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# Growing IL-18 field looks to enhance cell therapies via decoy evasion

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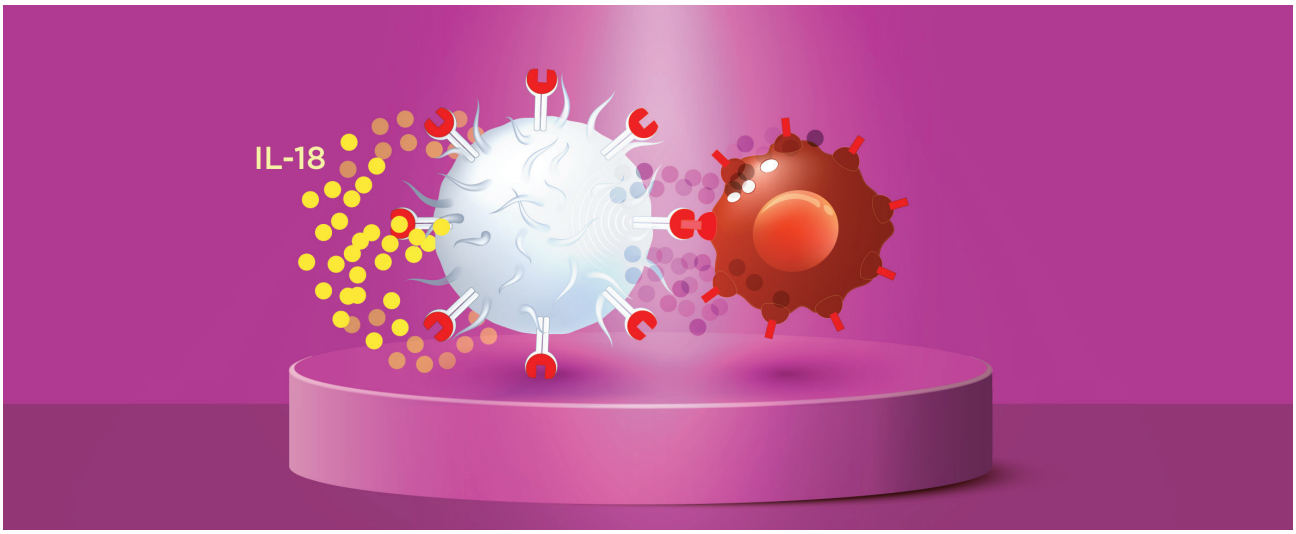


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Deals between major cancer cell therapy players and biotechs with strategies to promote IL-18 signaling unhampered by decoy receptors indicate the cytokine's next wave of innovation will combine the two approaches.

Interest in IL-18's capacity to boost tumor killing by immune cells has risen over the last five years through the convergence of multiple findings, including biomarker support for the cytokine's role.

"We're not a company based on cytokines, but we found this pathway to be highly expressed in patients resistant to immunotherapy," Pierre Ferre, VP of preclinical development at Compugen Ltd. (NASDAQ:CGEN; Tel Aviv:CGEN), told BioCentury.

Two major catalysts driving the interest were the 2017 preclinical finding that IL-18 increases the potency of CAR T cells, and the separate discovery in 2020 that the cytokine has a natural inhibitory decoy receptor, IL18BP, which thwarted earlier IL-18 cancer therapies but can be evaded through cytokine engineering.

Since then, research on the cytokine's role in cancer has expanded, and the number of companies with disclosed IL-18 cancer therapies has grown from two in 2020, to four in 2022, to at least nine in January 2024 (see Pipeline chart).

"The role we see it playing is, it can re-invigorate exhausted T cells and NK cells," Caroline Loew, CEO of Alkermes plc (NASDAQ:ALKS) spinout Mural Oncology plc (NASDAQ:MURA), told BioCentury. Mural launched in November with a focus on engineered cytokines including IL-18.

Both decoy-resistant IL-18 and IL-18-armored CAR T cell technologies are now in the clinic, the latter fueled by promising early clinical data from Carl June's team at University of Pennsylvania, which was also behind the 2017 preclinical finding.

