National Cancer Institute

Center for Cancer Research

ADVANCING BASIC, TRANSLATIONAL, AND CLINICAL RESEARCH:

A Strategic Plan for the Center for Cancer Research

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

The Center for Cancer Research conducts and supports research on cancer and HIV/AIDS across an integrated continuum of discovery, development, and delivery.

At the CCR, we leverage our scientific expertise and technological forces with key partners to achieve our vision of conducting basic, translational, and clinical research to prevent, cure, or make cancer a manageable, chronic disease.

Fulfilling our vision requires ingenuity and collaborations across:

- CCR laboratories and branches
- NCI divisions and offices
- Other NIH institutes
- Other Federal agencies
- Extramural laboratories at universities and biomedical research facilities
- Technology companies
- Pharmaceutical companies
- National and international biomedical consortia
- Combinations of the above

Advancing Basic, Translational, and Clinical Research: A Strategic Plan for the Center for Cancer Research is a dynamic document intended to inform, lead, and fuel discovery among CCR investigators and trainees, our colleagues throughout NCI, and the wider biomedical research community.

Advancing Basic, Translational, and Clinical Research:

A Strategic Plan for the Center for Cancer Research

For Internal Use Only

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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A Research Environment that Promotes Progress

Significant progress in cancer research is catalyzed in an environment that integrates basic and clinical research centrally, houses the latest technologies and resources, and promotes creativity, risk-taking, and long-term projects. The CCR provides such an environment. Our faculty of more than 250 principal investigators working on the campus of the National Institutes of Health (NIH) has access to the state-of-the-art NIH Clinical Center as well as the most advanced biomedical technologies and research laboratories available anywhere. Stable funding enables us to perform long-term, high-risk research that may be too complex or challenging for academia or private industry to take on. Our commitment to studying relatively rare but devastating cancers, and cancers predominant in medically underserved populations, has revealed astonishing findings that can also be applied to common cancers. Our ability to quickly redeploy resources to respond to urgent public need or newly identified health threats has led to discoveries in the treatment of cancer and HIV/AIDS. Much of our success is a result of collaborations with researchers in the private and public arenas who build upon the innovative findings made here at the CCR to develop and disperse new therapies to patients worldwide.

"You are given wide latitude on what you work on. The assumption is that you will work on important problems."

—Douglas Lowy, M.D., Chief
Laboratory of Cellular Oncology
CCR (*The Washington Post* 9/10/2007)

Directors' Message

Identifying High-Risk, High-Impact Priorities

Advances in the prevention and treatment of cancer and HIV/AIDS are the result of hard work, patience, ingenuity, careful planning, and significant investments of time and resources. As the National Cancer Institute (NCI) enters its eighth decade, it is clear that those investments have paid off. We now have within our reach both the fundamental knowledge to transform the way we treat and manage disease, and the ability to tackle the challenges that lay ahead, including decreasing the high mortality rates for some types of cancer and bringing more promising discoveries into practical, cost-effective patient use.

Capitalizing on these investments requires looking back at how far we've come and looking forward to identify the areas in which we can do our best work. The Center for Cancer Research (CCR) has made, and continues to make, critical advances in the global understanding of cancer and HIV/AIDS. As part of the NCI Intramural Research Program, the CCR conducts basic, translational, and clinical research—from fundamental research on the origins of cancer, to clinical trials that test promising discoveries, to development of novel therapies and prevention approaches to cancer and AIDS. But we don't do our work alone. Our goal is to work in tandem with our academic and industry colleagues to share discoveries made here as broadly as possible.

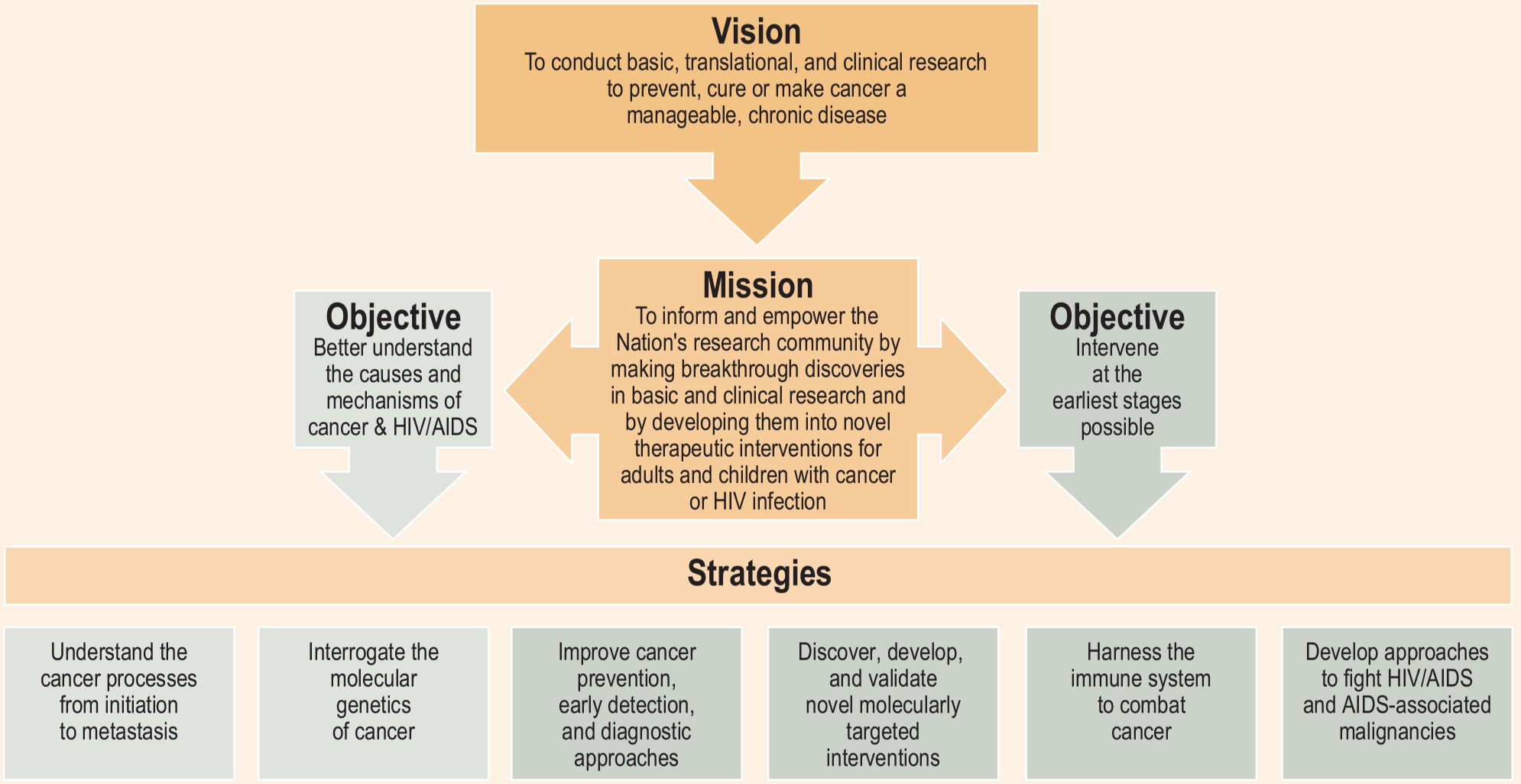
Ushering in a new era in which cancers are prevented or routinely detected at their earliest, most treatable stages, or managed through genetic profiling and other novel approaches, requires us to deepen our understanding of the biology of cancer and translate that knowledge into more effective, less toxic, and better tolerated therapies. Identifying the most promising avenues of research, as well as the greatest challenges, is critical to yielding major returns on our investments in the years ahead.

