How one cell transplant platform is poised to tackle complex diseases

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April 30, 2021 -- The biopharmaceutical industry has focused in recent years on the development of complex, cell-based therapies. But what goes into developing a successful cell therapy product? Lineage Cell Therapeutics CEO Brian Culley discusses the company's cell therapy technology with *ScienceBoard.net*.

The company's technology involves the transplantation of differentiated stem cells as part of an off-the-shelf allogeneic cell therapy and is based on controlling the differentiation of pluripotent stem cells. As the cells are grown and increase in number, Lineage scientists treat the cells in different ways, depending on what they want the final cell type to be.

Scientists in essence "control the lineage" of the cells that they are developing -- hence the company's name.

Culley joined the Lineage team two and a half years ago, and he sees great promise in the technology.

"I'm really excited about what the future may hold using this approach," Culley told *ScienceBoard.net*.

Transplantation science

Culley often refers to Lineage as a *cell transplant* company rather than a *cell therapy* company because the cells that it is developing have been manufactured to acquire specific functions and need to be delivered in the location of the cells they are replacing, such as the eye or spinal cord. This differs from companies and clinics that inject undifferentiated stem cells into a patient's circulatory system, he explained.

The company is currently developing three clinical-stage programs focused on the delivery of specialized differentiated cells. All the programs have one thing in common, Culley explained: they all rely on the large-scale manufacturing of a specific cell type from a pluripotent stem cell line.

OpRegen, Lineage's most established program, delivers human retinal pigment epithelium (RPE) cells to the subretinal space of dry macular degeneration patients to replenish dead RPE cells. Alternatively, Lineage's OPC1 therapy for spinal cord injury delivers oligodendrocyte progenitor cells (OPCs) -- glial cells that make up the spinal cord -- to replace damaged cells.

Lastly, Lineage's VAC2 cancer immunotherapy platform leverages dendritic cells, which are the body's most potent antigen presenting cells, as a means to carry specific messages to the immune system. Because dendritic cells are normally found in the circulatory system, the VAC2

therapy places dendritic cells derived from pluripotent stem cells into the blood for the treatment of tumors.

This platform technology differs from the company's other assets because the "message" or antigen can be designed for specific tumors, which permits the company to create a large number of therapies for different tumor types.

Early versions of VAC2 technology were used to explore treatment of acute myeloid leukemia, a blood cancer, and now the platform is being evaluated in a phase I/II clinical study of nonsmall cell lung cancer, a solid tumor.

"How can a cell therapy target both blood and solid tumors?" Culley asked. He answered that dendritic cells can be modified to carry a nearly endless number of antigens that target a wide breadth of tumor types, making the platform technology a truly transformative tool.

The challenge within the industry, Culley continued, is determining which antigens are the most powerful and relevant. With billions of potential antigens to select from, he explained that Lineage is partnering with companies that are focused on choosing effective antigens to help them deliver antigens and ensure that the tumor killing message reaches the immune system.

To this end, the company recently announced its first official license agreement for the technology with Immunomic for the treatment of glioblastoma multiforme.

"The VAC platform provides Lineage with the potential for many partnerships," Culley said.

Mastering the art of manufacturing at the gold standard level

The power of the platform is derived from the use of a single cell line -- as opposed to autologous cell therapies that harvest and modify a patient's own cells -- that make Lineage's off-the-shelf therapies more cost effective and therefore able to reach more patients.

Given the importance of being able to produce large batches of its cell therapy product, Culley explained that more than 50% of his staff is focused on the manufacturing side of the business.

"We really invest in manufacturing, because that's where we have a huge advantage," Culley said.

Lineage's manufacturing processes for its off-the-shelf cells are scalable. For instance, scientists can manufacture over 5 billion RPE cells in a single 3-L bioreactor. This is more than enough to service large phase III clinical trials. The manufacturing process can scale seamlessly for commercial production with the use of more and larger bioreactors.

Culley explains that with 3D cell growth in bioreactors, the company can control the differentiation of large amounts of cells. The company must demonstrate the purity of cells, meaning that they must prove to the regulatory agencies that they are indeed manufacturing the cells that they intended.

As it stands now, the regulatory agencies require only a few key measurements such as karyotyping (counting chromosomes) of the final cell products. Lineage shows that the pluripotent cells are below the level of detection (essentially zero) to ensure that cells are fully differentiated before being transplanted to a patient. As an industry, the regulators and industry scientists are still developing process development tools and defining quality standards.

Culley explained how Lineage conducts at least a dozen analytical methods to follow production processes and monitor in-process controls during manufacturing. They also monitor entire genomes of their cells to watch for genetic drift and confirm that the product is as they expect it to be each time. They also test for specific surface markers and conduct assays for specific cell functions of each cell type they produce.

"We levy a battery of tests against our cells to ensure that their activity, identity, purity, and all the other things you want are in place, as expected," Culley noted.

The company goes beyond what the agency currently requires of sponsors, Culley noted. But he believes that the bar will rise over time because the monitoring tools are better now than they used to be. So, it will become more reasonable for the U.S. Food and Drug Administration to demand greater control over manufacturing processes in the future.

Once regulators determine the set of quality and safety requirements for cell-based therapies, Culley noted that companies who are ahead of the game in their monitoring practices will be poised to enter the market quickly and successfully.

"I think there is going to be explosive growth in the field of cell therapy," he remarked.