Yale CANCER CENTER
A Comprehensive Cancer Center Designated by the National Cancer Institute

SMILOW CANCER HOSPITAL AT YALE-NEW HAVEN

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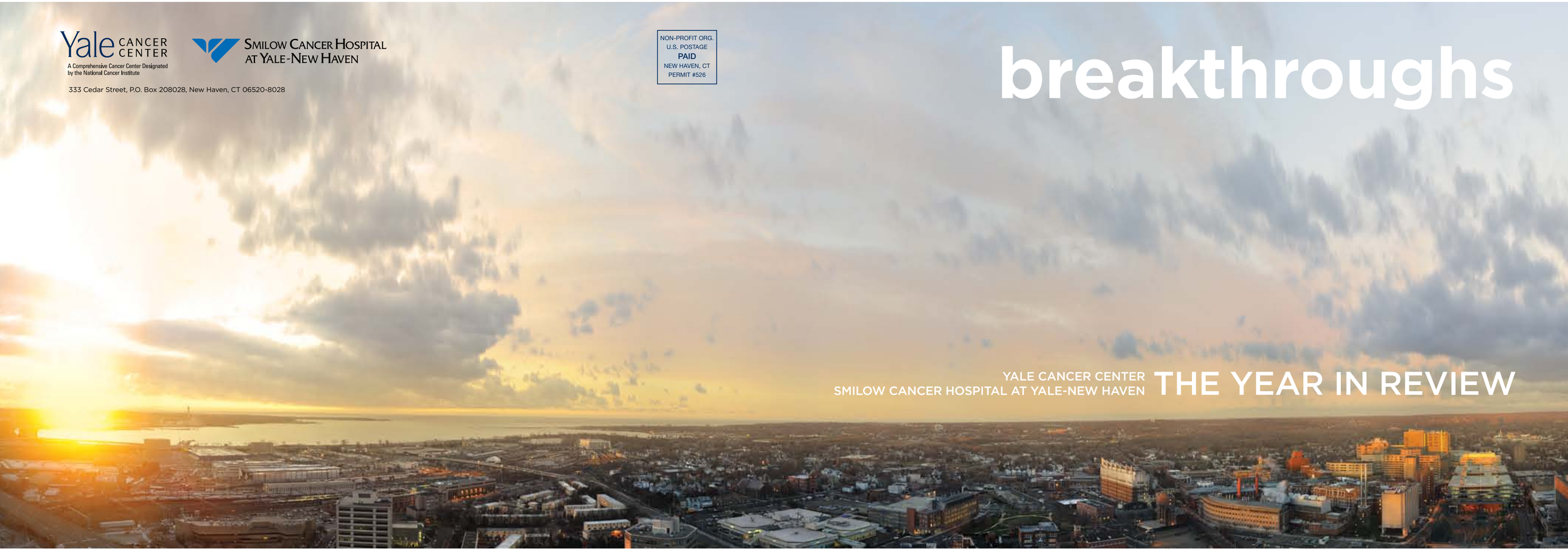

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THE YEAR IN REVIEW

yale cancer center

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The year 2012 was a breakthrough year for Yale Cancer Center and Smilow Cancer Hospital at Yale-New Haven. We saw a dramatic increase in participation in clinical trials and tremendous growth in our clinical, basic, population and translational research portfolio. We launched a new model of cancer care for the state of Connecticut with the integration of 8 Cancer Care Centers, and 23 new faculty members at these new sites. Our goal is to bring Smilow Cancer Care to within 35 miles of every resident in Connecticut so that all cancer patients have access to the most advanced treatment options, multidisciplinary cancer care, and supportive services that they need.

Research in cancer continues to excel as our access to genomic sequencing broadens. Each of Yale Cancer Center's seven research programs is seeing the positive impact of these efforts with exciting new projects that are helping to translate research from our labs to benefit patients at Smilow Cancer Hospital at Yale-New Haven. Equally important, tumor sequencing data from our patients is enriching our laboratory research and allowing our research teams new access to information on tumor types, and response to treatment.

Combined efforts from our Cancer Immunology Research Program and Developmental Therapeutics Research Program led to a landmark publication in the *New England Journal of Medicine* in June on the clinical effectiveness of the antibody therapy, anti PD1. Initial research conducted by Lieping Chen, MD, PhD led to the discovery of the immune molecules, and clinical research led by Scott Gettinger, MD and Mario Sznol, MD brought us promising results in patients with advanced lung cancer, renal cell cancer, and melanoma. The clinical trial results illustrate the significant impact that anti PD1 therapy is making in the lives of our patients with advanced cancers.

Yale Cancer Center and Smilow Cancer Hospital continue to focus on recruiting the very best clinicians and scientists to our team. In 2012, we welcomed Peter Schulam, MD, PhD, Chief of Urology and Director of the Prostate and Urologic Cancers Program from UCLA Medical Center and Wendell Yarbrough, MD, Chief of Otolaryngology and Director of the Head and Neck Cancers Program from Vanderbilt University.

Also joining our senior faculty were Lajos Pusztai, MD, from MD Anderson Cancer Center to lead our Breast Cancer Medical Oncology Program; Daniel Petrylak, MD, from NewYork–Presbyterian Hospital to lead our Prostate Cancer Medical Oncology Program; Joseph Paul Eder, MD, from AstraZeneca to lead our Early Drug Development Program; John Roberts, MD from Virginia Commonwealth University to lead our Sickle Cell Program; and Ted Tsangaris, MD from the Sidney Kimmel Comprehensive Cancer Center at the Johns Hopkins University Hospital as the Medical Director for Breast Services for Smilow Cancer Hospital Network.

> "As we move into the New Year, we will continue to expand our presence in Connecticut through our Care Centers and offer more innovative clinical trial opportunities to our patients."

As we move into the New Year, we will continue to expand our presence in Connecticut through our Care Centers and offer more innovative clinical trial opportunities to our patients. I look forward to sharing new research advances and outcomes from our laboratories and clinics with you in 2013.

Sincerely,

Tom Lynch

Thomas J. Lynch, Jr., MD
Director, Yale Cancer Center
Physician-in-Chief, Smilow Cancer Hospital
Jonathan and Richard Sackler Professor of Medicine

Expanding to Create a New Hybrid Model *for cancer care*

In 2012, Smilow Cancer Hospital at Yale-New Haven dramatically extended its ability to serve cancer patients throughout Connecticut by launching a network of Smilow Cancer Care Centers. The new network added 23 physicians, over 150 staff members, and seven pharmacists in eight community cancer care centers (Derby, Guilford, Hamden, New Haven, Orange, Sharon, Torrington, and Waterbury). Merging the state's largest private cancer practice, Medical Oncology & Hematology, P.C., and a Litchfield County practice, Connecticut Oncology Hematology, into Smilow Cancer Hospital created the largest cancer care delivery system in Connecticut.

Yale-New Haven Hospital's acquisition of the Hospital of Saint Raphael in September also created opportunities

for expansion of patient cancer care from Smilow. The acquisition created a single, 1,519-bed hospital for Yale-New Haven, with two main campuses, and added 400 medical staff members and 3,400 employees to Yale-New Haven. A Smilow Cancer Care Center continues to be located on the Saint Raphael Campus, and the busy radiation oncology practice at the campus was fully integrated into Smilow, adding three medical oncologists to the Yale Cancer Center faculty.

While the additional inpatient growth was not a direct need for cancer care at Smilow, its implications will continue to strengthen our inpatient cancer services available.

