Scaling Cell Therapies:

Revolutionizing Healthcare for a Future of Cures and Hope

Karthik Ramachandran, PhD
Chief Operating Officer & Co-Founder, Likarda

Cell therapies are heralding a transformative age in medicine, offering promising new avenues for treating a variety of debilitating diseases. As we shift our focus from merely alleviating symptoms to discovering potential cures, we enter a realm of unprecedented possibilities in healthcare. Millions of individuals worldwide grapple with chronic and life-altering diseases, such as diabetes, cancer, arthritis, and heart disease, all of which significantly impact their quality of life.

In response to this urgent need for effective treatments, breakthroughs in cell therapies are happening at an astounding pace. Pioneering biotech companies, both large and small, are at the forefront of these advancements, tirelessly working to develop innovative solutions. These trailblazers are dedicated to creating a better future for patients and their families, striving to transform the landscape of healthcare for generations to come.

However, as we race towards these groundbreaking therapies, it is crucial to recognize that their true potential can only be realized if they are accessible to the millions of patients in need. To achieve this, we must find ways to commercially scale their manufacturing processes. The ability to produce these therapies at a mass scale will not only bring life-changing treatments to countless individuals, but also usher in a new era of affordable and widely available healthcare solutions.

In this article, we will delve into the challenges and opportunities associated with creating scalable cell therapies, exploring the latest developments and technologies that can help make these revolutionary treatments a reality for patients around the world. Join us as we embark on this exciting journey to unlock the full potential of cell therapies and transform the future of medicine.

Scale-Out versus Scale-Up

The first thing to understand in scaling a process is the difference between scale-out and scale-up. The process of scaling out is simple in that the production process remains the same and is simply replicated. For example, if you're able to print a part using a 3D printer, you simply scale-out by purchasing more 3D printers to produce more parts. This can be a low-tech approach used for early process development and clinical batches, but to meet commercial demand, achieving economies of scale can be difficult. The process of scaling up is more complicated and requires more resources, planning, and development on the front end, but can achieve large-scale commercial production at a more reasonable cost point. An example of scale-up would be transitioning from bench-level flask-based cell culture to multi-liter bioreactors.

The best pathway for scaling a cell therapy further requires process development and thoughtful considerations about cell type, the growth/differentiation process of the cells, formulation/delivery technologies, equipment for cell growth/proliferation, delivery method (just-in-time vs cryopreserved), among other critical factors affecting manufacturability. It's important to ask these questions early as they can greatly affect downstream processes as a product goes from proof-of-concept to market.

Scalability in Cells

In considering the scalability of a manufacturing

Scaling Cell Therapies:

Revolutionizing Healthcare for a Future of Cures and Hope

process, the first thing to consider is the source of the cells: autologous (from the patient themselves) or allogeneic (from another donor). In an industry that is plagued by regulatory burden, autologous cells provide the least path of resistance as they come directly from the patient themselves. This alleviates or eases the need for immunosuppressive treatments, patient-to-patient cross contamination concerns (like disease transmission, graft-vs-host disease, etc.) and can lead to treatments that provide the strongest chances of success. However, producing an autologous cell therapy requires individual product manufacturing runs for each patient, increasing the logistics, manufacturing costs, and the complexities of controlling each batch individually.

Allogeneic cell therapies, on the other hand, offer the ability to take cells from a donor and produce treatments that could treat multiple individuals, even up to millions of individuals. More specifically, induced pluripotent stem cells (iPSCs) which are typically derived from adult cells, are reverted back to a stem cell like state where they can be differentiated to create a variety of cell types, in turn being able to be used to treat a variety of diseases. iPSC-based technologies are of high interest because they can easily be multiplied (proliferated) in commercial bioreactors or by other large-scale manufacturing processes. Allogeneic cells enable a future where cell therapies are more cost effective at scale and reach a broader number of people.

Scalability in Delivery Systems

To date, most cell therapies (whether autologous or allogeneic) have been directly injected either into the site of injury or systemically to treat diseases. For systemic diseases, this works well as can be seen in the successful use of CAR-Ts to treat hematologic cancers. However, this approach has had mixed results when injecting directly in targeted locations because the cells don't remain in place. One of our previous articles focuses on targeted cell therapy delivery along with discussing why cell homing doesn't work. Much like we deliver drugs in capsules, tablets, or particulate formulations that assist in drug absorption, distribution, function and clearance, cells also need delivery systems.

Microencapsulation technologies offer one formulation that enhances the function of the cell therapy and protects the cells from the immune system. Microencapsulation typically refers to injectable microspheres that contain the active ingredient—the therapeutic cells. Microspheres can be designed to be durable, lasting years, or degradable as a unique delivery modality like slow-release capsules. The question is: how to produce millions of cell-containing or therapy-containing microspheres at scale.

In cell therapies, the two most popular methodologies to microencapsulate cells in hydrogels are: 1) emulsion-based technologies or 2) droplet generator technologies. In emulsion-based technology, non-miscible fluids such as oil and water are used to create round droplets that contain the hydrogel and cells of interest. This methodology typically requires the utilization of oil or other non-miscible solvent that is compatible with both water and cells. Cells are highly sensitive to the products used in these processes and cell viability can be greatly affected by these solvents. The easiest way to think of this type of droplet generation is to take oil and water and mix them together in a bottle. You'll find little droplets of water floating in oil (or vice versa), which are then crosslinked to make the final product. One of the problems with approach is the inability to control the droplet size. This issue can be overcome by adding microfluidics where emulsion-methodology is occurs in size-constrained chambers. Along with poor cell viability, large-scale production is extremely

complicated with a microfluidic approach.

A more scalable form of microsphere generation involves extruding uncrosslinked hydrogels through a needle creating a droplet that falls into a bath for crosslinking. Alginate is the most popular material utilized for microencapsulation using this procedure. However, alginate is not biocompatible and is quickly rejected by the body. There are other materials available for encapsulation including hyaluronic acid, polyethylene glycol and polyvinyl alcohol, among others. These hydrogels crosslink too slowly so they are not readily applicable using the same manufacturing process as alginate. Likarda developed and patented its own unique process that enables leveraging the droplet generation approach, which is highly scalable, with these biocompatible hydrogels.

Wrapping Up

When considering all the options that can affect a cell therapy and its manufacturing process, it certainly can feel daunting. It's important to ask these questions early and develop a thoughtful process and understanding the cell therapy from start to finish. It's also important to recognize early that a cell therapy's failure may not be because of the cells, but because it's missing key manufacturing considerations like delivery systems, formulations, or storage when thinking about scale.

Have a Delivery System Issue?

If you believe you have a delivery system issue with a cell therapy currently in development, or you're planning on developing a new cell therapy and want to avoid delivery system issues, learn more about how Likarda's targeted delivery system can help you: **https://likarda.com/biologic-and-cell-solutions/**

Or book a call today with the Likarda team at **816.605.6440**.