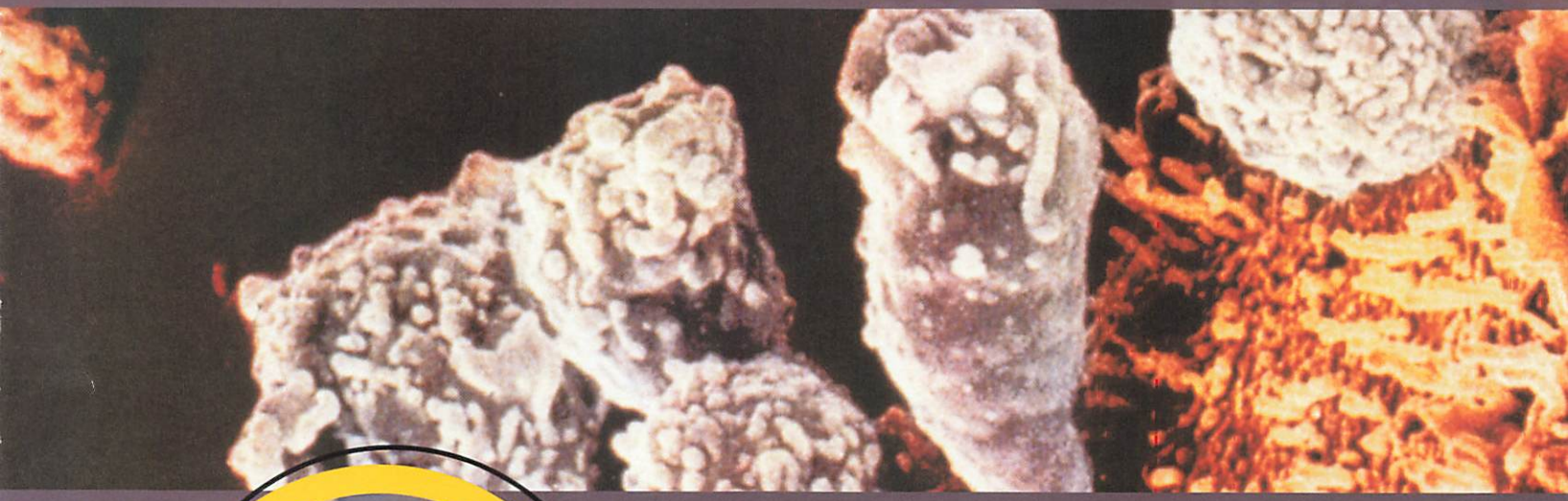
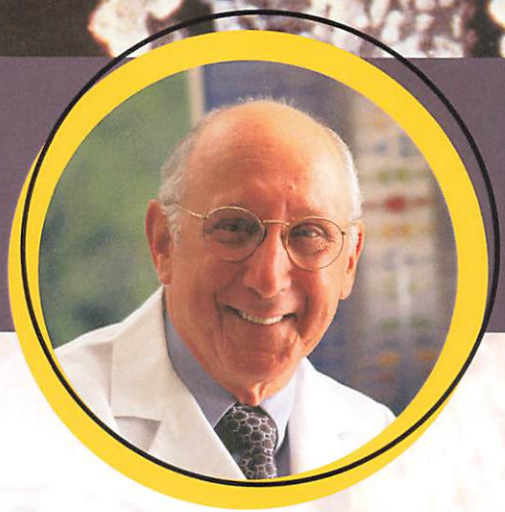
NATIONAL CANCER INSTITUTE
Center for Cancer Research

Past, Present, and Future of Cellular Immunotherapy:

Scientific Symposium Celebrating Steven A. Rosenberg's 50 years at NCI





September 26–27, 2024
Masur Auditorium, Building 10, NIH

Conference Program

Sponsored by the Center of Excellence in Immunology, Center for Cancer Research, National Cancer Institute