A Jan. 8 deal to develop cell therapies armored with decoy-resistant IL-18 is the clearest disclosed signal that the two approaches will soon be combined.

Simcha Therapeutics Holding Co. LLC said it was partnering with the Janssen Biotech Inc. unit of Johnson & Johnson (NYSE:JNJ) to develop, manufacture and commercialize decoy-resistant IL-18- armored cell therapies for an undisclosed number of programs, adding depth to the pharma's CAR T cell therapy franchise. The engineered cytokine company will receive an undisclosed upfront fee, and is eligible for option exercise fees and development and commercialization milestones.

Simcha CEO Sanuj Ravindran told BioCentury the collaboration is non-exclusive, enabling the company to combine its decoy-resistant IL-18 with other partners' cell therapies, including ones against the same targets. "We're actively considering other collaborations of a similar nature," he said.

The Dec. 19 announcement of a deal between Compugen and CAR T cell leader Gilead Sciences Inc. (NASDAQ:GILD) for the Israeli biotech's anti-IL18BP antibody didn't specify whether the partners will apply the decoy-blocking mAb to Gilead's cell therapies.

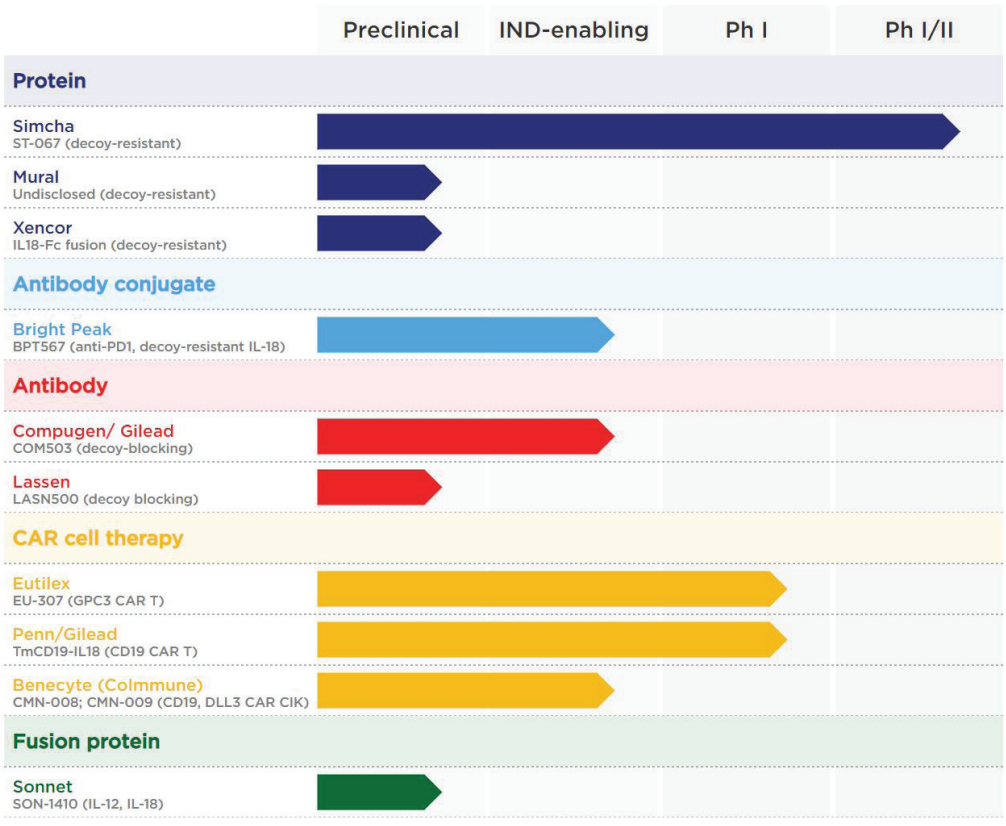
But Bill Grossman, SVP and therapeutic area head of Gilead Oncology, told BioCentury the understanding of IL-18 biology gained via the partnership will inform work at the company's Kite Pharma Inc. unit. "We can apply those learnings to our cell therapy programs," he said.

