

Yale Cancer Center

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MAGAZINE

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Peter Baker **photographer**
photographed at the Edge Fitness Club, Fairfield, CT

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yale cancer center

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Yale Cancer Center

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I continue to be inspired and excited by the incredible advances coming from the Yale Cancer Center labs and our translational research efforts at Smilow Cancer Hospital at Yale-New Haven. Our team had a wonderful presence at the American Society of Clinical Oncology (ASCO) meeting in June with over 50 abstracts presented, including impressive data on two phase I trials using immunotherapies for both advanced melanoma and bladder cancer, as well as a new combination immunotherapy study of melanoma treatment presented by Dr. Mario Sznol.

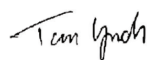
September's American Society for Therapeutic Radiology and Oncology (ASTRO) meeting was a great opportunity for Smilow Cancer Hospital to highlight our national leadership in radiation oncology research and treatment efforts. Dr. Lynn Wilson served as Chairman of the ASTRO Annual Meeting Scientific Committee that included 18 presentations and 15 poster presentations from Yale. Dr. Meena Moran presented new guidelines from ASTRO for breast margins, which you will read about in this issue of *Centerpoint Magazine*.

The leadership at Smilow Cancer Hospital evaluates our patient- and family-centered care efforts each day, including continuous review of patient satisfaction surveys and Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) scores. I am proud to announce that in our recent HCAHPS survey, our cumulative scores for our four Smilow Cancer Hospital units exceed the Yale-New Haven Hospital overall scores in all 32 domains. In addition, our Smilow units met or exceeded the 90th percentile ranking in 11 domains and met or exceeded the 50th percentile in 19 domains. We are very pleased with our progress and will continue to strive to improve our responsiveness to our patients and to steadily advance our performance over the coming year.

In September, we welcomed two new locations to our Smilow Cancer Hospital Care Centers group by integrating Oncology Associates of Bridgeport, Inc. and adding their Fairfield and Trumbull, CT offices to our network. We now have 10 Care Centers throughout the region for our patients to access Smilow Cancer Hospital quality care and our faculty physicians in convenient locations closer to home.

The upcoming year will be one of celebrations for us as we commemorate 40 years of Yale Cancer Center and 5 years of Smilow Cancer Hospital! I look forward to sharing those milestones with you in the next issue of *Centerpoint Magazine*.

Sincerely,



Thomas J. Lynch, Jr., MD

Director, Yale Cancer Center

Physician-in-Chief, Smilow Cancer Hospital

Exercise

as Adjuvant Treatment: the Links between Weight, Inactivity, and Breast Cancer



Evidence has been accumulating for 20 years showing that women who exercise have a significantly lower risk of developing breast cancer. In the past 10 years, researchers, including Melinda L. Irwin, PhD, MPH, Associate Professor of Chronic Disease Epidemiology at Yale School of Public Health and Co-Leader of the Cancer Prevention and Control Research Program at Yale Cancer Center, have considerably expanded that evidence, repeatedly showing that even after women have been diagnosed with breast cancer, they can substantially lower the risk of both recurrence and mortality by exercising and losing weight.

More recently, Dr. Irwin has found that this holds true even for women who don't become physically active until after their diagnosis. The difference is stark: women who exercise after diagnosis reduce their risk of death from breast cancer by 30 to 50 percent. Nor is it necessary to run marathons to gain these benefits. Dr. Irwin's observational studies show that moderate exercise, such as briskly walking for 30 minutes five days a week, can lower the risk of death from breast cancer by about 50 percent. More vigorous activity for 75 minutes a week, such as jogging or gym workouts, has a similar effect.

But the reverse is true as well, adds Dr. Irwin. Being overweight or obese increases the risk of developing breast cancer and dying from it. Similarly, women who gain weight after their diagnosis—and most do—put themselves at higher risk of recurrence and mortality. The difference, again, is stark: Dr. Irwin has shown that women who don't exercise after a diagnosis are more likely to die of the disease than women who initiate an exercise program after diagnosis.

Yet more than 65 percent of breast cancer survivors are overweight and don't exercise, despite the lethal consequences. So why isn't every breast cancer survivor pacing around her neighborhood or joining a gym? Dr. Irwin lists several reasons, each of which she is working to change.

First, clinicians remain skeptical. "Critics say the studies are observational," Dr. Irwin explained, "not randomized controlled clinical trials." Such critics suggest that exercise and weight loss are merely proxies for other unknown factors. For instance, active women who maintain a healthy weight may simply be more self-disciplined than other patients, and hence more likely to adhere to their treatment regimens, and hence more likely to survive. Or maybe active women tend to be nonsmokers or have more education, which can lead to better outcomes. Dr. Irwin notes that even if these explanations are true, they still underline the importance of physical activity and weight management in survivorship.

