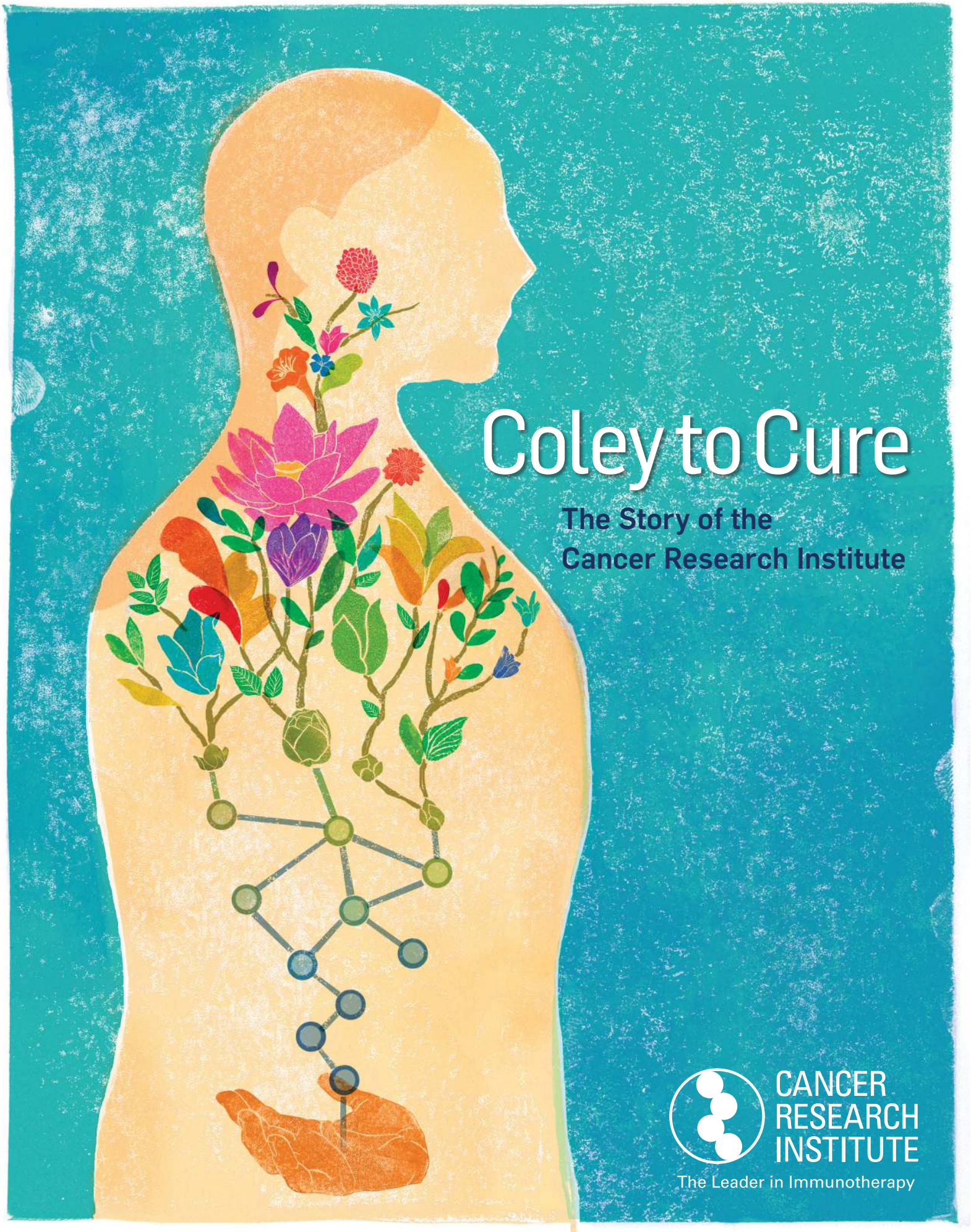

Coley to Cure

The Story of the Cancer Research Institute

CANCER RESEARCH INSTITUTE

The Leader in Immunotherapy

Coley to Cure

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CANCER RESEARCH INSTITUTE

The Leader in Immunotherapy

PROLOGUE

60 Years and Counting

The era of cancer immunotherapy has arrived. After years of only marginal recognition, the approach has finally captured the attention and respect of the scientific establishment as a whole. And rightly so: cancer immunotherapy offers the greatest hope of transforming cancer treatment in our lifetimes.

As the one institution that has consistently supported cancer immunology from the beginning, the Cancer Research Institute (CRI) is proud of the successes the field is now witnessing. Having *Science* magazine deem cancer immunotherapy the 2013 "Breakthrough of the Year" was fitting testimony to just how far we've come.

Yet, as we celebrate our contemporary successes and look optimistically toward the future, it is also appropriate to look back at where the field came from. Cancer immunotherapy did not spring to life out of nowhere in the past five years. It took decades of dedicated work by scientists and lay people who saw value in the approach and worked tirelessly to make it a reality. For many years, CRI was the only institution devoted to nurturing the field of cancer immunology. And it did so at a time when there was little interest from the medical establishment. If it weren't for CRI, cancer immunology as we know it today simply would not exist.

When CRI was founded in 1953, the mainstays of cancer treatment were surgery, radiation, and chemotherapy—just as they are today. The immune system and how it works to fight infection—to say nothing of cancer—was largely a mystery. No one but a handful of visionary individuals saw the potential of immune-based treatments for cancer, and the work these individuals pursued happened far out of the limelight. Yet from the beginning, the goal of CRI was nothing short of revolutionary: to conquer cancer just like smallpox and polio had been.

CRI's founders knew that reaching this goal would require steadfast financial commitment and sustained scientific research. For more than 60 years, CRI has provided these resources, allowing cancer immunotherapy to grow from a largely empirical, trial-and-error approach to a mature science backed up by deep knowledge of the immune system.

So intertwined are the histories of cancer immunotherapy and the history of CRI as an institution that it is impossible to tell the story of one without the other. In many ways, the story of the Cancer Research Institute *is* the story of cancer immunotherapy. Like any good story, this one comes with a cast of memorable characters, unexpected plot twists, and an ending that will leave you wanting more.

In addition to enjoyment and a greater understanding of what cancer immunotherapy has to offer, I hope readers will take from this tale a sense of the collaborative nature of science, and the role that institutions like CRI play in nurturing the decades-long process of scientific discovery. Thanks to the work of thousands of CRI-funded scientists, cancer immunotherapy is changing the face of cancer treatment, so much so that curing some forms of cancer is now truly within our reach. With continued financial support from the donors who make our work possible, CRI will continue to lead this important field well into the future.

JILL O'DONNELL-TORMEY, PH.D.
CEO and Director of Scientific Affairs

» Cancer immunotherapy offers the greatest hope of transforming cancer treatment in our lifetimes. «

COLEY TO CURE

The Story of the Cancer Research Institute

Mary Elizabeth Williams knew her odds of beating cancer were slim. The 37-year-old mother of two had been diagnosed with melanoma in 2010, and underwent surgery to remove a small patch of skin from her scalp. But in August 2011, her cancer returned with a vengeance, spreading to her lungs and back. The 5-year survival rate for metastatic melanoma is only 15%. Mary Elizabeth would be lucky to see spring.

That's when her doctor, Jedd Wolchok, of Memorial Sloan Kettering Cancer Center, proposed that she enter a clinical trial of two new immunotherapy drugs. The drugs work by boosting the immune system, empowering it to attack cancer cells.

Williams was skeptical at first, but the New York-based writer was willing to do almost anything for a chance to spend more time with her children. She began treatment in the fall of 2011. By January 2012, she knew the treatment was working.

"It was incredible," says Williams. "I didn't want to believe it. The tumor on my lung had disappeared. And the tumor on my back had completely receded." Two years later, she is in full remission.

OPPOSITE: *CRI's founder, Helen Coley Nauts (left), her father William B. Coley, M.D. (right), and leukemia survivor Emily Whitehead (center)*

■ *CRI Scientific Advisory Council associate director Jedd Wolchok, M.D., Ph.D., with Mary Elizabeth Williams at Memorial Sloan Kettering Cancer Center*

■ *In 2013,* Science *magazine voted cancer immunotherapy the "Breakthrough of the Year."*

Williams's story is dramatic, but it's not an isolated case. Williams was one of more than 80 patients to enroll in a clinical trial that has since made big waves in the oncology community. When Jedd Wolchok, the trial's principal investigator, presented results of the study at the June 2013 meeting of the American Society for Clinical Oncology (ASCO), the response was electric.

"Truly remarkable," is how Susan Swain, the past president of ASCO, put it, adding, "This kind of response has not been seen with immunotherapy before."

Science analyst Michael Becker was even more enthusiastic, proclaiming in July 2013, "The era of skepticism over use of the body's immune system to effectively treat cancer has officially come to an end. We are now firmly in the early stages of the cancer immunotherapy revolution."

In December 2013, *Science* magazine voted cancer immunotherapy the "Breakthrough of the Year"—hefty praise from America's top scientific journal.

If it is true that immunotherapy for cancer is entering a new phase of unprecedented progress, it is also true that such developments did not happen overnight. It took decades of basic research to make that hope a reality, and at the center of it all was one organization—the Cancer Research Institute (CRI).

For 60 years, CRI has dedicated itself to pursuing the science behind the immune response to cancer. At a time when immunotherapy was brushed aside by powerful leaders in the field, CRI took up the challenge of funding the research that would, over the course of six decades, put immunotherapy on the scientific map.

Thanks to CRI scientists, immunotherapy is beginning to join the ranks of surgery, radiation, and chemotherapy as a standard component of cancer treatment. And, with continued support from generous donors, CRI will be able to accelerate the pace of change, bringing more lifesaving immunotherapies to patients faster.

■ *James P. Allison, Ph.D., director of CRI's Scientific Advisory Council*

Checkpoint Blockade: A New Way to Fight Cancer

The immunotherapy that has garnered so much recent attention is known as checkpoint blockade. Antibodies are used to release the "brakes" on immune cells, revving them up. The approach takes advantage of the fact that the immune system already knows how to fight cancer, it just needs a little help.

Checkpoint blockade is the brainchild of James Allison, chair of immunology at The University of Texas MD Anderson Cancer Center in Houston, Texas, and current director of the Scientific Advisory Council at CRI. Like many therapeutic advances, it came out of a surprising laboratory finding.

