Melanoma Up Close

IN THIS ISSUE
Gene studies reveal new melanoma treatment targets
Clinical trials offer new hope
A Comprehensive Cancer Center
An integral part of one of the world’s most distinguished medical centers, Massachusetts General Hospital Cancer Center is chosen by more cancer patients than any other hospital in New England. Its commitment to eradicating cancer is fueled by scientific investigation conducted as part of the largest hospital-based research program in the United States.

Known for providing individualized, compassionate care to both adults and children, the Cancer Center comprises 18 fully integrated, multidisciplinary clinical programs and a vast network of support and educational services. The Cancer Center is consistently ranked as one of the best in the country by U.S. News & World Report, and its nurses were the first in the state to achieve Magnet status in recognition of the hospital’s exceptional nursing care.

Through a powerful synergy between scientists in the laboratories and physicians at the bedside, the Cancer Center fosters innovation in basic, translational and clinical research.

It is a founding member of the DF/HCC, a Harvard Medical School consortium designated by the National Cancer Institute as a comprehensive cancer center. This prestigious seven-member center forms the largest cancer research collaboration in the country. Also, Massachusetts General Hospital Cancer Center and Dana-Farber/Brigham and Women’s Cancer Center collaborate on joint clinical trials, education, training programs and quality of care improvements.

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Clinical Trials Provide Important Options for Patients
Dear Reader:

The summer months bring with them days at the beach, hours in the garden, long bike rides or hours spent in the yard. Relaxing, yes, but all of this sun exposure increases the risk of skin cancer.

Skin cancer is really more than one disease. Squamous cell and basal cell cancers are not generally life threatening, but a third form, melanoma, can be deadly if it invades beneath the skin.

Melanoma has become a major clinical and research focus for tremendous therapeutic energy at Massachusetts General Hospital Cancer Center and the Department of Dermatology. A specific melanoma-associated genetic profile exists, and we have an arsenal of targeted therapies, but we do not yet know which of these drugs will be most effective. Each cancer is characterized by a unique set of genetic changes; doctors who know a tumor’s precise genetic profile can use this information to tailor the best therapy for their patient. Profiling these tumors, determining which targeted therapy is most effective and finding new uses for existing targeted therapies reflect the Cancer Center’s goal of delivering personalized cancer medicine.

From this issue, you will learn about clinical trials — what is involved with each phase and who is eligible — and hear first-hand from patients who chose to enroll in trials. Our most advanced Phase I trials collect genetic information about the tumor, enabling us to identify new drug targets. Ultimately this information will help our doctors identify which drug to prescribe for a specific patient, the hallmark of tailored therapy.

You will also learn about our efforts to protect those who are genetically susceptible to melanoma, and about progress we have made in understanding and treating this difficult disease.

We hope you enjoy this issue of Synergy.
CenterPieces

Circulating Tumor Cells (CTCs) Can Reveal Genetic Signature of Dangerous Lung Cancers

Massachusetts General Hospital investigators have shown that a microchip-based device that detects and analyzes tumor cells in the bloodstream can be used to determine the genetic signature of lung tumors, allowing identification of those appropriate for targeted treatment.

A pilot study of the device called the CTC-chip, led by Cancer Center director Daniel A. Haber, MD, PhD and bioengineer Mehmet Toner, PhD, appeared in the July 24 New England Journal of Medicine and has garnered national media attention.

“The CTC-chip opens up a whole new field of studying tumors in real time,” says Haber, the study’s senior author. “When the device is ready for larger clinical trials, it should give us new options for measuring treatment response, defining prognostic and predictive measures, and studying the biology of bloodborne metastases, which is the primary method by which cancer spreads and becomes lethal.”

The paper’s co-lead authors are Shyamala Maheswaran, PhD, of the Cancer Center; and Sunitha Nagrath, PhD, of Mass General’s BioMEMS Resource Center; and Lecia Van Dam Sequist, MD, MPH, of the Cancer Center. Additional co-authors are Lindsey Ulkus, Brian Brannigan, Elizabeth Inserra, Sven Diederichs PhD, Daphne Bell, PhD, Subba Digumarthy, MD, Alona Muzikansky, MS, Jeffrey Settleman, PhD, and Thomas J. Lynch MD, all of the Cancer Center; Chay Collura, MS, and Daniel Irimia, PhD, both of the BioMEMS Resource Center; John Iafrate, MD, PhD, of Mass General’s Department of Pathology; and Ronald G. Tompkins MD, ScD, of Mass General’s Department of Surgery. The research was funded by grants from the National Institute of Health; the Doris Duke, Ellison and Monell Mass General’s Department of Surgery. The research was funded by grants from the National Institute of Health; the Doris Duke, Ellison and Monell Mass General’s Department of Pathology; and a $2-3 million grant from the Prostate Cancer Foundation of the BioMEMS Resource Center; and the National Cancer Institute.

Follow-up Treatment Reduces Breast Cancer Recurrence Risk

Women who receive letrozole (Femara) following tamoxifen treatment have a decreased risk of breast cancer recurrence — even when they begin the second drug up to seven years after tamoxifen treatment — according to Paul E. Goss, MD, PhD, director of the Breast Cancer Research Program at Massachusetts General Hospital Cancer Center and an Avon Foundation Senior Scholar. Letrozole is a member of a class of drugs called aromatase inhibitors that suppresses estrogen production. The effectiveness of tamoxifen, another estrogen blocker, decreases after five years, making it essential that women with hormone-dependent breast cancer have new treatment options. Women enrolled in the trial chose whether to receive letrozole, as opposed to being randomly assigned, which may have created a bias in the results. Nevertheless, says Goss, “Every woman who has previously taken tamoxifen should discuss these new results with her oncologist. The risk that hormone-dependent breast cancer will recur continues indefinitely, and our results imply that aromatase inhibition is effective whenever initiated.” Goss was lead investigator on the study, which appeared in the Journal of Clinical Oncology.

