Yale Cancer Center

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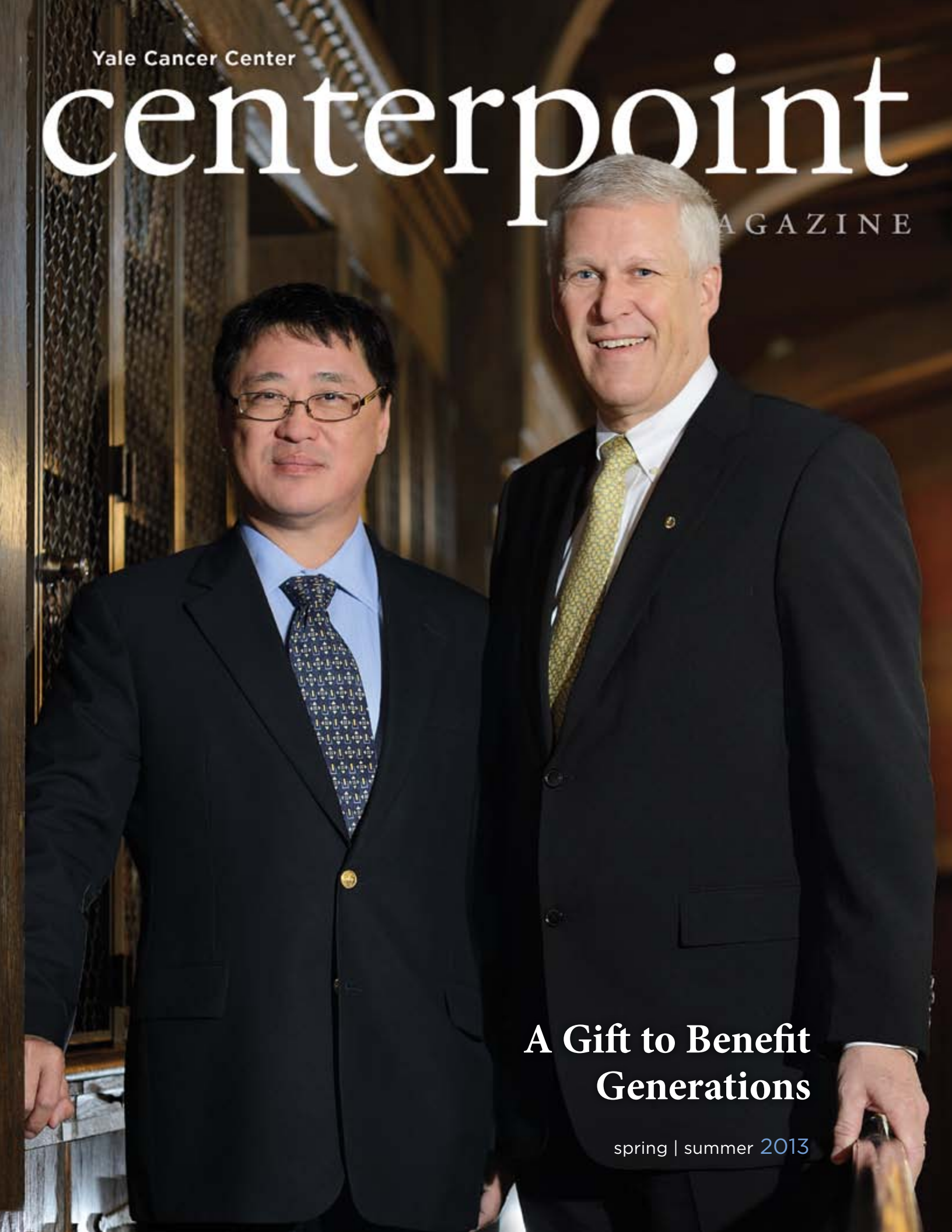

A Gift to Benefit Generations

spring | summer 2013

contents spring | summer 2013

departments

On the Cover
Lieping Chen, MD, PhD, the inaugural United Technologies Corporation Professor in Cancer Research and Louis Chênevert, Chairman and CEO of United Technologies Corporation and Chair of the Yale Cancer Center Advisory Board.

Peter Baker **photographer**

yale cancer center

Thomas J. Lynch, Jr., MD
Director

Kevin Vest, MBA, FACHE
Deputy Director, Administration and Clinical Affairs

Renee Gaudette
Director, Public Affairs and Marketing

art + Production

Greg Stewart
Art Director

contributors

Writers
Emily Fenton
Steve Kemper
Colleen Shaddox

Photographer
Peter Baker
pbakerphoto.com

Design
Ingenuity Design, Norwalk, CT
ingenuitydesign.com

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renee gaudette@yale.edu

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MAGAZINE

Centerpoint Magazine is published two times a year by Yale Cancer Center to inform the public and the Center's friends, volunteers, donors, and staff on current items of interest at Yale Cancer Center.

