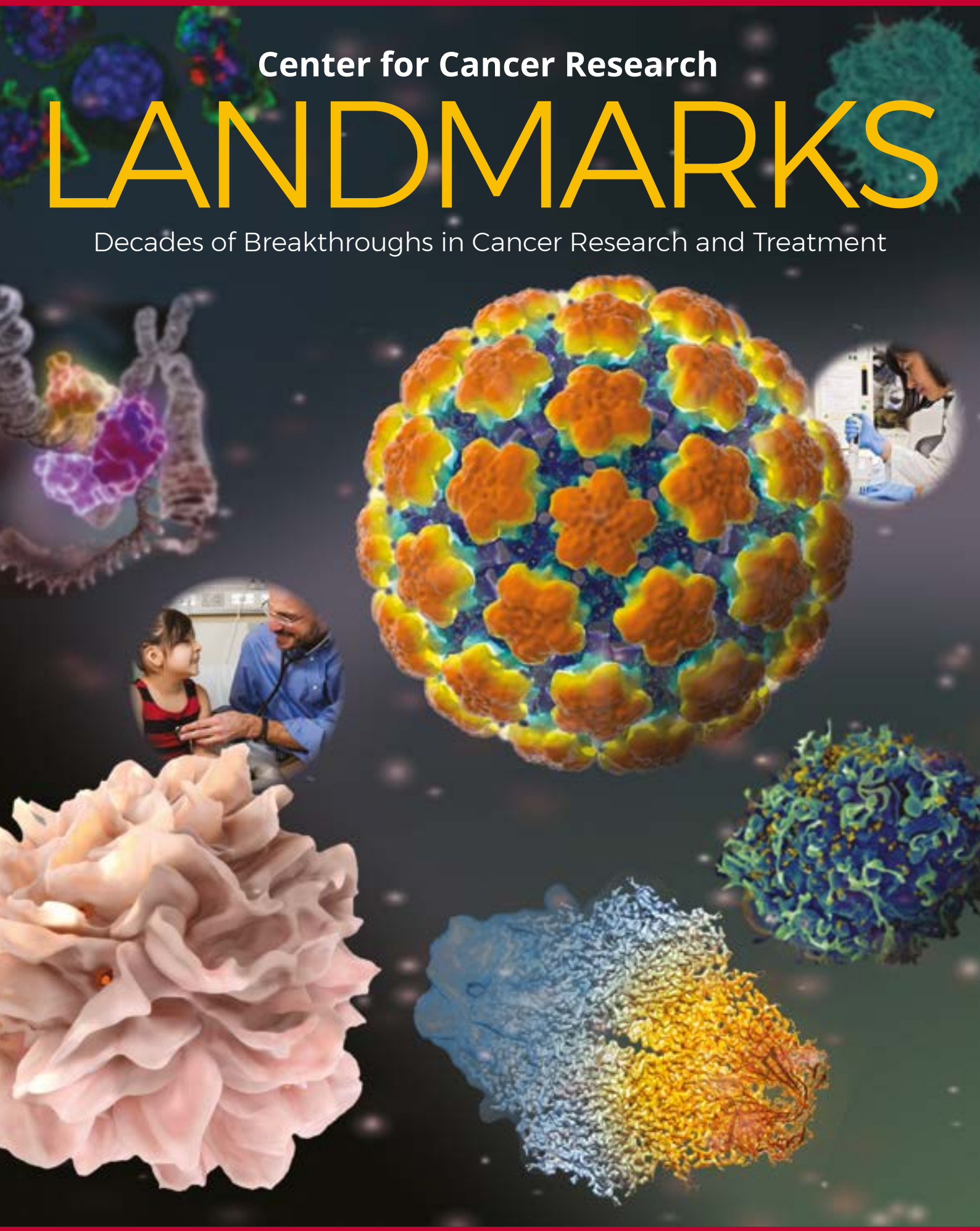
NIH NATIONAL CANCER INSTITUTE

Center for Cancer Research

LANDMARKS

Decades of Breakthroughs in Cancer Research and Treatment



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

NIH NATIONAL CANCER INSTITUTE

CENTER FOR CANCER RESEARCH

The Nation's Cancer Center

As part of the federally funded National Cancer Institute (NCI), the Center for Cancer Research (CCR) is the nation's cancer center. Located in the suburbs of Washington, D.C., our scientists are unlocking the mysteries of cancer and discovering new ways to prevent, diagnose and treat it. The CCR collaborates with academic and commercial partners and advocacy groups across the world in efforts to find treatments and cures for cancer through basic, clinical and translational research. Our physician-researchers translate these discoveries from the lab to the clinic, and we treat thousands of people from around the country every year with novel therapies through our clinical trials program at the National Institutes of Health Clinical Center. For more about our science, our training programs and our clinical trials, visit ccr.cancer.gov.

The **MISSION** of the CCR is to improve the lives of cancer patients by solving important, challenging and neglected problems in cancer research and patient care through:

- A world-leading basic, translational and clinical research and patient-care program
- An institutional focus on high-risk and long-term projects, unmet needs and pursuit of unexplored ideas
- Leadership and coordination of national disease networks and development of technology resources for the cancer community
- Partnerships with academic institutions, commercial entities and patient-advocacy groups
- Training of the next generation of the biomedical workforce

NOTE FROM THE DIRECTOR

The NCI Center for Cancer Research is at the forefront of cancer research – and has been for decades. Work from our basic and clinical investigators has led to fundamental insights into biological processes, the development of new cancer drugs, innovative vaccines and groundbreaking technologies that enable basic discovery and are used in the clinic every day to diagnose and treat patients.

In this publication we highlight some of our landmark discoveries over the years. They span the spectrum from basic research on how genes are expressed in cancer cells to advances in clinical care. They represent impactful research that has shaped and changed scientific fields and led to novel clinical applications that benefit patients. The remarkable discoveries highlighted in this magazine are a testimony to the creativity, ingenuity and persistence of CCR investigators. They are also a reminder of the extraordinary return on investment of federal funds allocated to maintaining and improving the well-being of our nation.

Why has CCR been so successful for so long? The short answer is that we do cancer research differently from most institutions. We have created an environment where our investigators can freely pursue what they consider to be the most important problems in cancer biology and treatment, and they can do so with limited time pressure. The intellectual freedom afforded to CCR scientists and the technological resources available to support them are unmatched. They enable projects that may be considered excessively risky in an academic or commercial setting but that fill an important niche in the biomedical landscape. The CCR's distinctive environment also combines basic and clinical research under one roof to foster interdisciplinary research to tackle the most difficult problems in cancer research.

Our science is driven by our curiosity and by our commitment to better lives. While we have reached many landmarks along the way, what motivates and inspires us is the knowledge that much remains to be done to prevent, diagnose and treat cancer. New landmarks are ahead, and we strive to reach them every day through our work in CCR.

Tom Misteli
Director, NCI Center for Cancer Research

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THE HPV VACCINE

Caption: Doug Lowy, M.D., and John Schiller, Ph.D., developed technology that led to vaccines against the two deadliest forms of cancer-causing HPV.

Credit: Rhoda Baer

Little did CCR researchers Doug Lowy, M.D., and John Schiller, Ph.D., know in the 1990s that their studies of two cancer-causing genes would lead to the first commercially available vaccine against the two deadliest forms of the cancer-causing human papillomavirus (HPV). Today, these powerfully effective vaccines have slashed HPV infection rates by 64 percent in the United States. As vaccination rates go up, there is already evidence of the potential to nearly eliminate HPV-caused cervical cancer in women coming of age and to prevent many other HPV-related cancers in both men and women.

In the 1980s, the connection between specific types of the HPV virus and cervical cancer became increasingly clear due to a series of laboratory and epidemiological studies conducted by NCI researchers and others. By the early 1990s, these discoveries inspired Lowy and Schiller to focus their research on developing a vaccine. Even though neither had prior experience in the field, they relied on the infrastructure of the NCI intramural program and its culture of intellectual freedom that allowed them to pursue high-risk, long-term projects.

