The deadliest aspect of cancer is its ability to metastasize, or migrate from a primary tumor to one or more distant sites. This is often the final, lethal step in the progression of solid tumors. In order to metastasize, a tumor cell has to complete many stages. It must lose its connections to its neighbors, invade through a matrix barrier, travel through the blood stream, survive in a new environment, and to reach a certain size, acquire its own blood supply. By the time cancer cells acquire these attributes, they have developed resistance to most standard therapies.

Because it is a complicated, multi-step physiological process with its own dynamics, metastasis has remained poorly understood. In 2006, the University of Chicago received an initial investment of nearly $20 million from the Virginia & D.K. Ludwig Fund for Cancer Research to launch a comprehensive center for metastasis research. In January, the Ludwig Center for Metastasis Research at the University of Chicago received another $90 million endowment from Ludwig. "Although metastasis is the leading cause of cancer deaths, accounting for 80 to 90 percent of cancer mortality, it has only recently become a major focus of research," said Center Co-Director Ralph Weichselbaum, MD, D.K. Ludwig Professor and Chair of the Department of Radiation and Cellular Oncology. "The endowment provides an unprecedented opportunity to make substantial progress in understanding and treating this fundamentally complex condition.

The Center brings together researchers from various areas of expertise—including molecular biology, cell biology, genetics, bioinformatics, chemistry, imaging, and medicine—to unravel what makes cancer susceptible to metastasis and what drives the process to completion once it has started. With knowledge about these aspects of cancer, therapy can be targeted to the metastatic process and individually tailored for each patient to avoid the toxicity of overly aggressive treatment.

To date, the University of Chicago team has made significant progress. "Ludwig funding has allowed us to carry out true bench-to-bedside research, in particular to develop novel nuclear receptor targeted therapies that have application in advanced breast, prostate, and ovarian cancers," said Center Co-Director Geoffrey Greene, PhD, Virginia and D.K. Ludwig Professor and Chair of the Ben May Department for Cancer Research at the University of Chicago. Dr. Greene’s group is studying the use of steroid hormone analogs and their receptors to treat metastases, determine their location, and deliver cancer-killing treatments directly to tumor cells. They have found that steroid receptors can provide accessible and highly specific targets, even in advanced metastatic disease. Another fruitful area of research has been in radiation therapy. "We’ve already had some success using prostate-targeted hormone-activated radiotherapy for patients with a limited number of metastases,” Dr. Weichselbaum said. “We completed small clinical trials involving patients with fewer than five metastases and no proven treatment options. At least 20 percent of those patients are still alive five years after their therapy. We are also developing genetic classifiers to identify those patients who are most likely to benefit from this approach.”

Additionally, Dr. Weichselbaum and colleagues are looking at ways to stimulate the immune system to boost the effectiveness of radiation therapy against cancers that are prone to relapse. He recently published a paper with Yang-Xin Fu, MD, PhD, professor of pathology, which showed in pre-clinical studies that combining high-dose sonication radiation therapy with immune modulators successfully suppressed tumor growth and amplified the anti-tumor effect. They now plan to translate these findings into analysis of patient samples and further test this novel combination therapy.

The Center also will continue promising studies of treatment, using highly focused radiation and other tools, for patients with oligometastases—a term coined by physician-scientists at the University of Chicago in 1994 to describe the intermediate state between localized disease with widespread metastasis.

University of Chicago researchers have also been studying the genes and processes involved in metastasis and developing and testing new targeted therapies. Marsha Rosner, PhD, Charles B. Huggins Professor of the Ben May Department for Cancer Research, is investigating the molecular mechanisms that underlie metastatic progression in breast cancer. Her laboratory discovered that the transcription factor BACH1 inhibits the metastatic suppressor Raf kinase inhibitor protein (RKIP). These findings illustrate that the BACH1-RKIP regulatory network plays an important role in establishing non-genetic tumor heterogeneity to drive breast cancer progression and metastasis, and may serve as a target for metastasis prevention or treatment.

Because of novel discoveries taking place at the University of Chicago and other Ludwig Centers, patients with metastatic disease may not be told that they have run out of options. Instead, they will receivehope and a realistic chance to beat cancer through the development of novel metastasis-focused treatments.

FROM THE DIRECTOR

In this issue of Pathways to Discovery, we are reporting on branches of science that have the potential to turn the tide in our fight against cancer. First, we are a leader in the study of metastasis, the deadliest aspect of cancer. A generous gift by the Ludwig Institute is enabling us to make substantial progress in understanding and treating this fundamentally complex component of cancer. Through these discoveries, patients with metastatic disease have new options and a realistic chance to beat cancer.

Cancer prevention and control, one of our strengths at the University of Chicago Medicine Comprehensive Cancer Center, is another area that can have a major impact on reducing the burden of cancer. The latest statistics on the world’s cancer burden have been published, and the picture it paints is grim. Cancer was the biggest cause of mortality across the globe in 2012, and cancer incidence is expected to rise by 57% over the next two decades. The report also mentioned that approximately half of all cancers worldwide could be avoided if our current knowledge about cancer prevention was put into practice.

In the fourth installment of our personalized medicine series, we describe advances in cancer immunotherapy. Triggering the body’s immune system to attack cancer or, at least, enhance the efficacy of other therapies, has the potential to revolutionize cancer treatment. Our investigators are leading the way by discovering the basic mechanisms by which cancer cells and immune cells in the tumor microenvironment communicate and pioneering new approaches to cancer immunotherapy.

