

centerpoint

Yale Cancer Center's community newsletter summer 2010

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



Pat Colucci-Coritt with her daughters, Lauren and Elizabeth.

Shedding Light on Sleep and Cancer

Yong Zhu points to the florescent fixture above his desk. "That completely changed our lifestyle," said Zhu, who is the co-Director of Cancer Prevention and Control Research Program at Yale Cancer Center and an Associate Professor of Epidemiology and Public Health. For most of human evolution, we woke up with the sun and slept at night. With the invention of the electric light, we could ignore the schedules our bodies have evolved to observe.

There were unintended consequences to burning the midnight oil. In the early 2000s, several studies established links between working the nightshift and some cancers. The strongest relationship was with breast cancer. In 2007, the World Health Organization named shift work as a probable carcinogen.

But this research could not tell us why shift workers had higher rates of cancer. Animal studies showed a link between malfunctions in circadian genes, the genes that regulate sleep cycles, and some cancers. Research findings in animals, however, often fail to translate to humans.

Zhu's research provides a critical missing piece to the puzzle. "Our work makes a link between the gene and the human cancer," explained Zhu. His group looked at all nine human core circadian genes in healthy volunteers and cancer patients. He found alterations in six of those genes were associated with breast cancer. He also determined eight circadian genes were associated with prostate cancer, and another four with non-

A Second Opinion Creates a Second Chance

When Pat Colucci-Coritt met with Dr. Clarence Sasaki, Chairman and Charles W. Ohse Professor of Otolaryngology at Yale, for a second opinion after being diagnosed with squamous cell carcinoma of the tonsil, she was shocked to learn that the cancer had extended to her tongue. She had not been aware of this previously, and was now faced with processing the news that her cancer had spread.

Pat had a surgical procedure known as a lymph node dissection performed in order to remove lymph nodes from the side of her neck where cancer cells may have migrated. She spent one night in the hospital following her surgery. She also underwent 28 subsequent radiation treatments under the care of Dr. Yung Son, Professor of Therapeutic Radiology at Yale, using brachytherapy. Brachytherapy is a technique that allows for the implantation of small radioactive seeds into or in close proximity to a tumor, which can provide radiation to tumors in a very specific and controlled fashion; in total 74 seeds were implanted in her tongue and throat.

As a psychologist, Pat's voice is important for communicating with her patients. Thanks to the carefully

planned and specific radiation treatment she received, her vocal chords were spared any damage from the treatment. Pat continued to see her patients throughout her treatment, even though her doctors forewarned her that there was a chance she may not be able to continue.

The day that Pat was scheduled for her lymph node dissection surgery, was the same day that her oldest daughter started high school. She explained that her diagnosis was a very difficult time for the entire family, but that her two teenage daughters played an important role in her recovery. She relayed any pertinent information regarding her treatment to them and the few times they came with her for treatment, Pat said Dr. Son explained everything in a way so that they could understand and wouldn't be frightened. For Pat his interaction with her children was a gift, as it was one less thing she had to worry about.

"I wanted to keep my life as normal as possible, and the team at Yale was amazing in enabling me to do just that. It was important to me to continue to participate fully in my girls' lives. I wanted to maintain the same level of involvement that I've always had. I

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Gifts that Change Lives

Everyone is touched by cancer in some way and there are many opportunities at Yale Cancer Center to help patients and families who will face a diagnosis of cancer. Each gift touches a life by funding innovative research, new treatments, and important patient services. Donors may never know the people that benefit from their philanthropy, but their generosity has a profound impact on the lives of so many. Without the support provided by people wishing to make a difference, cancer research and care would not be nearly as advanced as it is today. Your gift enables us to continue to make critical advances tomorrow.

Many donors choose to make a gift each year to Yale Cancer Center to honor friends and loved ones who have faced cancer. We encourage you to consider this as part of your philanthropy, possibly at a birthday, anniversary, or other important time.

Please use the enclosed envelope to make a gift to Yale Cancer Center. Remember, no gift is too small and each gift makes a difference.

If you have any questions, please call (203) 436-8527.