"With the Cancer Care Centers, we're bringing together Yale's academic cancer care model and the community care model throughout New Haven and to the entire state," said Arthur Lemay, the network's Executive Director. Combining the models, he added, strengthens both, and creates a new paradigm for cancer care in Connecticut. Patients at the Cancer Care Centers benefit from the comforts and convenience of seeing their doctor in a location close to home and avoid the hassles of travel.

"Yet they can also take advantage of all the things Smilow Cancer Hospital has to offer," said Anne Chiang, MD, PhD, Chief Medical Officer for the network and Assistant Professor of Medicine (Medical Oncology). "Patients have access to clinical trials and cutting edge therapies that aren't always available in community cancer centers. Their doctors will be able to freely consult experts with subspecialty expertise."

The Cancer Care Centers are also able to import specialty services from Smilow that enhance the practices: for instance, social workers, clinical dieticians, and genetic counselors.

"Unlike the usual affiliation relationship," said Dr. Chiang, "this is a true partnership. The physicians who practice in the community are Yale faculty, not affiliated faculty, and the employees in the Cancer Care Centers are also Smilow Cancer Hospital at Yale-New Haven employees."

Kert D. Sabbath, MD, a medical oncologist at the Smilow Cancer Care Center in Waterbury within the Harold Leever Regional Cancer Center, agreed. "I feel like an equal colleague with world class people, not an appendage at all." The integration with Smilow, he added, is "a win all around. It brings the resources of Smilow to my patients, and it gives me easy access to tremendous resources in terms of research, clinical trials, and thought leaders. It lets me practice at the level of a first-class university – and that benefits my patients."

The benefits of the Cancer Care Centers also flow toward Smilow. The Cancer Care Centers significantly increase the number of Smilow's patients. The average number of daily visits to medical oncologists in Smilow in one month was 148, compared to 226 in the Cancer Care Centers.

"We now have access to a broader pool of patients for clinical trials," said Dr. Chiang. The Cancer Care Centers also will help keep patients in-state who might otherwise be sent to New York or Boston for tertiary treatment. All of this, added Mr. Lemay, will make Yale more attractive to partnering with therapeutic drug development companies. The expansion will also help Yale maintain its National Cancer Institute designation as one of the country's 41 "comprehensive cancer centers."

> "This is a hybrid of community care and academic medicine that really hasn't been done on this scale before. It's an exciting time for all of us."

"This is a hybrid of community care and academic medicine that really hasn't been done on this scale before," said Johanna LaSala, MD, a clinician at the Smilow Cancer Care Center in Orange. "We're taking the best practices from two somewhat different cultures and melding them into something with a synergy for cancer care that gives patients a tremendous advantage. It's an exciting time for all of us."

The goal as the leadership of Smilow Cancer Hospital enters 2013: to make Smilow-quality cancer care available within 35 minutes of every cancer patient and their family in Connecticut. ●

Ashley, Justin, and Luke McDermott

ATTACKING CANCER, saving vision

When 14-month-old Luke McDermott was diagnosed with retinoblastoma, his doctor told Luke's parents that he would try to save the baby's life, eye and vision. "That's the order," he said. "If we have to, we will remove his eye to save his life."

A Smilow Cancer Hospital team was able to save all three, using an innovative treatment that delivers cancer-fighting drugs directly behind the eye where the tumor was located. Supraselective intra-arterial chemotherapy (SIAC) requires doctors to navigate arteries about the diameter of a strand of hair. Smilow is one of only a handful of hospitals offering this modality of delivering chemotherapy for retinoblastoma in the U.S..

The painstaking procedure can offer tremendous benefits, explained Miguel Materin, MD, Director of Ophthalmic Oncology at Smilow Cancer Hospital. There are not

many ophthalmologists who specialize in ocular cancer treatment, like Dr. Materin. He estimates there are about 300 such physicians in the world.

Though survival rates for retinoblastoma in the developed world are above 90 percent, traditional treatments could involve removal of the eye, systemic chemotherapy, radiation, and others. SIAC can successfully treat a retinoblastoma so that the eye can be saved. It also can render radiation unnecessary, sparing children the long term consequences of radiation treatment. Retinoblastoma typically affects children under the age of two, for whom radiation holds dangerous long-term consequences. Side effects for systemic chemotherapy – which circulates throughout the body as opposed to SIAC, which is delivered directly to the eye – can be severe in the short-term and include possible long-term risks.

Retinoblastoma is usually diagnosed after a parent notices leukocoria, a reflection from the retina that makes the pupil appear white, or when a child becomes cross-eyed. In Luke's case, his mother noticed one of Luke's eyes crossing at times. "It's probably just a lazy eye," Ashley McDermott thought. But when she called her pediatrician, he told her to take the baby to a pediatric ophthalmologist. The ophthalmologist saw a mass in Luke's eye and referred him to Dr. Materin.

Once a child is referred to the Ophthalmic Oncology Program at Smilow, things move quickly. We try to start the treatment within a week," said Dr. Materin. "It's a serious condition because it's a cancer and it can cause blindness too." The speedy response is also designed to make a difficult period of waiting as short as possible. "The anxiety of the family is very, very high," he said.

About 40% of retinoblastoma cases are hereditary, so genetic counseling is arranged for the patient's family. "We feel very confident that Luke doesn't have the germline mutation (the hereditary form of retinoblastoma)," Dr. Marterin said, based on Luke's age and other features of his tumor. Nevertheless, Luke's parents, brother Jack, 5, sister Cynthia, 3, and eventually the baby Ashley is carrying will all be tested for the mutation associated with retinoblastoma.

Within 48 hours of a referral, Dr. Materin will examine a child under anesthesia and have a brain MRI done. Following diagnosis, he'll meet with a family and go through the treatment options with them. The goal, of course, is to avoid radiation and eye removal if possible. There are several different chemotherapy delivery options. Some centers have strict preferences for a particular method.

"Here at Yale, we talk to the family. We spend a lot of time explaining the pros and cons of treatments. We give them our opinion," Dr. Materin said. "We decide based on each patient."

Though speed is critical, Dr. Materin is conscious that parents are bombarded with information and faced with hard decisions at an already stressful time. "It's terrible," he said. One way he offers support is by connecting parents with families who have already been through the experience.

Justin McDermott, Luke's father, recalled his shock on learning that his happy, active baby had cancer. "We really didn't believe it at first," he said. A high school teacher, Justin had to call his principal to say that he wouldn't be able to make a scheduled parent-teacher conference. "I was crying," he said. "That's when it really hit me."

"I really thought it helped a lot for us to be able to talk with another family," Justin said. Dr. Materin said that families always agree when he asks them to reach out to parents just beginning the process. They're eager to help each other. In fact, one family even started a foundation, Specs for Little Heroes, that helps when parents cannot afford the protective eyewear children may need after treatment.

Families are supported not only by each other but by a large medical team. When SIAC is delivered, up to 10 clinicians can be in the operating room, a state-of-the-art operating suite with biplane angiography, microsurgery, and MRI capabilities. This can all be done in one room without ever having to move the patient.

