National Cancer Institute

Center for Excellence in Immunology

Center for Cancer Research

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

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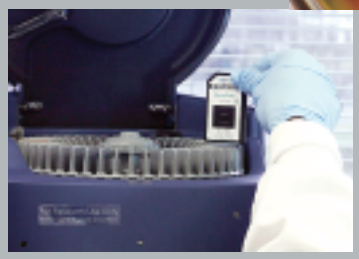
The Center of Excellence in Immunology



Letter from the Director

The Center of Excellence in Immunology (CEI), part of the National Cancer Institute's intramural research program in the Center for Cancer Research (CCR), is a community of scientists who integrate discovery with the development of novel, immune-based treatments for cancer and AIDS. Based in Maryland, on the Bethesda and Frederick campuses of the National Institutes of Health, the CEI is home to a critical mass and unique mix of basic, translational, and clinical scientists who work in multidisciplinary teams to aggressively pursue new approaches for the prevention and treatment of cancer and AIDS. Considered one of the leading communities of immunology researchers in the world, CEI scientists bring a distinguishing strength to the CCR. They already have produced many immune-based interventions that are offering relief to those with cancer and AIDS. Their integrated research also lays a strong foundation for new advances and brings hope for the future. The stories in this booklet provide a glimpse of their contributions to our progress against cancer.

Several key areas of research emphasis at the CEI are illustrated in this booklet, including cell-based therapy, immunotherapy with antibodies, cytokine-based treatments, as well as vaccines to prevent or treat cancer and HIV/AIDS. These research snapshots attempt to capture CEI's strategic use of the immune system to detect cancer earlier, diagnose it more precisely, and prevent or treat it more effectively-all with an eye toward the NCI Challenge Goal: To eliminate the suffering and death due to cancer by 2015.

The distinctive infrastructure of the NCI intramural research program is also captured in this publication. Here an enabling infrastructure empowers CEI scientists to do innovative work. Teaming within the NCI intramural program, they invent new tools or harness existing ones to translate their discoveries about cancer and the immune system into treatment interventions. Using cutting-edge technologies such as functional imaging, genomics, proteomics, CEI researchers drive their discoveries from the bench, to early phase clinical studies, all the way to a benefit for cancer patients. Ground-breaking advances in genomics, for example, were quickly applied to the molecular profiling of lymphoma and have revolutionized diagnosis and treatment for today's patients with this disease.

Another key attribute of the NCI's intramural research program that benefits CEI scientists is its longstanding support for high-risk research that has potential for making a major impact. Projects that might be considered too risky for industry or academia to provide prolonged funding are sustained at the NCI. Current clinical trials of adoptive cell therapy illustrate this well. Without NCI's two decades of support for cellular therapy research, cancer patients today might not be benefiting from the remarkable progress evident in treatment for advanced melanoma.

CEI has made impressive advances. Its success flows from a distinctive research environment: one in which a critical mass of able researchers unselfishly pool their diverse talents to create a "culture of the corridors" that fosters and produces a center of research excellence. As the Director of the CEI, I am privileged to share with you some of our accomplishments.

Robert H. Wiltrout, PhD.
Director, Center of Excellence in Immunology
Director, Center for Cancer Research
National Cancer Institute
National Institutes of Health

Spotlight on Center of Excellence in Immunology

A premier community of immunologists

In 2003, four Centers of Excellence emerged from a reengineering process that optimized the NCI's intramural research infrastructure. Through these new Centers, NCI's intramural researchers formed teams engaged in transnational research. CCR leads three of the Centers:

- **Advanced Biomedical Technology**
- **Immunology**
- **Molecular Oncology**

The CCR is home to one of the strongest immunology and virology communities in the world with renowned scientists performing basic, transnational, and clinical research. In 2003, the Center of Excellence in Immunology (CEI), a 250-member faculty headed by Dr. Robert Wiltrout, brought these investigators together within a collaborative unit to further the discovery, development, and delivery of novel immunologic approaches for the prevention, diagnosis, and treatment of cancer and cancer-associated viral diseases. This community of bench scientists and clinicians with a wide range of expertise, work as a think-tank, proactively mapping the future of immunology research at the CCR. With a global reach and vision, they have identified opportunities and barriers to progress and are collaborating with extramural investigators, academia, and the pharmaceutical industry worldwide to harness the power of the immune system to fight cancer and improve patient care.

Researcher Tom Shelton harvests a patient's tumor infiltrating lymphocytes after they have been activated and grown in vitro. *Photo credit: Rhoda Baer*

CEI members have made groundbreaking discoveries in the fields of cytokines, cellular and innate immunity, viral immunology, and immunotherapy, including cancer vaccines, immunotoxins, radioimmunotherapy, and cellular therapy. Their combined research has resulted in more than 4,700 publications in scientific journals since 1990. Having pioneered many of the approaches in use today, researchers in the CEI stand at the forefront of immunotherapy. Some of their bench-to-bedside research "firsts" include:

Cytokine-Based Therapy

Discovery of IL-2, plus a subunit of the IL-2 receptor complex, and JAK3, a kinase critical for IL-2 responses. These basic research findings have been translated to the clinic so that today, IL-2 is an FDA-approved treatment for metastatic renal cancer and melanoma. CEI members have also developed antibodies to the IL-2 receptor and used these for treatments of some forms of leukemia, autoimmune disease and graft versus host disease. This work was among the first to demonstrate the potential of monoclonal antibody therapy in treating cancer. Now numerous monoclonal antibodies are in clinical trials

Dr. Steven Rosenberg proudly displays his wall of illustrious alumnae, graduates of the Surgical Oncology Fellowship at CCR. *Photo credit: Rhoda Baer*

and monoclonal antibodies such as rituximab and trastizumab are routinely used for non-Hodgkin's lymphoma and breast cancer, respectively.

Adoptive Cell Transfer Therapy

A novel cell-based therapy that involves removing infiltrating immune cells from the tumor, activating them in vitro, and returning them to the patient. This approach has resulted in improvement in 51 percent of patients with metastatic melanoma that had not responded to earlier treatments (see page 31). Given the bleak prognosis for those with late-stage melanoma, these are remarkable and promising results.

Radio-Immunotherapy

CCR scientists coupled radioactive molecules with monoclonal antibodies to enable radio-immunotherapy for patients with refractory non-Hodgkin's lymphoma and T cell leukemia. They then partnered with pharmaceutical companies to develop a product that was both safe and efficacious in clinical studies in patients. This CCR effort yielded the first radio-labeled monoclonal antibody approved by the FDA as a cancer treatment.

Immunotoxin Therapy

Several immunotoxins generated at the CCR are in clinical trials. Treatment with BL22 resulted in a very high complete response rate among patients with hairy cell leukemia that was resistant to standard therapy. CCR scientists are also conducting clinical trials with the SS1P immunotoxin in mesothelioma, as well as ovarian and pancreatic cancer. Collaborations with the biotech company IVAX have also resulted in a Phase II multicenter trial treating malignant brain tumors with TP38, another immunotoxin.

