National Cancer Institute

Center for Cancer Research

explore
discover
translate

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

I am proud of the accomplishments of the NCI's Center for Cancer Research (CCR), a prototype for the horizontal and vertical integration needed by a research enterprise. Through their collaborative and cooperative activities, such as the NCI's Faculties and Centers of Excellence, CCR scientists and physicians bring together a strong basic science research program and advanced technologies to support innovative clinical research. Their strong relationships with national partners in key areas are making significant research contributions in the discovery, development and delivery of biomedical science. With compassion and talent, CCR reaches out collaboratively to cancer centers, cooperative groups, academe, and industry, working together toward a shared vision for 2015—the elimination of suffering and death caused by cancer.

Dr. Andrew von Eschenbach
Director, National Cancer Institute

Letter from the Director

The Center for Cancer Research (CCR), the basic and clinical research arm of the National Cancer Institute's intramural program, is a distinctive and effective community of scientists who integrate basic research discovery with the development of novel interventions against cancer and AIDS. Based in Maryland, on the Bethesda and Frederick campuses of the National Institutes of Health, CCR is home to a critical mass and a 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. Our efforts already have produced many new drugs and technologies that are improving the lives of Americans and rapidly advancing research, providing hope for the future.

Our distinguishing strengths span several key areas, including immunotherapy, molecularly targeted therapies for cancers and viruses, and vaccines against cancer and HIV/AIDS. We are developing strategies 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.

Our distinctive infrastructure enables us to be innovative and agile in our research. Here, talented scientists continuously invent new tools or harness existing ones to translate our discoveries about the nature of cancer and its progression into workable solutions aimed at intervening earlier in the cancer process. Using cutting-edge technologies-functional imaging, genomics, proteomics, and new approaches to drug development-our researchers are able to drive their discoveries from the bench, to early phase clinical studies, all the way to a benefit for cancer patients. Our scientists are encouraged to pursue high-risk research that we believe will make a major impact, but may be too difficult or risky for industry or academia to undertake.

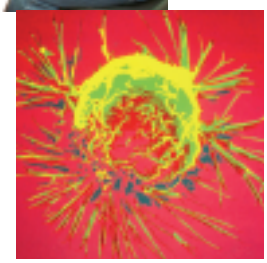
At CCR, we foster a collaborative environment. Our structure promotes and encourages multidisciplinary research teams in which each scientist brings his or her sophisticated expertise to bear upon the complex problems we face in cancer. We leverage our collective strengths to advance our understanding of cancer and HIV/AIDS. Through our Centers of Excellence, we have created focal points for integrating outstanding basic and clinical research, often in collaboration with researchers across the globe. Our newly established Center of Excellence in Immunology, for example, brings our researchers together with world-recognized exceptional extramural talent in immunology to discover and develop new immune-based therapies for the treatment of cancer. The Lymphoma and Leukemia Molecular Profiling Project is another collaborative approach that brings national and international scientists together to speed discovery in the promising area of patient profiling—constructing individual molecular snapshots of a patient's cancer that may then inform the choice of a most appropriate therapy. In neurobiology, the Glioma Molecular Diagnostic Initiative enables CCR oncologists and NCI Cooperative Groups to collect, study, and share glioma tissue samples and data analysis. In pediatric oncology, similar collaborations are under way for rhabdomyosarcomas.

I am extremely proud of the basic and clinical teams of scientists in CCR. This booklet enables me to share with you what I witness every day and what translates into a substantive return on the nation's investment in cancer research. The following pages provide glimpses of our patient-focused pursuit of cancer; they showcase several of our major accomplishments and demonstrate our longstanding commitment to excellence and integrity in research. We plan to build productively upon this strong foundation in the years ahead and will continue to share news of our progress with the scientific community and the American people.

Robert H. Wiltrout, PhD.
Director, Center for Cancer Research
National Cancer Institute
National Institutes of Health
Department of Health and Human Services

Introduction

The CCR promotes a collaborative research environment, which is integral to accelerating scientific progress.



HISTORY

The National Cancer Institute (NCI) was the first Institute created at the National Institutes of Health (NIH) in 1937. Its intramural research team assembled in 1939 through a merger of the Office of Cancer Investigations at Harvard University and a Washington, D.C.-based pharmacology division of the NIH. Both labs relocated to Bethesda. In 1948, the NCI was organized into three units: cancer control, intramural research, and extramural research. Soon after the National Cancer Act was signed into law in 1971, empowering NCI leadership to direct the National Cancer Program, the intramural program expanded under the Division of Cancer Treatment. Then, during a major reorganization of NCI in 1996, two new intramural divisions arose: Clinical Science and Basic Science. In 2001, these two Divisions merged into today's Center for Cancer Research, where basic and clinical science are seamlessly integrated with a mission to reduce the burden of cancer through exploration, discovery, and translation.

VISION

At CCR, we envision providing all cancer patients better options for cancer prevention, detection, diagnosis, and treatment. We focus on basic, translational, and clinical research with potential for yielding seminal discoveries in our pursuit of cancer. We translate novel therapies, approaches, and technologies into effective care for the patients in our clinical trials. We deliver our discoveries as meaningful advances that improve public health. We strive to see that all who could possibly benefit from participation in our early phase clinical trials are able to do so. As advances are made in our studies, we communicate them quickly and encourage broad incorporation across the oncology community to ensure better care for all patients. These efforts, and the dedication of purpose that drives our vision, will continue to be hallmarks of our work.

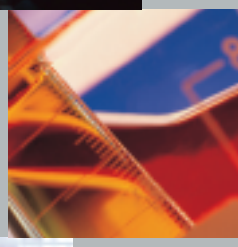
VALUES

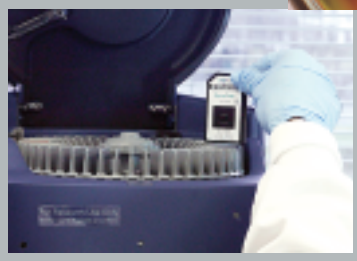
A commitment to scientific excellence and integrity serves as CCR's foundation. This sense of obligation is held individually and reflected collectively as we strive to fulfill our purpose in addressing emerging needs within cancer research in this country. We are committed to making meaningful progress solely for the greater public good—compassionate and effective care for all cancer patients.

CULTURE

The CCR promotes a collaborative research environment, which is integral to accelerating scientific progress. Our focus areas give us the flexibility to reassess and respond rapidly to emerging scientific needs and opportunities, leveraging the strengths of experts from diverse fields. This approach enables us to complement and interface with the activities of the extramural cancer research community. We are well poised to tackle complex scientific questions related to cancer and generate answers that will ultimately benefit patients and the public.

Doing Science at the CCR





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*

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."

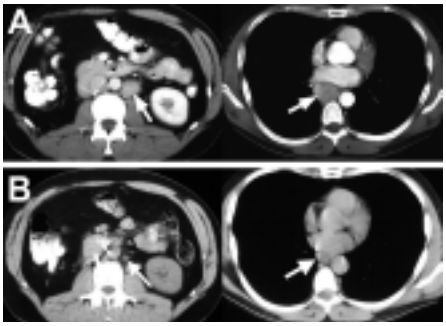
Thomas Waldmann

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'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.

VHL Gene Discovery Opens Door to Much More

During the past two decades, CCR researchers have made seminal discoveries about the genetic basis of kidney cancer



Serial Radiographs of a Patient Treated with High-Dose Bevacizumab, an anti-angiogenesis agent.
Panel A shows the pretreatment assessment (arrows indicate lymph-node metastases).
Panel B shows a radiograph obtained two years later, when treatment was stopped during a partial response.
(*N Engl J Med* 349;5 www.nejm.org July 31, 2003)

Once he saw that nearly all kidney cancers produce extra amounts of the angiogenic protein VEGF, CCR researcher Dr. Jim Yang launched the first clinical trial of an anti-VEGF antibody (bevacizumab or Avastin®) in patients with advanced-stage kidney cancer. The phase II trial showed that treatment with bevacizumab slowed tumor growth in these patients, paving the way for further testing of anti-angiogenesis agents in the clinic.

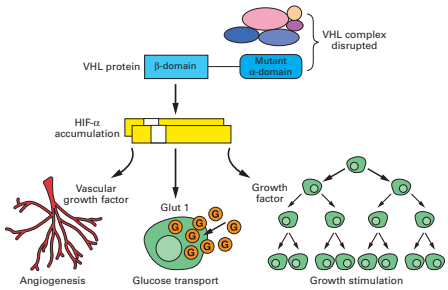
Gene Mutations in Kidney Cancers

Mutated Gene	Discovered	Linked to
VHL	1993	Clear cell renal cell carcinoma
c-Met	1997	Hereditary papillary renal carcinoma
BHD	2002	Chromophobe renal carcinoma

Their research has led to genetic tests for cancer susceptibility, understanding of molecular pathways in kidney cancer development, and discovery of important new drug targets. This remarkable success story began when NCI researchers observed that a segment of chromosome 3 was lost in the tumor tissue of patients with the most common form of kidney cancer, called clear-cell renal cell carcinoma (cRCC). Hoping to identify the gene responsible for this cancer that strikes more than 32,000 Americans each year, Drs. Berton Zbar and W. Marston Linehan assembled a team of basic scientists, clinicians, nurses, and pathologists. The group came together to study a less-common, inherited form of kidney cancer that develops in people who have von Hippel-Lindau (VHL) disease—an inherited multitumor syndrome. The team traveled around the country collecting blood samples and genealogic records from dozens of VHL families.

Their efforts paid off. They found the VHL gene, a critical tumor suppressor that is mutated in patients with this syndrome. Importantly, finding the VHL gene mutation enabled them to show that the same mutation was also a culprit in the more common, non-inherited kidney cancer, cRCC. The CCR investigators developed genetic tests to screen patients and families for VHL mutations, so that people at risk for the disease could receive counseling and earlier tumor screening.

They also used knowledge of the VHL gene to launch a series of major advances in understanding the molecular mechanisms responsible for kidney cancer, both at CCR and in laboratories around the world. CCR researchers found that mutations of the



Mutation in the VHL gene alters the VHL protein and the VHL complex, allowing HIF-α to accumulate in kidney cancer cells. This change encourages angiogenesis, increases glucose transport, and stimulates cancerous growth.

VHL gene lead to an accumulation of hypoxia-induced factor (HIF), which causes overproduction of vascular endothelial growth factor (VEGF), a protein that promotes new blood vessel formation (also known as angiogenesis) to feed a tumor. Today, agents targeting VEGF, other components of the VHL pathway, and Hsp90 (see page 8), are being tested in patients with kidney cancers at the NIH Clinical Center and in collaborative clinical trials between CCR and institutions in the United States and Europe.

CCR's identification of the VHL gene has led to new advances in other types of rare kidney cancers as well, making CCR a global resource for patients and their families affected by hereditary forms of these rare diseases. Working with scientists globally, CCR scientists have discovered new genes and their pathways, including the genetic changes responsible for Birt-Hogg-Dubé syndrome, hereditary papillary renal carcinoma, and hereditary leiomyoma renal cell carcinoma. Novel, evidence-based therapies for some of these rare cancers have entered clinical trials.

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

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.