The CCR Strategic Plan, *Advancing Basic, Translational, and Clinical Research,* contains the most compelling initiatives that the CCR will pursue over the next several years to make this new era in cancer care a reality. Developed by teams of CCR investigators, the plan sets forth six distinct yet highly interrelated objectives that fit squarely within the framework of the current *NCI Strategic Plan for Leading the Nation* and the *NIH Roadmap for Medical Research,* both of which chart far-reaching initiatives to reshape the way medical research is conducted. Like these plans, the CCR Strategic Plan articulates our commitment to deepen our understanding of cancer and HIV/AIDS and deliver effective therapies to improve public health.

It is our hope that each and every scientist, physician, and trainee at the CCR will be inspired to take on the challenges set forth in this plan. Doing so will lead us all toward new insights and research paths that unravel the complexities of cancer and HIV/AIDS and take us in unanticipated and exciting new directions.

Robert H. Wiltrout, Ph.D., Director
Scientific Director for Basic Research

Lee J. Helman, M.D.
Scientific Director for Clinical Research


Vision
To conduct basic, translational, and clinical research to prevent, cure or make cancer a manageable, chronic disease
Mission
To inform and empower the Nation's research community by making breakthrough discoveries in basic and clinical research and by developing them into novel therapeutic interventions for adults and children with cancer or HIV infection
Objective
Better understand the causes and mechanisms of cancer & HIV/AIDS
Objective
Intervene at the earliest stages possible
Strategies
Understand the cancer processes from initiation to metastasis
Interrogate the molecular genetics of cancer
Improve cancer prevention, early detection, and diagnostic approaches
Discover, develop, and validate novel molecularly targeted interventions
Harness the immune system to combat cancer
Develop approaches to fight HIV/AIDS and AIDS-associated malignancies

The Center for Cancer Research

Our Vision

Our vision is to conduct basic, translational, and clinical research to prevent, cure, or make cancer a manageable, chronic disease.

Our Mission

Our mission is to inform and empower the Nation's research community by making breakthrough discoveries in basic and clinical research and by developing them into novel therapeutic interventions for adults and children with cancer or HIV infection.

To achieve our mission, we:

- perform rigorous basic scientific research to discover the causes and mechanisms of cancer and to understand the molecular changes that occur in cancer initiation and progression;
- translate these advances rapidly from the laboratory to the clinic to develop lifesaving and life-prolonging interventions;
- develop innovative technologies that enable earlier and more accurate detection, diagnosis, and treatment;
- maintain a strong focus on rare cancers and cancers in underserved patient populations worldwide;
- share expertise, scientific data, and technologies to broaden the impact of our work and enhance productivity of the cancer research community in the U.S. and abroad; and
- provide an unparalleled scientific environment to cultivate and train the physician-scientists and biomedical researchers of the 21st century.

We are distinctly qualified to fulfill our mission through:

- a focus on long-term, innovative, and high-risk research with the potential for high impact;
- access to the state-of-the-art NIH Clinical Center that enables us to rapidly translate insights between the research laboratory and the bedside;
- committed partnerships between physicians and clinical trial volunteers that help advance research and provide patients with compassionate care and the latest therapies;
- application of findings, from intensified research into special populations and understudied cancers, to both rare and common cancers;
- the use of state-of-the-art technologies to bolster basic and translational research; and
- a distinctive, collaborative culture that catalyzes research advances and fuels additional discoveries to defeat cancer and HIV/AIDS.

The CCR Strategic Plan articulates our commitment to deepen our understanding of cancer and HIV/AIDS and deliver effective therapies to improve public health.

The HPV Vaccine: 25 Years in the Making

When scientists established the link between human papillomavirus (HPV) and cervical cancer in the early 1980s, CCR researchers set off to develop a vaccine against a form of cancer that, at the time, claimed the lives of more than 5,000 American women each year and today kills more than 270,000 women annually, 80 percent of whom live in developing countries. More than 25 years later, the FDA's approval of Gardasil® marked a victory for CCR scientists Douglas Lowy, M.D., and John Schiller, Ph.D., and their colleagues who laid the biological foundation for the HPV vaccine.

A unique feature of HPV is the ability of one of its component proteins, L1, to assemble itself into empty shells called virus-like particles (VLPs). Because they contain no viral genomic material, these particles cannot cause infection on their own. They can, however, mimic the presence of a viable virus and trick the immune system into mounting an anti-HPV immune response. Drs. Lowy and Schiller and their colleagues, in collaboration with the NCI Division of Cancer Epidemiology and Genetics, found that immunization with these L1-based particles could stimulate production of large numbers of antibodies; serum taken from vaccinated volunteers protected cultured cells from HPV infection in the laboratory. NCI licensed the VLP technology to Merck and GlaxoSmithKline (GSK), both of which subsequently developed HPV vaccines for clinical use. Both vaccines protect against HPV types 16 and 18, which cause up to 70 percent of all cervical cancer cases worldwide. Merck's Gardasil® also protects against HPV types 6 and 11, which cause 90 percent of genital warts. In Phase III clinical trials, both vaccines have been close to 100 percent effective at preventing the premalignant cellular changes caused by the relevant virus types. Thus far, in earlier trials, protection has remained solid after four years of followup. However, it appears that the vaccine does not clear HPV infections that have already become established.

The HPV vaccine, for women and girls ages nine to 26 years, was evaluated and approved in six months under the FDA's priority review process, which is used for products with potential to provide significant health benefits. GSK applied to the FDA for approval of its vaccine, Cervarix®, in 2007. Drs. Lowy and Schiller and their colleagues are exploring alternate ways of fighting or preventing cervical cancer, including the next generation of HPV vaccines and topical microbicides that might address some of the significant challenges of delivering a vaccine in the developing countries where it is most needed.

Adapted from CCR Connections, vol. 1, no. 1, 2007.

CCR has played an integral role in the development of many of the prevention and treatment approaches used today and continues to stimulate discovery in cancer and AIDS research worldwide.

Executive Summary

Overview of the CCR Strategic Plan

Advancing Basic, Clinical, and Translational Research is a series of six distinct yet highly interrelated objectives that the CCR will pursue over the next several years to help the NCI achieve its goal to reduce the burden of cancer on the lives of all Americans. As the basic and clinical research arm of the NCI's Intramural Research Program, the CCR is the center within NCI that conducts long-term, high-risk basic laboratory research in cancer and HIV/AIDS and translates promising findings into novel therapies through its in-house clinical research program and collaborations with external partners. In this capacity, the CCR has played an integral role in the development of many of the prevention and treatment approaches used today and continues to stimulate discovery in cancer and AIDS research worldwide. In this important role, it is imperative that the CCR identify and share its top priority objectives through its Strategic Plan.

A Basis for Priority-Setting

The CCR Strategic Plan sets the stage for the future by building on current cancer and AIDS research as well as several core beliefs and understandings. Among those beliefs is that a greater understanding of how cancers arise and behave will lead to improved or more effective prevention, detection, diagnosis, and treatment approaches. Another is that to understand the cancer process, we first need to understand the processes of normal cell growth and differentiation in order to compare disease initiation and progression. In addition, the recent sequencing of the human genome presents enormous opportunities for improved understanding and predicting cancer risk, prognosis, and responses to treatment. Likewise, the emerging fields of nanotechnology, genomics, advanced imaging, and proteomics will empower the research community to develop less invasive interventions at the molecular level, identify and characterize human proteins and their biological functions, and create new technologies to deliver precise treatments and predict therapeutic effectiveness.

With these and other challenges and opportunities as a foundation, the CCR developed six strategic objectives and corresponding action steps to form its Strategic Plan.

Aligning the CCR Vision with NCI, NIH

The CCR Strategic Plan, *Advancing Basic, Translational, and Clinical Research,* aligns with two visionary planning documents that came before it: the *NCI Strategic Plan to Lead the Nation* (2006) and the *NIH Roadmap for Medical Research* (2005). The CCR Strategic Plan articulates its path forward in the context of the NCI's stated goal of reducing the burden of cancer and the NIH emphasis on identifying the major roadblocks to scientific progress and initiatives to accelerate medical research to improve public health. Like these documents, the CCR Strategic Plan provides a framework of priorities that it should address to optimize its entire research portfolio and actively contribute toward achieving the vision of its parent institutions.