Preventive Cancer Vaccines

The development of vaccines to prevent cancer is another area of intense investigation at the CEI that is poised to deliver rich rewards. Basic research into the assembly of HPV, the virus that causes cervical cancer, has been translated into a vaccine designed to prevent the disease (see page 14). Results of Phase II trials showed a high level of protection against HPV infection, and Phase III trials testing this vaccine are in progress.

Therapeutic Cancer Vaccines

The ever-expanding field of therapeutic cancer vaccines also owes much to advances made by CEI researchers. They have identified numerous novel cancer antigens, devised novel approaches to vaccine design, improved vaccine delivery, as well as discovered ways to optimize vaccine-induced immune responses with cytokines and costimulatory molecules. CEI clinicians recently initiated a pilot study that was the first clinical trial to combine radiation and a cancer vaccine for treating prostate cancer. By showing that such combination therapy is safe and well tolerated, CCR is leading the way toward finding alternative treatments for patients with localized disease who receive radiation or surgery and then relapse. In several clinical trials, there is evidence that immune responses to vaccines were associated with prolonged survival. Several vaccines and combination protocols are being developed at NCI and are being evaluated at more than 60 cancer centers around the country for testing in clinical trials. At least two of these vaccines are progressing successfully from Phase II to Phase III studies.

Fueled by NCI's sustained support, the capacity to arrange global collaborations, and intellectual excellence in immunology, investigators in the CEI continue to break new ground to deliver more effective, less toxic treatments for cancer.

Drs. Jeffrey Schlom (seated), Philip Arlen (right) and James Gulley (left) evaluate the effectiveness of a breast cancer vaccine protocol. *Photo credit: Rhoda Baer*

A 50-Year Odyssey by a Quintessential Physician-Scientist

"Nowhere in the nation do I see the ability to do basic science, to take it to preclinical drug development and into the clinic as you can at the NCI. It is very exciting to see your patient get better with an agent that you've developed yourself. I cannot tell you how exhilarating it is to feel that you've made a difference."

Thomas Waldmann

Dr. Thomas Waldmann arrived at the NCI in 1956, just three years after the NIH Clinical Center opened. What was envisioned as a 2-year fellowship became a 49-year allegiance. He speaks with passion as he describes how the close proximity of patients to the research labs, the critical mass of scientists with a remarkable variety of expertise, and the sense of collaboration and comradery among researchers and physicians enticed him to stay. He describes the "culture of the corridors" of the Clinical Center as a unique interaction of infectious excitement and enthusiasm among basic researchers and clinicians who want to make a difference.

Dr. Waldmann is now unraveling the role of IL-15, a powerful cytokine that can prolong memory T-cells and produce a long-lasting immune response. *Photo credit: Rhoda Baer*

Dr. Waldmann and his colleagues Jing Chen Ph.D. (facing camera on left) and Hiral Patel, Howard Hughes Medical Scholar (back to camera on the right) examine a gel that confirms the purity of their preparation of IL-2 receptor. *Photo credit: Rhoda Baer*

Dr. Waldmann has made high-impact contributions towards understanding and treating an astonishing array of diseases and clinical disorders. He sums up his five decades at the NCI as a fascinating odyssey. Prior to 1980, he focused primarily on metabolism of serum proteins. This body of work led to insight into ataxia telangiectasia, myotonic dystrophy, familial hypercatabolic hyperproteinemia, Wiskott-Aldrich syndrome, allergic gastroenteropathy and intestinal lymphangiectasia (also termed Waldmann's disease). He then pioneered advances in how germ-cell tumors in the testis are diagnosed and treated, and how a type of human T cells, immune cells called "suppressors" that act as regulators, behave in immunodeficiency diseases and some forms of leukemia. He also devised a novel form of molecular

"One of the great aspects of the NCI is it allows you to experience serendipity. The chance observation in a patient that cannot be explained in the way we already think about a disease may open up a whole new scientific field!"

Thomas Waldmann

genetic analysis to improve diagnosis and treatment of leukemia.

In the late 1970s, a serendipitous discovery turned Dr. Waldmann and coworkers' attention to the newly born field of cytokines. Cytokines are a class of proteins that act as signaling regulators in the immune system. His group was trying to generate an antibody to CD4, a marker protein on the surface of T cells. They ended up instead with an antibody to an unknown protein. Quickly, they determined the protein was important to T-cell activation. So they cloned it and found it was part of the IL-2 receptor complex, where cytokines bind to effect signaling. With this finding, they characterized the first cytokine receptor, setting the stage for understanding the biology and biochemistry of this family of molecules.

Dr. Waldmann explains possible side effects to Carol as she begins her combination chemotherapy and immunotherapy. *Photo credit: Rhoda Baer*

Over the next 20 years, the Waldmann lab demonstrated that antibodies specific for this receptor were useful in treating adult T-cell leukemia, prolonging survival of transplant recipients, and treating multiple sclerosis. As part of an effort to unravel paradoxical observations in these trials, Dr. Waldmann co-discovered the cytokine interleukin 15 that is critical for the survival of yet another type of T cell, the "memory" T, named for its ability to remember past invasions and respond quickly to a pathogen's re-entry. Waldmann is translating these latest observations to the clinic by introducing IL-15 into cancer therapy, and into the design of vaccines for cancer and AIDS.

Dr. Waldmann carefully places an important paper in a safe place in his office. *Photo credit: Rhoda Baer*

"You'll see a patient and take that information into the laboratory. From the laboratory, you learn new insights that can be translated into rational drug development. The ability to move back and forth is very special here."

Thomas Waldmann

Dr. Waldmann's studies pioneered and propelled the use of monoclonal antibodies for immunotherapy. Today hundreds of new antibodies are in clinical trials, and the Food and Drug Administration already has approved about a dozen monoclonal antibodies, including Herceptin and Rituxan, to treat cancer and other diseases. For Waldmann, a chance discovery in the 1970s, pursued with a prepared mind and sustained commitment, has had a far-reaching impact.