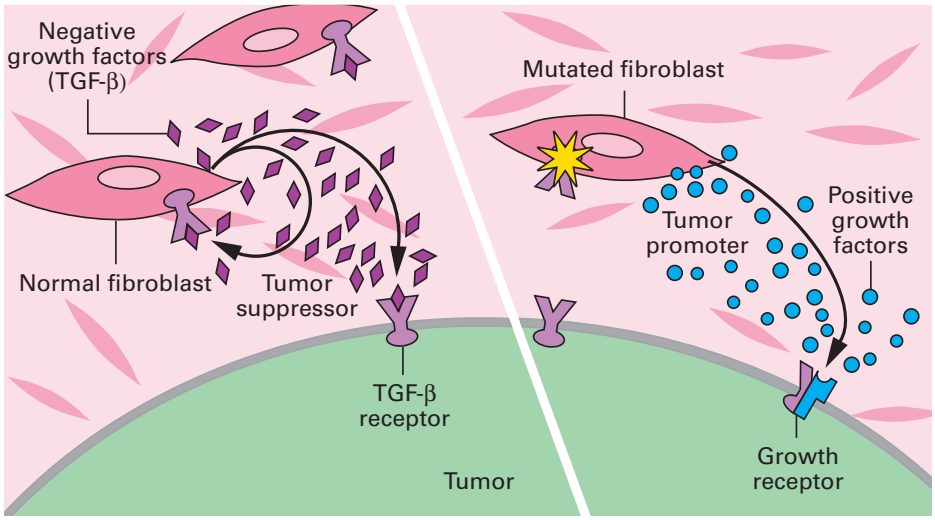
CCR has established a cooperative research agreement (CRADA) with Genzyme Corporation to develop TGF-β antibodies for testing in clinical cancer trials, both alone and in combination with other cancer treatments, such as chemotherapy and cancer vaccines. CCR continues with an active program to target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

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.

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



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.

Disarming Cancer's Chaperones—Bringing Hsp90 Inhibitors to the Clinic

Development of new cancer therapies at the CCR is no solitary pursuit

CCR's enabling infrastructure, which encourages investigator-initiated research, close ties between basic and clinical scientists, and seamless collaboration of intramural scientists with academia and pharma has produced yet another weapon in the oncologist's arsenal. Hsp90 inhibitors are emerging as a truly unique class of anticancer agents.

CCR researchers often collaborate with investigators at universities and cancer centers as well as with biotech and pharmaceutical companies. Each brings unique capabilities to design and move novel therapies into early phase clinical trials. The development of Hsp90 inhibitors illustrates this cooperative approach to drug discovery and development at the CCR.

Heat-shock protein 90 (Hsp90) is known as a molecular chaperone. In normal cells, it protects signaling proteins from damage by environmental stresses, including heat, chemotherapy, and radiation. During chemotherapy, but even in its absence, cancer cells are particularly dependent on Hsp90 for their growth and survival as this chaperone folds and protects from destruction several mutated proteins along with key signaling proteins. A drug that could inhibit Hsp90 would leave a cancer cell's signaling proteins vulnerable to breakdown and potentiate cancer cell death.

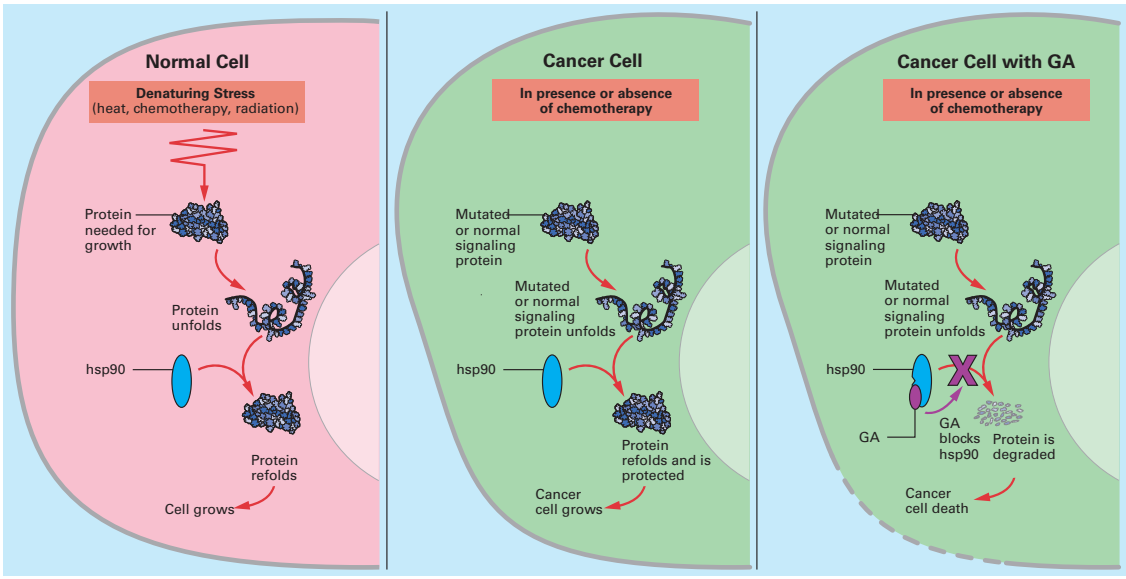
In the early 1990s, CCR scientist Dr. Len Neckers observed that an antibiotic called geldanamycin binds Hsp90, pulling it from its chaperone duties and exposing its bound proteins to degradation, resulting in cell death. Aware that Hsp90 was overexpressed up to 10-fold in cancer cells, Dr. Neckers immediately recognized the potential impact of his discovery for cancer patients. He turned his attention to better understanding the mechanism of action of Hsp90 in normal and cancer cells.

The geldanamycin in these experiments possessed antibiotic and antitumor effects, but was considered too toxic to use in patients. Undaunted, Dr. Neckers partnered with his neighbors in NCI's Developmental Therapeutics Program and the Cancer Therapy Evaluation Program to design geldanamycin derivatives that would preferentially kill tumor cells and be more tolerable to patients than geldanamycin itself.

Two analogs were selected and are being developed by the NCI in collaboration with Kosan Biosciences, which is producing the drug for clinical evaluation. Both agents (17-AAG and 17-DMAG) have shown antitumor activity in animal models of human

FDA-Approved Drugs Developed by NCI

Drug/Manufacturer	Use
Taxol® Bristol Myers Squibb	Treatment of cancerous tumors (e.g., breast and ovary)
Fludara (2-F-araA) Berlex Laboratories	Cancer chemotherapeutic drug
ZEVALIN® Coulter Corporation/ IDEC Pharmaceuticals	Treatment for non-Hodgkin's lymphoma First radioimmunotherapy approved by the FDA
ZENAPAX® Protein Design Labs/ Hoffman LaRoche	First humanized monoclonal antibody approved for transplantation
Kepivance™ Amgen, Inc.	Treatment to reduce the incidence and duration of severe oral mucositis
Vitravene® Isis Pharmaceuticals, Inc.	First antisense therapeutic approved for use in humans
Velcade® Compositions Millennium Pharmaceuticals/ Ortho Biotech	First proteosome inhibitor to be approved by the FDA
AIDS Test Kit nonexclusively licensed to multiple companies	First kit for detection of antibodies to HIV-1
Didanosine Delayed-Release Capsules Barr Laboratories	Treatment of HIV infection with ddI
Hivid® Hoffmann LaRoche	Treatment of HIV infection with ddC
NeuTrexin® MedImmune Inc.	Anti-parasitic agent that treats infection
Videx® Bristol Myers Squibb	Drug selectively inhibits HIV replication



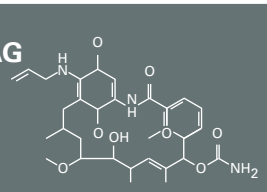
Cancer cells depend upon Hsp90 to protect mutated proteins from degradation.

cancers and are moving through twenty Phase I and II clinical trials at the NCI, the National Institute of Allergy and Infectious Diseases, several NCI-supported Cancer Centers, as well as at the Royal Marsden Hospital in the UK. In about half the Phase II trials, the analogs are being tested alone against cancers in which one or more Hsp90 client proteins are thought to play significant roles, such as cancers of the ovary, kidney, breast, and metastatic melanoma. Early results have been promising. Dr. William Figg, in CCR's Medical Oncology Branch, has established a cooperative research and development agreement (CRADA) with Locus Pharmaceutical to develop a new class of inhibitors based on the crystal structure of Hsp90. Several biotech companies have begun developing their own Hsp90 inhibitors as well.

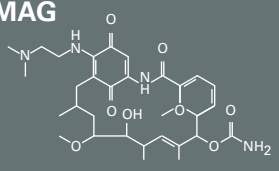
In the other half of the Phase II trials, 17-AAG is being tested in combination with nine different anticancer drugs or radiation therapy to enhance tumor cell killing in certain leukemias, multiple myeloma, and advanced solid tumors. The rationale for combination chemotherapy or a multimodality approach to treatment is based on scientific evidence. For example, radiation has been added because Dr. Neckers and Dr. David Gius found that treating cervical cancer cells with 17-AAG and exposing them to radiation alters Hsp90 function and results in greater tumor death than radiation alone. Similar independent cell studies of 17-DMAG by Drs. Kevin Camphausen and Philip Tofilon also showed enhanced tumor cell killing from a combination with radiation.

CCR's enabling infrastructure, which encourages investigator-initiated research, close ties between basic and clinical scientists, and seamless collaboration of intramural scientists with academia and pharma has produced yet another weapon in the oncologist's arsenal. Hsp90 inhibitors are emerging as a truly unique class of anticancer agents.

17-AAG



17-DMAG



CCR's Partners in Development of Hsp90 Inhibitors

Three major CCR programs—UOB, MOB, ROSP—partnered with DCT, CTEP, NIAID, Mayo, Memorial Sloan Kettering CC, Wayne State U, U of Pittsburgh, Ohio State U Hospital, Washington U School of Medicine, Royal Marsden Hospital-UK, COG

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 translational 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, translational, 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 vaccine in a patient with breast cancer. *Photo credit: Rhoda Baer*

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

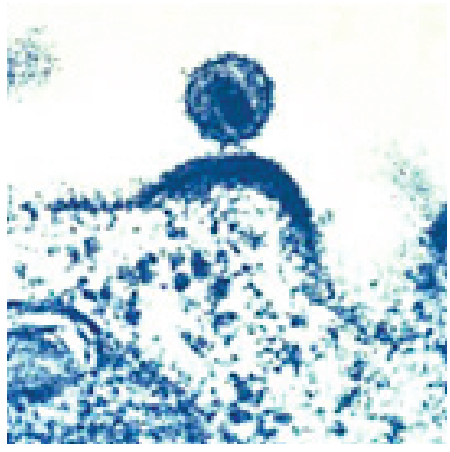
UNDERSTANDING of how HIV infects a cell

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.



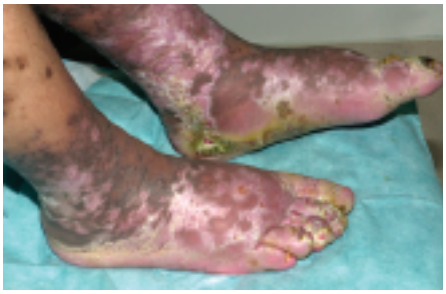
The virus that causes AIDS is shown budding out of a human immune cell.

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 RT 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

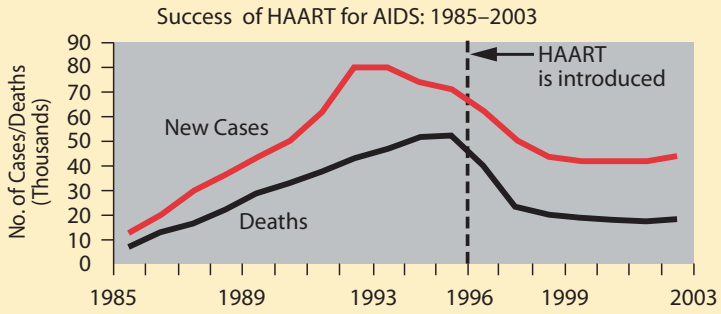
Uganda. As part of its long-term commitment to reducing the cancer burden for medically underserved populations worldwide, CCR researchers are developing new treatments for KS based on developing knowledge of how the Kaposi's sarcoma herpes virus (KSHV) causes the disease. Drs. Richard Little and Robert 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 anti-viral and other approaches for these AIDS-associated cancers.

