National Cancer Institute

Center for Cancer Research

Immunology

Making a Difference through Basic Discovery, Translation, and Clinical Care

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Fighting Cancer: From Prevention to Treatment

In 2003, the National Cancer Institute (NCI) announced a Challenge Goal: To eliminate the suffering and death due to cancer by 2015.

Key to this effort are strong programs in basic, translational, and clinical research to facilitate:

- *Basic discovery and new technologies*
- *Prevention and prediction of disease onset*
- *Early detection*
- *Development and use of treatments*

Robert Wiltrout, Director
Center for Cancer Research

The Center for Cancer Research and the NCI Intramural Research Program

The NCI Intramural Research Program (IRP) provides a unique environment to merge basic, translational, and clinical cancer research. The Center for Cancer Research (CCR) is the largest component of the NCI IRP, with a faculty of approximately 300 principal investigators (PIs). The mission of the CCR is to reduce the burden of cancer through exploration, scientific discovery, and the translation of research discoveries into successful treatments.

A combination of unique qualities defines the CCR, including:

- A critical mass of basic, translational, and clinical researchers creating a collaborative, interdisciplinary community
- A funding mechanism that supports high-risk research
- The capacity and mandate to study rare diseases and cancers of increasing incidence
- An infrastructure rapidly responsive to urgent public health needs
- Free medical care and travel expenses for patients
- An emphasis on training the scientists of the future
- A commitment to develop and distribute novel reagents and technology to the scientific community

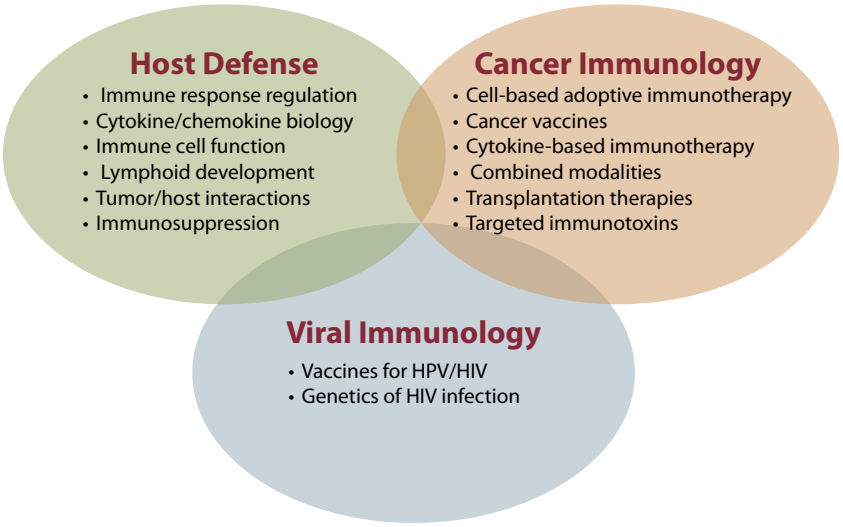
Researchers and clinicians in the CCR serve the scientific community and cancer patients through conduct of high-risk, distinctive research; generation and distribution of unique reagents and technology; training future scientists; and developing partnerships with investigators in academia and the biotechnology industry.

Immunology Research at the CCR: The Center of Excellence in Immunology

The Center of Excellence in Immunology (CEI) is one of four Centers of Excellence in the NCI IRP. The objective of these Centers is to create multidisciplinary venues that generate connections among diverse intellectual, financial, and physical resources to facilitate development of new initiatives, projects, and collaborations that reduce the burden of cancer.

The mission of the CEI is to foster discovery, development, and delivery of novel immunologic approaches for the prevention and treatment of cancer and cancer-associated viral diseases. Research interests of CEI faculty can be grouped into three broad and intersecting categories: ***host defense***, ***cancer immunology,*** and ***viral immunology***. These are described in the figure below. Some senior members of the CEI are listed in the accompanying table.