One of the complications for cancer patients who have undergone lymph node removal or radiation therapy is lymphedema—a build-up of fluid in the soft tissue of upper and lower extremities. There is no cure for this condition, but the University of Chicago Medicine now offers a surgery called lymphovenous bypass, which allows the lymph nodes to flow freely and decreases a patient’s swelling. Dr. David Chang, a recent addition to the other therapies, is one of the few surgeons in the country who performs it.

We are also featuring an inspirational story about a woman who was devastated to learn she had colorectal cancer soon after she became pregnant with her first child. But a team of doctors at the University of Chicago Medicine were unique in believing that they could save her baby. Read how their expertise treated her cancer, and also allowed for a normal pregnancy. As illustrated through these stories, the Comprehensive Cancer Center is using powerful science to break into areas that will lead to the most transformative changes in patient care.

Regards,

Michelle M. Le Beau, PhD
Director, The University of Chicago Medicine Comprehensive Cancer Center
Assistant and Marian Edelstein Professor of Medicine
Michelle M. Le Beau, PhD
Director, The University of Chicago Medicine Comprehensive Cancer Center
Assistant and Marian Edelstein Professor of Medicine
At the Forefront of Breast Cancer Surgery

T he University of Chicago Medicine is an accredited site for breast cancer care by the National Accreditation Program for Breast Centers. This distinction reflects the institution’s dedication to high-quality patient care and outcomes across multiple areas, including patient education, research, and survivorship programs, as well as consultations and treatment by breast surgeons, plastic surgeons, medical and radiation oncologists, and nurses. The hospital also boasts an American College of Radiology-accredited mammography facility which now offers same-day breast screenings and same-day diagnostic mammograms.

Breast cancer advances have long been a part of the university’s history. Researchers have been focused on the development of computer-aided diagnosis (CAD) methods for the detection and differential diagnosis of abnormalities on radiologic images for decades. One of the first cancer imaging programs in the nation was developed in 1994 and in 2010, Radiology Professor Maryellen Giger, PhD, and members of her research team, debuted an intelligent breast workstation for computer-aided diagnosis research team, debuted an intelligent breast workstation for computer-aided diagnosis (CADx) and quantitative image analysis, which reviews data from multimodality (CADx) and quantitative image analysis, that Column reviews data from multimodality and helps evaluate and characterize abnormalities on radiologic images for computer-aided diagnosis (CAD) methods in the condition, as there is no cure, and the protein-rich lymph fluid can cause infections. Historically, physicians have treated lymphedema with nonsurgical therapies, including compression garments, antibiotics, exercise rehabilitation, and massages. Dr. Chang is largely credited with pioneering and popularizing lymphovenous bypass and vasculature lymph node transfer in the United States, and is one of a few surgeons in the country who performs them regularly. These procedures are challenging and technical, requiring a high level of finesse. Lymphovenous bypass involves injecting a green dye that illuminates the lymphatic vessels as Dr. Chang views them with a sophisticated infrared camera. He traces the vessels on the skin and then makes several tiny incisions to reach them. Using microsurgical tools, he makes cuts in the vessels and nearby veins and then sews them together to bypass areas that have built-up fluid. As the lymph flows more freely, the swelling decreases. The entire procedure takes 4–6 hours, and patients are discharged in less than 24 hours.

Another exciting development in the surgical treatment of lymphedema that Dr. Chang has been involved in is microvascular lymph node transfer. Particularly for breast cancer patients who have lymphedema and also are in need of breast reconstruction, microvascular breast reconstruction and lymph node transfer can be combined to provide simultaneous breast reconstruction and treatment of lymphedema. In lymph node transfer, healthy vasculature lymph nodes (lymph nodes that have a rich blood supply) are microsurgically transplanted to an area of lymphatic injury to reestablish lymphatic connections. “The one thing that almost all my lymphedema patients appreciate after lymphedema surgery is improved quality of life,” Dr. Chang said. “This disease can be destructive to one’s lifestyle after already having survived cancer. Many patients are just incredibly thankful that they can reclaim their lives after surgery and return to doing the things they’ve always enjoyed.”

In addition to lymphedema surgery, Dr. Chang has developed a national and international reputation as an expert and an innovator in the field of breast reconstruction and attracts patients from all over the world. He has published numerous papers on this topic.

Silver Cross Hospital is launching the first multi-disciplinary Lung Cancer Conference in Will County. Patients will benefit from a team of experienced lung cancer specialists who will coordinate all aspects of care and planning so patients can begin treatment within the shortest time possible. Typically, patients who suspect they have or are already diagnosed with lung cancer meet with several different specialists before starting treatment, a process which can take several weeks or even months. With the one-stop Lung Cancer Conference, patients come to one location and a team of experts reviews their medical information and develops a plan of care all on the same day. The Lung Cancer Conference is held every Tuesday at the University of Chicago Medicine Comprehensive Cancer Center at Silver Cross Hospital.

Open Cancer Clinical Trials

Patient enrollment is under way for more than 350 clinical trials at the University of Chicago Medicine Comprehensive Cancer Center. A few of our newly launched clinical trials include:

- A Phase II/III randomized trial of two doses of MK-3475 versus docetaxel in previously treated subjects with non-small cell lung cancer–Michael Maitland, MD, PhD, principal investigator.
- A Phase II open-label, single-arm, two stage, multicenter trial of pracinostat in combination with azacitidine in elderly patients with newly diagnosed acute myeloid leukemia (AML)–Olatoyosi Odunsi, MBBS, MBB, principal investigator.
- A Phase II study of belzutuximab alone or in combination with TRC105 for advanced renal cell cancer–Walter Stadler, MD, principal investigator.
- Phase I study of imipetuzimab in combination with enbulin in patients with metastatic triple negative breast cancer–Rita Hundra, MD, principal investigator.