Yale Cancer Center
333 Cedar Street, PO Box 208028
New Haven, CT 06520-8028
yalecancercenter.org

Editorial Office
Yale Cancer Center
100 Church Street South, Suite 160
New Haven, CT 06519
renee.gaudette@yale.edu

director's letter

PETER BAKER

I AM INCREDIBLY GRATEFUL to Louis Chênevert and United Technologies Corporation for their investment in cancer research at Yale Cancer Center through their endowed gift of the United Technologies Corporation Professorship in Cancer Research. Endowed chairs are an important currency in academic medicine, as they allow leadership to recruit and retain the very best scientists and physicians to an institution. Dr. Lieping Chen, the first person to hold this professorship, is one of the brightest minds in cancer immunotherapy research. UTC's generous support will have a huge impact on Dr. Chen's ability to achieve innovative research breakthroughs to benefit and treat all cancer patients.

Earlier this year Yale Cancer Center welcomed the site review team from the National Cancer Institute for their evaluation of our Cancer Center Support Grant (CCSG). The grant summarizes the remarkable growth and investment in cancer care and cancer research that has occurred over the past three years, and highlights the continued strength in cancer research that has been a hallmark of Yale Cancer Center for nearly 40 years. The CCSG is the funding and award mechanism that establishes Yale Cancer Center as one of only 41 National Cancer Institute Comprehensive Cancer Centers. I am also pleased to report that our CCSG has been positively reviewed. We expect to receive our official award notification early this summer.

The leadership of Yale Cancer Center and Smilow Cancer Hospital at Yale New-Haven continue to focus on integration of our eight Smilow Cancer Care Centers and 23 faculty members at these centers, as well as the ever-expanding list of new faculty members on our main campus. Our goal is to create a unique, unified culture that benefits cancer patient care throughout our system. I am extremely pleased to report that we continue to have breakthrough patient satisfaction scores, and am grateful to the dedication of our nurses, physicians, social workers, and the entire patient care team who make a positive patient and family experience a priority each day.

I look forward to updating you on our CCSG renewal status with the National Cancer Institute, along with new research initiatives and clinical trial results in the fall issue of Centerpoint. Enjoy your summer!

Sincerely,

Tom Lynch

Thomas J. Lynch, Jr., MD
Director, Yale Cancer Center
Physician-in-Chief, Smilow Cancer Hospital

A GIFT TO BENEFIT GENERATIONS

Steve Kemper **writer** Peter Baker **photographer**

In cancer research, money translates into science that saves patients' lives. That clear equation recently inspired a gift of $3 million to Yale Cancer Center from United Technologies Corporation (UTC). The donation endows the United Technologies Corporation Professorship in Cancer Research. The first recipient is one of the Cancer Center's most accomplished scientists, Lieping Chen, MD, PhD, Professor of Immunobiology, of Dermatology and of Medicine (Medical Oncology) and Co-Director of the Cancer Immunology Program.

Dr. Chen is a pioneer in immunotherapy, a powerful weapon against cancer. His research into the ways that cancer cells trick the immune system into shutting off led him to discover an antibody that, when used to treat certain cancers, turns the immune system back on and drastically shrinks tumors. He has now turned his attention to difficult cancers, including those of the brain and prostate.

"What Lieping Chen is doing is remarkable," said Louis Chênevert, Chairman and CEO of UTC, and an enthusiastic supporter of Yale Cancer Center and Smilow Cancer Hospital at Yale-New Haven. The recent endowment is not the company's first gift to YCC. In 2008 UTC contributed $1 million toward construction of Smilow Cancer Hospital, which opened in 2009. Chênevert has also served on the Director's Advisory Board at YCC for 12 years and is currently its chair.

"Of all the things I do outside in terms of philanthropy and support," he said, "I get a lot of satisfaction being associated with Yale. It's truly a world class organization. Tom Lynch is not just a great doctor, he's a superb leader." Thomas J. Lynch, Jr., MD, is Director of YCC and Physician-in-Chief of Smilow.

"United Technologies Corporation and Yale Cancer Center share the same passion for excellence in research," said Dr. Lynch, "and we're extremely grateful for the partnership we continue to build together. UTC's generous support will have a huge impact on Dr. Chen's ability to achieve innovative research breakthroughs to benefit and treat all cancer patients."

Dr. Chen agreed. The endowment will provide him with the annual interest on the $3 million, which he expects to be between $130,000 and $150,000 per year. "For an active lab like mine, this will be a very important resource," he said. His research, he explained, is primarily funded by government grants, private foundations, and drug companies. "Most of those dollars come with very tight restrictions and rigid rules," he said. Such grants typically can be used only for things directly related to a specific experiment—for instance, to pay salaries or to buy lab animals and reagents.

Lieping Chen, MD, PhD, Louis Chênevert, Thomas J. Lynch, Jr., MD, and Dean Robert J. Alpern, MD

That contrasts with UTC's endowment. "This money is very flexible," said Dr. Chen. "We can buy anything we need — computer software, society memberships, sophisticated equipment for detailed analysis. We can send a star post-doc to a meeting to present his exciting results and get peer review about weaknesses or problems — that's the way to keep science moving forward. Most grants do not support any of those things, which are very important to keep the lab alive."

"IT'S A GIFT THAT WILL KEEP ON GIVING BECAUSE IT WILL FUND THIS PROFESSORSHIP FOR GENERATIONS TO COME."

