BioCentury
REPRINT FROM FEBRUARY 23, 2015

PRODUCT DEVELOPMENT

AGONIZING CANCER IMMUNOTHERAPY

BY JENNIFER RHODES, STAFF WRITER

Lycera Corp. is aiming to enter the increasingly competitive cancer immunotherapy space with oral small molecules that appear to be the first to simultaneously boost antitumor T cells and release the brakes on the immune system. If preclinical findings are borne out in the clinic, the molecules have the potential to augment — or even replace — PD-1 or PD-L1 inhibitors. They may also have synergy with adoptive cell therapies.

The molecules are the only disclosed agonists of RORgammaT. RORgammaT, also known as RAR-related orphan receptor C thymus-specific isoform, drives the activation and differentiation of CD4+ and CD8+ cells into IL-17-producing T helper type 17 (Th17) cells and cytotoxic Tc17 cells. Th17 and Tc17 are effector cells that promote inflammation, adaptive immunity and autoimmunity by producing IL-17 and other inflammatory cytokines such as IL-21.

There are a handful antagonists in development to treat autoimmune diseases, including a program Lycera partnered with Merck & Co. Inc. in 2011. But Th17 and Tc17 cells and the cytokines they produce also can have antitumor effects, which led Lycera to wonder if it could drive a durable antitumor response by turning on RORgammaT.

The biotech developed hundreds of synthetic agonists that are selective for RORgammaT and began evaluating them in cancer models. The first preclinical data, presented in November at the Society for Immunotherapy of Cancer meeting, showed increases in antitumor cytokines and Th17 and Tc17 cells, along with reductions in levels of regulatory cells that tamp down the immune response.

In both murine and naïve human T cells that were differentiated *in vitro* into Th17 cells, the addition of an RORgammaT agonist led the cells to produce significantly more GM-CSF, IL-17A and IL-17F than a dimethyl sulfoxide vehicle did ($p<0.05$).

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>
> GARY GLICK, LYCERA

The study also demonstrated target specificity, because the agonist did not significantly affect levels of IFN gamma, an antitumor cytokine that is not controlled by RORgammaT.

CBO Bruce Goldsmith said the results were duplicated in Tc17 cells.

In a second *in vitro* study, Lycera showed the agonist led to an increase in Th17 and Tc17 cells as measured by IL-17 mRNA, and a decrease in Treg cells, which suppress activation of the immune system.

"What you'd love to do is have more effector cells and fewer regulatory cells. That would in theory have more of an antitumor effect and a less immunosuppressive environment," said founder and CSO Gary Glick.

He said the company also has evidence that Th17 cells differentiated in the presence of an agonist have more "tumor homing properties" and are better able to penetrate the tumor than cells differentiated without the agonist.

SURPRISE EFFECT

A third *in vitro* study with a different RORgammaT agonist showed a surprising effect — the molecule reduced the expression of the immune checkpoint protein programmed cell death 1 (PD-1; PDCD1; CD279) on effector cells and made the cells less sensitive to that receptor's ligand — potentially releasing an important brake on the immune response.

Programmed cell death 1 ligand 1 (PD-L1; B7-H1; CD274) binds PD-1 on T cells and triggers a process that winds down an immune response, including reducing proliferation of the effector cells. In the tumor microenvironment, T cells overexpress PD-1 and a range of other receptors that bind to their corresponding ligands and act in concert to shut down T cells and block their antitumor effect.

The study showed murine and human effector cells treated with the agonist had about half as much PD-1 expression on the cell surface as cells treated with just a vehicle ($p<0.05$).

Cells that were differentiated with the agonist proliferated at the same levels whether or not PD-L1 was added. In contrast, cells differentiated without the agonist proliferated half as much with the ligand as without it.

"Cells differentiated in the presence of the agonist have a reduced sensitivity to checkpoint inhibition," noted Glick. Lycera is working to identify the mechanism by which the agonist reduced PD-1 expression and sensitivity.

BOOSTING CARS

Lycera also presented rodent data showing its agonists augmented adoptive cell therapies.

In a mouse model of lymphoma, mice receiving Tc17 cells that were differentiated *in vitro* in the presence of the agonist had significantly smaller tumor volumes at day nine compared with untreated mice and mice that received cells differentiated without the agonist ($p<0.01$). Goldsmith said the results were duplicated in mice given Tc17 cells, and Glick said the company has seen a similar antitumor response out to two months in a variety of tumor models, including lymphoma and melanoma.

