Summary

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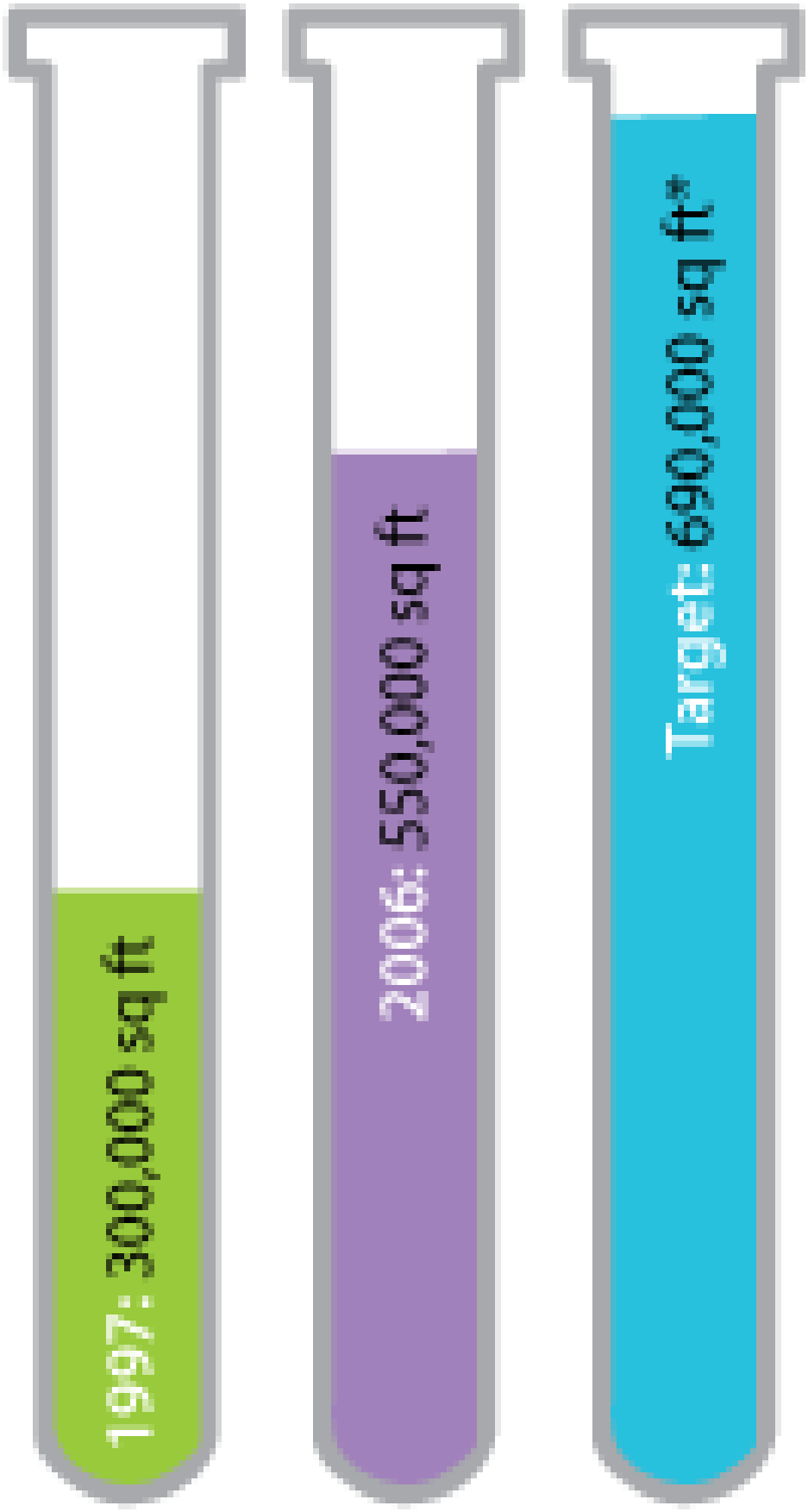
A decade ago, the Sloan Kettering Institute embarked on the largest effort to broaden and streamline its research activities in its 65-year-long history. Now the investment has put Memorial Sloan Kettering in a unique position to make discoveries that will further scientists' understanding of human disease, especially cancer — and to harvest the ripest fruits of such discoveries through investigation aimed at benefiting tomorrow's patients.