But she doubts the proxy theory, and points to one of her recent studies to illustrate why. About 70 percent of breast cancer patients take an aromatase inhibitor (AI) that impedes the production of estrogen, a known factor in breast cancer. AI therapy is effective, but about half of patients stop taking it because it gives them joint pain. Dr. Irwin just completed a study to see if this side effect could be modified by exercise—and patients reported diminished joint pain. Physical activity could help patients stick with AI therapy, and Dr. Irwin hopes to test that assumption soon.

Skeptics also want clear proof that exercise and weight loss affect biological markers associated with cancer. Such evidence is growing. The newest suspect is insulin: high levels of it have been implicated as a strong risk factor for developing and dying from breast can-

cer. A large clinical trial is studying whether the drug metformin, originally developed to cut the risk of diabetes by lowering insulin levels, can improve the rates of recurrence and mortality among breast cancer patients. Metformin can lower insulin by more than 20 percent.

This is an exciting possibility, yet Dr. Irwin notes that she and others have previously shown that exercise and weight loss can lower insulin by similar amounts. In fact, exercise and weight loss can also decrease levels of several other inflammatory biomarkers associated with cancer, including C-reactive protein (CRP).

That's what Dr. Irwin found in a recently completed study named LEAN (Lifestyle, Exercise, and Nutrition). She recruited 100 overweight breast cancer survivors who, over the course of six months, were given 11 half-hour counseling sessions, in person or by phone, on exercise and weight loss. Dr. Irwin found that patients who lost just five percent of body weight decreased their CRP by 30 percent—which means that a 200-pound breast cancer survivor who loses 10 pounds can significantly improve her prognosis.

"We need data like that to convince the clinicians," she said, "because they're the gatekeepers and the ones patients listen to. If they say, you really need to start an exercise and weight management program and here's one that's free and evidence-based, the patients are far more likely to take action."

Beth Perkins said the LEAN study changed her life. She was overweight, didn't exercise, and paid little attention to her diet. She was unaware of the links between weight, inactivity, and breast cancer. Because of the counseling by LEAN's project director, Maura Harrigan, MS, RD, CSO, a research associate at Yale School of Public Health and a certified specialist in oncology nutrition, Ms. Perkins began reading labels, eliminating pizza and Chinese take-out, and eating more fish, chicken, and fresh vegetables. She also began exercising, at first with difficulty, but was soon walking up to five miles per day. She lost 25 pounds. The study ended in 2013 but she still does CrossFit training three times a week and has lost another 15 pounds. These lifestyle changes transformed her. "I have much more energy," Ms. Perkins explained, "and an all-around better feel-

We need data to convince the clinicians because they're the gatekeepers and the ones patients listen to. If they say, you really need to start an exercise and weight management program...the patients are far more likely to take action.

ing about myself—more of a drive to move forward instead of falling backwards." Best of all, she remains cancer-free.

Right now clinicians are more apt to prescribe a pill or therapy covered by insurance. But Dr. Irwin believes that once physicians accept that exercise and weight loss can help their cancer patients live longer, they will insist that patients get counseling about these behaviors. And once that happens, insurance companies will start covering the costs as they do for other conditions, such as giving diet counseling to diabetes patients and cardiac

rehab to heart disease patients.

That's why, in addition to her observational and etiological studies, Dr. Irwin is devoting time to disseminating information. She and Ms. Harrigan have developed a book about weight loss counseling that they hope to distribute nationally through cancer hospitals and foundations. "Many breast cancer survivors do want to exercise and lose weight but don't know how to go about it," said Dr. Irwin.

As an example she points to a study she recently completed on women with ovarian cancer. No screening test exists for this difficult cancer, so it's usually diagnosed at a late stage, and patients tend to need chemotherapy for the rest of their lives. The diagnosis and treatment often lead to anxiety, depression, and cancer-related fatigue. Dr. Irwin did a trial similar to the LEAN study in which ovarian cancer patients received weekly telephone calls for six months to get counseling about lifestyle changes and exercise.

"We are analyzing the results right now," Dr. Irwin explained, "but I can tell you anecdotally that we've seen strong effects on quality of life—on lowering depression and cancer-related fatigue."

What's needed next, she added, are large-scale randomized clinical trials. Those are expensive, so the government is hesitant to fund them. Drug companies aren't interested because there's no potential profit. In the meantime, Dr. Irwin and other researchers will continue to demonstrate that women who exercise and control their weight have a better chance of avoiding breast cancer, escaping its recurrence, and living longer. ☺



Novel Gene Identified in Tanning Dependence

Exp Dermatol. 2014 Jul 16.

Researchers led by the Yale School of Public Health have for the first time identified a gene that appears to be associated with tanning dependence.

An exome-wide association study was conducted among 292 people, 79 of whom exhibited symptoms of tanning dependence. Researchers examined approximately 319,000 rare and common genetic variants primarily within the protein coding regions and found that a variation in one gene—known as patched domain containing 2 (PTCHD2)—was significantly associated with tanning dependence.