"By turning on this transcription factor and turning it into overdrive, we're able to turn on Th17 that lasts longer and gets into the tumor more and provides a longer response. We're also turning off simultaneously that immunosuppressive environment in the tumor," said Glick.

"One of the things we seem to be doing is reprogramming the effector cells to live longer, which allows them to carry out their effects more," noted Glick, who added that one of the problems with chimeric antigen receptor (CAR) T cell therapy approaches is that the engineered cells can die quickly.

The company is still exploring how the agonists prolong the life span of the effector cells, but Glick said it appears the agonist is reprogramming the cells to "have an enhanced stem-like quality."

"We're not going to build CAR Ts, but based on the data we've generated, one could imagine an agonist could significantly enhance the activity of CAR T cells and possibly lead to improved response rates," noted Glick.

MONOTHERAPY

Rodent data show Lycera's agonists also could have potential as monotherapy.

Data presented this month at a Keystone symposium showed an oral RORgammaT agonist given once daily reduced tumor volumes and lung and liver metastases in a mouse model of breast cancer, although it did not have the same effect on the ratio of effector cells to Treg cells seen in the *in vitro* studies.

Mice treated with the agonist did not have a significantly lower proportion of Treg cells compared with mice given the vehicle, but the company said increased IL-17A levels in the treated mice suggest the effector cells were more active and/or more plentiful in tumors.

In a mouse model of colon cancer, a third Lycera agonist given as monotherapy once daily led to significantly smaller tumor volumes at day 30 vs. vehicle alone ($p<0.01$). Significantly more treated than untreated mice were alive at day 40, the time the data were collected for the presentation ($p=0.001$).

Glick conceded that autoimmunity with its agonists is a concern, particularly given the role of Th17 and Tc17 cells and associated cytokines in autoimmune diseases. But he said the company has tested high doses of the agonists for several months in rodents and to date has found no evidence the agonists turn on the effector cells enough to generate an autoimmune response.

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NEXT STEPS

Lycera plans to select a lead small molecule oral agonist by the end of 1Q15 and to move the lead into the clinic by YE15, though the company is not yet providing details on its clinical development plan.

For early proof of concept, Glick said Lycera is exploring melanoma and lung cancers, "where other immunotherapies have worked very well." He said Lycera is also looking at RORgammaT expression in tumor types and is exploring which cancers correlate with either a very good or a poor response to RORgammaT-associated cytokines like IL-17.

For example, Glick noted that high IL-17 levels correlate with a good clinical response in ovarian cancer but are associated with a poor response in colorectal cancer.

"We want to integrate all three of those parameters to rationally select patients that would have the highest probability of responding to the agonists," said Glick.

Lycera plans to develop the agonists both as a single agent and as part of combination therapy with other immunotherapies including checkpoint inhibitors, radiation and/or chemotherapy.

"Since we presented this first data back in November, we've had a lot of inbound interest," said Goldsmith, who said Lycera is in discussions with potential partners. He declined to comment on timing for a potential deal, but said the company has fielded interest in the overall program, as well as interest selectively in the agonists as part of an *ex vivo* approach with adoptive cell therapies.

Paul Sekhri, who joined Lycera this month as president, CEO and a director, said he and the Lycera team are exploring raising capital, funding the program through partnerships, or both.

"Any and all of these might be ways to fund the company," said Sekhri, who was SVP of integrated care at Sanofi. "The most important factor is getting these compounds into the clinic and making sure we have enough capital to do that."

Lycera raised $21 million in a series A round in 2010. The company declined to comment on its cash position; however, Goldsmith said the company has "substantial support" from its existing investors.

As to the RORgammaT antagonist program with Merck, Glick said it is moving forward but declined to provide the stage of development or any milestones. bc

COMPANIES AND INSTITUTIONS MENTIONED

Keystone Symposia on Molecular and Cellular Biology, Silverthorne, Colo.

Lycera Corp., Ann Arbor, Mich.

Merck & Co. Inc. (NYSE:MRK), Whitehouse Station, N.J.

Sanofi (Euronext:SAN; NYSE:SNY), Paris, France

Society for Immunotherapy of Cancer, Milwaukee, Wis.

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Moisan, J. et al. "Novel oral RORgamma agonists demonstrate anti-tumor efficacy in the 4T1 breast cancer model." *Keystone Symposium – Tumor Immunology* (2015)