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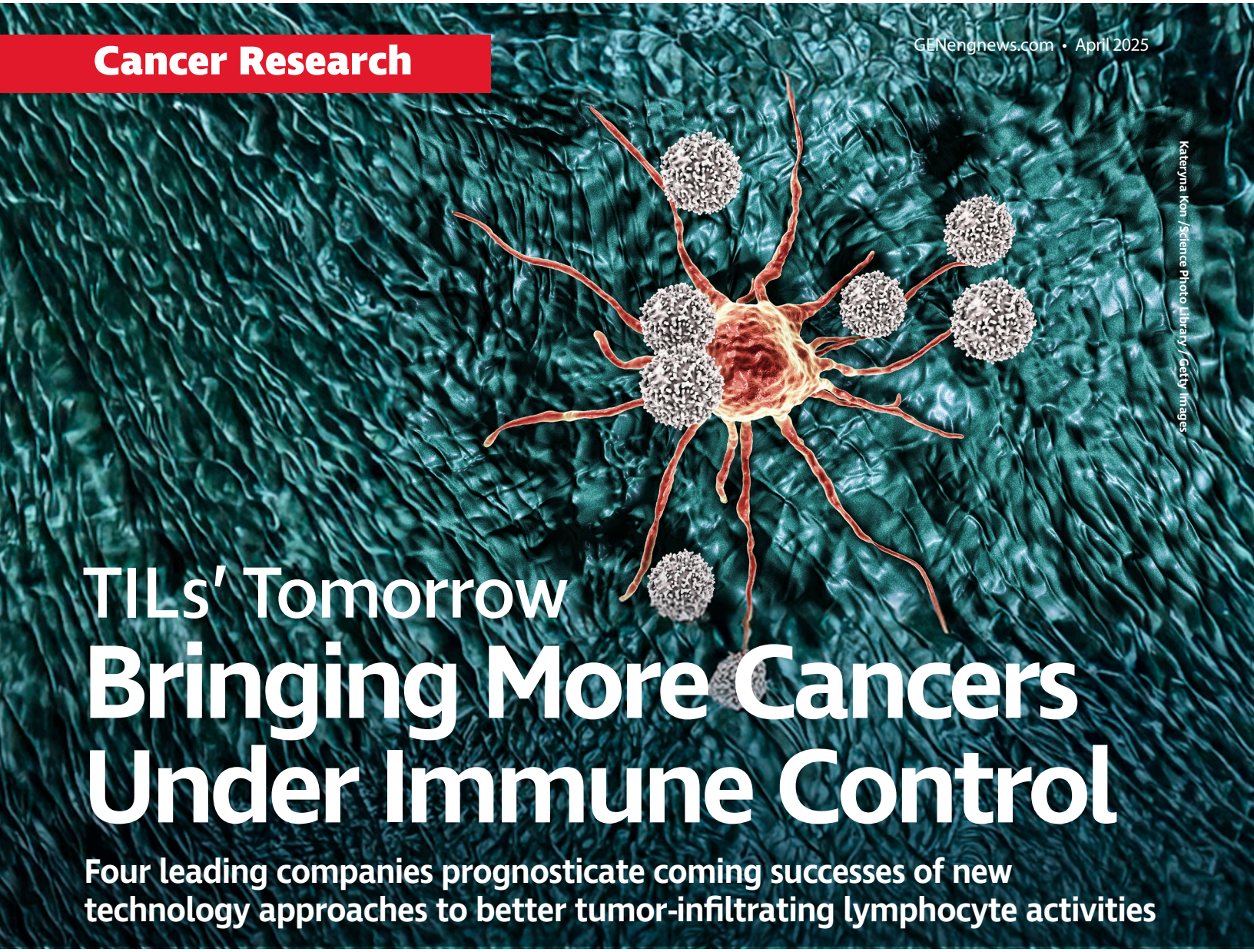

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TILs' Tomorrow
Bringing More Cancers Under Immune Control

Four leading companies prognosticate coming successes of new technology approaches to better tumor-infiltrating lymphocyte activities

By Tiffany Yesavage

Tumor-infiltrating lymphocytes (TILs) are a grouping of mostly T cells that enter tumors and elicit an initial immune response. But as Jason Bock, PhD, co-founder and CEO of **CTMC**, explains, "These cells have been fighting against the tumor, but the balance has shifted, and the tumor has gained the upper hand." He notes that traditional TIL therapy typically involves extracting the TILs from each patient's tumor, expanding and reinvigorating them, and then reinfusing them into the patient. In recent interviews with *GEN*, four leading companies shared their insights about the state of TIL therapy in 2025.