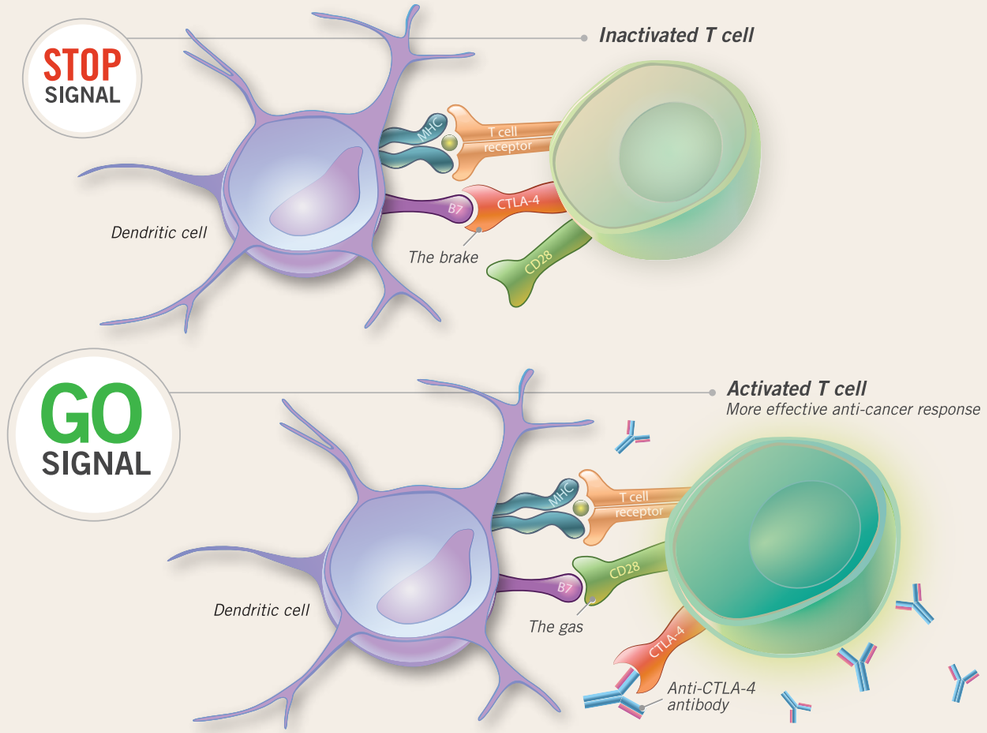
Back in the 1990s, while he was a professor at the University of California, Berkeley, Allison was exploring the signals that prod

» We are now firmly in the early stages of the cancer immunotherapy revolution.«

– MICHAEL BECKER

TAKING THE BRAKES OFF

T cells have stop and go signals, much like the brakes and gas pedal of a car. Checkpoint blockade antibodies like anti-CTLA-4 interrupt the stop signal on T cells, making them more active and prodding them to attack cancer cells.



T cells into killing their targets. T cells are immune system cells that recognize dangerous invaders by binding to tell-tale flags, called antigens, on their surface. Each T cell has a receptor that is specific for one particular antigen, with which it fits together like a lock and key. Additional receptors on the T cell provide the signals to attack.

Allison and colleagues had already shown that one such attack signal is provided by a receptor called CD28. Then, in 1995, they found that a receptor called CTLA-4 provided a different kind of signal. Unlike CD28, which prods T cells into action, CTLA-4 shuts them down.

Allison likes to use the analogy of a car: if the T cell receptor is the ignition switch, then the CD28 molecule is the gas pedal, telling the T cell to go; the CTLA-4 molecule is the brake, keeping the immune system in check so it doesn't speed out of control.

Allison realized that if the T cell's brakes could be temporarily let up, then the immune response to cancer might be strengthened. To let up the brakes, Allison and colleagues created an antibody specific for CTLA-4. The antibody binds to CTLA-4 on T cells and blocks its activation. They then injected this antibody into mice with melanoma tumors. To their great surprise, the tumors shriveled up and completely disappeared.

"It was amazing to think that just covering up this one molecule could have such a profound effect," Allison says.

Since Allison and colleagues first demonstrated the incredible power of anti-CTLA-4 antibodies to shrink tumors, interest in the approach has exploded. The first anti-CTLA-4 antibody, called ipilimumab (trade name Yervoy®, owned by Bristol-Myers Squibb), was approved by the FDA in 2011 for the treatment of metastatic melanoma, and is now being explored as a treatment for other cancers. A suite of additional checkpoint proteins are be-

» It was amazing to think that just covering up this one molecule could have such a profound effect. «

– JAMES ALLISON

James Allison, Ph.D., with CRI postdoctoral fellows Xingxing Zang, Ph.D., and Tsvetelina Pentcheva-Hoang, Ph.D., at Memorial Sloan Kettering Cancer Center

Jill O'Donnell-Tormey, Ph.D., CEO and director of scientific affairs at CRI

»We adapt like the immune system adapts.«

– JILL O'DONNELL-TORMEY

ing studied as well, including PD-1 and LAG-3. The hope is that by targeting several checkpoints at once, the immune system will be able to keep cancer under control, if not eliminate it completely.

"I really believe that immunotherapy is what holds the promise for durable control, not just of melanoma, but of many cancers," says Wolchok, who is conducting clinical trials of checkpoint antibodies and leading the charge of CRI's clinical program.

With clinical successes piling up daily, it's easy to forget that the first checkpoint blockade antibody was 15 years in the making. This was the time it took to bring Allison's basic finding from the bench to the clinic. What's more, Allison's discoveries built on the work of many other scientists, going back decades. At each point in that process, CRI was there, supporting the research on which our modern understanding of the immune system depends.

Fostering Collaboration, Accelerating Discovery

From the beginning, CRI's mission has been to enlist the power of immune system in the fight against cancer. The principal way that CRI has carried out this mission is through funding scientists to conduct basic laboratory and clinical research on the immune system. As knowledge has grown and the needs of the field have changed, however, CRI's funding strategies have evolved as well.

"We adapt like the immune system adapts," says Jill O'Donnell-Tormey, current CEO and director of scientific affairs at CRI.

Nowhere is this more evident than in CRI's most recent initiative, the Clinical Accelerator, designed to speed the development of new cancer immunotherapies. Scientists increasingly recognize that the most promising therapies will involve combinations of different drugs that work in complementary fashion to stimulate the immune system. At the same time, it has become clear that the existing model of drug development, which relies heavily on private pharmaceutical companies to conduct clinical

»The Clinical Accelerator has enabled partnerships with more than 15 biopharmaceutical companies, making available to CRI scientists more than 25 new drugs that can be combined and tested in the clinic.«

trials, is not well suited to testing these combinations in a smart and coordinated fashion.

"For reasons that have nothing to do with science, but everything to do with business," says Allison, "it's very difficult to get the proper pieces to come together in a way that makes the most sense."

This problem came to a head in the mid-2000s, when CRI researchers wanted to conduct a clinical trial of a novel drug combination and found it impossible to obtain the necessary agents. The trial had to be scrapped.

"That experience taught us that we needed a new way of working with companies," says O'Donnell-Tormey. "We needed a way to secure access to drugs."

That's when she, then scientific director Lloyd Old, and the CRI Board of Trustees decided to develop a better model. Their vision was to create a nonprofit venture capital fund that would provide CRI researchers with a seat at the bargaining table with pharmaceutical companies. In 2008, CRI hired financial manager and entrepreneur Adam Kolom to research and develop the strategy for this fund, and then to build it. Since then, the model

Adam Kolom, managing director of the CRI venture fund

GITR · AstraZeneca · MedImmune · CureVac the RNA people® · IMMUNE DESIGN · LUDWIG CANCER RESEARCH

has grown into a comprehensive strategy to speed up immunotherapy development.

Launched in 2012, the Clinical Accelerator is a one-of-a-kind, nonprofit drug development incubator that fosters collaboration among roughly 50 top academic researchers and a wide array of leading biopharmaceutical companies. By breaking down the natural competitive silos that tend to slow progress, the Clinical Accelerator helps to bring better immunotherapies to patients faster.

Funding for the trials comes largely from CRI's nonprofit venture fund, but by securing returns on investment from partner companies if drugs become successful, the model is designed to become self-sustaining over time. "It's a win-win-win situation," says Kolom, "providing significant and immediate benefits to patients, researchers, and industry."

The Clinical Accelerator has already yielded some impressive results. The program has enabled partnerships with more

BEGINNINGS:
William B. Coley & Helen Coley Nauts

WILLIAM B. COLEY (1862-1936) was a prominent surgeon affiliated with Memorial Hospital (now Memorial Sloan Kettering Cancer Center) in New York. In the 1890s, he made a series of observations that led him to a genuine, if underappreciated, medical breakthrough in the treatment of cancer.

It all went back to a single patient, a 19-year-old woman named Bessie Dashiell. In the fall of 1890, Bessie came to Coley complaining of a nagging pain in her right hand. After performing a biopsy, Coley learned that Dashiell had a rare and aggressive form of bone cancer called sarcoma. The condition called for immediate and drastic treatment: amputation of the arm below the elbow. Unfortunately, despite this treatment, the cancer rapidly spread and she died two months later.

Coley decided there must be a better to way to treat cancer. He searched through the medical records of The New York Hospital and stumbled across the remarkable case of a patient with inoperable sarcoma who experienced a complete remission shortly after coming down with a serious skin infection called erysipelas, accompanied by a high fever. Coley combed the medical literature and discovered a number of other cases of spontaneous tumor regressions that often seemed to coincide with a bout of erysipelas (a common post-operative infection in the days before antibiotics). Coley theorized that the infection had somehow caused these regressions through the action of a bacterial "toxin." He wondered whether inoculating patients with erysipelas could cure them of their cancers.

Coley performed the first of these inoculations in 1891 on a patient who had only weeks to live. To his amazement, the tumor regressed and the patient lived another 8 years. Coley continued to experiment with the treatment. Finding that administering live bacteria was difficult and often dangerous, Coley began to experiment with administering heat-killed bacteria.