Cancer Center Researchers Receive 2008 Challenge Awards for Transformative Prostate Cancer Studies

Two investigative prostate cancer research programs at Massachusetts General Hospital Cancer Center have been awarded The Prostate Cancer Foundation’s (PCF) 2008 Challenge Awards, supporting vital programs with $2-3 million grants. The programs are led by Daniel A. Haber, MD, PhD, director of the Cancer Center, and Matthew R. Smith, MD, PhD, director of genitourinary cancer research at the Cancer Center.

Designed to increase the impact of PCF funding, the Challenge Awards invest in large, multi-year projects with high potential for solving problems associated with advanced prostate cancer that may lead to better treatments.

Haber was awarded in the category of Progression Biomarkers for his team’s work on clinical and biological insights into prostate cancer derived from circulating tumor cells. This research may lead to more rapid development of new medications and may alert physicians of the disease progression at an earlier time. Cancer Center research team members include Richard J. Lee, MD, Shyamala S. Maheswaran, PhD, Sunitha Nagrath, PhD, Matthew R. Smith, MD, PhD, and Mehmet M. Toner, PhD.

Smith was honored in the Nutrition, Metabolism and Patient Quality of Life category for his work on the prevention of treatment- and disease-related morbidity during androgen deprivation therapy. The best available treatment for advanced prostate cancer is the removal of androgens, testosterone hormones that drive the growth and progression of prostate cancer. However, the medications used to reduce androgen in patients cause significant secondary illness. Smith and his team of investigators plan to study the health consequences of androgen reduction and will determine medical interventions to prevent the negative consequences of treatment.

Melanoma in Focus

Melanoma genetics research was the focus of a Massachusetts General Hospital Cancer Center event at the Governor’s Club in West Palm Beach, Florida, this spring. The Cancer Center’s Hensin Tsaio, MD, PhD, was the event’s guest speaker. Tsaio, who presented strategies for combating the alarming rise in the incidence of melanoma, is director of the Melanoma and Pigmented Lesion Center and director of the Melanoma Genetics Program at the Cancer Center. Tsaio’s research focuses on the use of genomic mapping techniques to determine the profile of individuals at high risk for developing melanoma. The hospital’s Melanoma and Pigmented Lesion Center is the oldest multidisciplinary clinic in the country dedicated to the care of cutaneous melanoma patients. The event was co-sponsored by the Richard David Kann Melanoma Foundation.
**Renewal of Magnet Status Honors Nurses**

This spring, the American Nurses Credentialing Center redesignated Massachusetts General Hospital as a Magnet Hospital through 2012. In 2003, Mass General became the first hospital in the state to achieve Magnet status. Fewer than five percent of the hospitals in the United States are Magnet-designated, and the renewed honor acknowledges the hospital’s continued high-quality patient care and innovations in professional nursing practice, which has also proven to have a direct correlation to attracting and retaining well-qualified nurses.

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**Palm Beach Dinner Shines Spotlight on Cancer Center**

Hospital supporters Dr. and Mrs. Kenneth Beer and Mr. and Mrs. Timothy Moran welcomed 115 physicians and friends of Massachusetts General Hospital Cancer Center to a cocktail reception and dinner at the Four Seasons Resort in Palm Beach, Florida. The reception served to introduce the Cancer Center to individuals who are committed to the fight against cancer and who are raising awareness of the patient care, research and education occurring at the Cancer Center.

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**Nurse Manager Receives National Recognition as Patient Advocate**

Karleen Habin, RN, nurse manager and supervisor for the Breast Cancer Clinical Research Program (BCCRP) at Massachusetts General Hospital Cancer Center, is one of the eight honorees to receive The American Cancer Society’s 2008 Lane Adams Quality of Life Award. This award promotes improved quality of life for individuals with cancer and their families through public recognition of compassionate and expert care providers.

Habin was honored for her role as patient advocate for the BCCRP, a nationally and internationally recognized program. She has used her personal breast cancer journey to empower and provide guidance to those facing a similar diagnosis. In her role, she spearheaded the creation of the first-ever Breast Cancer Resource Guide of Massachusetts, which was distributed free of charge and benefited a multitude of patients and families.

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**Breakthroughs in Addressing Treatment Side Effects**

An international research team led by David J. Kuter, MD, DPhil, director of the Center for Hematology at Massachusetts General Hospital Cancer Center, has shown that the novel drug romiplostim (Nplate) significantly improves platelet levels in patients with chronic immune thrombocytopenic purpura (ITP), a disorder in which the immune system destroys blood cells that help prevent bleeding. Kuter’s team will investigate the drug’s usefulness for treating other conditions of reduced platelet production, such as those caused by cancer and cancer treatment.

In an unrelated study that appeared in the April edition of Nature, a team of researchers led by Anders Näär, PhD, a cell biologist in the Center for Cancer Research at the Cancer Center, identified a mechanism that controls drug resistance to the fungal infections common in patients receiving chemotherapy and in transplant recipients treated with immunosuppressive drugs. These findings will lead the way to new drugs that may prevent drug resistance or that will make standard therapies more effective.