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Newly Available Clinical Trials from YCC

A Phase I Study of IPI-926 in Patients with Advanced and/or Metastatic Solid Tumor Malignancies

Principal Investigator: Scott Gettinger, MD

This trial will assess the success of targeting the Hedgehog (Hh) signaling pathway with IPI-926, an oral small molecule inhibitor of the Hh pathway. Evidence for elevated Hh pathway expression has been observed in several types of cancer, including basal cell carcinoma (BCC). It is believed that the Hh pathway is crucial for maintenance of the highly drug resistant cancer cell subpopulation that drives tumor growth and metastases, often referred to as 'cancer stem cells.' Two groups of patients are of particular interest: those with advanced BCC who have not been previously treated with a Hh inhibitor, and those with chondrosarcoma that can not be treated curatively. A handful of patients with other advanced solid tumors for which no standard options remain will also be enrolled.

For more information, please contact (203) 785-5702.

▶ **A Second Opinion** continued from page 1

didn't want to miss an open house at school, a band competition, or a dance recital," Pat said. "My doctors also knew it was important to me that I keep working and instead of discouraging me, they encouraged me. I was able to maintain my goal to continue working and did not miss any of my children's activities."

According to Pat, the most impressive part of her care was the multidisciplinary approach with which the team worked and how, together, they made decisions and coordinated her care. She described their partnership as comforting to her, and helped her feel confident in the treatment she was receiving; she knew that every treatment appointment was a step toward a cure.

"Going through this experience there are times when you question whether you are going to die, and whether or not you can beat cancer. What helped me get through the tough days were my family and friends. The support they provided me was unbelievable. The knowledge that people love and care for you is precious, and the treatment team at Yale was amazing."

Radiation treatment was the most challenging process for Pat because it burned her throat and tongue. While going through her radiation treatments, she met with Dr. Son weekly. She described him as very honest, caring, and warm. He encouraged her to 'live life' while undergoing treatment. "Dr. Son is a very special person, and his nurse, Dee, was always available, kind, and supportive, as were the radiation

An Open-label, Multi-center, non-Randomized Phase Ib Study to Investigate the Safety, Efficacy, and Pharmacokinetics of BAY 73-4506 "Regorafenib," Administered in Combination with Pemetrexed and Cisplatin in Patients with Advanced Nonsquamous Non-Small Cell Lung Cancer

Principal Investigator: Scott Gettinger, MD

Regorafenib (BAY 73-4506) is an oral multi-kinase inhibitor that targets angiogenic, stromal, and oncogenic receptor tyrosine kinases (TK). Regorafenib has been shown in preclinical studies to prevent the proliferation of tumor cell lines while promoting cell death. This trial will combine Regorafenib with Pemetrexed and Cisplatin in patients with advanced nonsquamous non-small cell lung cancer (NSCLC) to determine the safety and efficacy of Regorafenib in this patient population.

For more information, please contact (203) 785-5702.

technicians and support staff," Pat commented.

Having always taken care of others in her life, Pat found it challenging to accept help from friends and family. She eventually learned to let people help her, and that their involvement was their way of coping as well. Although she could drive herself, Pat allowed family and friends to drive her to and from appointments, and let them cook meals for her. She had counseled people not to 'sweat the small stuff' before, but never really knew what it meant to her personally until her treatment began. She realized that she needed to follow her own advice.

Shelley Jolie, RN, BSN, Nurse Coordinator for the Head and Neck Cancer Program was Pat's first contact at Yale. For Pat, Shelly was reassuring from the first phone call and continued to reassure her and boost her confidence whenever she needed. "My care team was treating my cancer, but in the process they were also giving me the strength I needed to beat this," Pat explained.

