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Oncologist Lawrence Fong, MD (center), who co-leads the UCSF Cancer Immunotherapy Clinic, consults with Gabriel N. Mannis, MD (left), and a patient.

Cancer Immunotherapy

Unleashing the Army Within

What if the human body possessed a powerful weapon against cancer, honed by millions of years of evolution? That's the idea behind immunotherapy, one of the most promising new approaches to fighting cancer. Instead of directly trying to poison cancer cells with chemotherapy, immunotherapy boosts the body's own immune system to attack cancer cells – the same way it kills viruses and bacteria.

Long before cancer immunotherapy made headlines by helping former President Jimmy Carter achieve remission from metastatic melanoma – a disease which often kills people within months – UCSF Department of Medicine faculty members had been working to translate an intriguing idea into remarkably potent therapies.

“Cancer immunotherapy has been something that people have thought about for decades, but the real excitement now is we've made the transition from pre-clinical studies and animal models to actually treating patients,” said oncologist Lawrence Fong, MD, Efim Guzik Distinguished Professor in Cancer Biology. He co-leads the UCSF Cancer Immunotherapeutics Program, established in April 2016, which includes both a clinic that offers the latest immunotherapy drugs to patients through

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The Department of Medicine is the largest of the 28 academic departments of the UCSF School of Medicine and is comprised of the following Divisions:

Cardiology

Clinical Pharmacology

Endocrinology/Metabolism

Experimental Medicine

Gastroenterology

General Internal Medicine

Geriatrics

Hematology/Oncology

HIV/AIDS

Hospital Medicine

Infectious Diseases

Nephrology

Occupational and
Environmental Medicine

Prevention Science

Pulmonary, Critical Care,
Allergy and Sleep Medicine

Rheumatology

From the Chair

The Changing Face of Cancer Treatment

In 1971, President Richard Nixon boldly declared a national “War on Cancer.” Nearly half a century since that declaration, the war has proved to be one of attrition. While there have been small victories, fundamental outcomes have not improved very much. Why? Despite the war, until recently our understanding of cancer was relatively primitive, and our weapons – primarily chemotherapy, radiation and surgery – have obvious limits.

In the past few years, we’ve turned a corner in this tragic and costly war. While in most of medicine the promise of precision medicine is just that, a promise, in oncology it feels very real. Our deepening understanding of the molecular underpinnings of cancer has created opportunities to develop new kinds of targeted therapies.

In this issue we profile some of the superb UCSF scientists and clinicians who are tackling cancer with new molecular tools, including those designed to unleash the power of the immune system. I am pleased that the work has attracted a number of generous donors, including Internet pioneer Sean Parker, whose Parker Institute for Cancer Immunotherapy is accelerating research in this exciting area.

Not only is the science evolving, but the new knowledge calls into question our organizational model for cancer. In the old days, cancer was defined by the organ in which the malignancy originated. And so there were lung cancers, colon cancers, breast cancers and prostate cancers, each with its own natural history, workup, prognosis, treatment options and specialists.

With our new discoveries and therapeutic armamentarium, does this organ-based grouping still represent the best organizational structure? Perhaps cancers should be organized by their genetic defect, or by their potential susceptibility to a given class of therapies. At UCSF, we are asking these hard questions, and coming up with novel answers. Today, patients with many different cancer types (as viewed through the traditional organ-system lens) might see Larry Fong and his colleagues in the UCSF Cancer Immunotherapy Clinic. Those with a given genetic profile might see Pamela Munster and her colleagues in the BRCA research clinic.

The progress is dizzying, and we are committed to marrying scientific advances with fresh thinking about care delivery. Our goal is to make it as easy as possible for patients to access the best treatments, to participate in cutting-edge clinical trials and to speed the discoveries we need to finally win the War on Cancer.

Sincerely,

Robert M. Wachter, MD

Professor and Chair, Department of Medicine

Holly Smith Distinguished Professor in Science and Medicine

Lynne and Marc Benioff Endowed Chair in Hospital Medicine



President Richard Nixon signing the National Cancer Act of 1971



Robert M. Wachter, MD

Alumni Profile: Dr. Margaret Callahan

‘We Can Offer Patients Hope’

When UCSF resident alumna Margaret Callahan, MD, PhD, began her medical oncology fellowship in 2009, treatment options for patients with metastatic melanoma were dismal. Only a tiny fraction of patients responded to therapies, and most died within months.

That landscape soon changed dramatically with the emergence of cancer immunotherapy – which has been particularly effective in melanoma patients, for reasons that are not yet understood.

“The conversations we have with patients today are very different,” said Callahan, now an assistant attending in the Melanoma and Immunotherapeutics Service at Memorial Sloan Kettering Cancer Center in New York, where she also completed her fellowship. “Today we have some really good options, and it’s very likely we’ll find a therapy that works for you. We can offer patients hope, and we have the drugs and the data to back it up. Many patients I treated during my fellowship are cancer-free or cancer-controlled – four, five, six years later.”

Callahan first learned about cancer immunotherapy in the early 2000s, when she was just starting her joint MD-PhD program at the University of Connecticut. “I was all set to go into genetics, but I heard a talk on immunotherapy and thought, ‘This is so cool!’” she said. “There were a lot of people who didn’t think it was such a great idea, but I saw that if we could understand the immune system better, we could mold it into a tool to fight cancer.”

Asking the Next Question

She earned her PhD in immunology along with her medical degree, then chose UCSF for her internal medicine residency. “My experience at UCSF was really foundational, and the skill sets I got there are imprinted on me,” said Callahan. “The program did a very good job of teaching residents to ask the next question. If something about a diagnosis doesn’t fit, we learned to ask what else could possibly explain it.



