The Fastest-Ever Medical Linear Accelerator Could Revolutionize Cancer Treatment

PHASER: Next-generation Radiation Therapy

Today, the quickest radiation treatments for cancer take several minutes per session. A large and clunky linear accelerator, which produces radiation, must mechanically rotate around a patient’s body, hitting a tumor from many angles as it bombards the cells in its path with high-energy beams. During that time—which can be as long as an hour and a half in some cases—it’s a given that the tumor will move at least slightly.

“We’re always trying to hit moving targets,” said Billy W. Loo Jr., MD, PhD, an Associate Professor in the Department of Radiation Oncology and SCI member. “Every part of the body moves all the time. Things move as you breathe in and out, the heart pumps, organs like the stomach squeeze, and people move around and wiggle.”

That movement means that non-cancerous cells invariably end up in the path of the radiation. And it’s why Loo is trying to make radiation therapy last less than one second instead of many minutes.

“What if we could give radiation nearly instantaneously? What if treatment could be given before any part of the body moves?” asked Loo. “That was the seed of the idea we came up with.” If radiation could be given quickly enough to “freeze” motion, Loo reasoned, then stronger, more focused beams could be given to the sites of tumors without having to worry about hitting the surrounding tissues when a patient moved.

Loo’s seed of an idea is now a large, interdisciplinary project that’s pushing the boundaries of physics, engineering, and radiation oncology at Stanford. It’s called PHASER—for Pluridirectional High-energy Agile Scanning Electronic Radiotherapy—and will be the fastest, most powerful radiation delivery system when it’s complete.

Loo is a physician-scientist who has a bioengineering background in addition to his radiation oncology training. He was familiar with ultra-fast CT scanners designed with fully electronic controls in place.

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PHASER is a more effective form of radiation therapy, with fewer side effects.
Message from the Director

Stanford Radiation Oncology is Exceptional

What distinguishes the Stanford Cancer Institute (SCI) is the quality and innovation that is embedded in our research and the resulting treatment options our clinicians are able to offer to patients seeking cancer care at Stanford.

The SCI, a National Cancer Institute (NCI)-designated Comprehensive Cancer Center, shares the NCI’s mission: to lead, conduct, and support cancer research across the nation. That mission has led the SCI to define eight research programs that encompass the broad efforts of our 462 faculty, representing 32 departments across the University.

The NCI has rated all eight programs in the highest tier, but our Radiation Biology program consistently receives the NCI’s highest rating, Exceptional.

As the cover article of our newsletter illustrates, this program is at the forefront of developing new technologies that will continue to significantly improve patient care. Those technologies result from basic science findings in the laboratories of SCI faculty in conjunction with research being carried out at the SLAC National Accelerator Laboratory. As highlighted in this issue, the physicists there are working together with our clinical colleagues to enable new technologies that will deliver faster and more precise radiation to patients.

Radiation Oncology has been a preeminent department at Stanford since its start more than 30 years ago. Today’s program builds on a long legacy that began in the 1950s when Henry Kaplan, MD, founding Chair of the Department of Radiology, developed the first high-energy linear accelerator for therapeutic use.

Dr. Kaplan’s inventive spirit continued under Malcolm Bagshaw, MD, the first Chair of the Department of Radiation Oncology, and was followed by Richard Hoppe, MD, who advanced the program’s intensive research and development efforts.

Today, under the leadership of chair Quynh-Thu Le, MD, the program is reaching new heights.

Beverly S. Mitchell, MD
Director
of mechanical components that physically slow down the imaging. Believing that the same thing could be done with the linear accelerators that produce radiation for cancer therapy, he reached out to colleagues at the SLAC National Accelerator Laboratory. As it turned out, Sami Tantawi, PhD, Professor, Particle Physics and Astrophysics, had just discovered new principles that would enable him to build a compact and far more efficient linear accelerator than ever before with the characteristics needed for this novel medical concept.

