

BioCentury

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PRODUCT DEVELOPMENT

CAR WINDOW

BY EMILY CUKIER-MEISNER, SENIOR WRITER

MaxCyte Inc. is collaborating with the Sidney Kimmel Comprehensive Cancer Center at The Johns Hopkins University to develop transiently expressed chimeric antigen receptor T cell therapies that may allow better control over the cells' therapeutic window. MaxCyte hopes the approach will enable the therapies to safely target antigens expressed on solid tumors.

Under a deal announced Tuesday, MaxCyte and the center will collaborate on preclinical development of CART cell therapies directed against solid tumor targets, starting with mesothelin. Other targets, as well as financial terms, are undisclosed.

MaxCyte will design and provide technology to manufacture the CAR T therapies, and retain the data and rights to resulting products. The partners will co-develop on-site manufacturing capability for the therapies at the center.

The partners expect to expand the agreement to include pre-IND studies and Phase I/II human proof-of-concept studies under terms that are not yet determined. The cancer center would be responsible for conducting the pre-IND and clinical studies and could submit an IND as early as next year.

Though chimeric antigen receptor therapies have achieved encouraging early results in hematologic cancers, they haven't been easy to adapt to treat solid tumors, in part because of the difficulty in finding suitable target antigens that aren't also expressed on normal tissues at levels that could lead to unacceptable levels of toxicity.

For example, CARs for solid tumors that target carbonic anhydrase IX (CAIX) have been associated with liver toxicity, and one patient with colon cancer died in 2009 after receiving a CAR against HER2 that caused pulmonary toxicity and edema followed by a cytokine storm.

Rather than giving up on antigens with limited but non-negligible expression on normal tissues, MaxCyte plans to mitigate their on-target toxicities with T cells that express CARs for a limited time. The therapies can be given repeatedly to sustain efficacy, and can be discontinued if toxicity develops.

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DOUGLAS DOERFLER, MAXCYTE

In MaxCyte's mRNA CAR platform, peripheral blood mononuclear cells are collected from patients by apheresis and put into a MaxCyte transfection instrument, where mRNA encoding the CAR is inserted into the cells by electroporation. The cells are then washed, aliquoted and cryopreserved for future administration.

President and CEO Douglas Doerfler said the resulting cells' CAR expression is highest immediately after administration and declines over 5-7 days. In contrast, virally transduced CAR T cells may multiply after administration and can persist for several weeks.

He said another advantage of using mRNA is that it can be delivered into cells after apheresis without selection or expansion, which would reduce expenses and cut manufacturing time from one to two weeks to a day. He said a single apheresis can supply enough cells for about eight doses of therapy.

The Kimmel Cancer Center's Leisha Emens said it remains to be seen what other advantages fresh cells might provide.

"The advantage in time is huge — we still have a lot to learn about what kinds of cells we need to use, and a lot of

preclinical work to do,” said Emens. She is principal investigator for the preclinical and proposed clinical program and associate professor of oncology at the center.

Doerfler said it is also easier and cheaper to produce therapies using fresh cells: “The facilities do not have to be as controlled as a biological manufacturing unit. You can use a stem cell lab, which has a much lower facility cost.”

MaxCyte’s partnership with Kimmel Cancer Center is the first that will use fresh cells.

Doerfler wasn’t aware of any other companies studying mRNA-expressed

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CANCER CENTER

CAR therapies in the clinic. However, several are using “suicide switches” to trigger the CAR cells’ destruction if they cause toxicity, and at least two — [Intrexon Corp.](#) and [Bellicum Pharmaceuticals Inc.](#) — are exploring small molecule approaches in the clinic to control the cells’ behavior.

EFFICACY QUESTION

Doerfler said MaxCyte chose mesothelin as the initial target for the collaboration because its expression profile is right for showing POC. Mesothelin is overexpressed in the majority of malignant pleural mesotheliomas and pancreatic and ovarian cancers, and is found in some lung, breast and gastrointestinal cancers. But it is also expressed at low levels on normal peritoneal, pleural and pericardial tissues.

“The selection of mesothelin was to prove the point that you could control this off-tumor, on-target toxicity in such a manner as to move the therapeutic index and have an antitumor effect without toxicity in normal tissue,” said Doerfler.

Whether any mesothelin-targeted CAR can be effective against solid tumors is still up for debate. Last week, some of the first data presented

for a CART therapy in solid tumors — CART-meso from [Novartis AG](#) and the [University of Pennsylvania](#) — showed hints of efficacy, but no complete or partial responses. The Novartis product consists of autologous T cells transduced with a lentiviral vector expressing a CAR directed against mesothelin (see “CAR Talk,” page 18).