UCSF resident alumna Margaret Callahan, MD, PhD, leads clinical trials of new immunotherapy drugs at Memorial Sloan Kettering Cancer Center in New York.

That’s served me well in so many different avenues.”

She also appreciated career guidance from Harry Hollander, MD, director of the residency program. Because she planned to complete a research-oriented fellowship, Callahan “fast-tracked” through residency – compressing her clinical training into two years rather than the usual three, and adding an extra research year to her fellowship. That required her to apply for fellowships just three months into her internship year.

“Dr. Hollander sat down with me early on, and made sure I was reflecting on decisions for my career pathway,” said Callahan. “He also helped me get all my paperwork in, and enabled me to have time to interview on the East Coast during my intern year, when I didn’t have a lot of control over my schedule. Those things aren’t small at all.”

“Maggie had all the intellectual energy one finds in top physician-scientists, coupled with the compassion

and kindness that convinced me that she would be a terrific clinical oncologist,” said Hollander. “In a very short time, she has made major contributions to the immunotherapy revolution which has swept over oncology.”

As a faculty member at Memorial Sloan Kettering, Callahan leads clinical trials of new immunotherapy drugs and combinations, and actively pursues many research questions. “I’d like to know why immunotherapy works for one patient but not another, and what we can do to improve activity and make side effects easier to tolerate,” said Callahan. “How can we improve our understanding of our patients’ immune systems so we can better deliver therapies that work? No one therapy will be the magic cure for all cancers, but there is lots of room to improve what immunotherapy can deliver.”

Callahan is married to Joseph Grosso, PhD, a cancer researcher. Together they have a young daughter, Olivia. ■

Immunotherapy

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clinical trials, as well as a laboratory that studies each patient's response to these agents. He is also co-director of the Parker Institute for Cancer Immunotherapy at UCSF (please see *Hacking Cancer* on page 8).

Uncloaking Tumor Cells

In the 1890s, a New York surgeon named William Coley, MD, began injecting cancer patients with bacteria, reasoning that an immune system stimulated to fight an infection would also be primed to attack cancer. He reported good results from using "Coley's Toxins," especially in patients with bone and soft tissue sarcomas. However, this controversial approach fell out of favor as radiation and chemotherapy advanced.

But a few tenacious researchers – including Fong and his UCSF colleagues – kept investigating the idea, playing pivotal roles in winning approval from the U.S. Food and Drug Administration (FDA) for novel immunotherapy drugs in 2010 and 2011.

"We've recognized over the last few years that carefully unleashing the immune system can have profound effects on tumors, an approach that was dismissed by most people for many years," said Alan Ashworth, PhD, FRS, president of the UCSF Helen Diller Family Comprehensive Cancer Center, E. Dixon Heise Distinguished Professor in Oncology and Senior Vice President for Cancer Services, UCSF Health. "This has revolutionized the way we think about treating cancer."

The immune system is built to attack invaders such as bacteria. But to prevent the body from attacking itself and causing autoimmune diseases such as rheumatoid arthritis and multiple sclerosis, the immune system has developed many brakes, also known as checkpoints. In part because cancer arises from the body's own cells, it has found ways to exploit this loophole, lulling the immune system into lowering its guns through mechanisms that are not yet fully understood.

"Cancer cloaks itself from the immune system and becomes invisible, so the immune system ignores it," said Ashworth. "The recent successes in

immunotherapy harness the notion that you can uncloak cancer. UCSF has worked in this area for a long time."

Bringing Immunotherapy to Patients

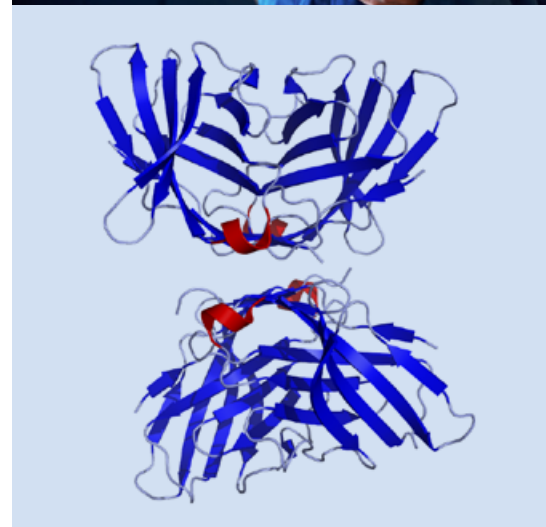
The development of some of the first immunotherapeutics illustrates UCSF's important role in the field. In the 1990s at UC Berkeley, immunologist James P. Allison, PhD, discovered that the CTLA-4 gene could tamp down the immune system, functioning like an off switch. One of Allison's graduate students, Matthew "Max" Krummel, PhD, now a professor in the UCSF Department of Pathology, conducted several experiments that applied this finding to prostate cancer.

In the mid-1990s, Jeffrey A. Bluestone, PhD, then an immunologist at the University of Chicago, discovered that CTLA-4 could restrain the immune system from causing autoimmune diseases and rejection of transplanted organs. Bluestone joined the UCSF faculty in 2000, and is now the president and chief executive officer of the Parker Institute for Cancer Immunotherapy and A.W. and Mary Margaret Clausen Distinguished Professor at UCSF.