Lowy and Schiller had previously studied two cancer-causing genes, or oncogenes, in the HPV genome that produce proteins, named E6 and E7, that can cooperate to render human cells cancerous. They knew that the presence of the oncogenes would complicate vaccine development. While vaccines at the time often used weakened or killed viruses, in this case, using any form of authentic HPV could potentially introduce the oncogenes into patients.

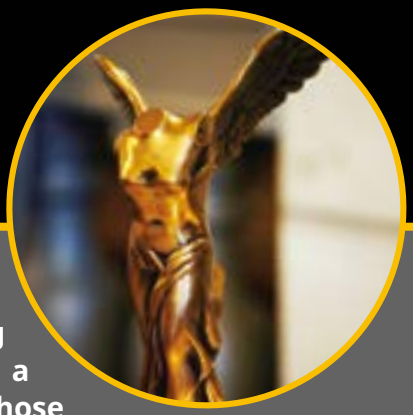
In their first attempt to develop a papillomavirus vaccine, the team discovered an alternative to using an intact virus in the vaccine. Remarkably, they found that multiple copies of the HPV protein L1 could spontaneously assemble into non-infectious virus-like particles (VLPs). Upon injection, these VLPs stimulated production of large quantities of antibodies and prevented viral infection in animal models. The VLPs were subsequently shown to be safe and highly immunogenic in trials

with human volunteers. These encouraging results attracted the interest of the pharmaceutical companies Merck and GlaxoSmithKline (GSK), who licensed the technology from CCR.

By 2006, interim results from a company-sponsored trial were so promising that the U.S. Food and Drug Administration (FDA) approved Merck's Gardasil for the prevention of cervical cancer and genital warts in women before the trial had finished. In 2009, Gardasil was approved for use in men to prevent anal cancer and genital warts, and GSK's Cervarix was approved for use in women to prevent cervical cancer.

After a decade on the market, HPV vaccines have been shown by numerous studies to successfully prevent infection by the HPV types known to cause most cervical cancers in nearly all vaccinated women. The vaccines also offer a strong potential for protection against vaginal, vulvar, anal, penile and head and neck cancers in members of both sexes.

Lowy, Schiller and their colleagues continue to be involved in research to prevent HPV infection and the cancers they cause in both women and men. In 2014 they were awarded the National Medal of Technology and Innovation for their work. In 2017 they were awarded the Lasker-DeBakey Clinical Medical Research Award for technological advances that enabled development of HPV vaccines for prevention of cervical cancer and other tumors caused by the human papillomaviruses.



In 2017 Lowy and Schiller received the Lasker-DeBakey Clinical Medical Research Award for their groundbreaking research. In announcing the award, the Lasker Foundation found that Lowy and Schiller "took a bold but calculated approach toward a major public health problem whose solution required them to vault formidable hurdles."

DISCOVERY OF TGF-β

In 1981, CCR scientists discovered a molecule that both promotes and inhibits cellular growth. By thoroughly characterizing that molecule, which they called transforming growth factor (TGF)-β, they demonstrated how different biological contexts can alter a signaling molecule's effect and revealed how TGF-β might be exploited to treat cancer. Nearly 25 years after the molecule's discovery, the first drugs designed to treat cancer by inhibiting TGF-β signaling entered clinical trials. Today, many such drugs are being evaluated in clinical trials for the treatment of cancer and other diseases.

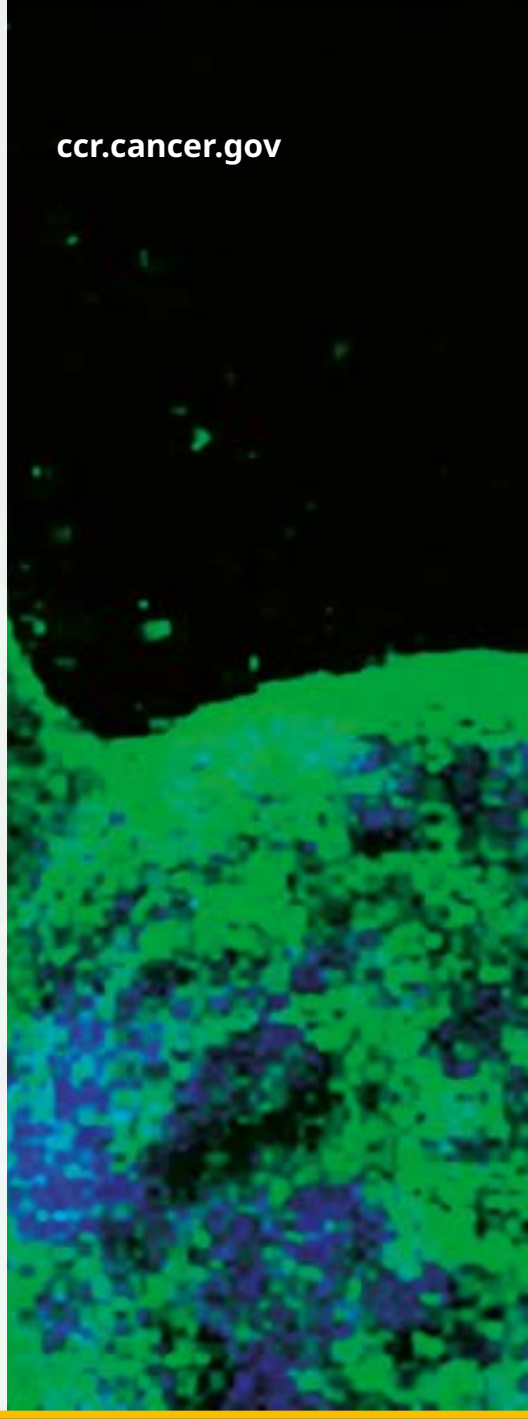
Caption: Anita Roberts, Ph.D., and Michael Sporn, M.D., discovered TGF-β's complex effects on cancer cells, wound healing and immunity.

Credit: NCI, NIH

NCI scientists, led by Michael Sporn, M.D., and Anita B. Roberts, Ph.D., in the 1980s, found TGF-β in cancerous cells and showed that it could make healthy cells malignant. Soon after, however, they made an unexpected discovery. They found that noncancerous cells produced the tumor-promoting factor too. To solve this puzzle, the NCI investigators undertook a major effort to isolate TGF-β from human blood cells and shared the purified protein with researchers around the world in the hope of elucidating its role in cancer.

Their subsequent experiments yielded surprising results. They confirmed that TGF-β can cause excessive cell growth, but in some situations they found it suppresses growth. The opposing functions made it difficult to imagine how to treat cancer by manipulating TGF-β signaling. However, Sporn, Roberts and their colleagues eventually exposed TGF-β's complex effects on cancer cells as well as its key roles in wound healing and immunity.

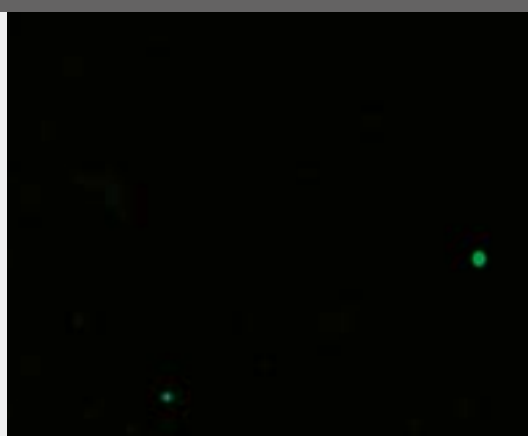
Because of its interactions with context-dependent signals, TGF-β generally promotes the growth and metastasis of advanced cancers but protects against early tumor formation. Working in animal models, CCR's Lalage Wakefield, D.Phil., who trained under Sporn and Roberts, later demonstrated that it is possible to block the tumor-promoting effects of TGF-β without affecting its normal tumor-suppressing activity.