Research Interests within the CEI



CEI Senior Leadership

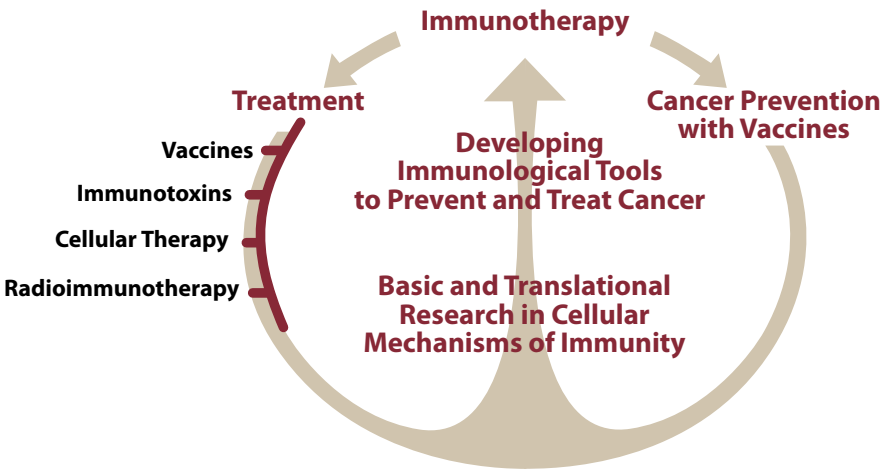
Jonathan Ashwell, M.D.
Jay Berzofsky, M.D., Ph.D.
Ronald E. Gress, M.D.
Allan Hildesheim, Ph.D.
Jeff Lifson, M.D.
Douglas R. Lowy, M.D.
Crystal Mackall, M.D.
Joost Oppenheim, M.D.
John R. Ortaldo, Ph.D.
Ira Pastan, M.D.
Marjorie Robert-Guroff, Ph.D.
Steven A. Rosenberg, M.D., Ph.D.
Lawrence Samelson, M.D.
Jeffrey Schlom, Ph.D.
Alfred Singer, M.D.
Mark Udey, M.D., Ph.D.
Thomas A. Waldmann, M.D.
Allan Weissman, M.D.
Jon Wigginton, M.D.
Robert Wiltrout, Ph.D.
Robert Yarchoan, M.D.

CEI scientists have made many contributions toward immunological approaches to prevent, treat, and cure cancer. This work spans the continuum from basic science discoveries to clinical research applications, illustrating high-impact contributions that have:

- Challenged or redefined existing paradigms
- Developed or employed novel concepts, approaches, methodologies, tools, and technologies
- Translated successfully into clinical practice

The CEI is built on a foundation of basic research that informs translational studies that are ultimately brought to the clinic. This has led to the development of several types of immunotherapies, including vaccines, radiotherapies, cellular therapy, and immunotoxins.

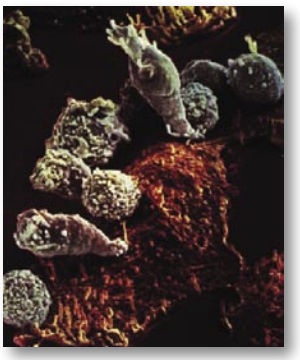
Program Overview



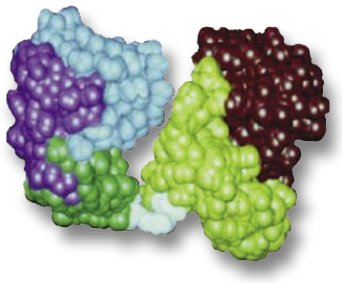
Advances in the Immunotherapy of Cancer

CEI investigators are performing exciting translational projects directed at the immunoprevention and immunotherapy of cancer. This work illustrates how long-term support of high-risk research can have tremendous impact in the development of novel treatments for cancer.

Cellular Therapy. Work from the Laboratory of Dr. Steven Rosenberg has been at the forefront of cell-mediated immunotherapy of cancer for two decades. His group pioneered the first successful immunotherapy of cancer, the use of interleukin-2 (IL-2) in the treatment of metastatic melanoma and kidney cancers. He has recently developed a cell-based therapy that resulted in improvement in 51 percent of patients with refractory metastatic melanoma. Given the poor prognosis for those with late-stage melanoma, these are remarkable and promising results.



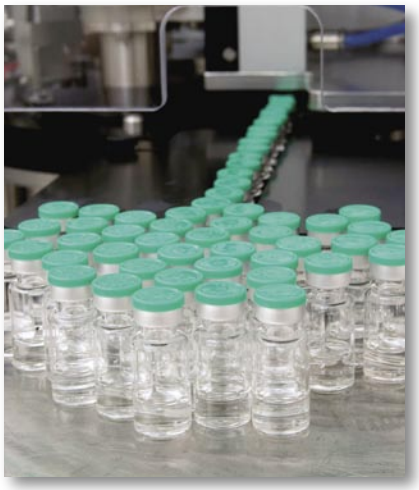
Immunotoxins. Over the past 15 years, Dr. Ira Pastan, a member of the National Academy of Sciences, has created a multidisciplinary program to create novel molecules, termed recombinant immunotoxins (RITs), that target specific antigens on cancer cells. These proteins consist of the Fab region of an antibody fused to the lethal portion of the bacterial toxin, *Pseudomonas exotoxin A*. Treatment with the RIT BL22 has resulted in complete remissions in a high percentage of patients with refractory hairy-cell leukemia.