While the precise function of PTCHD2 is unknown, its product is expressed mainly in the brain. People with one or more variants in PTCHD2 were about two thirds less likely to be classified as tanning dependent. Analogous to substance dependence, tanning dependence is defined by specific behaviors and symptoms, such as continued and frequent tanning despite adverse consequences.

Researchers Reveal Weakness in Defenses of Deadly Brain Tumor

Sci Signal. 2014 Aug 12.

Glioblastoma is a complex, deadly, and hard-to-treat brain cancer, but Yale researchers may have found the tumor's Achilles heel. The researchers discovered that targeting a protein crucial in the early development of the brain can block multiple signaling pathways implicated in glioblastoma growth. The approach also reduced human tumors in mouse models of the disease.

The new study shows that targeting this protein works in several ways. Inhibiting aPKC blocks a signal pathway that is the target of existing glioblastoma therapy. But it also blocks the action of some immune system cells called macrophages, which instead of attacking tumors, actively promote their growth.

Medicare-backed Breast Cancer Screenings Skyrocket, but do Patients Benefit?

J Natl Cancer Inst. 2014 Jul 16.

Breast cancer screening costs for Medicare patients skyrocketed between 2001 and 2009, but the increase did not lead to earlier detection of new breast cancer cases, according to a study published by Yale Cancer Center researchers. While the number of screening mammograms performed among Medicare patients remained stable during the same time period, the study focused on the adoption of newer imaging technologies in the Medicare population, such as digital mammography.

The research team explored trends in the cost of breast cancer screening. They identified the use of newer, more expensive approaches including digital mammography and computer aided detection, as well as the use of other treatment tools and subsequent procedures such as breast MRI and biopsy, between 2001-2002 and 2008-2009. They also assessed the change in breast cancer stage and incidence rates between the two time periods.

They found there was a large increase in the use of digital mammography technology, which is more expensive than standard film technology (\$115 vs. \$73 per mammogram) and has not been shown in clinical trials to be superior for women 65 years or older.

The team also found a considerable increase in the use of other newer, more expensive screening and related-adjunct technologies. As a result, Medicare spending for breast screening and related procedures increased from \$666 million (in 2001-2002) to \$962 million (2008-2009).

Sabotage as Therapy: Aiming Lupus Antibodies at Vulnerable Cancer Cells

Scientific Reports 4. Article No: 5958.

Yale Cancer Center researchers may have discovered a new way of harnessing lupus antibodies to sabotage cancer cells made vulnerable by deficient DNA repair. The study, led by James E. Hansen, MD, found that cancer cells with deficient DNA repair mechanisms were significantly more vulnerable to attack by lupus antibodies.

The genetic code that determines how a cell develops is written in DNA. Damage to this code can cause a cell to malfunction, die, or transform into a cancer cell. Normal cells are equipped to repair damaged DNA and preserve the genetic code, but many cancer cells have defective DNA repair machinery and accumulate genetic mutations.

This difference between normal cells and certain cancer cells creates an opportunity to develop therapies that damage DNA and only kill cancer cells that cannot repair the damage. However, DNA is sequestered inside cell nuclei, where delivery of therapies can be challenging. Yale Cancer Center researchers are finding that naturally occurring lupus antibodies just may be a solution to this problem. The researchers previously found that a lupus antibody called 3E10 inhibits DNA repair and sensitizes cancer cells to DNA damage, and they have now found that the DNA-damaging lupus antibody 5C6 is toxic to DNA repair-deficient cancer cells.

Defeating the Silencing of Tumor Suppressor Genes

One of the key features of tumors is that their rapid growth outstrips their blood supply, creating a low-oxygen environment known as hypoxia. In a fundamental finding of cancer biology, Yale Cancer Center researchers have recently shown that hypoxia triggers the silencing of tumor-suppressor genes and have identified a potential target to intervene in this process. Their work may open a therapeutic window for the development of new drugs to treat solid tumors.

About 20 years ago, Peter M. Glazer, MD, PhD, the Robert H. Hunter Professor and Chairman of Therapeutic Radiology, and Professor of Genetics at Yale, began studying hypoxia in earnest. He knew that the unusual tissue environment created by hypoxia profoundly changes the biology of cancer cells by stimulating blood vessel growth. He suspected that this challenging environment might also be one important

cause of the genetic instability that is the hallmark of cancer cells. He proved his theory in the lab, showing that cells growing in tumors have a higher rate of mutation than normal cells and that this is caused by hypoxia.