Bringing these discoveries to patients, Fong and Eric Small, MD, now the chief of the Division of Hematology and Oncology, Doris and Donald Fisher Distinguished Professor in Clinical Cancer Research, Stanford W. and Norman R. Ascherman Endowed Chair, and deputy director of the UCSF Helen Diller Family Comprehensive Cancer Center, led the first-in-human trials of the CTLA-4 inhibitor ipilimumab (also known as Yervoy), now an FDA-approved immunotherapy for melanoma. It functions by releasing the CTLA-4 "brake pedal," allowing the immune system to respond more aggressively to cancer.

Similarly, UCSF oncologist Adil Daud, MD, led trials of another checkpoint inhibitor that targets the PD-1 and PDL-1 antibodies. One of these agents, pembrolizumab (also known as Keytruda), has received FDA approval for use against advanced melanoma, non-small cell lung cancer and head and neck squamous cell cancer. It's the drug that former President Carter later received.

"One of the big turning points for the field of immunotherapy was learning the



Jeffrey A. Bluestone, PhD (top), discovered that the CTLA-4 gene (above) could restrain the immune system from causing autoimmune diseases and rejection of transplanted organs.

way these anti-CTLA-4 and anti-PD-1 antibodies each targeted just one molecule," said Fong. "By teasing apart different molecules that are important for controlling the immune system, you can hit specific molecules, rather than coming in with a sledgehammer that might hit multiple targets.

"Another watershed moment was when anti-PD-1 antibodies were approved for lung cancer, a disease which is essentially incurable and which kills people fairly quickly," said Fong. "We saw a clinical response with immunotherapy that is relatively free of side effects. Immunotherapy is absolutely now one of the pillars of cancer therapy, and, in the United States, the vast majority of lung cancer patients are now getting these immune checkpoint inhibitors. It has really



Inset: Eric Small, MD, led the first-in-human trials of the CTLA-4 inhibitor ipilimumab, a turning point for the field of immunotherapy. Above: Alan Ashworth, PhD, FRS, president of the UCSF Helen Diller Family Comprehensive Cancer Center, says that immunotherapy has “revolutionized the way we think about treating cancer.”

transformed medicine.”

In yet another groundbreaking investigation, Fong and Small led development and clinical trials of sipuleucel-T (also known as Provenge), the only FDA-approved cancer vaccine. It exposes a prostate cancer patient’s white blood cells to an antigen – a molecule that causes the immune system to produce an antibody against it – found in prostate cancer. These enhanced white blood cells are then re-infused into the patient, where they hunt down and destroy prostate cancer cells.

‘We’re Just Getting Started’

While many patients experience fewer side effects with immunotherapy than with conventional chemotherapy, others may suffer potentially life-threatening toxicities that require management in the intensive care unit. The UCSF Cancer Immunotherapy program has developed the expertise to manage patients through these challenging situations.

For example, one particularly potent immunotherapy approach is called chimeric antigen receptor (CAR) T-cell therapy. It involves extracting a patient’s T cells, genetically engineering them to

recognize an antigen found in their cancer, multiplying these souped-up T-cells and reinfusing them into the patient. In some cases, this approach can produce severe side effects, including high fever, nausea and organ failure. This is partly because CAR T-cells can attack not only cancer cells but normal tissues that contain the target antigen. Moreover, they can also stimulate so-called cytokine release syndrome, in which a patient’s highly activated immune system releases a storm of immune molecules.

“It really speaks to the strength and power of the immune system,” said Fong. “We walk that fine line of trying to suppress the immune response, while allowing the immune response to target the cancer cells. We have a team of investigators who manage patients across different clinical trials and are accustomed to identifying and treating cytokine release syndrome, for example, rather than assuming it’s an infection that requires an antibiotic.”

Immunotherapy has been incredibly effective for some patients, but is far from a silver bullet. When used as monotherapy, many immunotherapies lead to significant clinical responses in only 10 to 20 percent of patients. Yet some of these patients have extraordinary responses, living for

years when most patients treated with conventional therapies only survive for months.

Fong and his colleagues in the UCSF Cancer Immunotherapy Program are working hard to determine why some patients have astonishing responses to a particular immunotherapy, while others have little or no response. One component of this investigation involves neoadjuvant immunotherapy– giving patients immunotherapy prior to surgery, then intensively studying the genetic and immune profiles of tumor, lymph node and blood samples obtained during surgery.

“We use state-of-the-art immune assays and leverage the incredibly strong immunology community at UCSF to profile patient samples by multiple means,” said Fong. “One of our visions is to create a precision immunology clinic. If we understand mechanistically why some patients respond and some do not, we could use that to help guide treatment selection or patient selection for a particular treatment.”

“We’re moving to this holistic analysis of not just the tumor cell and its genome, but the microenvironment in the tumor and then the circulating

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Immunotherapy

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immune environment,” said Ashworth. “That provides a much more comprehensive picture of what’s going on in the person with cancer. It may be that only by modulating all of those effects do you get the best therapeutic effects.”

This approach may also yield clues about ways to effectively combine different kinds of immunotherapy drugs, or specific immunotherapy agents with conventional chemotherapy drugs, in a way that targets a patient’s specific type of cancer.