Loo launched a collaboration with Tantawi—and other colleagues with physics, engineering, imaging, and radiation expertise—to use the new linear accelerator principles in radiation oncology. Today, a prototype linear accelerator has been built—and is demonstrating world-record performance at SLAC—based on the collaboration.

But that advance alone isn’t enough to make Loo’s vision come true. He and colleagues have also been working on a design that eliminates the slow mechanical movement that other radiation systems relied on to direct the energy emitted by the linear accelerators. Rather than move a single linear accelerator in a circle, PHASER has a set of accelerators that can be quickly switched between to hit a tumor from many directions. And the controls that shape the beams of energy—previously in a mechanical fashion—have been redesigned to be fully electronic. Each piece of the puzzle shaves seconds, or minutes, off a standard radiation therapy session.

“The next major technological step is the integration of all these pieces to work together,” said Loo.

It will take about five years, he estimates, for PHASER to be ready to treat patients. But it will be worth the wait; when PHASER is deployed, it could upend radiation therapy. Not only would the fast, more targeted beams of radiation lead to fewer side effects because the radiation would have less off-target hits, but Loo’s basic research suggests that the radiation itself could be even more effective. In initial studies on mice, he and his collaborators have shown that the extremely fast form of radiation—even when it’s the same total dose—shrinks tumors with less damage to normal tissues. These experiments are possible to do in mice with existing customized accelerators, but requires PHASER technology to scale up to humans.

Because PHASER will be so fast, it also could allow hospital systems to offer treatment to many more patients in a day. In parts of the developing world, where there are limited places for patients to go for radiation therapy, this could be a huge advancement in cancer treatment.

“Once the machine is developed, the goal is to be able to have it accessible to anyone for the same cost as a standard accelerator,” said Quynh-Thu Le, MD, Professor and Chair of the Department of Radiation Oncology, and co-director of the SCI Radiation Biology Program. During each step of engineering, Le said, keeping costs low has been key.

The project, Le added, is showing where Stanford shines—cutting-edge, interdisciplinary work.

“We’ve always had this sense of innovation,” said Le. “Between the people in this department, at SLAC, and in the School of Engineering, we’re really leaders in this area.”
The Value of SCI Fellowships and Dedicated Mentors
From Mentor to Colleague

Ten years ago, Sukhmani (“Suki”) Padda, MD, was a medical student at Northeastern Ohio Medical University in Ohio interested in cancer research but not sure exactly what she wanted to pursue. In the hopes of getting exposure to clinical research experience after she graduated, she mass emailed just about the whole hematology/oncology faculty at Stanford. The first to reply: Heather Wakelee, MD, Professor in the Department of Medicine – Oncology, SCI member, specialist in thoracic oncology, and a big supporter of young researchers. Quickly, Wakelee became an invaluable mentor to Padda. “She has absolutely changed the trajectory of my career,” said Padda, now an Assistant Professor in the Department of Medicine – Oncology and SCI member. “I can say that very honestly. When you find someone who is as passionate and energetic as she is, you become attracted to the field and the work because of that person.”

A decade later, Padda and Wakelee still work together—now as colleagues in the Division of Oncology. And they both say their relationship, as mentor and mentee, has been invaluable.

“No person is going to solve cancer on their own. As an oncologist, I can only help a certain number of people in a day, a week, a lifetime,” said Wakelee, who has mentored a number of other junior clinicians and researchers. “If I can find other folks who are interested in helping and train them, we can help more people.”

After medical school, Padda worked as a research coordinator for Wakelee, helping to manage clinical trials of lung cancer drugs. The experience convinced Padda not only that she wanted to pursue a career in academic medicine, but that she wanted to focus her research on lung cancer, like Wakelee. The pair—both incredibly devoted to the work—found that they meshed well. To this day, they still joke about all the midnight emails they send back and forth.