Summary of the CCR's Strategic Objectives to Advance Basic, Translational, and Clinical Research

To understand the causes and mechanisms of cancer and HIV/AIDS, we will work to:

1. Understand the Cancer Process from Initiation to Metastasis. To interrogate the root causes of cancer, the CCR will conduct research into the tumor microenvironment and the larger biological system in which the tumor exists. Using the latest technologies, we will develop an integrated systems biology approach toward understanding ways in which cancers arise, progress, and metastasize, and establish a nationally recognized program in the promising yet understudied field of cancer stem cell and tissue stem cell biology research.

2. Interrogate the Molecular Genetics of Cancer. Genetic profiling is revealing a wide spectrum of genetic variations among individuals that can lead to cancer. Developing a deeper understanding of genetic susceptibility to cancer will require strengthening our expertise in epigenetics and chromosome biology, creating and using animal and human models to determine which genes give rise to and promote cancer progression, and using this knowledge to better predict patient response to prevention and treatment strategies.

To intervene at the earliest stages possible, we will work to:

3. Improve Cancer Prevention, Early Detection, and Diagnostic Approaches. Using knowledge gained through basic research, CCR scientists will develop less invasive, highly precise prevention and detection strategies, including advanced imaging techniques, to enhance early detection of both precancerous and cancerous lesions.

4. Discover, Develop, and Validate Novel Molecularly Targeted Interventions. Basic and clinical research findings will help to validate new molecular targets important for combating cancer at multiple stages. Increased knowledge of cellular changes will enable the search for new targets and help develop molecularly targeted therapies that, alone or in combination, are more effective and less toxic than standard treatments. We will streamline the early drug development process to move research advances into patient care more quickly.

5. Harness the Immune System to Combat Cancer. The CCR will leverage its strengths in immunology to fully understand the immune system's role in carcinogenesis, including the ways in which immune cells recognize and attack cancer cells. Focus will remain on stimulating immune responses to tumor cells, developing and evaluating immune-based therapies, and exploring the rational use of immunotherapies in combination with other therapies to treat and prevent disease.

6. Develop Approaches to Fight HIV/AIDS and AIDS-Associated Malignancies. Understanding the pathogenesis of HIV disease will assist CCR scientists in developing effective AIDS vaccines and drugs that work against the current drug-resistant viruses and prevent AIDS-associated cancer. With AIDS prevention as our primary goal, we will work to develop vaccines to prevent and treat the disease and develop immunotherapies and other approaches to keep the disease at bay and prolong life for people infected with HIV.

The plan presents several overarching themes meant to guide the work of every CCR investigator, regardless of his or her expertise, and to stimulate dialogue among colleagues.

Emerging Themes to Guide Research

The CCR Strategic Plan reflects the current state of cancer and AIDS research and is based on several core beliefs and understandings that have general acceptance in the research community. In addition to the six strategic objectives, the plan presents several overarching themes meant to guide the work of every CCR investigator, regardless of his or her expertise, and to stimulate dialogue among colleagues.

- To fully unravel the complexities of the cancer process, normal cell growth and differentiation must be studied and understood.
- Greater understanding of how cancers originate, progress, and behave will lead to improved or more effective prevention, detection, diagnosis, and treatment approaches.
- Prevention and early detection are key to disease control; adapting discoveries to prevent or intervene early in the disease process will help to make the greatest strides in reducing cancer incidence and mortality.
- Combining effective agents, including both conventional and molecularly targeted therapies, has led to greater efficacy against AIDS and several types of cancer and should be encouraged to develop less toxic and more effective treatments.
- An emphasis on individualized medicine, enabled through the mapping of the human genome and other research advances, will allow us to predict a patient's susceptibility to cancer and to use this knowledge to treat the disease on a personalized level.
- Surgery, chemotherapy, and radiation are likely to remain the staples of cancer treatment for many years; however, new molecularly targeted therapies that leave healthy cells unharmed are expected to one day routinely be combined with or replace today's standard therapies.
- Advanced biomedical technologies, such as nanotechnology, genomics, imaging, and proteomics, are essential to developing interventions at the molecular level, identifying human proteins and their biological functions, and creating instruments that deliver highly targeted treatments and predict therapeutic effectiveness.

Understanding normal cellular growth regulation and differentiation provides the foundation for unraveling cancer—a complex set of diseases that CCR scientists are striving to understand from multiple perspectives.

The CCR Strategic Plan to Advance Basic, Translational, and Clinical Research

The CCR Strategic Plan contains six distinctive yet highly integrated objectives to advance cancer and HIV/AIDS research over the next several years. The plan identifies a route for the CCR to take in pursuit of our mission by making breakthrough discoveries in basic and clinical research and translating them into novel therapeutic interventions for adults and children with cancer or HIV/AIDS.

To understand the causes and mechanisms of cancer and HIV/AIDS, we will work to:

1. ***Understand the Cancer Process from Initiation to Metastasis***
2. ***Interrogate the Molecular Genetics of Cancer***

To intervene at the earliest stages possible, we will work to:

3. ***Improve Cancer Prevention, Early Detection, and Diagnostic Approaches***
4. ***Discover, Develop, and Validate Novel Molecularly Targeted Interventions***
5. ***Harness the Immune System to Combat Cancer***
6. ***Develop Approaches to Fight HIV/AIDS and AIDS-Associated Malignancies***

To Better Understand the Causes and Mechanisms of Cancer and HIV/AIDS

The CCR will conduct and support basic, translational, and clinical research to gain a more complete understanding of the molecular, genetic, and cellular determinants of cancer and the mechanisms underlying susceptibility, tumor development, and recurrence.

Strategic Objective 1

Understand the Cancer Process from Initiation to Metastasis

Cancer is a complex, multistep process that can be interrupted at many stages, from initiation to disease progression to metastasis. While basic science exploration into the many factors that influence the cancer process has always been a major component of CCR research, it takes on increased importance today as accumulated knowledge and groundbreaking technologies such as imaging, nanotechnology, and metabolomics are enabling us to interrogate in precise detail the tumor microenvironment and the larger biologic system in which it exists. Within this area of basic research, the CCR will focus intently on the critical steps of cancer development to lay the foundation for intervening in the carcinogenic process.

Strategy 1.1—Understand the impact of the microenvironment and the surrounding biologic system on tumor development, metastasis, and recurrence

Significant progress has been made in dissecting the molecular pathways and mechanisms that have gone awry within malignant tumors. Capitalizing on these gains, the CCR will further explore the contributions of the biological system in which tumors reside—the microenvironment—and the larger system of which they are a part in order to determine the best points of intervention. The CCR will:

- elucidate mechanisms that influence tumor initiation, promotion, and progression, including those associated with lifestyle, the environment, inflammation, the immune system, host-tumor interaction in metastasis, wound healing, and angiogenesis;
- identify the distinguishing features within the microenvironment among dormant cancers, progressing tumors, and metastatic disease; and
- using animal models, examine how changes in the microenvironment and larger biologic system influence genetic susceptibility and resistance.

Strategy 1.2—Accelerate cancer stem cell research

The CCR will establish a nationally recognized program in cancer stem cell and tissue stem cell biology research to test the theory that some tumors contain small populations of self-renewing cells that give rise to all of the cells in tumors but are themselves resistant to conventional treatment. The CCR will:

- identify cancer stem cells and tissue stem cells and their distinguishing molecular characteristics in various organ systems;
- explore cancer stem cells and their progenitors as targets for cancer initiation, promotion, metastasis, and phenotypic heterogeneity;

- determine the impact of the micro- and macroenvironment on cancer stem cells and their role in cancer etiology, progression, and resistance to treatment; and
- use knowledge of cancer stem cells and tissue stem cells to develop better cancer interventions and therapies.

