HEMATOLOGY/ONCOLOGY

Lowell E. Schnipper, MD, Chief — The mission of the Hematology/Oncology Division is to provide the highest caliber of technologically expert and humane clinical care for men and women with cancer and benign hematological disorders. We aim to achieve this through the combined efforts of superior clinicians, leading-edge scientists and training programs of unsurpassed excellence. At the intellectual and clinical core of the medical center's Cancer Center, the Division oversees a large clinical program along with well-funded laboratory, translational and clinical research programs. Our goal is the delivery of unparalleled clinical care in an environment that emphasizes development of today's specialists and tomorrow's leaders. Sixty-five faculty members strong, the Division boasts diverse clinical, educational and scientific expertise that contributes to our leadership in benign hematology and solid and hematological neoplasms.

Research Highlights

Iron Overload Syndromes

A recipient of the Basil O'Connor Starter Award from the March of Dimes Research Foundation, Dr. Paula Fraenkel is among the Division's physician-scientists who've continued to make great progress this year. Dr. Fraenkel uses a state-of-the-art zebrafish research facility at BIDMC to identify genes important in iron transport and small molecule inhibitors that can mediate their function. Once the mechanisms for iron transfer/transport are fully understood, she plans to develop these molecules into new therapies for patients suffering from anemia of chronic disease, iron overload as a result of hemochromatosis, thalassemia and myelodysplastic syndrome. Dr. Fraenkel was recently awarded a five-year R01 grant from the National Institutes of Health to pursue this work.

Molecular Imaging

Under the leadership of Dr. John Frangioni, the Frangioni laboratory continues to focus on the first-in-human clinical testing of novel imaging systems and contrast agents for cancer detection. Over the past year, two new image-guided surgery devices, the mini-FLARE near-infrared fluorescence image-guided surgery system and the S-FLARE oxygenation imaging system, have been translated to the clinic and published in peer-reviewed journals. To date, over 250 patients have been imaged worldwide using FLARE technology. With the involvement of Dr. Hak Soo-Kim, a novel robotic chemistry system has been developed to aid in the discovery of peptidomimetic, small molecule, cancer-specific ligands for therapy of prostate cancer and breast cancer.

Resistance to Platinum in Ovarian Cancer

Dr. Pangagiotis Konstantinopoulos and Dr. Stephen Cannistra are tackling the challenging problem of resistance to platinum in ovarian cancers. They demonstrated a previously unrecognized role of the Keap1/Nrf2 pathway in mediating platinum resistance in epithelial ovarian cancer (EOC). Specifically, activation of this

Top: Xiao Zhen Zhou, MD, and Kun Ping Lu, MD, PhD

pathway was found in over half of EOCs with more common occurrence in the clear cell EOC subtype that is particularly chemoresistant. Of note, mutations of Keap1 gene were identified in 29% of clear cell and 8% of non-clear cell tumors. Also, activation of the Nrf2 pathway was associated with platinum resistance and shorter median overall survival. This study suggests that the Nrf2 pathway may be an important alternative target for preventing or reverting platinum resistance in this disease.

Pin1/Pin2 in Cancer and Alzheimer's

Under the leadership of Dr. Kun Ping Lu, the Lu lab has developed a method for generating conformation-specific antibodies. These antibodies are likely to be helpful in developing vaccines against the pathogenic protein conformation of Pin1 and in the early diagnosis and treatment of Alzheimer's and possibly other diseases.

