Actym Therapeutics, Inc.
www.actymthera.com

The next frontier in immuno-oncology

Actym Therapeutics' breakthrough platform addresses intractable immune pathways in the tumor microenvironment.

Across the solid-tumor spectrum, many patients are burdened with metastatic, immune-excluded or immune-desert tumors that do not respond to checkpoint monoclonal antibodies. Systemically administered therapies will be required to address these tumor types through direct activation of tumor-resident immune cells to elicit durable antitumor immunity.

Actym's microbial-based, tumor-targeting platform, STACT (*Salmonella typhimurium* (Attenuated) + Cancer Therapy), is capable of safely targeting well-characterized yet intractable immune pathways that are required to activate the immunosuppressive tumor microenvironment, but would otherwise be too toxic if systemically activated. Actym's therapies show a high degree of tumor-specific targeting in mice when delivered intravenously. After phagocytosis by myeloid cells, Actym's therapies deliver plasmids that encode either inhibitory RNA for potent knockdown of gene expression, complementary DNA encoding agonist proteins, or potent combinations of both. Actym's therapies are fully biodegradable and do not permanently integrate into the genome of the host cell.

Actym is focused on generating multiple product candidates along four tracks (**Fig. 1**):

- activation of stimulator of interferon genes (STING) (recent clinical data releases have shown that systemically administered STING will be required for optimal therapeutic effect);
- tumor-restricted delivery of immunostimulatory cytokines and other proteins;
- transforming growth factor-β inhibition alone and in combination with checkpoint blockade in a single therapy; and
- combinatorial targeting of immune pathways that would be too toxic if systemically activated.

In preclinical studies, Actym's therapies specifically targeted tumors in mice following systemic administration, stimulating both innate and adaptive immunity to the tumor. This resulted in a significant $CD8^+$ T cell induction in T cell-excluded tumors, leading to $CD8^+$ T cell-dependent complete responses and durable immunity in a rechallenge setting with two separate models. Actym's breakthrough approach is protected by multiple pending patent applications and is potentially beneficial across many tumor types.

The STACT platform has many advantageous features compared with other immuno-oncology therapies. Most importantly, STACT can be dosed systemically, whereas other stimulatory therapies, such as STING agonists, oncolytic viruses, mRNA-delivered cytokines, and toll-like receptor agonists, require direct intratumoral administration for optimal potency. While these intratumoral therapies require a systemic antitumor immune response to develop after local administration, STACT can stimulate immune responses in lesions across the body owing to its intravenous administration. Because of its auxotrophic nature, STACT can specifically enrich in tumors without the need for antigen targeting.

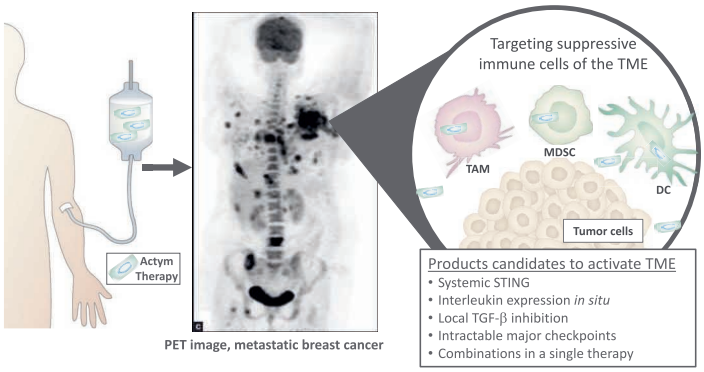

Fig. 1 | Systemic delivery, local effects. Tumor-specific localization and enrichment of the company's therapies enables IV administration to activate anti-tumor immune pathways that would otherwise be toxic if systemically activated. DC, Dendritic cell; MDSC, myeloid-derived suppressor cells; TAM, tumor-associated macrophages; TME, tumor microenvironment.

The highly attenuated STACT platform uses a low immunogenic vehicle that can be administered repeatedly, is well tolerated, and the effects of which are reversible with a simple course of antibiotics. It offers accelerated discovery cycle times and is highly feasible to manufacture and scale, without the need for a custom facility. "By introducing the innovative STACT platform, we are altering the paradigm of cell-based therapies to treat cancer," said Actym's president, CEO and cofounder Christopher Thanos.

Targeting TREX1

Actym's lead product candidate, STACT-TREX1, is a first-in-class, systemically administered STING pathway agonist, which targets the intractable immune checkpoint three-prime repair exonuclease 1 (TREX1) in phagocytic tumor-resident immune cells, such as tumor-associated macrophages, dendritic cells, and myeloid-derived suppressor cells.

TREX1 is an enzyme that degrades cytosolic DNA (a danger signal) and prevents it from binding to cyclic GMP–AMP synthase (cGAS) and activating the STING pathway. Mutations in TREX1 cause autoimmune diseases such as Aicardi–Goutières syndrome and chilblain lupus. Therapies that target TREX1 have broad applicability across a range of tumor types, but TREX1 is difficult to target with conventional therapeutic modalities.

By contrast, STACT-delivered RNA interference restricts the expression of TREX1 in the tumor microenvironment. As a result, cytoplasmic DNA accumulates, activating the STING–cGAS pathway (a key viral recognition pathway). Importantly, STACT-TREX1 limits STING activation of type I interferons to the hematopoietic compartment, unlike other STING agonists, which are taken up into all cellular components with different signaling outcomes.

STACT-TREX1 has shown potent antitumor activity in colon cancer models and induced protective immunity in cured mice. Importantly, STACT-TREX1 induces tumor-specific killer T cells. TREX1 knockdown overwrites the typical immune response to microbes and does not induce suppressive neutrophils or myeloid-derived suppressor cells.

Moreover, STACT-TREX1 demonstrates a significant improvement in safety over VNP20009—an attenuated *S. typhimurium* strain previously developed as a therapy for melanoma. STACT-TREX1 shows a greater than fourfold improvement in tolerability in mice compared with VNP20009. In addition, it is possible to achieve better colonization with higher doses of STACT-TREX1, which does not induce a toxic cytokine response at efficacious doses. Actym's core platform strain has been engineered to address the VNP20009 colonization limitations that were previously observed in a phase 1 trial.

Actym Therapeutics expects to initiate phase 1 clinical trials in 2020. "We look forward to establishing partnerships as the company develops our revolutionary platform with the hope of bringing significant benefit to patients," Thanos said.

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