To learn more about these or any other UCCC clinical trial, call toll-free 1-855-702-8222 for adult clinical trials or 1-773-702-6808 for pediatric clinical trials, or go to cancer.uchicago.edu and click on Search Clinical Trials in the blue box.
The Power of Mobilizing the Immune System for Cancer Therapy

HIGHLIGHTED AS THE “Breakthrough of 2013” by the leading scientific journal Science, cancer immunotherapy is finally getting the attention many in the field thought it long deserved. This breakthrough is not the result of one or two “eureka” moments. Instead, it is the culmination of more than two decades of insights made into the basic biology of immune cell action, followed by remarkable success in pre-clinical studies, anecdotes of impressive responses in individual patients and, finally, robust clinical trials.

Immunotherapy, the use of immune system components to treat cancer, encompasses diverse approaches from stimulating a patient’s immune system to attack tumor cells to administering immune system components such as antibodies as a cancer treatment. The identification of tumor antigens, which are the tumor-specific peptides or proteins that trigger an immune response, led to the development of specific therapeutic cancer vaccines against these antigens. Our current understanding of the complex immunoregulatory processes active in the tumor microenvironment (i.e., the cellular environment in which tumor cells interact with blood vessels, immune cells, and other cell types) has further accelerated immunotherapy development. In fact, anti-cytotoxic T-lymphocyte antigen (CTLA)-4 antibody (ipilimumab) treatment improved survival of melanoma patients by 20%.

It was approved by the U.S. Food and Drug Administration for the treatment of advanced melanoma in 2011. Recent studies of combination therapy with this anti-body and nivolumab, an antibody against the programmed death 1 (PD-1) receptor, in melanoma patients looks even more promising. These findings, and others, illuminate the potential of harnessing the immune system for cancer therapy and suggest that researchers are only scratching the surface of its promise.

At the University of Chicago Medicine Comprehensive Cancer Center, investigators are pioneering new approaches to cancer immunotherapy and discovering the basic mechanisms by which cancer cells and immune cells in the tumor microenvironment communicate. The laboratory of Yang-Xin Fu, MD, PhD, professor of pathology, is developing ways to mobilize the immune system for more robust anti-tumor therapy. In a recent report published in the journal Cancer Cell, they uncovered how tumors develop resistance to therapeutic antibodies that target oncoproteins such as HER2 and the epidermal growth factor receptor (EGFR). These antibodies, such as cetuximab and trastuzumab, are used to treat specific types of breast, head and neck, and colorectal cancer. Dr. Fu and his team demonstrated that immune modulation with the powerful cytokine interferon beta (IFNβ) controls antibody resistance in preclinical tumor models. This design of a next generation of antibody-based cancer therapy, which Dr. Fu compared to the combination of a muslce and a bomb, allows for stimulation of immune cells in the tumor microenvironment for sustained tumor destruction.

As Dr. Fu explained, “Tumors are heterogeneous, and traditional treatments will result in the outgrowth of a particular population that has become resistant to that treatment. To prevent tumor relapse, we now appreciate that you have to understand and mobilize the immune system.”

In a long-time collaboration with Ralph Weichselbaum, MD, D.K. Ludwig Professor and Chair of Radiation and Cellular Oncology, Dr. Fu also is identifying ways to use the immune system to enhance the anti-tumor effects of radiation therapy. Their recent work showed that blockade of the T-cell modulator programmed death-ligand 1 (PD-L1) made radiation much more effective at shrinking tumors in preclinical models. These findings suggest that radiation, T cells, and the PD-L1 signaling networks function together and could be exploited for designing potent combination therapies with immune modulators and radiotherapy.

Other promising advances in the field of immunotherapy have come from Comprehensive Cancer Center members Thomas Gajewski, MD, PhD, professor of pathology and medicine and leader of the Immunology and Cancer Program of the Comprehensive Cancer Center, and Hans Schreiber, MD, PhD, professor of pathology. Dr. Gajewski’s group focused on the regulation of anti-tumor immunity and recently showed that CD8+ T cells drive PD-L1 production and regulatory T cell accumulation in the melanoma tumor microenvironment, which are now being targeted therapeutically. Characterizing how tumors escape from host immunity is a major effort in Dr. Schreiber’s laboratory. They showed, in a 2013 study published in Cancer Cell, that tumor relapse is determined by how strongly tumor antigens are bound to the cell surface molecules that ultimately elicit an immune response such that only high-affinity interactions lead to cancer eradication. Additionally, all three laboratories collaborate extensively to tackle the biggest challenges in immunotherapy field.

A Conversation With... Yang-Xin Fu, MD, PhD

Professor of Pathology

If you were not a physician, what would your profession be?

I would still be a scientist

What is the most rewarding part of your job?

Developing a new idea to be tested and appreciated

Is there a professional goal that you have not yet accomplished?

A translational strategy or drug that can benefit many patients

If you had one piece of advice for someone considering your field, what would it be?

Be patient and be organized

Who inspires you?

Many great scientists

Where would you like to go on your next vacation?

A warm place

What is your favorite way to relax?

