Icell Kealex Therapeutics
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Enhanced immuno-viral therapy for solid tumors

Icell Kealex Therapeutics is developing oncolytic vaccinia viruses armed with T-cell-engaging antibody fragments that boost the virus's antitumor efficacy. The company is entering phase 1 trials for solid tumors with its lead product and is looking to partner with companies interested in clinical codevelopment of its wide-ranging therapeutic pipeline.

Icell Kealex Therapeutics (IKT), an oncology biotech startup based at the JLABS in Houston, Texas, is developing a novel oncolytic virus platform consisting of vaccinia viruses (VVs) that attack tumor cells by means of two distinct but complementary mechanisms[1–3]. In addition to using tumor cells to replicate and to infect other tumor cells via the standard oncolytic cycle, IKT's engineered VVs use their host cells to synthesize immunostimulating bispecific antibody fragments. Once secreted into the tumor microenvironment, these antibody fragments bind to uninfected 'bystander' tumor cells, turning them into targets for specific attack by the immune system. This two-pronged strategy helps to greatly improve the therapeutic efficacy of the virus.

IKT has dubbed its virus platform T-cell-engager-armed VVs (TEA-VVs).

In recent years, two of the most promising approaches to cancer therapy have been the use of oncolytic viruses to destroy tumors from within, and the development of cancer-specific immunostimulating strategies to engage the patient's own immune system to destroy tumor cells. The combination of both concepts into one therapeutic agent has emerged as a potentially powerful new way to target cancer, but to date only platforms combining oncolytic viruses with generic immunostimulating factors have been created. Even though some of these platforms are in advanced clinical testing, the generic nature of their immunomodulating activity has raised concerns about reduced efficacy and a lack of tumor specificity.

IKT's platform, being developed under an exclusive worldwide license from Baylor College of Medicine, circumvents these issues by arming the most potent VV strain available, the Western Reserve strain (TK and VGF double deleted), with highly tumor-specific T-cell-engaging antibody fragments to minimize the risk of side effects. The company is looking for partners interested in clinical codevelopment or licensing agreements. According to Shau-Tong Song, founder and CEO of IKT, the company's "platform of engineered, immunostimulating vaccinia viruses opens up a new and unique opportunity for fighting cancer from within. And in particular, we are excited about the potential for tackling solid tumors, one of the hardest challenges in the oncology field. With the right partners, we are poised to rapidly move a number of products into clinical studies and into market to deliver to patients the therapeutic benefits of our innovative platform as soon as possible."

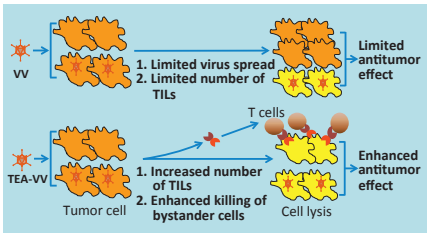

Figure 1: IKT's enhanced immuno-viral strategy for solid tumors. Unlike treatment with traditional vaccinia virus (VV) therapeutics, which results in the survival of large numbers of uninfected 'bystander' cells (upper panel), IKT's T-cell-engager-armed VV (TEA-VV) enables the immune system to target uninfected cells (increased numbers of tumor-infiltrating lymphocytes (TILs)) (lower panel).

TEA time for VVs

Oncolytic viruses—viruses capable of preferential replication within tumor cells—have been under development as cancer therapeutics for the better part of the past two decades. Vaccinia virus has emerged as an ideal viral backbone for engineering enhanced tumor-targeting capabilities, owing to its versatility and safety profile.

The mechanism of action of VV is a combination of the direct destruction of cells via virus-induced cell lysis and of immunostimulation in the tumor environment. Although cell lysis represents VV's main mechanism of action, its efficiency is variable, and large numbers of tumor cells—the so-called bystander cells—end up evading it. Immunostimulation, on the other hand, derives from two processes secondary to cell lysis. First, the presence of the oncolytic virus itself triggers the innate immune response, and second, tumor cell destruction results in the release of a number of factors such as cytokines that can have a strong but nonspecific immunostimulatory effect.

IKT has developed a platform, the TEA-VV that maximizes the tumor-fighting potential of VVs by using virus particles that have been engineered to take the immunostimulatory response to the next level. IKT's VVs secrete a so-called T cell engager consisting of two single-chain variable antibody fragments: a tumor-specific fragment, and a CD3-specific fragment. The tumor-specific fragment leads the T cell engagers to home to particular tumor cells, while the CD3-specific fragment binds CD3, coating the tumor cells with this T-cell-activation ligand and effectively turning them into targets for T cell attack (**Fig. 1**).

IKT's TEA-VVs offer a clear advantage over other oncolytic virus-based platforms and combination therapies. First, the company has enlisted the Western Reserve strain to maximize oncolytic potential, and second, the targeted sensitization of bystander cells by TEA-VVs specifically induces antitumor immunity without activating other innate immunity mechanisms that might enhance viral clearance. In addition, localized production of the T cell engager by TEA-VV infected tumors overcomes concerns with other bi-specific antibody based therapies over limited tumor penetration, short half-life, and the need for continuous systemic administration.

Partnering TEAs

IKT has developed a deep pipeline of TEA-VVs that express T cell engagers specific to a number of cancer-specific targets. The company's lead product, EpCAM-TEA-VV, targets epithelial cell adhesion molecule (EpCAM), a transmembrane glycoprotein expressed primarily in epithelial-derived neoplasms. EpCAM is a validated therapeutic target for a range of tumor types including breast cancer, non-small-cell lung cancer and prostate cancer. Manufacturing of EpCAM-TEA-VV is underway, and IKT is designing a phase 1 trial to be launched in 2018. Other cancer-specific targets in IKT's pipeline include fibroblast activation protein (FAP), ephrin type-A receptor 2 (EphA2), human epidermal growth factor receptor 2 (HER2), glypican 3 (GPC3) and ganglioside GD2.

IKT plans to move its lead product EpCAM-TEA-VV through phase 1 studies and is looking to identify partners to complete the clinical program; a phase 1 study of EpCAM-TEA-VV-loaded CAR-T cell therapy is already underway in China. All other products in the pipeline are available for codevelopment or licensing partnerships. As summed up by Song, "our flexible vaccinia virus platform in conjunction with our deep pipeline of TEA-VV products offers many opportunities for exciting partnerships with other companies in the oncology space, and we are looking to maximize this potential in the near future."

1. Yu, F. *et al.Mol. Ther.* **22**, 102–111 (2014).
2. Albelda, S.M. & Thorne, S.H. *Mol. Ther.* **22**, 6–8 (2014).
3. Song, X.T. *Discov. Med.* **16**, 261–266 (2013).

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