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ASH22 could be IL-18's watershed moment

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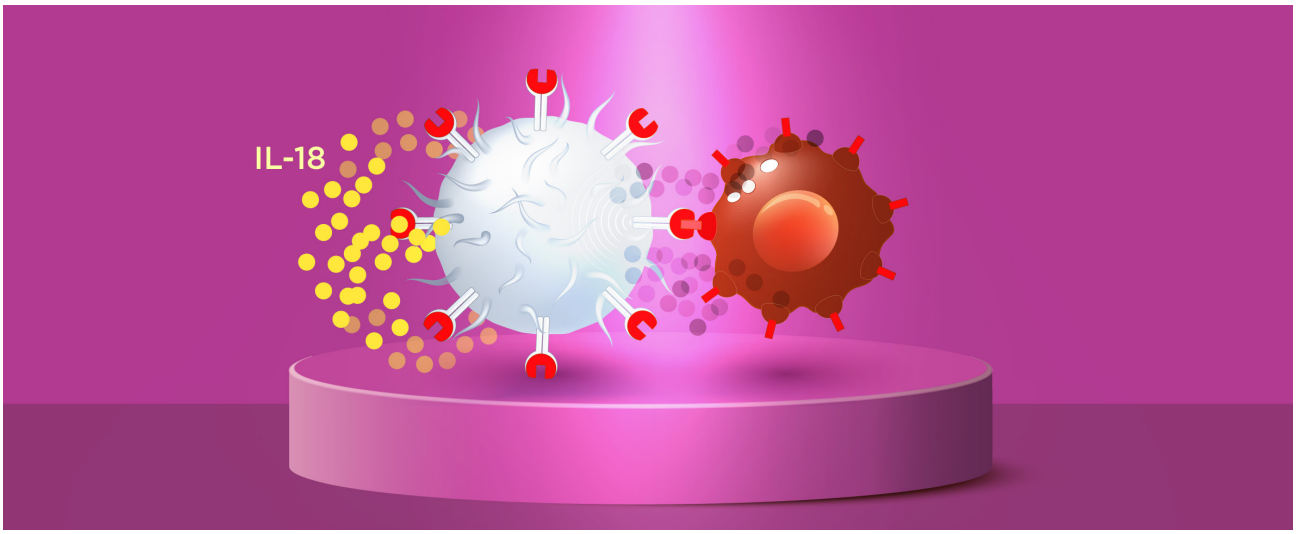

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A striking 100% overall response rate in a small CAR T cell study at ASH could be an inflection point for the still-small field of IL-18-based cancer immunotherapies. The IL-18-secreting CD19 CAR T therapy from cell therapy pioneer Carl June's lab could also address a growing unmet need: patients who've progressed after treatment with marketed CAR T therapies.

Lead study author Jakub Svoboda, an associate professor of medicine at University of Pennsylvania, told BioCentury that anti-CD19 CAR T cells have durable responses in 30-40% of third-line patients with relapsed/refractory diffuse large B cell lymphoma (DLBCL), and 40-50% of patients in the second-line setting, where two CAR therapies are approved so far.

"That leaves a large number of patients who will not achieve long term remissions. There's a significant room for improvement," he said.

In a Dec. 10 presentation at the American Society of Hematology (ASH) meeting, Svoboda and June's team will show the IL-18-secreting anti-CD19 CAR T therapy huCART19-IL18 — generated via an accelerated, three-day manufacturing process — produced four complete responses (CRs) and three partial responses (PRs) in seven evaluable patients with relapsed/refractory B cell non-Hodgkin lymphomas (NHLs), most of whom had progressed after treatment with marketed CAR Ts.

The clinical study built on translational research from multiple independent groups, kicked off by a 2017 *Cell Reports* study from June's lab, showing IL-18 enhanced IFNγ production, proliferation and tumor-killing activity of CAR T cells.