Watching movies or meeting old friends

"A translational strategy or drug that can benefit many patients"
Fitfully, the most recent analysis of global cancer statistics was released by the World Health Organization’s International Agency for Research on Cancer. The 2014 World Cancer Report, edited by Drs. Bernard W. Stewart and Christopher P. Wild, paints a grim picture of the worldwide cancer burden. Responsible for an estimated 8.2 million deaths in 2012, cancer was the biggest cause of mortality across the globe. In terms of incidence, cancer cases have increased by 11% in the last four years, to an estimated 14.1 million cases in 2012. Perhaps the most sobering statistic from the Report is that cancer cases are set to rise by 57% and reach close to 22 million over the next two decades. Developing countries are disproportionately affected by this increasing cancer burden, as more than 60% of the cases, and 70% of cancer deaths, occur in Africa, Asia, and Central and South America. This gap likely reflects their growing and aging populations, but also is likely deepened by a lack of screening programs and access to treatment. Even in higher income nations, the burgeoning cost of cancer care is putting remarkable strain on healthcare systems. For example, the total annual economic cost of cancer globally was estimated to reach US$1.16 trillion in 2010.

Cancer control and prevention is a major challenge, but the potential payoff is monumental. One of the most striking findings contained in the Report was that approximately half of all cancers worldwide could be avoided if our current knowledge about cancer prevention was put into practice. The modifiable behavioral and environmental factors that contribute most significantly to cancer include smoking, infections (namely hepatitis B and human papillomavirus [HPV] for liver and cervical cancer, respectively), alcohol consumption, obesity and physical inactivity, radiation exposure (sun and from medical devices), air pollution and other environmental factors, and delayed childbearing and not breastfeeding.

Researchers at the University of Chicago Medicine Comprehensive Cancer Center are trying to tackle cancer prevention and control, and health disparities, from many different directions. First, our global fingerprint is extensive, focusing on regions of the world such as Southeast Asia and beyond. For example, the University of Chicago Center for Global Health, launched as the Global Health Initiative in 2009 under the direction of Olufumilayo Oyadare, MD, Walter L. Palmer Distinguished Service Professor of Medicine and Director of the Center for Clinical Cancer Genetics, works with community-based organizations across Africa to facilitate advocacy and cancer research and training. In a partnership with the African Organization for Research and Training in Cancer, The University of Ibadan, Nigeria, and the University of Capetown, South Africa, they are providing accurate information on cancer prevention, detection, treatment, and palliative care, and reducing the stigma associated with a cancer diagnosis.

Global investigator-initiated research efforts include multiple NIH-funded projects of Habibul Ahsan, MB, MBBcSc, Louis Block Professor of Health Studies, Medicine and Human Genetics and Associate Director for Population Research of the Comprehensive Cancer Center, investigating gene–environment interactions in cancer risk and approaches to cancer prevention in Bangladesh. Brian Chiu, PhD, associate professor of health studies, is the principal investigator of the AsianLymph Taiwan Center, a component of the National Cancer Institute’s multicenter international-based study of lymphoma etiology in Asia, particularly examining environmental, chemical and viral exposure as well as genetic susceptibility.

A specific area of interest of the Comprehensive Cancer Center’s program in cancer prevention and control is cutting-edge research in behaviors that influence cancer risk. Andrea King, PhD, professor of psychiatry and behavioral neuroscience, is a leader in understanding the contribution of smoking and alcohol consumption to cancer risk, as well as developing smoking cessation programs such as Courage to Quit™ aimed at reducing the disparity in smoking quit rates in approximately 1,500 urban smokers in Chicago. As another example, Health4Chicago™ is a partnership between Comprehensive Cancer Center investigator Kenneth Alexander, MD, PhD, professor of pediatrics, and University of Illinois at Chicago researchers to promote child and adolescent health in Chicago schools by providing vaccinations for HPV, among others. As the World Cancer Report illustrated, the growing economic burden of cancer both nationally and globally is staggering. The cancer economics group in the Comprehensive Cancer Center, including Ya-Chen Tina Shih, PhD, associate professor of medicine; Rena Conti, PhD, assistant professor of pediatrics; Jonas de Souza, MD, instructor of medicine; David Meltzer, MD, PhD, associate professor of medicine; and Fabriczio Smeiniakas, PhD, assistant professor of health studies, is at the forefront of this critically important research area.

Ongoing research projects focus on the cost and use of on-label and off-label chemotherapeutic drugs in the United States, the impact of new technologies in the outcomes and costs of cancer care, the theoretical foundations of medical cost-effectiveness analysis, and the impact of healthcare reform on cancer costs and outcomes in the United States.

“The WHO Report highlights that the menace of cancer is rapidly spreading worldwide,” said Dr. Ahsan. “The Report also underscores the importance of prevention in tackling this impending pandemic. Comprehensive Cancer Center researchers, with increasing depth and breadth in cancer prevention research both locally and globally, are well poised to fight this global menace.”

The University of Chicago partners with the Pancreatic Cancer Action Network

Although pancreatic cancer is one of the deadliest cancers, there is hope that by advancing research and enhancing advocacy efforts, patient support services and awareness, significant progress will be made. Together, the University of Chicago Medicine and the Pancreatic Cancer Action Network (PanCAN) hosted a Breakfast, titled “February 20 to Take Off: From Program to Progress”, on February 18, 2014, at the University of Chicago Bombay Stede 5K Run/Walk to be held on April 26 in Lincoln Park at Montrose Harbor Event Honorary Chairs and Comprehensive Cancer Center members Irving Waxman, MD, Hedy Kindler, MD, and Mitchell Rosner, MD, were joined at the Breakfast by Laurie McCaskill, Chair of the PanCAN National Board of Directors (far left) and Julie Fleshman, President and CEO of PanCAN (far right).