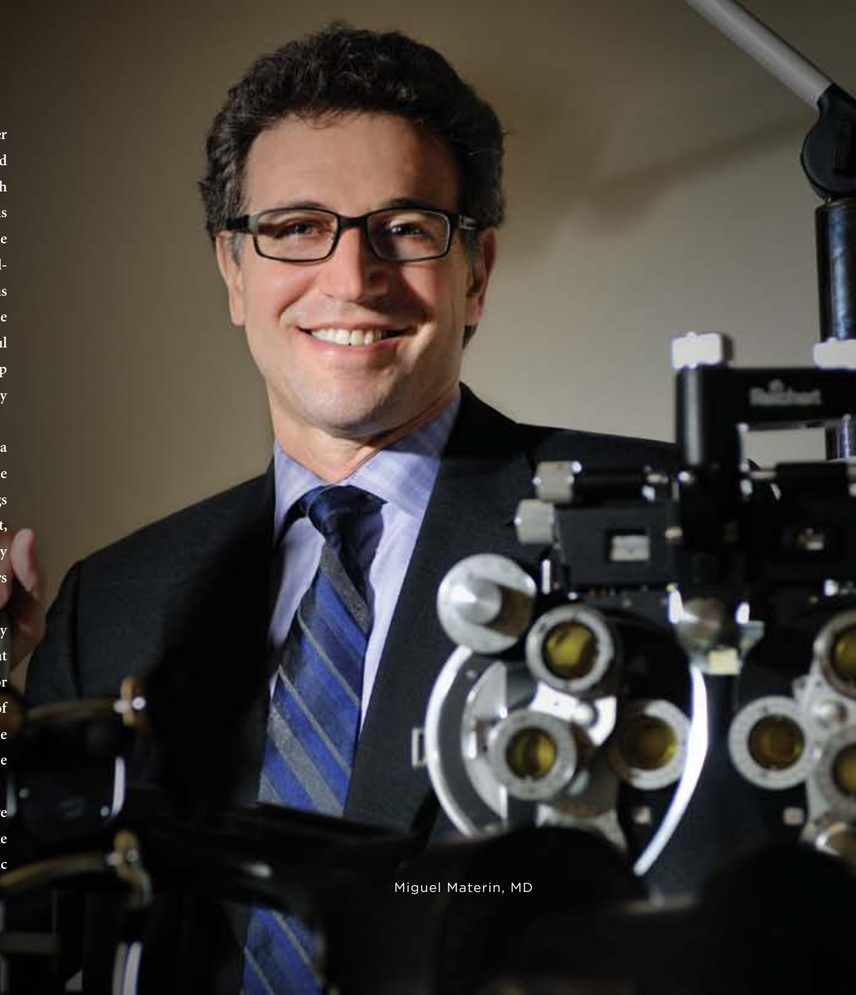
A pediatric anesthesia team will administer anesthesia. Jeremy Asnes, MD, a pediatric cardiologist, does the precise work of accessing the child's delicate femoral artery, which is at the groin. Then neurosurgeon Ketan R. Bulsara, MD, is tasked with threading the catheter up to the ophthalmic artery.

As Dr. Bulsara calls up images of Luke's procedure, the extremely delicate nature of this work is clear. A scan of Luke's skull shows that this is clearly a baby. "The smaller the vessel, the higher the risk of injury of the vessel," said Dr. Bulsara. He has three key assets to help him through the precise work: his equipment, his team, and his training. The imaging technology available in the unique operating suite at Smilow Cancer Hospital gives him real-time guidance. A team of doctors, nurses and technicians monitors the procedure and can warn him if anyone spots a danger. Finally, Dr. Bulsara is among a handful of neurosurgeons in the world who is dual fellowship trained in both skull base/cerebrovascular microsurgery and endovascular neurosurgery.

Once Dr. Bulsara reaches the ophthalmic artery, a dye is injected to make sure there is no spillage into the vessels supplying the brain. Then chemotherapy drugs are delivered for about half an hour. After one treatment, Luke's tumor shrank significantly. He needed only one additional treatment. Patients with larger tumors typically require more sessions.

The team recently published an article where they established for the first time through MRI imaging that drugs used in SIAC are delivered directly to the tumor via the ophthalmic artery. This was always the goal of the treatment, but the Yale team offered the first tangible proof using the unprecedented capabilities of the operating suite in Smilow Cancer Hospital.

Delivering chemotherapy drugs only where they are needed means that children are largely spared from side effects, said Farzana Pashankar, MD, the team's pediatric



Miguel Materin, MD

oncologist. She sees a potential to expand the program to serve more children. Currently SIAC is most often used to treat children with a tumor in only one eye. Dr. Pashankar believes the team may eventually develop the treatment to become a more viable option in children who have tumors in both eyes.

Follow-up is intensive for retinoblastoma. Children are examined monthly under anesthesia for two years following treatment. This creates a strong bond between families and the medical team. "The youngest child I've seen at Yale, she was five weeks at the time of the diagnosis with bilateral disease," Dr. Materin said. "I see the changes month after month, like when the child has a new tooth or when he or she is walking."

When Luke first saw Dr. Bulsara there was an instant bond. The boy "just lit up and was laughing and giggling," Justin said. It's as if Luke knew the surgeon was going to help him, he added.

Two months after his diagnosis, Luke is a happy, energetic toddler who likes to draw and roughhouse with his big brother and sister. As Luke and Jack sit rubbing noses and giggling, Ashley says she's glad that Luke will not remember his ordeal because it happened when he was so young. His parents have saved piles of notes and cards, however, particularly from Justin's students. They plan to make a scrapbook for Luke so that he can remember not how ill he was, but how many people were pulling for him to get well.

A SCIENTIFIC DETECTIVE STORY

"I call it a detective story," Peter M. Glazer, MD, PhD, Robert E. Hunter Professor and Chairman of Therapeutic Radiology and Professor of Genetics said. "It's been a roller coaster," James E. Hansen, MD, Assistant Professor of Therapeutic Radiology, and Dr. Glazer's main collaborator explained. Like many detective stories, this one combines mysterious occurrences, intriguing clues, unexpected plot twists, legwork (well, lab work), serendipity, and a surprise killer.

"About 15 percent of breast cancers and about 50 percent of ovarian cancers are linked to these inherited BRCA syndromes. It's a fairly substantial number of people. This antibody could act by itself on those as a targeted therapy. It also may work on some pancreatic and prostate cancers."

The story begins in the late 1980s with Richard Weisbart, a scientist at UCLA's medical school. While working on lupus, a terrible autoimmune disease, he identified a group of lupus anti-DNA antibodies. He wondered if he could use them to create a vaccine that would trick the lupus immune system into eliminating pathologic lupus antibodies. The best candidate for a potential vaccine was an antibody named 3E10, because it was nontoxic to normal cells and tissues.

Then 3E10 surprised him: he realized that it could penetrate cells and enter nuclei, with no toxic effects, a very rare ability among antibodies. Dr. Weisbart began to explore the possibility of using 3E10 as a molecular delivery vehicle.

"That's where I came into the scene," Dr. Hansen said, who began working with Dr. Weisbart as a post-doc after medical school at UCLA. "We were trying to use the antibody to carry therapeutic cargo proteins into cells. It worked well, but we didn't know how the antibody was getting into the cells. I started throwing everything I could think of at it, trying to block its uptake. Nothing worked until we started looking at nucleoside transporters."

Then came another big surprise – 3E10 seems to be following nucleosides into the nucleus, behavior by an antibody that had never before been seen or described.

At that point the scene shifted to Yale, because Dr. Glazer recruited Dr. Hansen to do his residency here and gave him lab space to continue probing the mysteries and possibilities of 3E10. Dr. Hansen decided to see if he could moderate the cell damage caused by radiation by loading 3E10 with molecules of Hsp70, a protein that helps cells cope with stress. He treated one lab dish of cancer cells with 3E10 fused to Hsp70. As a control, he treated another dish of cancer cells with 3E10 alone. He radiated both to see what would happen.