The next step was to discover the mechanism by which hypoxia causes genetic

instability. Dr. Glazer and his colleagues found that the DNA repair capability of cells is reduced when they are stressed by hypoxia. His group has spent the last decade teasing out the molecular steps by which this takes place. “One of the factors that contributes to tumor growth and progression – where tumors

become more malignant, metastasize and become resistant to therapy – is that many genes in the cancer genome are silenced long-term,” Dr. Glazer said. Many of the genes that appear to be turned off are tumor suppressor genes, which slow down or regulate cell growth or help maintain the integrity of

Peter M. Glazer, MD, PhD, the Robert H. Hunter Professor and Chairman of Therapeutic Radiology



PETER BAKER



the cell DNA. Dr. Glazer hypothesized that the hypoxic tumor environment might be one of the factors that stimulates the silencing of these genes.

In a study published in July in the journal *Cell Reports*, Dr. Glazer's group showed that hypoxia triggers the silencing of a critical tumor-suppressor gene known as MLH1 in colon cancer cells. They also found that lysine-specific demethylase (LSD1), one of the enzymes in cells that modifies the chromatin coating around the DNA, plays a role in this process. Chromatin protects and compacts DNA, much like the rubber coating wrapped around electrical wires. The study showed that when LSD1 is activated, the chromatin tightens, which leads to the silencing of MLH1. Because LSD1 is an enzyme, it is a potential target for drugs that may be used to inhibit it. "The first wave of chemicals that can inhibit enzymes like LSD1 have been synthesized, so that it's theoretically possible to develop a drug that could keep these tumor suppressor genes active or reactivate them," said Dr. Glazer, who has also found that BRCA1, another gene that plays a role in tumor suppression, is silenced by hypoxia.

Until now, Dr. Glazer's work has been in vitro, with cells grown in culture in the lab. The next step is to show that hypoxia turns off tumor suppressor genes in vivo in tumors growing in mice. His lab has developed a method of easily detecting when genes are silenced in cells in culture and is adapting it for tumors in vivo. He is also conducting genome-wide screening to individually knock out all the genes in the cancer genome in order to identify other factors that drive or maintain gene silencing. This could lead to additional therapeutic targets.

In the meantime, Dr. Glazer is beginning to translate his findings by testing existing small molecule chemical inhibitors of LSD1. He is planning on collaborating with the Yale Center for Molecular Discovery to either synthesize new molecules or identify better compounds that already exist. The finding that hypoxia leads to gene silencing means that it's probably one of the key factors in how cancers evolve and progress, so that they become more aggressive and resistant to chemotherapy and radiation therapy. While it may be just one of several ways tumor suppressor genes are silenced, it is a promising avenue that Yale scientists will continue to pursue. ☺



Closer to Free Ride Raises Over \$1.7 Million!

1. Robin Howell, RN with Diane Krause, MD.
2. Riders were welcomed with inspirational words from cancer survivor, Darriell Rolka.
3. Team Immune Brigade.
4. Dr. Thomas Lynch thanks our riders and volunteers for their dedication to Yale Cancer Center and Smilow Cancer Hospital.
5. Crossing the finish line!
6. Team MedOnc



Living with Hope: Breast Cancer Challenges a Family

When Heather Bruno learned that she had breast cancer, the news was devastating. She had no family history of the disease and her first mammogram was the one performed during the diagnostic process. As a single mom with three kids, she had things other than cancer on her mind, but that changed when she was diagnosed with stage IV breast cancer at the age of 42.

After feeling a lump in her left breast Heather made an appointment with her OBGYN who recommended having tests done in conjunction with the Smilow Cancer Hospital Cancer Care Center in Derby, CT. They performed a mammogram with ultrasound and did a biopsy. She left knowing in her heart that it was cancer. The biopsy confirmed this, and later she learned that it had metastasized to her bones. Since her cancer was widely spread, surgery was not an option and immediately she was put on hormone therapy. Her oncologist at the Care Center, Kevin R. Jain, MD, has been with her every step of the way.

"I cannot imagine going through this experience without him," Heather said. "The first day we met he told me we were going to become very good friends but I did not believe that was possible. Two years later I consider him, and the nurses at the Derby Care Center, more than friends, they are like family."

So far Heather has been on five different chemotherapy regimens. Most recently they discovered the cancer had metastasized to her liver and lungs, but she is not giving up hope. "I am amazed and in awe of Heather. She has found a balance between still living her life and remaining realistic. Taking the time to travel and be with her family is very important to her, and is not an easy task while combating advanced cancer," Dr. Jain said. "She truly is my hero."

Recently, Heather participated in Map-It, an initiative of Dr. Lajos Pusztai, Chief of Breast Medical Oncology at Smilow, for patients with metastatic breast cancer. Biopsies are analyzed through next-generation sequencing to look

for any mutations that can be targeted with FDA-approved drugs or investigational drugs. Three mutations were found in Heather's biopsy, but unfortunately one is not a therapeutic match for treatment, and one matched a therapy she had already tried. However, clinical trials are slated to start looking at the third mutation. For Heather, this is reason enough to hope.