Mini-Lecture Series Tackles Issues in Cancer Disparities Research

A series of mini-lectures on cancer disparities were launched at Chicago State University (CSU). The University of Chicago Medicine Comprehensive Cancer Center Office of Community Engagement and Cancer Disparities (OCECD), led by Karen E. Kim, MD, professor of medicine, partnered with CSU to develop the Chicago Southside Cancer Disparities Initiative, an infrastructure for cancer education, training, and outreach to improve the pipeline for increasing diversity in research. An aim of this Initiative is to create an interprofessional cancer disparities curriculum for CSU’s Master of Public Health (MPH) students and University of Chicago Pritzker School of Medicine students. The lectures were held January 30, February 26, and March 19, with another planned for April 23. The content from the mini-lectures will be integrated into the MPH curriculum at CSU and the Pritzker School of Medicine’s “Healthcare Disparities in America” course curriculum.
Four Comprehensive Cancer Center members have been honored with named professorships. A named professorship is the highest academic honor accorded by a university and is awarded only to the most distinguished scientists and clinicians.

1. Ernst Lengyel, MD, PhD, chair of the Department of Obstetrics and Gynecology, has been named the Arthur L. and Lee G. Herbst Professor of Obstetrics and Gynecology.
2. Jessica J. Kandel, MD, professor of surgery, section chief of pediatric surgery and surgeon-in-chief at the University of Chicago Medicine Comer Children’s Hospital, has been named the Mary Campau Ryerson Professor.
3. S. Diane Yamada, MD, professor in the Department of Obstetrics and Gynecology and section chief of gynecologic oncology, is the Joseph Bolivar DeLee Professor.
4. Irving Waxman, MD, professor of medicine and surgery, has been appointed a Sara and Harold Lincoln Thompson Professor.
5. Karen Kim, MD, professor of medicine, has been named as a Dean for Faculty Affairs in the Biological Sciences Division (BSD). Dr. Kim is the chair of the Department of Medicine’s Women’s Committee and director of the University of Chicago Medicine Comprehensive Cancer Center Office of Community Engagement and Cancer Disparities. She serves on numerous committees that support initiatives focused on mentorship, medical education, and diversity and inclusion. In her new role, Dr. Kim will work closely with the Dean’s office, alongside Dr. Melina Hale who also serves in this capacity, to identify goals and strategies to develop initiatives that support BSD faculty.
6. Marsha Rosner, PhD, Charles B. Huggins Professor and immediate past-chair of the Ben May Department for Cancer Research, was elected as a fellow of the American Association for the Advancement of Sciences (AAAS), the world’s largest general scientific society. Dr. Rosner is being honored for her distinguished contributions to the field of signal transduction, particularly for characterization of novel kinases and the function and regulation of the MAP kinase pathway. In February, she joined 388 newly elected AAAS fellows who were presented with a rosette and certificate at the AAAS Annual Meeting in Chicago.
7. Sonali Smith, MD, associate professor of medicine, has been invited to serve on the editorial board of the Journal of Clinical Oncology (JCo), the official journal of the American Society of Clinical Oncology. Dr. Smith is serving a three-year term, beginning in January.
8. Raymon Grogan, MD, assistant professor of surgery, was awarded a Paul Calabresi Career Development Award for Clinical Oncology (K12 grant mechanism) from the NCI. Under the mentorship of Kenan Onel, MD, PhD, associate professor of pediatrics, Dr. Grogan will further his work studying gene-environment interactions that modulate thyroid cancer heterogeneity. Dr. Grogan’s long-term goal is to characterize the heterogeneity of thyroid cancer and understand the mechanisms of this heterogeneity in order to eliminate over-diagnosis, reduce treatment of clinically insignificant cancers, and improve outcomes for aggressive forms of thyroid cancer.

Shooting Hoops for Cancer: Associates Board Holds Charity Basketball Tournament

On January 18, the University of Chicago Cancer Research Foundation Associates Board hosted “Sweat for a Cause,” their very first 3-on-3 Basketball Tournament at Francis W. Parker School. Teams of three to four players each competed against one another on half-courts for the championship spot in the men’s and women’s divisions. Proceeds from team registration will support immunology research at the University of Chicago Medicine Comprehensive Cancer Center. The players and supporters celebrated their victories on the court and fundraising success with an after-party at Benchmark sports bar. The Associates Board is a passionate and active group of young philanthropists dedicated to raising the funds necessary to aid in the prevention and cure of cancer.

Players and spectators alike cheered one another on with these encouraging signs during the tournament.
Pathways to Discovery

RESEARCH HIGHLIGHTS
The following represent some of the research accomplishments of University of Chicago Medicine Comprehensive Cancer Center members published December 2013–February 2014.

Metastasis Regulators RKIP and BACH1 Control the Metastatic Progression of Breast Cancer
Metastasis is the major cause of cancer-related deaths; yet, the molecular mechanisms underlying nongenetic variability in metastatic progression are not well understood. Dr. Matthew Snook, PhD, and Charles B. Huggins Professor of the Ben May Department for Cancer Research, charac-
tered a regulatory network that creates nongenetic heterogeneity in breast cancer cells, thereby promoting metastasis. Extending her group’s previous observations that the transcription factor BACH1 is negatively regulated by the metastasis suppressor Raf kinase inhibitory protein (RKIP), they identified a double-negative feedback loop in which BACH1 inhibits RKIP transcription, while RKIP represses BACH1. Dr. Rosner’s laboratory discovered that corepressors, such as histone deacetylases (HDACs) and the polycomb repressor enhancer-of-zeste, contribute to BACH1-mediated inhibition of BACH1 and RKIP expression. Further, they used single-cell analysis to validate their mathematical modeling and uncover a mutually repressive relationship between BACH1 and RKIP. These findings illustrate that the BACH1-RKIP regulatory network plays an important role in establishing nongenetic tumor heterogeneity to drive breast cancer progression and metastasis, and may serve as a target for metastasis prevention or treatment. (Lee et al., PNAS 111:11815-20, 2014)