"Then came the next bit of serendipity," Dr. Glazer described, though that's not what it felt like at first. "My first reaction," Dr. Hansen said, "was, 'Well, there goes my idea.'" The fused 3E10 and Hsp70 did cushion radiation damage to cells, but only slightly. The big surprise was the control dish – most of the cancer cells in it were dead. Acting by itself, 3E10 evidently had sensitized the cells to radiation. "The antibody hadn't previously been shown to be toxic to cells in any way," Dr. Glazer explained. "In fact it had been approved for a Phase I trial as a sort of vaccine for lupus, and people given that vaccine had no bad effects at all."

Mild-mannered 3E10, when teamed with radiation, turned into a killer of cancer. Drs. Glazer and Hansen began exploring the ramifications by running experiments in collaboration with Dr. Weisbart and with colleagues at Yale Cancer Center. They tested the antibody with chemotherapies and found that combining it with taxol had no effect on cancer cells, but combining it with doxorubicin amplified the chemical's killing force. Doxorubicin – like radiation but unlike taxol – targets DNA. "That told us that this antibody is probably interfering with DNA repair," Dr. Hansen said, "and follow-up experiments confirmed that."

3E10 wasn't finished springing surprises. Certain types of cancer, including breast and ovarian cancer, occur when DNA repair goes awry because of inherited BRCA-gene mutations. When the researchers tested the effects of 3E10 on cancer cells with those mutations, the antibody killed them outright. Dr. Glazer explained, "When cells lose the ability to repair DNA because of BRCA mutations, they become genetically unstable, causing a cascade of mutations that lead to cancer." Exposure to 3E10, an anti-DNA antibody, seems to further reduce the cells' ability to repair DNA. Since DNA repair is necessary to complete replication of cells – including cancer cells – 3E10 apparently kills cancer by choking off its ability to grow.

"About 15 percent of breast cancers and about 50 percent of ovarian cancers are linked to these inherited BRCA syndromes," Dr. Glazer said. "It's a fairly substantial number of people. This antibody could act by itself on those as a targeted therapy. It also may work on some pancreatic and prostate cancers."

Dr. Hansen suspects that 3E10 might also be providing clues to help solve the mystery of why patients with lupus tend to have lower rates of breast, ovarian, and prostate cancer. "A subset of breast, ovarian, and prostate cancers are associated with defects in DNA repair," Dr. Hansen said, "and it is tempting to speculate that lupus antibodies similar to 3E10 are protecting lupus patients against the development of such tumors."

The researchers' goal is to develop 3E10 into a cancer therapy, both on its own and in combination with radiation and chemotherapy. A lot of science and research remains to be done, but they think a clinical study is possible by 2015.

"It's too early to tell," Dr. Hansen said, "but I'm very excited about the possibility that 3E10 is just one of many cell-penetrating lupus antibodies with potential applications in cancer therapy." Dr. Glazer also expects more surprises. "One thing I've learned over the past 25 years is always to expect the unexpected," he said. "Let the data talk to you. If you're only looking for the predictable result, you'll often miss important things." ●

James E. Hansen, MD

Giving Caregivers an Opportunity to Reflect

The weekly schedule in hospitals includes many types of Rounds – grand rounds, patient rounds, teaching rounds – but when Schwartz Center Rounds were implemented at Smilow Cancer Hospital at Yale-New Haven in 2008, a completely new type of discussion began each month. Schwartz Center Rounds offer physicians, nurses, social workers, clergy, and other healthcare providers at the Hospital the opportunity to meet to openly and honestly discuss social and emotional issues that arise in caring for patients.

Hosted and moderated by Thomas Lynch, Jr., MD, Physician-in-Chief of Smilow Cancer Hospital, Schwartz Rounds gives caregivers an opportunity to share their experiences, thoughts and feelings on thought-provoking topics drawn from actual patient cases. Recent topics included: patient decision-making; fear of litigation; parenting at a challenging time; when a physician is the patient; difficult family situations; and patient suffering.

"Schwartz Rounds creates a crucial sense of community within our Hospital and reminds caregivers that they are not alone in their struggles with different patient situations. Ultimately, our discussions in Rounds help to strengthen the relationship between caregivers and patients," Lynch said.

During Rounds a panel of providers presents a case, and the challenges that developed during the patient's care. The patient is not identified and all personal information is kept confidential. Once the case has been presented, discussion develops and often points are discussed to help with the care of future patients, or to help the healthcare providers involved better cope with similar situations that may arise.

> "Discussing the human aspect of healthcare reminds us about the critical impact of illness."

"Discussing the human aspect of healthcare reminds us about the critical impact of illness and treatment on the patient and the family, as well as how these situations affect staff," Bonnie Indeck, LCSW, Manager of Oncology Social Work at Smilow Cancer Hospital, explained. "Schwartz Rounds gives our staff the ability to express their feelings and experiences and allows them to gain greater insight into their own responses and subsequently provide better connections with patients."

The Schwartz Center is a national organization founded by Ken Schwartz, a Boston healthcare attorney who died of lung cancer and found that what mattered to him most as a patient were the simple acts of kindness from his caregivers, which he said made "the unbearable bearable." He created the Schwartz Center in 1995 to ensure that all patients are treated with compassion. The Schwartz Center Rounds are a principal outcome of his vision, and are now in over 300 hospitals throughout the country.

(l to r) Karen S. Anderson, PhD; Scott J. Miller, PhD; Julie L. Boyer, PhD; Roy S. Herbst, MD, PhD

Brainstorming Ways to Bridge the Clinic and the Lab

The idea behind the Yale Cancer Center's Cancer Chemistry Colloquium is to bring together cancer biologists, chemists, clinicians, and other scientists from throughout Yale University to hear brief talks and brainstorm about how their research can be useful to each other and, eventually, to cancer patients. "We hope to encourage collaborations that develop new cancer drugs based on science being done in Yale labs," Julie L. Boyer, PhD, Associate Director for Translational Research Administration said. "This is at the heart of the translational research program at Yale Cancer Center – clinical evaluation of drugs based on Yale science for the benefit of cancer patients," said Roy S. Herbst, MD, PhD, Professor of Medicine and Pharmacology, Chief of Medical Oncology, and Associate Director for Translational Research.

The invitation-only group was organized by Boyer; Herbst; Karen S. Anderson, PhD, Professor of Pharmacology, Molecular Biophysics and Biochemistry; and Scott J. Miller, PhD, Irénée du Pont Professor and Chair of Chemistry.

Since June about two dozen researchers and clinicians have met each month in the living room of Provost Peter Salovey's house. The casual setting is intentional – the gatherings are meant to be relaxed and informal, to encourage participation and the free flow of ideas. Two presenters, usually a cancer biologist or clinician and a chemist, give short talks of no more than 15 or 20 minutes, leaving an hour for discussion, questions, and suggestions about how to work together. PowerPoint is banned.

"It's not a pitch or a shock-and-awe presentation," Dr. Miller said. "These are real conversations. It's people in a small room who can look at you and say, 'Wait a minute, I didn't know about that, back up.'"