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**Marathoners Kick It for Pediatric Cancer**

More than 125 members of the MassGeneral Marathon Team took the 112th Boston Marathon in stride to honor children fighting cancer. Formed in 1997 by Howard J. Weinstein, MD, chief, Division of Pediatric Hematology-Oncology, MassGeneral Hospital for Children, the team this year raised more than $650,000 for pediatric cancer, bringing total contributions over the past 11 years to over $5 million. Funds raised support research and programs to improve quality of life for pediatric patients and their families. Runners participate thanks to the generosity of John Hancock, which annually donates the numbers. This year about 50 members of the team participated in the Patient Partner program, where runners are carefully matched with patients, and runners have an opportunity to get to know their patient partner well before the marathon. This relationship culminates when runners present their patient partner with a marathon medal at a pasta dinner on the night prior to the marathon.
SCIENTIST HONORED AS THE RECIPIENT OF THE THIRD ANNUAL MASSACHUSETTS GENERAL HOSPITAL AWARD FOR CANCER RESEARCH

Massachusetts General Hospital Cancer Center is proud to honor outstanding scientists in the pursuit of eradicating cancer by scientific investigation. Recently, the Cancer Center awarded its third annual Massachusetts General Hospital Award in Cancer Research to Titia de Lange, PhD, Leon Hess Professor at Rockefeller University, for her pioneering studies on the structure and function of mammalian telomeres. Daniel A. Haber, MD, PhD, director of the Cancer Center, presented the award to de Lange prior to her seminar on Friday, April 4, 2008.

MAXIMIZING RESULTS FROM TARGETED THERAPY TRIALS

Determining the most advantageous uses of new “smart” or targeted drugs that home in on specific molecules within cancer cells will require sophisticated multidisciplinary clinical trials, according to Rakesh K. Jain, PhD, director of the E.L. Steele Laboratory of Tumor Biology at Massachusetts General Hospital. Successfully completing these complex trials, however, remains challenging.

In an article in Nature Reviews, Jain outlines factors that contributed to the success of his recent trials on anti-angiogenic therapy, a form of targeted therapy that uses drugs or other substances to stop tumors from making new blood vessels. Included among the points Jain outlines for a successful clinical trial are such features of Massachusetts General Hospital Cancer Center as collaborations with the National Cancer Institute and pharmaceutical industry; funding, infrastructure and access to advances in technology; dedicated patients and family members; and tight integration between the bench and bedside.

Jain was also recently elected to the Class of 2008 Fellows of the American Academy of Arts and Sciences (AAAS). AAAS is one of the nation’s oldest and most prestigious honorary societies and independent policy research centers in the country.

PHYSICIAN HONORED FOR COMMITMENT AND COMPASSION

David C. Harmon, MD, medical oncologist at Massachusetts General Hospital Cancer Center, was recently named the 2007 Excellence in Care Award recipient by the Leiomyosarcoma Direct Research Foundation (LDRF). This annual award honors Harmon’s dedication to finding a cure for leiomyosarcoma, a rare cancer of the smooth muscle cells, and his extraordinary compassion for his patients and their families. Harmon exemplifies the LDRF’s mission of advocating for more research and improving the quality of life for patients as they fight this disease.

DEVELOPMENT PROGRAM FOR ONCOLOGY SUPPORT STAFF

A team of care providers from Massachusetts General Hospital Cancer Center recently published the results of their study on the needs of oncology support staff in the Oncologist. The team included Barbara J. Cashavelly, MSN, RN, AOCN, nurse director of the Cancer Center; Karen Donelan, EdM, ScD, senior scientist in health policy at Mass General; Katie D. Binda, MSW, LICSW, director of the HOPES Program at the Cancer Center; Katherine A. Clair-Hayes, MSW, MA, LICSW, volunteer coordinator for Mass General; Johanna R. Mailhot, BS, of the Mass General Institute for Health Policy and Peter Maramaldi, PhD, MPH, LICSW, of Mass General.

This study reports on the group’s experience instituting the Support Staff Development Program, a training, education and support program at the Cancer Center. The intent of the study was to learn more about the experiences of non-licensed support staff in an oncology setting, something that has rarely been acknowledged or addressed. These personnel are front line staff who are often the first link between patients and their care team. Results showed that the emotional impact of this work on all staff must be recognized if institutions hope to minimize turnover and maximize high-quality care to patients and families.
“A SHINING LIGHT AMIDST THE DARKNESS”

The Cancer Center Honors the one hundred for Steadfast Commitment to Eradicating Cancer

On June 5, staff, donors and friends of Massachusetts General Hospital Cancer Center gathered to celebrate the first annual dinner in honor of the one hundred. The contributions of the one hundred reflect the diversity of talent and the life-changing compassion that can be found throughout the Cancer Center. Working together with a shared mission, these one hundred individuals and groups have been able to advance the field of cancer medicine and care through scientific discovery, patient care, philanthropy and volunteerism.

A nominator wrote of McCallum “Mac” Moore, “He greets a few hundred patients and visitors each day but makes each one feel special. For more than ten years, Mac has been, in many ways, the face of the Cancer Center.”

Mass General president Peter L. Slavin, MD (left), and event co-chairs Jay Minahan, Gina Barry and Tom Hamilton

DETERMINING THE GENETIC SIGNATURE OF LUNG TUMORS CAN HELP GUIDE TREATMENT

A new study in the May 20 Journal of Clinical Oncology led by Massachusetts General Hospital Cancer Center investigators found that early treatment with the targeted drug Iressa considerably improved the outcomes for people with non-small cell lung cancer. However, additional research is required before this approach can be routinely used to fight this disease.

Iressa works by disabling a receptor on the surface of lung cancer cells called epidermal growth factor receptor (EGFR), essentially halting a series of signals that can lead to cancer growth. Lecia Van Dam Sequist, MD, MPH, medical oncologist at the Cancer Center, led the first study in the US, in which patients with lung cancer were first tested for presence of an EGFR mutation in their tumor, and if positive, were treated with a targeted drug against EGFR. Patients with characteristic mutations in EGFR had vigorous responses to the drug.

“This is a pivotal in which the genetic makeup of a tumor is determined at the time a patient is first treated, and a targeted drug is then offered upfront, instead of waiting for failure of traditional chemotherapy drugs” says Sequist. “It is an exciting glimpse into what we hope is the future of cancer care. Instead of a ‘one size fits all’ therapy, we are moving toward finding the best treatment for each patient.”