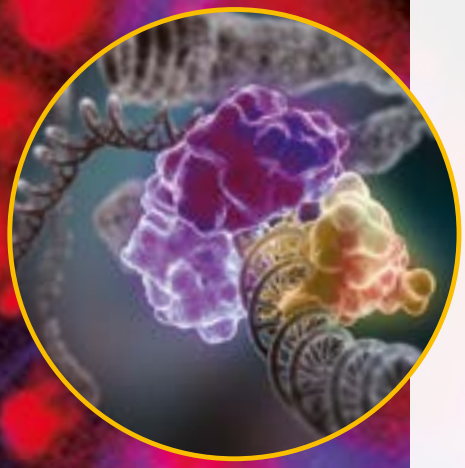
The discovery and characterization of TGF-β is one of CCR's many contributions to the deep understanding that scientists now have of cancer's elaborate signaling networks—knowledge that drives the development of targeted treatments.

Other CCR breakthroughs in cancer signaling include studies of the oncogene HRas by Doug Lowy, M.D., which demonstrated how mutations can convert a gene involved in normal growth regulation into a driver of cancerous growth; the discovery by George Vande Woude, Ph.D., that overactive signaling from the Met gene renders cells tumorigenic and metastatic; and the demonstration by Stuart Aaronson, M.D., that the HER2 gene can cause normal cells to behave like aggressive cancer cells. These genes can be critical lynchpins in different signaling networks and are the targets of several approved cancer treatments, as well as experimental drugs now under investigation.

Patients who receive high doses of conventional chemotherapy and radiation can suffer from painful ulcers in their mouths and throats that increase the risk of infection and make eating, drinking and speaking difficult. Thanks to the discovery of a growth-promoting molecule called keratinocyte growth factor (KGF) by CCR investigator Jeff Rubin, M.D., Ph.D., this side effect, known as oral mucositis, is now treatable. A modified version of KGF, called palifermin (Kepivance), speeds the healing of ulcers in the mouth and throat. In 2004, it was approved by the U.S. FDA for the prevention of oral mucositis. The drug also enables patients with blood cancers to better tolerate intensive cancer treatments prior to bone marrow transplants.



CHROMATIN PIONEERS



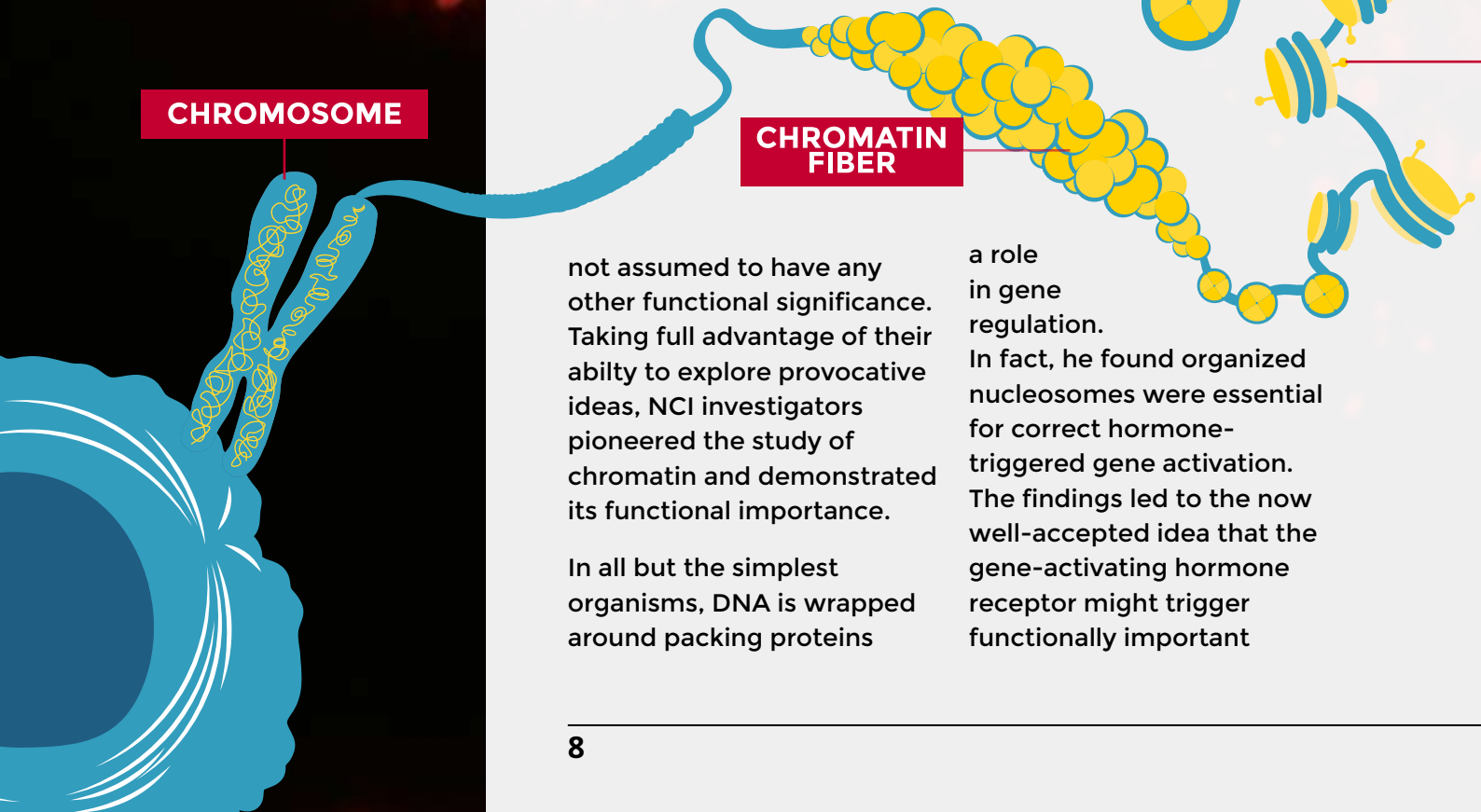
Caption: An enzyme repairs a broken DNA strand.

Credit: Tom Ellenberger, Washington University School of Medicine in St. Louis; Dave Gohara, St. Louis University School of Medicine

For much of the 20th century, scientists were fascinated by DNA. They probed its roles in gene activity and genetic inheritance using genetics, biochemistry and molecular biology. Most of these studies were conducted with DNA in its iconic double-helix formation. Meanwhile, it was well known that DNA in intact cells exists in a much more complex form known as chromatin, with many proteins required for its packaging. However, chromatin was mostly thought of as a means to package an organism's genetic material and was not assumed to have any other functional significance. Taking full advantage of their abilty to explore provocative ideas, NCI investigators pioneered the study of chromatin and demonstrated its functional importance.

In all but the simplest organisms, DNA is wrapped around packing proteins known as histones. A portion of DNA winds around eight histones to form a recurring structure called a nucleosome. In the mid-1980s, NCI researcher Gordon Hager, Ph.D., uncovered the first evidence that nucleosomes are carefully and predictably positioned along regulatory regions of DNA.