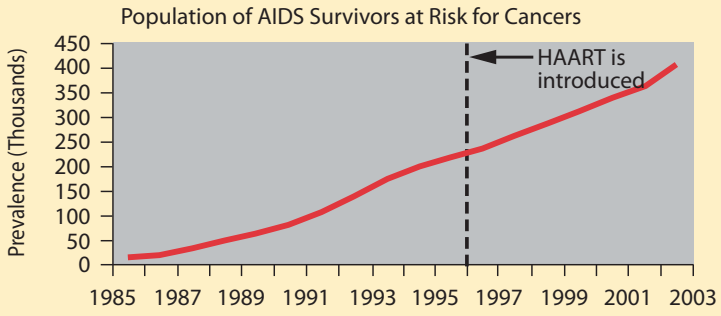


Kaposi sarcoma lesions most often develop in the patient's feet because they are often hypoxic (low oxygen). This condition induces replication in KSVH-infected cells.

Yesterday's Achievement



Today's Challenge

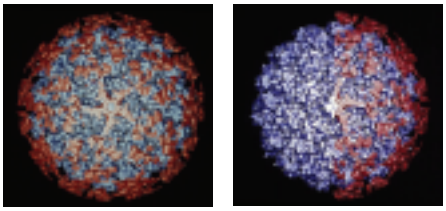


NCI'S AIDS VACCINE PROGRAM

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.

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



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.

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 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.

Compassionate Care for Rare Diseases, Rare Cancers

Xeroderma pigmentosum (XP) is a genetic condition that occurs in about 1 in a million people. It causes sensitivity to ultraviolet light and increases susceptibility to skin cancer-about 1,000 times the normal risk. CCR's Dr. Kenneth Kraemer has studied DNA repair abnormalities in people with XP for more than three decades. His laboratory has developed assays to measure DNA repair in human cells and has provided strong evidence that faulty DNA repair genes play a major role in the UV-caused skin cancer that occurs frequently in patients with XP. Through studies with XP patients at NIH, Dr. Kraemer found there are a number of different DNA repair genes responsible for this disorder. He has begun a molecular epidemiology study with scientists in NCI's Division of Cancer Epidemiology and Genetics to examine changes in the cancer risk from environmental exposures for carriers who appear normal yet have mutations in XP DNA repair genes.

Dr. Kraemer's work on XP is proving important to research on how human genes repair errors and to the study of skin cancer in the general population as well. His lab has demonstrated that as people in the general population age, their bodies are less able to repair UV-damaged genes. This inability may play a role in the higher incidence of UV-induced skin cancer as people pass age 50. In research with collaborators at M.D. Anderson Cancer Center in Houston, Dr. Kraemer found that a variation in one of the DNA repair genes occurs in 40 percent of the population. People who have this variation have an increased risk for a type of skin cancer called squamous cell cancer of the head and neck.

Over the past several decades, the Kraemer lab has collected cells from many XP patients who have come to NIH for help. By establishing cell lines from these patients and making them widely available, the Kraemer lab enables others to study these rare genetic conditions. The cell lines can be obtained through the NIH-supported NIGMS Human Genetic Mutant Cell Repository (http://locus.umdnj.edu/nigms) and the NIA Aging Cell Repository (http://locus.umdnj.edu/nia). Over the past 5 years, nearly 1000 shipments of these cells went to investigators worldwide.

Patients 9-year-old Ally Sufian and 11-year-old Emmanuel Tenga (front and center) traveled to NIH all the way from the Mwereni Annex School for the Blind in Moshi, Tanzania with their guardian Dastan Anthony (front, far right). They are receiving treatment for xeroderma pigmentosum, a rare disease that causes their eyes and skin to be damaged easily by the sun. Dr. Ken Kraemer (far right, back row) and his CCR team provided these two young patients free care, including specialized evaluations and treatments. *Photo credit: John Crawford*

Ally's caretaker puts salve on his hand, so he can apply it to his lips. *Photo credit: Bangor Daily News-Denise Farwell.*

ADDRESSING RARE CANCERS

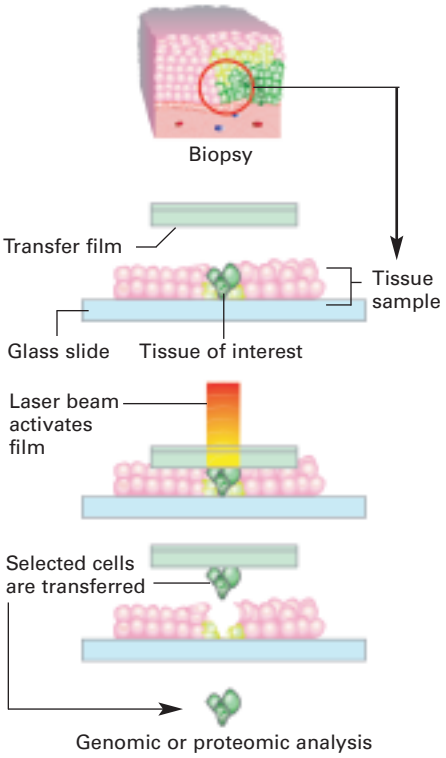
In addition to treating rare diseases, CCR's translational research teams also try to improve the detection, diagnosis, and treatment of rare cancers.

By applying advances in proteomics technology, CCR researchers have devised better prognostic tools for a rare childhood cancer called rhabdomyosarcoma (see page 25). Using their expertise in immunology, they have developed important new treatment options for hairy cell leukemia, a rare cancer (see page 11).

Exporting CCR Inventions

CCR scientists have created technologies to accelerate our capacity to prevent, detect, treat, and cure cancer

Laser-Capture Microdissection



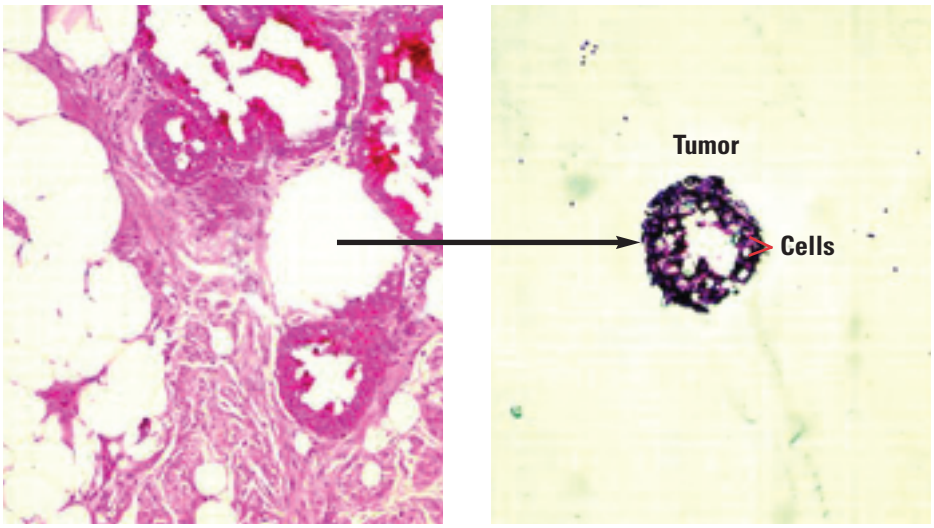
The technologies described on this page are used worldwide and are some examples of CCR's commitment to advancing cancer research through innovation and sharing of new technologies.

Innovations initiated at CCR in tumor pathology, molecular biology, and cytogenetics have contributed to oncology research in several ways. CCR rapidly deploys new technologies to the broader scientific community and provides training in these techniques. Often, CCR inventions are refined in collaboration with extramural engineers and biotechnology companies through licensing agreements. Three examples of inventions from the CCR are highlighted below.

Zeroing in on the Right Cells—Laser-Capture Microdissection

In 1996 Drs. Lance Liotta (now at George Mason University), Robert Bonner, and Michael Emmert-Buck invented laser-capture microdissection (LCM) to rapidly and precisely select specific cells from a biopsy sample. Diseased cells in a tissue sample are surrounded by a mixture of cell types, and isolating the target cells was a long-standing problem in pathology. However, LCM—using a low-energy laser beam and special transfer film—isolates normal, precancerous, and cancer cells for analysis and leaves behind unnecessary cellular information. Today, LCM is a well-established tool used throughout the world. The capacity to isolate molecules from a precise cell of origin has opened a floodgate of discoveries in genomics, functional genetics, and proteomics. In clinical trials, the technology is being applied to tissue biopsies obtained before, during, and after experimental therapy to determine the therapy's impact as early as possible. CCR makes state-of-the-art LCM instrumentation, technical support, and training available to NIH researchers and to researchers worldwide.

LCM selects a pure sample



In 1996 Drs. Lance Liotta, Robert Bonner, and Michael Emmert-Buck invented laser-capture microdissection (LCM) to rapidly and precisely select specific cells from a biopsy sample.

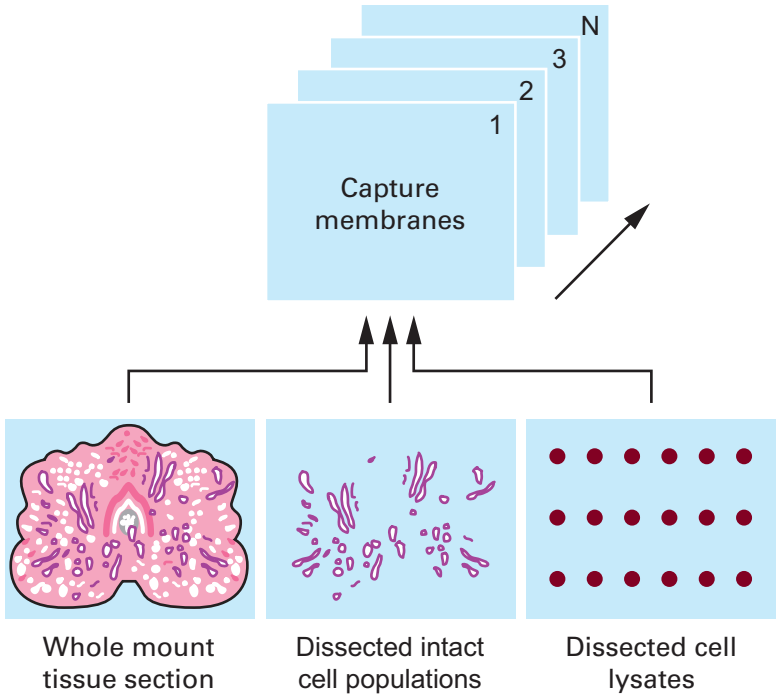
How to Profile Interacting Tissue Types—Layered Expression Scanning

Once they were able to segregate cell types with precision using LCM, CCR scientists wanted to be able to measure the molecular profile of each cell type in a tissue section, and they wanted a profile that preserved the two-dimensional relationship between interacting cells. Dr. Michael Emmert-Buck envisioned that such technology could enable an integrated genomics and proteomics analysis of tumor and normal tissue samples. Convinced that this technology would accelerate the identification of molecular targets, Dr. Emmert-Buck invented Layered Expression Scanning (LES) in 2000. This new technology uses a layered array of membranes coupled to antibodies, peptides, or DNA sequences that can capture targeted proteins, antibodies, or mRNAs as they cross the membranes.

Adding a Rainbow of Detail to Chromosome Viewing—Spectral Karyotyping (SKY)

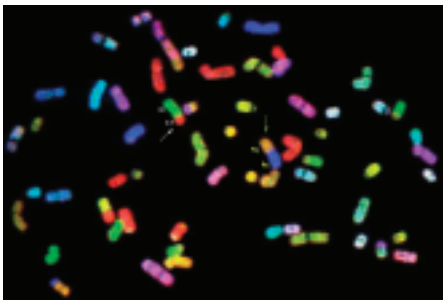
In 1996 Dr. Thomas Ried invented spectral karyotyping (SKY) and revolutionized the process of karyotyping. SKY translates computer-gathered light waves into a full-color palette and assigns each chromosome its own distinct hue. With all 23 pairs of human chromosomes identified by a different color, scientists can more easily examine the entire group of chromosomes for changes that could be associated with disease, such as missing or extra pieces of genetic material, or exchange of genetic material between chromosomes. Before this invention, karyotyping distinguished chromosomes using shades of gray--a much less effective approach. Dr. Ried has trained and collaborated with researchers in the United States and abroad to expand the use of this valuable method.