During the ensuing years, Padda landed an internal medicine residency, and then a hematology/oncology fellowship, both at Stanford, so the duo could continue their research collaboration. “I feel very blessed to have come across Heather as my first mentor in oncology, and it’s been an amazing relationship since then,” said Padda. Wakelee talked through research ideas with Padda and encouraged her to set her sights high, submitting research to conferences and journals and introducing her to leaders in the field of thoracic oncology.

Together, Padda and Wakelee have studied the gene mutations that cause lung cancers to grow, as well as how drugs can target those mutations to stop tumor growth. Their work is helping to inform clinicians how to best personalize treatments for lung cancers.

After her oncology fellowship, Padda found herself needing more time to finish research projects, so she applied for—and won—an SCI fellowship that supported her continued collaboration with Wakelee.

Padda’s continued research time thanks to the SCI fellowship has obviously paid off as she now works alongside her long-time mentor. “Over the years, I’ve gotten to see Suki evolve into a really independent and wonderful physician,” said Wakelee.
Drug Discovery
First FDA-Approved Treatment for Chronic Graft Versus Host Disease

The work of Stanford researchers has led to the first-ever approval from the Food and Drug Administration (FDA) for a drug to treat graft versus host disease (GVHD)—a potentially serious complication of hematopoietic cell transplants that utilize cells from a donor not related to the transplant recipient. Hematopoietic cell and bone marrow transplants (collectively referred to as HCT transplants) are used to treat some blood and bone marrow and other select cancers. Until now, doctors relied on corticosteroids to treat GVHD, but the long-term use of steroids causes many side effects, and GVHD frequently re-emerges when steroids are stopped.

“We’ve been looking for a long time for targeted effective therapies to get patients with chronic GVHD off steroids,” said David Miklos, MD, PhD, Associate Professor in the Department of Medicine-Blood & Marrow Transplantation (BMT), and an SCI member. “But other drugs, even those that showed early promise, have all ended up failing to show benefit in randomized clinical trials.”

GVHD is caused when immune cells from an unrelated donor start attacking the normal tissues of an HCT recipient. This can lead to painful, debilitating problems in organs from the skin and mouth to the liver and lungs, including itchy rashes, nausea and vomiting, muscle weakness, and breathing difficulty.

Miklos discovered that B lymphocytes—one type of immune cell—are critical to the development of chronic GVHD. Blocking B cell activity, he hypothesized, could prevent or treat the disease. Ibrutinib—a drug first developed to treat B cell cancers and already approved for multiple cancer types—was able to potently deplete B cells from an HCT donor. Miklos approached Pharmacyclics, the Sunnyvale-based company that makes ibrutinib, about launching a clinical trial of the drug for GVHD; the company agreed.

Last year, Miklos and his colleagues presented the results of that trial at the annual meeting of the American Society of Hematology. Sixty-seven percent of patients had improvements in their GVHD after taking ibrutinib; in 48 percent of patients, improvements lasted at least five months. The research was published in the September 2017 issue of the journal, Blood.

On the heels of the findings, the FDA granted a breakthrough designation to the drug, meaning it could move quickly through the approval process. In August, the FDA approved ibrutinib for the treatment of patients with chronic GVHD that has failed at least one systemic treatment.

Now, Miklos and his colleagues are working on a trial to see if ibrutinib is effective in patients with earlier stages of GVHD.

30 Years of BMT
The Stanford Blood and Marrow Transplant (BMT) Program celebrates 30 years of treating patients this fall. The program—the largest in Northern California—has been the designated provider for Kaiser Permanente in Northern California for over 20 years. It is also one of 20 programs nationwide to be named a Core Clinical Center for the NCI’s Blood and Marrow Transplant Clinical Trials Network.

Since Karl Blume, MD, founded the program in 1987, the team has developed the program into a national leader in offering patients the most efficacious treatment while managing and minimizing potentially life-threatening side effects. It is also a recognized leader in advancing science in the BMT field.