Over the next 40 years, Coley treated hundreds of patients with his toxins, many of whom obtained durable remissions. Unfortunately, Coley's work was not well-appreciated by the medical establishment at the time. No one—not even Coley—understood how the toxins worked, and they gradually fell out of use. It would only be much later that Coley's pioneering work would be recognized for the breakthrough it was. Today, Coley is known as the "Father of Cancer Immunotherapy." *(continued on next page)*

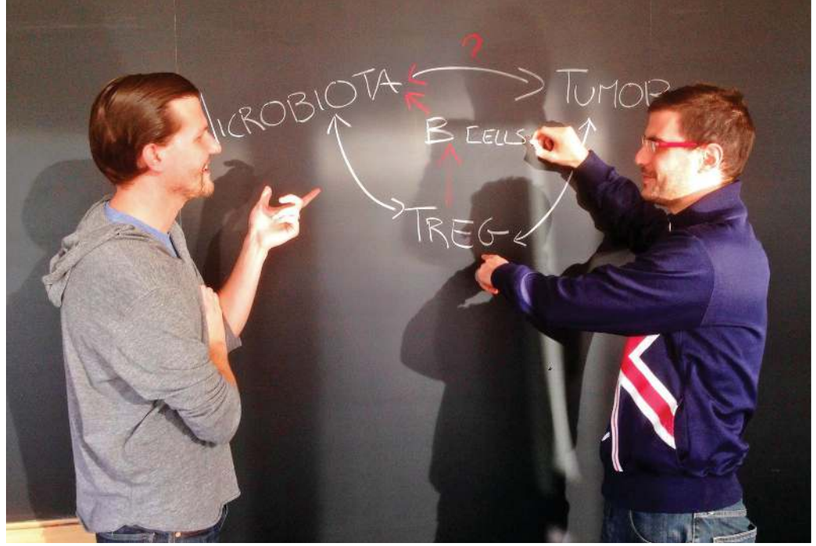
"Nature often gives us hints to her profoundest secrets, will but follow, may lead us on to the solution and it is possible that she has given us a hint which, if we of this difficult problem." —WILLIAM COLEY, 1891

(continued from previous page)

Helen Coley Nauts (1907-2001) rediscovered her father's work in 1939 in a barn on their Connecticut property and pored over his more than 15,000 papers for the next three years. Convinced that her father's toxin therapy had indeed worked, Nauts set out to revive its use. She faced a discouragingly uphill battle. In the early 1940s, the field of cancer treatment was dominated by radiation therapy. Radiation had the backing of prominent leaders in the field, including physician James Ewing, who had been William Coley's boss at Memorial Hospital. Compared to her father's approach, radiation therapy seemed to have immediate and consistent results, and was viewed as more modern and scientific. By the 1940s, Memorial had become known as "radium hospital."

In a few years, chemotherapy would come to the fore as a cutting-edge treatment for cancer, promulgated by another powerful figure at Memorial, Cornelius Rhoads. Rhoads became director of Memorial Hospital in 1939. During World War II he served as the chief of research for the Chemical Warfare Service, which discovered the potential of mustard gas as a chemotherapeutic agent. This wartime experience convinced Rhoads of the value of chemotherapy, and he became its most powerful and vocal advocate.

Nauts approached Rhoads about reviving use of the toxins, but was rebuffed. Undeterred, Helen decided her best bet for reviving use of the toxins would be to align her cause with scientific research. With $2,000 in seed money from Nelson Rockefeller and help from her good friend and businessman Oliver Grace, she started CRI in 1953 with the idea of sponsoring research that would one day validate her father's approach. Over the course of her tenure, she wrote more than twenty monographs analyzing her father's clinical data, and spoke to physicians all over the world about Coley's toxins. That immunotherapy is now a thriving field of cancer treatment has everything to do with the passion, commitment, and scholarship of Helen Coley Nauts.



■ *CRI postdoctoral fellows Noah Palm, Ph.D., and Nicola Gagliani, Ph.D., are investigating the role of bacteria and inflammation in cancer in the lab of Richard Flavell, Ph.D., at Yale University School of Medicine.*

than 15 biopharmaceutical companies, making available to CRI scientists a "spice rack" of more than 25 new drugs that can be combined and tested in the clinic.

But research doesn't—or shouldn't—end there. Insights generated from clinical trials need to feed back into basic laboratory research, which in turn will lead to new discoveries that enhance treatment. "It's a two-way street," says O'Donnell-Tormey.

To facilitate this exchange, CRI established in 2011 its Clinic and Laboratory Integration Program (CLIP), which provides much-needed support to researchers working at the intersection of basic and clinical research. Some of the most exciting questions in tumor immunology today are ones being pursued at this interface, and CRI is a leader in supporting this translational research.

With its innovative CLIP and Clinical Accelerator initiatives, CRI is well positioned to support research that, in the near future, will have a very real chance of curing certain types of cancer. How we got to this point is a story in itself, and leads us back to the Institute's beginning.

"By investing in young faculty and postdoctoral research fellows, CRI has fostered the next generation of cancer researchers who will make the future breakthroughs in cancer immunology."

– DANIEL A. HABER, M.D., PH.D.
Director, Massachusetts General Hospital Cancer Center

THE HARVARD MEDICAL SCHOOL

1890

1891
William Coley treats his first cancer patient with erysipelas vaccine.

1893
William Coley experiments with mixtures of heat-killed bacteria ("Coley's toxins") as a treatment for inoperable cancer.

1919
James Ewing, of Memorial Hospital, publishes *Neoplastic Diseases*, endorsing radiation as the best available treatment for cancer.

1939
Cornelius Rhoads becomes director of Memorial Hospital.

1943
NCI scientist Murray Shear isolates lipopolysaccharide (LPS) from bacteria in Coley's toxins.

1949
The first chemotherapy drug, nitrogen mustard, is approved by the FDA.

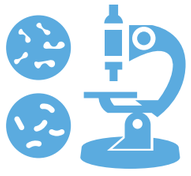
50s–60s HIGHLIGHTS

24

RESEARCHERS FUNDED

$730

THOUSAND AWARDED



RESEARCH AREAS

Coley's toxins

Non-specific immune stimulants (BCG)

Cell-surface antigens

Tumor-specific antigens

Viruses and cancer

1953–1969: Confirming Coley

In 1953, when CRI was founded, the immune system was still very much a mystery. Researchers knew something about the protective molecules, called antibodies, circulating in the blood, but very little about the cellular basis of immunity. Nothing was known about T cells, how they recognize antigens, or where they develop. They didn't even have a name. Our understanding of the immune system and its role in fighting cancer would gradually emerge over the next six decades, thanks in large part to the work of researchers funded by CRI.

In the early days of the organization, most of CRI's modest budget—$15,000 in 1953—went to funding research on Coley's toxins—the immune-stimulating bacterial products that William Coley had begun injecting into cancer patients back in 1891 (see Beginnings, p. 12).

CRI's first grant, in 1954, was awarded to Barbara Johnston, a physician at New York University-Bellevue Medical Center, for a clinical trial of Coley's toxins. Johnston's study was to be a large and definitive analysis of the cancer treatment. The toxins would be produced in Johnston's lab, and each batch of toxins would be tested on laboratory animals to ensure potency. Unfortunately, though some successes in combatting cancer were reported, the results were far from conclusive. Johnston encountered many of the same problems that Coley himself had experienced, namely, the results were inconsistent, and it was not possible to predict who would respond.

Having painstakingly pored through her father's clinical cases and tracked down the results of more than 900 patients treated according to her father's method, Nauts believed the toxins warranted continued use and investigation. Under her leadership, CRI continued to fund both clinical and basic research into bacterial toxins as a form of cancer treatment.

By the 1960s, however, the tide of mainstream cancer therapy had swung strongly toward radiation and chemotherapy, which had more consistently reproducible results. Lacking a medical degree or even formal scientific training, Nauts had a hard time convincing the wider medical community that her father's work might form the basis of a promising mode of therapy. Making matters worse, in 1965, the American Cancer Society added Coley's toxins to its list of "Unproven Methods of Cancer Management" — a compendium of quack therapies. By the end of the decade, it was clear that CRI needed to take a different tack if immunotherapy was going to get off the ground.

Enter Lloyd Old. Old was a young cancer researcher who had recently graduated from medical school at the University of California, San Francisco, and was doing postgraduate work at Sloan Kettering Institute in New York. Nauts met Old sometime in the late 1960s, and the two became fast friends and collaborators. Nauts was impressed by the work Old and his colleagues were conducting on non-specific immune stimulants such as Bacillus Calmette-Guérin (BCG), a weakened form of the bacterium that causes tuberculosis, commonly used as a TB vaccine. CRI began funding their research in 1967. Out of Old's lab emerged some of

Lloyd J. Old, M.D., with CRI founder Helen Coley Nauts. Old is considered the "Father of Modern Tumor Immunology."

» Science hadn't caught up with Coley. It was my responsibility to help Helen have science catch up with him. «

– LLOYD OLD

1950

1953
Helen Coley Nauts and Oliver Grace found the Cancer Research Institute.
Watson and Crick publish *Nature* paper on the structure of DNA.

1955
Henry L. Jaffe replaces Frances H. Bogatko as CRI medical director.

1957
Immunosurveillance hypothesis proposed by Burnet and Thomas.

1958
H. McLeod Riggins appointed medical director of CRI.

1959
Old, Benacerraf, and Clarke publish a paper in *Nature* showing that mice injected with BCG have increased resistance to tumor growth.

"Since 1982, the Cancer Research Institute has been a crucially important partner to Columbia University Medical Center. We look forward to many more years of productive, innovative partnership."

– LEE GOLDMAN, M.D.
Dean of the Faculties of
Health Sciences and Medicine
Executive Vice President for Health and
Biomedical Science,
Columbia University Medical Center

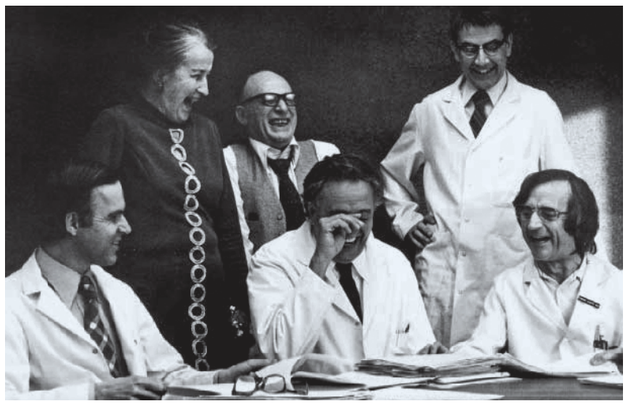
COLUMBIA UNIVERSITY MEDICAL CENTER

the earliest data showing that the immune system of mice could be stimulated to reject transplanted tumors—solid evidence that the immune system recognizes cancer. Old and colleagues also made the remarkable discovery that different types of immune cells could be distinguished by distinct markers on their cell surface, for example the CD8 marker that identifies "killer" T cells and the CD4 marker that defines "helper" T cells. This fact is so taken for granted today that it's easy to forget how unexpected and controversial it was at the time.

A few years later, Old and colleagues discovered the powerful chemical messenger, or cytokine, called tumor necrosis factor (TNF), which causes tumors to shrivel up and die when injected into mice. Produced by immune cells in response to bacterial toxins, TNF helped to explain William Coley's results and provided a dramatic illustration that the immune system could be stimulated to attack cancer.

Old was quickly establishing himself as a dominant force in the emerging field of tumor immunology. Perhaps not surprisingly, CRI eagerly enlisted his help in redefining its mission.

Lloyd Old and Helen Coley Nauts with members of the newly formed Scientific Advisory Council in the early 1970s



1970–1979: Seeding the Field of Tumor Immunology

In 1971, Lloyd Old became scientific director of CRI, a post he would hold for the next 40 years. One of the first things Old did was to use his scientific credentials to attract a group of world class immunologists to head CRI's Scientific Advisory Council. This group of experts—the cream of the scientific crop, including several Nobel laureates—would be able to speak with unimpeachable authority about immunology, and guide CRI knowledgeably.