Immunotherapy and Radiation Synergize to Promote Anti-Tumor Immunity
Radiation using high-dose ionizing radiation (IR) is a common approach for the treatment of primary and metastatic cancers; however, local relapses frequently occur. One hypothesis is that IR induces an immunoreactive response, which potentially promotes tumor regression but also can trigger resistance mechanisms that contribute to relapse. This hypothesis, and the potential of combining radiation and immunotherapy as a cancer treatment, was tested in preclin-
ical studies by Yang-Xiu Fu, MD, PhD, professor of pathology, and Ralph Weich- selbaum, MD, D.V. Ludwig Professor of Radiation & Cellular Oncology. Using colorectal cancer cell models, the research team found that the expression of PD-L1, a potent immune suppressor, was induced in tumor cells and in the microenviron-
ment following IR exposure. To test the functional significance of PD-L1 upregulation, tumor cells were cultured separately with IR and PD-L1 function-blocking antibodies in mouse models. Although each individual treatment had modest effects on cell proliferation and tumor growth, co-treatment with IR and anti-PD-L1 antibodies synergisti-
cally amplified the anti-tumor effect. Addressing the mechanism responsible, the investigators discovered that PD-L1 T cells were required for the efficacy of the combination therapy, and myeloid-derived suppressor cell accumulation in the tumor microenvironment was reduced by IR and anti-PD-L1 treatment. These data provide evidence for extensive crosstalk between T cells, IR signaling pathways, and the PD-L1/PD-1 immune response axis in cancer. They also support the translation of these findings into analysis of patient samples and the rational design of combi-
nation therapy with immune modulators and radiotherapy. (Deng et al., J Clin Invest 124:687-95, 2014)

Epigenetic Modifications Regulate Stem and Progenitor Cell Commitment during Eythrosity
Lineage commitment by hematopoietic stem and progenitor cells is characterized by induction of a well-defined transcriptional program that enables expression of genes that maintain the self-renewal compartment. Little is known, however, about the epigenetic changes that accom-
pany and may control lineage commitment and differentiation. Building upon technologies developed by Chun He, PhD, professor of chemistry, to map 5-hydroxy-
methylcytosine (5-hmC) modifications throughout the genome, Lucy Godley, MD, PhD, associate professor of medicine, sought to identify the global levels of 5-hmc modifications during erythropoiesis. Godley turned to a powerful human in vivo model system created and optimized by Amitha Wickrema, PhD, associate professor of medicine, and the investigators, including Bruce Lahn, PhD, William B. Graham Professor of Human Genetics, characterized dynamic changes in 5-hmc and 5-methylcytosine (5-mc) levels in a locus-specific focus of 5-hmc during erythroid differentiation. They analyzed the DNA los that gained 5-hmc modifications, and found that the genomic regions gaining 5-hmc were enriched for sites of specific transcription factor binding sites and correlate with activating histone marks. Importantly, leukemia patient-derived stem cells/ early progenitors contain mutations in the TET2 (encoding a methylcytosine dioxygen-
ase that converts 5-mc to 5-hmc) gene and demonstrated 5-hmc patterns, disrupting 5-mc patterns, impaired erythroid differentiation and augmented myeloid potential. These results establish hydroxymethylation as a critical epigenetic regulator of adult hematopoietic stem/progenitor cell commitment and differentiation. Further, given that epigenetic modulators are being pursued vigorously as anticancer drugs, extending these studies into clinically relevant preclinical models of myeloid malignancies will test their broader impact. (Madro et al., Cell Rep 6:231-44, 2014)

Anatomically Relevant Effects of MET/ON Inhibitor in Lung Cancer
Non-small cell lung cancer comprises the majority of lung cancers and is char-
acterized by multiple genetic alterations, including the amplification of the MET receptor tyrosine kinase and overexpres-
sion of the related BDNF kinase receptor. A study led by Ravi Salgia, MD, PhD, professor of medicine, in collaboration with Everett Vokes, MD, John E. Ultmann Professor of Medicine, addressed the efficacy of a potent dual MET/RON small molecule inhibitor (LY2016063) in anatomical and clin-
ical models of non-small cell lung cancer. The investigators found that LY2016063 was more effective than the tyrosine kinase inhibitor crizotinib (as approved treatment for advanced non-small cell lung cancer), and elicited distinct effects on downstream signaling, including reduced activation of the CBL, PI3K, and STAT3 kinases. Treatment with the dual kinase inhibitor also dramatically suppressed tumor growth in xenograft models by antagonizing cell proliferation and angiogenesis. These data provide preclinical evidence for the robust anti-tumor effect of targeting MET and RON using a dual kinase small molecule inhibitor in non-small cell lung cancer, and set the stage for testing this promis-
ing therapeutic strategy in clinical trials. (Kawada et al., Cancer Res 74:884-95, 2014)