A Promoter and a Suppressor of Tumor Growth: The Complex Biology of TGF-β

TGF-β (transforming growth factor-beta) was discovered three decades ago at CCR and has confounded and delighted researchers ever since

TIMELINE OF TGF-β COLLABORATIONS

1980s	
Identify and purify TGF-β	CCR
TGF-β promotes wound healing	CCR
Clone TGF-β	CCR/Genentech
TGF-β inhibits growth	NCI
1990s	
Crystal structures of TGF-β	NIDDK/NIDR
TGF-β mouse models	NINDS/NIDDK
First clinical trial with systemic TGF-β	NINDS
2000s	
CRADA to develop TGF-β antibodies	CCR/Genzyme
TGF-β blockers suppress metastasis	CCR
TGF-β switches from suppressor to promoter	CCR

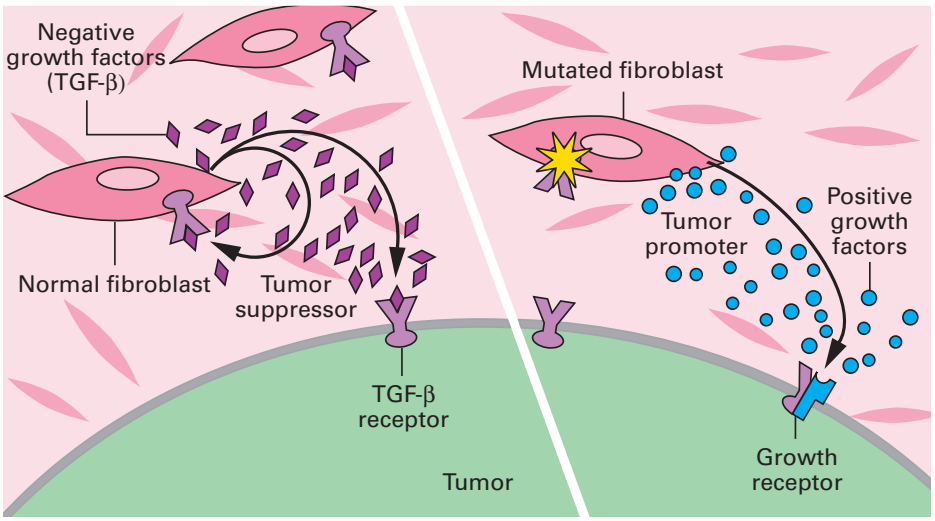
When Drs. Anita Roberts and Michael Sporn (now at Dartmouth Medical School) discovered and characterized TGF-β in 1981, they called it "transforming" because it can turn normal cells malignant, and because elevated levels of TGF-β predict poor outcomes in many types of cancer.

Dr. Roberts and her colleagues developed mouse models to study the TGF-β-signaling pathway in inflammation, fibrosis, and cancer. TGF-β regulates many cellular processes in normal cells, including tissue repair from injury. Intriguingly, mice lacking components of the TGF-β-signaling pathway heal faster from epithelial wounds and are protected against skin injury caused by ionizing radiation. CCR scientists are developing inhibitors of TGF-β to see if they can speed epithelial tissue repair following cancer radiotherapy.

Although TGF-β was originally discovered for its tumor-promoting activity, it has become clear that during the early stages of cancer development, TGF-β often acts as a tumor suppressor. Using a mouse model of human breast cancer, CCR's Dr. Lalage Wakefield demonstrated that TGF-β switches from tumor suppressor to tumor promoter, and it supports metastasis when a breast cancer changes from histologically low- to high-grade—a shift to more aggressive disease. Dr. Wakefield went on to make the unexpected finding that certain TGF-β inhibitors can selectively block the tumor promoter effects of TGF-β, without affecting its tumor suppressor activity. This discovery with mouse models suggests that TGF-β inhibitors might be useful to treat cancer metastasis in humans.

CCR has established a cooperative research agreement (CRADA) with Genzyme Corporation to develop TGF-β antibodies for testing in clinical cancer trials, both alone and in combination with other cancer treatments, such as chemotherapy and cancer vaccines. CCR continues with an active program to target TGF-β in cancer treatment, wound healing, and blood and immune system disorders.

Dr. Wakefield is committed to determining how TGF-β shifts from tumor suppressor to tumor promoter. "Understanding this problem will be critical if the TGF-β system is to be exploited effectively in novel approaches to the treatment of breast cancer."



During cancer progression, TGF-β signaling switches from producing growth negative to growth positive factors. Researchers are developing agents to selectively block this tumor promoting activity.

Dr. Roberts' leadership in creating a world-renowned center of expertise in TGF-β biology, was recognized by her recent award of the Leopold Griffuel Prize and the Federation of American Societies for Experimental Biology (FASEB) Excellence in Science Award.

Targeting the Virus That Causes Cervical Cancer: HPV Vaccine Will Have Global Impact

A vaccine to prevent cervical cancer is in final stages of testing

A vaccine to prevent cervical cancer, based on technology developed by CCR scientists Douglas Lowy and John Schiller, is in final stages of testing. This vaccine offers great hope for reducing the global burden of cancer.

Almost every cervical cancer in the United States and abroad is caused by infection with human papillomavirus, or HPV. Once NCI scientists in the Division of Cancer Epidemiology and Genetics (DCEG) established the link between HPV and cervical cancer, CCR scientists went to work to devise a vaccine against the virus. They found that multiple copies of a single HPV protein could assemble into non-infectious virus-like particles to form the basis of a vaccine. Immunization with these particles, they learned, could stimulate production of large quantities of antibodies that prevent virus infection in both animals and human volunteers.

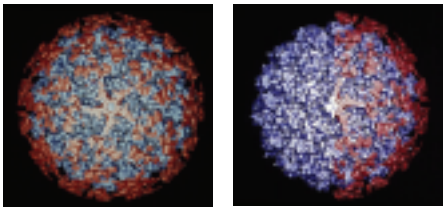
NCI licensed the technology to two pharmaceutical companies—Merck and Glaxo-Smith-Kline (GSK)—to develop HPV vaccines commercially. Both companies are running large-scale Phase III trials of their versions of an HPV vaccine. GSK's targets two HPV strains, 16 and 18, which together cause about 70 percent of all cervical cancers. Merck's targets strains 6, 11, 16, and 18. Phase II trials by both companies produced encouraging results. The VLP vaccines were 100 percent effective at preventing premalignant cervical abnormalities caused by the virus types in the vaccines, even up to four years after vaccination.

The NCI is performing its own Phase III trial of the GSK vaccine in Costa Rica, where cervical cancer rates are high. The NCI study is being run by DCEG's Allan Hildesheim and Rolando Herrero from the Fondacion Inciensa in Costa Rica. The women in the study will be followed for at least 6 years, to obtain information about the vaccine's long-term safety and the extent and duration of protection.

CCR's involvement in HPV vaccine development continues. Drs. Schiller, Lowy and colleagues have developed the first high-throughput assay to enable HPV vaccine developers to observe whether a vaccine can induce potentially protective antibody responses against other cancer-causing strains of HPV. They have made this assay available to other researchers to accelerate vaccine research.

In anticipation of approval of HPV vaccines, the Gates Foundation announced in June 2005 that it would grant $12.9 million to the World Health Organization, the International Agency for Research on Cancer, Harvard University, and the Program for Appropriate Technology in Health to create systems to ensure quality control in vaccine distribution, monitor the impact of different HPV vaccination strategies, and facilitate early introduction of the vaccines worldwide.

GSK and NCI are running a Phase III trial of an HPV vaccine to protect Costa Rican women from HPV infections that are linked to cervical cancer.



HPV L1 virus-like particles morphologically look very similar to authentic infectious [viral] particles except that they don't contain any DNA.