Old's next groundbreaking change was to establish a formal program to fund postdoctoral researchers working on the immune system and cancer. The idea behind the program was to train a new generation of immunologists, building support for immunotherapy from the ground up. If wider support for immunotherapy was lacking because mainstream cancer researchers lacked training in immunology, then CRI would help provide that training. Between 1971 and today, CRI has funded nearly 1,300 young investigators who have gone on to become leaders in the field.

A basic truth about scientific research is that you can't always predict where it's going to lead. No one knows this better than immunologist Rolf Kiessling, one of the first scientists funded as part of CRI's new postdoctoral fellowship program. In the early 1970s, Kiessling began his Ph.D. work intending to study T cell responses to cancer under the direction of Eva Klein at the Karolinska Institute in Sweden. He planned to inject mice with tumor cells to immunize them against the cancer and then study how T cells mounted an attack against a new tumor. But very quickly he ran into a problem. The immunized mice were capable of killing the cancer cells, but so were the control mice that hadn't been immunized. It was a kind of "background noise," he said, that he tried for many months to eliminate without success.

70s HIGHLIGHTS

208
RESEARCHERS FUNDED

$5
MILLION AWARDED

RESEARCH AREAS

Cytokines (interferon, IL-2, TNF)

Antibody structure and diversity

T cell biology

Natural killer (NK) cells

1960

1965
American Cancer Society adds Coley's toxins to list of "Unproven Methods of Cancer Management."

1968
Old, Boyse, and colleagues discover a cell-surface marker (CD8) that identifies cytotoxic ("killer") T cells.
Lloyd Old becomes a scientific advisor to CRI.

1970

1971
Lloyd Old named CRI scientific director.
CRI Postdoctoral Fellowship Program established.

1974
Osias Stutman publishes results with nude mice challenging the immune surveillance hypothesis.

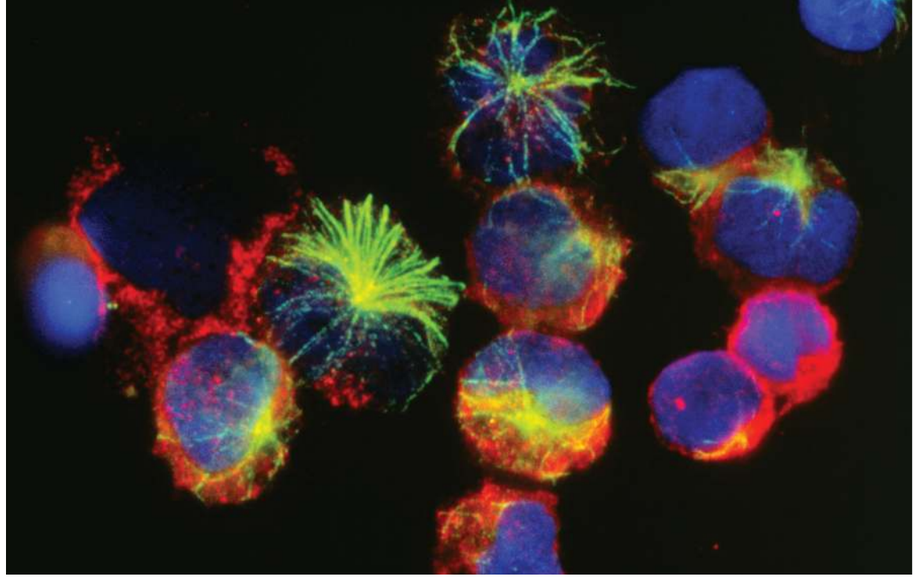
■ *Rolf Kiessling, M.D., Ph.D., of the Karolinska Institute (CRI postdoctoral fellow, 1977-1979)*

"I gradually became more and more interested in this background," says Kiessling, "and that's how my Ph.D. project took on a new angle, from studying T cell immune surveillance to studying the background noise."

This decision turned out to be quite fortuitous, since it was in studying this background noise that Kiessling would eventually discover and name a new type of immune cell—the natural killer (NK) cell. Kiessling's discovery electrified the scientific community and also addressed a controversy then brewing among researchers.

A basic tenet of the field of tumor immunology is the notion that the immune system routinely recognizes cancer cells and attacks them before they can form a tumor. Only when this system of "immunosurveillance" breaks down is cancer able to take hold in the body.

■ *Since 1971, CRI has funded more than 175 postdoctoral fellows in the labs of George and Eva Klein at the Karolinska Institute in Sweden, including Rolf Kiessling and Klas Kärre who discovered and characterized natural killer cells.*



■ *Natural killer (NK) cells are cells of the innate immune system that kill virally infected and cancerous cells.* Photo courtesy of Nancy Kerdersha, Ph.D., Harvard University

The theory of immunosurveillance was dealt a hefty blow in 1974 when a scientist named Osias Stutman published results of experiments with so-called nude mice. These mice, born without a thymus gland, were believed to lack a functioning immune system (since the thymus is where T cells develop). Stutman found that nude mice had no higher incidence of cancers than normal mice, thus casting doubt on the idea that the immune system routinely fights against cancer.

The results were discouraging to those working in the field of cancer immunology, but Kiessling's work helped to keep the hopes for immunotherapy afloat. It turns out that nude mice still have NK cells, and so they still have a partially functioning immune system. Kiessling's work showed that Stutman's conclusions were flawed.

NK cells are now known to play an important role in innate immunity against cancer, killing cancer cells before they can take hold in the body. Understanding and enhancing NK function is still an active area of research being explored by current CRI scientists.

"Over the past two decades, contributions by the Cancer Research Institute to Fred Hutchinson Cancer Research Center have provided crucial pilot support to launch the next generation of cancer pioneers."

– LARRY COREY, M.D.
President and Director, Fred Hutchinson Cancer Research Center

FRED HUTCHINSON CANCER RESEARCH CENTER

1975

Rolf Kiessling, together with Eva Klein and Hans Wigzell, identifies natural killer (NK) cells in mice.

Monoclonal antibody technology developed by Kohler and Milstein.

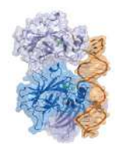
Carswell, Old, and colleagues announce discovery of tumor necrosis factor (TNF).

William B. Coley Award for Distinguished Research in Basic and Tumor Immunology established.

1978

CRI provides seed funding for trial of interferon-α in cancer patients, led by Jordan Gutterman.

Berendt and North demonstrate that endotoxin-induced tumor regression is dependent on T cells.



1979

Old, DeLeo, and colleagues link p53 tumor suppressor gene to human cancers.

BCG is reported by Alvaro Morales to be effective in the treatment of bladder cancer.

■ *In 1975, the William B. Coley Award was given to a group of 16 scientists deemed the "Founders of Cancer Immunology."* INSET: *The William B. Coley Award for Distinguished Research in Basic and Tumor Immunology*

■ *CRI investigator Joseph Sun, Ph.D., of Memorial Sloan Kettering Cancer Center, is studying NK cells.*

In addition to supporting young scientists just beginning their careers in cancer immunology, Old also recognized the importance of honoring more established scientists who have made fundamental contributions to the field. Thus was born the annual William B. Coley Award for Distinguished Research in Basic and Tumor Immunology.

The first Coley Awards were given, in 1975, to a group of 16 scientists deemed the "Founders of Cancer Immunology." These were the researchers whose earlier work laid the cornerstones of the field, without which later developments would have been impossible. The highly coveted Coley Award is now given annually.

By the end of the decade, under Old's leadership, CRI had gained increased scientific legitimacy. While understanding the basis of Coley's toxins was still a goal, this was incorporated into a larger strategy of building basic scientific knowledge. "Science hadn't caught up with Coley," Old used to say. "It was my responsibility to help Helen have science catch up with him."

1980–1989
How Do T Cells "See"?

By the late 1970s, thanks in part to the work of CRI scientists, it was clear that tumors were immunogenic, or able to provoke an immune response. But really nothing was known at the time about how the immune system was able to "see" cancer antigens—or any other antigens for that matter. Over the next decade, CRI-funded researchers studied basic aspects of how immune cells recognize and respond to antigens.

There are two main types of adaptive immune cells, B cells and T cells. B cells produce antibodies, which are released into the bloodstream where they seek out and destroy pathogens like heat-seeking missiles. "Killer" T cells, on the other hand, recognize and kill infected and cancerous cells at close range, by releasing a toxic payload directly onto a target.

By the mid-1970s, it was clear that in order to kill a target, T cells have to recognize and bind to two different things on the target cell's surface: an antigen and a molecule called MHC. The requirement for the presence of both antigen and MHC is known as "MHC restriction." The two scientists who worked this out were Rolf Zinkernagel and Peter Doherty, who would share the Nobel Prize in 1996. Zinkernagel is now a member of CRI's Scientific Advisory Council.

■ *Coley Award winners Philippa Marrack, Ph.D., and her husband, John Kappler, Ph.D., at the University of Colorado*

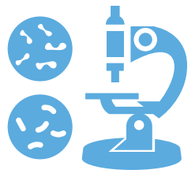
80s HIGHLIGHTS

493

RESEARCHERS FUNDED

$25

MILLION AWARDED



RESEARCH AREAS

T cell receptor

MHC

Dendritic cells

Antigen processing and presentation

HIV/AIDS

Cytokines

Pamela J. Bjorkman, Ph.D., of the California Institute of Technology (CRI investigator, 1989-1994)

» The antigen, they discovered, sat in the MHC molecule much like "a hot dog in a bun." «