The SIRT1 Protein Deacetylase Contributes to Skin Cancer Development
As an NAD-dependent protein deacetylase, sirtuin (SIRT1) controls cellular metabo-

lism, survival, and stress response, but conflicting data support its role as a tumor suppressor and oncogene depending on the tumor type and context. Yu-Ying He, PhD, assistant professor of medicine, sought to characterize SIRT1 action in ultraviolet B (UVB)-induced skin cancer using a mouse model with targeted deletion of the Sirt1 gene in keratinocytes. Surprisingly, Dr. He’s group identified a dual role for SIRT1 depending on gene dosage. Whereas heterozygous Sirt1 deletion promoted UV-induced skin carcinogenesis, homo-

zygous deletion suppressed tumor development but sensitized a resistant strain to chronic solar injury. They characterized the effect of Sirt1 deficiency on DNA damage repair pathways, and observed that gene dosage regulated distinct molecular networks controlling DNA repair and skin cell survival, consistent with its impact on tumorigenesis. These findings suggest that epithelial cells in the skin are exquisitely sensitive to SIRT1 levels, and that Sirt1 is a critical regulator of skin cancer development via modulation of DNA repair and survival pathway signaling. (Ming et al., Oncogene ahead of print, 2014)

EPSI Inhibition Sensitizes Lung Cells to Cisplatin
Cisplatin is a commonly used chemothera-
peutic drug for many types of cancer, but its use is frequently accompanied by devastat-
ning side effects, including neurotoxicity, renal toxicity, and ototoxicity. In an effort to understand the genetic mechanisms responsible for the toxic side effects of cisplatin, M. Eileen Dolan, PhD, professor of medicine, is using cell-based models and high-throughput technologies to map 5-hydroxymethylation as a critical epigenetic mechanism for β-catenin-induced tumor cell sensitization to this agent, as well as to cys-
taxin-based cell death. Her laboratory recently identified a common single nucleotide polymorphism (SNP) in the gene epigenomic growth factor receptor (EGFR) pathway substrate 8 (EPSI) associated with lower cisplatin-induced apoptosis and higher survival. Inhibition of EPSI expression using RNA interference and mithramycin treatment decreased the sensitivity of lymphoblastoid cell lines to cisplatin. Several non-small cell lung cancer cell lines and a bladder cancer cell line demonstrated increased sensitivity to cisplatin when EPSI levels were suppressed by RNA interference. Notably, an EGFR-mutant non-small cell lung cancer line is insensitive to EPSI inhibition with respect to cisplatin-induced cell death. Further characterization of this EGFR pathway component may lead to approaches to improve cisplatin treatment by enhancing tumor cell sensitivity and simultaneously minimizing its toxic effects on normal cells. (Gorici et al., PLoS One 8:48222, 2013)

This work was supported by National Institutes of Health grants CA141924, CA158006, CA158082, and CA15800, the American Cancer Society grant 1046, I11:391-96, 2014)
Expert Team Helps Woman Beat Colorectal Cancer and Deliver a Healthy Baby Girl

Just a few weeks after Michelle Jahnke learned she was pregnant with her first child, joy turned to sadness, then fear. The 30-year-old was diagnosed with stage 3 rectal cancer.

“The standard of care for her disease included combined chemotherapy and radiation therapy, followed by surgery and then adjuvant chemotherapy. Free physicians told Jahnke she was terminally ill, that her pregnancy; her unborn child would not survive radiation or surgery. One oncologist told her, ‘there is nothing I can do to help your baby.’”

But University of Chicago Medicine oncologist Blaise Polite, MD, MPH, assistant professor of medicine, told Jahnke and her husband, Mark, that a novel approach to therapy was possible—one that could treat the cancer and save their baby. To achieve that goal, Dr. Polite assembled a multidisciplinary team of experts that included four University of Chicago Medicine Comprehensive Cancer Center members. The University of Chicago Medicine physicians and surgeons collaborated closely to plan and implement each step of Jahnke’s treatment and the delivery of her child.

“My job was to figure out a way, first and foremost, to cure the cancer, but then also to come up with a way for Michelle to carry the baby to term,” Dr. Polite said. A nationally known expert in gastrointestinal cancer care, Dr. Polite works on a team of colorectal specialists that sees a high volume of cases and regularly designs individualized treatment plans for their patients. “We know there are different ways to successfully treat colorectal cancer,” he said.

During his first meeting with Jahnke, Dr. Polite explained that a new treatment protocol—chemotherapy alone before surgery—would soon be examined in a clinical trial for rectal cancer. Based on previous studies of babies born to mothers who had chemotherapy for breast cancer while pregnant; a careful review of the pharmacology with specially trained oncology pharmacists; and discussions with colleagues around the country, Dr. Polite believed giving chemotherapy at full doses to Jahnke during her pregnancy would be safe for her baby. He concluded that surgery and, if needed, radiation could wait until after the birth.

A University of Chicago Medicine obstetrician specializing in high-risk pregnancies used frequent ultrasounds to regularly observe the growth of Jahnke’s fetus throughout the pregnancy. He collaborated with Dr. Polite and other members of her medical team to monitor Jahnke’s overall health. Jahnke’s healthy baby girl was delivered by Cesarean section November 30, 2012, weighing six pounds. “Elana continues to thrive and is reaching all of her milestones,” Jahnke said.

Stanley Lucent, MD, associate professor of radiation and cellular oncology, determined that while the chemotherapy had successfully kept the cancer in check, radiation still was necessary. Jahnke elected to have proton therapy at a suburban location. Luain consulted with the proton center, reviewing and fine-tuning Jahnke’s treatment plan.

Jenalyn Turner, MD, PhD, Sara and Harold Lincoln Thompson Professor and associate chair of pathology, confirmed the diagnosis of rectal cancer. Due to Jahnke’s age (below 30), her tumor was sent out for genetic analysis to rule out any mutations linked to Lynch syndrome, which is associated with an increased risk of colorectal, ovarian, and endometrial cancer. Sonia Kupfer, MD, assistant professor of medicine, specializes in hereditary gastrointestinal cancer syndromes. In Jahnke’s case, “If upcoming advances in genetic testing give us more information,” Kupfer said, “we may be able to tell her more and help future generations of her family.”

