Incysus Therapeutics, Inc.
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Incysus Therapeutics: advancing science that makes sense

Harnessing the potential of γδ T cells, Incysus Therapeutics has developed two immunotherapy programs that are ready to be launched into the clinic.

In January 2015, with snowstorm Juno battering New York City and the subway closed for the first time in 110 years, biotech investor William Ho trekked through the blizzard, twenty blocks north from his office in Manhattan to the Waldorf Astoria to meet Lawrence Lamb, then a transplant immunologist at the University of Alabama at Birmingham.

The pair discussed using a then little-known type of immune cell, the γδ T cell, as an immunotherapy for cancer. Making their vision a reality today, the company has received US Food and Drug Administration approval for two investigational new drug (IND) applications, and is about to launch its first clinical programs, with Ho as CEO and Lamb as CSO.

While there has been much excitement over chimeric antigen receptor T cell immunotherapies, which have demonstrated remarkable responses in patients with haematological cancers, solid tumors present a far greater challenge. In blood cancers, tumor cells are part of the circulation, making them readily accessible to immunotherapeutic cells that also circulate. By contrast, solid tumors are densely packed, heterogeneous in nature and entwined with healthy organ tissue. Two major challenges for cell-based cancer therapies are achieving a high enough effector-to-target cell ratio to produce a therapeutic effect and designing a therapy that can recognize substantial differences in tumor cells within a single mass.

A combination approach

Incysus's approach is to combine standard chemotherapies with γδ T cell therapy. Chemotherapies are able to kill large numbers of tumor cells, but they also select for drug-resistant tumors that are difficult to eliminate and kill the very immune cells needed to target any residual cancer. The Incysus strategy is to genetically modify γδ T cells to survive use in combination with high doses of chemotherapy. These combinations enable the chemotherapy to break down the tumor and allow the modified γδ T cells to reach the high concentrations needed to kill off any remaining cancer cells (**Fig. 1**).

A crucial role for γδ T cells is to distinguish between the safe nonself, such as a pregnancy, and the dangerous self, such as cancer. γδ T cells bridge between the cells mediating innate immunity, such as natural killer (NK) cells, and cells of the adaptive immune system, such as the better-known αβ T cells. Similar to NK cells, γδ T cells respond to upregulated stress ligands and kill in the same manner. Unlike NK cells, γδ T cells recognize these antigens through both the natural killer group 2D (NKG2D) receptor and the γδ T cell receptor, allowing for an overlap in targeting.

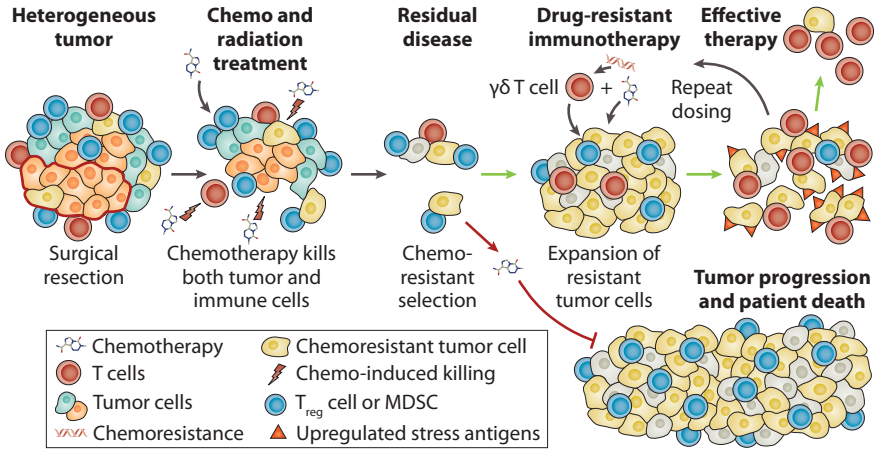

Fig. 1 | Drug-resistant immunotherapy by Incysus. MDSC, myeloid-derived suppressor cells.

Activated γδ T cells can act as professional antigen-presenting cells, and thus can directly phagocytose target cells, process tumor-associated antigens and cross-present the antigens to other T cells. In addition, γδ T cells produce cytokines that elicit stronger memory immune responses.

As a cell-based immunotherapy, γδ T cells have a key advantage: they can be given directly from donor to patient without generating graft-versus-host disease, unlike αβ T cells, which require extensive gene editing to remove major histocompatibility complex and T cell receptor genes. This means that Incysus can potentially create an off-the-shelf therapy, rather than personalizing the cell therapy for each patient.

In the clinic

Incysus is about to launch two clinical programs. The first, ICS-100, is exploring the use of allogeneic γδ T cells in patients with leukemia and lymphoma undergoing haploidentical stem cell transplantation. This therapy is a path toward a cure, but leukemic relapse remains at 51% in the first year, while infections with viruses such as cytomegalovirus and Epstein–Barr virus contribute to increased morbidity and mortality. The ICS-100 program will provide a high dose of γδ T cells early in the recovery period with the aim of not only reducing infections but also reducing the probability of relapse.

The second program, ICS-200, is based on autologous γδ T cells that have been genetically modified to express the *MGMT* gene, which confers resistance to alkylating chemotherapies. These Drug Resistant Immunotherapy (DRI) γδ T cells remain alive and functional even when combined with the chemotherapy. In this phase 1 trial, patients with newly diagnosed glioblastoma (GBM) will receive chemotherapy in combination with Incysus's novel DRI. The chemotherapy drives DNA double-stranded breaks that trigger a DNA damage repair cascade, activating responses to fix or eliminate cells with DNA damage. This process increases immune signals on cancer cells by up to 700% (even among chemoresistant cells), which γδ T cells use as a cue to eradicate any residual cancer.

In animal GBM models, chemotherapy alone offers a median survival time of 60 days. In combination with Incysus's DRI-modified γδ T cells, 80% of animals survived until 150 days, after which the animals were sacrificed and their brains analyzed, revealing that the DRI combination eradicated the tumors. The same combination also increased median survival in animals implanted with chemotherapy-resistant tumors by 41% ($P = 0.017$).

Incysus welcomes enquiries from patients and potential investors or collaborators to bring this novel therapeutic approach to the millions of patients with cancer whose lives could be transformed by a successful immunotherapy to treat solid tumor cancers.

contact
William Ho, President and CEO
Incysus Therapeutics, Inc.
New York, NY, USA
Tel: +1-646-600-6438
Email: info@incysus.com

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