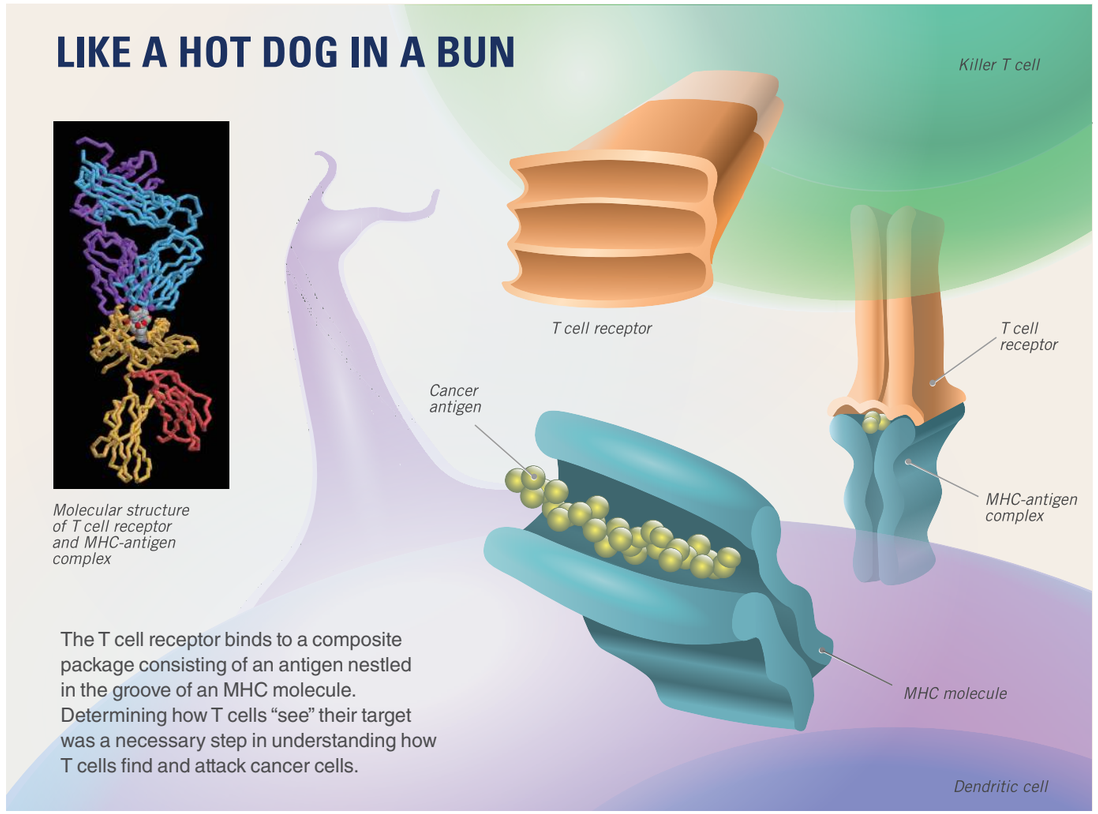
What was still not clear at the beginning of the 1980s was whether there were two T cell receptors or just one. "It was sort of a transatlantic thing," says Philippa Marrack, an immunologist at National Jewish Health and the University of Colorado, who was also the first woman to be appointed to CRI's Scientific Advisory Council. The Europeans, she says, were pursuing the idea that there were two different receptors, one for MHC and one for antigen. In the States, there was a bias toward the belief in a single receptor that recognized some combination of the two.

In 1983, Marrack and her husband, John Kappler, published a paper that strongly suggested there is a single T cell antigen receptor—work for which they received the 1993 Coley Award. Other groups, including one led by James Allison, had already isolated the receptor protein, and the gene for the receptor was cloned the following year.

Researchers next wanted to know: how can a single T cell receptor bind to two different targets, MHC and antigen? The answer to that question came in 1987, when Pamela Bjorkman, in collaboration with her advisors Don Wiley and Jack Strominger at Harvard, published an X-ray crystallography "picture" of an MHC molecule bound to antigen. The antigen, they discovered, sat in the MHC molecule much like "a hot dog in a bun." The MHC molecule then presented its cargo to the T cell receptor.

Bjorkman's precise molecular picture "nailed the issue about T cells recognizing a single entity that is antigen and MHC at the same time," says Marrack. By determining what a T cell "sees" on the surface of another cell, Bjorkman's work made it possible to target that interaction with therapeutic drugs and vaccines.

To support her promising work, CRI's Scientific Advisory Council gave Bjorkman an Investigator Award in 1989. The award couldn't have come at a better time, she says, right when she was starting up her lab at the California Institute of Technology. "It was $50,000 a year for four years, and that was just fabulous. What you really need when you're starting out is unrestricted money." CRI continues to fund research in the Bjorkman lab today.



In science, new answers lead to new questions. The next mystery to solve was how MHC got its cargo of antigen in the first place. The somewhat counterintuitive answer to that question was provided by Alain Townsend and colleagues working at Oxford. In 1989, Townsend proposed the idea that cells might continually chew up proteins and spit out little pieces to their cell surface, which they would then "present" to T cells of the immune system.

1980

1981
CRI begins funding Ralph Steinman's work on dendritic cells and cancer.

1983
Marrack, Kappler, Allison, and colleagues identify the T cell antigen receptor.

1984
Knuth, Oettgen, and Old demonstrate that T cells can be trained to recognize and attack an established tumor.

1985
Kary Mullis, Henry Erlich, and colleagues invent PCR.

1986
CRI Investigator Award program established.

Klas Kärre develops "missing self" hypothesis of NK activation.

1987
von Boehmer, Zamoyska, and Steinmetz show that the CD8 co-receptor is actively involved in antigen recognition by killer T cells.

1988
Rudd and Schlossman discover the biochemical initiators of T cell activation, CD4- and CD8-p56(lck) complexes.

1989
June and Thompson demonstrate the role of CD28 in T cell costimulation.

In 1990, CRI began funding Townsend to study this unorthodox idea. In the coming years, Townsend and other CRI-funded scientists would decipher the cellular machinery responsible for this antigen processing and presentation.

Still more important discoveries were yet to come in a decade already full of surprises. The conventional wisdom for many years was that immune cells called macrophages, which engulf pathogens at sites of infection and wounds, were primarily responsible for performing the task of antigen presentation. Slowly, and against much resistance from leaders in the field, a researcher named Ralph Steinman at The Rockefeller University would change all that.

In the early 1970s, Steinman became interested in a rare and somewhat strange-looking cell that no one before had previously noticed. He called the cell "dendritic" because of its coat of spiny tendrils (*dendron* is Greek for tree). Steinman proposed the highly unorthodox idea that dendritic cells crawled throughout the

» It was $50,000 a year for four years, and that was just fabulous.«

– PAMELA BJORKMAN

■ *Blaise Ndjamen, Ph.D., a CRI postdoctoral fellow working in the Bjorkman lab at Caltech, is studying antibody structure.*

"CRI fills a funding void in the biomedical community by providing resources for high-risk, high-reward projects that have direct impact on human therapeutics."

– MARC TESSIER-LAVIGNE, PH.D.
President, The Rockefeller University

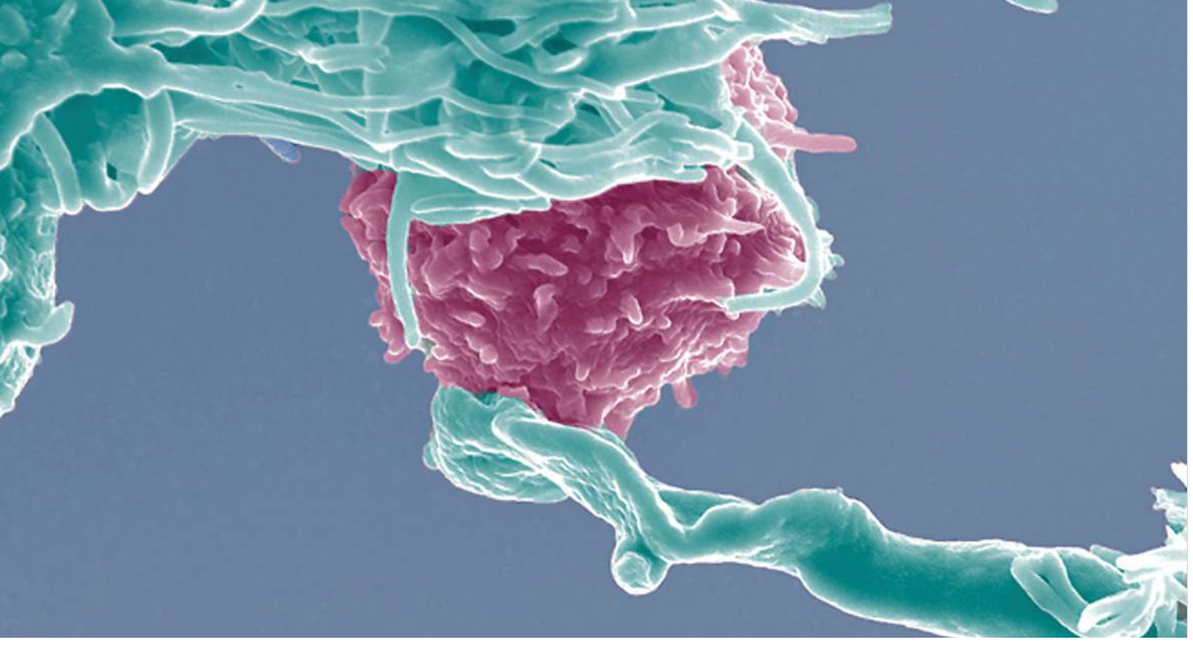
An Early Ally in the AIDS Epidemic

A nimble and forward-thinking nonprofit, CRI is able to recognize and respond quickly to emerging research needs. CRI became an early funder of AIDS research in the 1980s when immunodeficient individuals began to develop Kaposi's sarcoma, a rare type of skin cancer caused by a virus. CRI's scientific leadership recognized that important insights could be gained by understanding the nature of the immunodeficiency–cancer link, and quickly rallied behind this effort. In February 1983, CRI provided critical funds to help convene an important conference on Kaposi's sarcoma held at Cold Spring Harbor Laboratory in New York. The conference was attended by 34 leading scientists, including Robert Gallo, Donald Francis, James Curran, and Alvin Friedman-Kien, who were among the first to propose a retroviral cause of AIDS. That same year, CRI allocated $350,000 for new research projects devoted to AIDS. Then medical director Lloyd Old said at the time, "AIDS is a major concern and a major mystery—a compelling problem that merits a special CRI program." Together with the Gay Men's Health Crisis (GMHC), CRI funded the work of Bijan Safai, of Memorial Sloan Kettering Cancer Center, to develop a treatment for Kaposi's sarcoma.

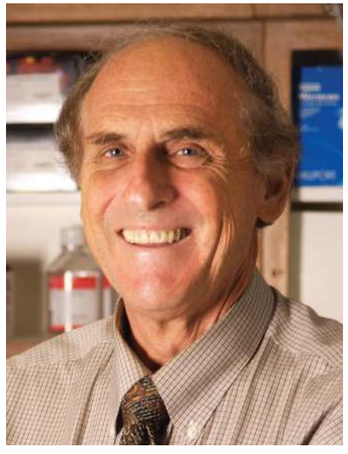
Recognizing the truly global nature of the epidemic, in the late 1980s and early 1990s, CRI became a steady funder of AIDS research in Africa, supporting several international symposia.

Since that time, CRI has provided nearly $6 million in funding to more than 50 researchers studying HIV. Work from these researchers has provided us with an evermore sophisticated understanding of how HIV acts to disrupt the immune system, paving the way for improved treatments not only for HIV, but also for cancer, allergies, and other immune-related diseases.

Photo of HIV budding courtesy of Jaisri R. Lingappa, M.D., Ph.D.



Dendritic cells (green) use their spiny tendrils to present antigens to T cells (red). Photo courtesy of Olivier Schwartz, Ph.D.



Ralph Steinman, M.D., of The Rockefeller University (CRI investigator, 1981-1983)

body and used their tendrils to present antigens to T cells. It was these unusual looking cells, Steinman argued, that were the best antigen-presenting cells in the body; if T cells are bloodhounds for pathogens and cancer, then dendritic cells provide the scent. Though roundly criticized at the time, we now know that Steinman's minority view was correct.