Strategy 1.3—Apply systems biology to the study of the cancer process

Progress in cancer research requires a full understanding of the complex networks associated with normal and neoplastic cell growth and differentiation. The CCR will embrace a systems biology approach—the analysis of cancer as a multifaceted biological system—using biological, chemical, physical, mathematical, and computational models. The CCR will:

- investigate cancer as a component of a complex biological network and apply this model to understanding the carcinogenic process;
- develop computational models of a spectrum of cancer processes to facilitate hypotheses that drive the development of novel interventions; and
- use a systems biology approach to understand the key molecular events that occur during aging at the level of the cell, organ site, and organism.

Impact

Discoveries in the basic science of cancer development and progression will provide new information about the many processes that contribute to these events in the cell and in the patient with cancer. A more comprehensive understanding of the abnormalities involved in the conversion of normal cells to malignant cells and how they progress will give rise to myriad discoveries, including the development of more accurate diagnostic tests. These tests will have the precision to assess the state of the microenvironment and identify the targets to help us develop personalized, informed prevention and treatment interventions for people with cancer.

From Basic Science Discovery to Drug Delivery: Relief from Treatment's Side Effects

Research discoveries made within the CCR often, by design, have their genesis in our labs but are carried forward by our partners—first in translational and clinical research and then in the extramural, industry, and academic communities. This translation is illustrated in the recent FDA approval of a drug to treat oral mucositis—painful sores in the mouth resulting from high-dose chemotherapy and radiation treatment—a drug which progressed from CCR labs to our own clinical trials, to the drug development stage involving the pharmaceutical company Amgen, and, finally, to adoption by the physician and patient communities.

For years, the CCR's Dr. Jeffrey Rubin and his former colleagues, Drs. Paul Finch and Stuart Aaronson, had been intrigued by the protective properties of keratinocyte growth factor (KGF), a naturally occurring protein that stimulates cell growth in the lining of the mouth and intestinal tract. The CCR team theorized that developing an artificial version of KGF could mimic the natural product in maintaining the mouth's epithelial barrier during chemotherapy and radiation treatment. Their commitment to this effort began to pay off when the new, purified agent they developed moved into early-phase research studies at the CCR and was proven safe for further study. Subsequent animal studies and early-phase clinical trials conducted elsewhere in the NCI showed that the drug, like natural KGF, was effective in stimulating healthy cells to divide and grow and thus alleviate the effects of cancer treatment. Finally, clinical trials proved that the drug, called palifermin, or Kepivance® by Amgen, actually decreased incidence and duration of severe oral mucositis and enabled patients to more easily eat, talk, and sleep, and finish their chemotherapy and radiation treatments. The drug was approved in late 2004 for use after high-dose therapy with bone marrow transplantation in patients with cancers of the blood, and Dr. Rubin envisions its approval for use in patients with other types of cancer as well.

Strategic Objective 2

Interrogate the Molecular Genetics of Cancer

Cancer is a disease involving diverse and dynamic changes in an individual's genetic material, or genome. Genetic profiling is revealing a wide range of genetic variations among people that can lead to cancer development and progression. The CCR will continue to conduct basic research to elucidate the influences of genetics and epigenetics—the processes critical for normal cell growth and differentiation—on cancer development to develop patient-specific approaches to cancer prognosis and treatment. Our work in this area will capitalize on our strong basic and clinical science infrastructure and use of advanced technologies to translate research into preclinical testing and clinical applications to improve all patient populations, including those with rare cancers and those with unequal cancer burden.

Strategy 2.1—Understand genetic susceptibility and the biology of cancer development

Changes in an individual's genes, including gene mutations, genetic modifiers, and polymorphisms, can alter his or her lifetime risk for cancer. To continue to elucidate the genetic factors that influence a person's risk for cancer, CCR scientists will:

- define the role of inherited or acquired genetic alterations, in combination with lifestyle factors and environmental exposures such as radiation and chemical elements, as important determinants of an individual's cancer susceptibility;
- identify new tumor suppressor genes and oncogenes and elucidate their mechanisms of action;
- identify gene expression patterns that enable early cancer detection and diagnosis, and selection of drug targets; and
- define genetic mechanisms that govern patient response or resistance to individualized treatments.

Strategy 2.2—Support the CCR's expertise in epigenetics and chromosome biology

Increased understanding of epigenetics—the study of heritable changes in gene function that occur without change in DNA sequence—and the intricacies of gene regulation and expression will provide new opportunities to develop novel intervention strategies. The CCR will:

- understand epigenetic inheritance both at the cellular and organism level;
- identify genetic and environmental factors that influence cancer epigenetics and the cancer epigenome;
- develop new technologies for interrogating chromosome structure, both at the macro and micro levels;
- use experimental model systems to further investigate the effects of chromatin structure, dynamics, and gene regulation on tumor development; and
- continue to advance scientific understanding and impact of RNAi and microRNA on the cancer processes.

Strategy 2.3—Maximize the predictive value of animal models to advance individualized care

CCR will investigate the impact of specific genetic alterations on cancer risk and development with emphasis on understanding the functional and mechanistic consequences of mutations and polymorphisms alone and in combination with environmental exposures. CCR scientists will:

- use genetically manipulated animal models to validate gene function and characterize mechanisms of action;
- exploit mouse models of cancer susceptibility to define gene-environment interactions;
- conduct cross-species genomic and proteomic comparisons of genetic and epigenetic mechanisms associated with carcinogenesis; and
- identify distinguishing characteristics between normal and cancer biospecimens using comparative molecular analysis among species.

Strategy 2.4—Use knowledge of genetics and epigenetics to predict patient response to cancer prevention and treatment

New and promising insights into the role of genetics and epigenetics in cancer will enable us to classify tumors at the molecular level and predict individual prognosis and therapeutic response. Accomplishing this requires research studies designed with sufficient statistical power to answer relevant scientific questions and access to sophisticated technology and bioinformatics. CCR scientists will:

- conduct human genetic studies to identify and validate key susceptibility genes and their modifiers using knowledge gained from gene expression profiles and protein fingerprints;
- explore the use of genomics to identify biomarkers and other tools for early cancer detection and diagnosis;
- support a robust and standardized approach to biospecimen procurement, stabilization, and processing;
- ensure that samples from all patients enrolled in clinical trials (with patient consent) are collected and analyzed to the fullest extent permitted by current and emergent technologies; and
- enhance bioinformatics resources to assist in data mining and promote the public release of high-quality data obtained from CCR research.

Impact

Molecular genetics is transforming our ability to determine an individual's risk for cancer, to accurately diagnose and predict prognosis and response to treatment, and to develop targeted prevention and treatment strategies tailored to the individual. Genetic and epigenetic research will continue to generate significant insights into the identification of molecular predictors of cancer and the molecular characterization of tumors and to give physicians the ability to recommend treatment based on the patient rather than on estimates based on large populations of patients.

CCR Discovery Leads to Genetic Tests for Kidney Cancer

The hypothesis that cancer is caused by an accumulation of mutations in cancer-causing genes has proven true in the CCR discovery of a prominent kidney cancer gene and subsequent genetic tests for families with an inherited form of the disease.

Fifteen years ago, the best medical advice for family members with an inherited kidney cancer was to be examined regularly to detect the cancer and treat it as early as possible. By 1993, that advice was about to change when the first gene shown to cause kidney cancer was discovered in the CCR laboratory of Drs. Marston Linehan, Berton Zbar, and their colleagues, transforming the way doctors diagnose and treat people with hereditary forms of the disease. Since the 1980s, the team has analyzed the genealogic records of families with von Hippel-Lindau (VHL) disease, a rare, hereditary disease that can cause the most common type of kidney cancer—clear cell renal cell carcinoma (RCC). More than a decade later they made the dramatic discovery of a single gene on chromosome 3—VHL—that causes both VHL and RCC. From that discovery, the CCR team developed genetic tests to screen patients and families for VHL mutations, enabling those at risk to seek counseling and early screening. The finding prompted the CCR to expand its understanding of the molecular mechanisms responsible for other types of kidney cancer, which led to the discovery of two other kidney cancer genes via studies of families with hereditary forms of kidney cancer. These and other discoveries have made the CCR a global resource for families with hereditary forms of kidney cancer.

