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EMERGING COMPANY PROFILE

TRuCs VS. CARs

BY VIRGINIA LI, STAFF WRITER

TCR2 Therapeutics Inc. is creating autologous T cell therapies that it thinks will have greater activity against solid tumors than CAR T therapies, and broader applicability than TCR therapies. The key to the approach is fusing tumor antigen recognition domains to T cell receptors, which retains the receptors' six intracellular subunits, as well as their natural shut-off mechanism.

The resulting therapeutics are referred to as T cell receptor fusion constructs (TRuCs). Lead candidate TC-210 is slated to enter the clinic in 2018 to treat solid tumors.

The main difference between TRuCs and chimeric antigen receptor (CAR) T cells is that the latter contain only the zeta subunit from an endogenous TCR, alongside a co-stimulatory domain. According to CEO Garry Menzel, CAR T cells quickly succumb to exhaustion because the zeta subunit cannot generate enough T cell activity.

"To get a sustained immune response against cancer, you need to recruit the full T cell receptor," he told BioCentury.

He also expects TRuCs to have a safety advantage because they should not induce cytokine release syndrome, an adverse event that has been common with CAR T cells in the clinic. "In its natural form, the T cell receptor has feedback loops to prevent overstimulation of a biological pathway, and we think that prevents over-release of cytokines," he said.

Autologous TCR therapies also signal through the full complement of TCR subunits. However, Menzel noted that TCR therapies target only antigens that are presented by the major histocompatibility complex (MHC), whereas TRuCs can be programmed to target any surface antigen.

He thinks that could open up a broader set of indications and translate into better efficacy. "Surface antigens typically present at a higher density than MHC-presented antigens, which may elicit a higher level of T cell activation," he said.

TC-210 targets mesothelin, a surface protein that is overexpressed in solid tumors including mesothelioma, ovarian, pancreatic and lung cancer.

TCR2 THERAPEUTICS INC.
Cambridge, Mass.

Technology: T cell receptor fusion constructs

Disease focus: Cancer

Clinical status: Preclinical

Founded: 2015 by Patrick Baeuerle

University collaborators: Massachusetts General Hospital; University Hospital of Ludwig-Maximilians-University; University of Freiburg

Corporate partners: None

Number of employees: 20

Funds raised: $44.5 million

Investors: MPM Capital, F2 Ventures

CEO: Garry Menzel

Patents: None issued

At the World Preclinical Congress on June 13, the company presented data from a mouse model of mesothelioma showing a single dose of TC-210 led to tumor eradication in all nine mice. The tumors did not grow back for at least 35 days. TC-210 also prevented growth of new tumors in three of five mice that were rechallenged on day 35.

In contrast, seven of nine of mice treated with a CAR T targeting mesothelin experienced tumor regrowth within 35 days.

The company also presented data from a mouse model of lymphoma showing T cells expressing a TRuC against CD19 produced more potent and durable antitumor responses than T cells expressing a 19-28z CAR or a 19-41BBz CAR.

TCR2 currently plans to partner the CD19 program to focus on solid tumors.

TCR2 also has a third TRuC against an undisclosed target on solid tumors. Menzel would not say when he expects it to enter the clinic.

Novartis AG and the University of Pennsylvania have huCART-meso, a CAR T therapy with a human anti-mesothelin binding domain, in Phase I for solid tumors.

In 2015, CART-meso, an earlier version of the therapy containing a murine anti-mesothelin binding domain, did not lead to any responses in the first six patients treated in a Phase I study. Although the study was recently completed, Novartis said it has no plans to report updated data and declined to say whether the program remains active. It also declined to compare either program to TC-210.

Six autologous TCR therapies are in the clinic for solid tumors. None target mesothelin.

At least three non-CART programs targeting mesothelin are in clinical testing for solid tumors. The most advanced is anetumab ravtansine from Bayer AG. The antibody-drug conjugate (ADC) is composed of a human HuCAL IgG1 mAb targeting mesothelin conjugated to the maytansinoid tubulin inhibitor DMR. It is in Phase II for malignant pleural mesothelioma.

Menzel said TC-210 can induce immune memory and thus could lead to more durable responses than ADCs. Bayer did not respond to requests for comment.

TCR2 raised $44.5 million in a series A round last year, which Menzel said will fund it through YE18 and enable start of its Phase I trial for TC-210. bc

COMPANIES AND INSTITUTIONS MENTIONED

Bayer AG (Xetra:BAYN), Leverkusen, Germany
Novartis AG (NYSE:NVS; SIX:NOVN), Basel, Switzerland
University of Pennsylvania, Philadelphia, Pa.
TCR2 Therapeutics Inc., Cambridge, Mass.

REFERENCES

Edelson, S. "CAR talk." *BioCentury* (2015)

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