should reimbursement be made dependent on outcomes?

Ultimately, these drugs must be developed in a more cost-effective manner. That's an area where technology providers and suppliers, like our company and others, can play a significant role by closing and automating systems, and by understanding the contribution of labor and overhead and possible economies of scale from reducing processes.

A big issue for companies working in these therapies are the regulatory hurdles. What insights can you share about regulatory issues for cell and gene therapy?

I think the regulatory groups have been encouraging. To a degree, there's competition among different regional bodies – in Europe and in the UK, in China and in Japan, in different ways and within different specialties.

We have seen that regulatory bodies have been very open and collaborative in acknowledging that cell and gene therapy is different. They are willing to put into place the appropriate regulatory system to enable the drugs to get to market, and to monitor them going forward.

The FDA's support on CAR-T technologies is a good example. Regulators are allowing flexibility in the normal hierarchy of how clinical trials are performed, particularly in phase II and III trails, but the companies must still address the FDA's post-marketing commitments and safety issues.

With the amount of strong research into developing, understanding and characterizing drug targets, and figuring out how to make these in production level volumes, this will be a constantly changing landscape. And, there will be many parts to patient treatment options going forward.

Do you think cell and gene therapy will be the core focus in the future for biopharma? Will it replace small molecules and biologics?

I don't think so. I think each type of drug product will find its niche. People tend to forget about small molecules, but they are still incredibly important in the market. Large molecules are also being developed for areas like neuro-degeneration. I think they'll have a continued role to play there.

Monoclonals and biopharmaceuticals have only started to make a significant impact in the last 15 to 20 years. Cell and gene therapies are just starting and have yet to obviously make a significant market impact. With that considered, who's to say what's next?

With the amount of strong research into developing, understanding and characterizing drug targets, and figuring out how to make these in production level volumes, this will be a constantly changing landscape. And, there will be many parts to patient treatment options going forward.

Avantor is excited to be involved in this groundbreaking new space to treat some of the most complex and difficult diseases the world faces. It's clear that cell and gene therapy can succeed as one more healing tool — as with other treatments that moved from theoretical possibilities to real results, we can clearly see the issues that need to be addressed, and we're ready to help get the next stage of development in motion.

About the author

Dr. Ger Brophy is Executive Vice President, Biopharma Production. In his current role, Dr. Brophy is responsible for developing and implementing Avantor's Biopharma Production offering to support the current and future needs of our customers. Prior to joining Avantor, Dr. Brophy held a variety of research and development, strategy, advanced systems, and business development positions with GE Healthcare Life Sciences, GE Healthcare Medical Diagnostics and Amersham for nearly 30 years. Dr. Brophy earned a Bachelor of Science in biotechnology, as well as a doctorate in molecular biology from Dublin City University in Ireland.

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