TargImmune Therapeutics AG
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TargImmune THERAPEUTICS

TAIMing cancer by harnessing the body's antiviral defences

TargImmune is developing first-in-class targeted apoptotic immune modulators (TAIMs) based on the Ta:RNA technology platform which mimics viral infection by selectively delivering viral-like double-stranded RNA to tumor cells and harnessing the body's antiviral defence mechanism against cancer.

Classical targeted agents such as tyrosine kinase inhibitors and monoclonal antibodies, as well as immunotherapies, including checkpoint inhibitors, have made a significant difference in the treatment of cancer. These therapies, however, have inherent limitations, which if addressed could provide substantial benefits to patients. TargImmune Therapeutics, headquartered in Basel, Switzerland, is pioneering a new category of cancer therapy that aims to address these limitations with the development of first-in-class targeted apoptotic immune modulators (TAIMs).

TargImmune's TAIMs comprise double-stranded RNA (dsRNA) packaged into nanoparticles that, when delivered to cancer cells, activate antiviral responses, including apoptosis of the target cells and a broader cytokine-mediated immune response directed against the tumor (Fig. 1). TargImmune's proprietary targeted RNA platform, Ta:RNA, uses linear polyethyleneimine (LPEI), which binds dsRNA through electrostatic interactions and creates stable dsRNA-LPEI polyplex nanoparticles that can be delivered systemically to reach tumors wherever they are in the body. Although LPEIs have been used to deliver oligonucleotides before, TargImmune's TAIM nanoparticles are unique in containing a linker element to which a variety of targeting moieties can be attached—making Ta:RNA a true platform technology.

These targeting moieties, which can be a variety of molecular types, are selected for their ability to bind to receptors that are overexpressed on the surface of cancer cells. Once Ta:RNA nanoparticles reach and bind to the receptors on cancer cells, they are internalized by endocytosis, releasing the dsRNA into the interior of the cell. Inside the cell the dsRNA is recognized by intracellular receptors, which initiate antiviral responses through multiple signaling cascades that drive both apoptosis and the release of cytokines. These in turn activate and recruit both innate and adaptive immune cells to the heterogeneous tumor, where they destroy additional cancer cells including those that do not overexpress the targeted receptor.

A cut above the rest

The Ta:RNA platform offers a number of advantages over classical targeted cancer therapies such as tyrosine kinase inhibitors and monoclonal antibodies, as well as newer anticancer agents including checkpoint inhibitors. Classical targeted therapies, directed against particular receptors or intracellular proteins, typically interfere with just one signalling pathway, which cancers can readily overcome through mutation or upregulation of alternative pathways. The effects of Ta:RNAs, by contrast, are multi-modal: they not only bind several intracellular proteins and activate multiple apoptotic pathways, but also elicit a cytokine-mediated attack by immune cells on the cancer cell, making the development of resistance less likely. The recruitment of both innate and adaptive immune responses to the tumor site also leads to a potent bystander effect, so that nearby cancer cells lacking the target of the Ta:RNA are still killed. Ta:RNA's bystander effect addresses the problem of tumor heterogeneity, which poses a challenge for other classical targeted therapies that kill just one type of cancer cell.

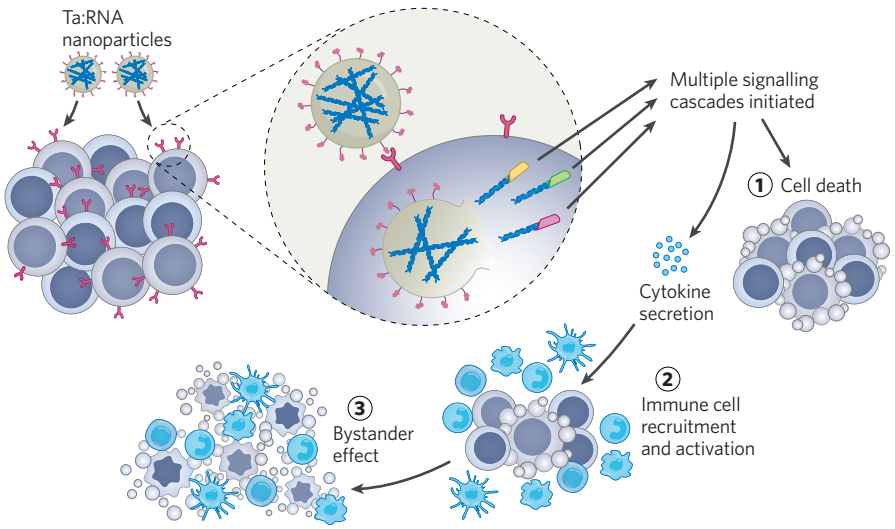

Fig. 1 | How targeted apoptotic immune modulators (TAIMs) fight cancer. Systemically administered TAIM nanoparticles are taken up by cancer cells that overexpress the target, initiating multiple signaling pathways that potently destroy cancer by three routes: apoptosis (1), recruitment and activation of immune cells (2), and bystander effects (3).

While immune modulators, including checkpoint inhibitors, have emerged as potent cancer therapies in recent years, they unfortunately only provide benefit to about 20% of patients. Checkpoint inhibitors require that tumors are 'hot', meaning that they show strong immune cell infiltration. Many tumors, however, remain cold, with little or no immune cell infiltration or inactive immune cells, rendering immune modulators ineffective. Ta:RNA treatment induces cytokine secretion, thereby both activating and recruiting immune cells towards cancer cells, switching tumors from cold to hot and priming them for combined therapy with immune modulators.

TargImmune currently has three Ta:RNA compounds in development. The lead compound, TAR001, is loaded with a moiety targeting the epidermal growth factor receptor (EGFR) overexpressed in many solid tumors, and is being developed for the treatment of a range of cancers.

TAR001's mechanism of action, including the killing of target cells and immune cell activation, has been demonstrated in vitro and in vivo. Promising preclinical in vitro and in vivo data show that TAR001 has anticancer activity as a systemically administered single agent as well as in combination with the checkpoint inhibitor anti-PD-1 antibody. TAR001 has a favourable side effect profile in exploratory studies in rats and cynomolgus monkeys, and GLP toxicology studies are ongoing with results expected shortly. TAR002 and TAR003, against undisclosed targets, are being investigated in a range of cancers, including prostate, breast, gastric and cervical.

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