Cervical cancer strikes nearly half a million women each year worldwide. It is the second leading cancer killer, claiming a quarter of a million lives annually. The vast majority of deaths occur in the poorest regions of the world—South Asia, sub-Saharan Africa, and parts of Latin America—where access to screening services and medical care is limited.

An NCI team of experts in virology, vaccine development, epidemiology, immunology, pathology, and cytology is helping to make cervical cancer prevention a reality.

The HPV prophylactic vaccine is highly immunogenic, prompting the production of antibodies that interfere with binding of the intact HPV virus to a patient's cells and entry through a receptor.

HIV/AIDS: NCI Responds Swiftly to a Public Health Crisis

A mysterious immunodeficiency disease

"In retrospect, our work was an ideal demonstration of what the Clinical Center is all about. A laboratory could do certain things and then, in effect, take the observation twenty feet down the hall into a clinical area and begin treating patients. That kind of interaction and that kind of ability is really very rare."

Former NCI Director Dr. Sam Broder: Interview with Gretchen Case of History Associates, Fall 1996

CCR'S AGILE INFRASTRUCTURE

IDENTIFICATION of HIV as causative agent for AIDS

DEVELOPMENT of first blood test for HIV infection

DISCOVERY of first antibodies to kill HIV

IDENTIFICATION of many retroviral proteins, new HIV reservoirs, immune system receptors that recognize HIV, and human genes that influence HIV susceptibility and AIDS progression

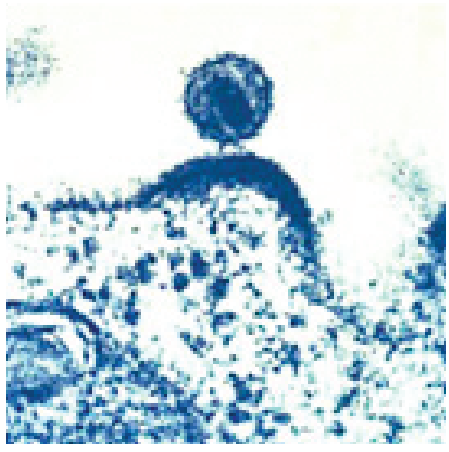
UNDERSTANDING of how HIV infects a cell

CONTRIBUTIONS to HIV vaccine development

PREVENTION and **TREATMENT** for AIDS-related cancers

In June 1981, the Centers for Disease Control (CDC) published the first report of five cases of a mysterious immunodeficiency disease. Two weeks later, a young man with a severe immune system disruption checked into the NIH Clinical Center with the help of an oncologist in NCI's Intramural Research Program. His condition was categorized as a rare disease—and later turned out to be one of the first cases of Acquired Immune Deficiency Syndrome (AIDS) in the United States. The AIDS epidemic spread quickly; by the end of that year more than 200 people had died of AIDS in the United States.

The medical community faced a public health crisis. The cause of the new disease was unknown and there were no means to treat or prevent it. Groundbreaking basic research by investigators in NCI's Intramural Research Program—and subsequent collaborations with industry—rapidly provided important answers. By 1984, Dr. Robert Gallo's group at NCI and a scientific team at the Pasteur Institute in France had discovered the virus now known as human immunodeficiency virus (HIV) and implicated it as the cause of AIDS. Intramural scientists also developed the first blood test to diagnose HIV infection and rapidly transferred materials to industry for the commercial production of a test that could be used for blood screening at the nation's blood banks.



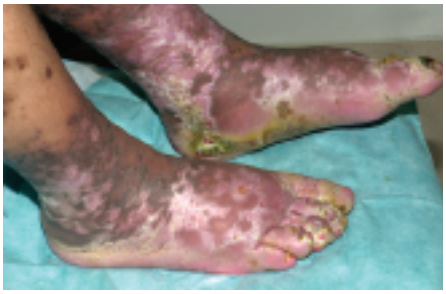
The virus that causes AIDS is shown budding out of a human immune cell.

Intramural researchers at NCI also played a key role in the development of the first drugs for treating HIV infections and AIDS. An NCI-funded researcher had already synthesized zidovudine (AZT) as a possible anticancer drug. Drs. Samuel Broder, Hiroaki Mitsuya, and Robert Yarchoan moved quickly to test AZT and other drugs: didanosine (ddI) and zalcitabine (ddC) for treating patients with AIDS. All three drugs were licensed for treating HIV infection, and today these agents are combined with protease inhibitors or non-nucleoside reverse transcriptase inhibitors in combination antiretroviral therapy, known as *highly active antiretroviral therapy* or HAART. This "cocktail" therapy has dramatically reduced the number of deaths and new cases of AIDS since its introduction in 1995. The number of annual deaths among people with AIDS in the United States has dropped to 15,600—less than one third the level at the height of the AIDS epidemic in 1995, when the disease killed 51,670 people in the United States.

Prior to the onset of the AIDS pandemic, a cancer known as Kaposi's sarcoma (KS) was a rare disease. With the spread of HIV, however, KS now accounts for 10 percent of cancers in countries such as Congo and

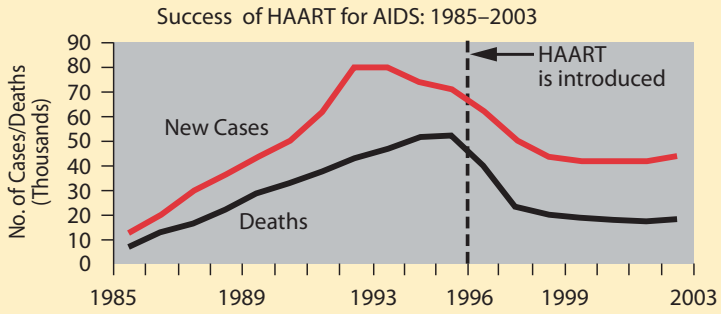
Uganda. As part of its long-term commitment to reducing the cancer burden for medically underserved populations worldwide, CCR researchers are developing new treatments for KS based on developing knowledge of how the Kaposi's sarcoma herpes virus (KSHV) causes the disease. Drs. Richard Little and Robert Yarchoan are conducting clinical trials using novel therapies to cut off the blood supply to the tumors (called antiangiogenic therapy) using agents such as thalidomide, bevacizumab, and a combination of IL 12—an agent with antiangiogenic and immunologic activity—and liposomal doxorubicin.

In developed countries, the growing population of people living with HIV infection and AIDS are living longer but still face significant health challenges. People infected with HIV are at a 20-fold increased risk for developing several forms of cancer, including KS, certain lymphomas, plus cancers of the cervix, liver, lip, mouth and pharynx, and several others. HAART therapy can reduce the incidence of some these cancers in HIV-infected patients, but others are becoming more common. Often, these cancers are caused by co-infection with other viruses, such as Epstein Barr virus or hepatitis C virus. CCR scientists are actively involved in developing antiviral and other approaches for these AIDS-associated cancers.