"Preclinically it was already pretty exciting, and we had our eyes out waiting to see what would happen" in the clinic, said Aaron Ring, founder of Simcha Therapeutics Holding Co. LLC and associate professor at Yale School of Medicine. "The initial data didn't disappoint at all."

Produced by innate immune cells such as dendritic cells, and received by a range of immune effectors including cytotoxic $CD8^+$ T cells, IL-18 has so far been a relatively minor focus of development activity in the Th1 cytokine cancer therapy space, which is dominated by programs delivering IL-2 and IL-12 (Figure 1).

About 10 years after GSK plc (LSE:GSK; NYSE:GSK) shuttered cancer studies for its recombinant IL-18 candidate iboctadekin for lack of efficacy, a 2020 paper from Ring's lab showed tumors limit IL-18's activity by upregulating the high-affinity IL-18 decoy receptor IL18BP, and that a decoy-resistant version of the cytokine had potent tumor-killing effects. The discovery formed the basis for Simcha, whose decoy-resistant IL-18 candidate ST-067 is in Phase I/II testing for solid tumors.

Other recombinant IL-18 programs in preclinical development for cancer include a decoy-resistant IL-18 program from Bright Peak Therapeutics Inc., and an IL-18/IL-12 fusion protein from Sonnet Biotherapeutics Holdings Inc.

Only one company, Seoul-based Eutilex Co. Ltd., has disclosed an IL-18-secreting CAR T cell program, targeting the liver cancer antigen GPC3; the company did not return requests for comment in time for publication. Penn has not yet announced a licensing agreement for huCART19-IL18.

Ring thinks the clinical data at ASH suggest decoy resistance may be less important when the cytokine comes from the CAR T cells themselves and acts in an autocrine and paracrine fashion, compared with systemic delivery of a recombinant cytokine. "It seems that by producing it in the microenvironment, it can outcompete the decoy receptor locally," he said.

He noted that huCART19-IL18's efficacy could also be attributed to its shorter manufacturing process, which cut expansion time down by three-to-four fold. "You're working with a more active, viable, stem like-product," said Ring.

Revved up response

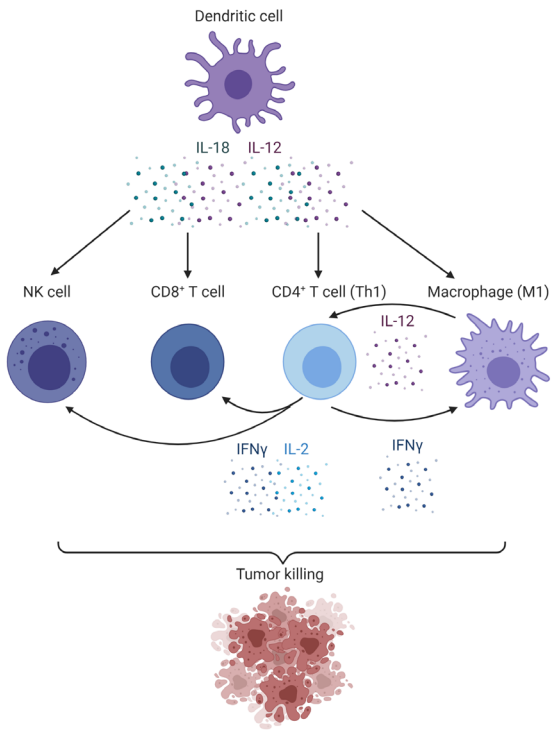
The patients' responses to huCART19-IL18, despite their challenging treatment histories, are an encouraging sign of the approach's potential.

The product, which Svoboda and June's team describe as a fourth-generation CAR T cell, consists of autologous T cells transduced with a lentiviral vector to co-express IL-18 and an anti-CD19 CAR with a 4-1BB costimulatory domain and a CD3ζ signaling domain.

Out of eight patients evaluable for safety, seven relapsed after prior CAR T treatment, and one had previously failed two attempts to collect adequate commercial CAR T product. Despite that history, he was able to produce enough cells for the huCART19-IL18 study. "He did not meet the assigned target dose, but exceeded the minimum infusible dose and was able to get treated, and he actually responded," Svoboda said.