CRI recognized early on that dendritic cells might one day be used to stimulate the immune system to recognize cancer antigens, and began funding Steinman's work in 1981. This line of research would come to fruition over the next three decades, in the form of the first dendritic cell-based vaccine for cancer.

For his work on dendritic cells, Steinman would eventually be awarded the Nobel Prize in 2011. Tragically, the announcement came three days after Steinman passed away from pancreatic cancer.

CRI funding has fostered breakthroughs that have had wide-ranging influence beyond the field of immunology. In 1979, CRI provided postdoctoral funding to a promising researcher at Stanford University School of Medicine for work on an MHC gene. That fellow, Henry Erlich, would eventually go on to head the laboratory at Cetus Corporation where, in 1985, he and Kary Mullis developed the polymerase chain reaction (PCR). By providing researchers with a way to amplify the amount of DNA in a sample from just a few molecules to billions of copies, PCR has revolutionized biomedical research.

1990–1999:
Finding a Needle in the Molecular Haystack

If the 1980s were focused on discovering how T cells "see," then the 1990s were geared toward understanding what, on cancer cells, the T cells were seeing. It was during this period that CRI scientists discovered the first tumor-specific antigens—those telltale fragments of protein that distinguish cancer cells from normal cells in the body. It all started with an unusual patient.

While serving as a young oncologist at a hospital in Frankfurt, Alexander Knuth cared for a middle-aged woman with metastatic melanoma. The patient, known as "Frau H," had already received aggressive treatment. Doctors removed her spleen, ovaries, and multiple lymph nodes, yet still the cancer continued to progress.

Given her dwindling chances, the patient was put on an experimental immunotherapy treatment designed to prod her body into mounting an immune response to the cancer. The treatment involved injecting her with weakened versions of her own cancer cells in the hopes that the cancer cells would die and release antigens for the immune system to see.

At first, the treatment seemed not to be working, since the patient's tumors continued to grow. But then, about two months later, the cancer began to disappear and the patient ultimately experienced a complete remission.

"That was a powerful experience for me as a young oncologist," recalls Knuth. "At the time, we were all thinking about radiotherapy

CRI Scientific Advisory Council members Alexander Knuth, M.D. (CRI investigator, 1989-1993), and Thierry Boon, Ph.D. (Coley Award winner, 1987)

> »At the time, we were all thinking about radiotherapy and chemotherapy and didn't really have a clue what immunotherapy could do.«
>
> – ALEXANDER KNUTH

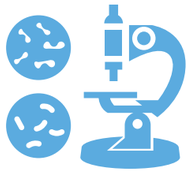
90s HIGHLIGHTS

616

RESEARCHERS FUNDED

$56

MILLION AWARDED



RESEARCH AREAS

Tumor-specific antigens

Cell signaling

V(D)J recombination

Dendritic cell-based vaccines

and chemotherapy and didn't really have a clue what immunotherapy could do. Then we witnessed this patient's dramatic response, and it was something very moving."

The unusual result also gave Knuth an idea. If he could understand how her immune system had recognized the cancer cells—what her T cells were seeing—then he would have solved one of the longest-running mysteries in tumor immunology.

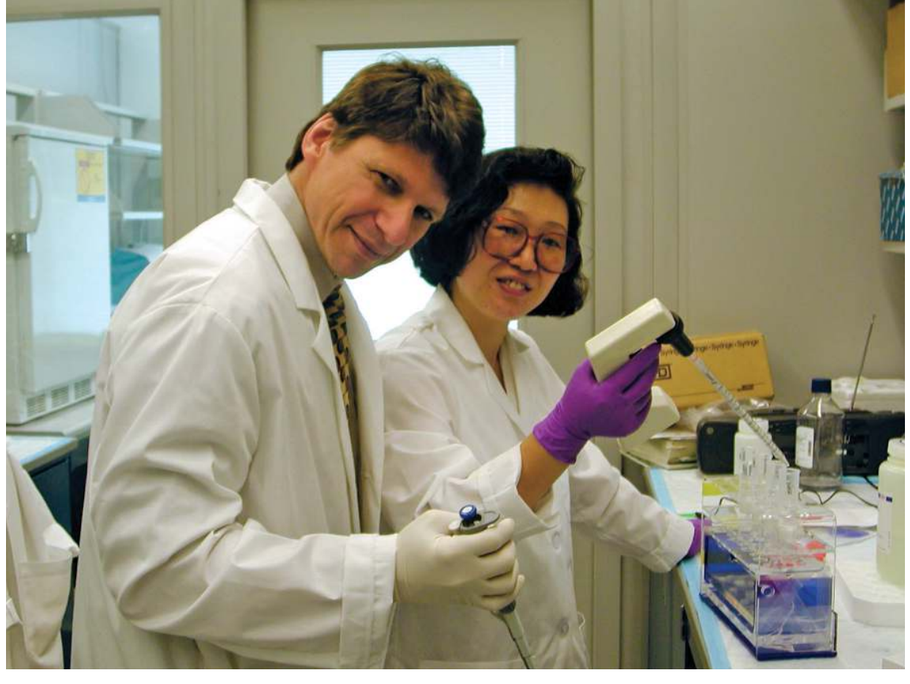
Knuth had a wealth of experience in coaxing T cells to grow outside the body, the starting point for this sort of investigation. But to find a cancer needle in the cell's molecular haystack, he would need some help. That's when he contacted Belgian molecular biologist Thierry Boon, who for a number of years had been studying tumor antigens in mice. With his extensive experience in molecular biology, Boon was the perfect person to help find the elusive tumor antigen hiding inside Frau H's cancer cells. Boon cut up Frau H's DNA into millions of pieces, inserted them into bacteria "cloning vectors" to produce protein, then systematically screened the proteins against her own killer T cells. When the T cells lit up with activity, he knew they had found a tumor antigen.

Boon called his tumor antigen MAGE (short for melanoma-associated antigen). It was the first tumor-specific antigen ever discovered. Others would soon follow, all isolated from Frau H's cells.

In total, it took eight years to isolate MAGE, and Knuth remarks that uninterrupted funding from CRI and CRI's partner, Ludwig Cancer Research, was crucial in sustaining the research. "Usually research grants are limited to a certain time period, like two to three years. With the support of the Ludwig Institute and the support of the Cancer Research Institute, continuity was enabled that no other funding institutions would give."

The discovery of MAGE was a lightning rod, reigniting one of the oldest dreams of immunology: a vaccine against cancer. The idea behind a cancer vaccine is simple: by presenting the immune system with a cancer-specific antigen, you stimulate the immune system to produce an immune response against cells that display that antigen, while sparing the body's normal cells. Such an approach would take advantage of what the immune system does best—targeting specific enemies and retaining a memory of the attackers for future protection.

Of course, more is required to generate an effective immune response than simply injecting a cancer antigen into the body. After all, when a patient has cancer, the immune system has failed to mount an adequate anti-cancer response. For that reason, in the early 1990s, researchers began to experiment with formulating cancer vaccines that were "souped up" with additional immune-stimulating chemicals. The question was: which chemicals would work best?



CRI Scientific Advisory Council member Drew Pardoll, M.D., Ph.D., with CRI postdoctoral fellow Yan Cui, Ph.D., at Johns Hopkins University School of Medicine

"When I began my career in cancer research in 1989, CRI was the only organization that believed in supporting junior researchers as the future of cancer immunotherapy…. Without CRI, I would not be doing this today."

– DREW PARDOLL, M.D., PH.D.
(CRI investigator, 1989-1992)
Johns Hopkins University

1990

David Raulet and colleagues report the generation of knockout mice with a targeted immune gene deletion.

Linsley, Clark, and Ledbetter identify B7 as the counterreceptor for CD28.

FDA approves use of BCG for superficial bladder cancer.

1991

Boon, Knuth, and colleagues announce discovery of first tumor-specific antigen (MAGE) in journal *Science*.

1992

Fu and Darnell report the discovery of the STAT gene family.

Allison, Raulet, and Gross demonstrate that blocking CD28 hampers T cell activation.

1993

Anjana Rao and colleagues report the identification of transcription factor NFAT.

Pramod Srivastava demonstrates the role of heat-shock proteins in tumor immunity.

Pardoll, Dranoff, Jaffee, Levitsky, and colleagues show that a vaccine composed of tumor cells irradiated and genetically modified to produce GM-CSF prevents tumor growth in mice.

1994

Houghton, Nathan, and colleagues provide the first demonstration that monoclonal antibodies can shrink tumors in cancer patients.

Bluestone and colleagues demonstrate that CTLA-4 is a negative regulator of T cell activation.

CRI associate director Glenn Dranoff, M.D., of the Dana-Farber Cancer Institute

CRI postdoctoral fellow Beth Stadtmueller, Ph.D., studies mucosal immunity.

In the early 1990s, a team of scientists led by Glenn Dranoff of the Dana-Farber Cancer Institute and Drew Pardoll of Johns Hopkins began to systematically test each then-known cytokine in a mouse model of cancer. Using genetic engineering techniques, they inserted the gene for a particular cytokine into tumor cells, irradiated the tumor cells to weaken them, re-injected the tumor cells into the mouse, and then watched for an immune response. By testing a dozen different cytokines in this way, they were able identify one that was particularly good at stimulating an immune response against cancer. It was called GM-CSF (granulocyte macrophage colony-stimulating factor).

Remarkably, right about the time that Dranoff and Pardoll obtained this result, Ralph Steinman reported that GM-CSF was, in fact, the primary growth factor for dendritic cells. Suddenly, it made sense why GM-CSF worked in this vaccine.

"It was sort of an 'aha' moment," says Pardoll. "Part of how these GM-CSF-transduced vaccine cells work is by inducing the proliferation of dendritic cells, which pick up tumor antigens and sort of start the whole ball rolling in terms of generating T cell responses."

This work would lead directly to the development of GVAX, a therapeutic cancer vaccine that is now being tested in clinical trials for a variety of cancers including pancreatic and colorectal cancers.

By the late 1990s, scientists had learned what really goaded dendritic cells into a frenzy of antigen-presentation: bits of protein, found on the surface of bacteria and viruses, called PAMPs (pathogen-associated molecular patterns). These PAMPs bind to Toll-like receptors (TLRs) on the surface of dendritic cells, triggering the release of powerful cytokines that alert the body to danger. Different TLRs recognize different PAMPs, and together a panel of more than a dozen TLRs provides dendritic cells with extremely sensitive "taste buds" for pathogens.

1995

Paul Rothman demonstrates a role for JAK-STAT signaling in malignancy.

1996

Allison and Krummel demonstrate that a monoclonal antibody directed against CTLA-4 results in rejection of melanoma tumors in mice.

CRI receives $20 million gift from The Atlantic Philanthropies.

1997

Chen, Old, and colleagues announce isolation of tumor-specific antigen NY-ESO-1.

Rituxan, the first monoclonal antibody for use in cancer (lymphoma), is approved by the FDA.