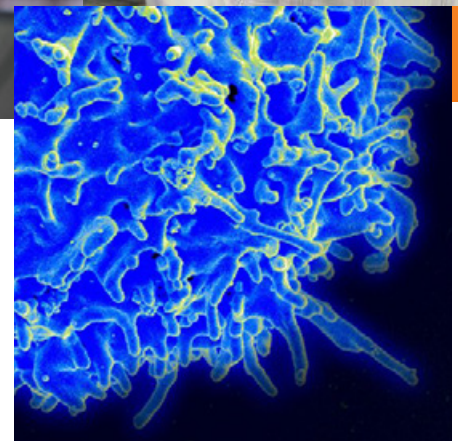
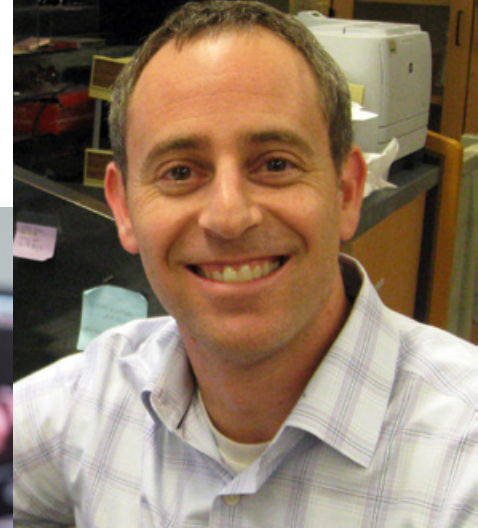
“So far, we’ve been targeting two molecules, but there are probably 30-plus molecules that are relevant for the immune system that we could target,” said Fong. “I tell people that we are just getting started with immunotherapy.”

From Cold to Hot

Cancer is an incredibly sophisticated foe, and it is likely that effectively administering immunotherapy is not as simple as removing a bottleneck in the immune system. “The crucial problem today, especially with PD-1, is that 40 percent of melanoma patients will respond to it, but the rest won’t,” said Daud, the UCSF oncologist who led clinical trials of PD-1 inhibitors and directs the Melanoma Program at the UCSF Helen Diller Family Comprehensive Cancer Center. “For most cancers, like colon, breast, lung and prostate cancer, PD-1 inhibitors only work about 10 to 20 percent of the time, and CTLA-4 has almost no activity at all.”

To better determine which patients are likely to respond to PD-1, Daud has teamed up with UCSF dermatologist and immunology researcher Michael Rosenblum, MD, PhD. Together they devised a novel way to extract, isolate and study T cells from patients’ tumors – something that had been done in mice, but not previously in humans.

T cells are the immune system’s foot soldiers, scouting out and destroying invaders. By interrogating T cells that specifically target cancer, Daud and Rosenblum found that many of these tend to be “exhausted” – meaning that they were able to find enemy tumor cells, but for some reason lost the



ability to kill them. They hope to discover ways to revive these exhausted T cells, restoring their natural ability to fight cancer.

Daud and Rosenblum also found that patients with “hot” tumors – those that were crawling with T cells – tend to respond well to a PD-1 inhibitor like pembrolizumab, while patients with “cold” tumors – those with few T cells on them – tend to be unresponsive.

“The question is, how do you take a cold tumor and make it hot?” asked Daud, noting that just revving up the entire immune system by giving more immunotherapy drugs doesn’t work. “It’s like trying to cook an egg in your kitchen. You can turn up the heat in your apartment, but the heat needs to be more targeted – otherwise you might burn your house down before the egg is cooked. What we’re trying to induce is immune rejection of the tumor, without causing collateral damage to your skin, colon and other organs.”

Daud had previous success with making tumors more visible to the immune system in the early 2000s, when he worked at the H. Lee Moffitt Cancer Center and Research Institute in Tampa. He and colleague Richard Heller, PhD, injected a gene called plasmid interleukin-12 (pIL-12) directly into melanoma tumors, then used electrical pulses to drive the gene through the tumor cell membrane. Once inside the tumor cell, pIL-12 caused the tumor cells to crank out a signaling protein that the immune system usually produces in response to emergencies like an infection. “It’s like a Code Blue

Oncologist Adil Daud, MD (above left), and dermatologist and immunology researcher Michael Rosenblum, MD, PhD (top), isolate and study T cells (above) from patients’ tumors.

that says, ‘Hey, something is seriously wrong – you’d better get over here quick!’” said Daud.

He recently launched a clinical trial that combines injections of pIL-12 with pembrolizumab, with the idea that the pIL-12 makes the tumor visible to the immune system, and pembrolizumab boosts the immune system’s ability to attack the cancer.

Daud, who joined UCSF’s faculty in 2008, leads a number of other immunotherapy trials, and is excited about the way that cancer immunotherapy has transformed the field. “It’s a time of incredible promise,” he said. “In 10 years, I think the basic treatment for cancer will be immunotherapy, and that we will add chemotherapy or targeted therapy to that as needed. Immunotherapy potentially offers a way out for some cancers that have been hard-core resisters, recalcitrant to whatever you can throw at them. It’s pretty amazing to be able to look people in the eye and say, ‘Hey, we think we can get rid of this tumor.’”

'Just Living My Life'

One of those patients is Bonnie Grear, a retired X-ray technologist who spends a lot of time doing yard work. In October 2015, she noticed what looked like a mosquito bite on her left calf. When it grew to the size of a dime, she showed it to her primary care physician at UCSF.

After undergoing several diagnostic tests, Grear was shocked to learn she had metastatic melanoma, which had spread to a lymph node in her groin. "It was very scary," said Grear, now 75. "I felt like someone hit me on the head with a brick, and I went into panic mode."

Her doctor referred her to the UCSF Melanoma Center, where she met with Daud and his team. They invited her to participate in the pembrolizumab and pIL-12 combination trial, which had shown early promise with other melanoma patients. "They answered every question, and I said, 'Let's take a chance,'" said Grear.