NATIONAL MEDIA SPOTLIGHT ON CARING NATURE OF CANCER CENTER PHYSICIANS

Massachusetts General Hospital Cancer Center’s longstanding focus on patient-centered care has received national media attention in recent weeks. In the June 23 issue of Newsweek, Cancer Center breast oncologist Lidia Schapira, MD, emphasized the importance of a humanistic approach to care and the need to routinely screen patients for emotional, social and psychiatric problems. Schapira currently is working with colleagues through the American Society of Clinical Oncology to establish a communication skills training program as an integral part of oncology training. Also recognized was the Cancer Center’s chief of Hematology-Oncology Thomas J. Lynch, MD, who has been instrumental in establishing the Schwartz Center Rounds, a multidisciplinary forum conducted in 145 medical institutions where caregivers discuss difficult emotional and social issues that arise in caring for patients.

A recent 90-minute PBS documentary, The Truth About Cancer, featured courageous stories of patients battling cancer, including a 38-year-old pancreatic cancer patient treated by David P. Ryan, MD, clinical director of the Tucker Gosnell Center for Gastrointestinal Cancers. Focused on the meaningful interaction between patient and caregiver, the original broadcast was viewed by 3.4 million people and more than 50,000 people watched the program online.
The Finnegan triplets – Dick, Paul and Kevin – describe themselves as “all different, and all wonderful.” Some of the differences are visible: they are fraternal triplets, so they don’t appear identical. Some are more discreet: only Dick has been diagnosed with melanoma. Yet the brothers share enough features to make them clearly brothers, and they share a genetic heritage — they are fair-skinned Irishmen — that makes them susceptible to melanoma.

Understanding the genetic makeup of people like the Finnegans is helping doctors and scientists at Massachusetts General Hospital Cancer Center work collaboratively to develop new ways to prevent and treat melanoma. This skin cancer is one of the most dangerous forms of cancer, and one that is growing faster than any other cancer.

“We have a much better understanding of genetic targets than just five years ago and are on the brink of a new generation of drugs specifically designed to hit these targets.” Donald Lawrence, MD
Although melanoma runs in some families, it is commonly thought to be caused by sunlight. According to David E. Fisher, MD, PhD, director of Massachusetts General Hospital Cancer Center’s Melanoma Program and chief of Dermatology at Massachusetts General Hospital, our sun exposure is an important reason behind the increase in melanoma. A person’s risk of developing melanoma doubles if they have sunburn early in life. Melanoma risk can, however, be diminished by managing exposure to the sun’s ultraviolet (UV) rays. Moreover, when detected early on, melanoma is frequently curable through surgical removal.

But once it spreads, melanoma can be extremely difficult to treat, concedes Donald Lawrence, MD, medical oncologist and clinical director of the Center for Melanoma in the Cancer Center. Melanoma is notoriously resistant to chemotherapy and radiation: “It’s the cancer that gives cancer a bad name,” explains Lawrence. At the Center for Melanoma, specialized expertise at all levels of care — from diagnosis and surgery in early stages to clinical studies and experimental treatments for people with more advanced disease — offers patients hope.

“In 35 years of research on advanced melanoma, not much has improved in treatment, but we’re changing that,” asserts Arthur J. Sober, MD, director, Center for Melanoma in the Cancer Center, whose research helped establish that just one blistering sunburn in adolescence doubles the risk of melanoma later in life.

Fisher, who is also director of the Cutaneous Biology Research Center, Lawrence and Hensin Tsao, MD, PhD, clinical director, Melanoma and Pigmented Lesion Center, are also conducting research to understand what makes melanoma tick genetically and how to develop new therapies that inhibit the genes known to drive melanoma. According to Lawrence, “We have a much better understanding of genetic targets than just five years ago and are on the brink of a new generation of drugs specifically designed to hit these targets.”

This genetic research lays the foundation for personalized medicine for melanoma patients. It will help them understand their risk of melanoma so that they may receive more preventive care, and it will also allow doctors to predict how aggressive a cancer may be and what drug will work best against it.

On the Front Line

On the front line of the war on melanoma, the Pigmented Lesion Center is the oldest continually operating multidisciplinary program in the country, founded in 1966.

“We’ve seen more than 4,000 melanoma patients,” explains Sober, “so we have experience in managing not only common forms but also very rare forms of the disease.” Specialized pathologists, called dermatopathologists, read biopsy slides and make the final determination on whether a pigmented skin lesion is a benign mole or malignant melanoma and provide information that helps the multidisciplinary care team decide on the best treatment.

Martin C. Mihm, MD, senior dermatopathologist at Massachusetts General Hospital and co-founder of Pigmented Lesion Clinic, is actively pursuing research into the nature of the inflammatory response and survival in melanoma patients as well as the mechanisms of metastasis. As co-director of the Melanoma Pathology Program of the European Organization for Research and Treatment of Cancer, Mihm is spearheading a worldwide study devoted to understanding not only the role of host immunity but also the evolution of the metastatic process and possible blockades to its development.

According to dermatopathologist Lyn Duncan, MD, in-depth pathology analysis will enhance the usefulness of the new targeted therapies since “dermatopathologists may look for specific biomarkers, potentially allowing for even more accurate determination of which therapies are best for a particular patient.” This evaluation of biomarkers, or drug targets, is an area of active research at the Cancer Center.

Immunotherapy is another clinical pathway being pursued by surgical oncologist Jennifer A. Wargo, MD, to treat melanoma and other types of cancer. Wargo is exploring the use of genetically manipulated T lymphocytes, a type of disease-fighting white blood cell that is part of the body’s natural immune system, to infiltrate and attack tumors in patients with metastatic melanoma. This cellular therapy has produced a clinical response in over half of treated patients, and holds promise for future research and treatment.