Layered Expresses Membranes



Spectral Karyotyping (SKY)

Karyotype of a normal cell.



SKY analysis of chromosomes prepared from a BRCA1-mutation associated breast carcinoma. Note that numerous chromosomes are involved in rearrangements, including chromosome breaks and chromosomal fusions. This pronounced genetic instability is a hallmark of BRCA1-associated cancers.

SKY translates computer-gathered light waves into a full-color palette and assigns each chromosome its own distinct hue. With all 23 pairs of human chromosomes identified by a different color, scientists can more easily examine the entire group of chromosomes for changes that could be associated with disease, such as missing or extra pieces of genetic material, or exchange of genetic material between chromosomes.

Investigating New Approaches: RNAi

Thousands of genes can be studied simultaneously using RNA interference

RNAi IS BEING USED TO:

- identify and validate new anticancer targets
- delineate pathways involved in cancer and related processes
- run high-throughput screens for drug discovery
- explore mechanisms of action of drugs
- generate new cell and animal models

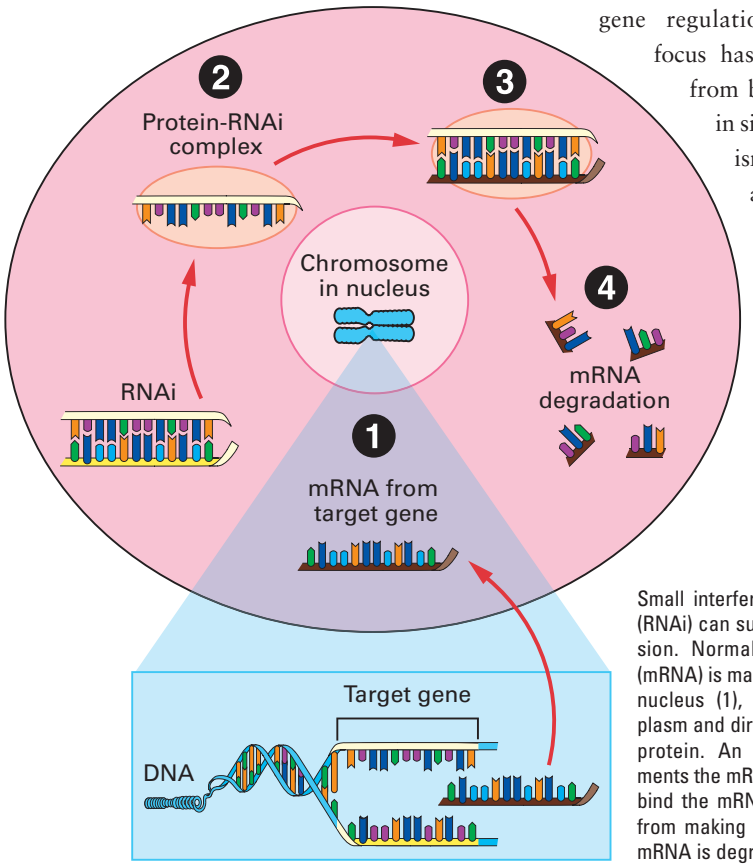
Thousands of genes can be studied simultaneously using RNA interference (RNAi) a powerful technique to silence gene expression. With RNAi technology, experiments that once took months or years are now performed in days or weeks. From an evolutionary perspective, this new technology exploits a cellular defense mechanism that recognizes and degrades the RNA of invaders such as viruses.

In addition to using RNAi technology as a tool to understand the regulation of gene expression and DNA repair, CCR researchers also explore cellular small RNAs directly to see how they contribute to gene regulation. CCR's dual focus has evolved directly from basic explorations in single-celled organisms. A few years ago, CCR's Dr. Susan Gottesman was exploring Escherichia coli bacteria as a model to develop methods to detect and characterize the function of small RNAs in gene regulation. She discovered the important ability of these small molecules to interact with specific protein-encoding RNAs and alter their regulation during stress responses and normal cellular metabolism.

Extending the findings of Dr. Gottesman and others, Dr. Shiv Grewal, who joined CCR in 2003, showed that short interfering RNAs seem to be equally critical regulatory molecules in the more complex cells of animals and plants. As a researcher at Cold Spring Harbor Laboratories, Dr. Grewal unveiled the role of RNAi in shepherding certain types of chromosomal complexes, called heterochromatin, to their correct places in the nucleus. His research achievement was selected as "Breakthrough of the Year 2002" by Science magazine. The link between RNAi and chromatin assembly has broad implications for genome organization and structure in organisms as distantly related as the fruit fly and humans.

RNAi technology has become a popular research tool because it allows scientists to discover the molecular effects of modulating expression at the level of individual genes or at the level of a gene cluster, but RNAi and the related small RNAs play equally important roles in vivo as molecular gene regulators.

CCR is making a significant investment in RNAi technology, to speed access, validation, and application of RNAi technologies from their present role as research tools to a possible future use in cancer therapy.



Small interfering ribonucleic acid (RNAi) can suppress gene expression. Normally messenger RNA (mRNA) is made from a gene in the nucleus (1), moves to the cytoplasm and directs the building of a protein. An RNAi that complements the mRNA sequence (2) can bind the mRNA (3) and prevent it from making protein. Instead, the mRNA is degraded (4).

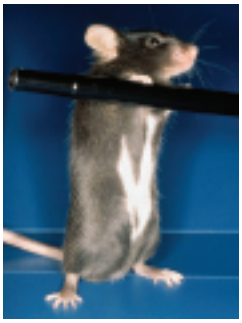
Building Better Cancer Models

CCR scientists are developing several techniques to take full advantage of the value of mouse models in advancing cancer research

Cancer is a genetic disease, so reproducing genetic alterations in mouse models allows scientists to study the impact of a specific change—and in some cases test new treatment approaches. CCR scientists are developing several techniques to take full advantage of the value of mouse models in advancing cancer research.

Recombineering

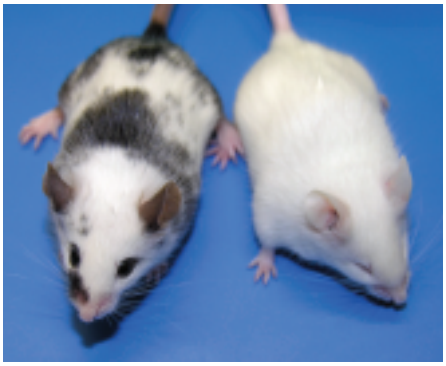
Making a mouse model of human cancer is complicated and labor-intensive, but Drs. Neal Copeland, Nancy Jenkins, and Donald Court have developed a new technology called "recombineering" that reduces the time required from years to weeks and makes genomic studies easier. They combined their expertise in the genetics of bacteria and mice to find a way around the most challenging aspect of traditional animal modeling. This involves "cutting and pasting" the DNA of interest into a form suitable for creating a transgenic mouse, a mouse who genome is altered by the transfer of one or more genes. Their recombineering technology—for recombination-mediated genetic engineering—adopts the strategy used by a virus that attacks bacteria to manipulate the DNA. Recombineering creates very specific gene-targeted mutations efficiently and rapidly and enables manipulation of long sequences of DNA, a major plus for scientists studying how a particular gene cooperates with other genes close by—or far away—to induce cancer. All of the reagents necessary to perform recombineering experiments are freely available from the CCR's Mouse Cancer Genetics Program; hundreds of labs worldwide now use the technique.



This mouse volunteer for recombineering technology helps CCR researchers develop better cancer models.

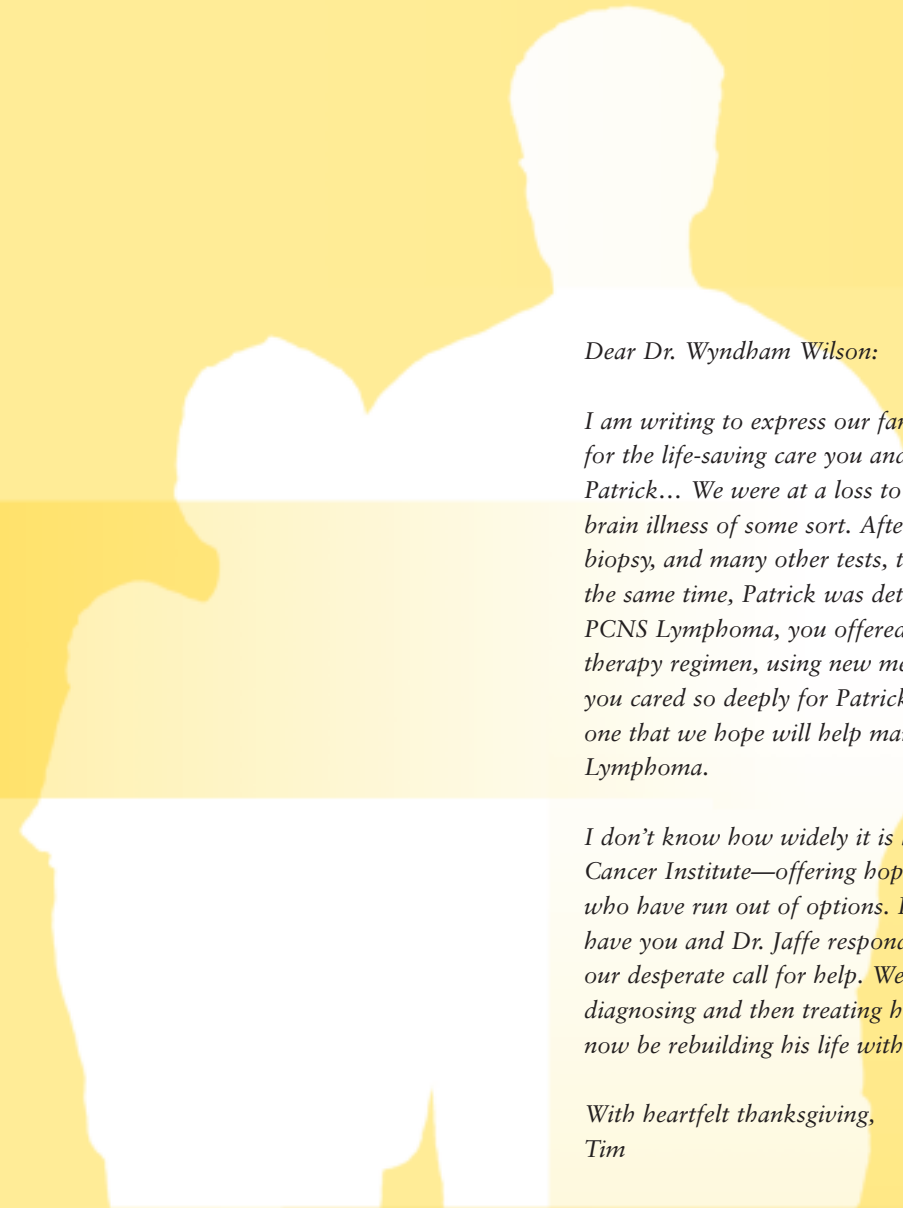
Sleeping Beauty

Drs. Adam Dupuy, Nancy Jenkins, and Neal Copeland recently discovered a new system to speed the way cancer-linked genes are found. The system involves reactivating once highly mobile transposons, genes that millions of years ago jumped from place to place within the genetic material of man and mice, but sit inactive today. Dubbed Sleeping Beauty, the new system reactivates these jumping genes and inserts them into or between genes, where they can turn other genes on or off and alter the amounts of proteins being made. Their discovery was made in mouse models, but researchers expect that the method will provide new insights into human cancer and its vulnerabilities. The Notch-1 gene, which was found in a mouse with T cell leukemia induced by Sleeping Beauty and is mutated in about 50 percent of humans with T cell leukemias, provides a good example how quickly cancer-linked genes can be located and validated in man. The new Sleeping Beauty system will be used to identify additional cancer-linked genes in melanoma, leukemia, lymphoma and in brain and breast cancer, among others.