According to Sloan Kettering Institute Director Thomas J. Kelly, the expansion and reorganization has been a massive undertaking, which within the next

five years is expected to yield an enterprise with about twice the research space it had when Dr. Kelly joined Memorial Sloan Kettering, in early 2002 (see the chart below).



Research Space — *Upon completion of the second ZRC building which is in the final stages of construction.

"The goal of this effort is twofold," he noted. "First, to build on the institute's traditional strengths by allowing its basic science program to grow. And second, to enhance opportunities for translational research," the type of investigation that integrates knowledge gained in laboratories and clinics, with the goal of developing new strategies to control or cure disease, or reduce people's risk of developing diseases in the first place.

"There has never been a better time to reinforce our commitment to biomedical research," Dr. Kelly added. The past decade has seen an explosion of knowledge about the genes and biological processes that may cause a cancer to arise, progress, and sometimes elude currently available treatments — an explosion that in many ways transformed the general understanding about the vast group of diseases known as cancer. (For example, not too long ago individual patients with glioblastoma, a common form of brain cancer, were largely assumed to have the same disease. Today, this and other cancer types are no longer viewed as single entities, but rather as a spectrum of diseases — each driven by a distinct set of genes and biological processes.)

"However, we are still ignorant about many aspects of cancer causation and progression," he explained, "and this is why basic research will continue to be vital as we work toward a definite solution to the cancer problem."

Advances through research are made only by the creative genius of individual scientists.

Progress in science and technology also laid the groundwork for exploring therapies that attack cancer in innovative ways — for instance, using genetically engineered white blood cells that can detect and kill tumor cells, or drugs designed to improve the precision of radiation therapy.

Craig B. Thompson, who served his first day as Memorial Sloan Kettering President on November 2, 2010, noted that research performed in Memorial Sloan Kettering laboratories has contributed many of the past decade's transformative developments. "In the coming

years, we will continue to strengthen the bridges between our laboratory and clinical scientists to fully realize the potential of all the extraordinary research that goes on here," he said.

Alfred P. Sloan, Sloan Kettering Institute Co-Founder

Dr. Kelly added that this decade will be "a golden era for clinical discovery" at Memorial Sloan Kettering, as both knowledge and research infrastructures are now in place to develop new therapies that are effective and safe, and that can be tailored to give maximum benefit for each patient.

Recruitments

Since 2000, more than 50 new research labs have been started at the Sloan Kettering Institute, some of which populated four newly established research programs (see Milestones 2000 to 2010), while others extended the scientific agenda of already-existing programs — in cell biology, molecular biology, immunology, and molecular pharmacology and chemistry.

> Sloan Kettering Institute has always had an exceptionally vibrant research community, renowned for its excellence in science. Today this community spans the entire discovery continuum — from the researchers who uncover the most basic cornerstones of life to those who realize the clinical potential of such findings — with creative interactions and collaborations taking place across the board.

At the Sloan Kettering Institute, new lead investigators are chosen with great care, Dr. Kelly said, because each recruit is regarded as a long-term commitment on the institute's part. "I see it as my main job to safeguard the high quality of our science by making sure we get the very best people to join us — and then to support their work and careers as well as we possibly can," he said.

And the Sloan Kettering Institute does attract many of the "very best people." A substantial number of the institute's approximately 60 senior members have been honored with the most prestigious awards bestowed on biomedical scientists in the United States. For example, 11 are members of the National Academy of Sciences (NAS), six are Howard Hughes Medical Institute (HHMI) investigators, and 13 are members of the Institute of Medicine (IOM).

One of these eminent scientists is immunologist James P. Allison, who, when he joined Memorial Sloan Kettering in 2004, had already earned his NAS and HHMI memberships, and had initiated a groundbreaking innovation in cancer therapy. (In 2007, Dr. Allison also was elected to the IOM.)

Thomas Kelly, Sloan Kettering Institute Director

> I'm excited to be working among people who are at the top of their fields. It's gratifying to know that you can always go knock on their doors and they're there for you.

Other prominent researchers joined the institute as junior investigators and have successfully advanced their careers at Sloan Kettering Institute. Laboratory scientist Scott N. Keeney, who established his own laboratory in 1997 when he joined the Molecular Biology Program, is today a Sloan Kettering Institute Member (a designation the institute bestows on senior faculty) and an HHMI investigator. Dr. Keeney's research has shed light on the basic mechanisms cells use to repair ruptures in their DNA. These studies suggest that similar repair mechanisms allow cancer cells to survive the DNA damage induced by etoposide, a commonly used chemotherapy drug. This survival could contribute to a patient's cancer becoming resistant to the drug. "Our discovery might enable the design of more-effective anticancer

Joao Xavier

therapies," Dr. Keeney noted.

