TILT Biotherapeutics Ltd.
www.tiltbio.com

Enabling solid tumor T cell therapies and checkpoint inhibitors with oncolytic adenoviruses

Oncolytic viruses developed to specifically destroy tumor cells are a potent form of immunotherapy, and consequently are finding their place in immunotherapy combination regimens. TILT Biotherapeutics' oncolytic viruses enable solid tumor T cell therapy and checkpoint-inhibiting antibodies.

T cell therapies, in which white blood cells are manipulated and propagated in the lab before being returned to the patient, have great potential as cancer treatments. This approach seems promising for the treatment of melanoma and blood cancers; however, clinical results for non-melanoma solid tumors—which account for over 90% of human cancers—are disappointing. Recruitment of T cells into solid tumors is thwarted by the highly immunosuppressive tumor microenvironment, which inactivates cells locally and prevents T cells from entering the tumor. Additionally, to prolong the viability and activity of the transplanted T cells, patients must be hospitalized for high-dose systemic pre-chemotherapy and post-conditioning interleukin-2 (IL-2) treatment, which causes severe toxicity and mortality.

TILT Biotherapeutics has come up with a clever solution: cytokine-coding oncolytic viruses.

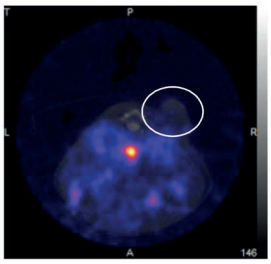
While working on oncolytic viruses at the University of Helsinki, Akseli Hemminki, professor of oncology, and his team took advantage of the European Advanced Therapy Access Directive to treat advanced solid tumors in 290 patients, using ten oncolytic viruses designed and constructed in their lab. "We very quickly saw a tremendous activation of T cells with the virus," said Hemminki. "A lamp went off in my head—oncolytic adenoviruses can make T cells fight solid tumors." Having already set up Oncos Therapeutics (now Targovax ASA), a more conventional oncolytic virus company, Hemminki established TILT Biotherapeutics in 2013 to optimize these patient observations and convert them into a T-cell-specific immunotherapy approach.

"What makes TILT technology unique is that it is based on observations in humans, not discoveries in mice or cell lines," said Hemminki. "Typically, drugs are developed in the lab and then taken into patients. We have done the opposite—converted patient data into a drug. Of course, now we must study the safety and efficacy of the new product in the clinic."

What TILT has done is engineer oncolytic adenoviruses (the most immunogenic virus type) to replicate only in cancer cells and, when they do so, to locally produce particular T cell immunostimulatory cytokines. This modifies the tumor microenvironment, overcoming the tumor's ability to suppress an immune response and significantly improving the efficacy of immunotherapy (**Fig. 1**).

TILT's lead product TILT-123, for example, is an adenovirus armed with tumor necrosis factor-α (TNFα) and IL-2, which TILT has found have the most prominent effects on T cells[1]. As well as having direct lytic effects through viral replication, a high concentration of virus in a tumor triggers acute danger signaling that is a 'fire alarm' to the immune system. "Presence of the virus per se activates pathogen-associated pattern receptors, and those signals are intensified by TNFα and IL-2, significantly increasing trafficking to and infiltration of the tumor by T cells," explained Hemminki, now TILT's CEO and CSO. "TNFα also has anti-tumor effects on its own, while IL-2 is important for retaining T cell activity at the tumor"[2].

Mock



TILT-123 (Ad5/3-E2F-delta24-hTNFα-IRES-hIL2)

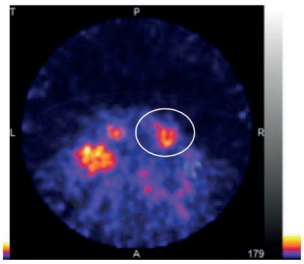


Figure 1: T cell trafficking to the tumor[2].

The viruses can be delivered directly to the tumor or intravenously and, once released from ruptured tumor cells, can travel through the blood system to tumors elsewhere in the body.

TILT's approach is synergistic with all forms of T cell therapy, and although there are several competing technologies, TILT-123 is the only product specifically designed with T cell therapies and checkpoint-inhibiting antibodies in mind. With tumor-infiltrating lymphocyte (TIL) therapy, for example, local production of TNFα and IL-2 in tumors obviates the need for a high dose preconditioning chemotherapy and after conditioning IL-2 treatment, thus significantly reducing toxicity[3]. The virus can also make chimeric antigen receptor (CAR) T cells—currently effective only in $CD19^+$ blood cancers—work in solid tumors. TILT is collaborating with Carl June's group at the University of Pennsylvania on work with this goal in mind[4].

Moreover, TILT's technology has the potential to realize the promise of checkpoint-modulating antibodies such as anti-PD1, which currently result in only a 10–50% response in solid tumors and do not work in immunologically silent tumors where the amount of TILs is low[5]. "Our virus can make silent tumors visible to the immune system, enabling checkpoint inhibitors to work," said Hemminki.

TILT Biotherapeutics, which retains close ties with the University of Helsinki's research group, is bringing TILT-123 and two other discovery-stage candidates to the clinic for the treatment of solid tumors in combination with cell therapies or checkpoint inhibitors (more information is available at the company's website). With preclinical proof-of-concept studies complete and EMA (European Medicines Agency) scientific advice and ATMP (Advanced Therapy Medicinal Product) classification obtained, phase 1 trials of TILT-123 in metastatic melanoma in combination with TILs are set to begin in 2018.

Additional trials are planned to test the efficacy of TILT-123 in combination with a checkpoint modulator (anti-PD1) and a CAR-T product in other solid tumor indications, including advanced melanoma, pancreatic cancer and ovarian cancer. TILT is looking to secure funding and establish new collaborations with industry leaders for this clinical development.

"Despite the recent approvals of targeted therapies and checkpoint-modulating antibodies, the challenge remains to extend treatment benefits to the more than 50% of patients who do not receive long-term positive effects from available drugs," said Hemminki. "Human data suggests that TILT technology may be the critical ingredient for unleashing the full power of T cells in eradicating advanced tumors."

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2. Siurala, M. *et al. Mol. Ther.* **24**, 1435–1443 (2016).
3. Santos, J. SITC 2016 abstr. 41 http://eventscribe.com/2016/SITC/TwitterPoster.asp?PosterID=75179 (2016).
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5. Cervera-Carrascon, V. SITC 2016 abstract 203 http://eventscribe.com/2016/SITC/TwitterPoster.asp?PosterID=75018 (2016).

contact
Aino Kalervo, Head of Business Management
TILT Biotherapeutics Ltd.
Helsinki, Finland
Tel: +358 50 321 74 54
Email: aino@tiltbio.com