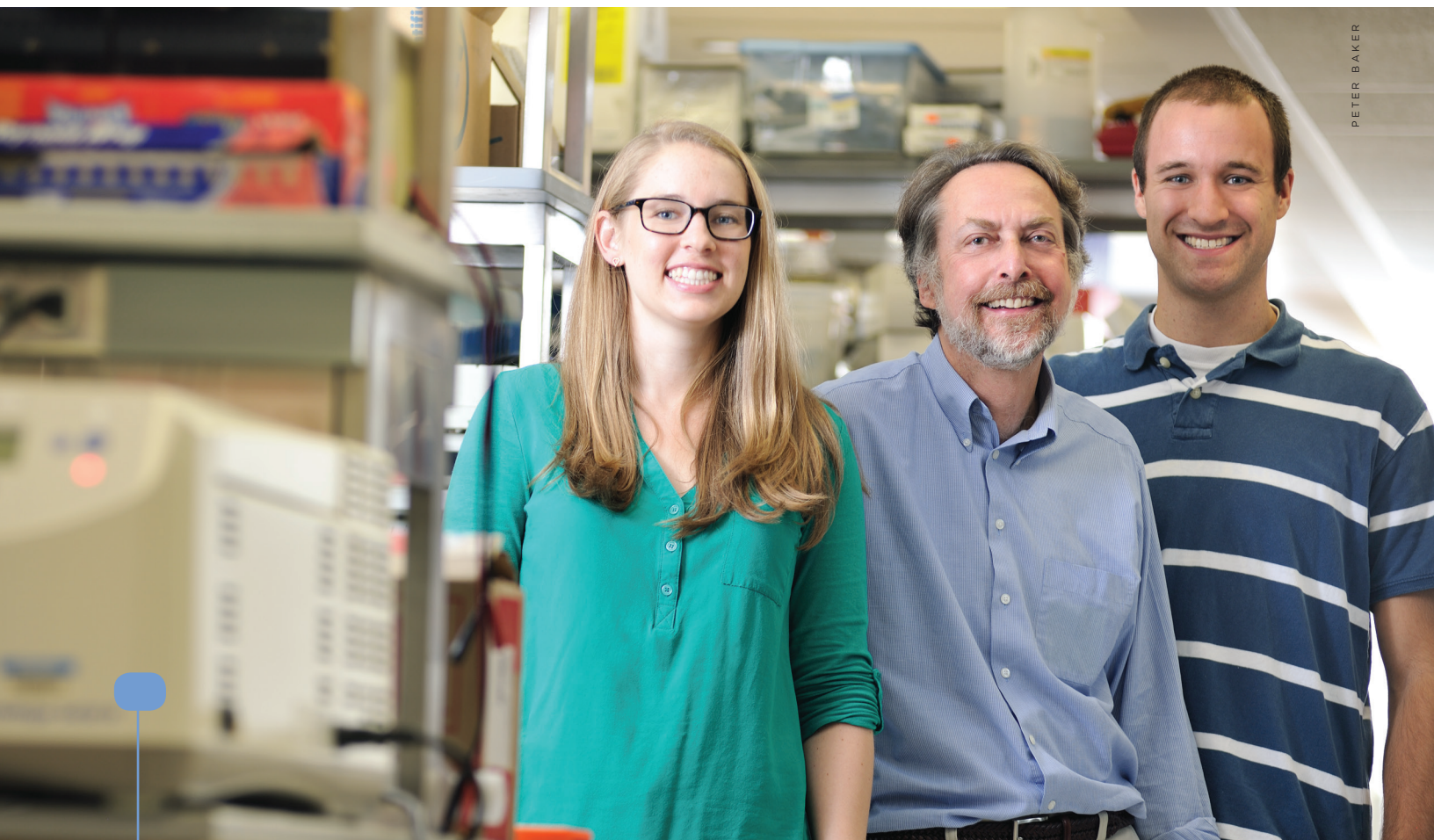
Heather commented that it does become discouraging - going through a treatment and experiencing the side effects, only to find out months later the cancer is still progressing. "I have to keep going," Heather said. "With every new treatment I hold out hope that this will be the one, because I will do whatever it takes to spend even one more day with my children."

Her son, 6 at the time, now 9, knows that his mom is sick. Heather said, "It is a common topic of conversation at our dinner table. It is a part of all of our lives." Treasured Time, Inc., an organization that orchestrates and plans moments for families battling life-threatening illnesses, gave Heather the opportunity to surprise her children with a trip to Disney World, something she would have never been able to do on her own. It gave them all a chance to be together and happy, memories they will always cherish.

There is no other place Heather would consider going to for care. The Smilow Cancer Care Center in Derby has brought her Smilow Cancer Hospital care and options closer to home. Feeling as though she is involved in and a part of her care was important, and she explained that Dr. Jain gives her the information needed to make decisions, and always has a plan of attack.