Since April 2016, she has received an intravenous infusion of pembrolizumab every three weeks. She also received injections of pIL-12 directly into the tumor on her leg. After two injections, however, the lesion shrank and became undetectable, so her doctors discontinued the injections. Her latest positron emission test (PET) scan showed that the tumor in her groin has regressed.

"Dr. Daud is very positive and has a sense of humor," said Grear. "He always explains things in a way that I can understand. He told me, 'I expect this PET scan to be a big fat zero,' and it was. The groin lesion is there, but it's like it's dead. I'm responding well to the treatment, and the results are pretty wonderful."

Grear initially lost her appetite when starting treatment, but regained it after a few months. Now she sometimes goes out to lunch after her infusions. She does experience fatigue, joint pain in her hip, and occasional light-headedness. "Those side effects are pretty common, but are really minor," she said. "If that's all I have, I'm grateful."

Grear will continue receiving pembrolizumab infusions for another year, then will be monitored every three

to six months for life. The hypothesis is that after two years of treatment, Grear's immune system will be sufficiently trained to keep the cancer in check on its own.

"It's a different paradigm from chemotherapy, where you always worry that the tumor may come back if you stop the chemotherapy," said Daud. "Immunotherapy is more like vaccination – it either works or it doesn't, but you don't just keep giving people more pneumonia shots. Once the T cells are running around, killing tumors, we're not inclined to keep giving a PD-1 inhibitor forever, because it does increase the chances of autoimmune side effects." The trial's initial results are promising: 18 months after stopping both the pembrolizumab and the pIL-12, 97 percent of patients who responded to the treatment remain in remission.

"I want to thank Dr. Daud and his team for making me part of this study," said Grear. "His expertise and enthusiasm keep my attitude very positive. There are patients who kick this, and they live for years after treatment. Hopefully I'm in that category. I'm just living my life, one day at a time, and am happy to be doing so well." ■

Melanoma patient Bonnie Grear (left) receiving an intravenous infusion, and (below) with her oncologist, Adil Daud, MD, who is investigating ways to increase response rates to immunotherapy.



The Parker Institute for Cancer Immunotherapy

In addition to advancing immunotherapy approaches in the clinic and laboratory, UCSF is now part of an even larger effort to exploit the immune system's full potential to treat cancer.

In April 2016, UCSF was named one of six major cancer centers – along with Memorial Sloan Kettering Cancer Center, Stanford Medicine, UCLA, the University of Pennsylvania and the University of Texas MD Anderson Cancer Center – to receive support from the Parker Institute for Cancer Immunotherapy. The institute was created by a \$250 million gift from the Parker Foundation, a private philanthropic organization established by Silicon Valley entrepreneur Sean Parker, who is perhaps best known for his roles as founding president of Facebook and co-founder of Napster.

UCSF immunologist Jeffrey A. Bluestone, PhD, A.W. and Mary Margaret Clausen Distinguished Professor, is president and chief executive officer of the entire institute. Lewis Lanier, PhD, chair of the Department of Microbiology and Immunology and holder of the J. Michael Bishop, MD, Distinguished Professorship, directs the UCSF center.

"We wanted to bring three things together: great science, great collaboration, and reduced bureaucracy that allows scientists to get back doing innovative science rather than constantly raising money," said Bluestone. "We're trying to bring all these pieces together to 'hack the system,' as Sean would say. We want people to take their most adventurous ideas and give them a try."

Bluestone spent decades investigating ways to rein in the immune system to prevent autoimmune diseases such as type 1 diabetes, which develops when the body attacks insulin-producing islet cells in the pancreas. One of the most feared side effects of powerful immunosuppressants is that they may stimulate cancer or infections, as organ transplant patients know all too well. And one of the biggest side effects of amping up the immune system to attack cancer is autoimmunity, including conditions such as diabetes, inflammatory bowel disease and lung

inflammation. "My whole career has been about checks and balances, tolerance versus immunity, on versus off," said Bluestone.

'A New Way of Doing Science'

As head of the Parker Institute, he now leads a bold enterprise that has made initial investments of \$10 million to \$15 million in each of the six Parker Institute centers. Collectively, the consortium has also created a common agreement that allows centers to share inventions and discoveries, manage intellectual property and create standardized ways to analyze data, collect tissue samples, and work collectively on clinical trials through a single Institutional Review Board.

The institute also partners with other nonprofits and the pharmaceutical industry to conduct innovative clinical trials – accessing novel and experimental drugs, testing them in combination studies, and using learn-as-you-go approaches to more quickly identify promising prospects. The Parker Institute collaborates with technology companies to bring new tools that are not yet commercially available to the centers, and create new machines specifically engineered to accelerate research.

Perhaps most importantly, the Parker Institute fosters deep partnerships among its six sites, more than 50 laboratories and 350 researchers. "Good collaboration is more than just common ideas and projects," said Bluestone. "It's about a sense of trust and collegiality. The best way to do that is to have people interact a lot together." Their retreats feature a "speed dating with data" component, giving each center five minutes to highlight their most exciting investigations. They also hold monthly lab meetings, the option to share manuscripts when they are submitted to a journal rather than waiting until they are published, and social gatherings at scientific meetings where researchers' families are welcome.

The Parker Institute is already pursuing ambitious ideas, including a cell therapy clinical trial that takes T cells from patients and uses CRISPR –



From left, Silicon Valley entrepreneur Sean Parker, UCSF immunologist Jeffrey Bluestone, PhD, and journalist Katie Couric at the Los Angeles launch of the Parker Institute for Cancer Immunotherapy in 2016. Bluestone is president and CEO of the national initiative.

a new gene-editing technique – to remove one of the immune system brakes and add a T-cell receptor that targets a tumor antigen. This combines the power of checkpoint inhibitors with T-cell therapy. "It's highly risky, because you're taking off the brakes on the cell, but we're doing our best to do it in a very safe way," said Bluestone. "We've invested millions of dollars for this trial, and it's not something that would be easily done through an NIH [National Institutes of Health] grant."