Induction of a single base-pair change by recombineering in mouse on left partially rescues coat color, eye size, and eye color. Originally, both mice (left and right) were homozygous for a single gene mutation.

Drs. Nancy Jenkins and Neal Copeland

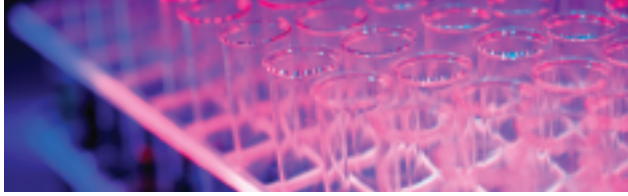


Dear Dr. Wyndham Wilson:

I am writing to express our family's deepest and heartfelt appreciation for the life-saving care you and your team provided for our son, Patrick… We were at a loss to understand what was clearly a serious brain illness of some sort. After weeks of hospitalization, MRIs, a brain biopsy, and many other tests, two top medical centers were stumped. At the same time, Patrick was deteriorating… Having correctly diagnosed PCNS Lymphoma, you offered to develop a state-of-the-art chemo-therapy regimen, using new medications. To us, it is miraculous that you cared so deeply for Patrick as to develop a new protocol for him—one that we hope will help many other young patients facing PCNS Lymphoma.

I don't know how widely it is known that you save lives at the National Cancer Institute—offering hope and treatment to people like Patrick who have run out of options. I will never forget what it was like to have you and Dr. Jaffe respond with such compassionate expertise to our desperate call for help. Were it not for the quick action you took in diagnosing and then treating his PCNS Lymphoma, Patrick would not now be rebuilding his life with a healthy future ahead of him.

With heartfelt thanksgiving,
Tim



From the Director for Clinical Research

The NCI intramural clinical program is an integral component of the nation's overall cancer program. We are the largest cancer-focused clinical research center (CRC) in the world performing patient-intensive clinical research focused on developing new approaches for prevention, diagnosis, and treatment of cancer.

As we move into the future, we will place particular emphasis on testing new science-based hypotheses that intensively study a disease or disease process. In addition, we will maximize our understanding of how to intervene in the disease process by interrogating cell signaling pathways within the body that are implicated in cancer's progression, using genetic, proteomic, and imaging tools.

The NCI clinical program routinely makes long-range commitments of resources to support high-risk, long-term basic and translational research. The close collaborations among scientists with diverse backgrounds enables the NCI clinical program to fuse new technologies with biology, to perform clinical studies that emphasize science-driven trials. Clinical studies are aimed at answering critical questions in a particular disease or disease process, and at identifying promising new therapeutic interventions that can then be confirmed in larger studies carried out at research centers across the country that are part of the NCI-supported extramural program.

Perhaps most importantly, the training programs within the CCR clinical program are dedicated to providing outstanding educational opportunities for the development of strong translational scientists and physician-scientists who can assemble and lead tomorrow's dynamic multidisciplinary teams to advance medical research.

The CCR clinical program is well poised to address the most complex patient-centered questions in cancer research. I look forward to guiding its research in the years ahead.

Lee J. Helman, M.D.
Acting Scientific Director for
Clinical Research
National Cancer Institute
Center for Cancer Research
National Institutes of Health
Department of Health and Human Services

The NIH Clinical Research Center provides the world's largest hospital dedicated solely to clinical research. It houses more than half of the NIH-funded clinical research beds in the United States. In fiscal year 2005, more than 1,000 new patients were enrolled on CCR clinical research protocols. All U.S. citizens are potentially eligible to enroll and are afforded easy, rapid access to the clinical trials process through various patient outreach and support services. Medical care is provided without charge and travel costs are covered for patients enrolled on clinical research protocols. For patients younger than 18 years participating in clinical research studies, parent or guardian travel is provided as well. Patients may also come from around the world to participate in CCR clinical studies of rare diseases or cancers. The Children's Inn and the Edmond J. Safra Family Lodge provide housing next to the Clinical Research Center, so that family members of patients undergoing evaluation and treatment can be near their loved ones.

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.

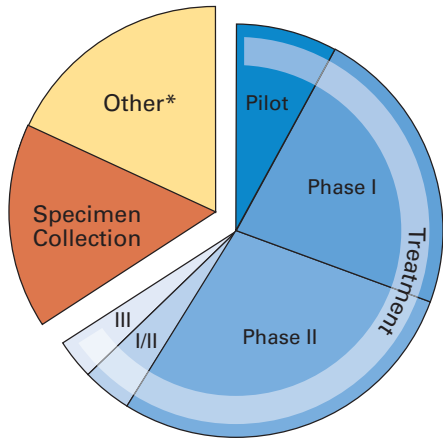
CCR scientists are translating discoveries at the bench into new diagnostic approaches and new targeted therapies, collecting molecular profiles for many cancer types and developing databases that eventually will serve the era of molecular medicine. CCR clinicians use a science-based rationale for treatment 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

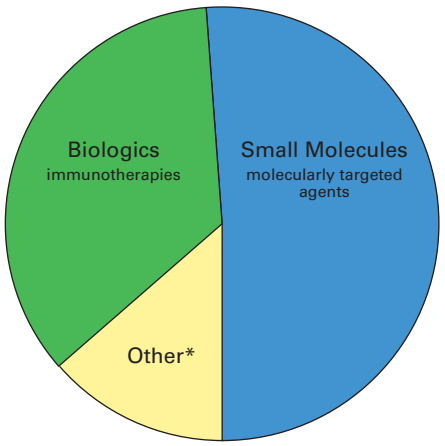


*Natural history, imaging, screening, follow-up, psychosocial, supportive care, epidemiology, surgery

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.

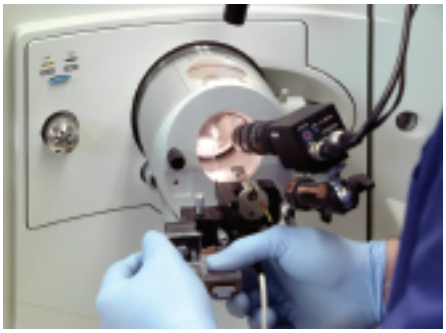
The Phase 0 Initiative

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.

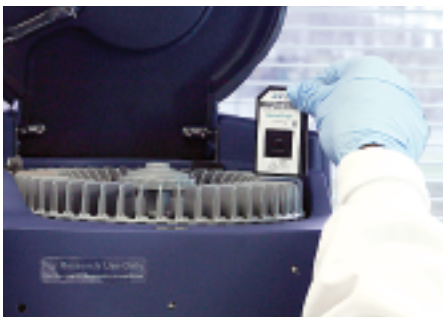
Clinical Trials: From Bench to Bedside

	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.

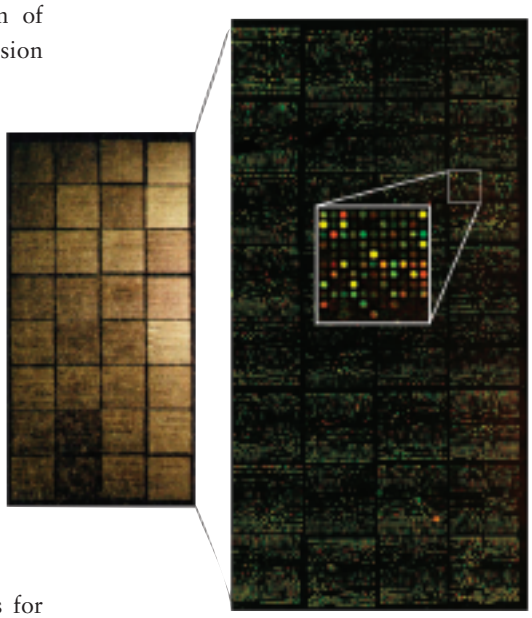
Patient Profiling

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



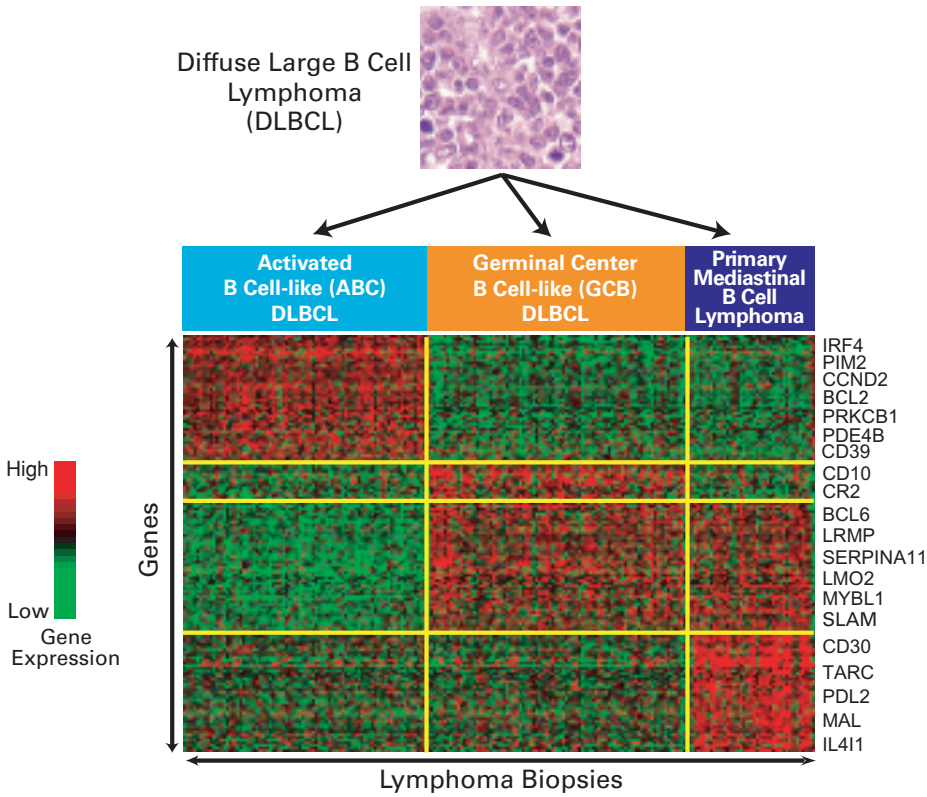
The lymphochip holds small, tethered DNA sequences (cDNAs) of known identity that represent the entire lymphocyte genome. Using complementary DNA binding, CCR researchers use this chip to study the gene expression of thousands of genes simultaneously. In the Lymphoma/Leukemia Molecular Profiling Project, 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.