Preventing cancer from occurring, or detecting it early when it is most curable, are focal points in the CCR's research program.

To Intervene at the Earliest Stage

Knowledge gained from the continuous study of the causes and mechanisms of cancer will be translated into development of novel interventions to prevent, diagnose, and treat cancer and to circumvent drug resistance and develop strategies to prevent HIV infection and treat AIDS-associated malignancies. Understanding the etiology of cancer greatly informs the prevention of cancers that are of infectious origin through a convergence of virology, cell biology, and immunology, the intersection of which is an area of strength within the CCR.

Strategic Objective 3

Improve Cancer Prevention, Early Detection, and Diagnostic Approaches

Preventing cancer from occurring, or detecting it early when it is most curable, are focal points in the CCR's research program. We will apply knowledge gained by understanding the causes and mechanisms of cancer and virology—outlined in Strategic Objectives 1 and 2—to developing new approaches, technologies, and drug targets both to preempt disease and to improve early detection and diagnosis through new technologies and information.

Strategy 3.1—Develop new cancer prevention strategies

Identifying the multiple steps in cancer development will enable us to target numerous points along the cancer continuum where we can prevent or interrupt the cancer process. New approaches using novel agents separately, in combination with one another, and in combination with standard interventions will be critical to preventing cancer. CCR scientists will:

- advance understanding of the effects of lifestyle (including physical activity and diet) and genetics on cancer prevention, initiation, and progression;
- uncover and compare the characteristics of precancers that are indolent (do not grow) with the cancers that progress;
- identify and validate promising molecular targets for cancer prevention in engineered animal models and reduce the toxicity of standard of care approaches, including chemotherapy and radiation, by exploring various combination strategies;
- identify prevention agents, such as vaccines, that are effective against precancerous conditions and at suppressing cancer or that are promising for people at high risk for developing cancer; and
- conduct mouse and human prevention studies in parallel to determine functionally significant molecular targets and predictive biomarkers.

Strategy 3.2—Develop and enhance early detection and diagnostic strategies

The ability to detect and diagnose cancer before it invades and metastasizes will dramatically improve the clinical management of the disease and save lives. To develop less invasive and more effective ways to detect and diagnose cancer earlier, CCR scientists will:

- advance the discovery and validation of biomarkers for early cancer detection, diagnosis, therapy, and followup for recurrence;

- rationally combine new technologies with existing approaches for greater impact and success in early detection and diagnosis;
- develop standards for the use of new technologies as they are created and applied to clinical questions;
- more accurately identify the determinants of cancer progression to ensure that early detection does not result in over-treatment of lesions with little or no propensity to progress to life-threatening illness; and
- employ animal models for early or precancerous disease for use in testing imaging methods.

Strategy 3.3—Improve imaging techniques to enhance early detection, diagnosis, and treatment

Imaging techniques play a vital role in the detection, diagnosis, and treatment of cancer. The development of more precise, noninvasive imaging tools will be critical for detecting and diagnosing cancer at even earlier stages than is now possible. To advance research to introduce promising new imaging approaches to the clinical setting, CCR scientists will:

- enhance the precision and use of anatomic, functional, metabolic, and molecular imaging—alone or in combination—to characterize and monitor tumors and their microenvironments, and enhance early detection of both precancerous and cancerous lesions;
- collaborate with bioengineers and other experts to develop new imaging instruments to direct focal therapies into early-detected lesions;
- coordinate expertise across the CCR to develop, test, and implement new imaging technologies and approaches—from applications at the nanoscale to testing in animal models and clinical trials;
- apply new and improved imaging technologies, approaches, and platforms to new or existing scientific problems, including cancer stem cells and metastatic dormancy; and
- conduct early-phase clinical studies with novel imaging agents to facilitate their translation to the clinic.

Impact

Dramatic developments in technology and a more complete understanding of the causes and mechanisms of cancer will enable us to provide more effective ways to prevent the disease. Advances in biomarkers and the promise of new approaches such as nanotechnology will make early detection and diagnosis of cancer and prediction of patient response to treatment even more precise. More exact imaging techniques will enable us to diagnose cancer earlier and evaluate treatment responses, ultimately giving physicians greater ability to select optimal therapies for their patients. Approaches currently used in early detection and diagnosis may be applied to new prevention strategies and to interventions to treat localized cancers before they spread.

A Personalized Approach to Diagnosing and Treating Cancer

The era of predicted, personalized medicine is being ushered in through the rapid advancement in new technologies and greater collaboration among scientists. Investigators at the CCR share the vision that in the near future all cancer patients will receive a molecular diagnosis that will help their oncologist guide their treatment choices. Diagnosing cancer at the molecular level requires the use of advanced technologies to analyze a patient's tumor. It can provide doctors with enough detailed information to tailor therapy to the individual patient, as opposed to providing standardized therapies that have proven effective based on studies in a large population.

Noninvasive detection approaches and early diagnosis of tumors will offer unprecedented opportunities to treat tumors before they become invasive and metastatic.

Under a standard microscope, the cancer cells of every patient with diffuse large B-cell lymphoma (DLBCL) look the same. But when the CCR's Dr. Louis Staudt and his team analyzed the genes of DLBCL patients using DNA microarray technology (a powerful new tool that allows researchers to determine which genes are active within cells) and combined the relatively new technique of genetic profiling, they found a startling difference—the discovery that the activity of as few as 17 genes out of thousands were determinative: investigators were able to predict whether patients with these genes would respond to chemotherapy, how fast tumor cells would divide, and from what type of normal lymphocyte (a type of white blood cell) the tumor originated. Many of the predictive genes a patient possessed suggest that a patient's immune response to the tumor is important for achieving a cure with chemotherapy. Since standard chemotherapy for the disease is effective in only 40 percent of patients, profiling gene expression in DLBCL patients' tumors may help clinicians decide which patients should pursue standard therapy and which should consider other options. The technique discovered and successfully validated in Dr. Staudt's lab could be applicable for routine use in the near future. Using genomic profiles of individual tumors will enable clinicians to make a more accurate diagnosis, prescribe the best treatment, and improve the patient's chances of long-term survival.

Strategic Objective 4

Discover, Develop, and Validate Novel Molecularly Targeted Interventions

Targeted cancer therapies are those that block the growth, spread, and progression of cancer by interfering with specific molecules. The CCR will conduct basic and clinical research around this promising area of research to validate new molecular targets or pathways important for combating cancer at multiple stages. With increased knowledge of cellular changes associated with cancer progression, we will develop molecularly targeted cancer therapies and approaches that are more effective and less toxic than the treatments available today. The CCR is committed to discovering potential lead compounds for clinical development and moving them rapidly into new cancer interventions safely and efficiently.

Strategy 4.1—Support the discovery and development of novel molecular targets

We will develop and validate novel molecularly targeted agents and search for new targets important in the cancer process. These steps are critical for improving diagnostics and generating effective therapeutics. CCR scientists will:

- facilitate the drug discovery and development process by leveraging the CCR's strength in cancer biology with expertise in chemistry and structural biology;
- develop rationally designed combinatorial therapies based on characterizing and targeting molecular networks that regulate tumor development;
- develop effective preclinical models for drug development, including those that establish predictive orthotopic models and genetically engineered mouse strains and that validate the use of the NCI Comparative Oncology Program in the early stages of the drug development process; and
- partner with academia, industry, and the extramural communities to discover and develop molecularly targeted drugs.

Strategy 4.2—Actively move research advances from the bench to the bedside

The CCR will support basic science efforts to develop new molecular targets and move them more efficiently through the development pipeline to deliver novel agents to the clinical setting. CCR scientists will:

- closely align the exploration and discovery phases of agent development with the performance of early-stage clinical trials by utilizing the resources and expertise of the NIH Clinical Center and NCI drug development initiatives, including the NCI Experimental Therapeutics Program (NExT), the Joint Development Committee, the NCI Chemical Biology Consortium, the Center of Excellence in Molecular Oncology, and the Molecular Targets Faculty;
- develop biomarkers and molecular imaging techniques to monitor the success of molecularly targeted agents and response to interventions;
- conduct clinical trials on molecularly based interventions to validate their effectiveness and move successful agents into larger, later-stage trials; and
- encourage partnerships with pharmaceutical companies to validate targets and advance the development process.

