Marengo Therapeutics
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# Activating T cells to fight cancer

**Marengo Therapeutics' breakthrough discovery in T cell receptor (TCR) activation blazes a new trail for safe treatment and long-term protection against cancer.**

Immuno-oncology (IO) has transformed cancer care to significantly benefit patients with both blood and solid-tumor malignancies. Despite recent advances, two-thirds of patients do not achieve durable responses to current therapies, which has been largely attributed to dysfunctional T cells. Marengo's deep understanding of T cell biology and receptor signaling has led to the discovery of novel multi-specific antibodies that target TCR variable beta (Vβ)-chain variants—powerfully activating the right T cells to fight cancer (Fig. 1).

"There is still a vast unmet need for effective and durable IO therapies that can overcome the dysfunctional T cell responses that develop in most cancer patients during the course of treatment," said Zhen Su, CEO of Marengo. "Our groundbreaking discovery, which is based on the right activation of the right T cells, builds on the foundations laid by T cell therapeutics such as checkpoint inhibitors, chimeric antigen receptor (CAR) T cells and T cell engagers."

"We have applied a precision IO approach by targeting specific Vβ-chain variants of the TCR, to activate subsets of a patient's own T cells. As a result, a patient's T cells are able to respond quickly, safely and effectively against solid tumors and enable long-term protection."

Activation of Vβ T cell subsets primes stimulation of clonally diverse populations of both $CD4^+$ and $CD8^+$ T cells directly through the TCR, turbocharging them to drive anti-tumor responses and long-term immunity.

To date, few T cell-activating antibodies have demonstrated functional memory and long-term protection as a single agent in a broad range of IO-sensitive and resistant solid tumor preclinical models. They have also been limited due to safety concerns. "A patient's own T cells are powerful—and even more so if activated in the right way," said Su. "Our approach mimics the natural, non-antigenic mechanism of TCR activation, much akin to bacterial superantigen-induced TCR activation."

Activation via TCR Vβ solves the current IO challenges of unleashing the right T cell quantity and quality. Furthermore, the technology allows for targeting of different Vβ variants for different therapeutic needs based on baseline Vβ frequencies and prevalence in tumor-infiltrating lymphocytes (TILs).

## Two T cell activation signals are better than one

Marengo's proprietary Selective T Cell Activation Repertoire (STAR) platform has a flexible design as a multi-specific fusion protein that binds specific TCR Vβ variants fused to a co-stimulatory signal. This further enhances the activation of the desired T cell subset and adjusts the T cell response to generate tailored effects for various therapeutic uses.

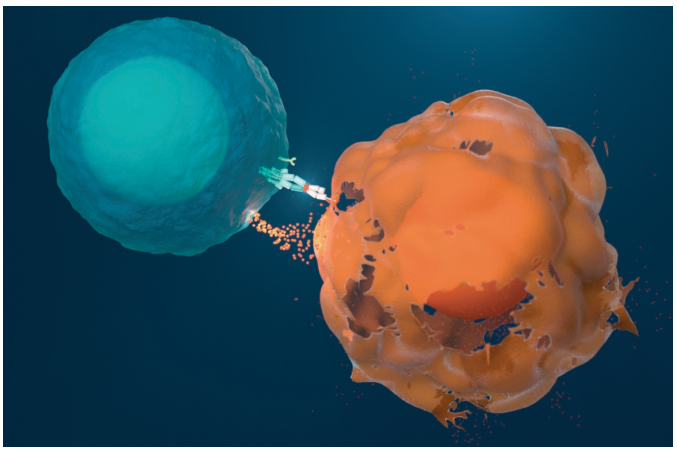

**Fig. 1 | Selective activation of T cells.** Marengo's unique approach uses anti-T cell receptor (TCR) variable beta (Vβ) antibodies that mimic natural modes of TCR activation.

The platform is dynamic and designed to plug novel T cell-activating discoveries and technologies into various therapeutic constructs to treat refractory cancers. Antibodies can also be designed with specific cancer-targeting domains that direct immune cells to less antigen-rich or 'cold' tumors that are more difficult to treat.

Marengo's candidate T cell activators have demonstrated promising findings to date, including a favorable safety profile, with limited cytokine release when cytotoxic cells were activated—further solidifying proof-of-concept around its unique approach.

## Phase 1 clinical trials on the horizon

Marengo's lead asset, STAR0602, is a fusion protein that binds to a specific region of TCR Vβ and delivers a unique activation signal on the same T cell, leading to a selective expansion of the targeted T cell subclones. This molecule has a confirmed mechanism of action and a strong safety profile, and has shown remarkable single-agent activity in a vast array of syngeneic mouse models, human TILs and organoids.

The compound will enter phase 1 clinical trials in the fourth quarter of 2022, and will focus on antigen-rich tumors in patients with advanced or metastatic solid cancers. Proof-of-concept could lead to an accelerated regulatory path.

Follow-on programs in pre-clinical development are aimed at generating a different T cell response either by delivering a different co-stimulatory signal or selecting a different TCR-Vβ subset, with an added customized second signal to achieve diverse immunological outcomes.

"The multi-dimensional platform and iterative process of our pipeline enable us to build on our learnings, apply them to our next compounds and take a faster path to the clinic," Su said. "Our flexible design, potent anti-tumor response and strong safety profile should enable us to optimize two more candidates by 2024." The compound STAR002 is designed to extend memory and will be developed in genitourinary (GU)-focused indications, while STAR003 turbocharges the T cell response for development in gastrointestinal (GI)-focused indications.

## Investing in long-term success

Marengo was launched with $80 million funding from its creator, Apple Tree Partners (ATP), which incubated its foundational scientific discovery. Su joined Marengo after six years at Merck KGaA as head of global oncology; he is known for establishing a strong pipeline and spearheading multiple drug approvals.

Marengo has been collaborating with King's College London to study the biology and immunological effects of its antibodies on various T cell subsets.

Marengo has cultivated a dedicated team of scientists who are well-versed in immunology and oncology and collectively committed to translating novel biological discoveries into valuable medicines. The company also prides itself on building and promoting a strong culture of innovation and resilience—two attributes that are critical to developing new approaches geared to overcoming longstanding challenges in the IO therapeutic landscape.

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