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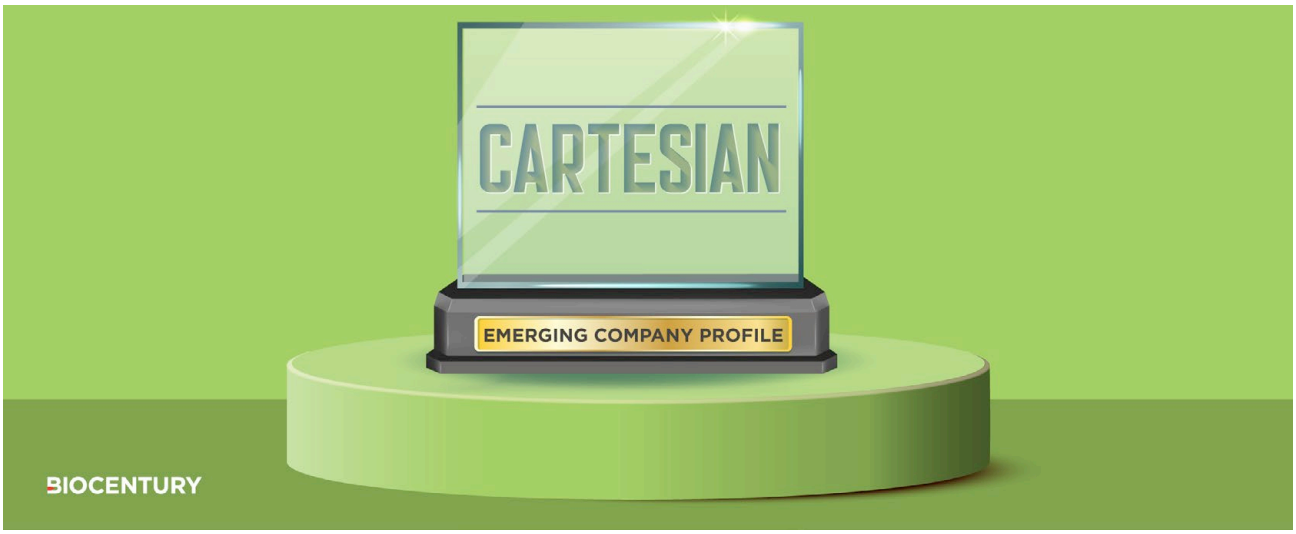
Cartesian expanding therapeutic window, disease settings for CAR T

BY STEPHEN HANSEN, ASSOCIATE EDITOR



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Cartesian's use of mRNA to drive expression of CARs in cell therapies may reduce the amplifying effect of DNA-based CAR therapies and associated toxicity, making its treatments more amenable to indications beyond cancer.

Launched in 2016, Cartesian Therapeutics Inc. is using mRNA, rather than lentiviral or CRISPR-based DNA engineering methods, to express the chimeric antigen receptor (CAR) in its cell therapies.

According to President and CEO Murat Kalayoglu, use of mRNA gives the CAR therapy a defined half-life because the transient expression profile of the mRNA means that in vivo cell expansion moderates, rather than amplifies, the CAR's expression on T cells.

"With the conventional approach you have a natural, logarithmic signal amplification. You've got huge amounts of proliferation, and as a result, massive CRS," Kalayoglu told BioCentury. Cytokine release syndrome (CRS) is a serious adverse event associated with traditional CAR T therapies.

"With mRNA expression, instead of an amplification of the signal, you have a dilution of the signal," Kalayoglu said. "Every time the cell divides with RNA cell therapy, the CAR on the surface of the daughter cell should be half of what it is on the parent cell."

That creates a "natural break" in total CAR signaling, he added. "The cell is still a CAR T cell. It is still finding, binding and killing its targets, but you can think of it as a traditional drug, where it has defined pharmacokinetics."

The advantage is a much larger therapeutic window. Kalayoglu said Cartesian hasn't observed any cases of CRS or neurotoxicity across studies in both multiple myeloma and generalized myasthenia gravis.

The therapy also doesn't require a preconditioning lymphodepletion regimen as needed by other CAR T therapies.

The drawback is an expected lack of durability of efficacy. But Kalayoglu said the benign safety profile allows for patients to be retreated when efficacy begins to wane. "You can always re-dose, and that's what we do."

Cartesian's lead program is Descartes-08, an autologous CAR T therapy targeting BCMA that is in a Phase IIa study in newly diagnosed MM patients and a Phase I/II trial to treat myasthenia gravis.

Because the lead program is autologous, it requires patients to undergo leukopheresis to obtain the T cells and then induce them with the mRNA construct. How attractive the dosing and administration profile will be to patients will depend the durability the efficacy.

In an upcoming Phase II study of Descartes-08 to treat myasthenia gravis, patients will receive six doses of the CAR T therapy once-weekly.

Kalayoglu said that based on the high-dose in the Phase I/II trial, one leukopheresis run can generate 12-18 doses of Descartes-08, equivalent to 2-3 full courses of the cell therapy. He said that if one treatment provides one year of disease remission, patients would have 2-3 years of therapy from one leukopheresis.

However, a much shorter durability profile would mean patients would have to undergo the burdensome process of extracting T cells more frequently, which could make the therapy less appealing, especially in a setting such as myasthenia gravis where patients now have relatively convenient treatment options from FCRN or C5 inhibitors with once-weekly or bi-monthly dosing.

The therapy's potential for a high level of efficacy, if it holds up with more testing, could help outweigh the burden of leukopheresis.

Data from two patients in the expansion cohort of the Phase I/II study of Descartes-08 showed reductions from baseline in MG-ADL score of 8 and 11 points at week 10, putting both patients in or near remission. Data were presented at the Myasthenia Gravis Foundation of America International Conference in Miami on May 10.

By comparison, recent data presented by UCB S.A. (Euronext:UCB) showed that in the Phase III RAISE study, patients treated with C5 inhibitor zilucoplan had a mean, placebo-adjusted reduction of 2.1 points in their MG-ADL scores, with 10% achieving a reduction ≥11 points at week 12. FCRN inhibitors have also shown mean, placebo-adjusted reductions of 2-3 points on MG-ADL score.

Cartesian isn't limiting itself to CAR T therapies. The biotech is also developing mRNA-engineered allogeneic mesenchymal stem cells (MSCs) that can deliver multiple payloads while acting as delivery vehicles to home to the diseased tissue of interest. Cartesian has started a Phase I/II study of Descartes-25, an engineered MSC therapy that expresses a bispecific mAb targeting BCMA and IL-12 to treat relapsed/refractory multiple myeloma.

The company also has preclinical programs targeting diabetic wounds, NET-related diseases and osteoarthritis.

COMPANY PROFILE
CARTESIAN THERAPEUTICS INC.
Gaithersburg, Md.

Technology: mRNA engineered cell therapies including CAR T cells

Origin of technology: National Institutes of Health (NIH)

Disease focus: Autoimmune, cancer

Clinical status: Phase I/II

Founded: 2016 by Murat Kalayoglu, Michael Singer and Metin Kurtoglu

Academic collaborators: Dana Farber Cancer Institute, University of Maryland

Corporate partners: Undisclosed

Number of employees: 22

Funds raised: $25 million

Investors: Schooner Capital, other undisclosed investors

CEO: Murat Kalayoglu

Patents: over 50 issued patents

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