After Jahnke finished treatment, she had colorectal surgery at the University of Chicago Medicine to remove the sigmoid colon as well as the majority of the rectum that contained the tumor. The pathology report after surgery showed no remaining tumor cells. As a proactive measure to reduce the likelihood of Jahnke later developing ovarian or endometrial cancer, she also underwent a hysterectomy and an oophorectomy at the same time as the colorectal procedure.

Today, Jahnke has a healthy baby girl and shows no signs of cancer. She recently visited with her physician team and expressed gratitude for her care: “I want to thank you so much from the bottom of my heart, my husband’s heart and my daughter’s heart. We are so appreciative to have had each and every one of you along with us on this journey. My daughter and I are here today because of all of you.”

Genomics Core Enables Research Using Next-Generation Sequencing

Modern medical and biological research relies heavily on genomics. Understanding why cancer occurs and how it progresses requires the ability to sequence DNA. Next-generation sequencing is one of the newest and most powerful tools that researchers use to analyze the function and structure of DNA, RNA, and proteins. “This sophisticated technology can monitor and explore the structure of genomes, the entire sequence of DNA within each cell of an organism. Located on campus in the Knapp Center for Biomedical Discovery, the Genomics Core Facility offers investigators at the University of Chicago Medicine Comprehensive Cancer Center the latest DNA sequencing equipment and computer analysis tools. This sophisticated technology can monitor and explore the genome in a fraction of the time that older approaches with lower accuracy required.

Within the past few years, the facility has made several major enhancements to its technical capabilities. In August 2012, it obtained an Illumina HiSeq2500, which was upgraded to an Illumina HiSeq2500 in February 2013. This instrument replaced the Illumina HiScanSQ and LiTech SOLiD™ SSx0/tm systems and allowed the Facility to provide services using the most advanced next-generation sequencing currently on the market. In addition, the HiSeq2500 features a faster sequencing mode, which boosts turn-around times for high-quality next-generation sequencing services.

“Next-generation sequencing has blossomed into the new way of doing science and is entering mainstream medicine,” said Pieter Faber, PhD, operational director of the University of Chicago’s Genomics Core Facility. “There are so many forms of whole genome analysis that now can be done.”

In addition to next-generation sequencing, the Facility also offers Sanger sequencing/genotyping, microarrays, and real-time PCR (polymerase chain reaction) services. With such large datasets being generated, the Genomics Core Facility works in tight partnership with the Bioinformatics Core Facility.

The most recent purchase in genomics is the Fluidigm C1 Single Cell Auto Prep System, a response to users’ need for single-cell genomics capabilities. This cutting-edge technique captures individual cells in order to analyze each cell’s DNA and RNA profile, providing an advantage over the current standard, which is to sample a population of cells that may or may not be a heterogeneous mixture. Dr. Faber suggests that single-cell genomics may be particularly useful for some fields, such as immunology, developmental biology, and cancer biology.

Taken together, all of these new capabilities are poised to help investigators use genomics to predict cancer behavior and response to therapy, which will ultimately help inform personalized cancer therapiers. For example, Thomas F. Gajewski, MD, PhD, professor of medicine, who investigates and develops new treatments for patients with melanoma, used the Genomics Core Facility recently for one of his experiments. He wanted to know why, in some melanomas, higher levels of T cells were present. Dr. Gajewski performed exome sequencing on the two tumor types (those with T cell infiltration and those without) and comparing the numbers of mutations in protein-coding regions between the two groups. He is also interested in identifying mutations in specific oncogene pathways and signaling/transcription networks in either group of melanomas that could explain immune exclusion.

The Genomics Core Facility is offering Comprehensive Cancer Center researchers, such as Dr. Gajewski, genomics capabilities that can help them answer many important basic and clinical questions. “We always feel like we operate at the edge of tomorrow,” Dr. Faber said. “And the technology is only improving.”

Comprehensive Cancer Center members receive access to shared resources at subsidized rates. For more information on eligible Core Facilities, go to cancer.uchicago.edu/research/core-facilities.
Gala Held to ‘Bet on a Cure’ for Cancer

The University of Chicago Cancer Research Foundation Auxiliary Board held its annual dinner in March at the Michigan Shores Club in Wilmette. More than 200 people attended the gala, which featured dinner, dancing, and a live and silent auction. The Auxiliary Board is dedicated to raising funds to aid in the prevention and cure of cancer, and at this event, they raised more than $175,000. For the third year, funds have supported the work of clinician scientists Jill de Jong, MD, PhD, assistant professor of pediatrics, Peter O’Donnell, MD, assistant professor of medicine, and Michael Spiotto, MD, PhD, assistant professor of radiation and cellular oncology. The emcee was NBC5 News anchor Rob Stafford, and the auctioneer was Alyssa Quinlan.

SAVE THE DATES!
The University of Chicago Cancer Research Foundation presents a list of upcoming fundraising events:

Kuhlman’s Krusaders Fundraiser
Sunday, May 4, 2014
Harry Caray’s Italian Steakhouse, Lombard, IL

WOMEN’S BOARD
Chicago Equestrians for a Cause
Sunday, September 7, 2014
Annali Farm, Antioch, IL

COMPREHENSIVE CANCER CENTER AND FOUNDATION
Shubitz Prize Recognition Dinner
Monday, October 13, 2014
Gleacher Center

WOMEN’S BOARD
Grand Auction
Saturday, November 22, 2014 (new date!)
Four Seasons Hotel, Chicago

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Support cancer research through the UCCRF:
cancer.uchicago.edu/donations