– Louis Chênevert

In the long term, keeping labs like Chen's alive leads to better care for cancer patients. That was another of UTC's motivations. The company is the largest employer in Connecticut, with workers at Pratt & Whitney aircraft engines, Sikorsky helicopters, Carrier air conditioning and heating systems, Otis elevators and escalators, and UTC aerospace systems.

"We have 27,000 employees in the state," said Mr. Chênevert, "and unfortunately nearly every family has had to deal with cancer, either directly or with relatives or friends. Yale is the only National Cancer Institute designated Cancer Center in Connecticut, and we believe that having it here benefits all the other hospitals in the state, because the advances that Yale develops in clinical trials wind up finding their way to other hospitals. Because of that, I can tell our employees that they and their families have a better chance if they are hit with cancer."

He added that he gets several letters a month from employees thanking him and UTC for supporting Yale Cancer Center and Smilow Cancer Hospital because treatment there saved a loved one's life. As an example he mentioned Mark Reitsma, the company's manager of Global Human Resources Support Operations, who was diagnosed with stage IV lung cancer in 2010 "and told to get his affairs in order." As a last hope he went to Yale, where he was placed on a clinical trial for a new Phase I drug. His cancer stabilized and he was able to resume bicycling — for the past two years he has completed Smilow's 100-mile Closer to Free ride.

Such stories are not uncommon at UTC, added Mr. Chênevert, which is another reason the company wanted to endow a professorship. "It's a gift that will keep on giving," he said, "because it will fund this professorship for generations to come. As long as Yale exists, somebody will be able to do things and do research that would not be possible without that grant. So my view is that our employees will benefit from this relationship for years to come."

FIGHTING BRAIN CANCER with NANOPARTICLES

Steve Kemper **writer** Peter Baker **photographer**

W. Mark Saltzman, PhD

The most common malignant brain tumor, glioblastoma multiforme (GBM), is also the most intractable and lethal. Even the most aggressive therapies barely slow its devastating progress — 96 percent of patients die within five years of diagnosis. Since more than 15,000 new cases of GBM are diagnosed in the United States every year, researchers and doctors are eager to find better ways of treating the disease.

One of the most promising new approaches has been developed in the Yale lab of W. Mark Saltzman, PhD, the Goizueta Foundation Professor of Biomedical Engineering, Chemical & Environmental Engineering & Physiology. In a breathtaking feat of biomedical engineering, Dr. Saltzman and colleagues, Dr. Toral Patel and Dr. Jiangbing Zhou, have devised a way to load anti-cancer agents onto nanoparticles and deliver them in high concentrations, via catheter, directly to the parts of the brain where the chemotherapy is needed, and also to regions of the brain that current therapies do not reach. The particles measure about 70 nanometers — smaller than the spaces between cells.

This brand-new method of transporting drugs into the brain will soon move from Dr. Saltzman's lab to the Brain Tumor Program at Smilow Cancer Hospital at Yale-New Haven, co-led by Dr. Saltzman's clinical partner, Joseph Massa Piepmeier, MD, the Nixdorff-German Professor of Neurosurgery. Drs. Saltzman and Piepmeier are now applying for FDA approval, and they expect clinical trials to begin within a year.

Dr. Saltzman's innovation is a sharp departure from current therapies for glioblastomas, including his own earlier designs. Before coming to Yale he worked on a drug delivery system now marketed as Gliadel®, a biodegradable polymer wafer packed with drugs that surgeons implant in the brain. The wafer slowly releases the drug. The method was an advance in treatment and remains in common use, but like every other therapy for GBM, its effect on survival rates has been slight.

"The problem with it," said Dr. Saltzman, "is that because of the dynamics of how drugs migrate in the brain, the drug can't penetrate very far from the site of the implant and get to everywhere it's needed."

To build a better way of delivering drugs, Dr. Saltzman decided he needed to radically shrink the drug-carrying wafer (about the size of a dime) to a size that could penetrate the brain. The literature suggested that the required measurement would be somewhere between 100 and 120 nanometers. In fact, after many experiments, Dr. Saltzman and his research team discovered that even this infinitesimal size was too large by 40 percent. They needed to create particles no bigger than 60 to 70 nanometers, including their cargo of drugs. They succeeded. The resulting degradable nanoparticles are the size of a virus — small enough to slip between brain cells.

"They can be pumped into the brain through catheters placed wherever the surgeon selects," Dr. Saltzman explained. "A technique called convection-enhanced delivery allows you to create fluid flow, which sweeps the nanoparticles deeper into the brain. When the infusion stops, the nanoparticles are still there, and they keep releasing their agents."

"Instead of giving someone a pill or injecting something in a vein and having it circulate," said Dr. Piepmeier, "you can put the drug in the highest concentration precisely where the tumor is invading the brain. This also minimizes toxicity and side effects."

Dr. Saltzman also wanted to design a delivery system that neurosurgeons could control and manipulate to do the most good for patients. That meant giving the surgeons a way to see what was happening in the brain during the infusion. "So we created particles that they can image by MRI to see if the particles are going where they should, at the right dose and volume," said Dr. Saltzman. At Smilow Cancer Hospital, he pointed out, the neurosurgical operating rooms are equipped with MRIs, which allows this imaging to be done during surgery.