Six patients from the lowest planned dose cohort of a Phase I study received doses of $1-3 \times 10^7$ cells to treat mesothelioma, pancreatic cancer or ovarian cancer. Four had stable disease by day 28. No cytokine release syndrome was observed. Cells persisted for at least 28 days in peripheral blood and showed evidence of trafficking to tumor sites as well as off-tumor, on-target sites, though these were not associated with overt on-target toxicities.

Data were presented at the [American Association for Cancer Research \(AACR\)](#) meeting on April 19.

Janos Tanyi, assistant professor of obstetrics and gynecology at the Hospital of the [University of Pennsylvania](#), introduced the presentation with a comparison to mRNA CARTmeso cells. Carl June and colleagues at the Abramson Family [Cancer Research Institute](#) at UPenn have started four clinical studies of mRNA CAR T therapies, two of which studied mesothelin-targeting CARs. In these trials, the cells were selected and expanded before electroporation.

Tanyi said mRNA CARTmeso therapy is a safe and feasible way to treat mesotheliomas and pancreatic adenocarcinomas. However, he said the university went on to develop its lentiviral approach because mRNA CARTmeso expression was detectable in peripheral blood for only one or two days after administration, and “the antitumor effect was very limited.”

Doerfler disagreed with Tanyi’s implication that mRNA CARTmeso cells would be ineffective. He said the duration of mRNA CARTmeso expression reported by Tanyi at AACR was based on a dose of about 10^8 cells, whereas data reported by June’s group in 2013 showed a dose of 10^9 mRNA CARTmeso cells was detectable up to seven days after administration.

June’s group published a case report in *Cancer Immunology Research* on two patients in Phase I trials of mRNA CARTmeso cells that were produced using MaxCyte’s technology. One patient with advanced malignant pleural mesothelioma had a partial response by modified RECIST criteria, but

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developed progressive disease six months later. The other patient, who had metastatic pancreatic cancer, had stable disease after receiving three weeks of therapy.

Both patients showed antibody responses consistent with epitope spreading related to tumor destruction, and an analysis of CARTmeso mRNA in the patient with pancreatic cancer suggested that the CAR T cells trafficked and persisted in tumor tissues.


“Dr. June showed two measurable responses in pancreatic cancer and mesothelioma with no attendant toxicities. In that initial cohort of patients, we were able to show some form of efficacy with no toxicity,” Doerfler said.

June is a professor in the Department of Pathology and Laboratory Medicine at UPenn’s Perelman School of Medicine and director of the translational research program at Abramson.

At the AACR presentation, discussant Michel Sadelain said the jury is still out on whether targeting mesothelin using CAR therapies can induce responses against solid tumors as dramatic as have been seen in early trials of hematologic cancers. Sadelain is director of [Memorial Sloan Kettering Cancer Center’s](#) Center for Cell Engineering and a scientific co-founder of [Juno Therapeutics Inc.](#)

“We know from these studies that responses are often excellent in the bone marrow, but less predictable in lymph nodes in particular,” Sadelain said at the meeting. “Until we see full-fledged efficacy, we cannot comment on safety — but so far so good.”

Doerfler declined to say how MaxCyte and the Kimmel Cancer Center’s initial mesothelin-targeted CAR construct may differ from UPenn’s CARTmeso construct.

MSKCC is also studying a mesothelin-targeted CAR T therapy in Phase I in combination with cyclophosphamide in patients with malignant pleural disease from mesothelioma, lung cancer or breast cancer. 

COMPANIES AND INSTITUTIONS MENTIONED

American Association for Cancer Research (AACR), Philadelphia, Pa.

Bellicum Pharmaceuticals Inc. (NASDAQ:BLCM), Houston, Texas

Intrexon Corp. (NYSE:XON), Germantown, Md.

The Johns Hopkins University, Baltimore, Md.

Juno Therapeutics Inc. (NASDAQ:JUNO), Seattle, Wash.

MaxCyte Inc., Gaithersburg, Md.

Memorial Sloan Kettering Cancer Center (MSKCC), New York, N.Y.

Novartis AG (NYSE:NVS; SIX:NOVN), Basel, Switzerland

University of Pennsylvania, Philadelphia, Pa.

REFERENCES

Beatty, G. “Mesothelin-specific chimeric antigen receptor mRNA-engineered T cells induce antitumor activity in solid malignancies.” *Cancer Immunology Research* (2013)

Cukier-Meisner, E. “Remote controlled CARs.” *BioCentury* (2015)