The Colloquium's main purpose is to bridge the gap between lab chemistry and clinical cancer science. Each side is learning from the other. "Cross-disciplinary conversations can turn on a light bulb for both sides," Dr. Anderson said. "Some collaborations have already come from it." For instance, Jaseok Peter Koo, PhD, Associate Professor of Medicine (Medical Oncology), and Scott Strobel, PhD, Professor of Molecular Biophysics and Biochemistry, are working together to screen compounds from Dr. Strobel's large collection of South American endophytes, to see if any hold promise as cancer drugs.

The meetings provide a communications shortcut. "We're neighbors," Dr. Miller said. "These conversations help us learn what's new as it happens rather than waiting six months to read it in the journals as if we're on opposite sides of the country."

The meetings can help focus or even redirect research. Dr. Miller mentions a talk given by Joseph "Yossi" Schlessinger, PhD, MSc, William H. Prusoff Professor of Pharmacology, Chair of Pharmacology, and Director of the Cancer Biology Institute, about ways to target the RAS mutations that make lung and pancreatic cancers resistant to chemotherapy.

> "Cross-disciplinary conversations can turn on a light bulb for both sides."

"It's not that the chemists were learning about it for the first time," Dr. Miller said, "but Yossi provided us with a sense of urgency, which can be helpful, because one of the toughest jobs is to decide what's most important. Given a choice between two equally interesting things chemically, if one of them has a chance to impact interdisciplinary science and one doesn't, that makes the choice easier."

"Many chemists want to work in clinically relevant areas and make an impact on human disease," Dr. Herbst explained. "I think these meetings get them more focused on that, and that's refreshing for them."

Everyone agrees that the meetings have been freewheeling and tremendously stimulating. In a way, the gatherings return these high-powered specialists to their undergraduate days when they could get together with other passionate people and simply brainstorm about science. "That's a very good point," Dr. Miller agreed. "It's a lot of fun to participate in something like this again, because it's so interdisciplinary."

An Innovative Vaccine Summons Cells to Fight Disease


Akiko Iwasaki, PhD

The sexually transmitted infection, genital herpes (herpes simplex virus 2, or HSV-2), is a widespread scourge with no cure. Attempts to design an effective vaccine have failed. Two researchers at Yale have discovered an innovative method of vaccination against HSV-2 that could not only stymie the disease, but might also be applicable against certain cancers.

The barriers to a vaccination against genital herpes begin with the infection's primary location. Memory T cells circulate in the body to fight infections, but for unknown reasons some sites obstruct entry by T cells, or perhaps fail to send out distress signals to summon them. These sites include the brain, the respiratory tract, the intestinal tract, and the entryway for HSV-2 – the genital tract.

Several years ago Akiko Iwasaki, PhD, Professor of Immunobiology and of Molecular, Cellular, and Developmental Biology, discovered that if T cells receive the right signals from the genital tract, they will rush in. "So we identified the chemokines responsible for sending the signals," Dr. Iwasaki explained, "and then decided to see whether we could artificially recruit the memory cells into the genital tract by topically applying those chemokines."

They tested the theory on a mouse model, using a strategy that Iwasaki and her co-author Haina Shin, PhD named "prime and pull." First they injected HSV-2 into the skin (prime), then they topically applied two chemokines to attract T cells (pull).

"And remarkably," Dr. Iwasaki said, "this was enough to get the memory cells to migrate there and stay for the long term. That's the most surprising thing – somehow they are programmed to stay." The T cells lingered for up to 13 weeks, providing protection against new viral challenges.

Dr. Iwasaki was also surprised by how the T cells protected the animals. In conventional vaccines, the antibodies and T cells target the epithelial cells and stop the virus from replicating in those cells. "That's what we expected," Dr. Iwasaki said, "but instead the T cells protected the neurons." The effect was to halt the infection's spread from the vaginal mucosa into the sensory neurons. Iwasaki suspects that this decreases the likelihood of new viral flare-ups. "That means a person won't ever be infected by a latent infection. The person might suffer an acute infection after encountering the virus for the first time, but that's it – no recurrent infections." So though a prime-and-pull vaccination would not cure HSV-2, it probably would provide life-long immunity.

Next Dr. Iwasaki wants to test whether the duration of protection can be extended by a booster application of antigens and chemokines. She will continue the research necessary to develop prime-and-pull to the level of clinical trials.

"In theory," she said, "this approach can be used with any vaccine to improve efficacy against chronic infections or localized tumors." She is especially hopeful about its use against HIV. T cell vaccines have been ineffective against the disease, she suspects, for the same reasons that conventional vaccines don't work against HSV-2 – the T cells are blocked from entering the genital tract. Dr. Iwasaki thinks the prime-and-pull strategy could overcome that.

"I bet we'll be able to protect women from becoming infected," she said, "or at least reduce the initial inoculum to a very low titer." She has started testing the possibility by collaborating with researchers across the country working on a vaccine for SIV, the simian model of HIV. Because HIV is an important co-factor in many cancers, effective vaccination against HIV would indirectly prevent the development of cancer.

She also foresees prime-and-pull as a weapon against cancer. Tumors, like the genital tract, put up barriers against T cells. The same method that works against HSV-2 could work against cancer by pulling T cells directly into the mass. Dr. Iwasaki is optimistic about using prime-and-pull against cancers that begin in restricted areas such as the cervix and breast. "My hope is that we could enhance current therapeutic strategies and better protect women from these cancers."

Valentina Greco, PhD

Stem Cell Regeneration and Tumor Growth Captured Live

For the first time, researchers at Yale Cancer Center have captured dynamic images of stem cell regeneration as it is occurring in animal tissue. Valentina Greco, PhD, Assistant Professor of Genetics and of Dermatology, and her colleagues in the Greco Lab used intravital microscopy to observe cell regeneration in real time in the hair follicles of uninjured mice. Their findings appeared last July in *Nature*. This breakthrough opens new opportunities to study the signals and pathways used by stem cells to turn cell growth on and off. Dr. Greco is researching how those signals malfunction and cause cells to proliferate wildly, producing tumors. "Using live imaging," she said, "we have a unique opportunity to study signaling in real time, and at the resolution of the single cell."

The genetic and molecular mechanisms used by stem cells to regulate regeneration aren't well understood. With microscopy, Dr. Greco and her colleagues have been able to put markers into stem cells, watch those cells in action, and identify components within them that respond to different signals and play different regulatory roles.

The Greco lab has begun to address whether stem cells and their signaling regulate tumor regression. They did so by treating mice with a carcinogenic treatment (DMBA) that induces a benign epithelial tumor called keratoacanthoma, which resembles squamous cell carcinoma. They chose keratoacanthoma because it grows and regresses, similar to hair follicles (keratoacanthoma typically disappears spontaneously). The researchers wanted to know if the tumor shrank because of signals from its stem cells and, if so, what signals and pathways were involved. They were able to identify the pathways and the signals being misregulated during the tumor's growth and regression. Next Dr. Greco and her colleagues hope to use live imaging to understand the mechanism that turns those signals off and on. Most tumors grow indefinitely, Dr. Greco said, because cancer "hijacks" cellular mechanisms. "The hope," she added, "is to switch off the mechanism that the tumor uses for growth – to uncouple that signal – and cause the tumor to regress."