This new system offers many other advantages as well. No incision is required, which also decreases the chance of complications such as infection. The infusion time is shorter — 30 minutes instead of two to six days — and the duration of drug release is much longer (more than 50 days).

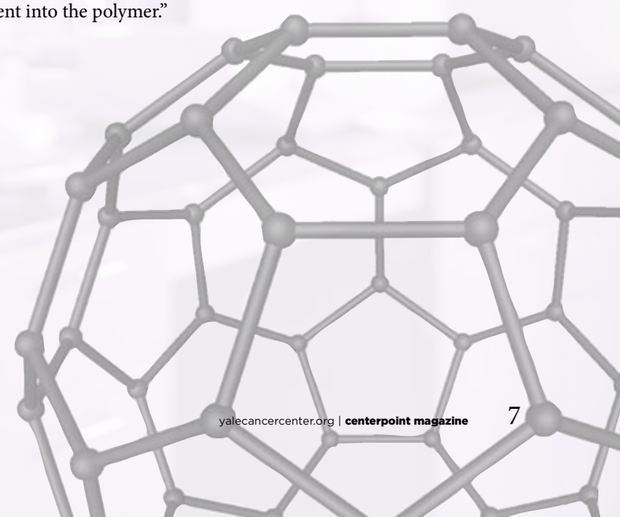
If the initial trials confirm that the particles can be controlled, distributed, and imaged, and that they release their cargo of drugs slowly over time, then patients with GBM will certainly benefit: their therapy will become less invasive and onerous, and their prognosis likely will improve.

"But the long term benefits could be even bigger," said Dr. Saltzman. If the clinical trial proves that nanoparticles carrying conventional chemotherapy can be deployed to fight brain tumors, he said, the broader applications could benefit patients with many other cancers. Dr. Piepmeier noted that it could be used to deliver local therapy to any solid tumor in the liver, breast, prostate, lung, or pancreas. "With other liquid agents," he said, "once you stop infusing, it's gone. But these particles reside at the site and persist for several weeks, so you get a much more robust and sustained release." The technique also opens possibilities for loading the particles with biological agents or therapies focused specifically on a tumor's genotype.

"Theoretically we could deliver whatever agent we want," said Dr. Saltzman. "We just have to figure out how to put that agent into the polymer."

In a breathtaking feat of biomedical engineering,

Dr. Saltzman and his colleagues have devised a way to load anti-cancer agents onto nanoparticles and deliver them in high concentrations, via catheter, directly to the parts of the brain where the chemotherapy is needed, and also to regions of the brain that current therapies do not reach.



A New Clinical Trial Gives Patients with Pancreatic Cancer *a Fighting Chance*

Emily Fenton **writer** Peter Baker **photographer**

Jeanne Czel went from enjoying retirement and playing golf in a benefit tournament in North Carolina, to a month later undergoing what would be one of the most difficult years of her life. It started with an uncomfortable feeling in her chest that she attributed to heart burn or acid reflux, although she had never experienced either before. She was still not feeling right, but had no alarming symptoms such as pain, or weight loss. Normally a very active person, when she started noticing loss of energy, she made an appointment to meet with her gastroenterologist. On July 21, 2011, after undergoing blood work, an MRI and a CT scan, Jeanne received a diagnosis of stage IV pancreatic cancer; it has metastasized to her liver and duodenum.

From there she began to research her options and on August 1 she met with Howard Hochster, MD, Professor of Medicine (Medical Oncology), and his team at Smilow Cancer Hospital. On August 5 she received her first of 23 intense rounds of chemotherapy. FOLFIRINOX is an innovative chemotherapy regimen that is in a phase II clinical trial for patients with advanced pancreatic cancer. FOLFIRINOX is the combination of 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin. Although Jeanne was not able to be part of the trial, due to the fact that she needed to start treatment immediately, she is being treated according to the trial guidelines.

"FOLFIRINOX is a very impressive treatment that can produce a dramatic response, but is very hard for some patients to handle," Dr. Hochster said. "Because pancreatic cancer spreads so rapidly it's a difficult disease to treat. Even if you are able to perform surgery, the cancer will most likely recur shortly after." Dr. Hochster commented that Jeanne's response to the treatment was remarkable.

Jeanne was able to follow the regimen for a year. Before undergoing the treatment she didn't want to know how bad the side effects would be. She knew it would be tough, but figured that knowing wouldn't help. "I didn't want it to dictate how I lived my life. I decided then and there to focus my energy on myself," Jeanne said.

Although she experienced side effects from the treatment, lack of energy being the main one, she continued to live her life and even traveled to Europe for two weeks. In June of 2012 it was determined that she could take a break from the chemotherapy, and was even deemed in remission. During this time she spent time golfing, and rode in the Closer to Free bike ride. Unfortunately, after 4 months her cancer progressed and she started chemotherapy again.

Dr. Hochster commented, "Not many pancreatic cancer patients have the opportunity to take a break of any length from treatment, but Jeanne's scans were normal and it looked as though she was in remission. For now we are keeping her cancer under control, but the future is uncertain. She is such a great example in that she is still living her life to the fullest and remains positive."