U.S. Department of Health & Human Services | National Institutes of Health

Agenda

Thursday, September 26

8:30 a.m.	**Welcome Remarks** James Gulley, M.D., Ph.D., Acting Co-Director, Center for Cancer Research, National Cancer Institute
SESSION I	From Cytokines to Cells for Melanoma Moderator: Nicholas Klemen, M.D., Center for Cancer Research, NCI
8:45 a.m.	**The First Effective 'Checkpoint' Therapy – Interleukin 2** Michael T. Lotze, M.D., University of Pittsburgh
9:00 a.m.	**The Early Preclinical Studies of LAK Cells, IL-2 and Other Cytokines** James Mulé, Ph.D., Moffitt Cancer Center
9:15 a.m.	**The Evolving Therapeutic Landscape of Metastatic Melanoma** Stephanie Goff, M.D., Center for Cancer Research, NCI
9:40 a.m.	**BREAK**
SESSION II	Antigen Discovery Moderator: Peter A. Prieto, M.D., Iovance Biotherapeutics, Inc.
9:55 a.m.	**Identification of Human Tumor Antigens Recognized by Tumor Infiltrating T Cells** Yutaka Kawakami, M.D., Ph.D., International University of Health and Welfare
10:10 a.m.	**Use of Personalized T Cell Antigen Screening Approaches to Develop Effective Adoptive Immunotherapies** Paul Robbins, Ph.D., Center for Cancer Research, NCI
10:35 a.m.	**Stocking the TCR Library Targeting Shared Neoantigens** James Yang, M.D., Center for Cancer Research, NCI
11:00 a.m.	**Exploring the Immunogenicity of Novel Sources or Tumor Antigens** Alena Gros, Ph.D., Vall D'Hebon Institute of Oncology
11:25 a.m.	**Targeting the Invisible: Novel T-Cell Strategies for Overcoming MHC-Loss in Tumor** Ken-Ichi Hanada, Ph.D., Center for Cancer Research, NCI
11:50 a.m.	**LUNCH & POSTER SESSION (FAES TERRACE)**
SESSION III	Bench to Bedside: TIL and T-Cell Receptor Therapy Moderator: Stephanie Goff, M.D., Center for Cancer Research, NCI
1:20 p.m.	**Introduction: Dr. Steven Rosenberg** Monica Bertagnolli, M.D., Director, National Institutes of Health
1:30 p.m.	**Neoantigen-Reactive TIL for the Treatment of Common Epithelial Cancers** Steven Rosenberg, M.D., Ph.D., Center for Cancer Research, NCI
1:55 p.m.	**Origins of TCR Gene Therapy for Cancer** Richard Morgan, Ph.D., Be Biopharma
2:10 p.m.	**Identification of Neoantigen Reactive T Cell Receptors from Tumor Infiltrating Lymphocytes** Maria Parkhurst, Ph.D., Center for Cancer Research, NCI
2:35 p.m.	**Identifying Tumor-Reactive TCRs for Therapy Based on NeoTCR Signatures** Frank Lowery, Ph.D., Center for Cancer Research, NCI
3:00 p.m.	**Enhancing TCR-based Cell Therapies with Chimeric Cytokine Receptors** Eric Tran, Ph.D., Providence Cancer Institute

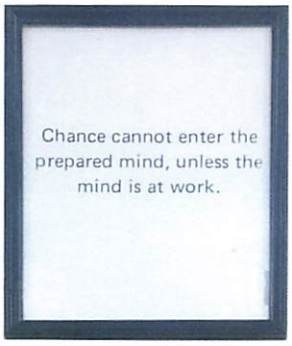
3:25 p.m.	**BREAK**
Session IV	**Bench to Bedside: Chimeric Antigen Receptor Therapy** Moderator: Rachel Beyer, Ph.D., Center for Cancer Research, NCI
3:40 p.m.	**The History of Gene Modified T-Cells: From Microinjection to CRISPR Technology** Patrick Hwu, M.D., Moffitt Cancer Center
3:55 p.m.	**Genetically Modified T-Cell Therapies for Hematologic Malignancies** James Kochenderfer, M.D., Center for Cancer Research, NCI
4:20 p.m.	**CAR T Cells for Solid Tumors: Charting a Path Forward** Crystal Mackall, M.D., Stanford University
4:45 p.m.	**ADJOURN** Surgery Branch alumni are invited to gather for a group photo and light refreshments. Location: Southwest Patio (Inclement Weather: FAES Terrace)

Friday, September 27

8:30 a.m.	**WELCOME**
SESSION V	**Advances in Checkpoint Inhibitor Blockade** Moderator: Mei Li Kwong, M.D., Center for Cancer Research, NCI
8:35 a.m.	**Origins of Checkpoint Inhibitor Therapy** James Allison, Ph.D., MD Anderson Cancer Center
9:00 a.m.	**PD-1 Pathway Blockade: State of the Art and Future Development** Suzanne Topalian, M.D., Johns Hopkins University
SESSION VI	**Optimizing Cell Phenotype for Clinical Translation** Moderator: Nikolaos Zacharakis, Ph.D., Center for Cancer Research, NCI
9:25 a.m.	**Engineering and Characterizing the Epigenetic Landscapes of T Cells with Curative Potential** Nicholas Restifo, M.D., Marble Therapeutics
9:50 a.m.	**Understanding and Leveraging Human Neoantigen-Specific T Cell Phenotypes to Improve Cellular Immunotherapy** Sri Krishna, Ph.D., Center for Cancer Research, NCI
10:15 a.m.	**Leveraging Potent T Helper Lymphocytes for Therapeutic Good Against Solid Tumors** Chrystal Paulos, Ph.D., Winship Cancer Institute at Emory University
10:40 a.m.	BREAK
SESSION VII	**Optimizing Tumor Microenvironment for Clinical Translation** Moderator: Stephanie Goff, M.D., Center for Cancer Research, NCI
10:55 a.m.	**Targeting the Microbiome to Promote Health and End Cancer** Jennifer Wargo, M.D. MD Anderson Cancer Center
11:15 a.m.	**Deep Investigations in the Tumor Microenvironment Pave the Way for New Cell Therapy Approaches** Rosandra Kaplan, M.D., Center for Cancer Research, NCI
11:30 a.m.	**Presentation of 50 Year Service Award to Steven Rosenberg, M.D., Ph.D.** Introduction by Deborah Citrin, M.D., Scientific Director for Clinical Research, Center for Cancer Research, NCI Award presented by Kimryn Rathmell, M.D., Ph.D., Director, National Cancer Institute
11:40 a.m.	**Closing Remarks** Steven Rosenberg, M.D., Ph.D., Center for Cancer Research, NCI

