

Full Text
OVID

JOURNAL OF
Immunotherapy

OFFICIAL JOURNAL OF INTERNATIONAL SOCIETY FOR
IMMUNOLOGICAL THERAPY OF CANCER

**WEB-BASED MANUSCRIPT
SUBMISSION NOW AVAILABLE!**
See journal Web site for details.
www.immunotherapy-journal.com

IN
SITE
AVAILABLE!

THE OHIO STATE UNIVERSITY LIBRARIES
Received on: 08-25-09
L-Bio Sci/Pharm Lib.
1270J682
V. 32
NO. 7

Walters Kluwer | Lippincott
Health | Williams & Wilkins

JOURNAL OF
Immunotherapy

OFFICIAL JOURNAL OF INTERNATIONAL SOCIETY
FOR BIOLOGICAL THERAPY OF CANCER

VOL. 32, NO. 7, September 2009

EDITOR-IN-CHIEF

Steven A. Rosenberg, M.D., Ph.D.
Bethesda, Maryland

ASSOCIATE EDITORS

Michael B. Atkins, M.D.
Patrick Hwu, M.D.
Michael T. Lotze, M.D.
Francesco Marincola, M.D.
James J. Mulé, Ph.D.
Nicholas P. Restifo, M.D.

EDITORIAL COORDINATOR

Lannah Lee
Phone: 215-253-3551
Fax: 215-220-3450
Email: journalofimmunotherapy@gmail.com

INTERNATIONAL SOCIETY FOR BIOLOGICAL
THERAPY OF CANCER

Sara Withington, Executive Director
55 E. Wells Street
14th Floor
Milwaukee, WI 53202-3823
Tel: (414) 271-2456; fax: (414) 276-3349
Email: info@isbtc.org

PUBLICATION STAFF

David Myers, Publisher
Jonathan Pine, Senior Executive Editor

EDITORIAL BOARD

Michael Atkins
Richard Barth
Ernest Borden
Alfred Chang
Robert O. Dillman
Mary L. Disis
Janice P. Dutcher
Alexander Eggermont
Soldano Ferrone
Bernard A. Fox
Michael S. Gordon
Ronald B. Herberman
Peter Hersey
Yutaka Kawakami
Ulrich Keilholz
Steven K. Libutti
Albert F. LoBuglio
Kim A. Margolin
James Lee Murray
Elizabeth A. Repasky
Licia Rivoltini
Pedro Romero
Michael Salgaller
Noriyuki Sato
Carmen Scheibenbogen
Craig L. Slingluff, Jr.
Paul M. Sondel
Mario Sznol
Walter Urba
Louis Weiner
Christine A. White
Jon M. Wigginton

Volume 32

Number 7

September 2009

Journal of Immunotherapy

Contents

Basic Studies

- 677 **High-avidity Autoreactive CD4⁺ T Cells Induce Host CTL, Overcome T_{regs} and Mediate Tumor Destruction**
Andrew G. Brandmaier, Wolfgang W. Leitner, Sung P. Ha, John Sidney, Nicholas P. Restifo, and Christopher E. Touloukian
- 689 **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
- 703 **Effect of Yeast-derived β -glucan in Conjunction With Bevacizumab for the Treatment of Human Lung Adenocarcinoma in Subcutaneous and Orthotopic Xenograft Models**
Wangjian Zhong, Richard Hansen, Bing Li, Yihua Cai, Carolina Salvador, Grace D. Moore, and Jun Yan
- 713 **Inhibition of Tumor Growth by Targeted Toxins in Mice is Dramatically Improved by Saponinum Album in a Synergistic Way**
Christopher Bachran, Horst Dürkop, Mark Sutherland, Diana Bachran, Christian Müller, Alexander Weng, Matthias F. Melzig, and Hendrik Fuchs
- 726 **Genetic Modification of T Cells With IL-21 Enhances Antigen Presentation and Generation of Central Memory Tumor-specific Cytotoxic T-lymphocytes**
Anjum S. Kaka, Donald R. Shaffer, Ryan Hartmeier, Ann M. Leen, An Lu, Adham Bear, Cliona M. Rooney, and Aaron E. Foster
- 737 **Activated T-cell-mediated Immunotherapy With a Chimeric Receptor Against CD38 in B-cell Non-Hodgkin Lymphoma**
Keichiro Mihara, Kazuyoshi Yanagihara, Misato Takigahira, Chihaya Imai, Akira Kitanaka, Yoshihiro Takihara, and Akiro Kimura