Jeanne plans to ride in the Closer to Free bike ride again this year on September 7th with her daughter, and just completed her first 5k run since being diagnosed with cancer. "The whole time I thought the body I had taken care of for so many years had betrayed me, but the same body that I thought had betrayed me, allowed me to undergo this grueling regimen," Jeanne said. She continues to golf, run, and ski, which she commented not a lot of people with stage IV disease of any kind can say. She considers herself to be a healthy person that happens to have a terminal disease.

She commented, "Research is so important in defeating this disease and it just might bring that 6% 5-year survival rate up to 10%, and then up from there." Her daughter and she are both part of the Pancreatic Cancer Action Network (PanCAN) and take part in fundraising. They both feel that Pancreatic Cancer Advocacy Day, held by PanCAN, is a special day because it focuses on raising awareness and speaking to legislators about funding more research in pancreatic cancer. Even though Jeanne tries not to look too far ahead, she remains a glass half full kind of person, and will watch her daughter walk down the aisle next month.

"I don't think about events that I might miss in the future, but focus on the fact that I am still here and living well with pancreatic cancer. There is nothing I want to do that I can't do. I hope that other patients see that it is possible to keep living life and that they seek out any options that provide them the opportunity to do better," Jeanne said. "I don't know why I got this disease, why I am still here, or how much longer I will be here, no one can answer those questions for me. I just know that if it wasn't for both my support systems, the one at Smilow and my close friends and family, I couldn't have done it. It all matters, all the prayers and well wishes, it all counts."

PETER BAKER

Jennifer Kapo, MD and Leslie Blatt, APRN

Helping Patients Feel Better, Inside and Out

Cancer does damage that never shows up on a scan: losing sleep because of pain; worrying that you'll be too exhausted to tour a college with your high school senior; seeing your illness as a test of faith – and wondering if you'll pass it.

Smilow Cancer Hospital at Yale-New Haven's Palliative Care Service treats cancer pain wherever it strikes: body, mind, or spirit. The keys to feeling better will be different for everyone depending on their illness and even more so on the myriad other circumstances of life. "What's unique about this team," said the Rev. Jane Jeuland, the team chaplain, "is that every member sees each patient within the context of their story." Palliative care addresses such wide-ranging concerns as the effect of cancer on a patient's family or career.

Making people feel better obviously has an enormous value in itself, says Jennifer Kapo, MD, the service's chief, and it also has a measurable impact on disease. She points to a study of patients with advanced lung cancer. People who received palliative care reported a higher quality of life and lived longer. YCC Director and Physician-in-Chief of Smilow Cancer Hospital, Thomas Lynch, MD, was a co-author of the paper published in The New England Journal of Medicine.

Andrew Putnam, MD, often sees fear on patients' faces when he introduces himself as a palliative care physician. The specialty is associated with end-of-life treatment. On the contrary, he explains, relieving pain can make it possible for patients to continue with an aggressive therapy that provides the best hope of defeating the cancer. The team can offer a range of pain-relieving strategies, from simple remedies, such as position changes and hot packs, to medication. Dr. Kapo plans to add complementary therapies, such as massage, for patients and their caregivers.

Physical, spiritual, and mental pain can interact, so a full interdisciplinary team reviews every case. When Leslie Blatt, APRN, started the service, her only partner was a physician. Today team members come from nursing, medicine, psychology, social work, and spiritual care.

Ursula Nehrt, PA, was seeing a patient who had received a terminal diagnosis. The woman's family had accompanied her to the appointment. "They were distraught," Ms. Nehrt remembered. She immediately called Rev. Jeuland, who came to pray with the family. "It was tremendously helpful," Ms. Nehrt said.

The program also offers psychological care. Psychologist Dwain Fehon, PsyD, sees palliative care patients – often right at Smilow in sessions arranged around their other appointments – for anxiety, depression, or other issues raised by their illness.

Though the team works with patients at all stages of disease, it does have a strong end-of-life component. Members follow patients who transfer to hospice programs in the community. Within five years, they plan to add a 10-bed palliative care unit at Smilow that would accommodate hospice patients as well as other patients who need intensive symptom management. Ms. Blatt says that her dream is to offer hospice care to patients in their homes.

The palliative care service recently received a $1 million gift from the Milbank Foundation to support clinical care, research, and education. Among other things, the gift will support a bereavement coordinator.