"One of the best decisions I've made in my life was going to Yale," Pat said. "They have an amazing team and there is a confidence and assurance that you feel as soon as you walk in the door that you just don't find anywhere else. Each medical breakthrough made at Yale helps patients like me have a second chance at living a healthy life. In combination with the high level of quality care provided at Yale, this disease doesn't stand a chance for much longer." ☺

Distinguished Immunobiologist Lieping Chen Joins Yale Cancer Center

Yale Cancer Center Director, Dr. Thomas J. Lynch, Jr., has appointed Lieping Chen, MD, PhD as Director of Cancer Immunology at the Center. Dr. Chen is an internationally known expert in cancer immunobiology. His laboratory work is focused on the understanding of molecular, biochemical, and structural aspects of cell surface molecule pathways and their functions in the control of innate and adaptive immunity and subsequent development of cancer.

"Lieping's appointment at Yale Cancer Center will ensure Yale continues as a leader in cancer immunobiology, not only in our basic science laboratories but in our clinics as well. His commitment to translating basic discoveries from the lab to develop new strategies to treat cancer using novel biologics in clinical trials will benefit patients at Smilow Cancer Hospital and throughout the world," Lynch said.

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JERRY DOMIAN

Lieping Chen, PhD, Director of Cancer Immunology.

Dr. Howard S. Hochster Welcomed to Yale Cancer Center

Howard S. Hochster, MD has been appointed Professor of Medicine in medical oncology, Medical Director of Gastrointestinal Oncology, and Associate Director of Clinical Research at Yale Cancer Center. Dr. Hochster joined Yale Cancer Center and Smilow Cancer Hospital at Yale-New Haven from New York University School of Medicine and the NYU Cancer Institute.

"Dr. Hochster's clinical and leadership experience and national reputation in gastrointestinal oncology will greatly benefit patients at Smilow Cancer Hospital. In addition to his clinical responsibilities, I am grateful to have his expertise in the role of Associate Director of Clinical Research as we continue to increase clinical trial opportunities for our patients," said Dr. Thomas J. Lynch, Jr., Director of Yale Cancer Center and Physician-in-Chief of Smilow Cancer Hospital at Yale-New Haven.

Dr. Hochster concentrates his clinical research on the study of new treatments, and combinations of therapies, for patients with advanced and relapsed colorectal cancer. He is a leader in translational research in development of targeted agents for GI cancers and expects to continue and expand this work at Yale Cancer Center. He has led national, pivotal clinical trials in the use of Bevacizumab and Cetuximab

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Howard S. Hochster, MD, Professor of Medicine in medical oncology, Medical Director of Gastrointestinal Oncology, and Associate Director of Clinical Research.

Yale CANCER CENTER answers

A Weekly Radio Program on WNPR – Connecticut Public Radio

Sunday Evenings at 6:00 PM

July 4, 2010

Ellen Matloff, MS

Understanding Your Cancer Risk

July 11, 2010

Hari Deshpande, MD and Clarence Sasaki, MD

Coping with Head and Neck Malignancies

July 18, 2010

Nina Kadan-Lottick, MD

HEROS: Pediatric Cancer Survivorship

July 25, 2010

Jill Lacy, MD

Treatment Strategies for Gastric Cancers

August 1, 2010

Susan Higgins, MD

Radiation Therapy for Gynecologic Cancers

August 8, 2010

Frank Slack, PhD and Joanne Weidhaas, MD, PhD

Cancer Genomics

August 15, 2010

Melinda Irwin, PhD

The Impact of Exercise on Cancer

August 22, 2010

Lawrence Solomon, MD and Leslie Blatt, APRN

Palliative Care for Cancer Patients

August 29, 2010

Raymond Russell, MD, PhD and Kerry Russell, MD, PhD

Cardiothoracic Chemotoxicities

For the latest schedule information and audio and written archives of all shows, please go to yalecancercenter.org/answers

► Dr. Lieping Chen continued from page 3

Throughout his career, Dr. Chen has played a leading role in the discovery and characterization of costimulatory molecules in the B7-CD28 and the TNF receptor/ligand superfamilies. His laboratory has made seminal contributions to the development of cancer therapeutic monoclonal antibodies against CD137, PD-1, and B7-H1, which are currently in clinical trials.

Prior to his appointment at Yale Cancer Center, Dr. Chen was a Professor of Oncology and Dermatology, Director of Research for the department of Dermatology, and Investigator in the Immunobiology Program at Johns Hopkins University School of Medicine.