Timeline* (1974–present)

Pre-1974



Over the years, this sign has hung above the door of every Rosenberg lab.

Members of the Surgery Branch staff outside Building 10 South (1975).

During his surgical training at the Peter Bent Brigham Hospital, Dr. Rosenberg encountered patients that formed the beginning of his journey in harnessing the immune system for the treatment of cancer. One was a man with spontaneous regression of metastatic gastric cancer.

SPONTANEOUS REGRESSION OF HEPATIC METASTASES FROM GASTRIC CARCINOMA

Steven A. Rosenberg, Md, Phd,* Edward Fox, Md, And Winthrop H. Churchill, Md

(*Cancer* 1972)

To deepen his scientific background, he left residency to successfully pursue a PhD in Biophysics at Harvard, studying the protein structure of human cell membranes.

Eager to search for cancer antigens on the membranes of cancer cells, Dr. Rosenberg joined the Public Health Service and became an Immunology Fellow in the Immunology Branch of the NCI.

SIALIC ACIDS ON THE PLASMA MEMBRANE OF CULTURED HUMAN LYMPHOID CELLS

Chemical Aspects and Biosynthesis

Steven A. Rosenberg And Albert B. Einstein, Jr.

From the Immunology Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20014

(*J Cell Biol*)

1974

Named Chief of the Surgery Branch, a position he has held continuously since July 1, 1974.

The Rosenberg Lab's initial studies attempted (unsuccessfully) to measure antibody responses to cancer. The limited survival of T cells *ex vivo* made in-depth study challenging.

IN VITRO GROWTH OF MURINE T CELLS

I. Production of Factors Necessary for T Cell Growth

II. Growth of in Vitro Sensitized Cells Cytotoxic for Alloantigens

Steven A. Rosenberg, Paul J. Spiess, And Susan Schwarz

From the Surgery Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20014

(*J Immunol*)

IN VITRO GROWTH OF CYTOTOXIC HUMAN LYMPHOCYTES

I. Growth of Cells Sensitized in Vitro to Alloantigens

John L. Strausser' And Steven A. Rosenberg

From the Surgery Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20014

(*J Immunol*)

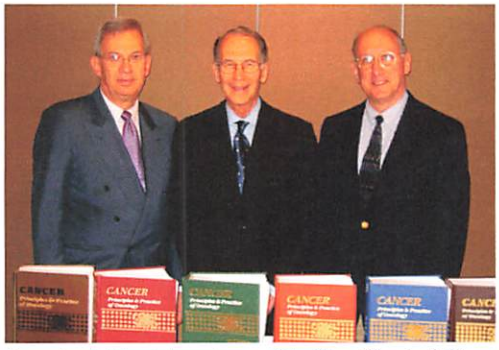
1976

Morgan, Ruscetti, and Gallo describe T cell growth factor (now known as interleukin-2) making longer-term laboratory study of human T cells possible

The focus of the Rosenberg lab shifted to the production and study of IL-2

*Timeline curated by S. Goff, M. Gaye and others, with material from NIH, NCI, and personal collections.

Nurses, technicians and scientists responsible for making and administering LAK in the Warren G. Magnusson Clinical Center and Ambulatory Care Research Facility.



The editorial trio at the release of the 6th edition in 2002.

"Perhaps we are at the end of the beginning of the search for successful immunotherapy for cancer."

John Durant,
President, Fox Chase Cancer Center
(*New Engl J Med*)

1980's

Pre-clinical work in the lab by Mike Lotze, Jim Mulé, and others led to study of lymphokine activated killers (LAK) in first-in-human trials.

1982

With Vincent DeVita and Samuel Hellman, published the first edition of Cancer: Principles and Practices of Oncology, setting a standard for oncology texts. The 12th edition was published in 2023.

1985

After dozens of attempts, a young woman with metastatic melanoma became the first patient to respond to immunotherapy. She remains disease free to this day.

1985

2014

Special Report

OBSERVATIONS ON THE SYSTEMIC ADMINISTRATION OF AUTOLOGOUS LYMPHOKINE-ACTIVATED KILLER CELLS AND RECOMBINANT INTERLEUKIN-2 TO PATIENTS WITH METASTATIC CANCER

(*New Engl J Med*)

"Thank you for allowing me the honor to play a small role in your extraordinary journey!"

