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Amunix unveils next-generation immuno-oncologic cancer therapy platform

A novel immunotherapy with extended serum half-life in a prodrug delivery format holds promise for overcoming the limitations of current BiTE therapies to treat a broad range of malignancies.

In recent years, treatment regimes that harness the immune system have shown promise for improving the clinical response in selected cancers, leading to substantial increases in survival for distinct subpopulations of patients. However, the prognosis over the past two decades for those with advanced solid tumors has not improved much, and there is still a considerable unmet need for new and more effective treatments. The field of immuno-oncology has emerged as one of the most fertile areas of research for therapies against such cancers, and the therapies being developed can be very specifically focused to attack malignant cells with differentiated cell surface antigens.

The development of bispecific T cell engagers (BiTEs) is one area of immunotherapeutic evaluation in which considerable progress has been made to tackle this challenge. The BiTE concept harnesses directed engagement of the highly cytotoxic capability of T cells coupled to a selective tumor cell target-recognition domain. There is a growing body of clinical evidence validating the effectiveness of such specifically targeted immunotherapeutics in fighting difficult-to-treat malignancies. Recent marketing authorization approval obtained for BiTE therapeutics for hematological malignancies has validated this immuno-oncology platform, and several new therapeutics based on the BiTE format have now entered the clinic for the treatment of hematological and solid tumor malignancies. Nevertheless, challenges remain, as the currently approved BiTE therapy requires vigilant dose administration via continuous infusion; this stems from concerns over an uncontrolled cytokine response, which, if left unchecked, could be potentially fatal.

Amunix is developing innovative strategies to overcome the inherent functional limitations of current BiTE therapies. The company maintains a primary focus on the design and development (at preclinical and clinical stages) of novel biotherapeutics with extended serum half-lives and payload delivery through the application of its patented XTEN (half-life extension), XDC (XTENylated Drug Conjugates) and ProTIA (Protease Triggered Immune Activators) technology platforms. The novel adaption of the XTEN half-life extension technology to create a long-acting, prodrug format under Amunix's recently unveiled ProTIA technology platform (**Fig. 1**) has yielded a unique class of bispecific T cell activators with long half-lives and the potential for superior safety compared to other bispecific formats.

"We are extremely confident that our design offers the optimal combination of our best-in-class XTEN half-life extension technology and payload delivery capabilities to the burgeoning field of immuno-oncology," said Volker Schellenberger, CEO and president of Amunix.

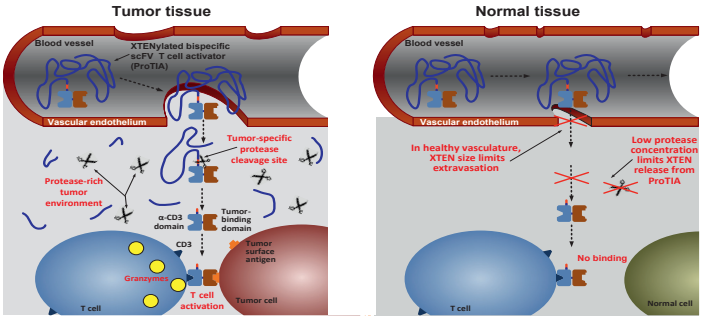

Figure 1: Representation of the ProTIA concept—tissue-specific delivery and activation.

Controlling the cell-killing cascade

The standard BiTE design embodies a hybrid molecular structure with three major components consisting of a defined single-chain antibody (scFv) binding to the targeted T cell receptor recognition moiety (α-CD3), and the selected scFv tumor-specific antigen recognition domain joined by a flexible linker. The individual binding domains of the BiTE structure facilitate the selective formation of a cytolytic synapse between tumor cells and T cells by bringing them into close proximity. The resultant activation of T cells elicits a cytolytic response by activating a highly effective tumor-cell-killing cascade.

This cytolytic effect must be rigorously managed by careful control of the therapeutic dose. One of the limitations of current BiTE therapeutic designs is that uncontrolled activation can lead to the 'cytokine storm' phenomenon, which, if not monitored and left unregulated, can prove fatal. Additionally, because of the narrow therapeutic dosing window and the short half-life ($t_{1/2}$~2–5 hours) of BiTE therapeutics, administration via continuous infusion remains the only viable route for treatment.

To overcome these limitations, Amunix has developed the ProTIA platform by applying XTEN technology to the bispecific scFv format. One benefit of this novel application is the significantly enhanced circulatory half-life through recombinant fusion to an XTEN protein polymer of defined length and sequence. The spatial bulkiness of XTEN serves not only to maximize circulatory half-life but also to minimize extravasation across the well-organized vasculature that is characteristic of healthy tissues. This reduces the potential for undesired uptake and activation in non-malignant tissues while simultaneously allowing for swift permeation into the tumor environment, which exhibits a significantly more leaky vasculature.

The company has further enhanced the molecular design by adapting it to a functional prodrug delivery format with the insertion of a protease cleavage site between the active payload and the adjoining XTEN peptide sequence. Upon migration across the tumor vasculature into malignant tissues, cleavage at the protease cleavage site by tumor-associated proteases releases the active bispecific payload. Following cleavage, the bispecific T cell activator becomes available to enable T cell activation upon formation of the cellular synapse with the tumor cell.

Amunix is currently completing preclinical evaluation of its lead ProTIA candidate AMX-168, with other candidates in early-stage evaluation. With the successful preclinical advancement of the ProTIA pipeline and an expected investigational new drug/clinical trial application (IND/CTA) filing by the end of 2017 for AMX-168, the company is planning for phase 1 evaluation of AMX-168 within the next 18 months.

"We are invigorated by our initial preclinical successes, and we envision wide-ranging opportunities for the first of our ProTIA molecules to come out of our discovery efforts," Schellenberger said. "We expect to continue to harness our ProTIA platform to accelerate the development of a broad pipeline of immuno-oncology therapeutics for a spectrum of currently difficult-to-treat malignancies, including ovarian, colorectal, lung, gastric, breast and other cancers."

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