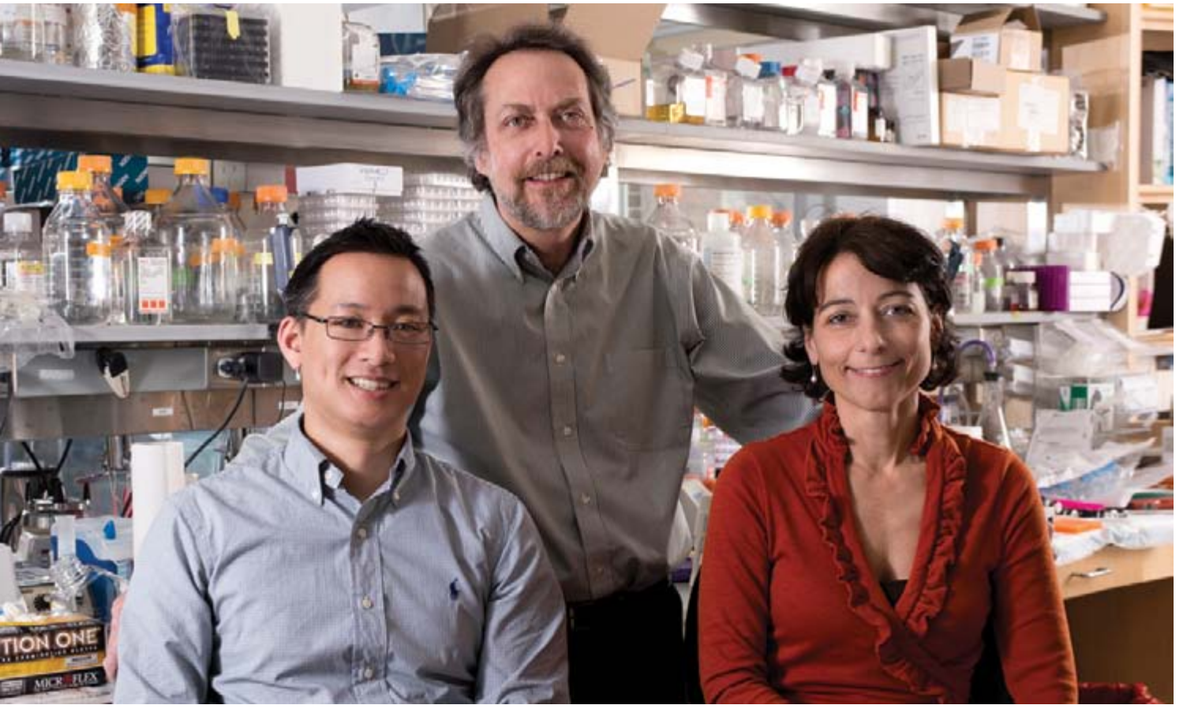
Dr. Kapo describes the team as "an extra layer of support" working with patients' primary oncologists. Today the team serves both inpatients and outpatients, though most cancer care is delivered on an outpatient basis. Jason Glombicki, a chaplain in training, is conducting a study to evaluate the need for spiritual care for patients receiving outpatient care.

Educating palliative care professionals is a key component of the service. Next year Yale will offer a fellowship in palliative medicine for physicians, also supported by the Milbank Foundation. The United States needs an estimated 10,000 more doctors specializing in palliative medicine than it currently has, according to Dr. Kapo.

The palliative care team plans to add a research component to determine the best ways to help patients and families. The team now holds a weekly meeting where members take turns presenting new information in the evolving field of palliative care.

One of Dr. Kapo's priorities is helping team members to support each other through their work, which can be emotionally draining. But that work is also immensely rewarding. Susan Crawford, LCSW, describes cancer as a "life-altering illness" for patients and their families. Yet at every stage of the disease, there is hope. "Our job is to help define for the patient and the family what their hope is," she explained.

> **"What's unique about this team** is that every member sees each patient within the context of their story."
>
> Reverend Jane Jeuland



PETER BAKER

Don Nguyen, PhD, David Stern, PhD, and Valentina Greco, PhD

Off to a Brilliant Start

Don Nguyen dreamed of a career in cancer biology research but knew there were no guarantees. Dr. Nguyen trained as a post-doctoral fellow at Memorial Sloan-Kettering Cancer Center, one of the best cancer institutes in the country. When it came time to establish his own laboratory, however, he faced a landscape of disappearing federal funding and intense competition.

Yale Cancer Center's Cadet Program is designed to help young scientists navigate that landscape. When he came to Yale, Dr. Nguyen received advice on equipping and staffing his lab. He won YCC pilot funding set aside for young investigators. That support allowed him to get impressive results in his study of lung cancer metastases – so impressive that he has since obtained an RO1 grant from the National Cancer Institute, a milestone achievement for an investigator. He also benefitted from informal help. "For a highly competitive institution with so many accomplished scientists, people are extremely collegial and generous with their time here," said Dr. Nguyen.

When he has questions, Dr. Nguyen can stick his head in the office next door and confer with fellow cancer biologist David Stern, PhD, who is a Professor of Pathology, Associate Director of Shared Resources at YCC, and leader of the Cadet Program. YCC has seen a huge influx of young faculty, with almost 100 assistant professors, half of whom were recruited in the past four years. "These are the individuals who are going to be running the cancer enterprise at Yale in the coming years," explained Dr. Stern.

"What drew me to Yale was the emerging cancer biology program that is growing across different departments," said Dr. Nguyen. Young faculty are typically attracted by the strength of Yale's resources, both human and technical, adds Dr. Stern. YCC scientists can access advanced genome sequencing and stem cell technologies and expect to collaborate with leading basic and clinical scientists.

Though YCC junior faculty are "extraordinarily strong" as scientists, they must also learn the work of managing a lab and establishing a reputation that will enable them to secure consistent funding, says Dr. Stern. A senior scientist tends to get a great deal of credit for any work that happens in a lab, thus overshadowing most of the accomplishments these younger researchers made in their post-doctoral years. "They're at risk of falling off the map," explained Dr. Stern.

Despite this vulnerability, the early years of a scientist's career are often the most productive. "They're at the top of their game. They have great bench skills and they're highly motivated."