—Linda T.

1986

A New Approach to the Adoptive Immunotherapy of Cancer with Tumor-Infiltrating Lymphocytes

Steven A. Rosenberg, Paul Spiess, Rene Lafreniere

(*Science*)

Tumor infiltrating lymphocytes (TIL) are more effective than LAK in mouse models of cancer (Science).

Tumor Infiltrating Lymphocytes (TIL) could eliminate liver and lung (not shown) metastases in mice.

1987

Suzanne Topalian and others described large scale expansion of human TIL, facilitating clinical experimental protocols.

Seen here during fellowship, Suzanne Topalian remained in the Branch as Senior Staff until 2006.

1988

First successful use of TIL in humans published in the New England Journal of Medicine.

1989

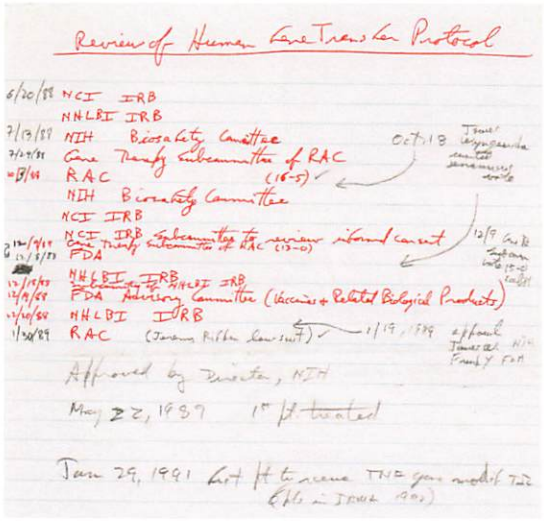
Special Report

USE OF TUMOR-INFILTRATING LYMPHOCYTES AND INTERLEUKIN-2 IN THE IMMUNOTHERAPY OF PATIENTS WITH METASTATIC MELANOMA

A Preliminary Report

Steven A. Rosenberg, M.D., P.D., Beverly S. Packard, Ph.D., Paul M. Aebersold, Ph.D., Diane Solomon, M.D., Suzanne L. Topalian, M.D., Stephen T. Toy, Ph.D., Paul Simon, Ph.D., Michael T. Lotze, M.D., James C. Yang, M.D., Claudia A. Seipp, R.N., Colleen Simpson, R.N., Charles Carter, Steven Bock, M.D., Douglas Schwartzentruber, M.D., John P. Wei, M.D., And Donald E. White, M.S.

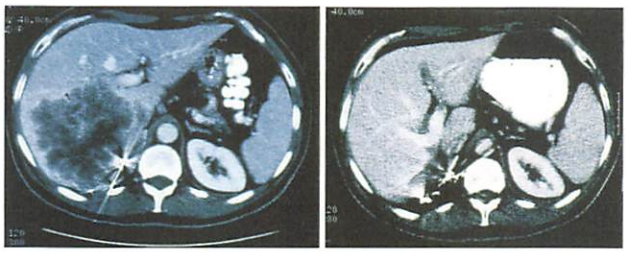
First administration of gene-modified cells, after a long, multi-layered review process and national conversation on the implications. TIL retrovirally transduced with neomycin phosphotransferase allowed tracking of transferred cells. Two years later, the team would attempt a functional modification of TIL by inserting a gene encoding tumor necrosis factor.



Weizmann Institute first describes immunoglobulin-T-cell receptor molecules, now known as chimeric-antigen receptors (CAR). In 1990, Dr. Zelig Eshhar joins the Rosenberg Lab on sabbatical.

1992

FDA approves IL-2 for metastatic renal cell carcinoma. Jim Yang and others performed a randomized trial to evaluate different doses in the Surgery Branch to explore the potential to reduce toxicity.



Resolution of a large hepatic metastasis after IL-2 therapy as seen by CT scan of a patient with kidney cancer.

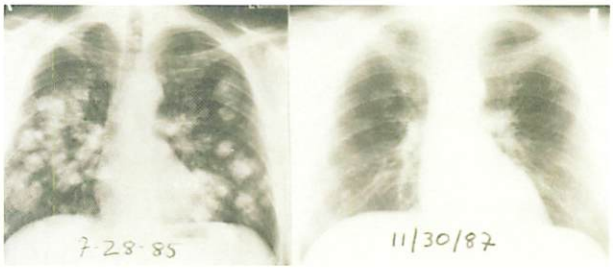
Jim Yang (bottom right) continues to spearhead the Branch's work in kidney cancer. Senior staff 2001.

1994

Yutaka Kawakami and others isolate a gene encoding a shared melanoma antigen recognized by T-cells (MART-1). Later T-cell receptors recognizing MART-1 would be isolated from a patient's TIL and utilized in trials of adoptive cell transfer with gene-modified peripheral blood.