“On November 2, 1987, the first adult patient received a bone marrow transplant at Stanford,” noted Robert Negrin, MD, Professor and Chief of the Department of Medicine-BMT, and co-leader of the SCI’s Immunology and Immunotherapy Research Program. “We joined our former patient in celebrating the 30th anniversary of that important day. Since then, over 7,000 other patients have received life-saving transplants by our outstanding team, who provide the most scientifically rigorous and compassionate care possible. Our team is very proud of what we have accomplished. We are also humbled by the many patients and their families who entrust their care to us at a most critical time in their lives.”
Clinical Trial Advances Treatment Of Neuroendocrine Tumors
SCI Researchers Help Show Efficacy of New Cancer Drug

Patients with advanced neuroendocrine tumors (NETs) may soon have a new treatment option, thanks to research conducted with support from the SCI. The phase 3 Neuroendocrine Tumors Therapy (NETTER-1) trial, which involved SCI researchers, concluded that the drug $^{177}$Lu-DOTATATE lengthened survival of patients with small intestine NETs by nearly three years. The results were published in the January 2017 issue of the *New England Journal of Medicine*.

“This is an especially exciting result,” said Pamela Kunz, MD, an Assistant Professor of Medicine – Oncology, SCI member, and author of the paper. “This has never been seen with other therapies for this disease; most other approved treatments have an absolute improvement of six to eight months.”

NETs are rare cancers that arise from cells of the endocrine or nervous system, which are found throughout the body. The most common locations for NETs are the lungs and gastrointestinal system. While most NETs are slow-growing, they can often go undetected for years, until they have already started to spread.

Octreotide, a drug commonly used to treat NETs, works by binding to the somatostatin receptor that’s found on the surface of most NETs. “It fits like a lock and key and slows down the cancer,” explained Kunz.

$^{177}$Lu-DOTATATE is based on a similar molecule to octreotide, except it also packs a powerful punch of radiation. In addition to fitting into the somatostatin receptor, the drug delivers radiation to the tumor. “This drug delivers radiation in a very targeted way to NETs; this is really the quintessential definition of a targeted radioisotope therapy,” Kunz said.

In the NETTER-1 trial, 229 patients with neuroendocrine tumors at 41 hospitals around the world were assigned to receive either high-dose octreotide alone, or a combination of standard-dose octreotide and $^{177}$Lu-DOTATATE. The study included 18 patients receiving their treatment at Stanford. After 20 months, 65 percent of those who had received $^{177}$Lu-DOTATATE were alive and their tumors had not grown, while the progression-free survival rate was less than 11 percent in the control group. After the same amount of time, 18 percent of patients receiving $^{177}$Lu-DOTATATE had their NETs shrink or disappear, while only three percent of those taking only octreotide had this response.

“This treatment is well tolerated and has the best chance of delaying progression. It is a significant advancement for patients with NETs, and for their families. This treatment is also an important contribution to the field,” said Kunz.

Similar molecules to DOTATATE, but bound to the radioactive molecule $^{68}$Ga instead of $^{177}$Lu, can be used for imaging studies to show exactly where NETs are located in the body, and combining these scans with targeted drugs like $^{177}$Lu-DOTATATE enables physicians to pinpoint who will benefit most from the treatment.

“This therapy is a great example of the emerging field of theranostics, in which we can both image and treat patients based on the same molecular target,” said Erik Mittra, MD, a Clinical Associate Professor in the Department of Radiology and SCI member who also worked on the NETTER-1 trial. “That, in turn, is exactly in line with the concept of precision medicine.”

Further work will aim to determine whether the drug works well in other types of NETs, demonstrate how it influences patients’ quality of life or overall survival, study side effects in more detail, and pinpoint how $^{177}$Lu-DOTATATE should be used in conjunction with other treatments.