Treating melanoma once it has metastasized, or spread, is challenging because there is no predictably effective treatment to date. The Cancer Center does offer very aggressive alternatives that are performed at only a few centers in the United States, but “there is no standard of care for advanced melanoma,” Lawrence notes. “We’re still searching for it, and we’re evaluating several new therapies in clinical trials.” (continued on page 8)
Like Sister, Like Brother

When Christine Wirtz was 22, her hairdresser noticed an irregular growth on her scalp and suggested she have it checked. Christine followed that advice, although she had ignored earlier suggestions to protect her fair, freckled skin from sunburns. The growth was diagnosed as a cutaneous melanoma. Fortunately, an examination of her lymph nodes at the time revealed that her melanoma had not spread.

When her younger brother went for a skin exam after her diagnosis, he was also diagnosed with melanoma. In the 13 intervening years, each has had numerous other melanomas.

“It’s more than just bad luck,” says Tsao, Christine’s dermatologist in the Pigmented Lesion Center. “When you see her history — the early age of diagnosis, the sheer number of tumors and having a brother with multiple melanomas — you know there’s something genetic going on, even if we don’t know which genes are involved. It’s vitally important to identify these genes so we can intervene with more intensive preventive care,” such as frequent body scans and biopsies of suspicious spots. The Center for Cancer Risk Assessment (CCRA) provides an important resource for families like Christine’s where there is an unusually high incidence of melanoma.

Tsao, who is also director of the Melanoma Genetics Program in the CCRA, is searching for risk genes in the DNA from about 200 families. “When we say gene, we actually mean a mutation or genetic variation that changes a gene’s normal function in a way that promotes cancer,” he clarifies. In addition to single genes, Tsao and other researchers are searching for combinations of genes that may increase melanoma risk.

Researchers know that a mutation in one gene, p16, raises a person’s risk of developing melanoma from 1.5 percent to 76 percent. Interestingly, faulty p16 also elevates risk for pancreatic cancer, which claimed the lives of the triplets’ two older brothers. As part of Dick Finnegan’s preventive care, his physicians keep watch on his pancreas, although his p16 status is not known.

Many of these risk genes normally function like a brake on the cancer engine. When mutations compromise the brake, some other trigger steps on the accelerator and drives the cancer forward.

“Actually cars usually have two braking systems, a normal and an emergency brake,” Tsao explains, “and this is similar for tumor suppressors, too. Each individual has two copies (one from mom, one from dad) of a gene. In patients who inherited the mutation in p16, the emergency brake is defective leaving the factory. The car is then vulnerable to any insults to the normal braking system since the backup is no longer available.”

Genetic Profiling in Tumors

Most melanomas, however, do not result from inherited gene malfunctions, but from sporadic changes that happen throughout life from UV radiation or during a tumor’s own evolution. These mutations often function as oncogenes, or cancer-promoting genes, that step on the accelerator and help cancer cells proliferate and spread.

Oncogenes make attractive drug targets because tumors often become “addicted” to them and go into withdrawal when deprived of their activity.

To identify these oncogenes and drugs that can inhibit them, Tsao collaborates with Jeffrey Settleman, PhD, scientific director of the Cancer Center and director of the Center for Molecular Therapeutics. They want to identify the genetic features in an individual’s tumor that make it particularly vulnerable to attack by a targeted drug. However, tumors vary widely in their pattern of mutations, and drugs may need to be tailored to the specific mutations present in the tumor.

To find potentially useful drugs, Settleman examines cells from different tumors for signatures that predict a cell’s sensitivity to a variety of drugs. He also investigates why not all tumors with a specific mutation respond well to therapy that targets it. Perhaps those tumors have other, overriding mutations. Settleman hopes to find markers for them that will aid in drug selection.

Working as a team, Cancer Center dermatologists, surgical oncologists, radiation oncologists, pathologists, medical oncologists, otolaryngologists and clinical research staff use their extensive expertise to help each patient fight his or her disease.
Attacking KIT

To expedite the process of getting effective drugs into the clinic, Settleman focuses on drugs already approved for other purposes or already in development, rather than starting from scratch with new designs.

Fisher’s research demonstrates the efficacy of this “re-purposing” of existing drugs. Recently, Fisher jumped on the observation that a rare, intractable form of melanoma affecting the mucosal membranes, palms and soles may contain mutations of a gene called KIT. An existing therapy, Gleevec, approved for certain leukemias and gastrointestinal tumors, was previously known to target KIT.

Several prior trials had failed to demonstrate the efficacy of Gleevec in melanoma patients, but for a new trial, Fisher and his colleagues selected only patients whose tumors contained a KIT mutation. “Our preliminary results showed a dramatic tumor shrinkage, for the first time demonstrating a successful oncogene-targeted therapy in metastatic melanoma,” Fisher says of the ongoing trial.

Lawrence is testing another targeted drug, Sutent, which also hits KIT, in a clinical trial for melanoma. “There’s every reason to be optimistic, but we still have lots of work to do,” Fisher says. KIT mutations are uncommon in melanoma, and researchers do not yet know if they have the right drugs to target other more common mutations.

Light Skin and Ultraviolet Risk

Because of the indisputable link between UV exposure and melanoma, Fisher is working to understand the molecular basis for that link. Using redheads as an example of a vulnerable, fair-skinned population, he studies how their skin differs from people who tan more easily.

His research drew from a gene called MITF that he had previously shown to function in skin cells called melanocytes, where it promotes pigmentation. When melanocytes develop deeper pigmentation, tanning results. Redheads lack that deep pigmentation pathway.

Fisher discovered that the direct target of UV radiation in skin was not melanocytes but keratinocytes, highly abundant cells on the outer layer of the skin. When UV rays damage those cells, keratinocytes release a hormone that stimulates the melanocytes’ dark pigment production. Redheads lack a functioning receptor for that hormone, so their melanocytes cannot respond to it, which explains their inability to tan.

Armed with that knowledge, Fisher selected a molecule that could bypass the non-functional receptor and applied it to skin in an animal model. The skin turned progressively dark brown without any UV radiation, creating protection from UV’s cancer-causing effects. Currently he is testing whether this or similar molecules can penetrate human skin, which is thicker.