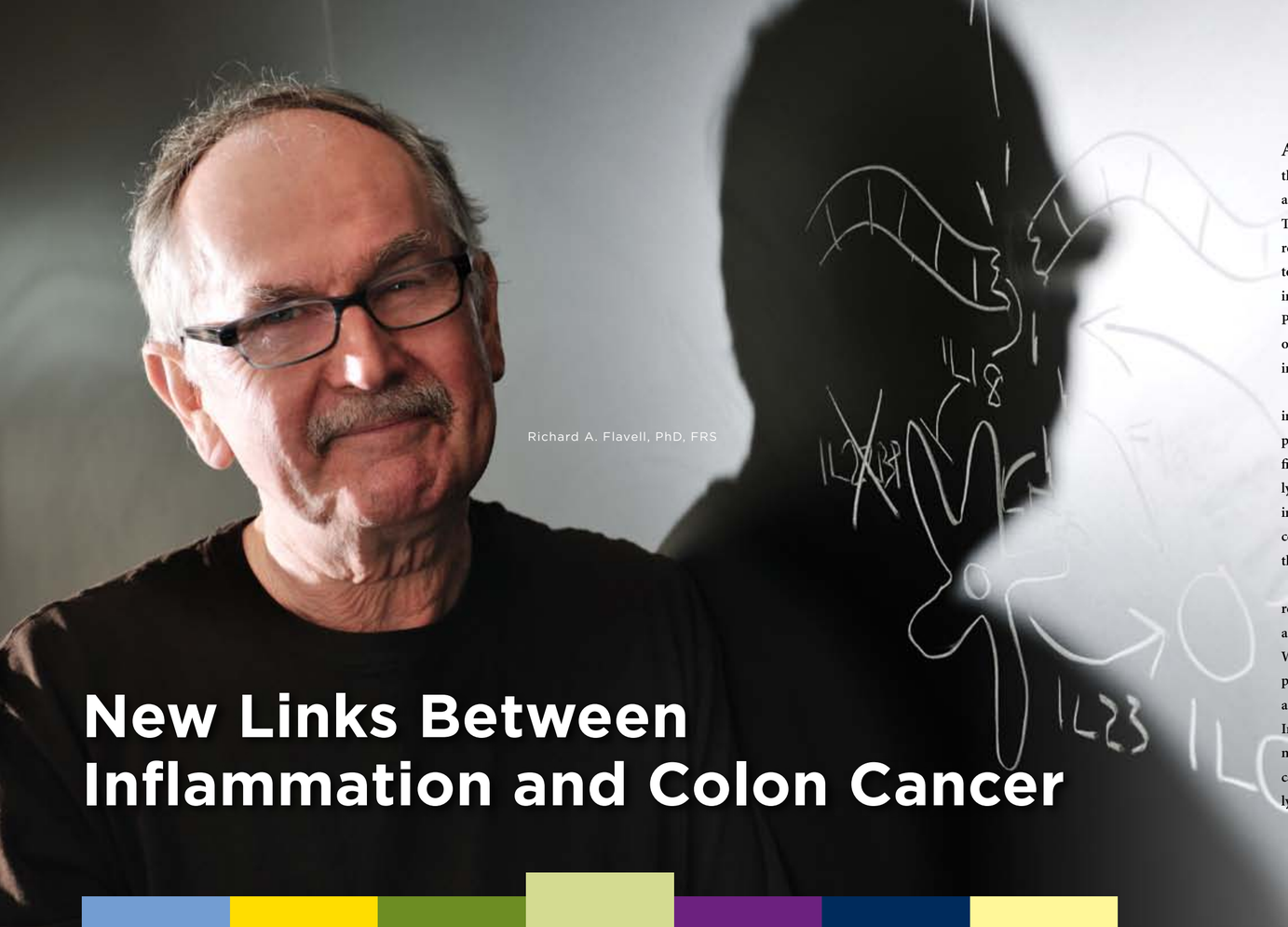
Because metastatic cancer cells behave in some ways like stem cells, researchers have long suspected a link between the two. The relatively recent discovery of cancer stem cells only partly resolves the issue, because it remains unclear whether cancer stem cells develop from normal stem cells that have gone bad, or from other mechanisms. Dr. Greco thinks the answer will differ depending on the type of tumor and its location.

"We now know that stem cells, which are apparently homogenous, contain a huge heterogeneity, with several subset populations," she said. This complexity, and the fact that stem cells live longer than other cell types, may account for the resurgence of cancer in patients who have received therapeutic treatment. A subset of stem cells that are aggressive might make the tumor grow, while another subset protects the mechanism used to fuel the tumor for the long term. If this latter subset survives therapy, those stem cells could become the engine that re-stimulates tumor growth.

> "This breakthrough opens new opportunities to study the signals and pathways used by stem cells to turn cell growth on and off."

The precise biological features of these stem cell subsets and their links to cancer must be understood before effective targeted therapies can be designed to block the ones that cause disease or its resurgence. That's why Dr. Greco is certain that basic biology remains crucial to cancer research. For her, the goal is to break the code of stem cell signaling.

"That's the way to understand dynamic behavior," she said. "My hope is to use live imaging to map the signaling pathways and to learn how they are integrated at the single cell level and how they influence behaviors in the process of tissue regeneration. You can imagine how that has a direct application in cancer, which utilizes all the major signaling pathways."



Richard A. Flavell, PhD, FRS

New Links Between Inflammation and Colon Cancer

Auto-inflammatory disorders arise when the body's innate immune system goes haywire and causes damaging inflammation of tissues. These disorders are one of the frontiers of cancer research. "Chronic tissue damage predisposes patients to the development of cancer, particularly in the intestine," said Richard A. Flavell, PhD, FRS, Sterling Professor and Chair of Immunobiology at Yale School of Medicine. Dr. Flavell is investigating how auto-inflammatory diseases are triggered.

One key seems to be a complex of proteins called the inflammasome. Dr. Flavell was lead author of a paper published in *Nature* last November that showed, for the first time, how the inflammasome and the intestine's lymphoid repair system are connected, and how irregularities within this connection cause uncontrolled cell division that promotes the growth of tumors in the colon.

In a healthy body, the inflammasome and the lymphoid repair system essentially idle in the background, an acquiescent state maintained by a regulatory mechanism. When damage occurs, the lymphoid cells produce a protein called IL-22, which fights invasive bacteria and repairs cells, but also can drive cell proliferation. In a healthy body, any excess IL-22 gets inhibited or neutralized by a binding protein from the inflammasome called IL-22BP. But when the inflammasome and the lymphoid systems detect damage to the intestine – for instance, when bacteria invades through a break in the epithelium – both move into high gear.

Dr. Flavell and his collaborators discovered that two things happen simultaneously. The inflammasome begins inhibiting production of the binding protein, IL-22BP, as the lymphoid cells begin pumping out extra IL-22 to fight the bacteria and fix the damage. So far, so good. "But the trouble with IL-22," Dr. Flavell explained, "is that after it has fixed the damage you're also risking the development of cancer, because if you have continuing division of the epithelium cells you can get mutations, and if you have mutations, you can get production of tumors. So IL-22 is a double-edged sword. It's very important for fixing damage but also hazardous because its continuing action can create tumors."