Through it all Heather has learned to live for today. Things that once seemed like inconveniences are now the best parts of her day. "Holidays are hard, and birthdays especially, but we have grown closer as a family. Some days I want to give up, but then I remember what I am fighting for," Heather said. "It is not an easy fight, nor is it fair, but it is one I am willing to battle." ☺





Training Tomorrow's Cancer Biologists

Molly Gale, David Stern, PhD, Professor of Pathology and Associate Director for Shared Resources at Yale Cancer Center, and Nathan Fons

While cancer research has led to significant advances in recent decades, there is still a pressing need to understand more about the fundamentals of cancer biology and to connect this information to new forms of treatment. Cancer research has identified a number of new therapeutic targets that drive the excessive growth of cancer cells. The ability to sequence tumor DNA and the huge amounts of data generated by new sequencing technologies have opened new opportunities for understanding the genetic makeup of each tumor, and the subsequent development of personalized treatments. “The overall challenge is to have analyses and therapies that will target cancer drivers for all cancers. This requires computational tools for deep analysis of tumors through

DNA sequencing and other methods, and the teamwork of cancer biologists working closely with cancer clinicians,” said David Stern, PhD, Professor of Pathology and Associate Director for Shared Resources at Yale Cancer Center. In response to this changing landscape, Yale Cancer Center is developing a new cancer-focused training program for PhD and postdoctoral students.

Training clinicians and scientists is one of Yale Cancer Center’s top priorities both in terms of its strategic vision and in its role as an NCI-designated Cancer Center. Yale is already educating cancer biologists through the Biological and Biomedical Sciences (BBS) program, an interdisciplinary doctoral program that spans the entire institution. The new Cancer Biology Training Program will build upon the foundation already offered by BBS. Academically, it will be similar to what is taking place – including a course on the cellular and molecular biology of cancer that has been offered for the past 20 years – but with the addition of expanded cancer-focused coursework and clinical components. “The new training components that we’re proposing will provide cancer PhD trainees with a real understanding of the practical issues seen in the clinic,” said Dr. Stern, who is slated to direct the new program.

Among the most novel aspects of the program are a Cancer Genetics/Clinical Translation Workshop and formal clinical mentorship by Yale Cancer Center clinicians. The workshop is a unique course that will deepen students’ clinical knowledge through coursework in

tumor resequencing, cancer pharmacology, and clinical practice topics, as well as attendance at some sessions of the Precision Medicine Tumor Board, which includes discussions between clinicians and biologists on the implications of tumor sequencing results.

“It’s a great context for PhD trainees to learn from on-the-ground examples of real-world tumor DNA sequencing,” Dr. Stern explained. “It gets them thinking about some of the practical challenges faced by clinicians in the context of real clinical discussions.”

The expertise provided by clinical oncologists will add depth to the program to better educate scientists, with results that may potentially find their way back to the clinic. For example, patients treated for lung cancer at Smilow Cancer Hospital have their tumors screened for two types of DNA mutations for which there is already an FDA-approved drug. However, only a small subset of lung cancer tumors have these mutations. At the same time, there is a great amount of DNA sequencing data available to researchers that may point to potential therapeutic targets for which drugs have not yet been developed. Collaboration between clinicians and scientists will foster the development of an understanding of tumor sequencing data that will ultimately benefit patients.

“It’s a great context for PhD trainees to learn from on-the-ground examples of real-world tumor DNA sequencing.”



Yale Cancer Center is currently applying for NIH funding and seeking private funds to formally establish and expand the program. In the meantime, in recent years, the Cancer Center has contributed funding to support cancer-focused doctoral and postdoctoral graduate students through the Yale Cancer Center

predoctoral fellowship training program and through the Leslie H. Warner postdoctoral fellowship program. One awardee, Nathan Fons, is a second-year PhD student. Nathan enthusiastically decided on cancer research after rotating through the lab of Ranjit Bindra, MD, PhD.

“It’s great that Yale has a focus for wanting to be a cancer biologist, instead of just molecular biology,” said Molly Gale, a third-year PhD student who was awarded a fellowship from the National Science Foundation. She noted that scientists in the Pathology Department, where she conducts her research, are in close contact with Yale Cancer Center clinicians and that students benefit by going to Yale Cancer Center Grand Rounds and talks in which oncologists discuss therapeutic approaches and investigators present their research findings. “It’s a cool place where the medical side and the research side are combining,” she said. “It’s great to learn firsthand how treatments are used and not just get it from the lab.”



PETER BAKER

New Surgical Guidelines for Early-Stage Breast Cancer

For more than 25 years, lumpectomy combined with radiation, also known as breast-conservation therapy, has been utilized as an alternative to mastectomy as a standard treatment choice for early-stage breast cancer. When surgeons remove a tumor during lumpectomy, they also remove a small amount of tissue surrounding it. However, the desirable width of this cancer-free margin has been a source of debate, which has led to high rates of second surgeries needed to remove larger margins of tissue.

