

SEPTEMBER 29, 2016

## EMERGING COMPANY PROFILE

### COMPOSITE T CELLS

By Lauren Martz, Senior Writer

While the specificity of  $\gamma\delta$  T cells gives them the potential to treat a broader array of cancers more safely than the  $\alpha\beta$  T cell therapies in the clinic, they may not persist long enough to benefit patients because of tumor evasion mechanisms. [Gadeta B.V.](#) has created an immunotherapy strategy that combines the desirable properties of both T cell types into a single product.

“We didn’t want to be another CAR T cell therapy company,” said Gadeta CEO Mark de Boer. “We wanted something to discriminate ourselves from the others.”

$\gamma\delta$  T cells comprise about 5% of the total T cell repertoire and are characterized by a unique set of TCRs. Whereas the  $\alpha\beta$  TCRs on most T cell therapies bind tumor antigens that can also occur on normal tissues,  $\gamma\delta$  TCRs bind markers found only on metabolically stressed cells such as tumor cells, producing a wider margin of safety, particularly in solid cancers. The problem with using  $\gamma\delta$  T cells therapeutically is that tumors have mechanisms for directly shutting them down, said co-founder and CSO Jürgen Kuball, who is also a hematologist and immunologist at [University Medical Center Utrecht](#).

Gadeta’s platform, dubbed “T cells engineered to express a defined gamma delta TCR” (TEGs), taps the advantages of both cell types by adding the tumor-sensing abilities of  $\gamma\delta$  T cells to  $\alpha\beta$  T cells, which proliferate and persist in advanced cancer patients. The company creates TEGs by using lentiviral gene transfer to express a  $\gamma\delta$  TCR on a patient’s  $\alpha\beta$  T cells, then enriching and expanding the new cells *ex vivo* before transplanting them into the patient. The idea is that the  $\gamma\delta$  TCR will redirect the  $\alpha\beta$  T cells to tumors.

In a 2011 study in *Blood*, Kuball and colleagues showed that  $\alpha\beta$  T cells expressing  $\gamma\delta 2$  — a  $\gamma\delta$  TCR specific for a marker of lipid/cholesterol pathway disturbance present in multiple cancers — lysed various leukemia, lymphoma and solid tumor cell lines with efficacy comparable to  $\gamma\delta$  T cells expressing  $\gamma\delta 2$ , and were not cytotoxic towards several normal human cell lines. In a humanized mouse model of leukemia, the engineered T cells decreased tumor growth to a greater extent than a conventional  $\alpha\beta$  T cell therapy.

Kuball said Gadeta also has unpublished data in mice showing that TEGs have higher and longer-lasting antitumor activity than conventional  $\gamma\delta$  T cells.

Gadeta plans to take its first  $\gamma\delta 2$  TCR candidate, TEG001,

GADETA B.V., Utrecht, the Netherlands

Technology:  $\alpha\beta$  T cells expressing high-affinity  $\gamma\delta$  TCRs for cancer cell therapy

Disease focus: Cancer

Clinical status: Preclinical

Founded: 2015 by Jürgen Kuball and Mark de Boer

University collaborators: [University Medical Center Utrecht](#)

Corporate partners: None

Number of employees: 10

Funds raised: €7 million (\$7.81 million)

Investors: [Medicxi Ventures](#), Baxalta Ventures, Utrecht Holdings

CEO: Mark de Boer

Patents: None issued

into the clinic early next year. The company will start with hematologic malignancies because Kuball’s group had already begun planning a trial for those before Gadeta was formed. But later it will explore solid cancers and expects to begin its first solid tumor trial in early 2018. Gadeta is also developing TEGs expressing different  $\gamma\delta$  TCRs.

de Boer said other plans could include combining TEGs with checkpoint inhibitors and creating allogeneic TEGs, which may be possible because, unlike  $\alpha\beta$  TCRs,  $\gamma\delta$  TCRs are not MHC-restricted.

At least three other companies have  $\gamma\delta$  T cell therapies in preclinical development for cancer, primarily in solid tumors.

[University Medical Center Utrecht](#) has filed applications on three patent families covering a large part of the  $\gamma\delta$  TCR sequence space and methods of identifying  $\gamma\delta$  TCRs for clinical use, and is in the process of licensing the IP portfolio to Gadeta. One of the patent families has received a notice of allowance in the U.S. ■

#### COMPANIES AND INSTITUTIONS MENTIONED

Gadeta B.V., Utrecht, the Netherlands

University Medical Center Utrecht, Utrecht, the Netherlands

#### TARGETS AND COMPOUNDS

MHC - Major histocompatibility complex

TCR - T cell receptor

#### REFERENCES

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