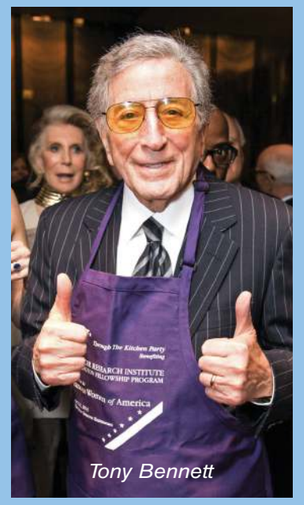
Mellman, Turley, and Lanzavecchia demonstrate that dendritic cells mature in response to microbial products, linking innate and adaptive immunity.

Choi and colleagues identify a new tumor necrosis factor family member TRANCE (RANKL).

Putting the "Fun" in Fundraising

Over the years, CRI has undertaken numerous fundraising efforts, and the CRI development team has shown as much creativity in planning events as our scientists have shown in designing experiments. From film and Broadway premieres, to golf outings, marathons, and bike tours, CRI fundraisers have set a high bar for attracting the attention and commitment of donors.

Throughout the 1970s and 1980s, event premieres were a staple of CRI fundraising. Alan Hirschfield, one-time CEO of both Columbia Pictures and Twentieth Century Fox, and also a former CRI trustee, was instrumental in arranging yearly film premieres to benefit CRI, including *Close Encounters of the Third Kind* (1977), *Return of the Jedi* (1983), and *Rhinestone* (1984). Broadway theater benefits included *Les Misérables* (1987), *Phantom of the Opera* (1988), *Miss Saigon* (1990), and *Mamma Mia!* (2001). A magic show featuring David Copperfield was held in 1996. These event premieres provided a crucial source of revenue for a young and growing organization situated in the heart of NYC.



For the past 30 years, the annual "Through the Kitchen" benefit has raised money for CRI's postdoctoral fellowship program. Conceived by trustee Lauren Veronis, the event has raised more than $10 million to fund promising young scientists focused on studying the immune system and its power to conquer cancer. CRI's annual golf outing celebrated its 20th anniversary in 2013. Long-time CRI board member Carlos Ferrer has championed the event every year from the beginning.

In June 2013, CRI celebrated the first annual Cancer Immunotherapy Month (CIM), to help raise awareness among patients and the public of immunotherapy's potential. As of 2014, CIM is a nationally recognized awareness event by the American Society for Clinical Oncology (ASCO), a major step forward in boosting the profile of both CRI and cancer immunotherapy.

With the discovery of PAMPs and TLRs, scientists had a new way of viewing the Coley phenomenon. It turns out that one of the PAMPs that TLRs specifically recognize is lipopolysaccharide (LPS), found in the cell wall of certain bacteria, and one of the main ingredients in Coley's toxins. A full century after Coley first experimented with bacterial toxins, the science of immunology had finally caught up with him.

Vaccinating Against Cancer?

Preventing cancer with a vaccine, like one for measles or flu, has always been a dream of tumor immunologists. With the discovery of cancer-causing viruses in the 1960s, that dream moved closer to reality.

CRI's support of virus research goes back to the earliest days of the organization, when Lloyd Old, Herbert Oettgen, and George Klein researched the connection between Epstein-Barr virus and Burkitt's lymphoma and nasopharyngeal cancer. Several additional types of cancer are now known to be caused by viruses, including liver cancer, cervical cancer, and certain leukemias.

Gardasil®, a vaccine designed to prevent cervical cancer, "grew out of research funded by CRI," says Ian Frazer, who conducted the research and received his first grant from CRI in 1999. Gardasil protects women against the two types of HPV that cause 70 percent of all cervical cancers, and was approved by the FDA in 2006. It represents one of the first effective preventative vaccines for cancer, and has the potential to save 275,000 lives a year worldwide.

Professor Ian Frazer of the University of Queensland, Australia

2000–2009:
Putting Vaccines to the Test

The discovery of tumor-specific antigens in the early 1990s answered the long-standing question of whether the immune system could recognize cancer. The answer was a resounding yes. Not surprisingly, these developments raised the old issue of immunosurveillance: if immune cells can recognize and kill cancers, then how do tumors ever form in the first place?

The year 2001 is known among researchers as the year that the immunosurveillance hypothesis was "resurrected." That is the year that CRI-funded researcher and Scientific Advisory Council associate director Robert Schreiber published his now famous article in *Nature*, documenting that mice bred to lack elements of a functioning immune system had a higher incidence of cancers. This research provided definitive proof that the immune system plays a role in keeping cancer in check. As Lloyd Old once said, "Stutman put the dagger into the heart of immunosurveillance, and Schreiber pulled it out."

But it did more than this. It also suggested an answer to the vexing question of why cancer cells sometimes—indeed, quite often—manage to evade detection by the immune system. Schreiber, along with Lloyd Old, Mark Smyth, and colleagues, proposed that immunosurveillance should be conceived as a kind of "immunoediting" process, with three distinct phases. In the first phase—elimination—the immune system provides effective control over incipient tumors, by eliminating the rogue cells. In the second phase—editing—the immune system acts as a kind of Darwinian sculptor, providing selective pressure on a developing tumor; those tumor variants that can more effectively evade detection are in effect selected by the immune system to survive and reproduce. In the third phase—escape—tumor cells with the most effective mechanisms of immune evasion begin to proliferate uncontrollably, eventually wreaking havoc on the body. Schreiber and colleagues called these steps the "Three Es" of immunoediting.

Schreiber's work provided a much-needed shot in the arm for the field of cancer immunology, and encouraged researchers that the time was right to put cancer vaccines to the test.

Recognizing the need for a collaborative, multi-pronged approach to cancer vaccine development, in 2001 CRI joined forces with Ludwig Cancer Research to form the Cancer Vaccine Collab-

CRI associate director Robert Schreiber, Ph.D., of the Washington University School of Medicine

"We are grateful to the Cancer Research Institute for its willingness to support some of the most innovative and creative work here and in the entire cancer immunology community."

– LARRY J. SHAPIRO, M.D.
Executive Vice Chancellor for Medical Affairs and Dean, Washington University School of Medicine

Washington University in St. Louis

A meeting of the CVC Trials Network in October 2013

orative (CVC). This centrally coordinated network of academic and clinical researchers was designed to enable a truly global approach to the problem of vaccine development. Made up of more than 50 scientists, from 30 institutions, in 10 countries, on 4 continents, the CVC would speed intellectual progress by conducting numerous studies in parallel rather than in sequence, and by pooling results.

A distinctive aspect of the CVC approach was its focus on one specific tumor antigen, called NY-ESO-1. As a protein that is found in many different types of cancer, but not in normal body cells (except the testes), NY-ESO-1 is an ideal candidate antigen around which to build a cancer vaccine. Focusing on one antigen also allowed scientists to compare results across studies. To date, more than 60 CVC trials have been conducted. In addition to expanding our knowledge of how to design effective cancer vaccines, the CVC trials network has become the new industry standard for collaborative clinical research, and remains a central pillar of CRI's Clinical Accelerator program.

"CRI is much more than a charity or funding agency; it is truly an incubator for fantastic science, research, and development."

– Sergio Quezada, Ph.D.
(CRI postdoctoral fellow, 2005-2008;
CRI investigator, 2011-2015)
Cancer Institute,
University College, London

Among the many valuable lessons to emerge from the CVC trials conducted so far is the importance of choosing the right adjuvant. Immunologists have long known that successful vaccines require an adjuvant—usually bits of bacterial protein that stimulate the immune system in a non-specific manner. In fact, it was this need for an adjuvant to jumpstart the immune response to an antigen that led to the fundamental discovery of Toll-like receptors (TLRs) in the first place.

CVC trials have shown that, indeed, TLR "agonists" are some of the most potent adjuvants for use in cancer vaccines, and these molecules are now being routinely included in clinical trials of vaccines.

CRI investigator Shane Crotty, Ph.D., of La Jolla Institute for Allergy and Immunology, is studying B cell memory.

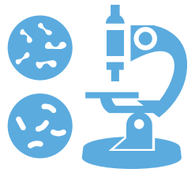
2000s HIGHLIGHTS

993

RESEARCHERS FUNDED

$175

MILLION AWARDED



RESEARCH AREAS

Cancer vaccines

Toll-like receptors (TLRs)

Regulatory T cells (Tregs)

CTLA-4, PD-1, LAG-3

Inflammation and cancer

2000
CRI Coley Award presented to Michael Pfreundschuh for his development of SEREX antigen screening technology.

2001
Cancer Vaccine Collaborative (CVC) established.
Schreiber, Old, Ikeda, Smyth, and colleagues revive the immunosurveillance hypothesis.

Cancer Vaccine Collaborative

2005
Dong and Weaver identify IL-17-producing CD4+ T cells, now known as Th17 cells.

2006
Gardasil® vaccine, developed by CRI-funded researcher Ian Frazer, is approved by FDA.

2007
Cancer Research Institute and Irvington Institute for Immunological Research merge.

2008
Oncophage, developed by Pramod Srivastava, is first therapeutic cancer vaccine to be approved for patients in Russia.

» With the successes of checkpoint blockades we now have a baseline of clinical activity on which to build with cancer vaccines and other combinatorial therapies. «

– JILL O'DONNELL-TORMEY

2010 to TODAY: Immunotherapy Comes of Age

By the second decade of the 21st century, CRI's strategy of funding basic research as a means to advance the field began to bear fruit. One example was Provenge® (sipuleucel-T), the first therapeutic cancer vaccine to receive approval from the FDA. Designed for use in patients with prostate cancer, Provenge consists of dendritic cells isolated from a patient's own body that have been incubated with a prostate cancer antigen, plus GM-CSF. Provenge was approved by the FDA in 2010, but the research that led to its development spanned more than two decades. In addition to the work of Pardoll and Steinman, Provenge was made possible by the insights of CRI postdoctoral fellow Curtis Ruegg. After completing his CRI fellowship in 1993, Ruegg joined the biopharmaceutical company Dendreon, which ultimately patented the product and brought it to market.

Following closely on the heels of Provenge was ipilimumab (Yervoy®), the anti-CTLA-4 antibody developed by James Allison and approved by the FDA in 2011. "Ipi," as the drug is affectionately known, was the first drug in history shown to extend the lives of patients with advanced melanoma. It became the model for the checkpoint blockade approach that is now transforming cancer treatment.

Having been instrumental in the development of checkpoint blockade, it was not surprising that Allison would be asked to take on a leadership position at CRI. Allison took the helm from Lloyd Old as director of the Scientific Advisory Council in 2011. Making this handoff was one of the last contributions that Lloyd Old made to a field of research that he helped to create. Old, the beloved father of modern tumor immunology, died of prostate cancer in 2011, at the age of 78.