1998

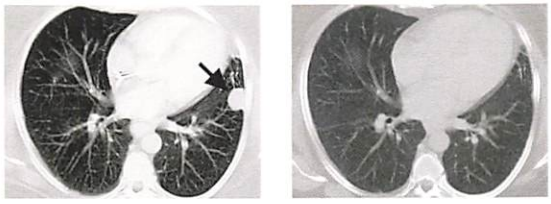
Success in early studies prompted large multi-institutional studies of high-dose IL-2 and FDA approves IL-2 for metastatic melanoma.



Resolution of multiple pulmonary nodules as seen on sequential chest X-ray of a patient with metastatic melanoma.

2001

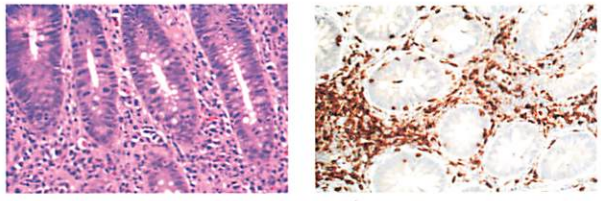
In collaboration with Jim Allison, began the first clinical trial utilizing anti-CTLA-4 monoclonal antibody. (Reported in 2003). Later observations by the Branch and others would identify a relationship between immune related adverse events and response.



Resolution of a pleural-based lung nodule after anti-CTLA therapy as seen by CT scan of a patient with metastatic melanoma.

2003

Mark Dudley and others report the addition of lymphodepletion prior to TIL transfer demonstrated an improvement in tumor response. Later studies would demonstrate that deeper lymphodepletion with the addition of total body irradiation did not further improve clinical response rates.



Immune/T-cell infiltrates in a patient with colitis after anti-CTLA4 therapy.

Michel Sadelain's laboratory reported successful use of CD19 CAR targeting of CD19+ leukemia cells *in vitro* and in murine studies. In 2007, James Kochenderfer joined the Rosenberg Lab to develop CD19 CAR for clinical use.

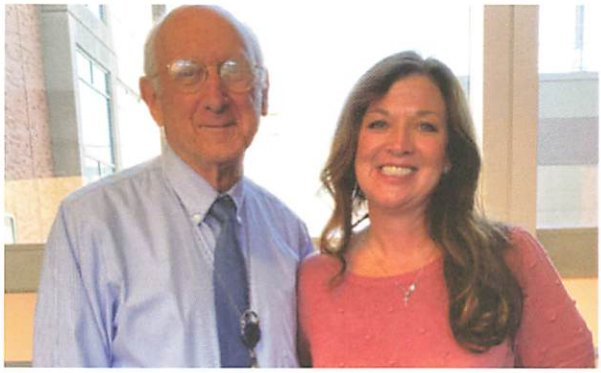
2004

Surgery Branch moves to new lab facilities in the Mark O. Hatfield Clinical Research Center.

As a Surgery Branch fellow, Marybeth Hughes isolated the MART F4 TCR. Seen here as a member of Senior Staff with Rick Morgan.

"It is with joy and gratitude that I add my name to the many patients to whom he has given a second life."

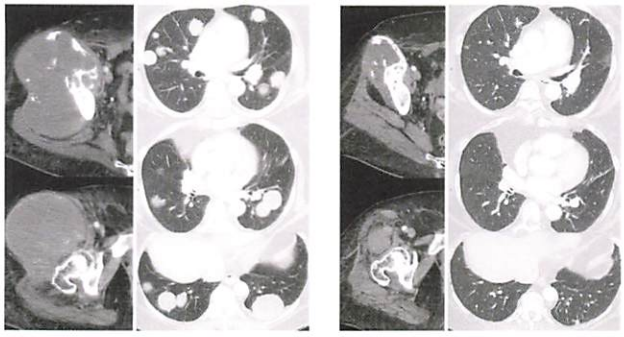
—Linda W.



"I have become a patient advocate because I wanted to find a way to pay it forward after having such a great response with TIL, and I owe that all to him!"

– Melinda B.

Pre-cells **+54 mo**



2006

Rick Morgan and others report the first demonstration of tumor regression with gene-engineered TCR (targeting MART-1).

2009

First patient with lymphoma successfully treated with CD19 CAR. (Reported in 2010)

2012

Cooperative Research and Development Agreement to transfer and develop CD19 CAR technology with Kite Pharma. This cell therapy would become axicabtagene ciloleucel.

2013

Paul Robbins and others develop a high throughput method to identify the potential immunogenicity of the products of cancer mutations. Later studies by Maria Parkhurst, Nikos Zacharakis, Drew Deniger, and others would highlight that the majority of common epithelial malignancies harbor immunogenic mutations, and with rare exceptions, are unique to each patient.

