

EMERGING COMPANY PROFILE

ADDING TO IMMUNE FUNCTION

BY EMILY CUKIER-MEISNER, SENIOR WRITER

Admune Therapeutics LLC is developing a heterodimeric complex of IL-15 to boost the immune system's response to cancer immunotherapies by increasing the number of antitumor lymphocytes overall and in the vicinity of tumors.

Tumors' responses to immunotherapy depend in part on the appropriate balance of immune cells that carry out an antitumor response vs. those that promote tolerance. President and CEO Sergio Finkielsztein said higher levels of tumor-infiltrating lymphocytes have been associated with better clinical outcomes, particularly in trials of checkpoint-targeting agents like PD-1 inhibitors.

"That is the whole hypothesis: checkpoint inhibitors and antibody-dependent cellular cytotoxicity are not going to do it on their own. You need to expand the relevant lymphocytes," he said.

Admune plans to begin a Phase I trial of hetIL-15 monotherapy to treat metastatic cancers this month and will seek multiple partners to test combinations, with anti-PD-1 and anti-PD-L1 agents "at the top of the list." The product is a complex of IL-15 with a cleaved soluble form of IL-15 receptor alpha chain (IL-15RA).

The IL-15/IL-15RA complex occurs naturally in both soluble and membrane-bound forms. It forms an activated complex by binding two additional receptor components: the IL-2 receptor beta chain (CD122; IL2RB) and gamma chain (CD132; IL2RG). Activating the receptor complex produces downstream effects that could increase tumor responses to immunotherapy, including proliferation of NK cells, CD8+ and CD4+ cells; migration of T cells to the periphery and tumors; and reduction of the proportion of Treg cells within tumors that could otherwise attenuate antitumor immune responses.

The product resulted from work conducted under a CRADA between **Marine Polymer Technologies Inc.** and NCI. Marine and NCI were studying ways of combining polymers with cytokines in oncology, which Finkielsztein said led to insights about how to stabilize IL-15. Instability had hampered the molecule's development as a therapeutic.

ADMUNE THERAPEUTICS LLC

Danvers, Mass.

Technology: Heterodimeric IL-15 complex for immunotherapy

Disease focus: Cancer

Clinical status: Preclinical

Founded: 2013 by Gessam Associates, Pilot House Associates and John Vournakis

University collaborators: [National Cancer Institute](#), Cancer Immunotherapy Network, [Sunnybrook Research Institute](#)

Corporate partners: Undisclosed

Number of employees: 10

Funds raised: Undisclosed

Investors: Gessam Associates, Pilot House Associates

CEO: Sergio Finkielsztein

Patents: 7 issued covering composition of matter, manufacturing, formulations and therapeutic applications related to heterodimeric IL-15/IL-15RA

"They discovered what was missing was a receptor — half the molecule. When they expressed both IL-15 and the receptor, the resulting molecule was incredibly stable," he said.

In 2013, NCI researchers published mouse data in *The Journal of Biological Chemistry* showing injection of the IL-15/IL-15RA complex induced proliferation of CD8+ T cell and NK cells more than IL-15 alone.

After Marine and NCI figured out a human cell line production process and subcutaneous delivery, Marine licensed the IP from NCI and spun out Admune to develop hetIL-15.

Finkielsztein said clinical experience with **Novartis AG's** Proleukin aldesleukin, a recombinant IL-2 to treat metastatic renal cell carcinoma (RCC) and melanoma, has provided proof of concept for expanding lymphocytes to attack tumors.

But IL-15 might be more active because IL-2 interacts with and expands Tregs, which dampen the immune response. IL-15 does not affect Tregs directly, but preferentially expands other lymphocytes that increase antitumor response. And animal studies suggest IL-15 may be less likely to cause capillary leak syndrome, an IL-2-related toxicity for which Proleukin has a black box warning.

“We have a history with IL-2 of expanding lymphocytes. Now we have a way to expand lymphocytes in a safe way,” said Finkielsztein.

Admune expects to focus on solid tumors so it can track infiltrating lymphocyte changes during therapy, he said.

Altor Bioscience Corp. also has an IL-15 product in the clinic for cancer. ALT-803 is an IL-15 mutant complexed to an Fc fusion protein of IL-15RA. It is in five Phase I/II trials to treat hematologic and solid tumors.

Finkielsztein said using the biological heterodimer, rather than a fusion protein, might reduce immunogenicity. However, Altor VP of R&D Peter Rhode said ALT-803 is not expected to be highly immunogenic because

it contains fewer non-host sequences and is dosed lower than commonly used therapeutic antibodies. He said the product also contains a mutation for increased agonist activity. 

COMPANIES AND INSTITUTIONS MENTIONED

Admune Therapeutics LLC, Danvers, Mass.
Altor Bioscience Corp., Miramar, Fla.
Marine Polymer Technologies Inc., Burlington, Mass.
National Cancer Institute (NCI), Bethesda, Md.
Novartis AG (NYSE:NVS; SIX:NOVN), Basel, Switzerland
U.S. Food and Drug Administration (FDA), Silver Spring, Md.

REFERENCES

Chertova, E. et al. “Characterization and favorable in vivo properties of heterodimeric soluble IL-15•IL-15Ralpha cytokine compared to IL-15 monomer.” *The Journal of Biological Chemistry* (2013)
Lou, K.-J. “Leveling cancer with IL-15.” *SciBX: Science-Business eXchange* (2014)

BIOCENTURY PUBLICATIONS, 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

All contents Copyright © 2015 BioCentury Publications, Inc. ALL RIGHTS RESERVED. All use of BioCentury and its contents by current subscribers is governed by the BioCentury User Agreement and by all others is governed by the BioCentury Terms of Use, unless a written agreement to the contrary has been executed by BioCentury Publications, Inc. No part of BioCentury or its contents may be photocopied, reproduced or retransmitted in any form without the written consent of BioCentury Publications, Inc., which may be requested from Reprints/Permissions at www.biocentury.com.

Trademarks: BioCentury®; BCIQ™; The BioCentury 100™; Because Real Intelligence is Hard to Find™; and The Clear Route to ROI™ are trademarks of BioCentury Publications, Inc.

Use of Images: Certain Images used in BioCentury Publications, Inc.'s Publications, Video Content, Websites, Services, Notices and/or Marketing Materials are licensed from Getty Images (US), Inc. Any such image of a person or object so displayed is being used for illustrative purposes only and any such person or object depicted, if any, is merely a model. For more information see “Use of Images” found under the “About Us” tab on the Homepage at www.biocentury.com.

All information provided through BioCentury Publications, Inc.'s Publications, Video and Audio Content, and Websites is gathered from sources that BioCentury believes are reliable; however, BioCentury does not guarantee the accuracy, completeness, or timeliness of such information, makes no warranties regarding such information, and is not responsible for any investment, business, tax or legal decision made or action taken in reliance upon such information.