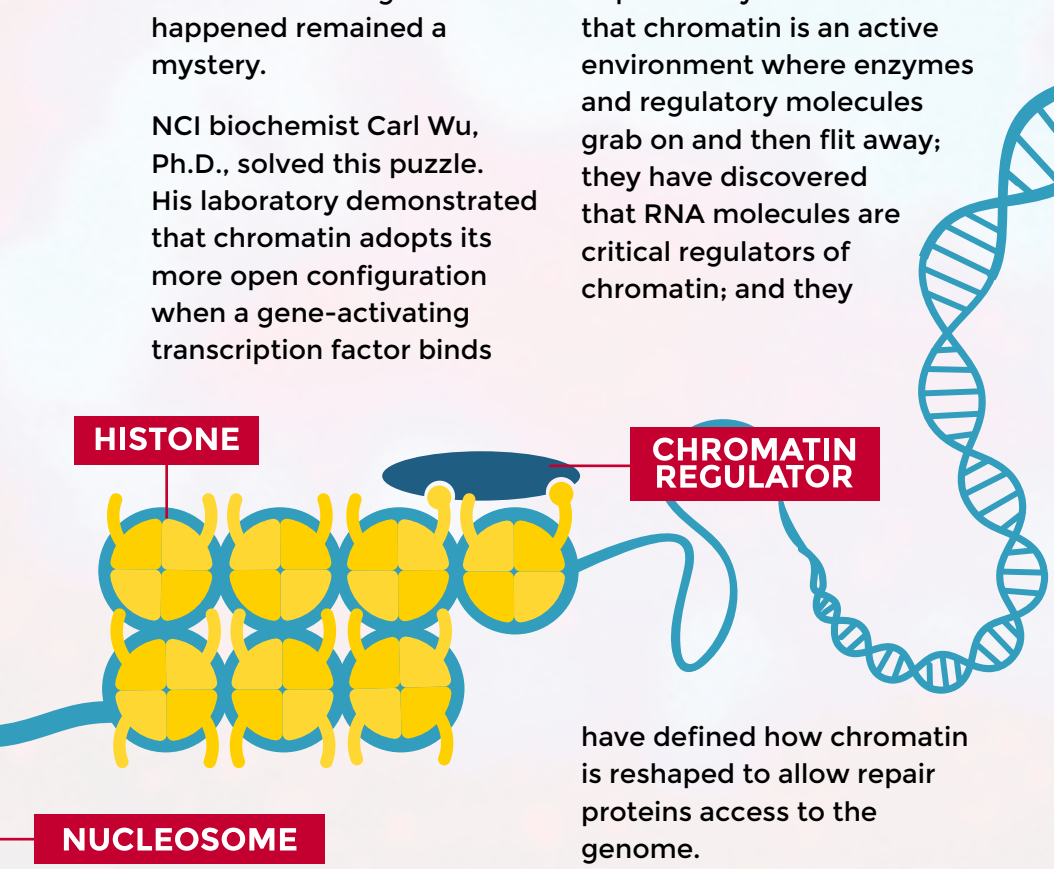
Analyzing DNA near a hormone-activated gene, Hager showed that nucleosomes there corresponded precisely to sites bound by that hormone, suggesting they had a role in gene regulation. In fact, he found organized nucleosomes were essential for correct hormone-triggered gene activation. The findings led to the now well-accepted idea that the gene-activating hormone receptor might trigger functionally important



chromatin changes. How that reconfiguration happened remained a mystery.

NCI biochemist Carl Wu, Ph.D., solved this puzzle. His laboratory demonstrated that chromatin adopts its more open configuration when a gene-activating transcription factor binds to its DNA. Later, Wu's lab discovered a protein complex called NURF that drives that change, shoving nucleosomes aside to make way for the enzyme that reads the DNA.

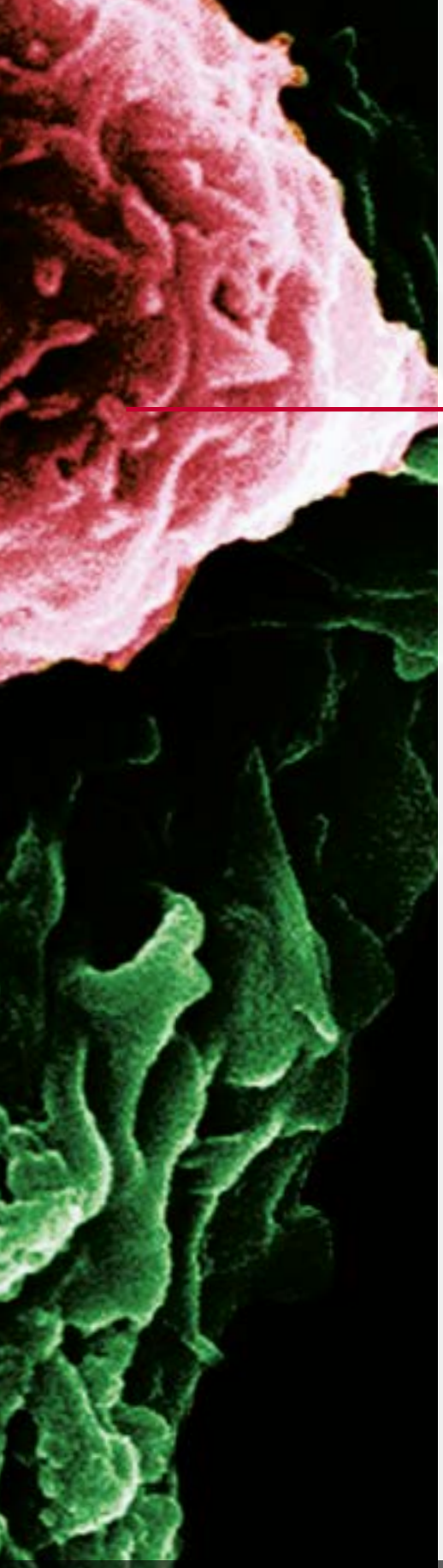
Since Hager and Wu's early discoveries, scientists at NCI and elsewhere have continued to find unexpected complexity in chromatin's structure, function and biological impact. They've learned that chromatin is an active environment where enzymes and regulatory molecules grab on and then flit away; they have discovered that RNA molecules are critical regulators of chromatin; and they have defined how chromatin is reshaped to allow repair proteins access to the genome.



NCI scientists' discoveries about chromatin's function in healthy cells have laid the groundwork for understanding chromatin's role in cancer and other diseases. Today, researchers are finding that mutations that disrupt chromatin are common in human tumors, and researchers are working to unravel the consequences of these changes.

CHROMATIN AND EPIGENETICS

Researchers in the field of epigenetics, which looks at changes in gene expression not due to the genetic code itself, are working to understand the full impact of these chemical marks and the cellular and environmental factors that influence them. Alterations in the form of epigenetic marks in a genome can have major consequences for cellular function, and many such changes have been linked to disease.



CYTOKINES AS THERAPY

Cytokines are small proteins that carry messages between cells and are known to play a critical role in the body's response to inflammation and immune attack. CCR researchers pioneered the therapeutic use of a class of cytokines called interleukins. In collaboration with academic and commercial partners across the country, CCR scientists have successfully led the translation of several interleukins with demonstrated therapeutic potential from the lab to the patient.

Interleukin-2 (IL-2), the first cytokine found to have therapeutic benefit, was discovered in 1976 by Robert Gallo, M.D., and Francis Ruscetti, Ph.D. The team demonstrated that this cytokine could dramatically stimulate the growth of T and natural killer (NK) cells, which are integral to the human immune response. This seminal work enabled researchers to grow and study T cells in the laboratory for the first time, changing the field of immunology forever.

Nearly a decade later, researchers led by Steven Rosenberg, M.D., Ph.D., successfully cured several patients with advanced metastatic renal cell cancer and melanoma by administering IL-2. It became the first U.S. FDA-approved cancer immunotherapy and is still used in clinical settings to treat metastatic melanoma and renal cancer. CCR researchers are currently investigating whether combining IL-2 with other cytokines is effective in treating patients with these cancers.

CCR research groups led by Crystal Mackall, M.D., and Ron Gress, M.D., characterized another cytokine, IL-7, as a master regulator of T-cell homeostasis or equilibrium.

