

EMERGING COMPANY PROFILE

TARGETED PHAGOCYTOSIS

BY VIRGINIA LI, STAFF WRITER

Alexo Therapeutics Inc. is developing variants of signal regulatory protein alpha that antagonize CD47 to increase macrophage phagocytosis induced by anticancer antibodies. Using the variants alongside antibody therapeutics could avoid on-target phagocytosis of healthy cells observed with more advanced CD47-targeting agents.

CD47 is a cell surface protein that is widely expressed on both normal and cancer cells. It allows cells to avoid phagocytosis by interacting with signal regulatory protein alpha (SIRPA) on macrophages.

President and CEO Jaume Pons said elevated CD47 expression is observed in many hematological and solid tumors and “correlates with aggressive disease and decreased probability of survival.”

However, blockade of CD47 signaling is not sufficient to induce macrophage phagocytosis, which also requires the delivery of a pro-phagocytic signal. Antibody therapeutics for cancer not only can deliver the required signal via binding of their Fc region to receptors on macrophages, but also can ensure the signal is targeted only to the cells that express the antibody’s target.

The result should be an increase in phagocytosis of cancer cells that spares healthy cells.

A 2013 paper in *Science* by **Stanford University** researchers described SIRPA variants that did not induce phagocytosis or reduce tumor growth by themselves but that showed “remarkable synergy” with several approved mAbs *in vitro* and *in vivo*.

SIRPA variants administered in combination with antibodies led to increased phagocytosis in three cancer cell lines compared to treatment with the antibodies alone. The variants were combined with Herceptin trastuzumab in a breast cancer cell line, Erbitux cetuximab in a colon cancer cell line and Rituxan rituximab in a lymphoma cell line.

The paper also described SIRPA variant CV1, which enhanced antitumor responses *in vivo* compared to antibodies alone when administered in combination with Rituxan or Lemtrada alemtuzumab in two separate mouse

ALEXO THERAPEUTICS INC.

South San Francisco, Calif.

Technology: High-affinity SIRPA variants that antagonize CD47

Disease focus: Cancer

Clinical status: Preclinical

Founded: 2015 by undisclosed founders

University collaborators: [Stanford University](#)

Corporate partners: None

Number of employees: 16

Funds raised: \$36 million

Investors: venBio, Lightstone Ventures, Longevity Fund, Stanford University

CEO: Jaume Pons

Patents: Undisclosed

models of lymphoma, and in combination with Herceptin in a mouse model of breast cancer. No notable toxicities were observed *in vivo*.

Alexo licensed exclusive, worldwide rights to its SIRPA technology from Stanford.

Pons said Alexo’s SIRPA variants are next-generation candidates that have “improved pharmacological properties” compared with the compounds described in *Science*. He declined to disclose details but did say yet-to-be published data on lead compound ALX148 showed a thousandfold higher affinity than wild-type SIRPA for CD47.

ALX148 is slated to enter Phase I testing next year. The Phase I study will evaluate ALX148 for safety as a single agent in patients with advanced solid tumors and hematologic malignancies for whom no treatment options are available. Future studies will combine the candidate with approved mAbs. Specific combinations and indications have yet to be determined.

At least three clinical compounds target CD47. **Trillium Therapeutics Inc.**’s SIRPαFc (TTI-621) is a fusion protein

comprising the CD47-binding domain of SIRPA and the Fc domain of IgG in Phase I to treat relapsed or refractory hematologic malignancies, acute myelogenous leukemia (AML) and myelodysplastic syndrome (MDS).

Forty Seven Inc.'s Hu5F9-G4 and Celgene Corp.'s CC-90002 are both anti-CD47 mAbs that are in Phase I testing for solid and hematologic cancers. Forty Seven also licensed its compound from Stanford. Alexo said that its IP does not overlap with that of Forty Seven.


Pons said Alexo's approach is designed to be safer than competing programs, which he noted have demonstrated single-agent activity but come with the risk of on-target toxicity resulting from phagocytosis of healthy CD47-expressing cells.

In non-human primates treated with SIRPαFc, Trillium observed transient leukocyte and platelet depletion and a dose-limiting toxicity of anemia, according to CSO Robert Uger. He noted that anemia is not expected to occur in humans because the compound does not bind significantly to human red blood cells.

Forty Seven CMO Chris Takimoto said Hu5F9-G4 has led to "transient, predictable and manageable mild anemia" associated with the first

priming dose in clinical testing so far, and added that higher maintenance doses have not led to further anemia.

Celgene declined to comment.

Alexo closed a \$36 million series A round last year led by venBio, where Pons is a venture partner. The company plans to use the A round to obtain Phase I data for its lead compound, after which it will seek partners for combination studies. 

COMPANIES AND INSTITUTIONS MENTIONED

Alexo Therapeutics Inc., South San Francisco, Calif.

Celgene Corp. (NASDAQ:CELG), Summit, N.J.

Forty Seven Inc., Palo Alto, Calif.

Stanford University, Stanford, Calif.

Trillium Therapeutics Inc. (TSX:TR; NASDAQ:TRIL), Toronto, Ontario

REFERENCES

Weiskopf, K., et al. "Engineered SIRPα variants as immunotherapeutic adjuvants to anticancer antibodies." *Science* (2013)

BIOCENTURY INC.

NEWSROOM

pressreleases@biocentury.com

SAN CARLOS, CA

+1 650-595-5333; Fax: +1 650-595-5589

CHICAGO

+1 312-755-0798; Fax: +1 650-595-5589

WASHINGTON, DC

+1 202-462-9582; Fax: +1 202-667-2922

UNITED KINGDOM

+44 (0)1865-512184; Fax: +1 650-595-5589

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