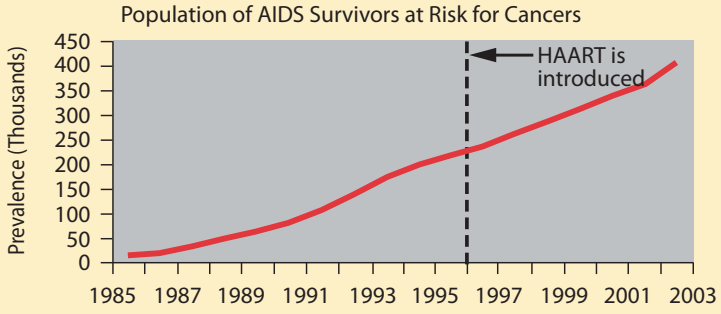


Kaposi sarcoma lesions most often develop in the patient's feet because they are often hypoxic (low oxygen). This condition induces replication in KSHV-infected cells.

Yesterday's Achievement



Today's Challenge



NCI'S AIDS VACCINE PROGRAM

In addition to conducting its own intramural research, the NCI's AIDS Vaccine Program, headed by Dr. Jeffrey Lifson, saves the research community millions of dollars and speeds research progress by developing and providing a broad range of novel reagents, assays, and analytical methods to U.S. and international researchers who study AIDS and cancer. It has more than 4,300 reagents (cell lines, proteins, antibodies, viruses). More than 139,000 vials have been shipped to scientists from the United States and 63 foreign countries.

Clinical Trials at the NIH Clinical Center

Clinical research, an integral part of the CCR, is conducted in the new NIH Clinical Research Center (CRC) on the Bethesda campus of the NIH. This facility contains state-of-the-art diagnostic and therapeutic capabilities to support clinical research programs in pediatric and adult oncology conducted by clinical investigators in laboratories or branches of the CCR. In fiscal year 2005, there were more than 30,000 total outpatient visits and over 1,000 in-patient admissions to the CCR clinical research program.

Throughout the day-to-day care of cancer patients, CCR clinicians train the next generation of radiologists, oncologists, surgeons, pharmacologists, and nurses for careers in clinical research. Several CCR training programs lead to board certification in cancer specialties (see Training, pg. 32).

AVAILABLE CCR CANCER TRIALS

CCR's cancer trials open for enrollment are available at: http://www.cancer.gov/clinicaltrials.

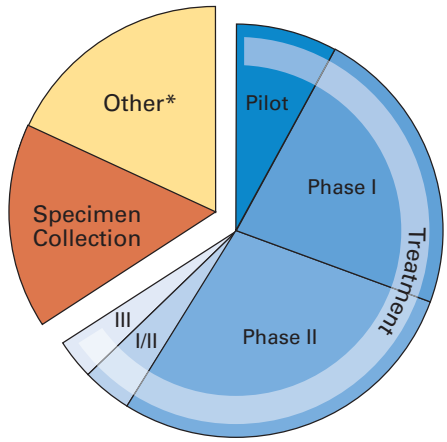
CCR scientists are translating discoveries at the bench into new diagnostic approaches and new targeted therapies, collecting molecular profiles for many cancer types and developing databases that eventually will serve the era of molecular medicine. CCR clinicians use a science-based rationale for treatment planning. With a patient-focused approach to treatment research, they evaluate a patient's case history and the expression profiles of cancerous tissues—when available—along with evidence-based pharmacological data. Clinicians try to match patients with the appropriate available trials. The overarching goal is to detect and diagnose cancers earlier and more accurately and treat patients more effectively than is possible with standard treatments.

With the laboratory bench down the hall from the patient's bedside, CCR scientists can take a new agent that shows promise in an early phase study and return to the bench to improve its stability, or to develop a better way to deliver the drug, or to design better imaging agents to help monitor its action in the body. Areas of ongoing science-based trials include: early detection, immunotherapy, adoptive cell transfer therapy, molecular targets, innovative combination treatment regimens, drug resistance, local therapy, cancer genetics, and molecular profiling.

New Territory

Approximately two-thirds of the clinical research studies at CCR are testing novel treatments for cancer (see Figure 1). The rest are natural history studies, specimen collection, imaging and screening trials, plus follow-up, psychosocial, supportive care, epidemiology, and surgery trials. Many of the new treatments are small molecules or biological agents (see Figure 2) developed at the CCR or in collaboration with academic or industry partners.

Figure 1

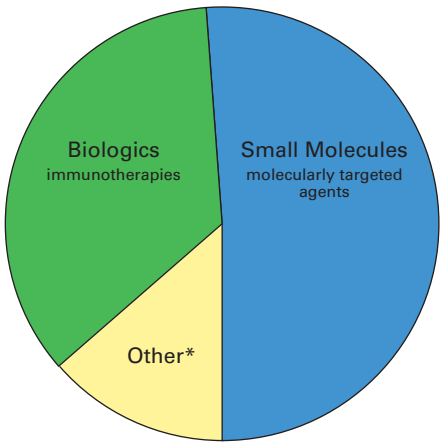


*Natural history, imaging, screening, follow-up, psychosocial, supportive care, epidemiology, surgery

The majority of the treatment trials at CCR are early phase studies. CCR focuses on proof-of-principle research. These small trials answer some of the basic questions about optimizing a new drug's effective dose and manner of delivery. Well before any new agent is placed in a Phase I trial, though, massive preclinical data has been collected and studied carefully in anticipation of moving the treatment to patients. CCR researchers undertake these high-risk, high-impact studies to develop new agents and deliver them as stable and effective drugs. Occasionally CCR works collaboratively with pharmaceutical companies to improve the composition of their new agents.

New protocol concepts undergo rigorous,

Figure 2



*Transplant, cell therapy, radiation, radiofrequency ablation, gene therapy, surgery, exercise

timely reviews via relevant boards and committees. Modifications are made as recommended to ensure optimal trial designs that protect patient safety during discovery and refinement of new and effective cancer treatments. The CCR has an administrative infrastructure to oversee and maintain all aspects of the highest quality and ethical clinical research, including regular refresher-training in clinical research, patient privacy safeguards, research nursing and data management support, statistical evaluation, and outreach programs to promote and support patient accrual.

A Step-by-Step Process

Clinical trials, or research studies in which humans participate, are conducted in phases. There are many types of trials, including treatment, prevention, detection, diagnostic, and quality-of-life. The majority of trials under way in the CRC are treatment trials designed to test the safety and effectiveness of new drugs, biological agents, techniques, or other interventions in people who have been diagnosed with cancer. These trials evaluate the potential clinical usefulness of a therapy or compare an investigational treatment against standard treatment, if there is one.

Phase I trials generally involve a small number of patients. These trials find a safe dosage, decide how the agent should be given, and observe how the agent affects the patient's body. Cancer patients who have no known effective treatment options are eligible for Phase I trials. Study participants are divided into cohorts, and each cohort of participants is treated with an increased dose of the new therapy or technique.