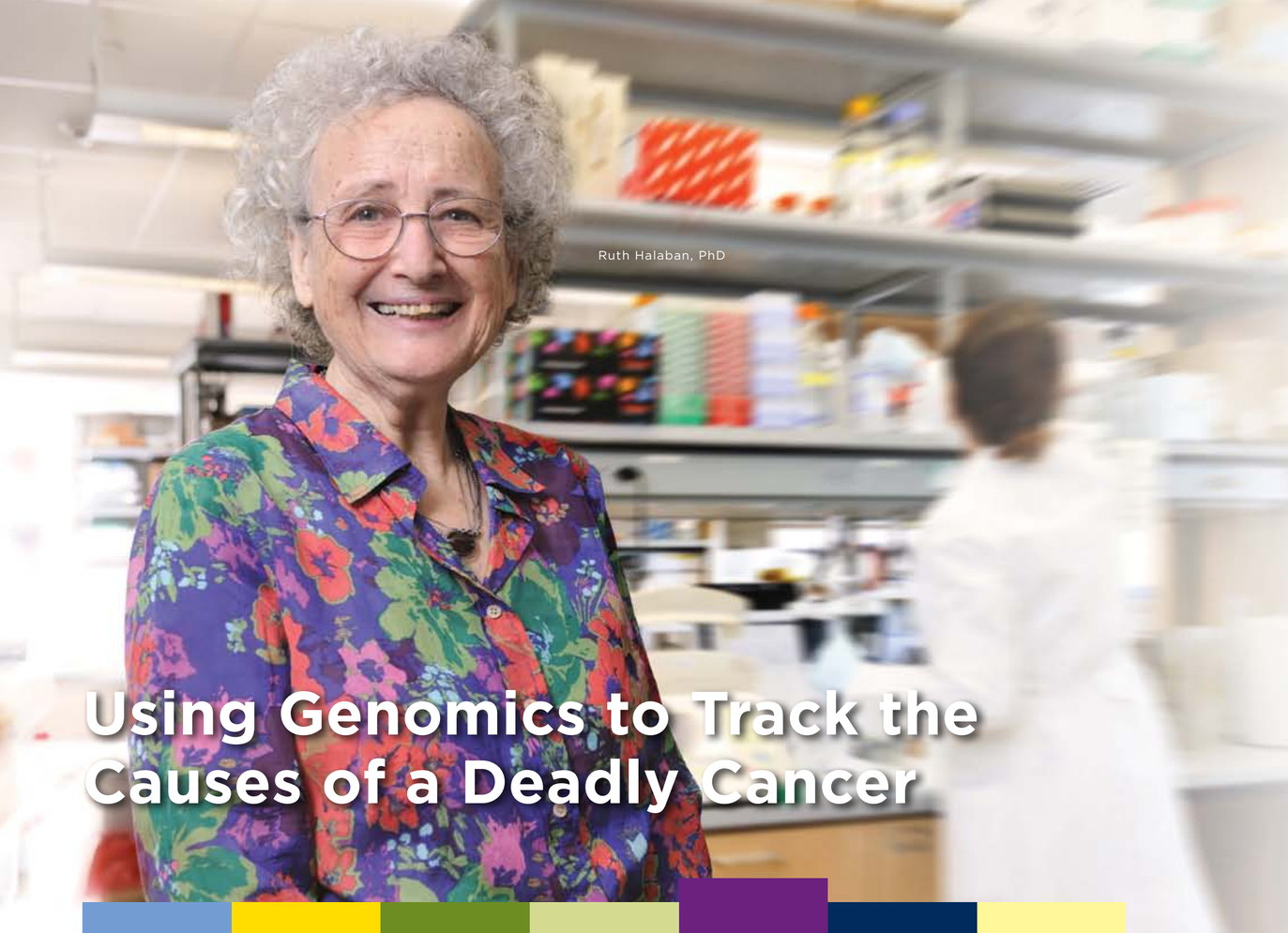
When the system works normally, the body protects itself by limiting its exposure to IL-22. To do this, the inflammasome and the lymphoid system once again work in tandem. Once the damage is fixed, the lymphoid cells slow production of IL-22 and the inflammasome stops inhibiting the binding protein, IL-22BP, which resumes its job of neutralizing IL-22. But Dr. Flavell and his collaborators discovered that if the inflammasome fails to sense that the damage has been repaired and continues to inhibit IL-22BP, then the uncontrolled IL-22 stimulates excessive cell proliferation. The consequence is tumors – more of them, and larger as well.

"In other words, IL-22 produced after the repair is fixed is severely hazardous to the intestine and is pro-carcinogenic," Dr. Flavell said. "The same pathways that are important for healing can also promote tumors." He noted that IL-22 has been considered as a potential therapeutic drug, a prospect that, in light of Flavell's findings, now looks potentially risky.

Dr. Flavell's other intriguing finding is that this system of defense and repair requires interaction and cooperation between three different cell types: the lymphoid cells, which make the IL-22; the epithelium, where the damage occurs and the inflammasome is activated; and the dendritic cells, which make IL-22BP after getting signals from the inflammasome. A drug therapy to fix a malfunction might need to target all three components. "That's the complication," Dr. Flavell said.

Dr. Flavell and his collaborators, Samuel Huber, Nicola Gagliali, and Clara Abraham, have already confirmed their basic findings on human cells. Next they intend to test their findings on clinical samples drawn from patients at Smilow Cancer Hospital, and to further their understanding of how inflammatory damage to the intestine can lead to colon cancer.

"Our findings open the door for targeted therapies, which may enable us to control wound healing and avoid cancer development or progression."



Ruth Halaban, PhD

Using Genomics to Track the Causes of a Deadly Cancer

Researchers at Yale Cancer Center are using powerful DNA sequencing machines to map genetic landscapes and locate the mutations that cause cancer. Melanoma, one of the most common and deadly cancers, is a priority.

In 2012 Ruth Halaban, PhD, Senior Research Scientist in Dermatology, and her collaborators sequenced the exomes of 147 melanomas, the largest sequencing project ever done on the disease. They were looking for recurring mutations – that is, mutations that change a protein at exactly the same place again and again.

The scientists discovered several recurrent mutations that were previously unknown. One of them was responsible for about 9 percent of sun-exposed melanomas – a mutation in a gene called RAC1. In every instance, the mutation occurred when a single amino acid was replaced by another. That was all it took to lock the gene's signal permanently on, which enhanced normal cells to multiply and disperse.

"The percentage of melanomas produced by this mutation may not look like a lot," Dr. Halaban said, "but it's the third most common mutation behind the BRAF and NRAS genes, and it hadn't been described before."

Pinpointing the gene and the mutation gives researchers a clearer target for designing a therapy specific to this cause of melanoma. Melanoma patients with a faulty BRAF gene, for instance, are now treated with vemurafenib, a new drug targeting that mutation. Dr. Halaban hopes that something similar will be developed for RAC1 as cancer treatment becomes more personalized.

Equally important, the researchers discovered that the RAC1 mutation is triggered by UV radiation, the first time a direct link has been shown between a frequently sun-damaged gene and melanoma. The BRAF and NRAS mutations, though known to be implicated in melanoma, don't show the signature of UV damage. Dr. Halaban and her colleagues, by contrast, found UV damage on the mutated RAC1 gene - clear evidence that UV radiation alters the gene, which then drives toward malignancy.

In a healthy body, the pigment cells that regulate skin pigmentation are kept relatively immobile in the skin. But when RAC1 mutates, the pigment cells not only begin to divide faster, they escape their environment and migrate out to distant sites.

"That's a bad sign," said Dr. Halaban. "The RAC1 mutation is the gas that accelerates the car, and it won't shut off, which causes cell proliferation and migration that leads to melanoma."