Strategy 4.3—Identify and validate rationally based combination therapies and multimodality approaches

Guided by evidence that the rational combination of treatments is often more effective and less toxic than individual interventions, CCR will cultivate a leadership role in identifying combinations of agents and/or modalities that work through complementary mechanisms to interrupt cancer development and progression. The CCR will:

- support translational research focused on developing novel agents for use alone or in combination with other agents, or in combination with chemotherapy, radiation, surgery, and/or immunotherapy;
- facilitate the testing of combinations of agents in the *in vitro* and preclinical settings with a clear path to early-phase clinical trial design and implementation; and
- partner with the NCI Division of Cancer Treatment and Diagnosis to facilitate the translation of successful intramural clinical studies into later-phase trials.

Impact

Molecularly targeted therapies will provide effective ways to personalize cancer treatment, reduce treatment side effects, and improve the quality of life of people living with cancer. The CCR's focus on developing a more coordinated approach to the chemistry aspect of drug development will be essential to achieving this goal. In addition, streamlining the process for moving agents to clinical trials will encourage greater industry collaboration.

Putting Natural Compounds to Work Against Cancer

The CCR is in a unique position to access the enormous chemical diversity of NCI's Natural Products Repository for use in molecularly targeted high throughput screening for the development of new natural product-based chemotherapeutic drugs. Though this approach to new agent discovery is high risk and requires a long-term commitment of resources, through the efforts of the CCR's Molecular Targets Development Program (MTDP), it has paid off in the development of several promising new agents. Under the direction of James McMahon, Ph.D., the MTDP provides leadership for converting the CCR's basic sciences advances into drug leads for molecular target evaluation. Researchers in the program use the Natural Products Repository and other chemical and biodiversity repositories to facilitate the discovery of natural products and synthetic compounds that may serve as bioprobes for chemical genetics, proteomics, target validation, and potential lead compounds for clinical development.

Targeting DNA's Double Helix to Kill Cancer Cells

Topoisomerase 1 (Top1) is an essential enzyme that enables tightly coiled DNA to unwind and open up so that transcription and replication can take place, and to close back up again, restoring the DNA double helix. The CCR's Dr. Yves Pommier, Chief of the Laboratory of Molecular Pharmacology, received an NIH Merit Award for his comprehensive approach to devising drugs that block that action and selectively kill cancer cells. Dr. William Bonner, of the same laboratory, developed and patented an antibody to a histone called H2AX. This histone is known to form complexes with broken DNA. Bonner's antibody will be used to monitor the DNA-damaging activity of new agents called idenoisoquinolines that are entering clinical trials at the CCR.

Dr. Bonner has patented his antibody to phosphorylated H2AX and will test it in upcoming Phase 0 and Phase I clinical trials of select idenoisoquinolines. If successful, this antibody-monitoring approach will enable clinicians to verify that a DNA-damaging drug has hit its molecular target.

For many years, the natural drug camptothecin was the only drug that could attack topoisomerase 1. In the early 1990s, Dr. Pommier and his colleagues were the first to propose that camptothecin traps the enzyme and DNA in open conformation by taking advantage of a key difference between cancer cells and normal cells: cancer cells will die if the DNA breaks remain open too long, while healthy cells can wait out this cycle unharmed. The team hypothesized that the longer the double helix is open, the more fatal the damage to cancer cells it becomes. In 2005, the team's hypothesis proved correct when they solved the crystal structure of the three-way complex of camptothecin, Top1, and DNA. They also showed that many natural anticancer drugs such as Taxol and some antibiotics use the same mechanism, demonstrating that researchers should look for new agents that can keep this DNA structure open longer. While camptothecin is effective, Dr. Pommier's team searched for other drugs that were stable in the blood longer and could trap DNA-Top1 complexes in open formation for a longer period. In collaboration with NCI's Developmental Therapeutics Program, they found a group of drugs called idenoisoquinolines that traps the complexes even better. Of the more than 400 of these new drugs found through screening at NCI, eight lead compounds are in high-priority development by NCI and at least one has been licensed to a drug company for further development.

Strategic Objective 5

Harness the Immune System to Combat Cancer

The immune system has the capability to successfully attack tumors. Although its exquisite specificity can be used to selectively target cancer cells with minimal collateral damage to normal cells, the frequency of the immune system's effective responses remains limited. The CCR will leverage its strengths in immunology to better understand the immune system's role and function in cancer progression, develop new "immunotherapies" (cancer vaccines and therapeutics that stimulate the immune system), and move these discoveries into early-phase and advanced clinical trials. We will place significant emphasis on the rational use of immunotherapies in combination with other novel or conventional therapies and on their use in the premalignant stage as a means of preventing and interrupting the cancer process.

Strategy 5.1—Understand the basic science of immunology in cancer

Designing effective immunotherapies requires detailed knowledge of the ways in which immune cells identify their targets, become activated, and ultimately destroy those targets. To enhance our efforts to understand the basic science behind the role of the immune system in the cancer process, CCR scientists will:

- identify and understand the mechanisms by which immune cells recognize and attack cancer cells;
- identify the ways in which molecular and cellular mechanisms communicate with one another to initiate immune cell recognition;
- explore receptor-initiated signaling as it relates to lymphocyte activation and differentiation;
- elucidate the ways in which immune cells activate under normal circumstances and after chemotherapy; and
- discover strategies to activate the immune system to increase effective responses.

Strategy 5.2—Identify immune system components that inhibit or enhance cancer initiation and progression

Identifying ways in which the immune system responds to, or ignores, invading disease is essential for using immunotherapy as a complement to, or in place of, today's standard care. The CCR will:

- identify inflammatory or immune cells and their products that promote or limit tumor growth in animal models and humans;
- identify immunologic checkpoints that hinder effectiveness of immunotherapy and discover pathways by which checkpoints can be bypassed; and
- identify mechanisms by which tumor cells avoid immune surveillance.

Strategy 5.3—Optimize immune system response to target tumor cells

A major goal of immunotherapy is to enhance the immune system's ability to fight invading disease. To make this response as effective as possible, CCR scientists will:

- define optimal conditions for inducing therapeutic antitumor immune responses;
- identify and evaluate cytokines that influence both tumor growth and transforming events in cells within and outside of the immune system for potential use as immunotherapy targets; and
- develop approaches to activate the immune system and maintain a sustained response in patients with cancer.

Strategy 5.4—Develop, evaluate, and implement novel immune-based therapies and spearhead new combinatorial approaches

Immunotherapy used in combination with chemotherapy, radiation, and surgery shows promise in some types of cancer. To optimize immunotherapy's effectiveness, CCR scientists will:

- identify new targets for monoclonal antibodies, vaccines, and immunotherapy, including tumor antigen discovery;
- discover novel biologics or treatment approaches such as vaccines, recombinant immunotoxins, antibodies, and adoptive therapies that impact known cancer targets;
- advance the use of science-based, rationally designed immunotherapies in combination with other novel agents or conventional therapies for maximal patient response;
- strengthen the CCR's ability to obtain drugs for combinatorial therapies through alliances with NCI's Cancer Therapy Evaluation Program and pharmaceutical companies;
- evaluate the use of agents developed for other diseases to prevent and treat cancer, and vice versa; and
- conduct early-phase clinical trials of promising novel agents or combinations of agents and approaches developed within the CCR or elsewhere in defined patient populations.

Impact

Advances in immunology research have significant implications that can be integrated into multiple initiatives across the CCR and will impact other strategic priorities outlined in this plan. Continued commitment to this critical area of research will result in novel strategies and rationally based combination therapies for the delivery of more effective, less toxic treatments that have the potential to revolutionize cancer treatment and become the standard of care.

