Forty Seven to Gilead: "Eat me"

Gilead's latest cancer immunotherapy acquisition, a $4.9 billion buyout of Forty Seven, gives the biotech giant access to a pipeline of CD47-targeted monoclonal antibodies (mAbs) and other related binding molecules to fight cancer.

Forty Seven's lead drug is magrolimab, a mAb against CD47, the 'do-not-eat-me' cue that tumor cells use to evade the immune system's macrophage-mediated killing. The mAb blocks recognition between CD47 on tumor cells and its binding partner, signal regulatory protein (SIRP)-α, on macrophages.

Forty Seven is a spinout of Stanford University; it went public in 2018. In December, the company announced results from a phase 1b trial for magrolimab in combination with the chemotherapeutic agent azacytidine, for myelodysplastic syndrome and acute myeloid leukemia, at the American Society of Hematology meeting. The combination therapy was "highly active and well-tolerated" in both groups of patients.

The acquisition further boosts Gilead's cancer immunotherapy pipeline, mostly obtained from its purchase of Kite Pharma in 2017, before the first approval of its chimeric antigen receptor (CAR)-T cell therapy Yescarta. Former Kite cancer immunotherapy assets KTE-X19, KITE-718 and KITE-439 are in clinical testing by Gilead. "Magrolimab complements our existing work in hematology, adding a non-cell therapy program that complements Kite's pipeline of cell therapies for hematological cancers," says Gilead chairman and CEO Daniel O'Day.

Forty Seven has plans to advance two experimental medicines into clinical testing that target other parts of the same immune signaling pathway. One approach is to target cKIT, a cell growth factor found on hematopoietic stem cells, which blocks an 'eat-me' signal to macrophages. Forty Seven's anti-cKIT antibody, FSI-174, has shown anticancer effects in combination with magrolimab in animal testing. The other is anti-SIRPα antibody FSI-189, which is expected to enter phase 1 testing this year.

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γδ T cells bring unconventional cancer-targeting to the clinic — again

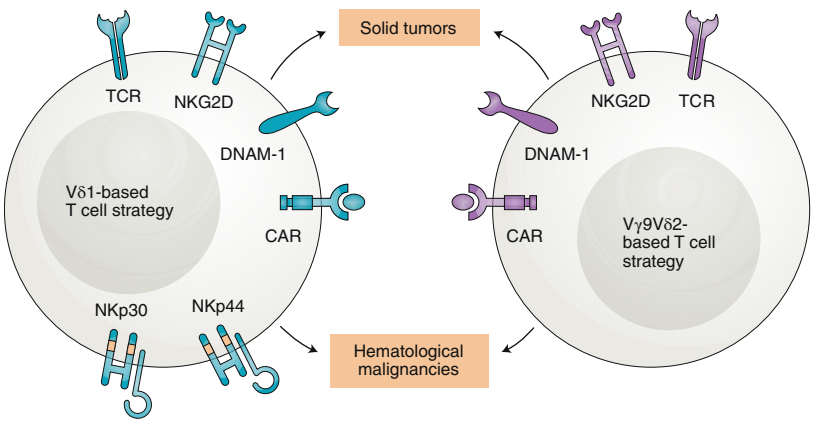
A growing number of companies seek to unleash these unusual T cells against cancer.

The December announcement from Imcheck Therapeutics of a $53 million financing round co-led by Pfizer Ventures has heightened the buzz around γδ T cells. Together with at least nine other biotech companies, Imcheck is developing cancer immunotherapies involving these strange cells that bridge innate and adaptive immunity (Table 1). "There's a new burst of interest in γδ T cells," says Dieter Kabelitz, a Kiel University immunologist. These immune sentinels combine the cell-killing power of the familiar αβ T cells with their own unique tumor recognition abilities. After a series of failed clinical trials in the 2000s, a second wave of therapies is exploiting recent discoveries with novel therapeutic approaches.

γδ T cells are innate effectors: a battle-ready first line of defense against pathogens and cancer. Although they do not require positive selection in the thymus, they have much in common with αβ T cells: they are long-lived, express a T cell receptor (TCR) for target recognition, can have immunological memory, and "are potent killer cells," says Kabelitz. One difference is that most circulating γδ T cells find their targets by detecting metabolic or other abnormalities. They sense small, non-peptide antigens called 'phosphoantigens', present in infected cells or tumor cells, that ultimately lead to γδ T cell activation. They "recognize when things are off, when things are aberrant," says University of Iowa γδ T cell researcher Craig Morita.

The antitumor potential of γδ T cells emerged in 2001, when King's College London immunologist Adrian Hayday reported that γδ T cells prevent mice from developing skin cancer. But exactly how γδ T cells recognize cancer wasn't understood when therapy trials began, mostly repurposing existing drugs. It was known that phosphoantigen metabolites of the mevalonate cholesterol biosynthesis pathway could activate the main type of γδ T cells in circulation:Vγ9Vδ2 cells.. Moreover, scientists noted that certain bisphosphonate drugs for treating osteoporosis activate γδ T cells because the drugs block the mevalonate pathway, resulting in phosphoantigen buildup. A series of cancer clinical trials testing bisphosphonates as γδ T cells activators followed.

But cancer trials failed: in at least six trials, bisphosphonates with low-dose interleukin-2 (IL-2) proved safe but ineffective. That was also true for bromohydrin pyrophosphate, a phosphoantigen analog, in trials by Innate Pharma. Although γδ T cells expanded in vivo, they disappeared from the circulation



Tissue resident (left) and circulating (right) γδ T cells suppress tumors differently. New cell therapies and antibodies exploit these different mechanisms. Adapted with permission from B. Silva-Santos, S. Mensurado & S. B. Coffelt, *Nat. Rev. Cancer* **19**, 392–404 (2019), Springer Nature.