PsiOxus Therapeutics Inc.
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Turning tumor cells into drug factories

An intravenously administered oncolytic virus platform delivers combinations of therapeutic genes specifically to solid tumors to enable a potent anticancer immune response while minimizing systemic toxicity.

PsiOxus Therapeutics aims to be the world's leading cancer gene therapy company to deliver medicines of value to patients with cancer. The company focuses on the discovery and development of innovative treatments for solid tumors using its proprietary, intravenously administered, tumor-specific immuno-gene therapy (T-SIGn) virus platform. The early-stage and clinical-stage products are capable of simultaneously expressing combinations of genes locally at the tumor site, potentially allowing for treatment with therapeutics that are prohibitively toxic or poorly tolerated using systemic approaches.

The cornerstone of the T-SIGn platform is the enadenotucirev virus. Enadenotucirev is a clinical-stage, highly potent, broad-spectrum oncolytic virus with the potential to target the vast majority of solid tumors. Enadenotucirev retains its cancer-killing activity in the blood and selectively replicates in tumor cells and not within normal, noncancerous tissue. Efficient intravenous delivery of enadenotucirev has been demonstrated clinically, together with tumor-specific replication, demonstrating its potential as a systemic therapy for cancer. PsiOxus and Bristol-Myers Squibb are jointly funding a clinical trial administering a combination of nivolumab and enadenotucirev to try to expand the range of patients who respond favorably to checkpoint inhibitor therapy.

In the T-SIGn next-generation platform (**Fig. 1**), enadenotucirev acts as a vector system for the delivery of up to four therapeutic transgenes to cancer cells. The transgenes can encode antibodies or antibody fragments, bispecific or multispecific antibodies, secreted immunomodulators such as cytokines or chemokines, or membrane-integrated ligands such as T cell-engaging ligands or other ligands that are bound to the tumor cell membrane. Additional transgene approaches may also be possible and are the subject of ongoing research. In each case, the objective is to express the genes only in the tumor, thus achieving very high concentrations in the tumor microenvironment but with very low systemic exposure, thereby creating therapeutics anticipated to be capable of selectively destroying tumor cells through attracting immune cells.

At the time of viral replication in the tumor, the DNA-encoded transgenes are transcribed into mRNA, which in turn is translated into proteins that are produced at the tumor site. "In effect, the T-SIGn virus products turn tumor cells into drug factories," said John Beadle, CEO of PsiOxus. "This results in biological anticancer therapeutics acting locally within the tumor microenvironment."

Tumor-targeted T cell responses

The first T-SIGn virus is NG-348, which is designed to drive T cell immune responses at the tumor site. NG-348 encodes two immunomodulatory membrane-integrated T cell proteins: a membrane-anchored, full-length human CD80 and a membrane-anchored antibody fragment specific for the T cell receptor CD3 protein. When expressed together on the surface of NG-348-infected tumor cells, these two proteins provide both the T cell receptor and costimulatory activation signals required to activate tumor-infiltrating CD4 and CD8 T cells in an antigen-independent manner.

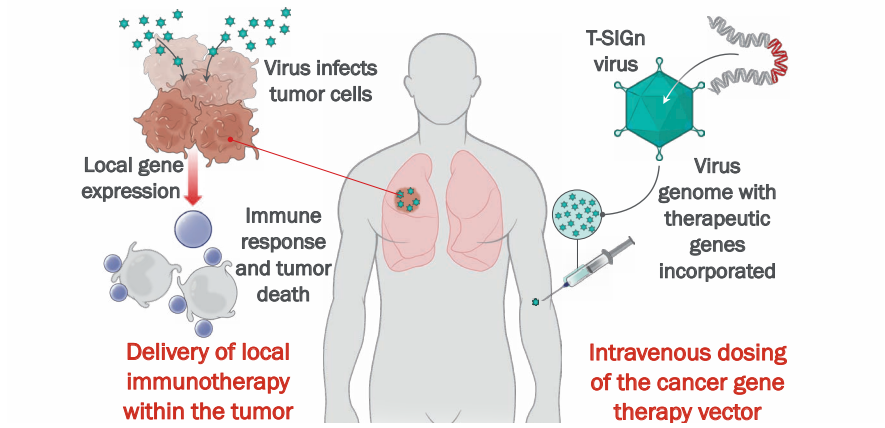

Fig. 1 | The tumor-specific immuno-gene therapy (T-SIGn) virus platform.

In essence, this approach is the mirror image of chimeric antigen receptor (CAR)-T cell therapies, which modify the patient's T cells ex vivo, whereas NG-348 modifies tumor cells in situ. And unlike CAR-T therapies, NG-348 is an off-the-shelf product that does not require autologous cell processing, does not require selection for any given tumor-specific antigens and is directed toward solid tumors. In 2016, Bristol-Myers Squibb was granted exclusive worldwide rights to NG-348. Last year, NG-348 was the first T-SIGn program to achieve approval for use in human clinical trials.

Preclinical products illustrate broad potential

Currently, there are four T-SIGn viruses in preclinical development. These products include NG-350A, an antibody-based virus with an investigational new drug (IND) application and a clinical trial planned to start later this year; NG-aFAP, an antifibroblast activation protein, stromal cell-targeting, bispecific antibody-producing virus; NG-aEpCAM, an anti-epithelial cell adhesion molecule, tumor-cell-targeting, bispecific antibody-producing virus; and NG-347, a combination virus of cell-bound and secreted immunomodulators with a clinical trial planned to start in 2019.

NG-347 is armed with three transgenes: secreted interferon-α (IFNα), secreted macrophage inflammatory protein-α (MIP1α) and membrane-bound CD80. Secreted MIP1α is a chemokine that drives inflammatory cell recruitment and the release of other pro-inflammatory cytokines. IFNα is a potent type I interferon that is regulated by the stimulator of interferon genes (STING) signaling pathway and acts to stimulate macrophage, natural killer cell and dendritic cell activation and drive immune effector cell-mediated cytotoxicity in solid tumors. NG-347 allows IFNα to be expressed directly within the tumor, bypassing the STING pathway. Membrane-bound CD80 acts as a costimulatory ligand to enhance T cell activation.

Research is ongoing to discover and develop additional novel T-SIGn viruses that express gene therapy combinations. "PsiOxus is committed to creating a broad gene therapy pipeline both by developing programs internally and with strategic partners who are also deeply committed to explore and develop new areas for T-SIGn gene therapy," Beadle said. "At PsiOxus we choose to fight cancer alongside all of those patients who did not choose that fight and are excited by the potential to deliver gene therapy medicines to cancer patients."

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