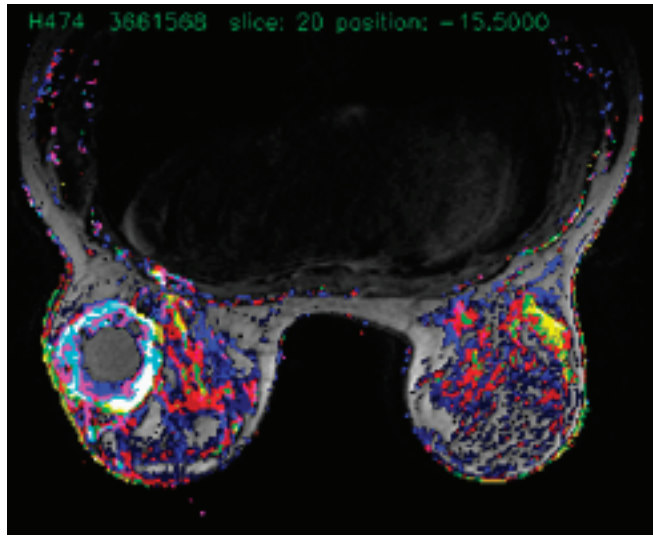
Lymphoma and rhabdomyosarcoma are just two examples of cancers being studied by CCR scientists by using genomic or proteomic profiles of individual tumors. By improving patient profiling, clinicians will be able to make a more accurate diagnosis, prescribe the best treatment, and improve the patient's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

Imaging: In Man, Mice, and Molecules

Using less invasive imaging technology, CCR clinicians visualize physiological processes in living tissue in real time and, with unprecedented vividness and accuracy, examine activities such as blood flow, oxygen consumption, or glucose metabolism as they take place in a cancer patient. New imaging contrast agents such as nanoparticles track cancer cells to sentinel lymph nodes to detect metastasis. Hypoxia is measured and monitored noninvasively in mouse models, and cellular complexes are studied to better define a normal cell. Here are some examples of the role imaging plays in clinical care and research at CCR.

DCE-MRI Captures Microvasculature

Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) generates color maps that reflect the microvasculature of the tumor. In this illustration, DCE-MRI depicts the cancer as a rim of highly vascular tissue.



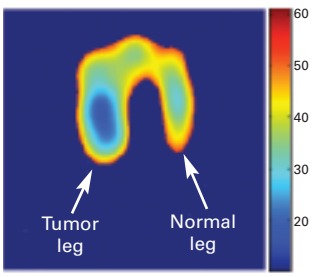
EPRI Noninvasively Measures Hypoxia

The presence of hypoxia (low oxygen) in human tumors points to tumor aggressiveness. Using electron paramagnetic resonance imaging (EPRI) in mouse tumor models, CCR scientists can make real-time noninvasive measurements of oxygen levels.

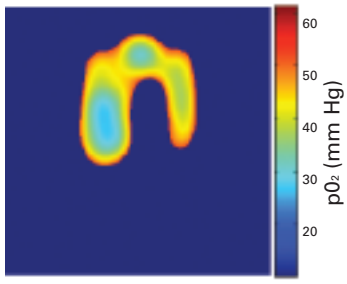
The EPRI AIR image to the left compares oxygen levels in a tumor-bearing vs. normal leg of the mouse breathing normal air. The oxygen level in the tumor-bearing leg is much lower (hypoxia) than the normal one. The HIGH image on the right shows oxygen levels in both legs after the same mouse was switched to high oxygen (carbogen), which increased oxygen levels in both the tumor-bearing and the normal leg.

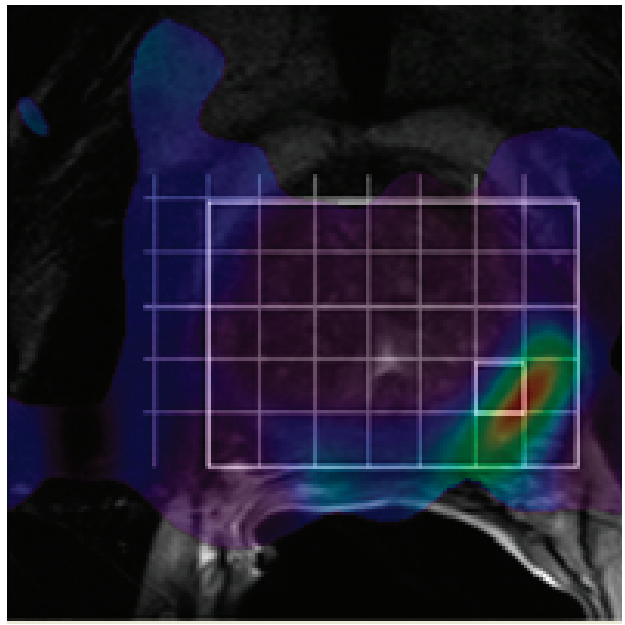
Dr. M. Krishna and RBB team

AIR: 21% Oxygen



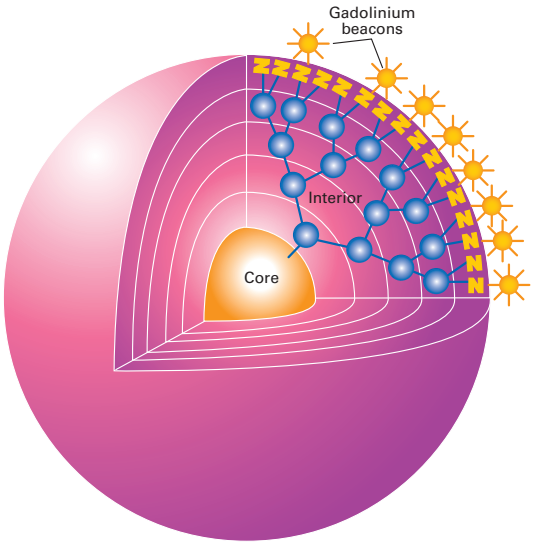
HIGH: Carbogen – 95% Oxygen





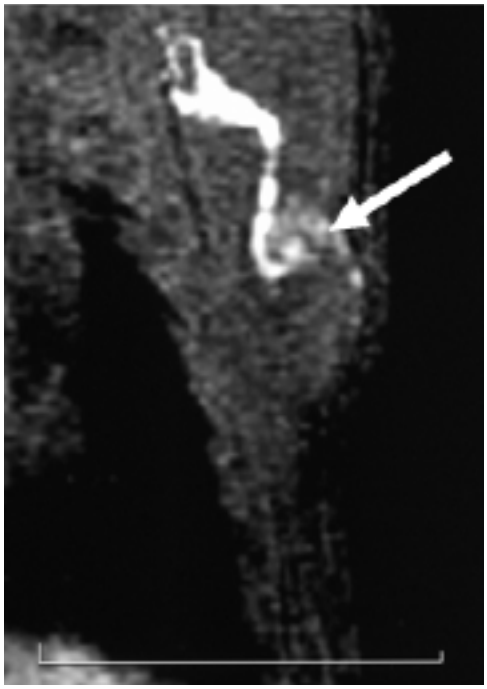
Color Map Implicates Cancer

This is a spectroscopic color map of an MRI of the prostate, showing the relative concentrations of choline and citrate. (Choline is produced by tumors, while normal prostate produces citrate.) In this map, the green/red colors indicate regions with a high choline-to-citrate ratio indicative of prostate cancer.



CCR's Gadolinium-Labeled Dendrimer

Dendrimers are man-made branching nanoparticles about the size of an average protein. CCR scientists attached gadolinium to the surface as a "marker" molecules to "light up" its location.

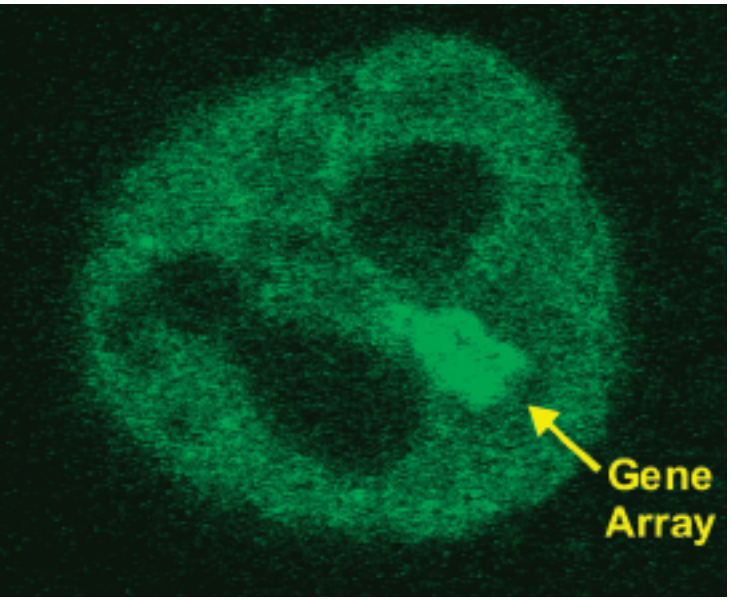


CCR's Dendrimer Detects Metastasis

Evaluation of the sentinel lymph node is a surgical procedure widely used to determine if tumor cells have spread to other sites in the body. CCR investigators hope to spare patients unnecessary surgeries by developing a noninvasive alternative approach.

In this picture, the gandolinium-labeled dendrimer was injected around the tumor, where it then drained away from the tumor through the lymphatic vessels, which appear as a bright white trail. The arrow is pointing to the sentinel lymph node, which is only partially filled with gadolinium because cancer cells have spread to that area, blocking the uptake of the dendrimer.

Drs. H. Kobayashi, P. Choyke, and M. Brechbiel



FRAP Images the Genome

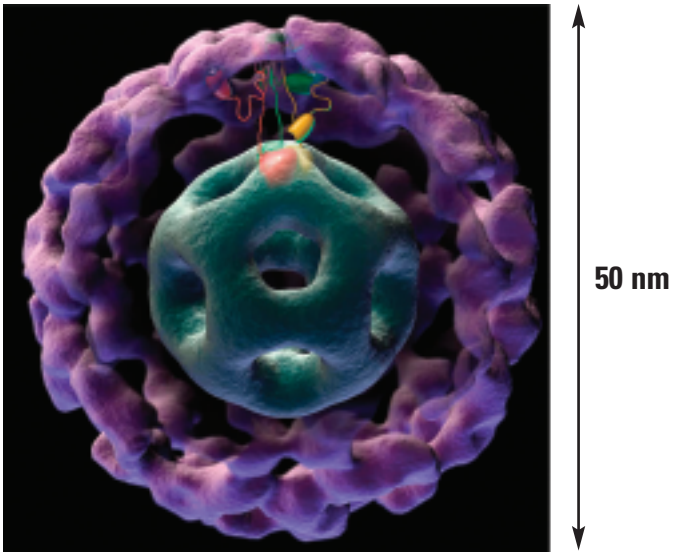
Using a technique called fluorescence recovery after photobleaching (FRAP), CCR scientists observe tagged regulatory proteins called glucocorticoid receptor (GR) molecules as they interact with their target DNA regulatory sites. (The bright green light seen in this photo occurs where they interact). Using this approach, the team discovered that the binding interaction lasts for only a few seconds.

Dr. G. Hager team

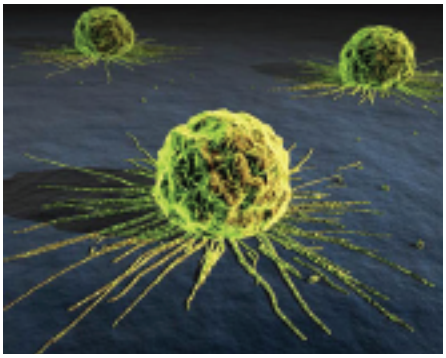
Electron Microscopic Imaging Informs Model

This is an illustration of the pyruvate dehydrogenase complex, a highly efficient cellular machine that is critical to supply cells with energy. Using high-resolution electron microscopic imaging of individual frozen complexes, CCR researchers derived a model to show the positions of distinct components of this machine.

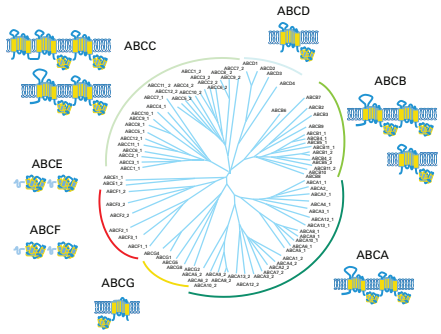
Drs. J. Milne and S. Subramaniam



Unraveling ABC Transporters



CCR researchers are beginning to unravel how cancer cells develop resistance to chemotherapy.