Becoming a manager and courting fame can be vexing for scholars who want to concentrate on science. "The need to devote time to financial planning and lab management rather than only focusing on scientific projects is challenging," said Katerina Politi, PhD, another cancer biologist in the Pathology Department studying mutations associated with drug resistance in lung cancer. But she's realized it's "part of the new role" and is doing her best to excel at these ancillary skills. Dr. Politi and Valentina Greco, PhD, in the Department of Genetics, have organized junior faculty development programs, including a retreat where they can consult with senior faculty and administrators as well as an organizational psychologist on the dynamics of managing lab personnel.

All departments throughout Yale University and the School of Medicine have programs to mentor young faculty, says Dr. Stern. The YCC Cadet Program works to augment these and to get scientists together across departments to enable them to excel in the increasingly interdisciplinary world of cancer research. It is particularly important to link basic scientists with faculty who care for patients so that research focuses on the areas where it can best advance clinical care. Providing a platform within YCC encourages young scientists to focus their work on cancer.

"The Yale Cancer Center Cadet Program builds bridges," said Dr. Greco, noting that she's a geneticist with an appointment in the dermatology department who regularly interacts with biologists. "It creates a community, which is vital to young scientists as they start."

Her lab developed a method to watch stem cells regenerate tissue in real time in living animals, an achievement with the potential to improve understanding of how cancers develop. Dr. Greco says that many senior faculty are helping her along the way, notably Daniel DiMaio, MD, PhD, YCC's Scientific Director. But regular meetings with peers are also valuable. "A mentor is anybody who has gone through a process that I haven't yet," she explained. As her career progresses, she'll continue to seek the kind of collegiality she's enjoyed as a cadet. "You can go faster and be more effective," Dr. Greco said.

"The Yale Cancer Center Cadet Program builds bridges. It creates a community, which is vital to young scientists as they start."

Valentina Greco, PhD

The Weight of Disease

Tobacco will soon be displaced as the main cause of cancer deaths in the United States. This might be reason for celebration, if smoking was not being supplanted by yet another preventable cause of cancer: obesity and its sidekicks — unhealthy food and lack of exercise. About a third of the estimated 1.6 million new cases of cancer last year stemmed from tobacco use, but another third were linked to obesity, inactivity and poor diet.

"So we know how to prevent about two-thirds of the current cancer burden in the United States," Susan T. Mayne, PhD said, head of the division of Chronic Disease Epidemiology and Associate Director for Population Sciences at Yale Cancer Center, whose research has traced the role of diet in several forms of cancers. "Exercise, fruits, vegetables, whole grains: that's the same message we've been giving for a long time. But it's not changing behavior — the prevalence of obesity keeps going up."

Indeed, the nation's collective waistline has been steadily expanding for several decades, though recent research has found that the rate may be leveling off. At the moment, one in every three U.S. adults is obese, and another third are overweight. If projections hold, 78 percent of Americans will be overweight by 2020.

Yale researchers have demonstrated that the links between cancer and obesity can be broken, or at least weakened, through interventions and individual willpower. Cancer risk can be drastically cut by reducing one's waistline. A growing number of publications have also reported associations between exercise, healthy eating, and a reduced risk of breast and colorectal cancer recurrence.

This year about 42,000 U.S. women will be diagnosed with endometrial cancer, the most common form of uterine cancer. Scientists have long suspected a link between excess weight and endometrial cancer. Recent research by scientists at the School of Public Health has not only documented that link but also found troubling proof that the foundations of endometrial cancer may form as early as a woman's 20s.

Until this research, this form of cancer was assumed to be caused by postmenopausal changes in a woman's body. Now Herbert Yu, MD, MSc, PhD, a member of the Yale Cancer Center Cancer Prevention and Control Research Program, and several collaborators have found compelling evidence that correlates the risk of developing endometrial cancer with weight long before menopause begins.

"We found a cumulative effect from the age of 20 or 30," Dr. Yu said. "If young women become obese and maintain obesity, they have a much higher risk of developing the cancer than do women who become overweight in their 40s or 50s. And the longer you are obese, the higher your risk."

The increased risk is not trivial. Overweight women are twice as likely to develop endometrial cancer as women of normal weight. For obese women, the risk is four times greater. The study also found that overweight women tend to develop the disease at a younger age.

These findings, funded by the National Cancer Institute (NCI), held true across all racial and demographic categories among the 1,333 women studied. The genetic analysis of the data is still under way.

"But unfortunately," explained Dr. Yu, "based on preliminary data, there are no strong linkages to genetic factors for endometrial cancer." Unfortunate because that makes a genetically engineered remedy unlikely.

"It seems that environmental factors, especially lifestyle, contribute significantly to the disease," Dr. Yu said. "But that could be good, because lifestyle can be modified by diet and exercise."

Dr. Yu also reported another troubling finding: "The sample size is very small for those who went from being obese to being normal weight," he said. "But those who went from normal weight to overweight or obese are a huge number. It seems that once you're obese or overweight, it's very hard to reverse it."

Yale researchers have demonstrated that the links between cancer and obesity can be broken, or at least weakened, through interventions and individual willpower.