1962 — Conducted groundbreaking studies leading to the development of monoclonal antibodies

1976 — Discovered IL-2 and demonstrated it is a T-cell growth factor

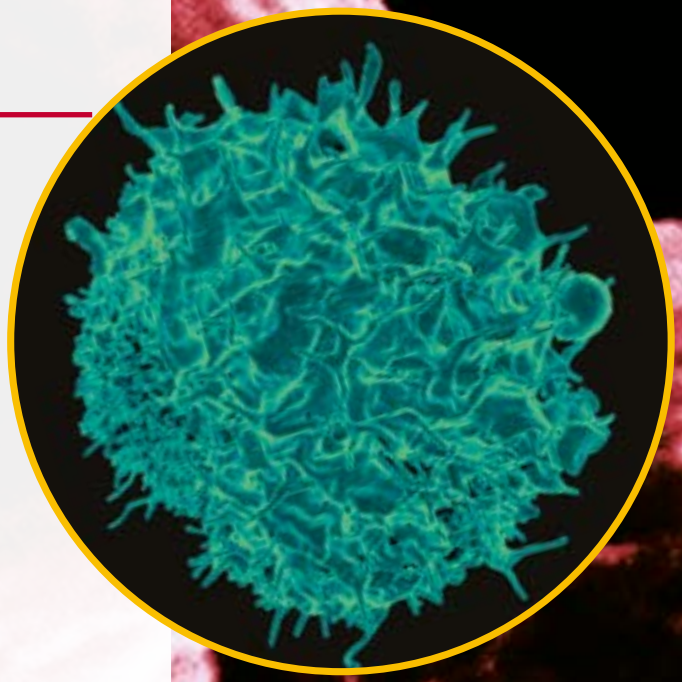
1984 — Cloned the alpha subunit of the IL-2 receptor

1985 — Used IL-2 to develop the first effective immunotherapy cancer treatment

In the first human clinical trial with IL-7, they found that the cytokine drives regeneration of T cells that are critical to the immune system but become depleted during chemotherapy. IL-7-based therapies also might restore immune function in other immunocompromised individuals, such as those with HIV and the aged, and might enhance the activity of vaccines and other cancer immunotherapies (see Development of Cancer Immunotherapy, p.12).

A third cytokine, IL-15, was co-discovered in CCR in 1994 by Thomas Waldmann, M.D., and his team. Like IL-2, it triggers the production of immune cells that attack and kill cancer cells. CCR collaborated with the NCI's Division of Cancer Treatment and Diagnosis and the National Institute of Allergy and Infectious Diseases to produce clinical-grade IL-15 for first-in-human testing in clinical trials across the U.S. Coming full circle, it was Waldmann's group that initiated the first IL-15 clinical trial in 2011. The results of the trial, published in 2015, showed IL-15 dramatically increased growth and activity of T and NK cells. Studies investigating the potential for IL-15 to enhance the effectiveness of vaccines against viruses that cause cancer and autoimmune diseases are underway.

The success CCR researchers have had in developing therapeutic cytokines is a reflection of the highly collaborative nature of CCR research, both among NIH colleagues and with academia and the commercial sector.



Caption: A colorized scanning electron micrograph of a T lymphocyte used in immunotherapy.

Credit: National Institute of Allergy and Infectious Diseases, NIH

1988 Discovered and cloned the first chemokine, IL-8

1989 Created a single-chain recombinant immunotoxin

1994 Co-discovered IL-15

1994 Discovered JAK3 and demonstrated it is activated by IL-2

DEVELOPMENT OF CANCER IMMUNOTHERAPY

More than 30 years ago, NCI intramural scientists began to explore the heretical idea that a patient's immune system could be harnessed to fight cancer. The objective was to amplify and unleash the body's natural ability to recognize and destroy cancer cells. The resulting field, now called immunotherapy, has made important advances in cancer treatments using monoclonal antibodies and cytokines, as well as cell-based therapies.

CCR scientist Michael Potter, M.D., conducted groundbreaking research that led to the development of monoclonal antibodies, for which he received the 1984 Albert Lasker Award for Basic Medical Research. His findings laid the foundation for the use of monoclonal antibodies to successfully treat several types of cancer. One approach, developed by CCR researcher Ira Pastan, M.D., coupled a monoclonal antibody to a toxin to deliver it to cancer cells. The resulting immunotoxin has been an effective therapy for patients with hairy cell leukemia and has shown promise in the treatment of other hematologic cancers, as well as liver and mesothelin-based cancers.

Monoclonal antibodies have also become the agent of choice to block key immune checkpoints, which limit the capacity of the body to kill cancer cells. In 2003, CCR investigator Steven Rosenberg, M.D., Ph.D., was amongst the first to show that checkpoint blockade drugs could lead to cancer regression. This approach is now used worldwide in the treatment of many types of cancers.

In the mid-1980s, Rosenberg discovered that treating cancer patients with the cytokine interleukin-2 (IL-2) reduced or eliminated tumors in some patients. Several other cytokine-based

2001 — Demonstrated that the immunotoxin BL22 induced remission in hairy cell leukemia

2003 — Showed the administration of a checkpoint inhibitor can mediate cancer regression

2006 — Reported first successful gene therapy of any cancer in humans

2010 — Determined T cells expressing CARs could be used to successfully treat cancer

therapies developed by CCR researchers soon followed (see Cytokines as Therapy, p. 10).

Rosenberg's team went on to pioneer cell-based cancer therapies by using IL-2 in a different capacity. T cells, which are key infection-fighting cells in the body, were isolated from a patient's tumor and grown in the laboratory with IL-2, a potent T-cell growth factor. These cells were then re-infused into the patient. While this proved an effective treatment for some patients, the researchers discovered they could improve these results by genetically engineering T cells to recognize proteins specific for the patient's cancer cells.

One outcome of these early adoptive cell therapy studies was the development of chimeric antigen receptor (CAR) expressing T cells. T cells isolated from a patient's blood are modified to express a CAR that will ideally enable the cell to recognize and destroy specific types of cancer cells. Rosenberg's team was the first to show that CAR T cells recognizing CD-19 are useful in the treatment of some blood cell cancers.

While the initial components necessary to develop CAR T-cell treatments were painstakingly developed at NCI, they are now widely used, and numerous laboratories have since demonstrated the benefits of this approach in the treatment of a variety of cancers. What started decades ago as a speculative idea in CCR laboratories is now common practice in hospitals around the world.

Caption: Steven Rosenberg, M.D., Ph.D., with Linda Taylor, the first cancer patient he cured using immunotherapy.

Credit: NIH Record

2010 — First use of IL-7 to treat cancer in humans

2013 — Developed method to identify and target unique mutations in cancer cells from individual patients

2014 — Reported epithelial cancers can be successfully treated using adoptive cell therapy

2015 — "First-in-human" clinical trial of IL-15

GENOMIC CLASSIFICATION OF TUMORS

While it is current practice today to molecularly characterize tumors based on their genetic fingerprints, CCR investigators were among the first to classify tumors based on genetics. As a result, treatments are now being tailored to an individual's specific cancer subtype, and new therapies are being developed to target the vulnerabilities of different types of cancer cells. Major CCR successes in this area have improved the classification of kidney cancers and lymphomas and have laid the foundation for what is now called precision medicine.

Historically, kidney cancer was considered a single disease with a poor prognosis in its advanced stages. Hoping to find clues about the disease's origins that might lead to targeted therapies, CCR investigators Marston Linehan, M.D., and Berton Zbar, M.D., set out in the 1980s to search for its genetic causes.

They established a hereditary cancer program to recruit patients with rare genitourinary cancers to the NIH Clinical Center and launched large-scale genetic studies. After analyzing the DNA of thousands of patients, the team linked mutations in the VHL gene to the von Hippel-Lindau syndrome that predisposes people to developing tumors in many organs, including the kidneys. The VHL gene is also commonly mutated in non-inherited cases of clear cell renal cell carcinoma, the most common type of kidney cancer. Understanding the VHL pathway has provided the foundation to develop a number of novel approaches to therapy for this disease.

Linehan and his colleagues went on to identify and characterize a number of different genes that are mutated in different forms of kidney cancer. Determining which mutations are present helps doctors predict how aggressive a patient's cancer is likely to be and assists in recommending an appropriate treatment. Identifying the pathways disrupted by these mutations has also pointed toward strategies for developing new therapies, including immunotherapy.

