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Innovations
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REPRINT FROM OCTOBER 12, 2017

EMERGING COMPANY PROFILE

CHEMO-PROOF T CELLS

By Lauren Martz, Senior Writer

T cell therapies have shown unprecedented efficacy in hematologic malignancies, but haven't produced the same results in solid tumors and have dangerous toxicities. By combining engineered, drug-resistant γδ T cells with chemotherapy, Incysus Ltd. has hit upon a strategy that may be safer and more effective against solid tumors than conventional T cell therapies.

The αβ T cells most T cell therapies use are antigen-specific and may not eliminate the entire tumor. Incysus relies on γδ T cells because they do not require antigen processing to detect target cells, and they penetrate and kill solid tumors more effectively than αβ cells.

"γδ T cells are like a bridge between the innate and adaptive immune response. They can kill like natural killer cells, then become antigen-presenting cells when activated," said Incysus CEO and co-founder William Ho.

According to Ho, one reason T cell therapies fail is that large numbers of the cells are destroyed by the immunosuppressive tumor microenvironment before they reach the tumor. Chemotherapy can kill Tregs, making that hostile environment penetrable, but it kills effector T cells as well.

To overcome the problem, Incysus creates γδ T cells that are chemotherapy-resistant. Using its Drug Resistant Immunotherapy (DRI) technology, the newco engineers allogeneic or autologous γδ T cells to express MGMT, a DNA damage repair protein responsible for chemo resistance in cancers. It uses only γδ T cells from the Vδ2 subset because they are all interferon-producing cells with antitumor properties; the Vδ1 subset contains both interferon-producing and immunosuppressive lineages.

"We hijack a tumor's own resistance mechanisms and genetically engineer them into γδ T cells so they can survive co-dosing with high dose chemo," Ho said. Chemotherapy shrinks the tumor and kills Tregs, enabling the MGMT-expressing cells to penetrate the tumor and eliminate the remaining cancer cells.

The modified γδ T cells have two additional advantages: all cancer cells express the NKG2D ligands that γδ cells target, and chemotherapy up-regulates those ligands; and γδ T cells don't produce pro-inflammatory IL-6 and so are unlikely to cause cytokine storms, making them safer than αβ T cell therapies.

INCYSUS LTD., Hamilton, Bermuda
Technology: Drug-resistant γδ T cells delivered in combination with chemotherapy
Disease focus: Cancer
Clinical status: Preclinical
Founded: 2016 by William Ho, Lawrence Lamb and H. Trent Spencer
University collaborators: University of Alabama at Birmingham
Corporate partners: None
Number of employees: 1
Funds raised: Undisclosed
Investors: Undisclosed
CEO: William Ho
Patents: One issued covering the combination of chemotherapy with immune cells, including γδ T cells and NK cells

At the 2017 American Association for Cancer Research (AACR) conference, Incysus presented data showing that in a mouse model of glioblastoma, 80% of animals simultaneously treated with its γδ T cells and temozolomide survived through the 150 day study, whereas all mice treated with either therapy alone died. The combination also increased survival in mice with temozolomide-resistant glioblastomas compared with temozolomide alone.

Incysus plans to submit an IND for its autologous γδ T cells plus temozolomide in glioblastoma by early next year.

While the newco ultimately plans to test allogeneic γδ T cells in solid tumors as well, its first trial of allogeneic cells will be in a more established indication. The newco submitted an IND for allogeneic γδ T cells in leukemia or lymphoma patients undergoing stem cell transplantation last month, and hopes to begin a Phase I/II trial early in 2018.

Incysus is in partnering discussions with undisclosed entities for both programs, and has begun raising funds in a series A round.

According to Ho, Incysus was launched last year with a seed round in the low single-digit millions, based on work from Emory University, the University of Alabama at Birmingham and Children's Healthcare of Atlanta Inc.

At least four other companies — GammaDelta Therapeutics Ltd., Adicet Bio Inc., Gadeta B.V. and Lymphocyte Activation Technologies S.A. — have γδ T cell-based therapies in preclinical development. According to Ho, no other companies have engineered drug-resistant γδ T cells.

COMPANIES AND INSTITUTIONS MENTIONED

Adicet Bio Inc., Menlo Park, Calif.

American Association for Cancer Research (AACR), Philadelphia, Pa.
Children's Healthcare of Atlanta, Atlanta, Ga.
Emory University, Atlanta, Ga.
Gadeta B.V., Utrecht, the Netherlands
GammaDelta Therapeutics Ltd., London, U.K.
Incysus Ltd., Hamilton, Bermuda
Lymphocyte Activation Technologies S.A., Cantanhede, Portugal
University of Alabama at Birmingham, Birmingham, Ala.

TARGETS

IL-6 - Interleukin-6
MGMT - O6-alkylguanine alkyltransferase
NKG2D (KLRK1; CD314) - Killer cell lectin-like receptor subfamily K member 1

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