“It has been a long road getting this compound to market, and the excellent results of the NETTER-1 trial are a great outcome of all the work that many people around the world have put in for many decades,” said Mittra.
How Social Media is Being Leveraged to Prevent Cancer
Tweeting to Help Smokers Quit

Craving a cigarette? Try pulling out your phone and messaging a private social network group of other people who are trying to quit smoking. That’s the idea behind Tweet2Quit, a novel intervention aimed at helping people quit their addiction to nicotine. It’s the brainchild of SCI member Judith Prochaska, MD, PhD, Associate Professor of Medicine in the Stanford Prevention Research Center, and her colleague, Connie Pechmann, MBA, PhD, a professor of marketing at UC-Irvine’s Paul Merage School of Business. Together, they were recently awarded a $2.5 million grant from the National Cancer Institute to further study their Twitter-based approach.

Despite decades of evidence that smoking cigarettes is harmful, over 35 million Americans continue to smoke, and cigarettes remain the leading cause of preventable death in the U.S. and worldwide. Tobacco accounts for nearly one in three cancer deaths. The key reason: nicotine cigarettes are highly addictive, making it difficult to quit smoking. Seven in 10 smokers report wanting to quit, yet only seven in 100 are successful in doing so in any given year.

“Most smokers have tried to quit on their own, without long-term success. They know the how-to’s for quitting smoking, but it’s challenging to stay smoke-free, and relapse is common,” said Prochaska.

In a first study of Tweet2Quit, participants were provided the nicotine patch and a link to the National Cancer Institute’s smokefree.gov online resources, and they were encouraged to set a quit date within one week of the study’s start. If they were randomized to the Tweet2Quit intervention arm, participants also were linked to a private Twitter group of 20 smokers. Within the Tweet2Quit intervention, a daily tweet provided evidence-based discussion topics on quitting smoking and individualized feedback encouraged participation. Beyond those two automated prompts, members were free to chat among themselves.

“What the group provides is both immediate support and camaraderie from a virtual network and longer-term accountability,” said Prochaska.

Early results suggest that Tweet2Quit doubles the number of smokers who are able to quit; in a randomized controlled trial of 160 smokers, only 20 percent of those in the control group were tobacco-free at 60 days, compared to 40 percent of people assigned to a Twitter group.

Now, with their new grant, Prochaska and Pechmann are engaging nearly 1,000 participants, tracking their smoking behaviors for six months, and asking questions about who Tweet2Quit serves best. They’re also testing whether women-only groups are more helpful than co-ed groups for women smokers trying to quit.

The study, Prochaska said, is yielding unique detailed information on the process of quitting smoking. The private Twitter groups provide a treasure trove of information to mine: all the conversations between the participants.

“We’re kind of like flies on the wall in these groups,” said Prochaska. “With participants’ permission, we have all the dialog viewable and available for analyses.”

Before Prochaska and Pechmann began designing Tweet2Quit, they studied existing Twitter accounts that aimed to provide information or support on quitting smoking.

“There’s lots out there that’s not evidence-based,” said Prochaska.

But Tweet2Quit provides participants in each group with the type of advice they might get from a doctor—without requiring insurance or a doctor’s visit. That means it can reach smokers who may be missed by other interventions.
SCI Mourns the Loss of John Freidenrich

We were greatly saddened by the recent death of John Freidenrich, one of the truly great friends of Stanford University and the Stanford Cancer Institute (SCI). In 2006, John attended a Stanford School of Medicine retreat and rode home with Phil Pizzo, who at that time was Dean.

Their conversation turned to the importance of translational research and the role of the newly-form Stanford Cancer Institute in promoting such research. John always said it was the most expensive ride he had ever taken! The result has been an enduring partnership among John, his wonderful wife, Jill, and the SCI that has enabled tremendous expansion of cancer research and care over the past decade.

We will always remember John's terrific sense of humor and his devotion to Stanford as we continue our quest to improve the treatment of patients dealing with cancer—with much of our work originating from the beautiful Jill and John Freidenrich Center for Translational Research.

Generous support from Jill and John Freidenrich has allowed the SCI to perform groundbreaking translational research.