Compugen will receive $60 million up front, plus $30 million if FDA clears the program's IND as the partners expect next year. The deal includes $758 million in milestones, as well as royalties in the low double digits.

Early signs of success for IL-18-armored CAR T cells, however, suggest it's possible that decoy evasion may be less critical for cell therapies that produce their own cytokines locally than for systemic delivery of protein-based therapies.

A June 2023 update from June's Penn team on its HuCART19-IL18 cells, which made a splash at the 2022 American Society of Hematology (ASH) meeting, showed a three-month overall response rate (ORR) of 82% in 11 evaluable patients, six (55%) of which had complete responses. All patients were alive at a median follow-up of 12 months.

## Company IL-18 programs in oncology




*Source: BCIQ, ClinicalTrials.gov, company websites • CAR - Chimeric antigen receptor; CIK - Cytokine-induced killer cell*

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"There's a growing consensus of the importance of IL-18 signaling in tumor immunotherapy," said Simcha founder Aaron Ring, an assistant professor at Fred Hutchinson Cancer Research Center, whose lab discovered the IL18BP mechanism and evasion strategy while at Yale University. "The critical question is, if IL-18 is good, is decoy-resistant IL-18 better, given what we know about the binding protein in the tumor microenvironment?"

### Modality matrix

Companies with disclosed IL-18 cancer programs are divided into those delivering decoy-resistant IL-18 proteins, those blocking IL18BP with mAbs, and those incorporating IL-18 into cell therapies or fusion proteins without disclosed decoy-resistance strategies.

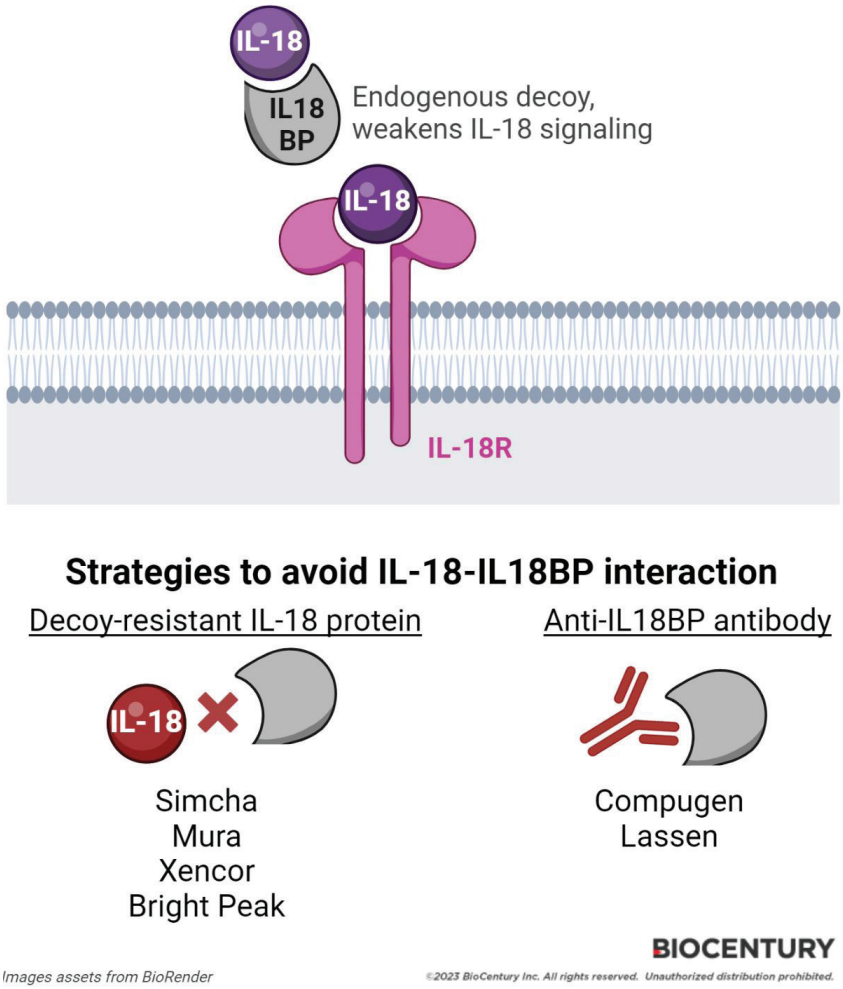
"There's more than one way to exploit this biology," Ring said.