In the 1990s, CCR investigator Louis Staudt, M.D., Ph.D., began searching for molecular distinctions that might predict the clinical course of an aggressive blood cancer called diffuse large B cell

lymphoma (DLBCL). DLBCLs look the same under the microscope, and although some patients respond well to chemotherapy, no one could predict who might benefit from a more aggressive approach.

Taking advantage of CCR's support for open-ended discovery, Staudt created a novel DNA microarray termed the lymphochip and used it to analyze the activity of thousands of genes in tumor biopsies from patients with DLBCL. Interrogating their data, the team identified two main subtypes of DLBCL, each with a characteristic molecular profile that is now recognized as a distinct cancer type by the World Health Organization. The discovery explained why patients respond differently to chemotherapy and enabled researchers to develop new strategies for eliminating the more difficult-to-treat subtype, activated B-cell (ABC) DLBCL.

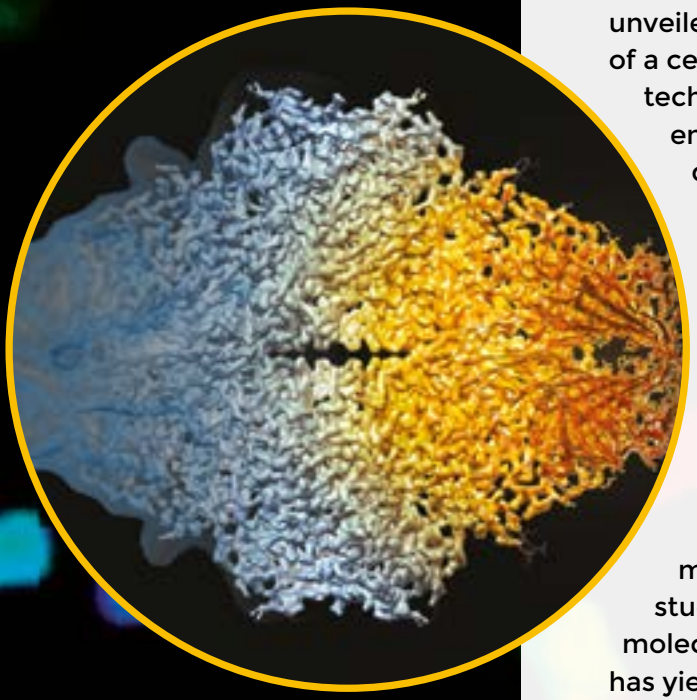
Most significantly, this discovery coincided with the development of the drug ibrutinib that specifically inactivated an enzyme called BTK, which Staudt showed is a lynchpin in the ABC form of the disease. In clinical trials conducted with Wyndham Wilson, M.D., Ph.D., a close colleague of Staudt, patients with ABC DLBCL had frequent responses to ibrutinib, some quite durable, whereas ibrutinib was ineffective against most other DLBCL tumors. Staudt and Wilson are extending this precision medicine paradigm to other forms of lymphoma and are devising combination regimens that are tailored to the molecular abnormalities of each lymphoma subtype.

Caption: Marston Linehan, M.D., discusses treatment with a patient. Linehan is a pioneer in the study of the genetic basis of kidney cancer.

Credit: Rhoda Baer

Technology developed by CCR investigators Lance Liotta, M.D., Ph.D., Robert Bonner, Ph.D., and Michael Emmert-Buck, M.D., Ph.D., in 1996 paved the way for the large-scale molecular analysis of a range of cancers. The method, called laser capture microdissection, enables the isolation of tumor cells from the surrounding normal tissue in a sample to help determine the genetic difference between the two. As researchers view the sample through a microscope, they trace the desired cells with a laser. This allows for the precise separation of tumor cells from the healthy or precancerous tissue that surrounds them. The technique was an important step forward for genomic classification because it damages neither the structure of the cell nor its chemistry. It also leaves surrounding cells intact, thereby enabling extraction of pure cells from the desired location.

CELLULAR IMAGING



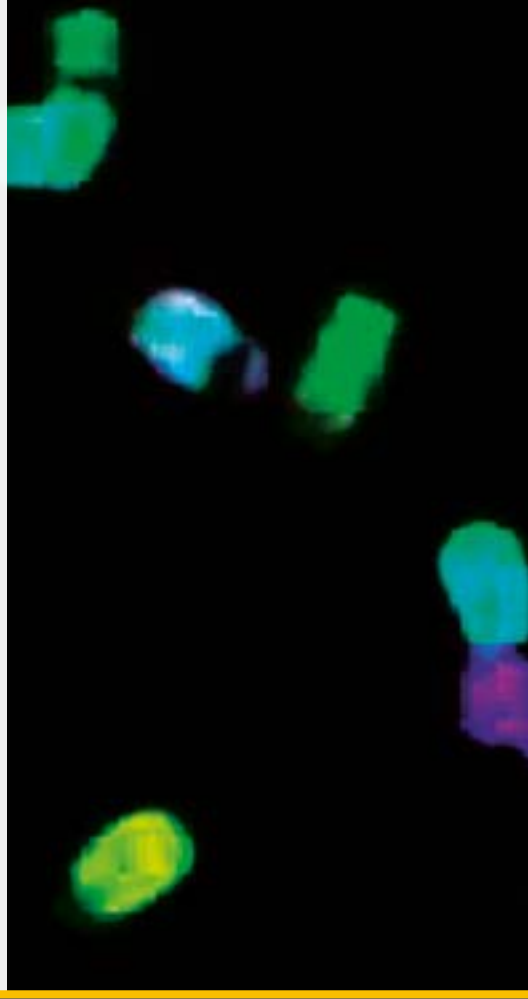
Caption: This composite image of the beta-galactosidase molecule shows how cryo-EM's resolution has dramatically improved in recent years.

Credit: Veronica Falconieri, Sriram Subramaniam, CCR, NCI, NIH

A unique aspect of CCR is an interest in the development of new methods and technology to drive discovery. Innovative imaging methods developed and refined within CCR have revealed atomic-level structures of biological molecules and unveiled dynamic views of a cell's interior. These technologies have enabled groundbreaking discoveries at the subcellular level that are driving the design of new treatments and diagnostics for cancer.

For decades, X-ray crystallography has been the primary mainstay of structural studies of biological molecules. The technique has yielded molecular structures at a very high resolution but only worked optimally with molecules that could be crystallized without destroying the integrity of the molecule itself. CCR investigator Sriram Subramaniam, Ph.D., and his team have now made it possible to obtain the same type of high-resolution structural information for many molecules that are incompatible with X-ray crystallography through his use of cryo-electron microscopy, or cryo-EM. Cryo-EM could become an important part of accelerating drug discovery. It was named "Method of the Year" by *Nature* in 2015 and in 2017, was recognized by the Nobel Prize in Chemistry.

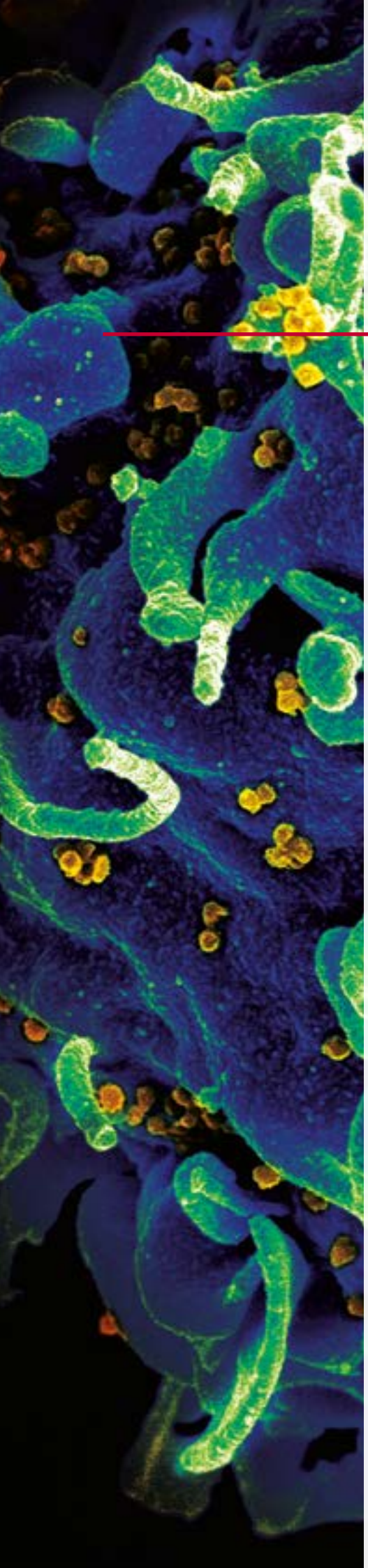
To visualize molecules with cryo-EM, purified proteins are flash-frozen in liquid nitrogen and bombarded with electrons to capture a molecular image. In 2015, the Subramaniam laboratory reported the highest-resolution image ever produced with the technique, visualizing the structure of a bacterial enzyme with a level of detail previously achieved only with X-ray crystallography. Since then, his group has produced extraordinarily high-resolution structures that offer insight into how potential targets for new cancer therapies work and interact with compounds that block their function. This type of information is expected to help guide the design of new drugs for patients.