Exercise remedies

Melinda L. Irwin, PhD, MPH, Associate Professor in the division of Chronic Disease Epidemiology and Co-leader of the Cancer Prevention and Control Research Program, has shown that exercise and weight loss not only help to lower the risk of cancer, they also can greatly improve a patient's recovery and survival chances.

Indeed, the numbers are startling. In a 2008 study of 933 women with breast cancer, Dr. Irwin found that women who began exercising moderately after diagnosis lowered their risk of death from cancer by 45 percent compared to their inactive peers. Breast cancer patients who reduced their physical activity were four times more likely to die of the disease. Irwin also learned that obese women tend to have high levels of insulin and insulin-like growth factors, which encourage cells to proliferate, leading

to breast cancer. Exercise lowers these levels and curtails the growth of tumors.

How much exercise is necessary to lower the risk of recurrence and death? Observational studies during which women were asked how much they exercised after diagnosis showed that 30 minutes, five days a week, of "moderately intensive" activity such as brisk walking, was associated with about a 50 percent lower risk of death, explained Dr. Irwin.

"To put in perspective how important this lifestyle behavior is," noted a 2011 report from the American Society of Preventive Oncology, co-authored by Dr. Irwin, "physical activity is associated with a reduction in risk of recurrence by 30 percent to 50 percent, an effect comparable to chemotherapy and hormonal therapy; however, many patients and clinicians may not appreciate its benefit for survival."

The report recommends making exercise and weight loss part of cancer therapy but adds that such programs are rare, "despite the fact that obesity, weight gain and physical inactivity are common in cancer patients before and after a cancer diagnosis."

Dr. Irwin suspects that most people still believe, or prefer to believe, that cancer is caused by things beyond their control, such as family history or genetics. "But we know that a majority of cancers — at least 30 percent, maybe more — are related to our health behaviors: our diet, our weight and our level of physical activity," she said.

Echoing Dr. Yu, she added that this is potentially good news, because it means that people have more control over their risk of getting cancer or, if they are diagnosed with the disease, of avoiding a recurrence. Dr. Irwin calls a cancer diagnosis a "teachable moment," because the disease may motivate people to change unhealthy habits.

"We need a new approach rather than just giving people information about exercise and diet," said Dr. Mayne. "The strategies that are important for reducing the risk of cancer are equally important for reducing the risk of many other chronic diseases. We need to teach people how to make good food choices, how to incorporate physical activity into their daily lives — how to be healthier."

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Q+A

meet the physician

Erin W. Hofstatter, MD

You're focused on the care of women who are at high genetic risk for developing breast cancer. How should these women be monitored?

Women who are at increased risk of breast cancer due to an inherited genetic mutation, such as BRCA1 or BRCA2, have a variety of options to manage or reduce their risk of developing breast cancer. For some women, close surveillance with annual mammograms, annual breast MRIs and semi-annual breast exams is an appropriate choice, with a goal of finding a breast cancer as early as possible if it develops. Other women may opt to have prophylactic mastectomies (preventative removal of the breasts), which significantly reduces the risk of breast cancer development. BRCA mutations are known to increase the risk of ovarian cancer as well, so careful monitoring and removal of the ovaries by the age of 40 should be considered as well. Decision-making for cancer prevention in the setting of a BRCA mutation can be complicated for patients and providers alike, and recommendations should ultimately be tailored to the individual patient.

How is the treatment of women who are BRCA+ different?

Currently, the standard chemotherapy and hormonal treatment options for women with BRCA-related breast cancers are not different than for other women with breast cancer. However, abundant research is underway to find treatments that can specifically target the BRCA gene mutation in the treatment of breast cancer, such as platinum chemotherapy agents and PARP inhibitors. We will soon be opening a clinical trial for BRCA-related breast cancers, specifically studying the role of platinum chemotherapy in these patients.

One of your clinical trials is looking at the use of black cohosh as a therapeutic agent. How was this discovered for treatment?

Black cohosh is a plant-based herb that has been used for centuries for a variety of ailments, including menopausal symptoms. Inspired by my colleagues Elena Ratner, MD and Mary Jane Minkin, MD of gynecology, who often use this agent for management of hot flashes in breast cancer patients, I found compelling data in the literature suggesting that black cohosh was not only safe but had potential to be an effective agent for breast cancer treatment and prevention. Not only does there appear to be an anti-cancer effect in breast cancer cells in the laboratory setting, but there is observational evidence of a protective effect from breast cancer recurrence in those women previously diagnosed with cancer, and a preventive effect in healthy women as well. Given that black cohosh has few side effects, and can potentially help with menopausal symptoms, I became interested in studying this specific agent to prove an anti-cancer effect.

Who is eligible and would potentially benefit from participating in the black cohosh clinical trial?

In general, eligible women are those who have been newly diagnosed with DCIS (ductal carcinoma in situ) of the breast and who have not yet undergone surgery. Study participants are asked to take black cohosh for 2-5 weeks prior to their planned surgery. We will study the effect of black cohosh on the breast cancer cells before and after treatment with black cohosh, with a goal of demonstrating reduced cancer cell proliferation. We are hopeful that this trial will be a first step in identifying the role of black cohosh in the treatment and prevention of breast cancer.

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