2014

Eric Tran and others report the first patient treated with TIL selected for neoantigen reactivity.

2015

TCR-transduced lymphocytes targeting a cancer germline antigen, NY-ESO-1, mediated durable clinical regressions in patients with metastatic melanoma or sarcoma.

2015

Awarded the American Cancer Society Medal of Honor.

With his wife, Alice, members of Senior Staff (Rick Sherry, Jim Yang, Nick Restifo, Stephanie Goff, Steve Feldman, and Paul Robbins) and their partners at the Medal of Honor Gala.

2016

Brief Report

T-CELL TRANSFER THERAPY TARGETING MUTANT KRAS IN CANCER

Eric Tran, Ph.D., Paul F. Robbins, Ph.D., Yong-Chen Lu, Ph.D., Todd D. Prickett, Ph.D., Jared J. Gartner, M.Sc., Li Jia, M.Sc., Anna Pasetto, Ph.D., Zhili Zheng, Ph.D., Satyajit Ray, Ph.D., Eric M. Groh, M.D., Isaac R. Kriley, M.D., and Steven A. Rosenberg, M.D., Ph.D.

(*New Engl J Med*)

A case report in the New England Journal of Medicine details partial tumor regression using autologous TIL recognizing mutated KRAS. Combined with resection of a progressing tumor, the patient described remains alive without disease to this day.

2017

FDA approved CD19 CAR products from both Kite Pharma and Novartis (working with the University of Pennsylvania) for patients with diffuse large B cell lymphoma or acute lymphocytic leukemia.

A Class II-restricted TCR inserted into CD4+ lymphocytes mediated tumor regression in patients with a variety of epithelial cancers.

"You've done what others thought impossible, and I am forever grateful."

—Celine R.

"I hope my experience has helped further the research and treatments that will give people their lives back. It's been exciting to track the research as immunotherapy becomes more common."

—Hannah L.

"...allowed me to see the birth of my six grandchildren."

—Doug A.

2018

Nikos Zacharakis and others report a complete response to neoantigen selected TIL + pembrolizumab in a patient with metastatic breast cancer.

Global online and print coverage of the Branch's Nature Medicine report.

Began studies utilizing personalized TCR targeting cancer mutations. The Branch's Vector Production Facility, founded by Steve Feldman in 2008, transitioned to support small scale, individualized transient TCR production, under the direction of Rachel Beyer.

"The team that Dr. Rosenberg has assembled is amazing."

– Judy P.

Initial TIL space, Warren G. Magnuson Clinical Research Center.

The research manufacturing space on 3W in the Hatfield Clinical Center created over 1000 cell products for Surgery Branch protocols over 16 years of operation.

"Your steadfast direction saved not only my life but gave my children the opportunity to have their dad with them through their teen years."

– Bill H.

2019

Parisa Malekzadeh, Peter Kim, Drew Deniger and others demonstrated broad immunogenicity of mutated TP53.

2020

Sri Krishna, Frank Lowery and others demonstrated a correlation of clinical response and stem-like CD8+ cells in patients with melanoma treated with TIL.

2021

Noam Levin and others identified human TCRs targeting RAS mutations.

2021

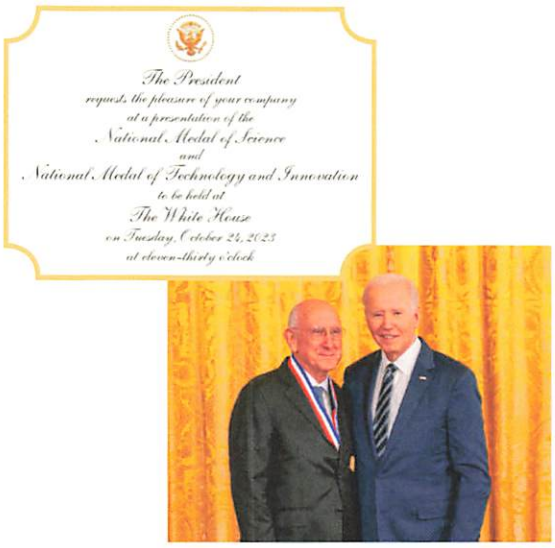
Stephanie Goff and others reported the Surgery Branch's single institution experience with TIL for patients with melanoma. Dr. Rosenberg's long relationship with Iovance helped guide the development of lifileucel, which would be approved in 2024.

2022

For the first time, the Surgery Branch began manufacturing clinical cell products outside the laboratory spaces of Building 10 in a new modular facility designated T30. The TIL lab has been a critical part of the bench-to-bedside cycle of the Branch's ambitious translational program since the beginning, making rapid advances in the modern era under Mark Dudley, John Wunderlich, Rob Somerville, and Hyunmi Halas.

Modular manufacturing facility (T30) for Surgery Branch investigational cell products.

2023



Awarded the National Medal of Technology and Innovation by President Biden "for transforming the way we treat cancer and advancing our progress toward ending cancer as we know it."