“Because of this new understanding of how sunlight induces pigmentation, we might be able to safely regulate production of pigment as a cancer prevention strategy,” Fisher says, meaning that redheads may some day be able to tan. It is too early to know whether this strategy will work in humans, but work in that direction is progressing.

The Ultimate Protection

Ultimately, Fisher emphasizes, the quickest way to reduce melanoma deaths is to catch the disease early when it is localized and curable by surgery. “Better still, avoid sun exposure and do not intentionally expose yourself to ultraviolet radiation, such as indoor tanning salons.”

“I wish that I had protected my skin when I was younger,” reflects Christine. “If I had, I might still have melanoma because of my genetic risk, but not as many recurrences.”

While people like Christine and Dick may now spend more time in the shade, physicians and researchers at the Cancer Center are working together to shed light on this disease and to offer patients the best treatments possible.

Does Melanoma Run in Your Family?

Most melanoma occurs as a result of ultraviolet exposure, but some people are at higher risk because of a family history of the disease. If you have one or more of the following risk factors, a genetic counselor may be able to determine if you need additional screening or guidelines to help protect you from developing melanoma:

- Multiple family members on the same side of the family diagnosed with melanoma
- Individuals in the family with multiple primary melanomas (not melanoma that has spread from another location)
- Individuals in multiple generations affected with melanoma
- Pancreatic cancer (in some families)

Although inherited melanoma is rare, genetic counseling and genetic testing for people who may have a hereditary predisposition to the disease could save lives. If you have questions or would like to arrange for a consultation in the Center for Cancer Risk Assessment, please call 617.724.1971.
Aggressive Therapies
Keep An Outdoor Enthusiast Active
I was a red-haired, fair-skinned boy who played in the sun, played lots of sports and got lots of sunburns,” says George Brewster, 67, acknowledging that the same risk-taking spirit that led to several rollerblading accidents probably also put him at risk for melanoma. But being a fitness buff also made him a good candidate for aggressive therapies in Massachusetts General Hospital Cancer Center’s Center for Melanoma. Rarely performed elsewhere, these therapies have kept his melanoma in check.

In 2001, while recovering from a rollerblading accident, he noticed a suspicious growth on his injured right leg that his Cancer Center doctors subsequently diagnosed as melanoma. Members of his care team surgically removed it, but Brewster kept checking for new sites because he knew that having had one melanoma meant another unrelated one could likely occur. That indeed did happen, over and over, but he caught each new growth early.

Because for many years the melanomas were confined to his right leg, he eventually chose to have a procedure called isolated limb perfusion, in which his doctors isolated blood flow from his leg with a bypass machine and treated it with extremely high doses of chemotherapy delivered at high temperatures. This approach protects the rest of the patient’s body from the heat and drugs.

Although this procedure is effective in some patients, Brewster’s melanoma recurred, this time in his abdomen. Because he was in superb physical condition and otherwise healthy, his interdisciplinary team recommended immunotherapy — interferon and interleukin — to stimulate his immune system to attack the melanoma cells. While immunotherapy “melts away” some tumors, it has no impact on others for reasons doctors have yet to determine. Fortunately for Brewster, all signs indicate he is in the small minority of patients who benefit from this approach, and he hopes to continue enjoying his outdoor activities for many years to come. — Cathryn Delude
With summer in full swing, many people are trading a day at the office for a day outdoors. While time spent outdoors can be good for body and soul, says Donald Lawrence, MD, clinical director of the Center for Melanoma at Massachusetts General Hospital Cancer Center, sun protection is critical. Skin cancer is the most common form of cancer. Melanoma, the most dangerous form of skin cancer, is on the rise, especially in women between the ages of 20 and 29.

“While it is not clear exactly what causes skin cancer,” says Lawrence, “we know that ultraviolet radiation from both sun exposure and tanning beds damages the skin cells. If the damage does not repair itself, cells grow uncontrollably, leading to cancer. Tanning is most definitely not a good idea.”
A CONVERSATION ABOUT TANNING AND SKIN CANCER WITH DONALD LAWRENCE, MD

Q. What causes skin cancer?
A. Skin cancer, like all cancer, is caused by genetic changes that disrupt the normal growth and death cycle of cells, causing them to reproduce uncontrollably. While scientists don’t yet know all the reasons for these changes, we have identified major culprits.

Ultraviolet radiation from the sun or from tanning beds plays a significant role in causing melanoma and other skin cancers. Fair-skinned individuals and redheads are at particularly high risk because of the ways in which their skin differs from people who tan more easily. There are known inherited genetic changes in families that confer a higher-than-average risk for melanoma, but these changes account for fewer than 12 percent of all melanoma cases. What’s important to note is that a behavior change can save your life: protect yourself from the sun.

Q. How is melanoma treated?
A. The best treatment for melanoma is surgical removal of the mole or lesion while it is confined to the surface area of the skin. Melanomas that have grown into the deep layers of the skin may spread to the liver, lungs, bones and brain. These cancers are highly aggressive, and they typically don’t respond well to standard treatments such as chemotherapy.

Research at the Massachusetts General Hospital Cancer Center is opening the door to more successful melanoma treatments, including targeted or “smart drug” therapies, immunotherapy and cellular therapy. Through laboratory and preliminary clinical trial work, we are identifying which targeted therapies, or smart drugs, are most effective in treating advanced melanoma. These and other research efforts will give us a better understanding of preventing and treating melanoma.

Q. Are all skin cancers dangerous?
A. If skin cancer is removed before it invades the body, then it poses no danger. That being said, there is no such thing as an innocent melanoma. Basal cell and squamous cell skin cancers are relatively slow growing and don’t tend to invade the body. Melanoma, however, can be very aggressive and is a difficult disease to treat once it gets below the skin’s surface. The good news is that it’s 100 percent curable if removed while still confined to the outer layers of the skin.