TIL therapy gains FDA approval in 2024

Brian Gastman, MD, executive vice president of medical affairs at **Iovance Therapeutics**, highlights how the company's TIL therapy, called lifileucel, was the first to be approved by the FDA in February of 2024. The current indication is for adult patients with unresectable or metastatic melanoma previously treated with a PD-1 inhibitor.

Gastman recalls the registrational trial that led to this historic FDA approval. "It is incredible if you think about it. That trial enrolled extremely refractory melano-

ma patients. Many of them had up to nine or ten lines of previous therapy."

Despite the grim outlook for the enrollees, the trial demonstrated an overall response rate of 31%. Even more impressive has been the exceptionally long duration of many responses with Iovance's TIL therapy—often exceeding 10 years.

Iovance is primarily focused on scaling up techniques developed by the National Cancer Institute in the 1990s. "For a long time, the problem was not the technology but the scalability," notes Gastman. "What Iovance has done is scaling to bring the therapy to the masses."

What is the key to Iovance's success? "We hire experts in cell therapy who view this not only as a job but as a mission," he stresses. He also emphasizes the company's ability to attract investors and the tight coordination of its manufacturing and clinical processes.

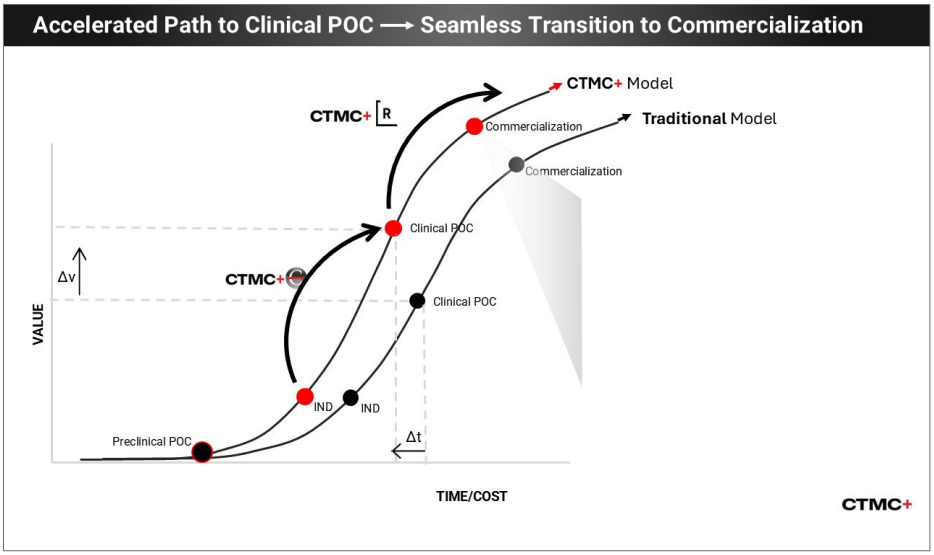
Gastman highlights that the company is also completing a pivotal trial for non-small-cell lung cancer with lifileucel as a second line of treatment. "Preliminarily, we see very encouraging results. Our goal is to get FDA approval for lifileucel in lung cancer."

He also mentions the company's current frontline validation study in which patients with melanoma receive a PD1 inhibitor with or without lifileucel. Ultimately, this could lead to approval for treatment in patients with metastatic or unresectable disease who have not been treated with any drug.

Iovance has expanded its clinical trials for lifileucel to include indications such as cervical, endometrial, and head and neck cancers. "Our experience in the next year may outpace the entire world's history of TIL therapy in a very short period of time," predicts Gastman. "No one has been here before because of the size and scope of what we are doing."

Pursuing engineered approaches

Bock explains that there are two broad forms of TIL therapy. First, there is the traditional approach that does not require engineering. "This type of TIL therapy has efficacy by itself," he notes. "It is a baseline platform that you can build off."