Radioimmunotherapy. Using monoclonal antibodies to the IL-2 receptor, Dr. Thomas Waldmann, also a National Academy of Sciences member, has pioneered treatments for cancer and other immunological diseases. Waldmann and colleagues cloned the alpha chain of the IL-2 receptor (IL-2R) and generated antibodies to it. These antibodies, when conjugated with radioisotopes, are effective tools for treatment of T-cell leukemia and, in their unmodified form, T cell–mediated autoimmune disorders, including multiple sclerosis and noninfectious uveitis. This work has propelled interest in using monoclonal antibodies for immunotherapy, with hundreds of antibodies now in clinical trials.

Another important advance in the radioimmunotherapy of cancer was the development of tiuxetan by investigators in the Radiation Oncology Branch of the CCR. This bifunctional chelating agent has been used to facilitate radiolabeling of monoclonal antibodies specific for antigens on cancer cells. This advance resulted in the development of Zevalin, the first radiolabeled antibody that the FDA approved for use in humans. In the past five years, Zevalin has become an invaluable addition to treatment options for recurrent and refractory non-Hodgkin's lymphoma (NHL).

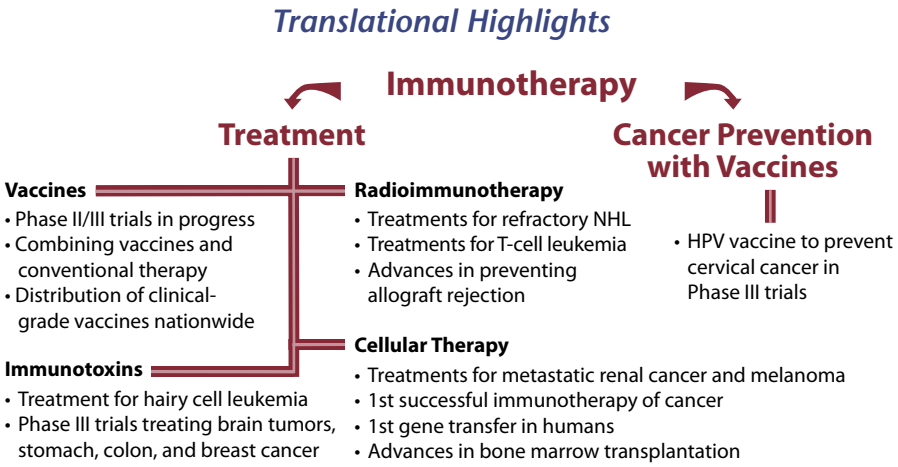
Developing Therapeutic Vaccines for Cancer. The development of therapeutic cancer vaccines represents an investment by the CCR in the future of cancer treatment. CEI researchers, including Drs. Jeffrey Schlom, Jay Berzofsky, Crystal Mackall, Steven Rosenberg, and Thomas Waldmann, have collectively published more than 1,000 peer-reviewed articles in this field in the past decade. Vaccines designed and developed at the CCR are currently being tested in Phase II and III clinical trials at more than 60 cancer centers throughout the U.S.



Prophylactic Vaccines for HPV-Associated Cancers. Cervical cancer is the third most common cancer among women worldwide, and is caused by infection with a subset of human papillomaviruses (HPVs). Researchers at the CCR discovered that the major papillomavirus structural protein can self-assemble into virus-like particles (VLPs) that are highly immunogenic. Based on these findings, CCR investigators Drs. Douglas Lowy and John Schiller, in collaboration with researchers from the Division of Cancer Epidemiology and Genetics from the NCI IRP, designed a vaccine to prevent infection with HPV. Results of Phase II trials demonstrated a high level of protection against HPV infection, and Phase III trials are currently underway.

This vaccine has the potential to eliminate up to 150,000 deaths annually from cervical cancer, as well as an additional 75,000 deaths if the vaccine also prevents other cancers attributable to HPV.