This tree diagram shows the many different ABC transporter proteins that are present in humans. They are organized into seven groups (ABCA-ABCG). Around the outside are examples of the different forms of the transporter proteins in the membrane of the cell. Some transporters act as individual proteins, and other pair up to form an active pump.

For several years, a multidisciplinary team at CCR, including Drs. Susan Bates, Tito Fojo, John Weinstein, Michael Gottesman, William Figg, and Michael Dean, has provided oncologists fundamental knowledge on how cells handle and become resistant to chemotherapy drugs through a phenomenon called multi-drug resistance (MDR). CCR scientists defined and cloned the human MDR1 gene 20 years ago, and showed that it was an energy-dependent pump that actively removes multiple anticancer drugs from cancer cells. Today they are working on several fronts to circumvent or reverse MDR.

MDR1 is now known to be one of 48 ATP-binding cassette (ABC) transporters, a group of proteins embedded in the cell's membrane that regulate traffic of molecules such as hormones, lipids, and drugs, in and out of the cell. Over the years, CCR researchers have discovered 31 of these 48 ABC transporter proteins. Because they transport toxic materials out of cells, mutations in many of these proteins can confer resistance to cancer drugs in humans.

In 2004, Drs. Gottesman, Weinstein and coworkers showed that they could predict drug sensitivity or resistance based upon gene expression profiles of individual ABC transporter genes in cancer cells. Along with the drug resistance they expected to find, CCR researchers were surprised to see that some of the ABC transporters could even increase the effectiveness of a drug. Dr. Michael Dean has gathered the discoveries in this area into a Web-based, searchable, publicly available database (http://www.ncbi.nlm.nih.gov/books), the human ATP-Binding Cassette Transporter Superfamily, which serves researchers worldwide who wish to design novel therapies either to evade or exploit the action of ABC transporters.

Digging more deeply into the effects of specific transporter proteins, Dr. Bates' lab recently cloned the gene for a new ABC transporter, ABCG2, from human cancer cells that are highly resistant to mitoxantrone, an antibiotic used to treat cancer. These studies have led to the indentification and preclinical testing of several inhibitors of ABCG2.

Many genetic variants-called single-nucleotide polymorphisms (SNPs) have also been identified within the ABC transporter genes. CCR scientists are using sophisticated technology to investigate the role of these SNPs. To date genetic variants in 18 of the 48 ABC genes are associated with inherited diseases such as cystic fibrosis, retinal degeneration, and anemia, and many of these discoveries came from the Dean lab.

The Bates' lab recently demonstrated that just a single SNP can change ABCG2's activity and may well alter a patient's response to chemotherapy through cellular resistance or altered pharmacokinetics. With additional research, these data will inform rational drug design of molecularly targeted agents that can prevent drug resistance.

CCR researchers are discovering and validating targets, developing novel agents to impede those targets, and quickly evaluating the new agents in early phase trials that include information on each patient's ABC transporter profile. CCR's long-term focus on multi-drug resistance is moving towards making individualized treatment a reality for cancer patients.

Reducing Cancer's Unequal Burden

Preventive medicine and advances in medical technology have improved life expectancy and overall health for many Americans. However, not everyone is benefiting equally. African Americans, Hispanic Americans, Asian Americans/Pacific Islanders, and American Indians/Alaska Natives continue to face worse outcomes for some cancers, as compared to the U.S. population as a whole. The Center for Cancer Research (CCR) serves the larger NCI effort to meet this public health challenge.

Probing the Biology of Disparities

When African-American women develop endometrial cancer, they experience poorer survival rates than Caucasian women. To study this health disparity at the biological level, CCR investigator Dr. John Risinger collaborated with Dr. Larry Maxwell at the Walter Reed Army Medical Hospital in Washington, D.C. First, the researchers analyzed data from four clinical trials, focusing on the survival rates of African-American women and Caucasian women who had Stage III, Stage IV, or recurrent endometrial cancer. The scientists found that the African-American women had a 25 percent greater chance of dying than the Caucasian women with the same stage of disease. Next, they focused on endometrial cancer tissue samples and compared sets from these two populations that were matched according to stage, tumor grade, and cell type. Comparing gene expression patterns in the two groups, the researchers focused only on matched sets of samples for advanced-stage cancers and observed differences in the expression profiles between African-American and Caucasian cancer patients. The investigators believe that this study demonstrates the complex interplay that exists in individual patients among multiple factors such as genetics, the environment, and culture, all of which may contribute to differences in gene expression. It remains for researchers to determine if expression profile differences among specific cancer patient populations can consistently yield biomarkers capable of informing the design of better therapies for those at higher risk for poor outcomes.

Patient Navigator Academy Workshop

Patient navigation is the support and guidance offered to the cancer patient and their families from the time of "abnormal finding," through the necessary cancer diagnostic tests, to completion of treatment. The NCI funds a number of Patient Navigation Research Programs and Pilot Projects in disadvantaged areas across the United States. Joining NCI in this area, the CCR collaborated with the NCI's Center to Reduce Cancer Health Disparities and the Division of Cancer Treatment and Diagnosis, and together they sponsored the first Patient Navigator Academy in the spring of 2005 at the newly opened NIH Clinical Research Center. The Academy provided NCI-funded patient navigators with an overview of cancer, its treatment and psychosocial impact on individuals, and an overview of clinical trials and resources available to help them access cancer clinical trials. The participants received hands-on training on how to search for appropriate open cancer clinical trials for their patients; they also shadowed a nurse to observe the clinical trials process at NCI.

When African-American women develop endometrial cancer, they experience poorer survival rates than Caucasian women.

A Patient Navigator is an experienced advocate from the patient's community —often a lay person, social worker, or nurse—who helps the patient choose a doctor, arrange transportation, assess treatment options, and see that the patient follows the prescribed care regimen and returns for follow-up appointments.

Countering Cancer's Side Effects

Tempol applied to the scalp before whole brain radiation dramatically reduces hair loss.

For their discovery of KGF that led to Amgen's development of Kepivance, the Rubin-Aaronson-Finch team was among the top-five nominees for the "Inventor of the Year" award from the Intellectual Property Owners Association, and they received the 2005 Mid-Atlantic Regional Excellence in Technology Transfer Award from the Federal Laboratory Consortium.

Kepivance enables this cancer patient to suffer less from mouth sores, a common side effect of high-dose chemotherapy. *Photo credit: Rhoda Baer*

Improving quality of life for cancer patients undergoing treatment is an important part of CCR's commitment to excellence. Research projects to minimize the side effects of chemotherapy and radiation are an integral part of our work.

Preventing Hair Loss From Radiation Therapy

Complete alopecia (hair loss) is a universal side effect of whole-brain radiation therapy. Hair loss can have a negative effect on patient self-image and quality of life, and contributes to anxiety about treatment. Dr. James Mitchell, Chief of CCR's Radiation Biology Branch (RBB), and his team have identified and characterized a new class of antioxidants called nitroxides, chemically stable organic compounds with an unpaired electron. Dr. Mitchell's group has shown they can protect against radiation-induced damage. Preclinical animal studies demonstrated proof of principle that one of the nitroxides, Tempol, could protect against radiation-induced hair loss. A Phase I clinical trial evaluating topical application of Tempol to patients' scalps before they were treated with whole-brain radiotherapy for brain metastases was recently completed. The study showed that Tempol, applied this way, protected against hair loss and was safe and well tolerated. Encouraged by these results, a Phase II study is currently under way to evaluate an improved gel formulation of Tempol, which is expected to provide better protection because of a more uniform application of the drug to the scalp.

Preventing Oral Mucositis

Many cancer patients who are treated with high doses of chemotherapy and radiation develop oral mucositis (OM). The resulting sores in the mouth can cause severe pain, limit the patient's ability to eat, drink and speak, and increase the risk of serious infection. While physicians have attempted to counteract the effects of OM with painkillers, antibiotics and intravenous replacement of nutrition and fluid, nothing has been available to prevent or reduce the severity of this common complication of cancer treatment-until now.

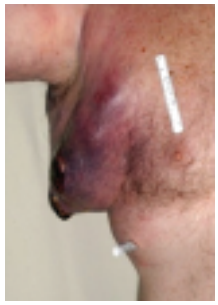
In December 2004, the FDA approved the use of a new drug called Kepivance (palifermin) to treat OM. This new agent evolved directly from the basic research of CCR investigator Dr. Jeffrey Rubin and his former NCI colleagues, Drs. Paul Finch and Stuart Aaronson. Following Dr. Rubin's purification of keratinocyte growth factor (KGF), several studies established that recombinant KGF reduces damage to the mucosa. An intact mucosa, in turn, limits a patient's pain and chance of infection by maintaining the epithelial barrier. In a recent clinical trial, treatment with Kepivance, a modified version of the naturally occurring KGF, decreased the incidence and duration of severe OM in patients with cancers of the blood who were given intensive chemotherapy and radiation prior to bone marrow/blood cell transplants. Patients who received Kepivance reported fewer symptoms of OM, required less pain medication and were better able to eat.

Training T Cells To Attack Cancer

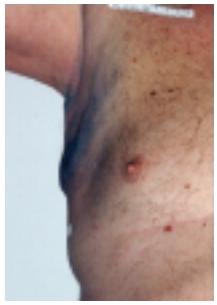
A critical component of the CCR's strength in translational research is an infrastructure that facilitates bench-to-bedside-to-bench research at the clinical center. This environment is enabling CCR's physician scientist Dr. Steven A. Rosenberg to develop and refine an innovative approach to immunotherapy. 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



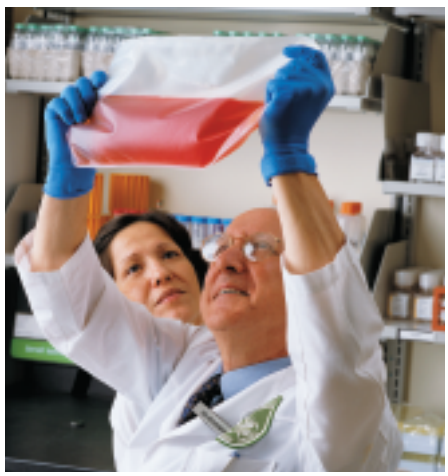
After treatment

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.

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*

Teaching the Art of Inquiry

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

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 translational 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 translational 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.
- **Translational 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

Illustrious Alumnus: Dr. J. Carl Barrett

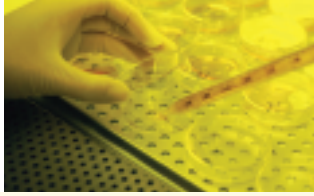
As founding director of the Center for Cancer Research in 2001, Dr. J. Carl Barrett realized his vision for establishing and promoting translational research within the intramural program of the NCI by merging the basic and clinical scientific communities together to accelerate their progress against cancer.

Dr. Barrett provided transformational leadership to the cancer research community and to NCI. Undaunted by the complexity of cancer, he approached the development of the CCR with a vision and a strategic plan. Top scientists have joined NCI's intramural research program in large part out of respect for the scope of Dr. Barrett's inquiry, the depth of his analysis, and his egalitarian management style. Without comprising his staunch support for basic research, Dr. Barrett re-engineered NCI's intramural research program into a translational center of excellence, where clinicians and basic researchers today work side by side for the patient's benefit. His creation of Faculties and Working Groups fostered interdisciplinary approaches to complex problems.

His successful leadership achieved success by adhering to several key principles: strong commitment to basic science exploration and discovery; encouragement of collaboration and partnerships in recognition that complex scientific problems benefit from the contributions of multidisciplinary teams; dedication to excellence in mentoring and training; and promotion of innovation in thought and approaches to unraveling the biology of cancer.