Simcha's ST-067, in Phase I/II testing for solid tumors, is the most advanced decoy-resistant IL-18 protein therapy. The company is testing ST-067 as a monotherapy, and in combination with anti-PD1 mAb Keytruda pembrolizumab.

Other decoy-resistant IL-18 programs include preclinical technologies from Mural and Xencor Inc. (NASDAQ:XNCR).

Mural is using its Picasso protein engineering platform to dial out IL18BP binding, and its half-life extension domains to increase tumor residency. The company plans to nominate a candidate this year.

Loew thinks the compound could have complimentary activity with other cytokines such as IL-2, the focus of Mural's lead program, but said it's important to first study it as a monotherapy.




*Images assets from BioRender*

"The path of going immediately to combination without understanding the components is extremely fraught," she said. "But we've had a lot of interest from folks who would like to develop this in combination."

Xencor presented on the antitumor activity of its IL-18 targeting agents, fused to Fc domains to improve stability, at the 2023 Society for Immunotherapy of Cancer (SITC) meeting. The presentation included a potency-reduced version of the cytokine fused to a PD-1-targeting agent, which showed improved tolerability compared with the full-potency variant in non-human primates.

A company with a similar bivalent strategy is Bright Peak Therapeutics Inc., whose preclinical antibody conjugate BPT567 links a decoy-resistant IL-18 to LZM009, a clinical anti-PD1 mAb from Livzon Pharmaceutical Group Ltd. (HKEX:1513; SZSE:000513). The compound simultaneously blocks PD-1 and stimulates the IL-18 receptor on the surface of PD-1+ T cells.

In contrast, preclinical mAb candidates from Compugen and Lassen Therapeutics Inc. block the interaction between IL-18 and IL18BP, unleashing

the activity of endogenous IL-18 instead of delivering exogenous cytokine signals (see Diagram).

Compugen's Ferre thinks the "sweet spot" for this strategy may be cancers with inflammasome signaling, which promotes IL-18 secretion in the tumor microenvironment. "This is why we think it's an interesting pathway, because the inflammasome is activated in many tumors," he said.

Ferre thinks the company's candidate COM503, slated for an IND submission this year, will be dosed every two, three or four weeks like other antibody therapies, which he believes will be more convenient for patients than typical dosing regimens for engineered cytokines.

He believes an IL18BP-blocking approach may also have a wider therapeutic window than systemic IL-18 delivery. "When you dose a cytokine, it hits cells in the circulation first," which can result in unwanted inflammation outside the tumor, and insufficient activity within the tumor, Ferre said.

Compugen's hypothesis is that by relying on endogenous production of IL-18, COM503's will be activity constrained to the tumor microenvironment.

Simcha and Compugen's different views on the selectivity of IL-18 receptor expression, an ongoing debate in the field, shape their respective thinking on therapeutic modalities and targeting strategies.

According to Simcha's Ravindran, IL-18 "acts on antigen-experienced T cells, not on quiescent T cells, like other cytokines might." As a result, "IL-18 acts more like an amplifier than an on-switch," which increases the safety of exogenous cytokine stimulation, and expands its therapeutic window.

Compugen believes IL-18 sensitivity is more widespread among T cells, making it both safer and more feasible to depend on tumor IL-18 production for activity. "In our data, the IL-18 receptor is expressed in many subtypes of T cells. We're taking the chance that the potential will be broad," Ferre said.