Dr. Chen received his Medical Degree from Fujian Medical College in Fuzhou City, China and completed his internship and residency training in Medicine at Fujian Union Hospital and Beijing Union Medical College and followed with his PhD from Drexel University in Philadelphia, Pennsylvania. After a postdoctoral fellowship at University of Washington-Seattle, Dr. Chen spent seven years in research and development in Oncology Drug Discovery at the Bristol-Myers Squibb Pharmaceutical Research Institute in Seattle, Washington and six years in research and education at the Mayo Clinic in Rochester, Minnesota before joining Johns Hopkins.

Dr. Chen has published more than 250 scientific papers, review articles, and book chapters, and has edited two books. He has delivered more than 150 seminars and invited lectures and has served on many committees and advisory boards for the United States Government. He is a member of the American Association of Immunologists, American Association for Cancer Research, Federation of Clinical Immunology Societies, and the International Society for Biological Therapy of Cancer. Dr. Chen is also a co-founder of the Amplimmune Biotechnology Company based in Bethesda, Maryland. ♻️

Healing Garden Provides a Place to Reflect



For patients needing a quiet place and some fresh air, the Healing Garden on the 7th floor of Smilow Cancer Hospital at Yale-New Haven offers a perfect respite. Surrounded by trees, grass, and the sound of water, patients have a place to go to forget they are in a hospital, often times receiving aggressive treatments for their disease.

Recently enjoying a break in the garden, Tony and his wife, Heidi, explained that they had tried visiting the garden once before, when it was still under construction. They said it was worth the wait and are amazed at how beautiful the location is. Tony is receiving radiation therapy in the lower level of Smilow. "I wanted to be sure to take everything in as we walked along the path. I have just started to feel better and can enjoy things more now. It's a peaceful place where my wife and I can spend time together," Tony explained.

With water flowing through the middle of the garden, patients can listen to running water while sitting on one



of the many beautifully crafted wooden benches that are placed along the outline of the path. The entire garden is lighted for nighttime use, and provides an unobstructed view of the New Haven skyline. It is easily accessible for staff to bring patients that are unable to visit the garden themselves, but want to enjoy the open space.

This unique garden was made possible largely by donations from individuals and corporations. Benches, trees, and even a sun shade trellis were supported through the fundraising campaign for use in the garden. Tony commented that the connotation of the garden as 'healing' has a real significance to him as he himself is in the healing process and is beginning to feel stronger; it means a lot to him to see all the generous donations people made.

Donna Cochrane and her friend discovered the Healing Garden at the suggestion of her husband's nurse. They use it as a place to meditate and pray while Donna's husband is in the ICU at Yale-New Haven Hospital after suffering injuries from a fall. "It's a beautiful spot at a time when I need some beauty in my life," Donna said. "The sound of the water is so soothing, and I am able to forget about where I am for awhile."

The Healing Garden at Smilow Cancer Hospital at Yale-New Haven is more than beautiful benches, trees, and flowers. It provides a space where, if only for a brief moment, patients, spouses, and family members can feel like they are somewhere else, away from treatments and exam rooms, and enjoy a rare moment of peace. ☺



ALL PHOTOS THIS PAGE BY PETER BAKER

Cancer Boutique Open at Smilow

This spring the Boutique at Smilow Cancer Hospital at Yale-New Haven opened as a new resource for cancer patients to find a helping hand moving forward. The boutique makes life easier for patients facing a diagnosis of cancer, and the side effects of treatment, by giving them a convenient place to find items such as breast prostheses, canes, scarves, fashion advice, and educational information.

Located on the first floor of Smilow Cancer Hospital at Yale-New Haven, the boutique is designed to be an open and welcoming spot where patients can feel comfortable no matter what stage of treatment they are in. Linda Secher was asked to come on as a consultant during the planning phase of the boutique, and she remains the driving force behind the boutique.

Bonnie Indeck, Director of Patient and Family Services at Yale Cancer Center, is one of the many people responsible for referring patients to the boutique. She commented that for patients, feeling confident in their appearance is an important step in the cancer journey and that the new boutique allows them to do just that.