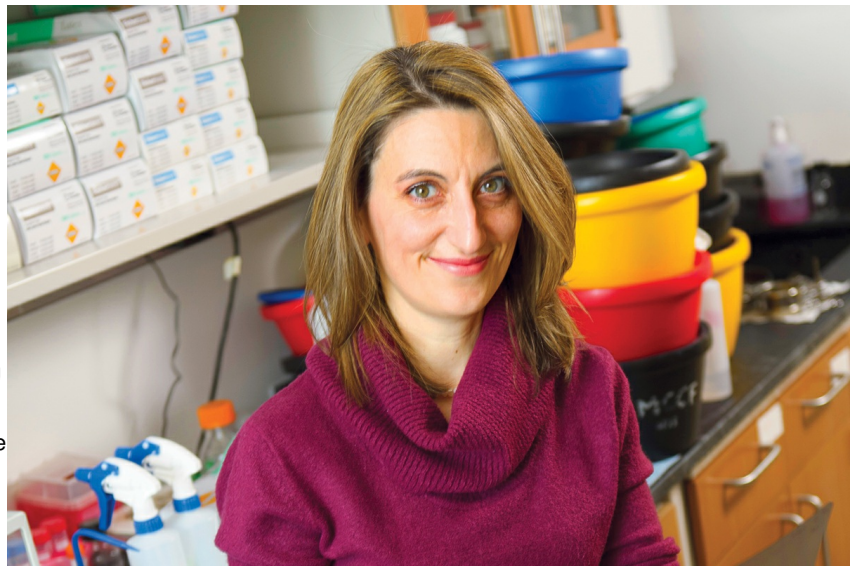
About 80 percent of the lead researchers the Sloan Kettering Institute has recruited since 2000 started at the junior level, as Dr. Keeney did. For example, the Sloan Kettering Institute's Developmental Biology Program has since its inception recruited nine new investigators, eight of whom started as junior researchers. "It's been so rewarding to see what scientific questions the best young people in my field are focusing on, and how they bring these questions to the next level," said developmental biologist and Program Chair Kathryn V. Anderson. "And it's been wonderful to then sit back and watch these people succeed."

Strengthening Expertise and Technology for Research

According to laboratory researcher Alan Hall, who chairs the Cell Biology Program, one resource that sets Memorial Sloan Kettering apart from other research centers is the Sloan Kettering Institute's 36 core facilities, which provide a wide range of expert services and research technology.

"No other institution I know of provides equivalent support for its scientists," said Dr. Hall, who had conducted research at a number of leading biomedical institutions, in Europe as well as in the United States, before joining Memorial Sloan Kettering in 2006. "By constantly pushing the limits of what scientists can accomplish, our professional support staff foster highly productive, cutting-edge research."

Over the course of the past ten years, research support has been augmented to accommodate the Sloan Kettering Institute's growing scientific community and to maintain technologies at the leading edge. Some new services were introduced — notably, facilities dedicated to the development of small molecules for cancer therapy — while many existing facilities were expanded, both in the numbers of people who serve on their staffs, and in their laboratory spaces, equipment, and technology.



Elisa de Stanchina heads the Sloan Kettering Institute's Antitumor Assessment core facility.

Laboratory scientist Andrea Ventura, of the Sloan Kettering Institute's Cancer Biology and Genetics Program, said strong research support is a key to success for a start-up lab such as his, which he launched two years ago. The lab explores how molecules called microRNAs act on genes to either promote or halt cancer progression, with the ultimate goal of exploiting these molecules for therapy.

"We have already generated eight transgenic mouse strains that lack individual microRNAs, and we are now in the process of analyzing them," he noted, adding he could "only have dreamt of doing such experiments" without the support of Sloan Kettering Institute's Antitumor Assessment and Mouse Genetics facilities and its Genomics Core Laboratory.