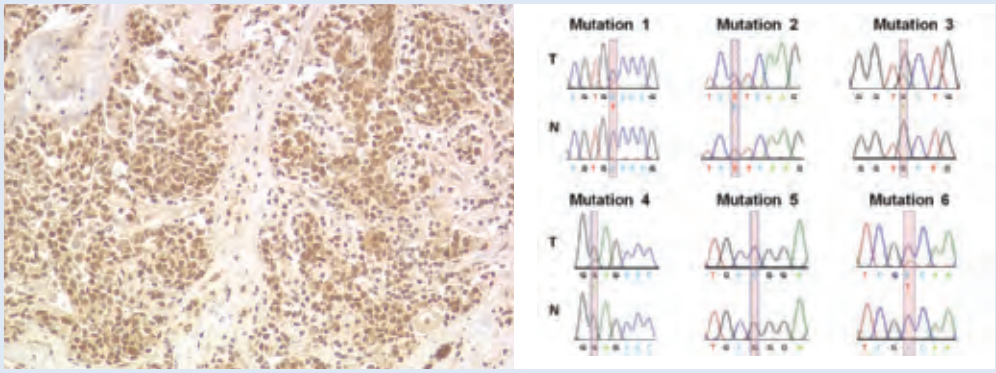
DNA Damage, Repair and Cancer

Dr. Ralph Scully and his colleagues are exploring the relationships between double strand

Faculty

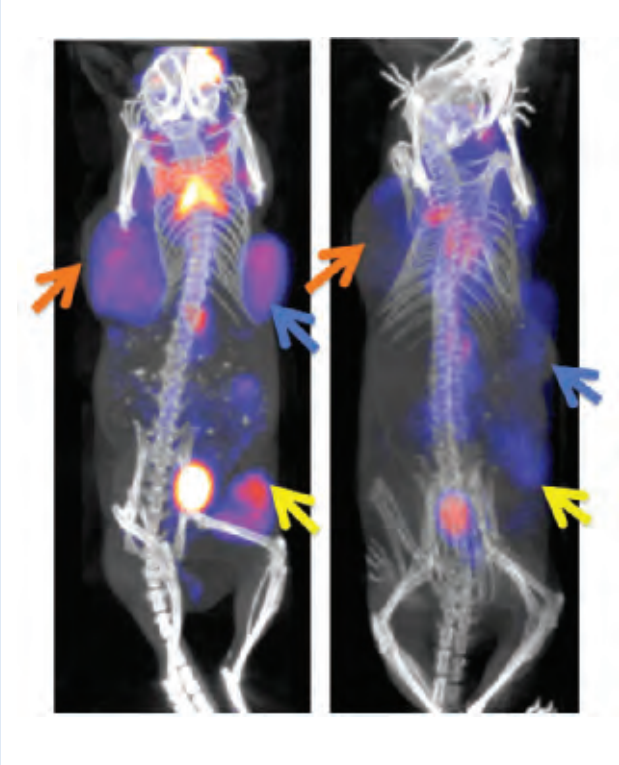
Jon Arnason, MD
Michael B. Atkins, MD
David Avigan, MD
Steven Balk MD, PhD
Kenneth Bauer, MD
Stuart Bless, MD
Rupal Bhatt MD, PhD
Vassiliki Boussiotis MD, PhD
Glenn Bubley, MD
Elizabeth Buchbinder, MD
Andrea Bullock, MD
Mary Buss, MD
Stephen A. Cannistra, MD
Lisa Cavacini, PhD
Shao-Yong Chen, MD
Daniel Cho, MD
Hak Soo Choi, PhD
Amy Comander, MD
Steven Come, MD
Daniel Costa MD, PhD
Reed Drews, MD
Alexander Ebralidze, PhD
Mark Exley, PhD
Laurie Feldman, PhD
Paula Fraenkel, MD
John V. Frangioni MD, PhD
Marc Garnick, MD
Michael Goldstein, MD
Christina Herold, MD
Mark Huberman, MD
Rinath Jeselsohn, MD
Robin Joyce, MD
Walk Kagan, MD
Kerry Kilbridge, MD
Susumu Kobayashi MD, PhD
Pangagiotis Konstantinopoulos MD, PhD
Stephen Landaw, MD
Roger Lange, MD
Tae Ho Lee, PhD
Elana Levantini, PhD
James D. Levine, MD
Lequn Li, PhD
Bing Lim MD, PhD
Fangbing Liu, PhD
Kun Ping Lu MD, PhD
David F. McDermott, MD
James Mier, MD
Rebecca Miksad, MD
Kim-Son Nguyen, MD
Susan Pandya, MD
David Panka, PhD
Aric Parnes, MD
Lucia Pastorino, PhD
Akash Patnaik MD, PhD
Hanna Radomska, PhD
Jacalyn Rosenblatt, MD
Diane Savarese, MD
Lowell Schnipper, MD
Ralph Scully MB, PhD
Dimitrios Spentzos, MD
Jennifer Stone, MD
Ryan Sullivan, MD
Arthur Sytkowski, MD
Daniel Tenen, MD
Sheila Thomas, MD
Nadine Tung, MD
Dimitrios Tzachanis, MD, PhD
Gerburg Wulf MD, PhD
Anyong Xie, PhD
Min Ye, PhD
Xiaocong Yu, PhD
Xin Yuan MD, PhD
Pu Zhang, PhD
Xiao Zhou, PhD
Jeff Zwicker, MD