CTMC's website notes that the company was created to bring together the leading complex biologics manufacturing technology organization and the leading clinical cancer center to enable innovation from academia and biotech to accelerate cell therapy's impact for cancer patients. IND: Investigational New Drug; POC: Proof of concept.

A second class of emerging TIL therapies involves genetic engineering. This may require CRISPR to knock out genes or genetically engineered viruses that express specific genes.

"The way we work at CTMC—a joint venture between the MD Anderson Cancer Center and **Resilience**—is that companies come to us with their genetic engineering ideas or concepts and proprietary methods and approaches," explains Bock. "Then, we are able to combine those elements into our TIL platform and come up with a robust way to produce TIL that has demonstrated efficacy in the clinic."

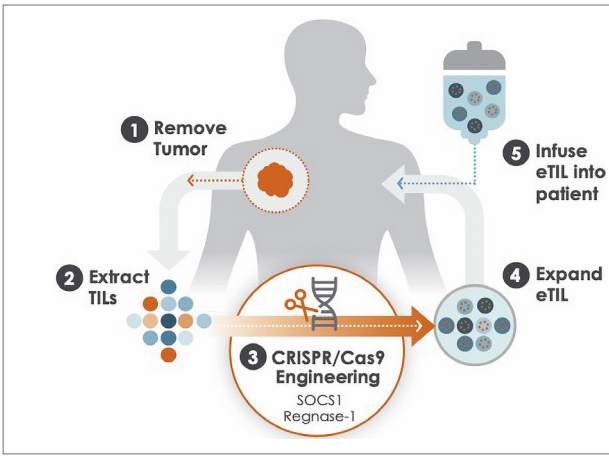
CTMC believes that it has the most successful platform for producing engineered TILs. "We have this consistent and efficacious TIL platform. When they work with us, companies don't have to spend all their time trying to make high-quality TILs because we already have that," says Bock.

The organization has also optimized its platform to require less tumor material, and TILs can now be collected with a less invasive needle biopsy instead of surgical resections. "That makes the process more manageable for patients, easier to implement on the clinical side, and opens up access," notes Bock.

CTMC currently has a portfolio of TIL projects it is working on, ranging from relatively large multi-site studies to earlier-stage clinical trials. The organization also supports its partners with early clinical trials at MD Anderson.

CRISPR-engineered TILs

Anna Truppel-Hartmann, MD, chief medical officer of **KSQ**, explains how the company is leveraging CRISPR-Cas9 technology to produce its engineered TILs—called eTILs. "Ultimately, our goal is to enhance each patient's personalized immune response through this engineered approach," she says.



KSQ's eTIL approach involves removing TILs from each patient and knocking out genes such as SOCS1 and Regnase-1 with CRISPR/Cas9 engineering.

Truppel-Hartmann notes that not all patients respond to traditional, unmodified TIL approaches. Furthermore, un-engineered TILs are often unable to overcome tumor immunosuppression in solid tumors. "We believe T-cell therapies for the treatment of solid tumors require functional enhancements to overcome some of these challenges," she adds.

She explains how KSQ has developed a proprietary drug discovery engine called CRISPRomics® that identifies the top therapeutic gene targets within the genome. "We believe one of our biggest differentiators is the strength of our targets," she notes.

The biological insights provided by the CRISPRomics platform have allowed the company to identify the *SOCS1* and *Regnase-1* genes as important targets. "These two genes act as powerful brakes that restrain the ability of T cells to overcome the immunosuppressive tumor microenvironment," she explains.

In preclinical studies, the inactivation of *SOCS1* and *Regnase-1* has been shown to play a critical role in TIL biology by enhancing post-infusion TIL engraftment and the destruction of solid tumors. Ultimately, KSQ's eTILs undergo gene editing with CRISPR-Cas9 to inactivate *SOCS1* and *Regnase-1*.

Truppel-Hartmann highlights KSQ's lead eTIL program, KSQ-001EX, a single-edit eTIL product with an inactivated SOCS1 gene. It is currently being investigated in a clinical Phase I/II study. "We believe inactivation of SOCS1 will help our eTILs engraft, persist, infiltrate, recognize, and kill tumors more effectively," she adds.