To fully understand a biological molecule's involvement in health or disease, scientists also need to understand how it behaves in its natural context. In the early 2000s, the laboratory of Tom Misteli, Ph.D., started devising methods to visualize how genes behave in living cells. The group developed techniques using fluorescent tags to observe gene-regulating proteins in action and used the tags to show that the protein activities are surprisingly dynamic. They also created complementary approaches to track the locations and motion of genes themselves. Those tools led to the discovery that genes have particular three-dimensional positions within the cell nucleus and their spatial organization has a profound impact on their level of activity. In 2009, Misteli's team discovered that some genes reside in different places inside cancer cells than in noncancerous cells. Following these displaced genes may one day help clinicians diagnose disease.

The imaging and visualization methods developed by CCR scientists have propelled studies of the mechanisms that drive cancer and have influenced imaging as well as other aspects of diagnostic and clinical areas of oncology. As researchers have proven, when the unseen becomes visible, our understanding of biology gains sharper focus.

Diagnostic labs around the world rely on a method developed at CCR to visualize chromosomes and diagnose disease. The method, developed by Thomas Ried, M.D., in 1997, is called spectral karyotyping (SKY). It paints different chromosomes with distinctly colored fluorescent probes so that each one can be easily identified. SKY is particularly useful in cancer cells, whose broken and mixed up chromosomes can make other methods of chromosome identification nearly impossible.



THE FIRST AIDS DRUGS

Faced with the burgeoning HIV/AIDS epidemic in the 1980s, NCI's intramural program developed the first therapies to effectively treat the disease. The NCI efforts drew upon its established expertise in virology, tumor biology and the immune system and was enabled by the inherent flexibility of the NIH intramural research program to respond quickly to new crises. The discoveries of NCI researchers in the early days of HIV/AIDS were vital in transforming HIV infection from a fatal diagnosis to the manageable condition it is for many today.

Patients with the mysterious immune disorder now known as AIDS had been arriving at the NIH Clinical Center since 1981. When the human immunodeficiency virus (HIV) was identified by Luc Montagnier, M.D., at the Pasteur Institute in Paris, and then shown by NCI's Robert Gallo, M.D., in 1984 to be the cause of AIDS, NCI scientists were poised to rapidly act on the discoveries.

At the time, there were almost no effective antiviral drugs for any disease, and it was unclear whether stopping HIV from replicating was feasible or would allow patients' immune systems to recover from an infection. But NCI's Samuel Broder, M.D., Hiroaki Mitsuya, M.D., Ph.D., and Robert Yarchoan, M.D., searched for compounds that inhibited viral growth in the laboratory and then immediately initiated first-in-human trials at the NIH Clinical Center to test them in patients. NCI's strong industry collaborations helped speed patient access to the new drugs.

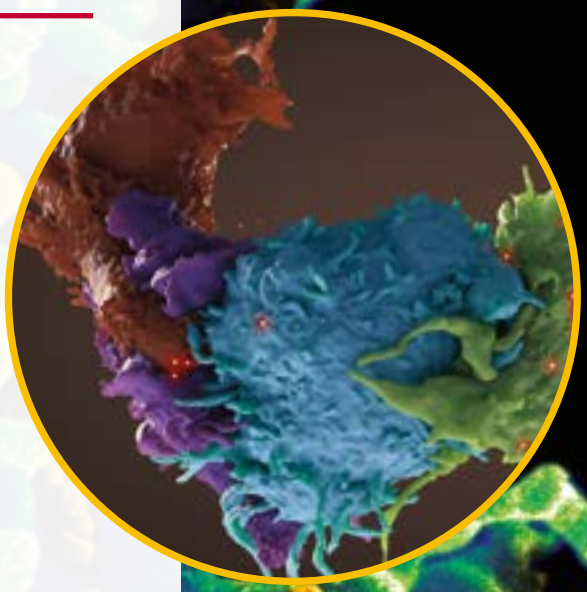
The NCI researchers first focused on a viral enzyme called reverse transcriptase that HIV needs to multiply. They developed an assay to test the utility of drugs against HIV and gathered a number of promising compounds to test. Azidothymidine (AZT), a compound first synthesized by Jerome Horowitz, Ph.D., in 1964 as an anti-cancer drug, was among the drugs initially tested. In a preliminary clinical trial done largely in the NIH Clinical Center, NCI scientists showed that AZT could improve the immune function of AIDS patients. In a randomized trial, it was subsequently shown to improve survival of AIDS patients. In 1987, it became the first drug approved by

the U.S. FDA for treatment of the disease. AZT was subsequently shown to markedly reduce the perinatal transmission of HIV.

Because AZT was not entirely effective by itself, NCI scientists continued to develop and test other drugs to treat AIDS, including the reverse transcriptase inhibitors didanosine (ddI) and zalcitabine (ddC). These became the second and third drugs approved by the FDA for AIDS. Combining AZT with one of these drugs improved the effectiveness of antiretroviral therapy.

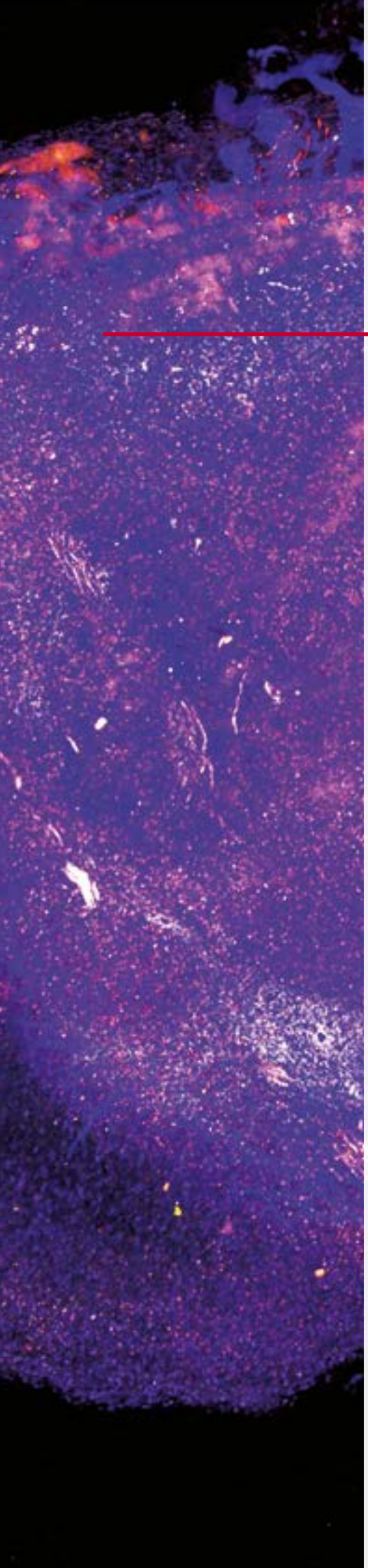
Unfortunately, patients often developed resistance to these drugs. As researchers learned more about HIV in the following years, they were able to develop drugs that attacked the virus in new ways. NCI scientists helped map out the structure of another essential viral enzyme, the HIV protease, to guide the design of a new class of HIV drugs. When combined with reverse transcriptase inhibitors, protease inhibitors, developed in the mid-1990s, dramatically suppressed replication of the virus, often reducing it to undetectable levels.