“The problem is that though we have the long-term data establishing that breast-conservation therapy works, it was variable as to how those original trials defined a negative margin,” said Meena S. Moran, MD, Associate Professor

Meena S. Moran, MD
Associate Professor
of Therapeutic Radiology

of Therapeutic Radiology, who has also held several national roles with the American Society for Radiation Oncology (ASTRO) over the last decade.

Thanks to the efforts of a multidisciplinary panel led by Dr. Moran and Monica Morrow, MD, Chief of Breast Surgery at Memorial Sloan Kettering Cancer Center, there are now consensus guidelines on margins in breast cancer surgery that are likely to reduce unnecessary re-excision for many patients. The panel’s recommendations were

published by ASTRO and the Society of Surgical Oncology (SSO). In spearheading this initiative, Dr. Moran reasoned that “unless we have some kind of a statement that’s backed by national organizations, practicing physicians are still going to routinely take their patient back for a re-excision because there is no guideline or recommendation to support not taking them back for narrow margin widths.” The consensus guidelines were made possible by a research grant from the Susan G. Komen Foundation with significant administrative support from SSO.

Lumpectomy is performed in 60 to 75 percent of new breast cancer cases in the United States. When the tumor and surrounding tissue is removed, the surgeon or pathologist douses the outer part of it in ink. By examining thin slices of the tissue under a microscope, the pathologist can measure the distance between the ink, which is the edge of the specimen that the surgeon cuts, and where the cancer cells are. Positive margins mean that cancer cells extend to the edge of the tissue, where the ink is, while negative margins mean that no cancer cells can be found in the ink.

Until now, anywhere from 23-50 percent of women undergoing this surgery are reported to have also undergone re-excision in order to obtain wider negative margins, with the notion that there is less risk the cancer will recur. However, studies do not support the benefits of this practice. There are also several downfalls associated with additional surgery, including risk of complications and infection, increased stress for the patient, poorer cosmetic outcome, higher conversion to mastectomy rates and increasing healthcare costs.

The scientific basis of the new guidelines are based on a meta-analysis of data from 33 studies published between 1965 and 2013 that included more than 28,000 patients with early-stage breast cancer who were treated with breast-conservation therapy. The recommendations delineate how wide the negative margins should be and how this affects the risk of a recurring cancer in the

same breast. The consensus panel of breast experts also outlined how factors such as biological characteristics of the tumor, the patient’s age, and additional therapies (for example hormonal therapy, radiation therapy and chemotherapy) should be considered in conjunction with margin widths when deciding whether or not to recommend further surgery. In the case of positive margins or if ductal carcinoma in situ (DCIS) is associated with an invasive tumor, the guidelines note that the risk of recurrence in the same breast is double or more. But when the tumor cells are away from the ink (i.e. no ink on tumor), the panel did not find any value in increasing the margin width to 1mm, or 2mm, or 5mm. Dr. Moran noted that separate guidelines pertaining to DCIS will be released in the near future.

She stressed that the guidelines are intended to diminish unnecessary re-excisions. That is not to say that re-excisions are never indicated. If a surgeon does recommend a second surgery, there should be a discussion between the patient and physician as to why it is indicated and should be weighed in the context of the risks and benefits of additional surgery. At the same time, pathologists should continue quantifying margins, so that clinicians can use this information to inform their recommendations. “Hopefully, we have provided some rationale to support not routinely taking back patients for re-excision,” said Dr. Moran, adding that the guidelines are already being widely adopted by surgeons and radiation oncologists. ☺



PETER BAKER

Q+A

meet the physician

Patricia M. LoRusso, DO

Associate Director of Innovative Medicine

The Associate Director of Innovative Medicine is a new role. What does the position mean to you?

First I would like to say how excited I am to be part of the Smilow Cancer Hospital family and to join Dr. Paul Eder as we continue to build the Phase I clinical trials program. The amount of energy and passion that emanates from the Smilow team is contagious. The Associate Director of Innovative Medicine role is one that I feel fits well with my goals. My long-standing area of expertise is in translational medicine and early therapeutics, and bringing this skillset and embracing the Smilow community with a robust Phase I program is a natural extension for me. Most important, I look at this new position as much more than a title, but as an exciting challenge. Yale has many gifted scientists and I will know I am succeeding when we enhance the integration of the clinical and scientific communities to bring forward novel therapies to make a difference for our patients.

When did you decide to narrow your clinical focus on Phase I trials? Why?

I studied oncology because I wanted to find drugs to treat cancer. In my youth, I was personally touched by this disease and came to know of it as an “enemy” that I wanted

to fight. I had a dream of finding a drug to cure the disease. Obviously that “one drug” dream was unrealistic. However, I was fortunate early in my career to work with a mentor that focused exclusively on preclinical drug development. That experience launched my career as a medical oncologist in the Phase I arena. It was actually a childhood dream come true!

What are the targets of the SU2C Melanoma-MRA Dream Team?