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Cultivating Basic Research Alongside Translation

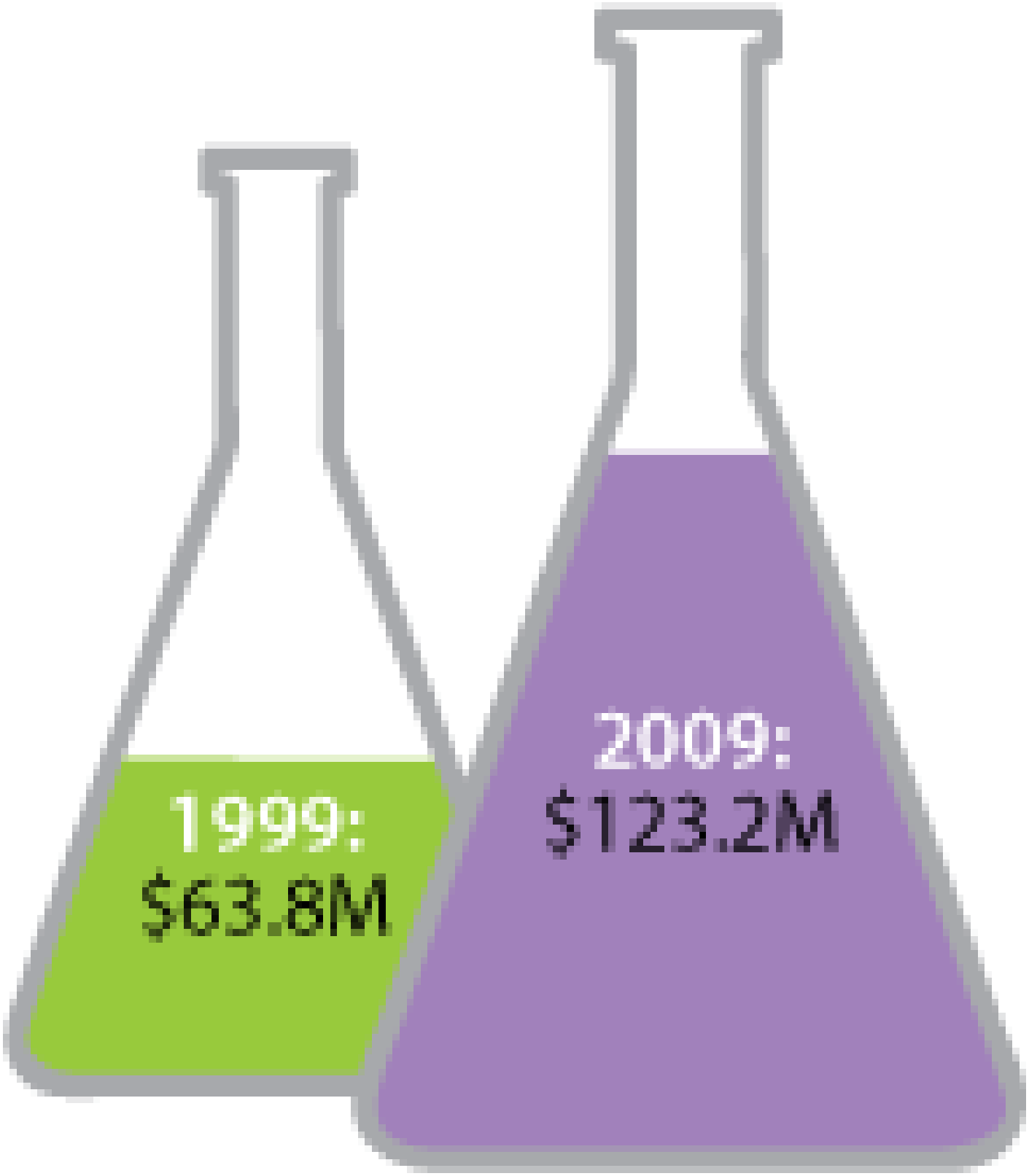
"From the first day I walked in [in 1996], I knew this was a place where people love to interact and share ideas about science," said Dr. Anderson. Much has happened at the Sloan Kettering Institute since that day. With the addition of new laboratories and programs, many areas in which the institute's investigators traditionally excelled — such as developmental biology, molecular genetics, and structural biology — have been strengthened, and programs incorporating newer disciplines such as computational biology have been established.

Opportunities have also grown for basic scientists to see their work translated into clinical applications, or to actively take part in this endeavor. When Dr. Anderson began her research career by investigating the cellular mechanisms that guide a fruit fly's development, the relevance of those mechanisms for human disease was "still somewhat theoretical," she said, but that relevance has now become more obvious.