(continued next page)

Lippincott
Williams & Wilkins
Wolters Kluwer
Health

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.

Contents *(continued)*

- 744 A Novel Mouse Model for Evaluation and Prediction of HLA-A2-restricted CEA Cancer Vaccine Responses**
Antonella Conforti, Daniela Peruzzi, Patrizia Giannetti, Antonella Biondo, Gennaro Ciliberto, Nicola La Monica, and Luigi Aurisicchio

Clinical Studies

- 755 HSCT Recipients Have Specific Tolerance to MSC but not to the MSC Donor**
Mikael Sundin, A. John Barrett, Olle Ringdén, Mehmet Uzunel, Helena Lönnies, Åsa-Lena Dackland, Birger Christensson, and Katarina Le Blanc
- 765 Vaccination of Renal Cell Cancer Patients With Modified Vaccinia Ankara Delivering the Tumor Antigen 5T4 (TroVax) Alone or Administered in Combination With Interferon- α (IFN- α): A Phase 2 Trial**
Robert J. Amato, William Shingler, Madusha Goonewardena, Jackie de Belin, Stuart Naylor, Jaroslaw Jac, James Willis, Somyata Saxena, Joan Hernandez-McClain, and Richard Harrop

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.

Address for non-member subscription information, orders, or change of address: Lippincott Williams & Wilkins, P.O. Box 1580, Hagerstown, MD 21741-1113; phone 800-638-3030 (outside the United States 301-223-2300); fax 301-223-2400. In Japan, contact LWW Igaku-Shoin Ltd., 3-23-14 Hongo, Bunkyo-ku, Tokyo 113-0033; phone 81-3-5689-5400; fax 81-3-5689-5402. In Bangladesh, India, Nepal, Sri Lanka, and Pakistan, contact Globe Publications Pvt. B-13 3rd Floor, A Block, Shopping Complex, Naraina Vihar, Ring Road, New Delhi, 110028; phone 91-11-579-3211; fax 91-11-579-8876.

Lippincott Williams & Wilkins cannot be held responsible for errors or for any consequences arising from the use of the information contained in this journal. The appearance of advertising in this journal does not constitute an endorsement or approval by Lippincott Williams & Wilkins for the quality or value of the product advertised or of the claims made for it by its manufacturer.

PERMISSION TO PHOTOCOPY ARTICLES: This publication is protected by copyright. Permission to photocopy must be secured in writing from Lippincott Williams & Wilkins, 351 West Camden Street, Baltimore, MD 21201, FAX: 410-528-8550; or Copyright Clearance Center (CCC), 222 Rosewood Dr., Danvers, MA 01923; FAX: 508-750-4470; or UMI, Box 49, 300 North Zeeb Road, Ann Arbor, MI 48106-1346; FAX: 313-761-1203.

Article and issue photocopies and 16-mm microfilm, 35-mm microfilm, and 105-mm microfiche are available from UMI, 300 North Zeeb Road, Ann Arbor, MI 48106-1346.

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.
From the *Surgery Branch of the National Cancer Institute; and
†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.

Reprints: James N. Kochenderfer, Surgery Branch of the National
Cancer Institute, NIH 10 Center Drive CRC Room 3-3888
Bethesda, MD 20892 (e-mail: kochendj@oncolit.nih.gov)

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.