The Stand Up to Cancer (SU2C) – Melanoma Research Alliance Dream Team is a team I co-lead with Jeffrey Trent, PhD. The overall focus is to utilize a personalized medicine approach to treat metastatic non-V600 malignant melanoma. Aside from immunotherapy, there are no effective therapeutic options available for patients. We are evaluating the genetics of the tumor and trying to identify the best drug(s) available to treat our patients that will match the tumor profile. We have assembled a world-class team of investigators and, in collaboration with several pharmaceutical companies who are supplying targeted agents, we are working together to make a difference not only in the treatment, but also in the basic biologic understanding of melanoma.

What Phase I trials do you plan to open at Smilow?

The primary focus of the Phase I trial portfolio at Smilow has been on novel immunotherapeutic agents. My area of focus has primarily been on small molecule and monoclonal antibody targeted agents. One of the attractions for me joining Smilow was their tumor profiling capabilities, which have become a necessary tool for early drug development. I believe these capabilities will enhance our ability to grow our novel drug portfolio and bring a rapid expansion of treatments available to patients in the Smilow community. My hope is that, over the next several months, our patients will have access to a much broader portfolio of novel therapeutics that will hopefully lead to a positive outcome in both quality of life and survival.

Kerin Adelson, MD

Kerin Adelson, MD joined Smilow Cancer Hospital as Chief Quality Officer earlier this year. In this new role, Dr. Adelson is charged with overseeing the patient safety and quality initiatives at Smilow Cancer Hospital and at our 10 Care Centers; advancing clinical informatics, including EPIC and Care Pathways; and developing a robust research program in quality cancer care.

Dr. Adelson is a medical oncologist specializing in breast cancer and formerly practiced at Mount Sinai, where she was the Director of Ambulatory Quality for the Mount Sinai Cancer Network. She is a graduate of the University of California and received her Medical Degree from Yale School of Medicine. Dr. Adelson completed her residency and internship at Mount Sinai and a fellowship in Clinical Quality at the Greater New York Hospital Association.



Amy Davidoff, PhD

Amy Davidoff, PhD recently joined the Yale School of Public Health as a senior research scientist in the Department of Health Policy and Management. Dr. Davidoff is a health economist and health services researcher. In the past several years she has applied this research to individuals with cancer and their treatment, with specific expertise in lung, colorectal, and hematologic malignancies.

Dr. Davidoff's recent research efforts have examined the relationship between supplemental insurance in the Medicare population and the economic burden of cancer, and how Medicare coverage influences access to oral and parenteral chemotherapy and supportive care medications. Ongoing research focuses on reimbursement policy, as well as early evaluation of the impact of the Affordable Care Act on cancer survivors. At Yale, she is also affiliated with the Yale Cancer Outcomes, Public Policy, and Effectiveness Research (COPPER) Center and Yale Cancer Center's Cancer Prevention and Control Program.



Saral Mehra, MD, MBA

Saral Mehra, MD completed an advanced fellowship in Head and Neck and Thyroid Cancer at Beth Israel Medical Center with a special emphasis on reconstructive surgery including the use of free tissue transfer through state-of-the-art microvascular surgical techniques before joining Yale School of Medicine's Department of Surgery earlier this year.

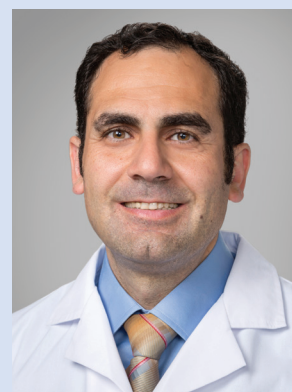
Dr. Mehra is an Assistant Professor of Surgery (Otolaryngology) and a member of Smilow Cancer Hospital's Head and Neck Cancer Program. His clinical practice focuses on treating patients with head and neck and thyroid diseases, particularly cancer, including advanced reconstruction and rehabilitation. While trained in treating advanced and recurrent cancers, he also has special training in minimally invasive techniques such as salivary endoscopy for salivary stones and salivary gland diseases, laser surgery, and robotic surgery.



Amer Zeidan, MBBS, MHS

Amer Zeidan, MBBS, MHS, has been appointed Assistant Professor of Medicine (Hematology) at Yale Cancer Center. Dr. Zeidan completed a hematology/oncology fellowship and a clinical research fellowship in myelodysplastic syndromes at Johns Hopkins University where he also earned a Master of Health Science (MHS) degree in Clinical Investigation. Dr. Zeidan received his MBBS degree from the Faculty of Medicine, University of Jordan, Amman, Jordan.

Dr. Zeidan's clinical interest is in the management of hematologic malignancies. The focus of his clinical/translational research is the development of novel therapies for myelodysplastic syndromes and myeloid hematologic malignancies. In addition, Dr. Zeidan also has an interest in effectiveness and outcomes research in hematologic malignancies and will be working with the Yale Cancer Outcomes, Public Policy, and Effectiveness Research (COPPER) Center.



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