During her career, Linda has opened 24 cancer boutiques, or 'appearance centers,' across the country, including at Dana-Farber Cancer Institute and UCLA's Jonsson Comprehensive Cancer Center, and so she knows what it takes to make a cancer boutique work for patients. In addition to treatment-related items, such as for women undergoing breast surgery and wigs, the boutique also carries gift items, including slippers, purses, and hats.

"What this boutique does for Smilow is make it a truly comprehensive hospital. In addition to providing patients with top medical care, the

resources available in this boutique ensure that the whole body is being cared for," Linda explained. "Being a part of this boutique is very rewarding for me personally as well. If I can help take a little stress away from someone undergoing cancer treatment, then I know I have done a good job."

Lymphedema, an abnormal buildup of fluid that causes swelling most often in the arms or legs is a side effect that can occur after treatment for breast cancer. The boutique offers products such as 'lymphedema sleeves' to help manage these symptoms. For patients losing their hair during treatment, they can receive a free 'buzz cut' as well.

"This boutique is one-stop-shopping for patients and supplies them with many of the things they will need to begin down the road of recovery. From sun-protective



clothing to motivational items, patients have access to products that will encourage them to feel good about themselves," Bonnie said.

The boutique is certified to do fittings for breast prostheses and can assist with billing insurance companies for their services and products. Bathing suit prostheses are also available. The boutique is open Monday-Friday, and Saturday by appointment. "We will try to accommodate our patient's needs and be flexible over the coming months," Linda said. The boutique is open to all patients in the region, not just those being treated at Smilow Cancer Hospital. ☺

in colorectal cancer, and maintenance Rituximab for the treatment of low-grade lymphoma.

Previously, Dr. Hochster was Professor of Medicine at New York University School of Medicine in the divisions of Medical Oncology and Clinical Pharmacology and Director of the Gastrointestinal Cancer Program at the NYU Cancer Institute. He has also served as the Principal Investigator for the Eastern Cooperative Oncology Group at NYU for the last 16 years.

Dr. Hochster is a fellow of the American College of Physicians and a member of the American Society for Internal Medicine, American Society for Clinical Oncology (ASCO), and American Association for Cancer Research. In addition, Dr. Hochster serves as the associate editor for the journal, *Gastrointestinal Oncology*, and on the editorial board of *Current Colorectal Cancer Reports*.

Dr. Hochster graduated from the Yale College with BS and MS degrees in chemistry and received his Medical Degree from Yale School of Medicine. He completed his residency in internal medicine at New York University – Bellevue Hospital and his fellowship in medical oncology and hematology at New York University Medical Center. He was subsequently awarded a Fulbright Fellowship and worked at the Jules Bordet Cancer Institute in Brussels, Belgium to study clinical pharmacology and early clinical drug development. ☺



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Hodgkin's lymphoma. Breast and prostate cancer are both affected by hormones; therefore Zhu suspects the circadian genes regulate hormones.

Zhu has proven there is a genetic susceptibility to some cancers through irregular circadian genes. But earlier studies tell us all shift workers are at risk for some of these same cancers. So what is to blame -- heredity or environment? Both, Zhu believes. "The interaction between genetics and lifestyle probably plays the most important role," he said.

Proposed role of the circadian clock in tumorigenesis is illustrated in Figure 1.