"The Parker Institute is a new way of doing science that's incredibly powerful," said Alan Ashworth, the The UCSF Helen Diller Family Comprehensive Cancer Center president. "The idea that you partner major institutions and leading scientists with access to resources without all the administrative burden of very complicated grant application procedures is the thing of the future."

"We need science that's high-risk and making big bets, but we also need administrative structures that are willing to take risks," said Bluestone. "Does that mean we could fail? Sure, but I'd love to take a chance of being great rather than average in perpetuity." ■

Faculty Profile: Dr. Lawrence Fong

Transforming Cancer Treatment

For oncologist and immunotherapy pioneer Lawrence Fong, MD, cancer is personal. His father died of lymphoma when Fong was in college, inspiring a lifelong focus on cancer.

"I became really intrigued by the complexity and power of the immune system, and one of my medical school professors was interested in cancer immunotherapy," said Fong, now the Efim Guzik Distinguished Professor in Cancer Biology. "That really planted the seed of thinking about using the immune system to treat cancer."

Fong, a San Francisco native, grew up in the Russian Hill neighborhood. He received his medical degree from Stanford University School of Medicine, and completed internal medicine residency at the University of Washington in Seattle and medical oncology fellowship and postdoctoral fellowship in pathology at Stanford. In 2002, Fong joined the UCSF faculty, collaborating with other researchers who shared an interest in tumor immunology.

Fong worked closely with Eric J. Small, MD, now the chief of the Division of Hematology and Oncology, Doris and Donald Fisher Distinguished Professor in Clinical Cancer Research, Stanford W. and Norman R. Ascherman Endowed Chair, and deputy director of the UCSF Helen Diller Family Comprehensive Cancer Center.

Fong, Small and their colleagues brought some of the first immunotherapy drugs from the lab to the clinic. They identified a protein called prostate acid phosphatase, using it as a target for a prostate cancer vaccine called sipuleucel-T or Provenge – now approved by the U.S. Food and Drug Administration (FDA) for treatment of prostate cancer. They also led first-in-human trials of ipilimumab, also known as Yervoy, now an FDA-approved immunotherapy for melanoma. It works by lifting immune system "brakes" associated with CTLA-4, enabling the immune system to aggressively pursue cancer.

Persevering through Lean Times

Although the potential of cancer immunotherapy has intrigued physicians for more than a century, its clinical usefulness has only recently been demonstrated. "I joke that four or five years ago, the field of cancer immunotherapy was a little bit of a support group for people who were diehards, thinking this approach would really work," said Fong. "It was a very difficult time, not only because of cynicism from our peers, but because it was very difficult to get grants from the NIH [National Institutes of Health]. I certainly would not have predicted that we'd be treating so many different cancers with immunotherapy, and that companies would have invested billions of dollars to develop immunotherapy drugs."

Today, Fong is the co-leader of the UCSF Cancer Immunotherapeutics Program, and directs its Cancer Immunotherapy Clinic, where patients can access the latest new drugs through clinical trials. The program also includes a cancer immunotherapy laboratory, which rigorously studies patients' responses to novel agents.

"The program has been an outstanding success, and is a testament to Larry

Fong's skills both as a researcher and a clinician," said Alan Ashworth, PhD, FRS, president of the Helen Diller Family Comprehensive Cancer Center and E. Dixon Heise Distinguished Professor in Oncology. "It allows UCSF to provide patients with access to new treatments, and to do it at scale."

"It's such an exciting time," said Fong. "As a family member of someone who died from cancer, I want to be able to offer effective treatments to patients. The pace of development has really accelerated, and we can go from ideas to actually treating patients with some of our concepts in not that long a period of time.

"I have some of the most fulfilling relationships in my life with my patients. We tend not to talk about the mundane, but rather about pretty significant questions. You learn a lot about a person in that context, and I'm privileged to help guide patients through their disease."

Outside of medicine, Fong enjoys mountain biking and spending time with his family. He is married to Nina Loh, MD, a radiologist with the Palo Alto Medical Foundation. Together they have three children: Grant, Mara and Alana. ■

Lawrence Fong, MD, led some of the first clinical trials of immunotherapy, and continues to be a pioneer in this rapidly advancing field.



New Department Chair Profile: Seeing the Big Picture

Robert M. Wachter, MD, who was appointed the chair of the UCSF Department of Medicine last October, has had an astonishingly diverse and influential career.

"It's what happens when a political science major becomes an academic physician," said Wachter, who holds the Holly Smith Distinguished Professorship in Science and Medicine and the Lynne and Marc Benioff Endowed Chair in Hospital Medicine. "Every eight to 10 years, I have been able to jump into a really interesting issue and make a contribution."