Phase II trials are designed to evaluate the effectiveness of the drug in a larger group of participants using the dosage determined to be safe in Phase I trials. Researchers often focus Phase II trials on cancers for which no effective treatment exists and/or cancers that are most likely to show a response to therapy. If an acceptable percentage of the patients respond well to the drug in a Phase II trial, the agent will go forward to a phase III trial.

Phase III trials typically involve large numbers of participants in order to determine whether a new therapy or technique is more effective or less debilitating than a standard treatment. These trials are conducted at multiple institutions around the country, including community settings. The results of Phase III trials guide health care professionals and people with cancer in making treatment decisions.

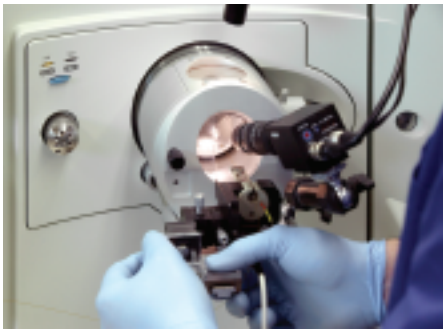
The Phase 0 Initiative

As part of CCR's role in developing and testing new agents, the CCR is partnering with NCI's Division of Cancer Treatment and Diagnosis (DCTD) to launch a Phase 0 Initiative. CCR's strength in integrated research and its clinical program will be combined with DCTD's expertise in drug development and its relationships with pharmaceutical companies to create a joint-program in drug development that will perform "first-in-human studies," mini-trials called Phase 0 trials. These studies will validate the initial scientific rationale that is driving researchers to promote a new protocol by gathering pharmacological data directly from human volunteer patients. The goal is to subject promising new agents to sophisticated, preliminary human toxicity (pharmacokinetic and pharmacodynamic assays) and then, based on the results, select those that are most likely to succeed through Phase I, II, and III trials.

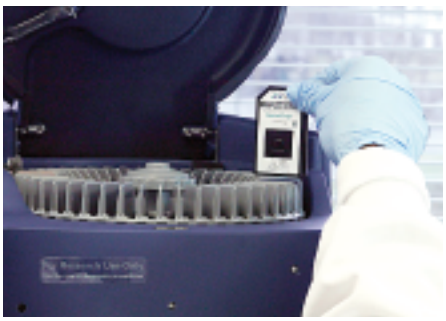
Clinical Trials: From Bench to Bedside

	Phase 0	Phase I	Phase II	Phase III
Avg. Years	0.5	1.5	2	3.5
Est. No. of Patients	6–10	20–100	30–200	150–5000
Purpose	Validate molecular target	Determine safe dose, side effects	Evaluate effectiveness, side effects	Confirm effectiveness, monitor adverse reactions

Exploring the Power of Molecular Profiling



A CCR researcher loads a protein lysate to mass spectrometry equipment in search of unique protein profiles or marker proteins (called biomarkers).



A CCR researcher uses a gene chip to study cancerous tissue samples for changes in gene expression.

"My basic vision is that every cancer patient receive a molecular diagnosis," says CCR's Louis Staudt. "Then we could steer each patient to the optimal therapy, based on the characteristics of his or her tumor."

The pace at which scientific discovery and its application to patient care is advancing has been aided by new technologies and far-reaching collaboration among scientists. Gene expression profiling and improved imaging techniques are two areas that have had huge impacts on clinical research, enabling scientists to envision a near future when enough detail can be gleaned about each patient's cancer to provide the right intervention for the right reason at the right time.

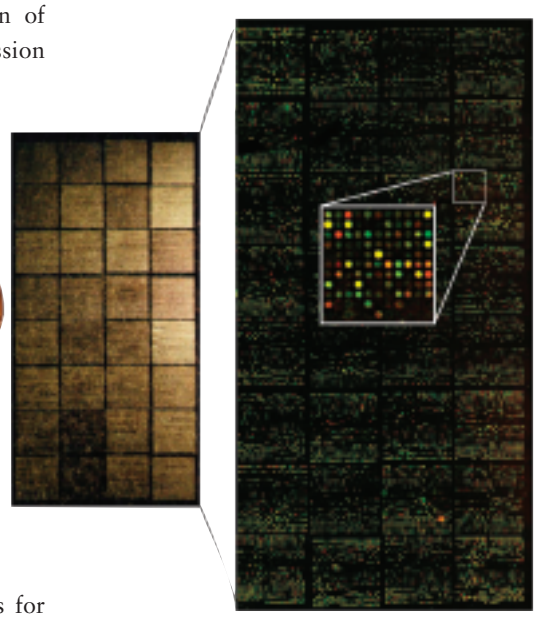
Patient Profiling

Gene expression profiling or genomics (studies of the structure and function of multiple genes) and protein expression profiling or proteomics (analysis of complete sets of proteins to determine their interactions and functions) are powerful new tools in biomedical research that CCR scientists are using to find differences between normal and cancer cells and to understand how healthy cells become malignant. With these technologies, clinicians are moving to more targeted, science-based strategies for early detection and diagnosis, prognosis, and individualized therapy. CCR investigators are identifying different patterns of gene and protein expression in cancer cells. These technologies and their patterns—molecular profiles—are already improving the diagnosis and management of cancer.

Profiles Inform Therapy

Dr. Wyndham Wilson developed a novel treatment strategy for patients with diffuse large B-cell lymphomas (DLBCL) called Dose-Adjusted EPOCH-Rituximab (DA-EPOCH-R). Results from several studies suggest that this new therapy may become the treatment of choice for DLBCL because cure rates increased by 20 to 30 percent when compared to results with standard treatment. An international Phase III trial is now under way to carefully compare DA-EPOCH-R to the standard. Already prelim-