Ferre's SITC presentation showed the company's anti-IL-18BP mAb modified the tumor microenvironment, but not the periphery, in mouse models of cancer, while an engineered IL-18 increased serum inflammatory cytokine levels and lymphocyte activation markers.

Although Mural has opted for an exogenous cytokine strategy, Loew said the company's research team thinks both sides of the debate have merit. The team thinks IL-18 is selective for antigen-experienced T cells over other T cells, but also affects innate immune cells such as macrophages and dendritic cells.

"While this may support therapeutic efficacy, it may also have an impact on tolerability," she said. "We are closely monitoring this in preclinical testing, as well as considering biomarker and mitigation strategies for future clinical studies."

## "THE CRITICAL QUESTION IS, IF IL-18 IS GOOD, IS DECOY-RESISTANT IL-18 BETTER?"

### AARON RING, FRED HUTCH

Ring said his lab tested an IL18BP-binding approach, but ultimately saw stronger efficacy by agonizing the IL-18 receptor directly. "We made inhibitors of the binding protein and patented them, but in our hands, the effect was pretty modest."

However, he added, "different strategies may have unique advantages in different indications."

### Cell reception

Among IL-18 programs without a disclosed decoy mitigation strategy, cell therapies are the primary modality.

The most advanced data on IL-18-armored CAR T cells comes from the Penn team's ongoing Phase I study of HuCART19-IL18, but the university has another Phase I study of a similar product, dubbed TmCD19-IL18, which lists Gilead's Kite unit as a collaborator.

The program is part of Gilead's December 2022 acquisition of Tmunity Therapeutics Inc., through which Kite gained access to armored CAR T technology developed by Tmunity's founders at Penn.

"This study is seeking to support the rationale for using IL-18 armoring to enhance T-cell proliferation, INFγ production, and cytolytic activity (including Cytotoxic T cell and NK cell mediated cell killing)," Gilead spokesperson Tracy Rossin told BioCentury in an email.

Eutilex Co. Ltd. (KOSDAQ:263050) has a GPC3-targeted, IL-18-secreting CAR T cell therapy EU-307 in Phase I testing for hepatocellular carcinoma (HCC). The company presented preclinical data on the candidate at the 2023 American Association for Cancer Research (AACR) meeting.

Benecyte Inc., formerly CoImmune Inc., licensed preclinical CAR cytokine-induced killer (CIK) cell therapies targeting CD19 and DLL3 from Memorial Sloan Kettering Cancer Center (MSKCC), where they were developed by Renier Brentjens, now deputy director and chief of medicine at Roswell Park Comprehensive Cancer Center.

MSKCC also has an ongoing Phase I academic study of an IL-18-armored CAR T cell therapy. Dubbed CD371-YSNVZIL-18,

its CAR targets CLEC12A for acute myelogenous leukemia (AML).

Sonnet BioTherapeutics Holdings Inc. (NASDAQ:SONN) has a preclinical fusion protein, SON-1410, that delivers both IL-12 and IL-18 signals as a payload attached to an albumin-binding human single-chain antibody fragment (scFv) that increases the compound's half-life and concentration in tumors.

In Oct. 2022, Sonnet and Janssen announced a partnership to preclinically test three of the biotech's cytokine fusion proteins, including SON-1410, in combination with the pharma unit's cell therapies. Financial details were not disclosed.

Whether the IL-18 is decoy-resistant or not, companies can armor cell therapies by engineering them to express their own IL-18; co-deliver an IL-18 agent as a separate compound, as in the Sonnet deal; or tether the cytokine to a cell therapy's surface via a linker.

Simcha's Ravindran noted that combining a separate IL-18 compound with a marketed CAR T cell offers the opportunity to reach patients more quickly.

"While our deal is specifically around armoring CAR T cells, and that's an approach we will seek to complete more collaborations around, we also believe that combining with IL-18 in a co-delivery setting can make sense," he said.

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