Milestones 2000-2010 — A decade devoted to advancing research at the Sloan Kettering Institute

"Back then, we had to ask ourselves, 'How can I prove that my findings are relevant for cancer?'" Dr. Anderson explained. "Today, we simply ask what is the best way to figure out how a cellular process works, knowing that what we learn will almost certainly apply to cancer biology."

Research findings made in several Sloan Kettering Institute laboratories — including Dr. Anderson's lab, which currently investigates the genes that control development in a mouse embryo — have shed light on the cellular processes that allow normal tissues to take shape and grow. These processes can also be co-opted by tumors.



Federal Research Awards Granted to the Sloan Kettering Institute — Sums include all federal research expenditures on awards made directly to the Sloan Kettering Institute, excluding awards made to another institution and subcontracted to the Sloan Kettering Institute.

For example, researchers in the lab of Alan Hall, Chair of the Cell Biology Program, are investigating a group of proteins called Rho, which dictate how normal cells divide and move around within a tissue. When inappropriately activated in tumors, these proteins can promote cancer progression and metastasis.

“When I first came here, I was impressed by the tremendous research program Harold and Tom were building,” Dr. Hall said, referring to the effort then-Memorial Sloan Kettering President Harold Varmus and Dr. Kelly had undertaken to simultaneously cultivate basic and translational research at Sloan Kettering Institute. “They recognized the need to keep an open mind about the opportunities basic science might afford in the future, while exploiting the knowledge we already have.”

In 2004, when Dr. Allison joined the Sloan Kettering Institute as Chair of its Immunology Program, one of his goals was to integrate the program’s clinica and scientific expertise, encouraging basic scientists to engage in translational research. “The main reason I came here was to be fully involved in exploring the clinical potential of discoveries made in my lab,” he said. “I wanted to learn as much as possible from a clinical study, and then take that experience back to my laboratory” for further research. “I considered a number of leading cancer centers across the country,” he added, “but none compared to Memorial Sloan Kettering in terms of providing a climate where translation can thrive.”

Research in Dr. Allison’s laboratory is focused on the molecular mechanisms by which the immune system’s T cells can be activated to defend the body against challenges such as cancer or infections. In the 1990s, Dr. Allison discovered that a protein called CTLA-4 inhibits T cell activation and can act as a brake on T cells’ ability to track down and kill tumor cells.

He later worked with a team of Memorial Sloan Kettering clinicians — led by medical oncologist Jedd D. Wolchok — and with a biotechnology company to develop an antibody therapy that releases this brake by interfering with CTLA-4. The drug, ipilimumab, is the first success in a series of efforts to develop treatments that act by enhancing the immune system’s inherent ability to recognize and attack cancerous cells.

Scott Keeney with research fellow Liisa Kauppi, who is pursuing her postdoctoral training in his lab.

New Opportunities for Collaboration and Translation

As construction began on the Mortimer B. Zuckerman Research Center, SKI adopted new ways to advance therapeutic innovation at Memorial Sloan Kettering.

Learn more →

Today thousands of people have been treated with the drug, which holds high promise for the treatment of several cancer types. In June, ipilimumab was shown to be the first therapy to improve survival in patients with advanced melanoma — and the estimated survival benefit to patients receiving the drug was remarkable, with a 25 percent survival rate four years after treatment.

Dr. Allison and colleagues are now investigating — in mice — what he and many others believe will be the next generation of cancer therapy: treatments that combine immune therapy, such as ipilimumab, with drugs targeting specific genes or proteins that drive cancer progression. In addition, the investigators continue to explore the molecular fundamentals that make T cells able to defend the body from foreign intruders, hoping their research will instigate innovation in cancer therapies.

“Until we’ve objectively improved our understanding of how T cells are regulated, we won’t find new or better ways to manipulate them in the clinic,” Dr. Allison noted, adding that this approach once led to the discovery of CTLA-4, the protein that ipilimumab targets. “Had I set out to search for a molecule we could manipulate to trigger a patient’s immune response against a tumor, I would never have found it,” he affirmed.