Lymphochip



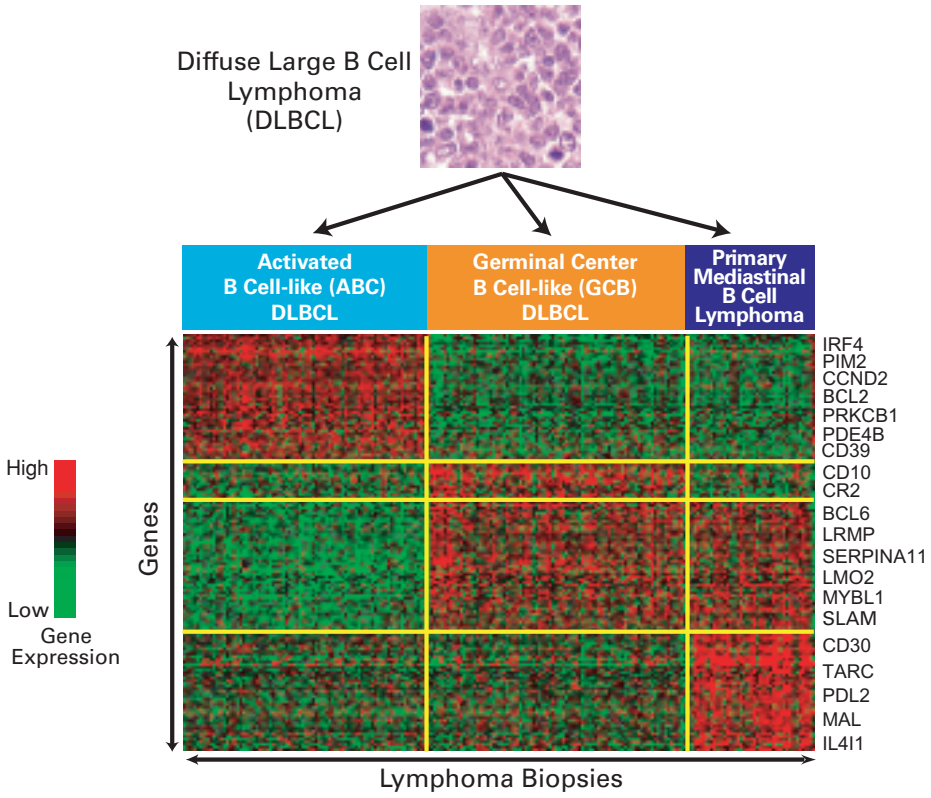
The lymphochip holds small, tethered DNA sequences (cDNAs) of known identity that represent the entire lymphocyte genome. Using complementary DNA binding, CCR researchers use this chip to study the gene expression of thousands of genes simultaneously. In the Lymphoma/Leukemia Molecular Profiling Project, the Lymphochip will help CCR researchers define the genomic profiles of all types of human lymphoid malignancies.

inary insights are being gained from biomarkers in this trial. For some patients whose biomarkers predict a poor response to standard treatment, these same biomarkers do not predict failure with DA-EPOCH-R. Such discoveries show how individual profiles may be used to guide treatment choices for a patient.

Dr. Louis Staudt used genomic technology to explain why some patients with diffuse large B-cell lymphomas (DLBCL) live longer and respond better to therapy than others. Under the microscope, the DLBCL cancer cells from every patient look the same. The Staudt lab profiled the genes expressed in patients with DLBCL and found important differences, leading him to identify three molecularly and clinically distinct subclasses of the disease: germinal center B-cell-like (GCB), activated B cell-like (ABC), and primary mediastinal B-cell lymphoma (PMBL).

These lymphoma subclasses arise in B cells at different stages of maturation and follow different molecular pathways that lead to cancer development. Their discovery revealed new molecular targets and new treatment approaches based on subclass. Dr. Staudt's group is developing new therapies to inhibit the NF-kB pathway, which is critical to cancer growth and survival in two of the DLBCL subclasses, ABC and PBML. These new therapies are being tested in the clinic by Dr. Wilson's team.

Genomic Profiling of DLBCL



The genomic profiling of diffuse large B-cell lymphoma provides clear proof of principle that microarray technology can reach beyond a tissue slide and dramatically improve a clinician's ability to diagnose lymphoid malignancies more precisely.

Profiles Inform Prognosis

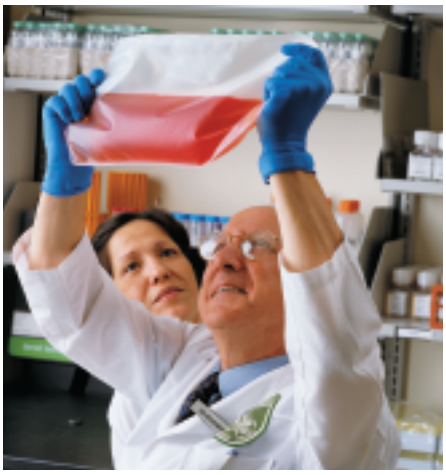
Until recently, there was no reliable indicator to predict treatment outcomes for children with rhabdomyosarcoma (RMS), a fast-growing, highly malignant soft tissue tumor—yet treatment fails 30 percent of these young patients. Clinicians may now have their indicator. Using proteomics technology, Drs. Lance Liotta and Lee Helman and their research teams, in collaboration with the Food and Drug Administration, the Children's Oncology Group, and other extramural partners, identified a molecular profile of RMS tumors that responds well to therapy. Using reverse-phase protein microarrays and antibodies that indicate the presence of a dozen key signaling proteins in the cell, the Helman-Liotta teams examined tumor samples from children with non-metastatic and metastatic forms of this cancer. CCR clinicians found a strong correlation between successful treatment and suppression of a cellular system called the "AKT/Target of Rapamycin pathway (AKT/mTOR)," a major regulator of cell growth. Patients with AKT/mTOR suppression profiles, which resembled the ones produced by treatment with the immunosuppressant rapamycin, had the best prognosis. Further analysis of the children's tumor profiles identified key proteins—such as 4E-BP1, and the phosphorylated forms of 4E-BP1 and AKT—that could completely segregate responders from non-responders.

Lymphoma and rhabdomyosarcoma are just two examples of cancers being studied by CCR scientists by using genomic or proteomic profiles of individual tumors. By improving patient profiling, clinicians will be able to make a more accurate diagnosis, prescribe the best treatment, and improve the patient's chances of long-term survival.

Training T Cells To Attack Cancer

In a mouse model, Dr. Nicholas Restifo has demonstrated that T cells that mature *after* being returned to the mouse's body are better tumor killers. This insight is being applied to improve the ex vivo enhancement phase for TILs.

Drs. John Wunderlich and Rosenberg converse as the TILs are excised from the patient's cancerous tumor. *Photo credit: Rhoda Baer*

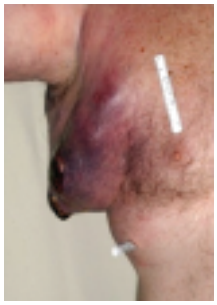


Dr. Rosenberg and Azam Nahvi inspect the growth of a patient's TILs and estimate when they will be ready for harvesting. *Photo credit: Rhoda Baer*

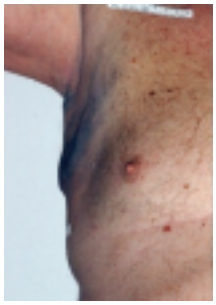
A critical component of the CCR's strength in transnational research is an infrastructure that facilitates bench-to-bedside-to-bench research at the clinical center. This environment is enabling CCR's physician scientist Dr. Steven A. Rosenberg to develop and refine an innovative approach to immunotherapy. By closely coordinating the roles of the pathologist, surgeon, and nurses, the Rosenberg team, in experimental studies of their new approach, is saving lives, producing dramatic results in patients with advanced melanoma.