CCR's Commitment to Rare Cancers Has Broader Applications

In the late 1990s, an experimental immunotoxin called BL22 was shown to put 11 of 13 patients with the rare hairy cell leukemia—whose cancers no longer responded to standard chemotherapy—into complete remission. Developed in the laboratory of Dr. Ira Pastan, Chief of the CCR's Laboratory of Molecular Biology, the immunotoxin delivered a deadly poison to tumor cells while leaving healthy cells unharmed. The results were viewed as remarkable but were just the beginning of what could be accomplished in other, more common types of cancer in this promising new field of cancer research.

"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 see at the NCI. It is very exciting to see your patient get better with an agent that you've developed yourself."

—Thomas Waldmann, M.D., Chief
Metabolism Branch
CCR

The BL22 treatment in Dr. Pastan's landmark study was a version of Pseudomonas exotoxin A—a bacterial toxin he had identified 15 years earlier as a promising potent cancer-cell killer. Genetically modified by Dr. Pastan and his colleagues, Drs. David FitzGerald and Robert Kreitman, the antibody portion of BL22 binds to the CD22 protein found at high levels on the surface of many kinds of leukemia cells, killing them. Over more than three decades, Dr. Pastan has identified proteins uniquely expressed on the surface of cancer cells, including mesothelin, expressed at very high levels in ovarian, pancreatic, and other types of cancer, so that antibodies can be developed that bind only to these proteins. Drugs attached to the protein-targeting antibodies can thus selectively obliterate tumor cells. BL22 and other immunotoxins are currently being tested—some in collaboration with academic institutions and pharmaceutical companies—to evaluate their effectiveness in other types of cancer as well. Aided by computer technology, Dr. Pastan and his team are continually working to refine immunotoxins and adjust the way they are given to patients so they are more potent and less likely to be inactivated by the patient's own immune cells.

Strategic Objective 6

Develop Approaches to Fight HIV/AIDS and AIDS-Associated Malignancies

Great progress has been made in HIV/AIDS research since the earliest days of the epidemic. Along with the National Institute of Allergy and Infectious Diseases (NIAID), NCI maintains a significant HIV/AIDS research program, concentrating specifically on HIV and AIDS-associated malignancies, including Kaposi's sarcoma, non-Hodgkin's lymphoma, and other types of cancer for which people infected with HIV are at extremely high risk. The CCR will focus on developing effective vaccines for the prevention and treatment of HIV/AIDS, on strategies to mitigate the frequent mutations that result in resistance to antiviral drugs, and on developing novel antiviral and immune-based therapies to keep the disease at bay and prolong life for people with the disease. We will continue to elucidate the pathogenesis of HIV disease, AIDS-associated malignancies, and viral-induced tumors, with emphasis on identifying new viral and host factors as targets for improved antivirals and enhancing prevention, detection, diagnosis, and treatment options for AIDS patients worldwide.

Strategy 6.1—Understand the pathogenesis of HIV disease, including malignancies

We will stimulate research to improve understanding of the causes and mechanisms of HIV disease, AIDS, and AIDS-associated malignancies to identify potential points of intervention. CCR scientists will:

- conduct basic research into virus structure, genetics, and interaction with cellular factors;
- understand virus-host interaction in the pathogenesis of AIDS and virus-induced malignancies, and mechanisms by which malignancies develop as a result of HIV infection;
- continue to identify mechanisms by which HIV infection causes immune dysregulation and immune deficiency; and
- identify susceptibility and resistance genes as well as genetic modifiers in patients using cutting-edge tools and approaches.

Strategy 6.2—Develop effective prevention strategies for HIV disease and subsequent AIDS-associated and viral-related malignancies

With AIDS prevention as the ultimate goal, the CCR will use our expertise in cancer vaccines, T cell immunology, mucosal immunology, and retrovirology to develop effective strategies to control or inhibit HIV infection and, in turn, prevent AIDS-defining malignancies, other malignancies that arise in HIV-infected patients, and other viral-induced malignancies. CCR scientists will:

- discover and develop prophylactic vaccines to prevent HIV infection and infection with oncogenic viruses that cause AIDS malignancies;
- promote research into the optimal induction of HIV neutralizing antibodies, mucosal immunity, and cytolytic T cells;

- optimize vaccine response through investigation of immune dysregulation;
- identify and develop chemoprevention as well as microbicidal and antiviral agents to prevent HIV transmission; and
- conduct clinical trials of promising HIV/AIDS prevention strategies.

Strategy 6.3—Develop effective therapies for HIV infection and AIDS-associated malignancies

In addition to pursuing prevention strategies, we will continue to develop novel interventions to treat HIV/AIDS. We will focus on the growing challenge of drug resistance, develop drugs that will be effective against the current drug-resistant viruses, and conduct clinical trials of new therapies for HIV-related diseases. The CCR will:

- develop therapies for AIDS-defining malignancies, other malignancies that arise in HIV-infected patients, and other viral-induced malignancies, focusing on pathogenesis-based treatments;
- understand the basic mechanisms of resistance to antiviral drugs and develop strategies to prevent emergence of drug resistance using animal models and performing clinical studies;
- discover and develop therapeutic vaccines and immunotherapies that enable the immune system to fight HIV infection;
- identify and validate novel targets for therapies and develop innovative strategies for established targets;
- study drug-drug interactions used in treatment of AIDS by conducting clinical trials of therapeutic agents on HIV-related diseases; and
- improve access to screens for antivirals by improving the quality and quantity of the CCR's chemical libraries.

Impact

Until we find a cure for HIV/AIDS, prevention is the best course of action. Accomplishing our stated objectives will improve understanding of the basic mechanisms of HIV viral pathogenesis and provide valuable information for the development of effective vaccines to prevent or treat HIV infection and AIDS-associated malignancies.

The Promise of Adenovirus as an HIV Vaccine

The lack of an HIV vaccine more than 25 years after AIDS was identified is not due to a lack of research effort. Indeed, developing an HIV vaccine has been one of the largest—and complex—scientific problems of the last 20 years. Perhaps the biggest obstacle is the nature of HIV infection itself. Led by Marjorie Robert-Guroff, Ph.D., researchers in the CCR Vaccine Branch are pooling knowledge of cancer and retrovirus vaccines to understand not only what immune system responses are required to fight off infection with the virus but also how to develop a vaccine that will elicit those responses.

In addition to attacking the very cells the body relies on for defense against infection, HIV replicates rapidly and inaccurately, allowing new strains to arise quickly. This characteristic allows HIV to evade immune response by quickly changing its protein makeup, a viral advantage that also explains the appearance of drug-resistant strains of HIV following a period of treatment. The virus always manages to stay ahead of the immune system or drug treatment attempts to control it. For the past two decades, Dr. Robert-Guroff and her colleagues have been interrogating the immune responses required to fight off HIV infection with a singular focus on developing an effective HIV vaccine. For the fundamental building block of their vaccine strategy, they have turned to the adenovirus, a common human virus that can be genetically altered to trick the immune system into thinking it is seeing HIV and thus into building robust HIV immune responses. Theirs is a unique approach among many other HIV vaccine efforts, and their recent work in nonhuman primate models of HIV suggests that it has a high potential for success. Human testing is expected to begin on this adenovirus-based HIV vaccine within the next two years.

"If you look at discovery, most things—in one way or another—have come out of, or were somehow touched by, the intramural program."