Meanwhile, the company's second eTIL program is KSQ-004EX, a dual-edited TIL in which both *SOCS1* and *Regnase-1* genes are inactivated. "This combined deletion enhances the anti-tumor functionality of eTILs by many hundred-fold, leading to a potential best-in-biology enhancement in anti-tumor functionality," she says. KSQ-004EX just entered Phase I clinical development, with an IND clearance at the end of 2024.

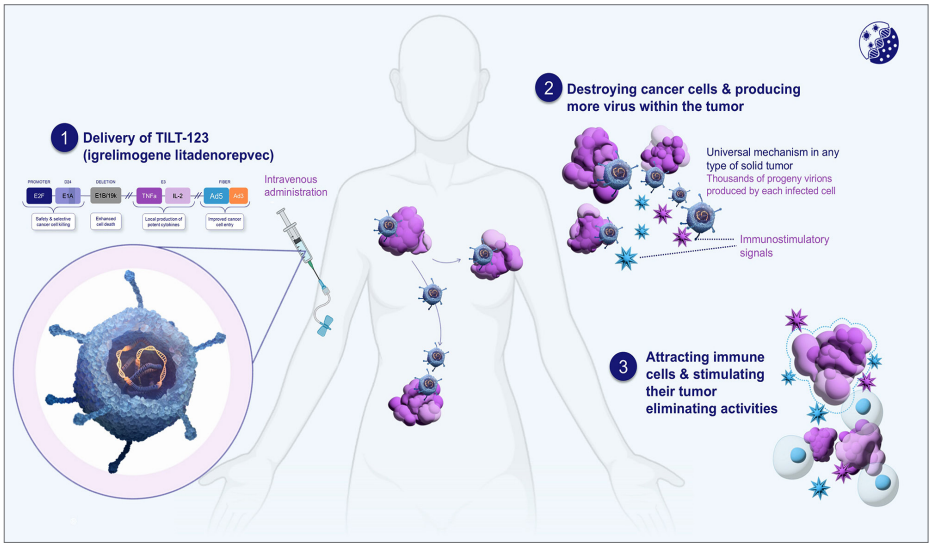
Genetically engineered viruses aid TILs

João Manuel Santos, PhD, head of Translational Medicine at **TILT Biotherapeutics**, explains how the company genetically engineers viruses to enhance lymphocyte activity.

TILT's lead asset, called TILT-123, is a genetically engineered adenovirus. "From the very beginning, TILT-123 was designed to support and enhance the anti-tumor function of lymphocytes, including TILs," he notes.

When patients receive TILT-123 intravenously, tumor cells are infected and destroyed by the virus. Meanwhile, infected tumor cells are also instructed to produce two well-known lymphocyte-stimulating factors—interleukin-2 and tumor necrosis factor—further alerting the immune system to attack the tumor and infected cells.

"TILT-123 prepares the tumor and its surroundings so that, when the patient receives an infusion of TILs, these can function better in destroying the tumor," explains Santos.



TILT Biotherapeutic's TILT-123 intravenous adenoviral treatment. The virus encodes for genes that lead to enhanced cancer cell killing, the local production of potent cytokines, and improved cancer cell entry.

He notes that the combination of TILT-123 and TIL therapies is often a good match. "Furthermore, the effects of TILT-123 in the tumor go beyond lymphocytes, thus indirectly affecting other immune cell types as well," he adds.

TILT is currently developing TILT-123 for cancer patients across several clinical trials. The treatment is being used as a monotherapy or in combination with immune checkpoint inhibitors or adoptive TIL therapies. The company has two Phase I clinical trials combining TILT-123 and TIL therapy for metastatic melanoma. Santos notes how one of these trials "completed accrual with results showing safety and promising activity in this patient population."

The company is also developing intravenous TILT-123 in combination with pembrolizumab for patients with platinum-refractory/resistant ovarian cancer. TILT is currently moving to Phase II with this combination.

Expanding to all solid tumors

Bock is optimistic about the future of engineered TIL therapy. "Thus far, TILs have largely been applied to skin cancer and melanoma," he notes. "But the good news is that we don't have to make different TIL for different indications like lung, renal, cervical, and pancreatic cancer. The next big step will be indication expansion to see how many different solid tumor types these can work in." GEN