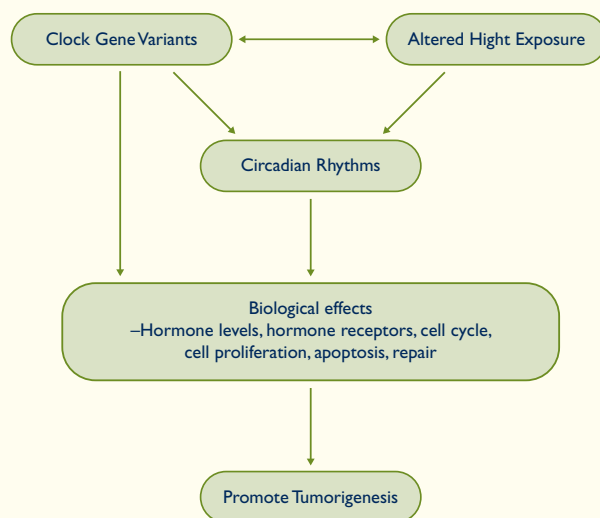


Figure 1

The irregularities Zhu found associated with cancers were both genetic and epigenetic. In other words, some of the alterations were irregularities in the DNA, irregularities that are present at birth. Epigenetic changes, however, affect the way a cell functions without changing the structure of its DNA. Epigenetic changes may result from environmental exposures.

Zhu is looking at large population samples to find out if shift work conclusively causes epigenetic changes. He's often crunching his data until 1 a.m., under that florescent light. For the purpose of his research, however, that's not considered shift work. He's looking at a large group of volunteers in Denmark who work the overnight shift.

Meanwhile, he's continuing laboratory research to examine exactly what's happening on a cellular level when altered circadian genes lead to the development of cancers. A clear understanding of the process will give medicine a chance to interrupt it -- to engineer drugs that would be especially effective combating cancers associated with particular genes.

Shakespeare wrote about "sleep that knits up the raveled sleeve of care." Zhu explains that circadian genes do knit up imperfections. They play a role in cellular

repair functions. When these functions are working well, the body repairs faulty DNA or induces defective cells to die. The sleep-cancer connection may occur because that repair function is disrupted, leaving malignancies free to develop.

There are immediate practical uses for Zhu's research. For example, someone carrying one of the circadian gene alterations associated with increased risk might choose a profession where daytime schedules are common.

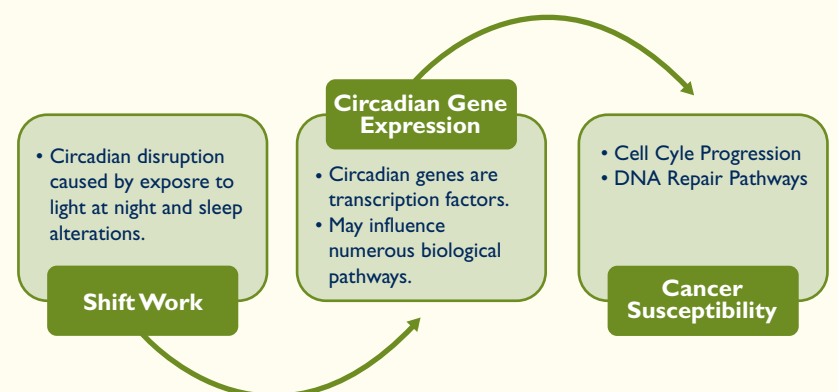
That is increasingly difficult, however. Night hours were once associated with specific careers, such as health-care, factory work, and some service industries. But according to the U.S. Bureau of Labor Statistics, more jobs are becoming night jobs. Globalism is creating a need for more white-collar workers to abandon their 9-to-5 schedules to interact with distant colleagues.

Zhu also found that alterations in certain circadian genes predict a patient's risk of recurrence. This could be helpful information for patients and their oncologists when deciding how aggressively a cancer should be treated, he explained.

Zhu has begun publishing his landmark findings. Earlier this year, the press picked up on his discovery that alterations in the so-called CLOCK gene put women at higher risk for breast cancer. The effect was especially strong in women with estrogen- or progesterone-receptor negative tumors, which are typically aggressive.

"I began getting emails from all over the world," Zhu said. Many were from women who worked night shifts and had been diagnosed with cancer. One came from a woman who works in a dark room and wondered whether her dim quarters put her at risk.

Zhu thinks that's a good question and hopes to look at light exposure in future research. He was attracted to this work because of the enormous number of good



questions it presents. Most circadian genes were discovered only within the past 10-20 years. Furthermore, the tools to analyze their actions on a molecular level continue to evolve. That provides tremendous promise to investigate circadian genes and by understanding them to devise better treatments and even prevention strategies for common cancers. "We've got a lot of work to do," Zhu commented. ☺