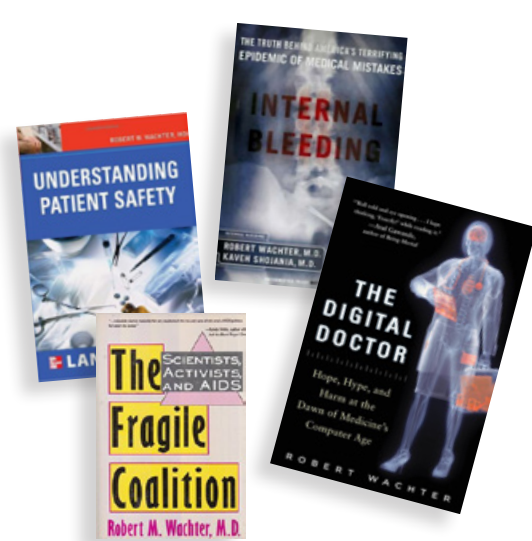
His first book, *The Fragile Coalition: Scientists, Activists, and AIDS*, chronicled the contentious Sixth International Conference on AIDS held in San Francisco in 1990, and through it, the influence of patient activism on health care policy. In 1996, Wachter and then-Chair of the Department of Medicine Lee Goldman, MD, co-authored a *New England Journal of Medicine* article that coined the term "hospitalist," describing a new kind of expert who specializes in the care of hospitalized patients. With about 50,000 hospitalists in the U.S. today, hospital medicine is the fastest growing specialty in the history of modern medicine.

In 1999, after an Institute of Medicine report estimated that nearly 100,000 people died annually due to medical errors, Wachter wrote two bestselling books, *Internal Bleeding: The Truth Behind America's Terrifying Epidemic of Medical Mistakes*, and *Understanding Patient Safety*, urging systemic changes to prevent mistakes.

"I try to listen and learn, see the big picture, and tell a story that helps people better understand something that's important," said Wachter.

Reimagining Health Care

His most recent efforts have focused around the promise and perils of the digital health revolution. Several years ago, Wachter found himself pitching stories to his wife, author and *New York Times* journalist Katie Hafner, about how



"I try to listen and learn, see the big picture, and tell a story that helps people better understand something that's important."

Robert M. Wachter, MD (above), the new chair of the UCSF Department of Medicine, is a pioneering leader in patient safety, hospital medicine and digital health.

health information technology was radically changing the practice of medicine. Then Wachter learned about an egregious medication error at UCSF Medical Center: a teenager received a 39-fold overdose of a common antibiotic, ordered through the computerized prescribing system. "That error wouldn't have happened if we were still paper-based," he said. "I came home and said, 'Honey, I need to write a book about this.'"

That book, published in 2015, is *The Digital Doctor: Hope, Hype, and Harm at the Dawn of Medicine's Computer Age*. "Just six or seven years ago, health care was primarily an analog, three-ring-binder industry, and now we're primarily a digital industry," said Wachter, noting that this huge shift includes both the widespread adoption of electronic health record systems as well as consumer-facing devices and software, such as Fitbits and smartphone apps. "At the same time, we're under massive business pressures to make patient care better, safer, more satisfying and less expensive."

Medical informatics is potentially an invaluable tool for increasing health care value, but the field is still in its infancy. "I don't think we have any idea what the end of the movie looks like," said Wachter. "The disruption in industries like print journalism, taxis and hotels was massive, and people in those industries didn't know what hit them until it was too late. UCSF's excellence, impact and reputation will increasingly be determined by the ability to use information technology to enhance and transform our work across all of our missions."

Some of UCSF's strengths in this area include its excellence in digital health, leadership role in precision medicine, and strong history of industry partnerships, whether with biotechnology firms or technology startups. Add to that UCSF's proximity to leading technology companies in San Francisco and Silicon Valley, its participation in a UC-wide data sharing network, and its history of innovation, and Wachter sees the Department of Medicine's potential to become an international leader in applying digital tools to advance clinical care, research and training.

Rather than just digitizing analog processes, Wachter sees this as an opportunity to reimagine the entire process of health care. "Instead of just taking a paper chart and creating a digital version, we should be thinking, 'Is this the right way to record data about patients?'" he said. "Where things get massively better is when people say, 'Let's do this in an innovative way that takes advantage of new digital tools.' That's the core job we all have, and we're in an incredibly good position to do that."

Finding Joy at Work

Growing up on Long Island, Wachter was inspired by his father, a successful small businessman who did not attend college. "He was really funny, cared deeply about people, and had boatloads of emotional intelligence," said Wachter. "One of the things I learned from him is if you're not having fun, you're not getting it right. I want to promote an environment in which people take their work seriously, but can also say, 'I had

fun and did something interesting and important today.”

Wachter received his undergraduate degree in political science and government from the University of Pennsylvania, then earned his medical degree from Penn’s Perelman School of Medicine. He completed residency and chief residency in internal medicine at UCSF and a Robert Wood Johnson Clinical Scholar fellowship at Stanford, then joined the UCSF faculty in 1990, based at Zuckerberg San Francisco General Hospital and Trauma Center. He served as internal medicine residency director from 1992 to 1995, then ran the medical service at UCSF Medical Center. He was founding chief of the Division of Hospital Medicine, which grew from its first faculty member in 1995 to about 70 today.

“My overall vision is that our department should be the world’s leader in providing better, safer and more efficient care at the lowest cost, producing trainees that are excellent in all those things, and having a research agenda that advances our ability to deliver that and advances the science of medicine and health,” said Wachter. “My fundamental job as a leader is to create an environment where spectacular people want to be here and are inspired to do their best work. So much of the work is about listening to people, forging relationships and gathering consensus.”

One of the biggest challenges he sees for the Department of Medicine is its sheer size. “I am excited about using new tools to communicate,” said Wachter, who was an early adopter of Twitter and blogging. He also looks forward to simultaneously pursuing the multiple missions of patient care, education and research, particularly with UCSF Health as a robust partner. “I love interesting challenges that require a lot of balancing in an environment that’s rapidly changing,” he said.