—John E. Niederhuber
NCI Director

Cross-Cutting Commitments: Maintaining a Foundation for Long-Term Success

Success of the six objectives in the CCR Strategic Plan is dependent on the commitment of CCR and NCI leadership to foster an innovative and creative research environment. By its charter, the CCR supports both investigator-initiated research and multidisciplinary translational research teams that pursue high-risk, high-impact research. Several critical components contribute to this distinctive culture and underpin the plan's strategic objectives:

Maintain strong support for basic, translational, and clinical research. One of the CCR's distinguishing strengths is its ability to move discoveries made in the lab into the clinical setting as rapidly as possible so that interventions quickly reach patients. To make this translational research process as seamless as possible, the CCR will:

- strongly support basic science exploration and discovery which provides the foundation for translational and clinical research;
- more closely align the exploration and discovery phases of novel agent development with the initiation of early-stage clinical trials on promising approaches to validate their effectiveness;
- advance successful agents into larger, later-stage trials by partnering with the NCI intramural and extramural communities, other NIH institutes, industry, academic researchers, pharmaceutical companies, and our patient volunteers;
- maintain a focus on research into rare and underserved patient populations to develop novel therapies for understudied cancers; and
- support a robust clinical trials program involving the volunteer support of our patients, well-trained clinicians versed in the mechanics of clinical trials administration, and the participation of our nurses, social workers, and administrators.

The Translational Research Pipeline— Bringing Cancer Discoveries to the Public

By definition, translational research is the advancement of promising basic laboratory discoveries into preclinical studies and, if successful, into clinical trials to test for safety and efficacy, with the hope of their being fully developed into new cancer drugs, therapies, medical instruments, and methodologies for use by the public.

- Early in the translation process, promising discoveries are moved into initial testing through Phase I and II clinical trials involving a small number of patient volunteers to evaluate what dose is safe, and how and when an agent should be given.

Continued on next page

The Translational Research Pipeline

Continued from page 33

- Later-stage trials (Phases III and IV) compare the intervention with standard therapy and further evaluate its long-term safety and effectiveness in larger populations.
- Scientists are now conducting very early Phase I trials, which expose patients to less toxicity, can be performed in less time with fewer patients and help researchers weed out drugs that are not producing desired effects much more quickly.

The majority of work in the CCR takes place early in the translational process as scientists work to rapidly advance discoveries to early-phase clinical trials. The CCR collaborates closely with other NCI divisions, industry, and pharmaceutical companies to move early-stage drug and technology discoveries forward. The CCR eventually licenses its discoveries so that the later stages of development, FDA approval, and movement into the marketplace can take place and improve patient care.

Encourage internal and external collaboration. Solving the complexities of cancer requires scientists to move beyond their own disciplines and explore new ways to conduct team science. The CCR's partnerships with scientists at universities, medical schools, hospitals, government agencies, and other nonprofit and for-profit research facilities in the United States and abroad, and its Centers of Excellence, faculties, and working groups successfully cut across organizational boundaries to foster collaborative research. To further support these relationships and develop new partnerships, CCR will:

- recognize, review, and reward team science to encourage talented independent investigators to join multidisciplinary initiatives;
- improve exchange and sharing of patient biospecimens and data by promoting collaborative interactions between basic scientists and clinicians; and
- serve as a model of multidisciplinary research for the extramural research community and explore approaches to working more seamlessly with this community.

Develop and share technologies and expertise. CCR investigators have access to the latest technologies, specialized expertise, and technical support in imaging, animal sciences, analytical and protein chemistry, genetics and genomics, structural biology, and other areas. The CCR encourages its investigators to take full advantage of the technologies and research support available to them and is committed to sharing its expertise through training and consultation and encouraging new uses for core facilities as our research priorities evolve. The CCR will:

- support the development, evaluation, and sharing of novel, cost-effective technologies—including imaging, genotyping, and gene expression—that enable basic research discovery and permit rapid, accurate patient diagnosis;
- enhance the range of technologies available to researchers, including gene expression profiling, single nucleotide polymorphism (SNP) analysis, comparative genomic hybridization, DNA sequencing, and related assays, in addition to novel technologies;
- create an accessible, systematic, secure, and centralized biospecimen procurement and processing center to coordinate the analysis of human samples collected during clinical trials; and
- ensure that bioinformatics support is available to CCR investigators through expansion and sharing of resources, increased training and integration of computers, and the provision of software and personnel to assist in the mining of data.

A Commitment to Rare and Understudied Cancers

A significant portion of the CCR's research portfolio is devoted to the study of rare cancers—those cancers that affect fewer than 15 in 100,000 people and whose incidence is fewer than 40,000 new cases in the United States per year. These include cancer of the thyroid, uterus, pancreas, and others, some of which have rising rates. Cutting across all areas of research, the CCR is committed to studying rare and understudied cancer for several reasons, both practical and ethical. Among them, many rare cancers are highly lethal, their study may be informative about the etiology of more common tumors, and some have disproportionately high incidence in certain medically underserved populations. Altogether, the total incidence of all rare tumors is substantial and places a heavy burden on public health. In addition, as part of the NCI, the CCR has a mandate to devote resources to new and emerging health threats and to cancers that may not have the population base to be profitable in the commercial arena. Some of the earliest AIDS therapies including highly active antiretroviral therapy (HAART) were the result of this commitment. More recently, the vaccine against human papillomavirus (HPV) originated with CCR researchers may one day eliminate cervical cancer, a significant health problem among underserved women here and in the developing world.

Train and mentor the next generation of investigators. The CCR is home to one of the strongest cancer and HIV/AIDS research communities in the world. It is imperative that we maintain a robust core of scientists and physician-scientists through active recruitment, training, and mentorship to ensure the next generation of laboratory and clinical leaders. To continue to provide top scientists the opportunity to develop and refine skills, CCR will:

- support recruitment, training, and mentoring of postdoctoral fellows, junior investigators, and physician-scientists into existing and emerging areas of research;
- focus on retaining and rewarding accomplished postdoctoral fellows and staff scientists to encourage their long-term contribution to research through pursuit of both traditional and nontraditional career paths; and explore a "team track" career path;
- provide extramural researchers opportunities to train at CCR labs and encourage CCR staff to continue their education through course work within and outside of NCI; and
- reach out to local communities to nurture middle- and high-school-age students with interests in the health sciences.

Training the Next Generation of Cancer Researchers at the CCR

As the CCR ponders its highest research priorities, it is important to ask: Who will carry out the research that will bring us to the future we envision? Training the next generation of cancer researchers is a major part of the CCR mission. Over the years, scores of CCR trainees have gone on to become leaders in the cancer research workforce in the United States and in other countries. The CCR provides training opportunities for researchers ranging from summer internships for our youngest scholars while still in high school to more extensive programs for between 800 and 1,000 recent college graduates (postbaccalaureates) and postdoctoral fellows who train under the direction of CCR scientists each year. The CCR offers course work in basic, translational, and clinical research, all with an interdisciplinary, collaborative focus that provides access to expertise and resources though partnerships with leading universities and research institutes.

"The legacy of CCR is greater than the education of this medical oncologist/molecular pharmaceuticologist. It provides an environment where one can be mentored and further develop one's medical, scientific, and analytical skills to make fundamental discoveries that ultimately will benefit patients around the globe."

—CCR alumnus Patrick Johnston, M.D., Ph.D.
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Acknowledgements: CCR Strategic Planning Participants

The CCR Strategic Plan is the work of CCR leadership and staff, with review and input from the CCR Advisory Board and NCI Board of Scientific Counselors. The following are participants of the small-group discussions that formed the basis of the plan.

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The CCR Strategic Planning Process

In 2006, the CCR began a series of strategic planning meetings with CCR investigators who were charged with identifying specific initiatives that would make the greatest contribution to cancer and AIDS research within six priority areas. These group discussions resulted in the development of action steps for each area, the identification of commitments that should be honored and cut across all six objectives, and the emergence of common themes which will be critical to the implementation of the entire plan. The CCR Director solicited input on the initial draft of the plan from the CCR community, the CCR Advisory Board, and a working group of the NCI Board of Scientific Counselors (BSC). With the approval of the full BSC, the CCR finalized its Strategic Plan in the fall of 2007. Implementation will proceed as budget allows and as emerging needs and opportunities are balanced. *The CCR Strategic Plan is intended to be a dynamic and flexible document that will evolve with cancer and HIV/AIDS research and will continually challenge our community to remain on the cutting edge of scientific discovery and development.*

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