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JOURNAL OF
Immunotherapy

OFFICIAL JOURNAL OF INTERNATIONAL SOCIETY
FOR BIOLOGICAL THERAPY OF CANCER

VOL. 32, NO. 7, September 2009

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Journal of Immunotherapy (ISSN: #1524-9557) is published nine times a year in January, February, April, May, June, July, September, October, and November by Lippincott Williams & Wilkins, 16522 Hunters Green Parkway, Hagerstown, MD 21740-2116. Business and production offices are located at 530 Walnut Street, Philadelphia, PA 19106-3621. Periodicals postage paid at Hagerstown, MD and at additional mailing offices. Copyright © 2009 by Lippincott Williams & Wilkins.

Annual Subscription Rates: *United States* - \$600 Individual, \$1585 Institution, \$282 In-training. *Rest of World* - \$700 Individual, \$1867 Institution, \$296 In-training. Single copy rate \$206. All prices include a handling charge. Subscriptions outside of North America must add \$14 for airfreight delivery. United States residents of AL, CO, DC, FL, GA, HI, IA, ID, IN, KS, KY, LA, MD, MO, ND, NM, NV, PR, RI, SC, SD, UT, VT, WA, WV add state sales tax. The GST tax of 7% must be added to all orders shipped to Canada (Lippincott Williams & Wilkins' GST Identification #895524239, Publications Mail Agreement #616346. Subscription prices outside the United States must be prepaid. Prices subject to change without notice. Visit us online at www.lww.com.

Website: www.immunotherapy-journal.com

Postmaster: Send address changes to *Journal of Immunotherapy*, P.O. Box 1550, Hagerstown, MD 21740.

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This journal is listed in *Index Medicus*/MEDLINE Current Contents/Life Sciences Scisearch, Biomedical Database, BIOSIS, EMBASE/Excerpta Medica, Chemical Abstracts, and Current Awareness in Biological Sciences.

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Construction and Preclinical Evaluation of an Anti-CD19 Chimeric Antigen Receptor

James N. Kochenderfer,* Steven A. Feldman,* Yangbing Zhao,* Hui Xu,* Mary A. Black,*
Richard A. Morgan,* Wyndham H. Wilson,† and Steven A. Rosenberg*

Summary: T cells can be engineered to express the genes of chimeric antigen receptors (CARs) that recognize tumor-associated antigens. We constructed and compared 2 CARs that contained a single chain variable region moiety that recognized CD19. One CAR contained the signaling moiety of the 4-1BB molecule and the other did not. We selected the CAR that did not contain the 4-1BB moiety for further preclinical development. We demonstrated that gammaretroviruses encoding this receptor could transduce human T cells. Anti-CD19-CAR-transduced CD8⁺ and CD4⁺ T cells produced interferon- γ and interleukin-2 specifically in response to CD19⁺ target cells. The transduced T cells specifically killed primary chronic lymphocytic leukemia (CLL) cells. We transduced T cells from CLL patients that had been previously treated with chemotherapy. We induced these T cells to proliferate sufficiently to provide enough cells for clinical adoptive T cell transfer with a protocol consisting of an initial stimulation with an anti-CD3 monoclonal antibody (OKT3) before transduction followed by a second OKT3 stimulation 7 days after transduction. This protocol was successfully adapted for use in CLL patients with high peripheral blood leukemia cell counts by depleting CD19⁺ cells before the initial OKT3 stimulation. In preparation for a clinical trial that will enroll patients with advanced B cell malignancies, we generated a producer cell clone that produces retroviruses encoding the anti-CD19 CAR, and we produced sufficient retroviral supernatant for the proposed clinical trial under good manufacturing practice conditions.

Key Words: chimeric antigen receptor, gene therapy, CD19, T cell, gammaretrovirus, adoptive T cell therapy

(*J Immunother* 2009;32:689–702)

Approximately 22,000 people die because of B cell malignancies each year in the United States.¹ Patients with some B cell malignancies including mantle cell lymphoma and chronic lymphocytic leukemia (CLL) cannot be cured by therapies such as conventional chemotherapy and monoclonal antibodies,^{2,3} but some patients with these diseases can achieve prolonged disease-free survival after allogeneic stem cell transplantation.^{4–6} Unfortunately,

allogeneic stem cell transplantation is limited by significant transplant-related mortality and a shortage of suitable donors.^{2,6,7} In patients with B cell malignancies that relapse after allogeneic stem cell transplantation, infusion of allogeneic donor lymphocytes can induce remissions.^{8–10} The effectiveness of these lymphocyte infusions provides a rationale for attempts to develop other cellular immunotherapies for B cell malignancies.

Adoptive transfer of autologous T cells that are cultured from tumor infiltrating lymphocytes can cause regressions of advanced melanoma in humans.^{11,12} Because tumor-reactive T cells cannot be reliably cultured from most of human tumors, methods have been developed to engineer T cells to express genes encoding tumor antigen-specific T cell receptors.^{13,14} Adoptive transfer of these genetically modified T cells is a promising approach to cancer immunotherapy.¹⁵ Another approach to adoptive T cell therapy is to engineer T cells to express chimeric antigen receptors (CARs).^{16,17} CARs are made up of an antigen-recognizing receptor coupled to signaling molecules that can activate T cells expressing the CAR.^{18–20} The antigen-receptors most commonly incorporated into CARs are single chain variable region moieties (scFv) that consist of the light chain and heavy chain variable regions of a monoclonal antibody joined by a peptide linker. Murine models have shown that T cells transduced with retroviruses encoding CARs can protect mice from tumor challenges in vivo.^{21,22}

Our group has completed a phase I clinical trial in which patients with ovarian carcinoma were treated with T cells that were transduced with a CAR that was specific for the ovarian carcinoma-associated antigen α -folate receptor.²³ No objective tumor regressions were seen.²³ The CAR used in this clinical trial incorporated the Fc receptor- γ cytoplasmic signaling chain without any costimulatory molecules such as CD28 or 4-1BB. More recent work in mice has demonstrated that CARs containing the T cell receptor (TCR)- ζ cytoplasmic signaling chain had superior in vitro function and in vivo antitumor efficacy than CARs containing the Fc receptor- γ cytoplasmic signaling chain.²⁴ In addition, in vitro studies with human cells and murine in vivo studies have shown that incorporating the signaling domain of CD28 into CARs enhances function and in vivo antitumor efficacy.^{22,25–27} Signaling of the 4-1BB costimulatory molecule has been shown to enhance T cell proliferation and persistence,^{28,29} and 4-1BB signaling enhanced the function of CARs in vitro.^{30,31} Thus, significant advances in CAR design have occurred since our last clinical trial using CAR-transduced T cells.

CD19 is a promising target for antigen-specific T cell

Received for publication January 6, 2009; accepted April 21, 2009.
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†Metabolism Branch of the National Cancer Institute, National Institutes of Health, Bethesda, MD.

This work was supported by intramural funding of the Center for Cancer Research, National Cancer Institute, NIH.

Financial Disclosure: All authors have declared there are no financial conflicts of interest in regards to this work.

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