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EMERGING COMPANY PROFILE

Silverback: Taking on tumoral myeloid cells

BY ELIZABETH S. EATON, STAFF WRITER

Silverback's antibody-based conjugates stimulate innate and adaptive immunity by turning myeloid cells against tumors, while overcoming resistance to checkpoint inhibitors and other T cell-targeting immunotherapies.

"When you are able to appropriately and potently activate myeloid cells, the tumor microenvironment is completely reprogrammed," Valerie Odegard, CSO of Silverback Therapeutics Inc., told BioCentury. "The inflammatory nature of the response allows for T cells and other immune cells to then infiltrate those tumors in a way that wasn't possible previously."

According to Peter Thompson, who invented the company's immunomodulatory conjugate platform, checkpoint inhibitor-resistant tumors often have lower levels of infiltrating T cells but are replete with myeloid cells. Thompson is co-founder, chairman, president and CEO of Silverback and a partner at OrbiMed, which developed the technology and invested in the start-up.

While myeloid cells are ordinarily immunosuppressive, recent strides in the field have shown how switching the cells to a tumor-targeting phenotype also enables them to coordinate a T cell attack (see "Flipping the Switch in Immuno-Oncology").

Silverback's compounds achieve this dual result by linking tumor-targeting antibodies to a small molecule immunotherapy payload, such as a TLR8 agonist. The conjugate binds FGCR on tumor-associated myeloid cells to activate them; the payload then augments myeloid cell activation and stimulates adaptive immunity by activating dendritic cells, which in turn drive expansion of $CD8^+$ T effector cells. Silverback declined to disclose whether it modifies the antibody's Fc domain.

Because the compounds require tumor and myeloid cells for activation, they are only active inside tumors. Thompson said this feature allows them to recapitulate the efficacy of intratumorally injected immunotherapies, while avoiding the restrictions posed by hard-to-access tumors and the severe side effects associated with TLR8 agonists and other systemic immunotherapies, such as cytokine release syndrome (CRS).

SILVERBACK THERAPEUTICS INC.
Seattle, Wash.

Technology: Tumor-targeting, antibody-based immunotherapies for myeloid cell activation

Disease focus: Cancer, autoimmune, infectious

Clinical status: Preclinical

Founded: 2016 by Peter Thompson and Badreddin Edris

University collaborators: None

Corporate partners: None

Number of employees: 35

Funds raised: $55 million

Investors: OrbiMed Advisors, Celgene Corp., Alexandria Venture Investments

CEO: Peter Thompson

Patents: None issued

Silverback's lead compound, SBT6050, is a HER2-targeting mAb linked to a TLR8 agonist. The company plans to take it into the clinic for HER2-positive solid tumors next year; Thompson said initial trials will include cancer types that have been shown to not respond to checkpoint inhibitors, as well as patients who didn't respond to those therapies.

Odegard said Silverback chose TLR8 as a target because it is expressed only on myeloid cells, and in particular on dendritic cells that drive durable, adaptive immune responses. The company chose HER2-positive tumors as the lead indication because they are frequently immunosuppressive and have high myeloid cell counts.

In an abstract published ahead of the American Association for Cancer Research (AACR) meeting in April, Silverback reported data showing SBT6050 activated tumor-associated myeloid cells and decreased tumor growth in a mouse model of HER2-positive colon cancer. Mice whose tumors completely disappeared were resistant to tumor rechallenge.

Thompson said Silverback also has therapies in preclinical testing for fibrosis and infectious disease. "This ability to systemically administer a compound that then is locally active can be applied both in and outside of oncology."

He declined to disclose how many products are in the company's pipeline or what the products target, but said Silverback is considering partnerships to help develop its entire pipeline.

According to BioCentury's BCIQ database, at least three companies have TLR8 agonists in the clinic for cancer. At least two others, Faron Pharmaceuticals Oy and Macrophage Pharma Ltd., are reprogramming tumor-associated macrophages at the transcriptional level to make them immunostimulatory.

Odegard said Silverback combines these two strategies — TLR8 agonism and myeloid reprogramming — into a single compound that directs both arms of the immune system against tumors.

The company has raised $55 million from OrbiMed, Celgene Corp. and Alexandria Venture Investments. Thompson said Silverback is looking to close a series B later this year.

COMPANIES AND INSTITUTIONS MENTIONED

American Association for Cancer Research (AACR), Philadelphia, Pa.
Celgene Corp. (NASDAQ:CELG), Summit, N.J.
Faron Pharmaceuticals Oy (LSE:FARN), Turku, Finland
Macrophage Pharma Ltd., Windsor, U.K.
OrbiMed Advisors, New York, N.Y.
Silverback Therapeutics Inc., Seattle, Wash.

TARGETS

FCGR - Fcγ receptor
HER2 (EGFR2; ErbB2; neu) - Epidermal growth factor receptor 2
TLR8 - Toll-like receptor 8

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