■ *Ipilimumab (Yervoy®) was approved by the FDA in 2011 for the treatment of metastatic melanoma.*

As effective as checkpoint blockade antibodies can be, not everyone responds to them in the same way. Why some patients experience cure-like responses, while others do not, researchers cannot yet say. One tantalizing clue has come from work done by Jedd Wolchok. In a 2011 study, he found that melanoma patients with antibodies in their blood that recognize the NY-ESO-1 tumor antigen were almost twice as likely to respond to ipilimumab as patients without these antibodies. Wolchok's work suggests that measuring a patient's immune profile might enable doctors to effectively tailor immunotherapies to the patients who are most likely to benefit from them.

Much more research is needed to figure out combinations of immunotherapies that will work for all patients, but CRI's scientific leadership thinks we are well on our way. "With the successes of checkpoint blockades we now have a baseline of clinical activity

"Dana-Farber's legacy of scientific excellence would not be possible without the partnership of the Cancer Research Institute."

– EDWARD J. BENZ JR., M.D.
President and Chief Executive Officer,
Dana-Farber Cancer Institute

DANA-FARBER CANCER INSTITUTE

2010

CRI venture fund launched to support clinical research.

Sipuleucel-T (Provenge®) prostate cancer vaccine approved by FDA.

2011

Clinic and Laboratory Integration Program (CLIP) launched.

Ipilimumab (Yervoy®) is approved by FDA for use in metastatic melanoma.

June, Kalos, and colleagues successfully use chimeric antigen receptor (CAR) T cells to treat patients with leukemia.

The Clinical Accelerator

2012

Clinical Accelerator program launched.

2013

CRI and AACR join forces to create the journal *Cancer Immunology Research*.

Results of phase I trial of ipilimumab and nivolumab for advanced melanoma show cure-like responses in nearly 50% of patients.

CRI names June as Cancer Immunotherapy Month.

Cancer immunotherapy dubbed "Breakthrough of the Year" by *Science* magazine.

2014

CRI receives $15 million gift from the Anna Maria and Stephen Kellen Foundation.

CRI investigator Peter Savage, Ph.D., of the University of Chicago, is researching Tregs.

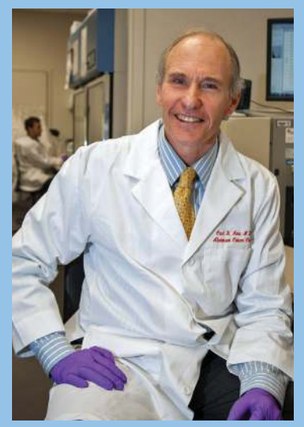
on which to build with cancer vaccines and other combinatorial therapies. It is exciting to look to a future where cancer immunotherapies hold out hope of response rates of 50 percent or higher in many cancers," says O'Donnell-Tormey.

Even as immunotherapies have come to the market in recent years, CRI has continued to fund basic research. One important area that has emerged in the past decade is the role of regulatory T cells (Tregs) in tamping down the immune response. Tregs are important for reining in the immune system, so that it doesn't attack the body's own cells. But they can also blunt an incipient anti-cancer immune response. Understanding and modulating the balance between attack and restraint remains an ongoing focus of research for CRI investigators.

A second major focus is inflammation—the redness, heat, and swelling that occur around areas of infection or injury and are part of wound healing. Long considered an asset in the fight against cancer, going back at least to Lloyd Old's work on tumor necrosis factor, inflammation has emerged in recent years as a double-edged sword in cancer. As part of a targeted immune response, short-lived inflammation may indeed help nip cancer in the bud. Chronic inflammation, on the other hand, if it goes on for years, can actually promote cancer, as research on inflammatory bowel disease and colon cancer shows. The 2013 Coley Award was given to Michael Karin, professor of pharmacology at the University of California, San Diego, for his groundbreaking work on signaling pathways used in inflammation. CRI is currently funding numerous researchers who are studying the role of the body's microbiota—its natural microbial flora—in inflammation and cancer. Figuring out how to sort good inflammation from bad is a key challenge for the next decade of research.

Engineering CARs

A powerful approach to cancer treatment involves removing T cells from a patient, engineering them in the lab to recognize cancer antigens, and then re-infusing them into the body. This approach, known as chimeric antigen receptor (CAR) T cell therapy, has been used successfully to treat patients with leukemia.



Carl June, M.D., of the University of Pennsylvania, who joined the CRI Scientific Advisory Council in 2013, is a leading expert on the technique. His team at Penn recently made headlines with several dramatic cancer cures. Eight-year-old Emily Whitehead was cured of her leukemia in 2011 after being treated with June's CAR T cell approach. CRI is currently funding a clinical trial of CAR therapy for patients with pancreatic cancer.

CAR therapy builds upon a long history of work on adoptive T cell therapy by other CRI-funded scientists including Philip Greenberg, Michael Kalos, and Michel Sadelain.

Michael Karin, Ph.D. (right), was the recipient of the 2013 Coley Award.

Looking Ahead

CRI scientists are rightly proud of what they have accomplished since Helen Coley Nauts rediscovered her father's work in a Connecticut barn more than 60 years ago. But they also know there is much more work to be done to make cancer immunotherapy an effective treatment for all cancers.

CRI Scientific Advisory Council associate director Ellen Puré makes the point explicitly. "I hope nobody walks away thinking 'Okay. Now we have all these cancer immune therapies, and they're in the clinic. So we're done, right?' Because that is so not true. We have a lot more to do and a lot more to learn."

As it has for decades, CRI will continue to fund the basic science and clinical research that, in time, will yield important therapeutic breakthroughs. By investing in today's young researchers, and fostering crucial collaborations between nonprofit scientists and industry, CRI will help ensure that the cancer therapy pipeline is full of promising new treatments.

And that is key. Because ultimately the goal of CRI-sponsored research is not simply to advance science, but to help cure patients suffering from a terrible disease.

"Scientifically, of course, it's very satisfying to see the field that I have dedicated my life to come into the mainstream," says Jedd Wolchok. "But seeing people enjoy their lives after having benefited from a clinical trial—nothing's better than that."

» Seeing people enjoy their lives after having benefited from a clinical trial – nothing's better than that. «

– JEDD WOLCHOK

Honoring Our Donors

None of the lifesaving research that CRI supports would be possible without the generous financial contributions of our donors—individuals, foundations, and corporations. CRI honors those donors by being responsible and strategic about how we invest these funds.


Sophie Stenbeck

Individuals: From the thousands of individuals who make one-time donations, to the many families who give yearly in memory of a loved one, to our trustees who give generously of both their time and money, no gift to CRI goes unappreciated. It is individuals who originally put CRI on the path to success, and who continue to make a difference in the life of the organization. CRI would not be here without the early contributions of philanthropist Nelson Rockefeller, for example, who provided seed funding for the organization back in 1953. Gifts from founding chairman Oliver Grace and his family, Julian Robertson, Wade Thompson and his family, Sean Parker, and Sophie Stenbeck among others, have ensured that CRI can maintain and expand the crucial work of bringing life-changing immunotherapies to patients faster.

Corporations and Foundations: Philanthropic gifts from corporations and foundations have also been key to CRI's success. Corporations such as Bristol-Myers Squibb, Genentech, and MedImmune, and foundations such as the Ambrose Monell Foundation, the Edith M. Schweckendieck Trusts, the Florence and Edgar Leslie Charitable Trust, the F.M. Kirby Foundation, the Hagedorn Fund, the Marion Esser Kaufmann Foundation, the Oliver S. and Jennie R. Donaldson Charitable Trust, the Whiting Foundation, and the Wildflower Foundation—to name just a few—have helped sustain CRI's mission over the years by providing steady annual support. Some gifts, by virtue of their size and timing, have dramatically altered the scope and scale of CRI's activities. Most notably, in 1996 and 2000, The Atlantic Philanthropies presented CRI with two gifts totaling $40 million. These gifts, which more than tripled CRI's annual budget, enabled the Institute to establish the Cancer Vaccine Collaborative (CVC), the first and for nearly a decade the only clinical network of its kind. In 2014, the Anna Maria and Stephen Kellen Foundation pledged $15 million to support clinical trials being conducted through the CVC Trials Network, providing the necessary seed money to get CRI's innovative Clinical Accelerator running at full speed.

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A meeting of CRI's Board of Trustees

» Building the field of cancer immunology meant thinking at least a decade ahead.«

–LLOYD OLD

CANCER RESEARCH INSTITUTE

Scientific and Clinical Achievements

CRI scientists have been instrumental in the following scientific discoveries and clinical advances:

- CD8+ "killer" T cells
- Natural killer (NK) cells
- Tumor necrosis factor (TNF)
- Antibody structure and diversity
- Somatic recombination
- T cell receptor
- CD28/B7
- MHC structure
- Dendritic cells
- p53, the first tumor-suppressor protein
- Polymerase chain reaction (PCR)
- Cloning of HER2/neu oncogene
- Perforin, the "lethal hit" cytokine
- STAT gene family
- MAGE, first tumor-specific antigen
- NY-ESO-1 tumor-specific antigen
- Immunoediting hypothesis
- BCG as treatment for bladder cancer
- Natural killer T (NKT) cells
- Th17 cells
- CTLA-4 and checkpoint blockade
- Gardasil®, preventative cancer vaccine
- Provenge®, first dendritic cell vaccine
- Oncophage therapeutic cancer vaccine
- Chimeric antigen receptors (CARs)

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CANCER RESEARCH INSTITUTE

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2.	New York University Medical Center	$9,894,634	
3.	Harvard Medical School	$9,591,895	
4.	The Rockefeller University	$8,637,903	
5.	Karolinska Institute	$7,761,782	
6.	Dana-Farber Cancer Institute	$7,511,152	
7.	Weill Cornell Medical College	$6,969,166	
8.	University of California, San Francisco	$6,854,927	
9.	Stanford University	$6,605,675	
10.	Washington University School of Medicine	$6,436,475	
11.	Yale University School of Medicine	$6,195,174	
12.	Roswell Park Cancer Institute	$6,043,678	
13.	Johns Hopkins University	$5,236,524	
14.	University of Chicago	$4,505,165	
15.	University of Washington	$4,097,417	
16.	Columbia Presbyterian Hospital	$3,949,047	
17.	University of Pennsylvania	$3,691,138	
18.	The Scripps Research Institute	$3,639,239	
19.	Fred Hutchinson Cancer Research Center	$3,555,799	
20.	Massachusetts General Hospital	$3,465,373	
21.	Krankenhaus Nordwest	$3,329,828	
22.	University of California, San Diego	$3,220,017	
23.	Mie University School of Medicine	$3,219,250	
24.	University of California, Berkeley	$3,107,102	
25.	Centre de Lutte Contre Le Cancer Nantes	$2,824,500	
26.	Immune Disease Institute, Inc.	$2,792,917	
27.	University of California, Los Angeles	$2,719,071	
28.	Massachusetts Institute of Technology	$2,701,859	
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