He said it's unclear if this patient's improved manufacturing outcome was related to huCART19-IL18's design, but between the product's two major innovations — a shorter manufacturing process and IL-18 secretion — he thinks the former is more likely to contribute to improved manufacturability.

Figure 1



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Another patient received a low dose (3 x 10^6 cells) of huCART19-IL18 without lymphodepletion, had a PR, and then received a second infusion of the cells that led to a CR. "The idea that IL-18 was able to drive activity without lymphodepletion is really exciting," Ring said.

The two other patients with PRs, one of whom had progressed to CD19-negative disease, both transitioned to alternative therapies.

All patients with CRs had ongoing responses, and all the treated patients remained alive, at a median follow-up of eight months.

Svoboda said huCART19-IL18's toxicity profile "appears to be in line with" marketed CAR T cells. His team reported cytokine release syndrome (CRS) in four out of eight patients (50%), with a median duration of 5.5 days; two patients required anti-

cytokine therapy. Two out of eight patients (25%) experienced neurotoxicity.

The authors also presented data on CAR T cell expansion and persistence in each patient; in one patient, the cells were detectable at almost 300 days.

Svoboda said it's too early to try to link response profiles to biomarkers such as CAR T persistence, but said the group will be exploring correlative biomarker analyses in both peripheral blood and biopsies at various time points, including a biopsy at day 14 after huCART19-IL18 infusion.

Turning 18

Advocates of IL-18 tout its improved safety relative to other cytotoxic T cell-stimulating cytokines like IL-12.

"It's not an on-switch, it's an amplifier," Ring said. "It's amplifying the activity of the CAR T cells, but not bystander T cells, like IL-12 would do."

That selectivity is partly due to the lack of IL-18 receptor expression on naive or quiescent T cells that haven't been recently exposed to cognate antigen.

"T cells acquire the ability to respond to innate signals only after they've been licensed by antigen," Ring said, which can provide selectivity in the tumor microenvironment. "If you haven't seen your cognate antigen in a long time, chances are you're not tumor-reactive."

Another factor shaping IL-18's activity profile is that it signals through the adaptor protein MyD88, instead of the JAK/STAT pathways downstream of many other cytokines. The NFκB signals downstream of MyD88 are not sufficient for immune activation on their own; instead, they amplify other forms of activation, Ring said.

In addition to TCR activation, IL-18 can also amplify signals from other cytokines, such as IL-12, IL-15 or IL-2, and from NK cell activators such as Fc receptors or NKG2D. "Adoptive NK cell therapies are coming to the fore, and the idea of adding IL-18 on top of those therapies is exciting," said Ring.

An ASH presentation from Affimed N.V. (NASDAQ:AFMD) researchers and Katy Rezvani's group at University of Texas MD Anderson Cancer Center shows AFM13, an innate cell engager-conjugated NK cell therapy pre-activated with IL-12, IL-15 and IL-18, led to complete response rates of up to 71% and an 83% overall survival rate at a median of eight months follow-up in 30 lymphoma patients.

While some studies have suggested IL-18 can have pro-tumorigenic effects, Ring thinks it's likely that chronic, low-grade IL-18 production in a tumor would have a very different activity profile than the "alien physiology" of IL-18 produced by CAR T cells, or delivered at high-doses via recombinant cytokine therapy.

"We need to dissociate in our mind what may be happening endogenously, and what we can do pharmacologically," he said.

Simcha's decoy-resistant IL-18 is "well-suited to pair with multiple modalities of immunotherapy, including with cell therapies," which opens the door to partnering opportunities, Simcha CEO Sanuj Ravindran told BioCentury in an email.

"We're highly motivated to broaden the breadth of potential that decoy-resistant IL-18 holds, and if we can do a better and faster job through partnering with others that have complementary expertise and technologies, then that's what we'll do, and in fact have already begun exploring," he said.

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