Q. How can I protect myself?
A. The most important thing is to protect yourself from sun exposure in the middle of the day, when ultraviolet rays are strongest. If you use tanning beds, my advice is simple: stop. If sun exposure is inevitable, wear clothing that covers your arms and legs, a hat, sunglasses and a generous coating of sunscreen with a UVA/UVB rating of at least 35.

Q. How can I tell if I have melanoma?
A. Check your skin once a month for any changes, especially for new growths or changes to existing moles. If you are a parent, check your child’s skin as well. Even young children are vulnerable to melanoma. Make sure to check your scalp and even places that are not exposed to the sun, such as the bottoms of your feet and the palms of your hands. If you notice any of the following changes, visit your doctor for a more thorough examination:

- **Asymmetry**: one half of the mole does not match the other half
- **Border**: edges are ragged, blotched or blurred
- **Color**: uneven or mottled colors, including brown, black, tan, red, white or blue
- **Diameter**: mole is larger than the size of a pencil eraser or is growing
- **Evolution (or elevation)**: a mole that changes or that has different thicknesses or heights

Very rarely, melanoma occurs inside the eye or in the mucous membranes of the nose or mouth. Regular checkups with your dentist and optometrist will help screen for disease in these areas.

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Interview by Katie Marquedant
Navigating Toward Hope

Clinical Trials Provide Important Option for Patients
“I jumped at the opportunity to work with Dr. Penson on a new approach to treating ovarian cancer,” says 44-year old Erika Meng of her participation in a Phase II clinical trial at Massachusetts General Hospital Cancer Center. Meng, who works as an agricultural resource economist in Mexico, returned to Massachusetts to live with her family after her Cancer Center oncologist Richard T. Penson, MD, MRCP, clinical director of the Gillette Center for Gynecologic Oncology, told her of the new trial that was targeted for her disease. “The trial showed promise and went beyond the standard chemotherapy I had undertaken,” she says.

Clinical trials offer patients and their families an important option at any stage or with any type of cancer. Designed to improve existing therapies by extending lives or reducing side effects, these trials make available drugs that demonstrate, after rigorous testing, the most promise for patients.

**Mapping the Future of Cancer Care**

The Cancer Center’s administrative director of clinical trials, Glenn C. Siegmann, MS, has a map of the known cancer-causing cellular pathways in humans. This map, explains Siegmann, indicates many potential targets for cancer drugs. These targets are opportunities in cellular activity where cancer-causing changes can be stopped, corrected or exploited. Scientists know that the map is just the beginning: many more targets may be hidden in the complexity of cell function.

To complicate matters further, according to Siegmann, “Not all of these pathways are active in every type of cancer. Finding out which ones are active and in which cancers and then targeting them with the appropriate drug is the challenge.” Alternatively, the target may be fixed, but the drugs may be faulty or simply the wrong type for that particular target.

Fortunately, explains Siegmann, laboratory and clinical research at the Cancer Center is designed to optimize the chances of success. Because targeted therapies or smart drugs, which affect a particular cancer-causing change within the cell, have shown such promise, the Cancer Center focuses its new drug research on these types of therapies.

**Where the Path Begins**

All drug discovery begins in the lab, where scientists like Jeffrey E. Settleman, PhD, Cancer Center scientific director and director of the Center for Molecular Therapeutics, cultivate different types of cancer cells and then treat them with prospective drugs. In addition to determining whether the drug kills the cancer cell, Settleman investigates the reasons for success or failure. These studies open the possibility of identifying new targets, more effective drugs or drug combinations that may lead to the control or destruction of the cancer. Promising approaches are then tested in animal models before moving to clinical trials.

Clinical trials occur in four phases. Phase I, which usually involves 20 – 30 patients, helps determine how a new drug or combination of drugs should be given (pill, injection, intravenously), how often and what dose is safe. The second phase studies how well the new drug works and focuses on a particular type of cancer in 30 – 100 patients. Phase III trials test the new treatment in comparison to the current standard of care. Patients are randomly assigned the current standard or the new treatment. At this stage, the same trial may be offered at many cancer centers nationwide. Hundreds or even thousands of patients may be enrolled. Phase IV studies, which are not always done, monitor the long-term effects of the new treatment. All trials are strictly monitored and must adhere to government regulations that protect the safety of patients. Patient eligibility for clinical trials is a scrupulously reviewed process that takes into account age, health, response to prior treatment, stage of disease and, most importantly, the patient’s willingness to participate in the trial and understanding of their rights and of the parameters of the study.

The Cancer Center partners with the Harvard-wide DF/HCC to have one of the region’s largest clinical research programs and offers many Phase I and Phase II trials that are not available at other cancer centers. In addition, the Cancer Center is a leading provider in New England for Phase I clinical trial studies and Phase II treatment studies for gastrointestinal cancer patients. This vibrant clinical trials program, built on a synergistic relationship among patients, doctors and laboratory researchers, continues to build a better future for people with all forms of cancer.

**New Hope and Extra Care**

Patients enrolled in clinical trials at the Cancer Center discover, as Erika did, that participation strengthens the relationship between patient and caregiver. “He’s sticking with me throughout this,” she says of Penson. “There’s never been any question that it was otherwise.” According to Bruce A. Chabner, MD, clinical director of the Cancer Center, there’s an additional benefit as well. “If patients qualify for a clinical trial and make the decision to participate in one,” he says, “they can expect to be treated beyond the standard care they get at a hospital that does not offer a clinical research component.”