Wachter will continue to serve as an attending physician on the hospital wards four weeks per year. “It allows me to write and speak effectively about the health care system, plus it energizes me tremendously,” said Wachter. “Our housestaff and students are so smart, and the patients are fantastically interesting.”

Outside of medicine and politics, Wachter’s passions include golf, piano and tweeting (@Bob_Wachter). He and his wife have three grown children: Doug, Benjy and Zoë. ■

Appointments

Michael Chen was appointed associate chair for finance for the UCSF Department of Medicine. He is responsible for departmental finances, clinical revenue, the faculty compensation plan and research administration. Chen earned his law degree from UC Berkeley’s Boalt School of Law and has served at UCSF in various roles, including division manager of the Division of Hematology/Oncology, director of finance for the medical service at Zuckerberg San Francisco General Hospital and Trauma Center (ZSFG) and chief financial officer of the Department of Medicine.



Mitchell Feldman, MD, MPhil, was appointed chief of the Division of General Internal Medicine based at UCSF Health sites, leading a diverse faculty of more than 70 clinicians, educators and researchers. He earned his BA from Johns Hopkins, an MPhil from Cambridge University and completed his medical degree and internal medicine residency at UCSF. His research has focused on the identification and management of behavioral issues in medical patients and mentorship in academic medicine. Feldman is co-editor of the *Journal of General Internal Medicine* and lead editor of *Behavioral Medicine: A Guide for Clinical Practice*. He has also served as associate vice provost for faculty mentoring at UCSF since 2006, establishing the UCSF Faculty Mentoring Program.



Beth Harleman, MD, was appointed associate chair for faculty experience for the Department of Medicine. She will lead efforts to recruit and retain exceptional faculty, expand faculty development and promote satisfaction, engagement and diversity throughout the Department. Harleman completed her medical degree, internal medicine residency and chief residency at UCSF. A general internist based at ZSFG, Harleman co-created and ran the UCSF School of Medicine capstone course, Coda. She also served as associate chair for strategic planning for the Department, promoting leadership, integration and collaboration across the Department. A dedicated educator, Harleman also continues to serve as associate program director for the Internal Medicine Residency Program.



Maria Noveler, MA, MPA, was appointed associate chair for administration for the UCSF Department of Medicine. She oversees human resources, academic affairs, space, information technology, facilities, communications and leadership of the central administration and division manager teams. Noveler earned master’s degrees in international affairs and finance from Columbia University and in public policy from Osaka University. She previously served as administrator for the UCSF Division of Hospital Medicine, helping to advance efforts in quality, safety, value and “lean” methodology. In 2017, she received the Holly Smith Award, the highest service award given by the UCSF School of Medicine. ■



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Donor Profile: *Peter Michael Foundation*

Raising a Glass for Research

With expertise in everything from technology to wine, Sir Peter Michael is a Renaissance man. The engineer and entrepreneur's accomplishments include founding several technology companies, including Quantel, which transformed television graphics. He later co-founded Classic FM, the first commercial radio station in the United Kingdom, and established a luxury hotel and restaurant in England. He was knighted by Queen Elizabeth II in 1989.

While working in Silicon Valley in the 1970s, he fell in love with Northern California. Michael bought a ranch in Calistoga and established the Peter Michael Winery, which he runs with his son and daughter-in-law, Paul and Emily Michael. His vineyards produce some of the world's top wines – a Peter Michael Cabernet Sauvignon Napa Valley Au Paradis 2012 was chosen as Wine Spectator's 2015 Wine of the Year.

He also established a philanthropic foundation to support innovative treatments for prostate cancer. The Peter Michael Foundation hosts dinner auctions across the United States, with exquisite meals prepared by famed chefs like Thomas Keller. "People come from all across the country for the food and wine," said Walter B. Menzel, the foundation's chief executive officer and executive



Sir Peter Michael (left), an entrepreneur, philanthropist and founder of the Peter Michael Winery, supports cancer immunotherapy research at UCSF through the Peter Michael Foundation, which hosts dinner auctions across the country to raise funds for prostate cancer research. Paul and Emily Michael (above), Sir Michael's son and daughter-in-law, help run the winery and foundation.

director. "They come as guests, and leave as friends." The proceeds from these events support cutting-edge prostate cancer research at four top cancer centers across the country, including UCSF.

Even before its potential became widely known, the Peter Michael Foundation began supporting cancer immunotherapy. For the past six years, the Foundation has funded a postdoctoral research fellow in the lab of Lawrence Fong, MD, Efim Guzik Distinguished Professor in Cancer Biology, who directs the UCSF Cancer Immunotherapy Clinic and co-leads the Cancer Immunotherapy Program of the UCSF Helen Diller Family Comprehensive Cancer Center. "The resources from the Peter Michael Foundation have made a big impact on our research program," said Fong. "They provided consistent support year after year at a time when cancer immunotherapy was not the high-visibility field that it is now. This allowed us to make continued progress positioning our

program for even greater successes."

These research projects have included identifying biomarkers that may help determine which patients are most likely to respond to immunotherapy, and studying whether combining immunotherapy treatments could lead to more robust clinical responses.

"We fund really smart people who are working on innovative, high-risk projects," said Menzel. "Immunotherapy has great promise. We've all read about 'super-responders' – people who are right in the sweet spot, and the cancer is completely gone [after receiving immunotherapy]. But those people are few and far between. What was it in that patient and that treatment protocol that connected so effectively, and can you replicate that at scale?"

The Peter Michael Foundation (petermichaelfoundation.org) hopes its support hopes their support will improve the efficacy of immunotherapy for more patients. ■