2024

Article

ADOPTIVE TRANSFER OF PERSONALIZED NEOANTIGEN-REACTIVE TCR-TRANSDUCED T CELLS IN METASTATIC COLORECTAL CANCER: PHASE 2 TRIAL INTERIM RESULTS

Maria Parkhurst, Stephanie L. Goff, Frank J. Lowery, Rachel K. Beyer, Hyunmi Halas, Paul F. Robbins, Todd D. Prickett, Jared J. Gartner, Sivasish Sindiri, Sri Krishna, Nikolaos Zacharakis, Lien Ngo, Satyajit Ray, Alakesh Bera, Ryan Shepherd, Noam Levin, Sanghyun P. Kim, Amy Copeland, Shirley Nah, Shoshana Levi, Neilesh Parikh, Mei Li M. Kwong, Nicholas D. Klemen, James C. Yang & Steven A. Rosenberg

(*nature medicine*)

Proof of concept of objective response using personalized gene-engineered TCR, a Branch-wide effort relying on clinical, laboratory, and manufacturing expertise.

Looking ahead

Surgery Branch and the Rosenberg Lab will move to the new Surgery, Radiology, and Laboratory Medicine (SRLM) wing of the NIH Clinical Center.

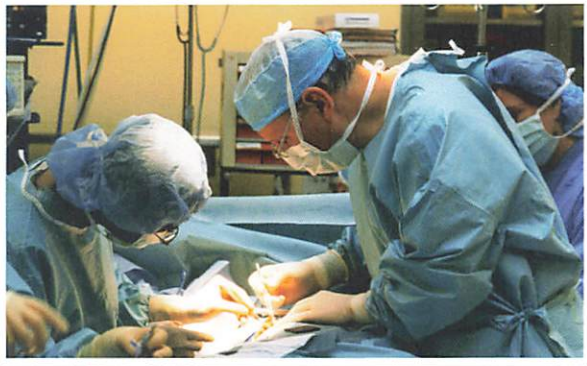
Mentorship

Since arriving in 1974, Dr. Rosenberg has mentored a steady stream of clinical and laboratory fellows in the Surgery Branch and in the Rosenberg lab.

Former fellows are now scattered from coast to coast and across the globe running academic labs, in private industry, and clinical leadership positions

"The world is, and will always be, a better place because of the compassion and curiosity for progress that your work has instilled in the world."

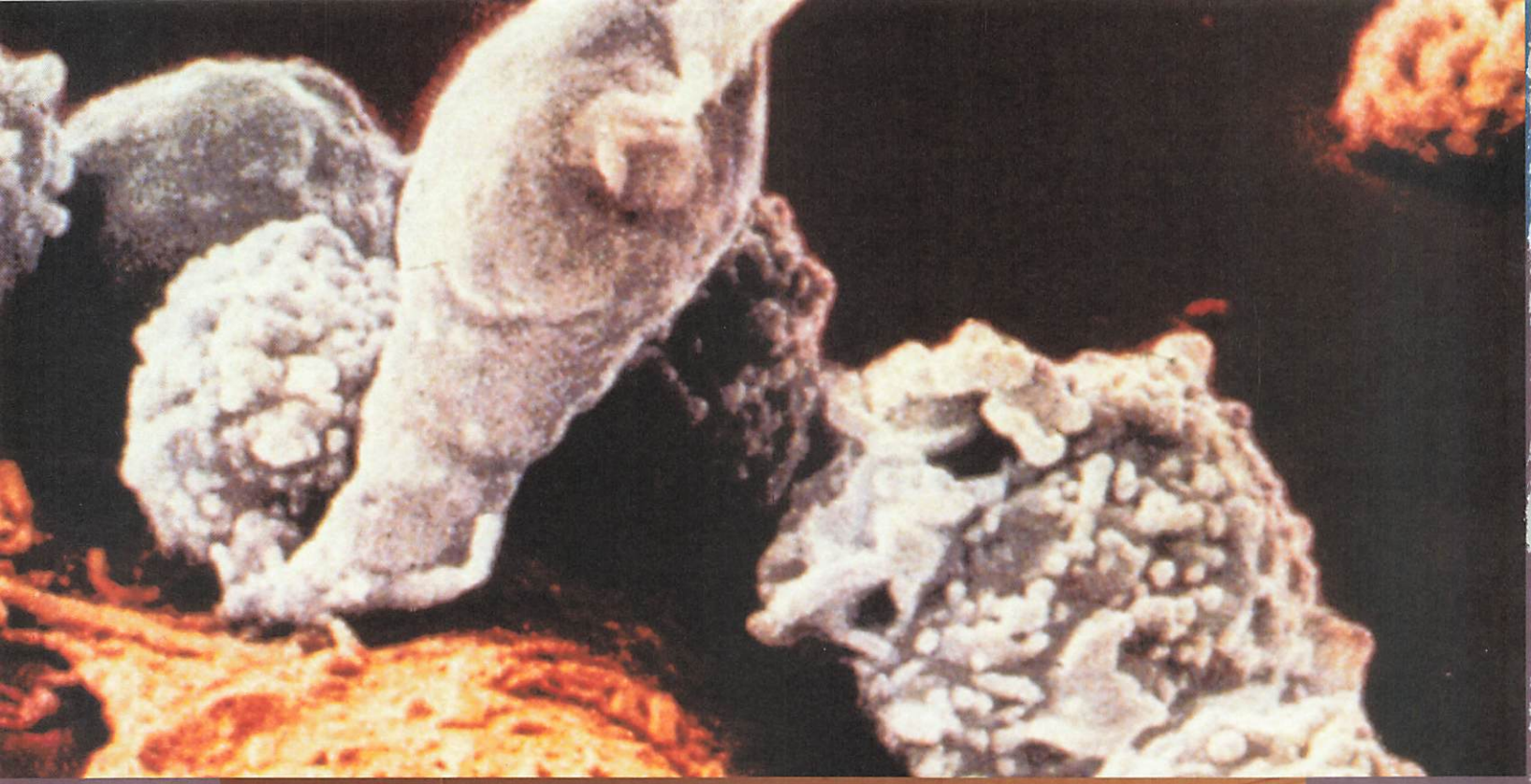
—Michael C.

