

REPRINT FROM NOVEMBER 5, 2015

TRANSLATION IN BRIEF

UBER CAR

As researchers tinker with combinations of antibody fragments and accessory molecules to optimize chimeric antigen receptor (CAR) T cells, a study from Michel Sadelain's group at [Memorial Sloan Kettering Cancer Center](#) has shown that adding a costimulatory molecule to sit alongside the CAR produces greater potency and persistency in killing tumor cells than fusing multiple domains to create ever more complex CAR molecules. The new format could yield a third-generation product that prevents T cell exhaustion, lasts longer than earlier iterations, and has greater potential for making inroads into solid tumors.

Sadelain is director of the center for cell engineering and head of the gene transfer and gene expression laboratory at MSKCC and a scientific co-founder of [Juno Therapeutics Inc.](#) (NASDAQ:JUNO).

First-generation CAR molecules involved an extracellular domain derived from an anti-CD19 antibody and an intracellular signaling domain from CD3, and were succeeded by second-generation constructs that amplified T cell activation by adding a costimulatory domain, often derived from CD28 or [tumor necrosis factor receptor superfamily member 9 \(4-1BB; TNFRSF9; CD137\)](#).

Sadelain told BioCentury that he wanted to combine the two domains into a single therapy because the CD28 domain was more effective at boosting the initial T cell response, whereas the 4-1BB domain was more effective at prolonging T cell persistence, which compensated over time for the lower tumor-killing potency it imparted.

His team systematically tested the effect of different combinations of costimulatory signals in CAR T cells, either by adding extra costimulatory domains to create triple-fusion CARs or expressing a separate full-length costimulatory molecule alongside a second-generation CAR.

The combinations contained double fusions of an anti-CD19 extracellular domain with either a CD28 cytoplasmic domain or a 4-1BB cytoplasmic domain, or a triple fusion of all three domains. As an alternative, full-length 4-1BB or CD80 cassettes were co-expressed on T cells containing either the anti-CD19/CD28 or anti-CD19/4-1BB double-fusion CARs.

In a mouse xenograft model of CD19-positive leukemia, the optimal combination was produced by cells that co-expressed

"These CAR T cells have a potent antitumor profile, good expansion properties, good persistence properties, less exhaustion markers, and on top of that they make IFN β ."

Michel Sadelain, Memorial Sloan Kettering

the full-length 4-1BB with the anti-CD19/CD28 CAR, which produced the highest rate of tumor killing and persisted the longest of all the formats tested. In addition, that combination decreased expression of [programmed cell death 1 \(PD-1; PDCD1; CD279\)](#) and other T cell exhaustion markers compared with the other combinations.

Sadelain's team also discovered that the T cells containing the optimal combination expressed type I interferon response genes and secreted interferon β (IFN β) after attacking the tumors, which suggested the cells induced innate and adaptive responses against the tumor. Results were published in *Cancer Cell*.

Sadelain told BioCentury, "These CAR T cells have a potent antitumor profile, good expansion properties, good persistence properties, less exhaustion markers, and on top of that they make IFN β , which we think will be very useful based on the known antitumor effects of IFN β against a range of tumors, including solid tumors."

He added: "Because the cells have all these attributes, we anticipate smaller T cell doses may be effective."

Sadelain said the team has filed patents on the methods, initiated manufacturing of the cells, and plans to test the next-generation CAR T cells in the clinic in 2016. He added the team is in discussions with an undisclosed biotech to co-develop the therapy. *Zhao, Z., et al. "Structural design of engineered costimulation determines tumor rejection kinetics and persistence of CAR T cells." Cancer Cell (2015)*

— Stephen Parmley

EDITORIAL & RESEARCH

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

Editor: C. Simone Fishburn, Ph.D.

Associate Editor: Michael J. Haas

Senior Writers: Lauren Martz; Stephen Parmley, Ph.D.

Staff Writers: Selina Koch, Ph.D.; Mary Romeo;
Karen Tkach, Ph.D.; Mark Zipkin

Director of Research: Walter Yang

Copy Editor: Claire Quang

BioCentury®; Because Real Intelligence is Hard to Find™; BCIQ™; The BioCentury 100™; and The Clear Route to ROI™ are trademarks of BIOCENTURY PUBLICATIONS, INC. All contents Copyright © 2016, BIOCENTURY PUBLICATIONS, INC. ALL RIGHTS RESERVED. No part of BioCentury's Publications or Website may be copied, reproduced, retransmitted, disseminated, sold, distributed, published, broadcast, circulated, commercially exploited or used to create derivative works without the written consent of BioCentury. Information provided by BioCentury's Publications and Website is gathered from sources that BioCentury believes are reliable; however, BioCentury does not guarantee the accuracy, completeness, or timeliness of the information, nor does BioCentury make any warranties of any kind regarding the information. The contents of BioCentury's Publications and Website are not intended as investment, business, tax or legal advice, and BioCentury is not responsible for any investment, business, tax or legal opinions cited therein.

CORPORATE, SUBSCRIPTIONS & PRIVACY

BioCentury's mission is to provide value-added business information & analysis for life science companies, investors, academia and government on the strategic issues essential to the formation, development and sustainability of life science ventures.

BioCentury Publications, Inc.
BioCentury International Inc.

MAIN OFFICES

PO Box 1246
San Carlos CA 94070-1246
+1 650-595-5333; Fax: +1 650-595-5589

CORPORATE

Chairman: Karen Bernstein, Ph.D.

President & CEO: David Flores

Vice President/Commercial Operations: Thomas Carey

Vice President/Administration & CFO: Bennet Weintraub

Publisher: Eric Pierce

Executive Editor and Director, New Ventures:

Joshua L. Berlin

Senior Director/Commercial Operations:

Tim Tulloch

Senior Director/Operations: Julia Kulikova

Director/Business Intelligence: Chris Dokomajilar

Director/Multimedia Operations: Jeffrey Fitzgerald

Director/Multimedia Business Development:

Jamie Gould

Director/Digital Product Manager: Ravid Lazinsky,

Director/Marketing & Promotional Services:

Greg Monteforte

Director/Administration & Human Resources:

Susan Morgan

Production: Jenny Nichols

SUBSCRIBER SERVICES

Subscriber Services: subscribe@biocentury.com

Account Managers: Orlando Abello; Matt Krebs;
Michelle Ortega; Ron Rabinowitz

BUSINESS SERVICES

Accounting & Billing: finance@biocentury.com

Conferences: conferences@biocentury.com

Data Solutions Support:
support@biocentury.com

Privacy Policy: privacy@biocentury.com

Reprints/Permissions:

businessservices@biocentury.com

PRIVACY & ADVERTISING

In accordance with its Privacy Policy, BioCentury does NOT sell its customer information or usage data to third parties.

BioCentury does NOT sell advertising in the BioCentury, BioCentury Innovations or BioCentury Week in Review. BioCentury is pleased to acknowledge its conference partners and sponsors through unpaid promotional announcements in its publications. BioCentury MAY accept paid promotional messages from sponsors, which are displayed only on BioCentury's websites.