Dr. Halaban pointed out that none of these new findings would have been possible a decade ago, before high-speed sequencing. "You also need money to run the samples," she said, "people who know how to operate the machines, surgeons and clinicians to give you tissue

> "The SPORE created a community of investigators and clinicians that otherwise wouldn't have the opportunity or funding to relate their talents to melanoma."

specimens, experts in bioinformatics and biostatistics to analyze these millions of data points and tell you what's there, and basic scientists to interpret the results and validate the function of the mutant protein. The whole collaboration at Yale is amazing."

As another example of this advantage, she points to the Yale SPORE (Specialized Programs of Research Excellence) in Skin Cancer, a multidisciplinary research program that she directs as principal investigator. The program's funding by the National Cancer Institute was renewed in August for another five years and $11.5 million.

"The SPORE created a community of investigators and clinicians that otherwise wouldn't have the opportunity or funding to relate their talents to melanoma," Dr. Halaban explained. "Before the SPORE, two or three people here worked on melanoma. Now we have about 80 working on several major projects related to this cancer."

Cary P. Gross, MD

Using "Big Data" to Scrutinize New Cancer Therapies

Once a new drug or procedure has been clinically tested and approved by the FDA, doctors and patients often rush to use it. "But just because a treatment is new doesn't mean it's better," said Cary P. Gross, MD, Associate Professor of Medicine and Director of the COPPER (Cancer Outcomes, Public Policy and Effectiveness Research) Center at Yale Cancer Center. "Even if a treatment is effective for patients enrolled in a clinical trial, sometimes it's not better for patients outside the research setting. We often don't know the true risks of these new therapies until they are used in actual clinical practice."

COPPER's researchers apply scientific skepticism to new medical treatments and technologies being used on patients. "As the practice of medicine enters the digital age, there is increasing interest in analyzing the resulting 'Big Data' – large databases that contain important clinical information from thousands or even millions of patients, but have been stripped of patient identifying information. We analyze 'Big Data' to determine what happens to cancer patients in actual clinical practice who are receiving these new approaches," Dr. Gross said.

For example, one of the more than 30 papers published last year by COPPER researchers showed that a drug frequently given to breast cancer patients – trastuzumab – increased the risk of heart failure in older women by up to 20 percent when combined with anthracycline, a common chemotherapy. As with many new drugs, the use of trastuzumab climbed steeply, from 2.6 percent of women with breast cancer in 2000 to 22.6 percent in 2007.

So why was the drug being used among increasing numbers of older women even though the risks were unclear? There was little data available to inform decisions. Researchers typically prefer not to complicate cancer trials by including patients who have other medical conditions. Such patients are often older, with problems such as diabetes, heart disease, or kidney damage that can make them more susceptible to complications from new cancer treatments. Yet the treatments get approved on the basis of trials that exclude them. "The patients in research studies often don't reflect the patients we see in actual clinical practice," Dr. Gross explained.

Dr. Gross was the lead author of another COPPER paper published last year that looked at brachytherapy, an increasingly popular treatment for women with breast cancer. The standard therapy for women with breast cancer is surgery followed by radiation. In brachytherapy, by contrast, radiation is delivered to localized sites in high doses via a catheter. It's highly targeted, and takes less time. Consequently more and more women have been opting for it.

Dr. Gross and his colleagues looked at data on about 30,000 breast cancer patients nationwide, one year after they received radiation treatment. In some areas of the country up to 70 percent of women got brachytherapy

"But just because a treatment is new doesn't mean it's better."

(the national average was 16 percent). They found that, compared to women who received external beam radiation, brachytherapy patients were roughly twice as likely to have complications, specifically skin and wound problems related to incisions for the catheters. "Our study doesn't close the door on brachytherapy," Dr. Gross said, "but it does show the importance of looking at outcomes to see if a new therapy really is better and should be widely used."

"The ability of the scientific community to generate new knowledge is dramatically outpacing our ability to test whether these new treatments are effective," Dr. Gross explained. "Once a new treatment appears to be effective in a trial setting, we shouldn't stop studying it. We need to bridge the gap between research and clinical practice, using 'Big Data' to help our patients make informed choices about their care. When patients are making critically important decisions about their health, we need to be able to say 'data shows that for patients like you – a 75 year old women with stage III breast cancer and a history of disease and diabetes – therapy X tends to work better than therapy Y' We don't have that capability yet, but we are on the cusp of a new era that will get us there in the not-too-distant future."

Abhijit A. Patel, MD, PhD

Detecting Cancer from a Blood Sample

In the near future it may be possible to detect cancer from DNA in a blood sample, a "liquid biopsy." That is one of the implications of a recent paper by a team of scientists from Yale. Using a technique called "ultra-deep sequencing," they were able to detect extremely low levels of tumor-derived mutant DNA in the plasma of cancer patients. "I hope that this will provide a clinically useful tool in the future," said Abhijit A. Patel, MD, PhD, Assistant Professor of Therapeutic Radiology at Yale School of Medicine. "Ultimately we want to use this for purposes such as early detection of cancers."

The researchers used 117 samples of plasma from 30 patients with non-small cell lung cancer. The samples were taken before, during, and after treatment, then run through a sequencer that analyzed them for DNA containing tumor-specific mutations. To eliminate false positives due to sequencing errors, the researchers designed a strategy that essentially proofread each DNA sequence by checking the forward and reverse strands against each other. This produced an analysis of ultrafine sensitivity – just one variant in 5,000 molecules – that identified mutant DNA released by the tumors.

The method opens tantalizing possibilities for detecting cancer through blood-borne DNA. The advantages are many, noted Patel. For instance, DNA is highly specific, unlike the protein biomarkers now used to spot some cancers. Most protein biomarkers are present in small amounts even in healthy people, and these biomarkers can sometimes be elevated due to conditions other than cancer. "But it would be very unlikely to find a mutation in a cancer-related gene in someone's blood if they didn't have cancer," Dr. Patel explained. "Tumor-specific mutant DNA in the blood would be highly unusual in a healthy person, so we expect the false positive rate to be very low. Specificity is very important when developing a screening test."

DNA-testing of blood could also deliver a more comprehensive diagnosis of a patient's mutation profile. A biopsy provides information about an individual tumor sample, a keyhole view. But what if that tumor mutates? What if the patient has multiple tumors in different phases and locations? A blood-based analysis of DNA mutations may be able to detect all of this, revealing the whole landscape and giving doctors a roadmap to direct treatment.

"Based on the mutation profile that you find in the blood," Dr. Patel said, "you might have enough information to tell you that a certain targeted therapy would be most effective."

In their paper, Dr. Patel and his colleagues offer some evidence that plasma sequencing might also be used diagnostically to assess whether a treatment has failed, is working, or is losing effectiveness – based on changes in tumor DNA levels in the blood.

> "The method opens tantalizing possibilities for detecting cancer through blood-borne DNA."

Dr. Patel is especially excited by the possibility of using this technology for early detection. Most cancers are characterized by distinctive mutations. "People at high risk, such as those with a strong family history of cancer or an extensive smoking history could be tested for a broad panel of tumor mutations. If a particular set of mutations suggestive of cancer was found, the patient could be worked up to determine what is going on. You could use the test to find the needle in the haystack – a small tumor in a more curable stage."

He and his collaborators are now widening their search for mutations found in other cancers, including colorectal, pancreatic, and ovarian cancers. He believes they eventually will be able to test for many others.

The sequencing costs have dropped to less than $100 per sample and will keep dropping. Dr. Patel cautions that much remains to be done before the test reaches the clinic, but the potential to help patients is clear. "My hope is that eventually blood-based DNA testing may become a routine part of an annual physical."

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