By enabling effective interactions among NCI intramural scientists and investigators in the extramural divisions, in other NIH institutes, academic institutions, and industry, Dr. Barrett has increased CCR's ability to lead within the oncology community.

The importance of mentorship and training as articulated by Dr. J. Carl Barrett continues to be a core value at CCR. This attribute attracts successive generations of able young researchers who help to keep CCR rich in talent and innovation. *Photo credit: Rhoda Baer*



Milestones of NCI's Intramural Research Program 1950s–1990s

DR. ALAN RABSON

Dr. Alan Rabson's 50-year imprint on NCI's intramural research is remarkable. His vision and leadership promoted outstanding science and established excellence in mentorship. And his imprint on CCR and other NCI activities continues today.

A pathologist by training, Dr. Rabson reported to the NIH clinical center in 1955 and never lost his compassion for the patient. Known as the "heart and soul" of NCI, Alan Rabson has served as a constant source of support and inspiration for dozens of staffers, researchers—and patients—who have come through the doors of CCR and the NIH clinical center over the years.

In 1975, he was named Director of NCI's Division of Cancer Biology, Diagnosis, and Centers, where he served until his appointment as NCI Deputy Director in 1995. During his career at NCI, Dr. Rabson held clinical professorships in pathology at Georgetown University Medical Center and The George Washington University in Washington, D.C., and at the Uniformed Services University of the Health Sciences in Bethesda, Md. In 1987, he became a member of the Institute of Medicine.

"Al Rabson embodies the true meaning of research commitment and excellence, always putting NCI, its people, and its mission first."

—Dr. Andrew von Eschenbach
Director, NCI

In 2005, at the annual retreat for intramural investigators, NCI introduced the Alan Rabson Award "in recognition of his dedication and enthusiasm for NCI and its intramural program during his 50-year tenure at NCI." Dr. Susan Gottesman was the first recipient. Dr. Steven Rosenberg will accept the second award in January 2006.

"As my first Division Director, Dr. Rabson provided a nurturing environment for scientific growth, challenged me to look at complex problems in different ways, and through his actions, demonstrated that mentoring and training were among his strongest core values."

—Dr. Robert Wiltrout
Director, NCI-CCR

THE 1950s

NCI's intramural program mounts efforts to understand and combat cancer using chemotherapy. Unlocking of the genetic code launches molecular biology. Researchers explore structures and activities between and within cells and develop sophisticated techniques for growing cell and tissue cultures.

1953 Full-scale clinical research begins in new NIH Clinical Center.

First patient receives hormone treatments for prostate cancer.

First patient admitted to the Clinical Center

1955 Intramural program coordinates first national voluntary cooperative cancer chemotherapy program.

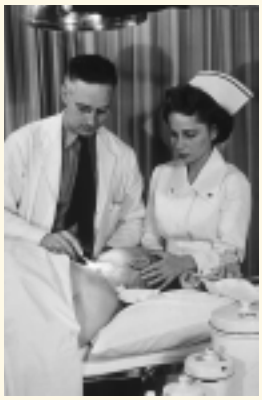
First successful chemotherapy for malignancy

Chemotherapy tests

in a solid tumor. Large doses of methotrexate (a folic acid antagonist), achieves total cure of choriocarcinoma, a rare cancer of the placenta, until then invariably fatal.

First randomized clinical trial for cancer chemotherapy.

Sarah Stewart links viruses and cancer



Surgery

1957 SE polyoma virus demonstration that viruses can cause cancer in animals.

1958 Successful culture of patient's tumor cells for study in vitro.

THE 1960s

Basic and clinical scientists team to improve cancer chemotherapy. Combination chemotherapy is initially scorned. Intramural drug development program evolves. The field of medical oncology emerges. As microscopes improve, viruses—long suspected of causing cancer—become visible. A major NCI virus program opens viral oncology as a fertile area for cancer research.

1961 Viral Oncology lab investigates the relationship of viruses and human cancer.

First successful treatment of acute lymphocytic leukemia (ALL), a childhood malignancy

1962 First task force is launched to tackle acute leukemia.

Frei and Freireich introduce intensive combination chemotherapy against strong resistance from The National Cancer Advisory Board and the scientific community, who call the approach "unconscionable."

1964 First successful treatment of a major systemic cancer—acute lymphocytic leukemia (ALL), a childhood malignancy—with intensive combination chemotherapy.

1965 First use of adjuvant therapy occurs.

H. Stewart and T. Dunn—mouse pathologists

1965 "Life Island" debuts: the first clinically usable germ-free isolated environment for immune-suppressed patients.

NCI clinicians successfully treat an adult tumor—disseminated advanced Hodgkin's disease—with a four-drug combination therapy called MOPP. Successful treatment for Hodgkin's disease leaps to 80 percent survival rate.

1966 Testing of suspected cancer-causing chemicals is standardized.

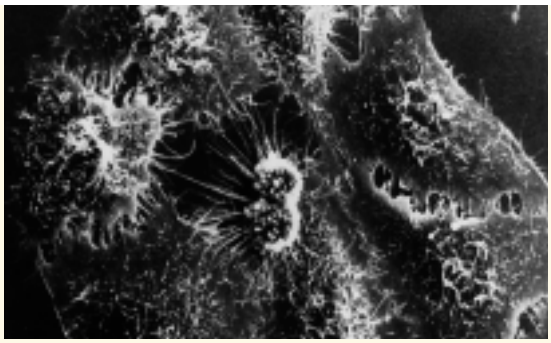
1969 Working in the cancer virus program, Robert Huebner and George Todaro formulate the concept of the oncogene.

Rare autosomal dominant Li-Fraumeni syndrome that predisposes person to cancer is first described.

THE 1970S

The pursuit of cancer intensifies, largely through the efforts of philanthropist Mary Lasker and businessman Benno Schmidt. In 1971, President Nixon endorses a War on Cancer. Advances in research technology enables discovery of the molecular basis of genetic regulation. Recombinant DNA techniques help NCI researchers localize genes and define modes of inheritance. Scientists recognize that cancer involves several genetic changes.

President Nixon endorses a War on Cancer

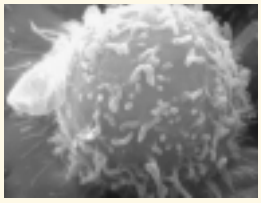


SEM of virus-infected cancer cells

1972 Intramural research wins 10 of 17 Lasker Awards.

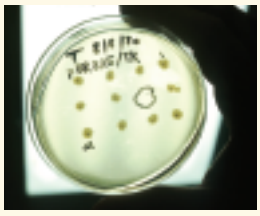
1975 New hybridoma technology produces monoclonal antibodies.

1976 Interleukin-2 (IL-2), a growth factor that stimulates proliferation of T cells is discovered.



EM of lymphocyte

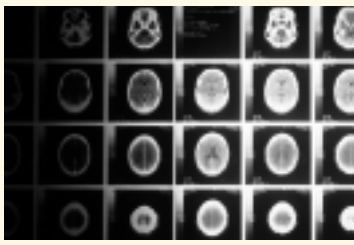
1979 First human RNA virus—human T-cell lymphotrophic virus or HTLV-I is discovered. A related virus, HTLV-2, is isolated from patients with patients with hairy-cell leukemia.



Recombinant technology

THE 1980s

Imaging technologies such as CT, MRI, PET, and ultrasound allow clinicians to visualize tumors or other abnormalities not accessible with a physical examination or with X-rays alone. Geneticists develop new tools for exploring and manipulating DNA. Intramural researchers begin to explore the role of specific cancer-causing oncogenes. Immunologists explore the workings of the immune system and its complex relationship with cancer. Genetic engineering facilitates the study of genes. NCI



CT-scan

plays a critical role in identifying the causative agent of AIDS. Research on cancer and AIDS remain intertwined. Viruses become research tools.

1980 Discovery of HTLV-3, better known as human immunodeficiency virus, or HIV.

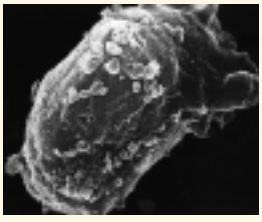
Discovery of receptor for IL-2, and development of a monoclonal antibody that binds to it (anti-Tac).

1981 First AIDS patient admitted to the Clinical Center.

Germ-free room

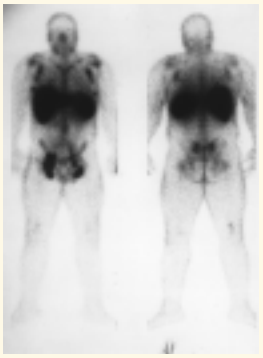
Demonstration of the superiority of limb-sparing surgery to amputation for sarcoma patients.

1984 Lasker Award for fundamental research into the genetics of



Lymphocyte with AIDS cluster

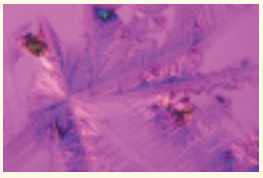
DNA sequencing gel



Use of radiolabeled monoclonal antibodies

immunoglobulin molecules, which paved way for the development of hybridomas and monoclonal antibodies.

1985 First AIDS antibody test is released.



Chemotherapy

1987 Intramural research program develops AZT, the first FDA-approved antiretroviral drug to be used as a treatment for AIDS.

1989 A foreign gene is inserted into human tumor-infiltrating lymphocytes.

THE 1990s

Study of cellular mechanisms leads to recognition that cancer is a disease of genetic instability, with inherited syndromes only accounting for 30 percent of the cases. During this decade of the Human Genome Project and the Cancer Genome Anatomy Project, CCR scientists establish more links between chromosomes, gene mutations, and predispositions for cancer. Genetic variations and post-transcriptional modifications play critical roles in cancer progression.

1990 First gene therapy in a patient occurs. A copy of a normal gene was inserted into a child's white blood cells to reverse her immune deficiency disease (CCR and NHLBI).

Dr. Phillip Pizzo named Washingtonian of year for helping start NIH Children's Inn and Camp Fantastic.

1991 First cancer gene therapy occurs. Two patients receive transfusions of special cancer-killing cells armed in the laboratory with an inserted gene capable of producing tumor necrosis factor (TNF).

Murine anti-Tac, prolongs renal allograft survival in humans.

1992 Intramural research program spearheads development of Taxol (paclitaxel), an anticancer drug extracted from the bark of the Pacific yew. Taxol receives FDA approval for ovarian cancer treatment.

Taxol

1993 Identification of the human cancer gene that is mutated in populations with the inherited cancer syndrome called von Hippel-Lindau (VHL) disease. Discovery that same VHL mutation develops in sporadic (nonhereditary) cases of clear cell carcinoma.

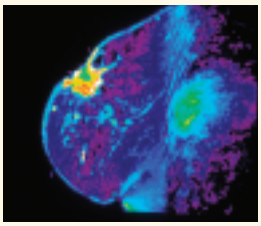
1994 Clinical trials run by the NCI's intramural program at the NIH Clinical Center are posted on the World Wide Web for the first time.

Normal VHL protein function identified as suppressor in tumor development.

1995 A major NCI reorganization adds the Division of Basic Sciences and the Division of Clinical Sciences to the intramural research program.

1996 In partnership with government, academic, and industrial laboratories, NCI launches the Cancer Genome Anatomy Project to assemble the first full index of genes involved in cancer.

1997 Humanized anti-Tac (daclizumab, Zenapax) receives FDA-approval as treatment to prevent human allograft rejection.



Breast MRI

Identification of the gene for the hereditary cancer syndrome, hereditary papillary renal carcinoma: the c-Met proto-oncogene.

1998 CCR radiologists and surgeons develop a Telemedicine approach to support oncology practices in remote areas of the United States and in Europe.

Web Sites With More Information About CCR

CENTER FOR CANCER RESEARCH

http://ccr.cancer.gov

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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NIH Publication No. 06-5736
Printed October 2005