The number of AIDS-related deaths in the U.S., which exceeded 40,000 in 1995, declined rapidly after the introduction of this combination therapy, called highly active antiretroviral therapy (HAART). HAART has dramatically reduced AIDS mortality and transmission of the virus in many parts of the world where there has been ready access to the medication. It has also markedly reduced the development of the many AIDS-related cancers that are associated with immunodeficiency. CCR scientists have continued to study the virus, including malignancies such as Kaposi sarcoma that are related to and influenced by HIV infection, and patients living with HIV today have even more treatment options.



Caption: An HIV-infected T cell (blue, green) interacts with an uninfected cell (brown, purple).

Credit: Donald Bliss, National Library of Medicine, NIH; Sriram Subramaniam, CCR, NCI, NIH



PRECISE CLINICAL IMAGING OF TUMORS

A major challenge in cancer treatment is to precisely locate and monitor tumors in the body so that the tumors can be killed without harm to surrounding cells. In the past decade, multidisciplinary teams of CCR researchers have helped design breakthrough imaging technologies that enable a closer understanding of where and how tumors grow in the human body. One of these imaging technologies, now known as UroNav, is revolutionizing clinicians' ability to accurately diagnose and treat prostate cancer.

The imaging tool UroNav, also called MRI/ultrasound fusion-guided biopsy, overlays an advanced magnetic resonance image (MRI) of the prostate, done at initial diagnosis, with an ultrasound image performed at the time of biopsy. This image fusion technology dramatically improves the accuracy of locating potentially cancerous prostate regions that require biopsy. Standard multi-needle methods of prostate cancer biopsy have randomly sampled large areas of prostate tissue, which increases the likelihood of false-negative or false-positive results.

MRI/ultrasound fusion biopsies permit more precise biopsies of abnormal-appearing prostate tissue.

A prototype of the new method was patented by CCR researchers in 2007. After extensive testing at NIH, the investigators combined forces with InVivo, a subsidiary of Philips Healthcare, to build a commercial version of the prototype. Now known by the name UroNav, the device enables three-dimensional, real-time visualization of prostate tumors during biopsy. Released to the market in 2013, UroNav, and other devices based on the same technology, may soon replace the current standard of care for prostate cancer detection and diagnosis.

A year after its release, UroNav was included in *U.S. News & World Report's* list of the top ten most notable medical advances in the past 25 years. Clinical testing is underway to determine whether such devices may also be used to guide localized laser ablation of scattered, small prostate tumors as an alternative to full prostate removal or irradiation.

Another imaging tool developed by CCR researchers helps in the identification of treatment-resistant tumors. The method, called electron paramagnetic resonance imaging (EPRI), is similar to an MRI in that it uses a magnetic field to reveal properties of atoms. In the case of EPRI, however, the primary focus is on free radicals, which are uncharged molecules with a free electron. EPRI indirectly detects the low oxygen levels characteristic of growing tumors that occur in a wide range of cancers. Tumors with inadequate oxygen supply, called hypoxic tumors, are more resistant to radiation and chemotherapy and have an increased risk of metastasis than tumors with normal oxygen levels.

In 1998, CCR researchers used EPRI to create the first map of oxygen content in tissues and tumors of mice. In 2008, the team demonstrated that EPRI, when used in conjunction with MRI, provided detailed, three-dimensional information about the exact location of treatment-resistant tumors in living organisms in real time, thus creating a roadmap to help target treatments to these tumors. Today, CCR continues to explore EPRI as a noninvasive way to detect tumor hypoxia in patients.

Caption: Peter Pinto, M.D., and Peter Choyke, M.D., use UroNav to improve accuracy of prostate cancer imaging.

Credit: Rhoda Baer

AWARDS AND ACCOLADES

NATIONAL ACADEMY OF SCIENCE MEMBERS

- Sankar Adhya
- Susan Gottesman
- Shiv Grewal
- Doug Lowy
- Ira Pastan
- Michael Potter*
- Maxine Singer*
- Lou Staudt
- Thomas Waldmann
- Sue Wickner
- Carl Wu*

NATIONAL ACADEMY OF MEDICINE MEMBERS

(formerly the Institute of Medicine)

- Michael Gottesman
- Richard Hodes
- Elaine Jaffe
- Claude Klee*
- Marston Linehan
- Doug Lowy
- John Niederhuber*
- Ira Pastan
- Steven Rosenberg
- Thomas Waldmann
- Sam Wells*
- Carl Wu*
- Stephen Katz*

AMERICAN ACADEMY OF ARTS AND SCIENCES MEMBERS

- Sankar Adhya
- Donald Court
- Michael Gottesman
- Susan Gottesman
- Shiv Grewal
- Claude Klee*
- Michael Lichten
- Glenn Merlino
- Stephen O'Brien*
- Ira Pastan
- Maxine Singer*
- Thomas Waldmann
- Sue Wickner
- Carl Wu*

LASKER AWARDS

- Robert C. Gallo (1982,1986)*
- Doug Lowy and John Schiller
- Michael Potter*
- The NIH Clinical Center

NATIONAL MEDAL OF TECHNOLOGY AND INNOVATION

- Doug Lowy and John Schiller

*** No longer with NCI**

PRESIDENTIAL EARLY CAREER AWARDS FOR SCIENTISTS AND ENGINEERS

- James Gulley
- Dan Larson

SERVICE TO AMERICA MEDALS

- Steven Rosenberg: 2015 Federal Employee of the Year
- Thomas Waldmann: 2009 Career Achievement Award
- Doug Lowy and John Schiller: 2007 Federal Employees of the Year

ARTHUR S. FLEMMING AWARD

- Elise Kohn
- Lance Liotta*
- Tom Misteli
- Andre Nussenzweig
- Carole Parent*
- Shyam Sharan
- Lou Staudt

NIH DISTINGUISHED INVESTIGATORS

- Susan Gottesman
- Shiv Grewal
- Doug Lowy
- Tom Misteli
- Andre Nussenzweig
- Ira Pastan
- Lou Staudt
- John Schiller
- Giorgio Trinchieri
- Thomas Waldmann
- Sue Wickner
- Carl Wu*

FORMER TRAINEES WHO WON A NOBEL PRIZE

- Robert Lefkowitz* (mentor: Ira Pastan)
- Daniel Nathans* (mentor: Michael Potter)
- Harold Varmus* (mentor: Ira Pastan)

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LANDMARKS COVER ART CREDITS

LEFT SIDE FROM TOP TO BOTTOM:

Title: Killer T cells surround a cancer cell
Credit: Alex Ritter, Jennifer Lippincott Schwartz and Gillian Griffiths, NIH

Title: Enzyme repairing DNA
Credit: Tom Ellenberger, Washington University School of Medicine in St. Louis; Dave Gohara, Saint Louis University School of Medicine

Title: Terry Fry, M.D., and patient
Credit: Daniel Soñe

Title: Dendritic cell with HIV
Credit: Donald Bliss, National Library of Medicine, NIH

RIGHT SIDE FROM TOP TO BOTTOM:

Title: T lymphocyte
Credit: NIAID, NIH

Title: Researcher in CCR lab
Credit: Rhoda Baer

Title: Human papillomavirus
Credit: Veronica Falconieri, CCR, NCI, NIH

Title: HIV infecting a human cell
Credit: Seth Pincus, Elizabeth Fischer and Austin Athman, NIAID, NIH

Title: Improving resolution by cryo-EM
Credit: Veronica Falconieri, Sriram Subramaniam, CCR, NCI, NIH

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