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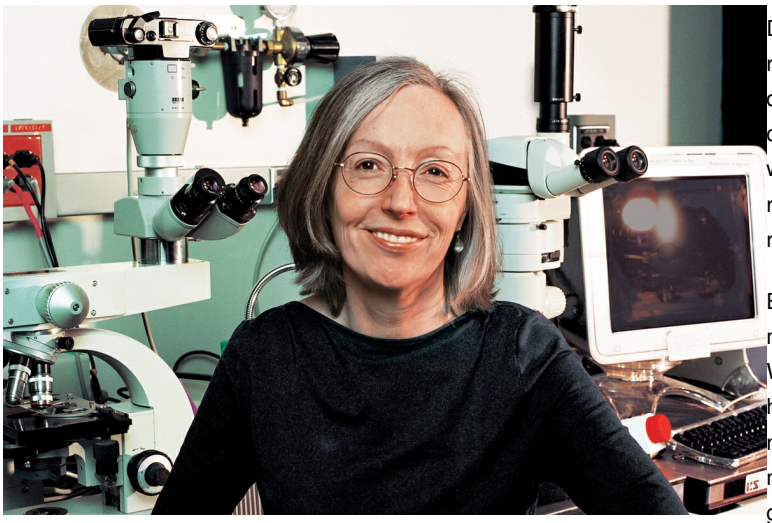
Shaping the Next Generation of Researchers

One evening in October, Scott Keeney stood before a whiteboard facing an audience of postdocs — researchers who have earned a doctoral degree and are undertaking the final years of training needed to become the head of an academic research team. He was jotting down some of his best advice

on how to prepare for a faculty job interview. “I could have used an introduction like this myself when I was a postdoc about to enter the job market,” Dr. Keeney said, as he started the session. “Before my first interview, I had little idea of what to expect or how to prepare.”

> The postdocs and students who train in our labs are those who generate the most creative ideas, and their success is the center of our academic mission.

Currently more than 400 postdoctoral researchers are working in Sloan Kettering Institute labs, which amounts to half of the institute’s academic community. As part of the Sloan Kettering Institute’s recent expansion, several efforts have been introduced to support postdocs in their training, and to help them secure future employment — whether as scientists in academia or the biotechnology industry, or as research professionals pursuing alternative career paths.



Kathryn Anderson, Sloan Kettering Institute Developmental Biology Program Chair

Dr. Keeney and many of his faculty colleagues meet with the institute’s research trainees on a regular basis to share their experiences and to discuss various career challenges. This forum is part of an extensive career development program offering a host of services — from writing workshops to networking events. In addition, the Sloan Kettering Institute recently implemented new mentoring guidelines to foster stronger relationships between postdocs and their faculty advisors.

But academic training, education, and mentoring is a long-established mission of Memorial Sloan Kettering. Together with their colleagues at the Weill Cornell Medical College (WCMC), Sloan Kettering Institute faculty have engaged in graduate training since 1952. In the past decade, the number of graduate students training at the Sloan Kettering Institute has more than doubled (see chart below), with the addition of several graduate training programs — including one in Computational Biology and Medicine, offered jointly by Memorial Sloan Kettering, WCMC, and Cornell University; and one in Chemical Biology, a collaboration between Memorial Sloan Kettering, WCMC, and The Rockefeller University. And six years ago, when Memorial Sloan Kettering obtained degree-granting status from New York State for the first time, the Center launched a PhD program of its own, the Gerstner Sloan Kettering (GSK) Graduate School of Biomedical Sciences.

*Includes all students who were enrolled in PhD and MD-PhD graduate training programs affiliated with the Sloan Kettering Institute

GSK offers students firsthand exposure to cutting-edge science as well as to the realities of clinical practice at Memorial Sloan Kettering. Its innovative curriculum was created on the premise that “solving many of the big questions in biomedical research today will require being conversant in multiple areas of science and medicine,” said Sloan Kettering Institute Molecular Biology Program Chair Kenneth J. Marians, who serves as Dean of GSK. Some in the first class of GSK students are expected to graduate this spring. (Last year, the school was one of 23 across the nation to receive a grant from the Howard Hughes Medical Institute in support of graduate training that brings research and medicine together.)

“Ten years from now, I hope to see all the students and postdocs who have learned science in my lab pursue rewarding careers, wherever they choose to go,” said cancer biologist Andrea Ventura, who oversees and guides research done by three postdocs and three graduate students in his laboratory.

“This is my biggest goal, more important than publishing papers, because I can’t think of a greater satisfaction than knowing I’ve helped shape a new generation of scientists.”

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