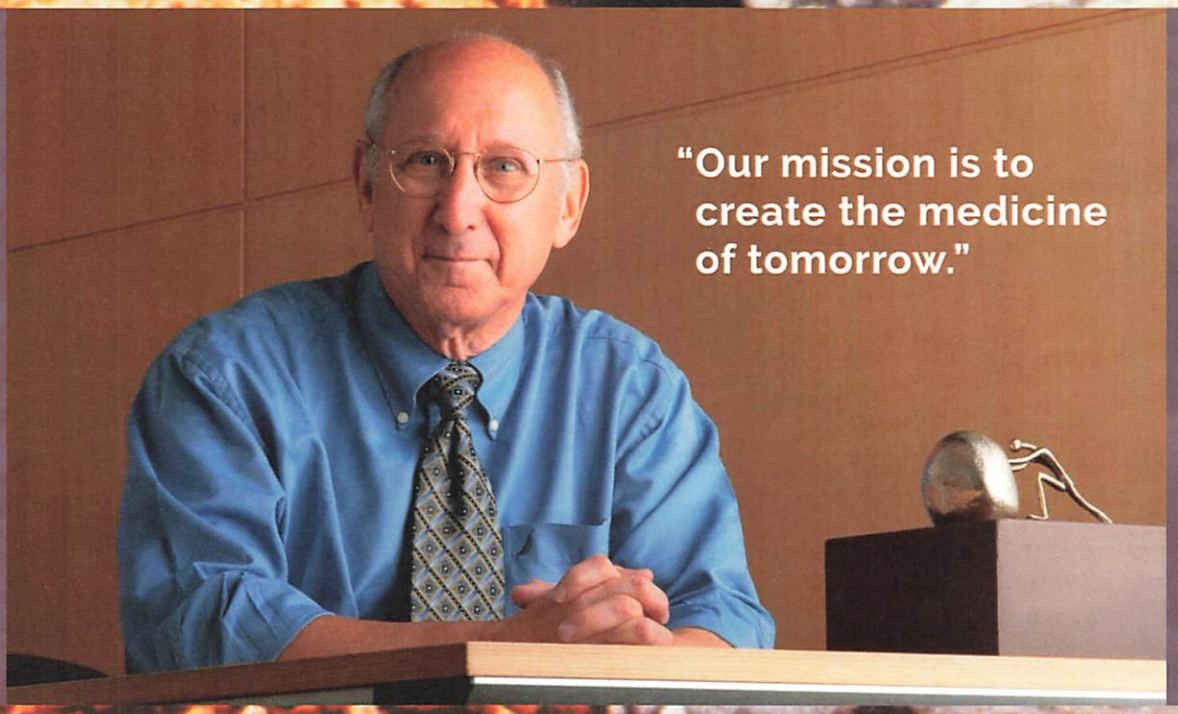


"There were probably, and I am not exaggerating, 40 days in the first 40 years of my work here that I was in town not traveling, that I was not in this hospital... I would come in Saturdays, Sundays to go over research with some of the fellows... or see patients, and that kind of life requires support. There are not a lot of wives who I think would handle that kind of commitment outside the home, but Alice did. She has been a vital part of all I have done.

She really takes care of so much that enabled me to work at that level. But it was a family thing, I have three daughters [Beth, Rachel, and Naomi] who were growing up as all of this was happening... it takes a family, and I doubt I could have done it without their support."

Edited excerpt from an interview by former fellow, Peter Attia




"Our mission is to
create the medicine
of tomorrow."