A summary of immunotherapy treatments originating in the CCR is illustrated in the figure below:



Advances in Cytokine Research

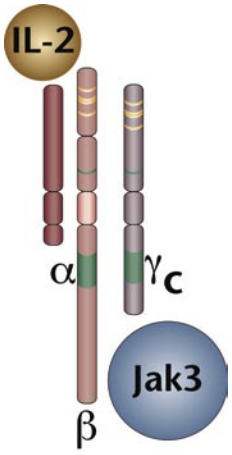
Cytokines are critical to the development and function of the immune system and integral to tumor biology. CEI investigators have contributed groundbreaking work in the discovery, characterization, and immunotherapeutic potential of these important mediators of immunity. This includes discovery/co-discovery of numerous cytokines and chemokines (e.g., IL-1, IL-2, IL-3, IL-6, IL-8, IL-15, TGF-β, and MCP-1), as well as important advances in understanding cytokine signaling and biology. This work, summarized in the table below, has fueled several treatments for some cancers and has potential for the treatment of others.

Applications and Potential Uses of CCR Cytokine Discoveries

Cytokine	Potential Treatment Application
IL-2	Metastatic renal cancer* Metastatic melanoma* Leukemia†
IL-2 Receptor Blockade	Autoimmune disease† GVHD*
IL-7	Modulation of immune reconstitution following cytotoxic therapy Lymphocyte restoration
IL-12	Adult and pediatric cancers
IL-15	Cancer and HIV/AIDS
IL-15 Receptor Blockade	Autoimmune disease Cancer immunotherapy
TGF-β Receptor Blockade	Leukemia

*FDA-approved treatments; †Used in the Clinic.

There are several cytokines that are distinct areas of emphasis by CEI faculty. These include IL-2, IL-7, IL-15, TGF-β, and several chemokines. This work has facilitated some notable bench-to-bedside advances. For example, the figure below illustrates contributions of CEI faculty in the continuum of basic, translational, and clinical research on IL-2.



Basic Research in Immunology Supporting Prevention and Treatment of Cancer: Interleukin 2, Bench-to-Bedside

- Discovered IL-2
- Identified and cloned alpha chain of IL-2 receptor
- Cloned JAK3, kinase critical for IL-2 responses
- Discovered use of IL-2 to treat metastatic renal cancer and melanoma
- Combined IL-2 with adoptive immunotherapy to treat renal cancer and melanoma
- Developed humanized antibodies to alpha chain of IL-2R to treat some leukemias, autoimmune diseases, and GVHD

Advances in Cell-mediated Immunity

Clinical and translational efforts in the CEI toward immune-based treatments for cancer are supported by outstanding basic research programs in lymphocyte biology. Within the CEI are several internationally renowned laboratories dedicated to understanding development and regulation of the cellular components of immunity, as well as events underlying immune cell transformation. These accomplishments are summarized below.

Novel Insights into Cellular Immunity

Progenitor Cell

Development:

- The importance of Evi9 in normal lymphoid development
- Key role of cKrox in thymocyte differentiation into the CD4 lineage

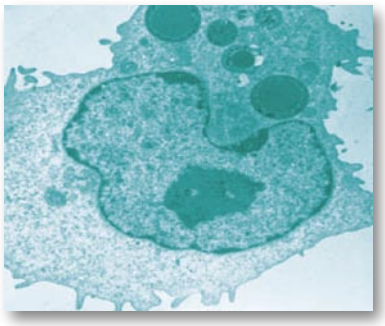
Functional T Cell → **Survival:**

- Discovery of activation-induced T-cell apoptosis
- The role of DNA damage in lymphocyte survival and transformation
- TCR ubiquitylation and events critical for TCR trafficking
- Enzymes key to protein ubiquitylation and degradation

Effector Activity:

- Mechanisms mediating costimulatory signals between the TCR and CD28
- Discovery and characterization of a novel class of adaptor proteins important in signaling through immunoreceptors
- Development of means to visualize real-time signaling through the TCR in single, living cells

The CEI also has a strong program directed toward the study of key innate immune constituents such as natural killer (NK) and NK T- cells, with an emphasis of on the role of these cells in the development of cancer. Contributions to this field by CEI faculty include:



- Co-discovery and characterization of NK cells
- Characterization of a novel Ly49 NK receptor family
- Demonstration that NK cells do not rearrange their T-cell receptor genes
- Discovery that tissue-associated NK cells can mediate anti-metastatic activity in the liver and lungs
- Development of a novel model for regulation of NK receptor expression
- Demonstration that NKT cells can mediate immunosuppression