Dr. Rosenberg's goal is to optimize each patient's immune response, so that immune operatives called T cells will circulate throughout the patient's body, recognize markers on the surface of a tumor, and attack and kill the cancer cells. They are testing this approach, called "adoptive cell transfer therapy" against melanoma and kidney cancer.

The scientists identify a specific kind of T cell called tumor-infiltrating lymphocytes (TILs) that the patient's immune system has generated in response to his or her cancer. These TILs are removed from the patient's tumor right after the tumor is removed. This population of TILs is then tested against tumor samples from the patient, and the most potent TILs are collected and expanded in the laboratory, or ex vivo. Meanwhile, the patient is given chemotherapy drugs to eliminate any ineffective T cells that remain in the body, so that the enhanced population of TILs being grown ex vivo will have the chance to rebuild the patient's immune system. Once the TILs have multiplied to sufficient numbers in the lab, they are returned to the patient along with a high dose of interleukin-2 (IL-2), a protein that stimulates the immune system.



Before treatment



After treatment

The researchers have faced many hurdles in developing this therapy—all of which they've been able to overcome. At first, the TILs did not last long enough in the body to do their work, they could not multiply into large enough numbers to be effective, and they failed to reach the target cancer cells. Dr. Rosenberg's team solved these formidable problems one by one.

In their most recent experimental study, 35 patients with metastatic melanoma underwent the adoptive cell transfer process. Fifty one percent of the patients responded—Three experienced a complete response and 15 had a partial response lasting from 2 months to 2 years. Over half of these patients entered the study with tumors resistant to chemotherapy and all but one were resistant to high-dose IL-2 therapy. This study is a dramatic proof-of-principle that immunotherapy has tremendous potential against cancer that has advanced to stages once considered beyond help.

Teaching the Art of Inquiry

The Office of Training Education, headed by Dr. Jonathan Wiest, plays an integral part of the CCR mission to support young scientists as they become independent researchers. In addition to managing about 900 post-doctoral and 150 post-baccalaureate students, the program supports the next generation of clinical investigators, minority researchers, and high-school and college students who come to CCR to work as summer interns.

Individuals at every level of training experience scientific enrichment. CCR investigators-in-training have access to cutting edge technologies and computational services along with exceptional online library resources to fortify their pursuit of cancer's biology. They are groomed in the essentials for the conduct of ethical and informative clinical and laboratory research and in the skills needed for lab management. They also receive training in writing professional papers and presenting their data. The CCR has taken several steps to broaden the training experience across the NIH campus. Investigators can participate, for example, in transnational fellowships in molecular pathology, radiation sciences, biostatistics, or chemistry.

CCR's labs and clinics at the clinical center are equally important training grounds for clinical fellows—young oncologists, radiologists, and surgeons who have decided to specialize in cancer care. They come to NCI for up-to-3-year rotations that permit them to combine clinical experience with investigator-initiated research in nearby labs.

- **ACGME Clinical Residency in Anatomic Pathology**—offers training and research opportunities in anatomic pathology, emphasizing the art of establishing clinical correlations to disease mechanism.
- **ACGME Medical Oncology Fellowship**—provides transnational research training in medical oncology. Fellows develop their expertise over a 3-year period. This is the oldest training fellowship in the intramural program.
- **ACGME Pediatric Hematology/Oncology Fellowship**—pairs the Johns Hopkins University and the NCI Pediatric Oncology Branch to prepare researchers adept in laboratory and/or clinical research in this area.

Some resources useful to CCR's postdocs include:

- **Fellows Editorial Board**—run by the fellows, provides editorial services and review for scientific papers.
- **transnational Research in Clinical Oncology (TRACO)** is a course for postdoctoral fellows to enable strong collaboration between basic and clinical scientists to develop novel approaches for the treatment of cancer. This Web-cast course has been adapted for training young investigators in Spain.

More information on training opportunities at CCR can be found at:

CCR Office of Training and Education: http://ccr.nci.nih.gov/careers/office_training_education.asp

Training Opportunities at NCI: http://www.cancer.gov/researchandfunding/fellowships

Research and Training Opportunities at NIH: http://www.training.nih.gov

CCR POSTDOCTORAL FELLOWSHIPS AND TRAINING PROGRAMS

ACGME Clinical Residency Programs:

- Residency in Radiation Oncology
- Residency in Anatomic Pathology
- Residency in Dermatology

ACGME Clinical Fellowship Programs:

- Medical Oncology
- Johns Hopkins University/ NCI Pediatric Hematology/Oncology
- Hematopathology
- Cytologic Pathology

Additional Clinical Fellowship Programs:

- Surgical Oncology
- Urological Oncology
- HIV and AIDS Malignancy
- Gynecologic Oncology
- Neuro-Oncology

Translational Fellowships:

- Multidisciplinary Fellowship in Breast Cancer Research
- Gynecologic Cancer Foundation/ NCI Fellowship in Gynecologic Oncology
- Postdoctoral Fellowships in Radiation Sciences
- Biostatistics/Mathematics Training Fellowship (Informatics Training Program)
- Program for Interdisciplinary Training in Chemistry (PITC)
- Comparative Molecular Pathology Research Training Program
- University of Cambridge/ GlaxoSmithKline Oncology Fellowship

Basic Science Fellowships:

- Cancer Research Training Awards
- Visiting Fellow Program

Web Sites With More Information About CCR

CENTER FOR CANCER RESEARCH

http://ccr.cancer.gov

For information on CEI research
http://home.ccr.cancer.gov/coe/immunology

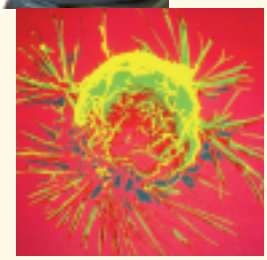
Office of the Director
http://ccr.cancer.gov/about/default.asp

Office of the Clinical Director
http://ccr.cancer.gov/trials/clinical_director.asp

Office of Communications
http://ccr.cancer.gov/news/ooc.asp

Office of Science and Technology Partnerships
http://ccr.cancer.gov/research/ostp/

Office of Training and Education
http://ccr.nci.nih.gov/careers/office_training_education.asp



PATIENT INFORMATION ON CANCER AND CLINICAL TRIALS

Open NCI Clinical Trials
http://www.cancer.gov/clinicaltrials

How to Refer a Patient
http://bethesdatrials.cancer.gov/professionals/refer.asp

NCI Cancer Information Service
http://cis.nci.nih.gov/
1-800-4-CANCER (1-800-422-6237)
For deaf and hard-of-hearing 1-800-332-8615

Understanding Cancer Series
http://www.cancer.gov/cancertopics/understandingcancer

Clinical Studies Support Center (CSSC)
http://ccr.cancer.gov/trials/cssc/staff/services.asp

ADDITIONAL LINKS

National Cancer Institute (NCI)
http://www.cancer.gov

Working at the NCI
http://www.cancer.gov/aboutnci/working

National Institutes of Health (NIH)
http://www.nih.gov

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