Erika agrees that the care she received was extraordinary. “Every step of the way, Dr. Penson shared with me what the trial was exploring and how it was proceeding. Many people watched over me. There were many scheduled blood labs, for example, to monitor the medication as it moved through my system. Even my hair follicles were tested.” (continued on page 16)
More Uses for Existing Drugs

Launching a new drug can take a decade of research and hundreds of millions of dollars, and many drugs that looked promising in the lab turn out to have little or no impact at the bedside. To bring hope to today’s patients, Cancer Center scientists are looking to expand the usefulness of existing targeted therapies. To do this, says Siegmann, the Cancer Center focuses its efforts on understanding exactly how these new drugs work and on identifying the patients who are most likely to benefit from them. This information will help scientists find new and better uses for targeted therapies that have already received FDA approval. Gleevec, for instance, was originally developed to target a pathway known to lead to chronic myeloid leukemia. Subsequently, researchers discovered it affects a second pathway, a finding that has made Gleevec useful in fighting gastrointestinal stromal tumors (GIST). In a clinical trial currently under way at the Cancer Center, Sutent, which has been approved for use in kidney cancer and GIST, is being used in clinical trials for some melanoma patients since scientists know this second pathway is also involved in a specific type of melanoma. Other Cancer Center studies are aimed at uncovering ways targeted drugs can be used in lung cancer, sarcoma, kidney and brain cancer.

In addition to finding new cancers impacted by the drugs and helping to match the right drug to the right patient, these studies will lead to a new understanding of how cancer cells eventually overcome the effects of targeted therapies. Already, this research has led to a second generation of these drugs that target two cancer-causing pathways instead of the single-pathway blockade of earlier targeted therapies.

“Understanding the mechanism of this drug resistance is key,” says Settleman. “Subtle differences in the chemistry of the drug will be important. Rather than prescribing a drug cocktail, we’ll change drugs when necessary to stay ahead of the tumor’s resistance. In this way, cancer becomes a chronic disease that we can keep in check.” Ongoing studies will identify new targets for existing drugs, new targets to support drug development and new combinations of therapies.

Doctors and patients agree that clinical trials are the most viable way to uncover new treatments. “It is my hope that there can be more trials involving many new therapies that help an even larger number of people like me,” says Erika. “This is how progress will finally be achieved in the fight against cancer.”

Jeffrey W. Clark, MD, medical director for clinical trial programs at the Cancer Center, stresses that people like Erika who participate in clinical research are vital to improving cancer care for generations to come. “It is to each of them,” he says, “that we owe the greatest gratitude.”

Joining a Clinical Trial

Information on available clinical trials, including eligibility criteria, is available at massgeneral.org/cancer/clinical_trials and at other cancer-related websites such as the National Cancer Institute (cancer.gov/clinicaltrials) and CenterWatch Clinical Trials Listing Service (centerwatch.com). However, the best way to learn about a suitable clinical trial is by asking your doctor, who can provide you with support and guidance through each step.
Rubin Sugarman went to a dermatologist near their home in Wellington, Florida, in 2002 to have a doctor take a look at an unusual spot on his chest. He and his wife Estelle worried it might be a skin cancer. A biopsy report proved them correct, and indicated that Rubin had Stage III melanoma, meaning the dangerous skin cancer had invaded his body.

Within days, the couple flew back to their home in Newton, Massachusetts, so Rubin could be treated at Massachusetts General Hospital Cancer Center. Arthur J. Sober, MD, director of the Center for Melanoma, surgically removed Rubin’s tumor, which had spread to his chest and abdomen. Rubin’s prognosis was excellent, but he continued to see Sober every three to six months for checkups.

Four years later, Rubin began to complain about pain in his back. Thinking the pain was orthopaedic in nature, he went to a spine specialist who performed an MRI and an X-ray on his back. The results were a shock to the Sugarmans: the cancer had metastasized to an area around his spine. Rubin returned to the Cancer Center and was treated by Donald Lawrence, MD, clinical director of the Center for Melanoma, but his health declined quickly. An otherwise vibrant and healthy man, Rubin died 10 months later, last year, at age 80.

“We always thought of melanoma as skin cancer and had no idea that melanoma could spread to other parts of his body the way it spread in Rubin’s body,” says Estelle.

During Rubin’s illness, he and his wife discussed giving a large gift to the Cancer Center to advance cancer research. After her husband’s death, Estelle created the Rubin and Estelle Sugarman Melanoma Endowed Fund to support the melanoma research of Lawrence and Hensin Tsa0, MD, PhD, who is director of the Melanoma and Pigmented Lesion Center and director of the Melanoma Genetics Program at the Cancer Center.

“My hope is that this donation will enable discoveries that will save the lives of future melanoma patients,” says Estelle.

Tamar Morad

The generosity of donors like the Sugarmans makes a profound difference in the lives of cancer patients. To find out how you can help people battling this disease, please contact Kate Todd, director of Development for Massachusetts General Hospital Cancer Center, at 617.726.0402, or kstodd@partners.org.

Making a donation to the Cancer Center online is easy. To make your gift today, visit us at massgeneral.org/cancer/help/donate.asp.
Shane King’s first steps drew proud applause from his parents, his older brother Casey and his medical team at the Francis H. Burr Proton Therapy Center at Massachusetts General Hospital for Children Cancer Center. It was July 2007, and 13-month-old Shane was in the middle of treatment for rhabdomyosarcoma, a rare cancer that originates in the skeletal system and can manifest itself in various organs, including the prostate, which is where Shane’s cancer was found.

Shane’s specialized care team involved a pediatric oncologist, genitourinary surgeon, pediatric urologist, radiation oncologist and nurses who supported him and his family through a rigorous 43-week course of chemotherapy, surgery and proton therapy, a precisely targeted form of radiation not available anywhere else in New England.

“The nurses who cared for Shane chose to work with him based on a connection with him and with his condition,” recalls Shane’s mother Julie. “His pediatric oncologist related to our family as a physician and as a mother. It felt personal. We had a team.”

Today, Shane is free from chemo and catheters. A rambunctious two-year-old who loves trains and the Red Sox, Shane can’t wait until he’s big enough to join his brother Casey in pre-school. - Andrea Gimler