Training Tomorrow's Scientists and Clinicians

Members of the CEI have demonstrated a strong commitment to training the next generation of scientific leaders. Many leading researchers and clinicians trained with scientists in the CEI. These "alumni" include a Surgeon General, 2 Nobel laureates, 7 members of the National Academy of Sciences, 3 NIH Institute Directors, an NIH Director, an NIH Deputy Director, 13 NIH Lab/Branch Chiefs, 16 directors in biotechnology companies, and 124 department chairs/chiefs in academic institutions across the United States. Worldwide, CEI trainees head a total of 158 departments in academia and industry.

Future Directions

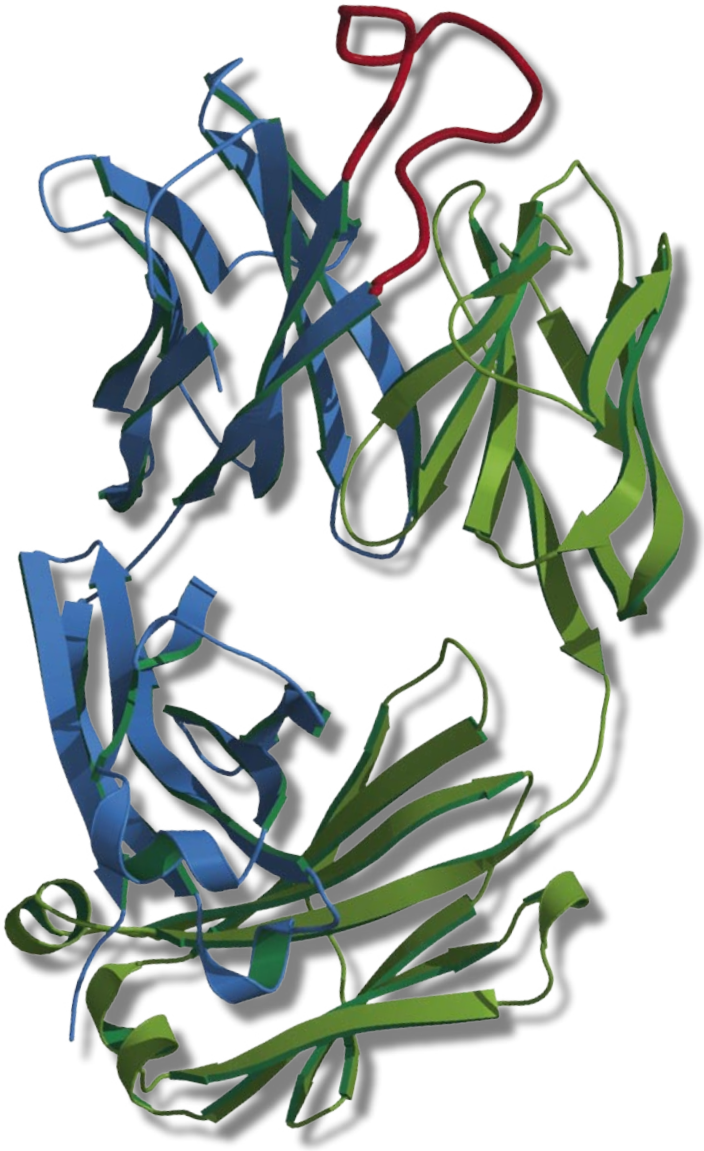
The CEI faculty has used the unique combination of resources in basic science and clinical expertise in the CCR to make breakthrough discoveries that have contributed to immunological treatments for some cancers.

Some strategies for the future include:

- Support basic research and provide incentives for outgrowth of translational and clinical studies
- Continue emphasis on training the scientists of the future
- Facilitate synergistic interactions in the CCR immunology community to develop new immunotherapeutics
- Develop a new program focused on inflammation and cancer
- Create partnerships with the NCI Cancer Prevention Program to develop and deliver vaccines and other potential immunotherapeutics to populations with high-risk, pre-neoplastic conditions
- Forge partnerships with the academic and biotechnology communities

For More Information

Information on research at the CCR and the CEI can be found at http://ccr.nci.nih.gov/ and http://home.ccr.cancer.gov/coe/immunology/, respectively. Dr. Diana Linnekin can also be contacted at dlinnekin@ncifcrf.gov for additional information on CEI research and activities.



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