Targeting Signaling Pathways in Breast Cancer — There is an unmet need to improve the outcome for women with metastatic breast cancer. In collaboration with Dr. Lewis Cantley, Dr. Gerburg Wulf discovered a new role of the enzyme PI3Kinase for BRCA1-related estrogen-receptor negative breast cancer. Namely, she found that PI3K-inhibition caused not only a slowing of cell growth but also a dramatic increase in DNA damage repair mechanisms. Based on this discovery, her group examined the therapeutic efficacy of a pan-class IA PI3K-inhibitor, NVP-BKM120, and found a striking anti-tumor effect in a mouse model of BRCA1-related breast cancer. Importantly, this effect was synergetic *in vivo* with an inhibitor of DNA damage repair, the PARP inhibitor Olaparib. Translating these findings into an early phase clinical study, Drs. Wulf and Cantley are now leading a study in women with breast cancer scheduled to open in 2012.



Figures show a clear cell cancer with positive staining for Nrf2 (left panel) and Keap1 mutations identified in epithelial ovarian cancer (right panel). Courtesy of Pangagiotis Konstantinopoulos, MD, PhD and Stephen Cannistra, MD.

break (DSB) repair and cancer predisposition. The major hereditary breast/ovarian cancer predisposition genes, BRCA1 and BRCA2, have established roles in DSB repair by homologous recombination. Our accomplishments this year include: discovery of a mutagenic pathway of HR that is independent of BRCA1, development of a novel tool for triggering replication-associated DNA damage, identification of new mechanisms of action of BRCA1 in the repair of replication-associated DNA damage and development of a multi-photon laser/real-time imaging system for kinetic analysis of the DSB response in mammalian cells.



These images illustrate a decrease of F-18-Deoxyglucose uptake in breast cancers treated with the combination of a PI3Kinase-inhibitor and Parp-inhibitor (Olaparib). Mice were imaged before and after only three daily treatments, the repeat scan was obtained within three hours after the third treatment. This mouse had multiple synchronous primary tumors, labeled in the before and after images with blue, orange and yellow arrows. Decrease in percent FDG-uptake was 65% (tumor with orange arrow), 55% (tumor with blue arrow) and 64% (tumor with yellow arrow). Images courtesy of Gerburg Wulf, PhD.

Sequencing BRAF Mutations in Circulating Melanoma Cells

Dr. James Mier's lab has developed an exquisitely sensitive assay that allows detection of a minor population of cells harboring the BRAFV600E mutation in a 1,000- to 10,000-fold excess of cells with the wild type gene. This enables analysis of blood for circulating tumor cells, a signal suggesting high likelihood of relapse.

Clinical Highlights

Cancer Clinical Trials Office

In conjunction with the Cancer Center, the Division undertook a reorganization of the Cancer Clinical Trials Office (CCTO). The change, orchestrated by Dr. Steven Come and Ms. Joni Pitcher, the Executive Director of the BIDMC Cancer Center, developed formal research pods that are staffed by regulatory and research personnel, creating a seamless interaction between operations and research compliance. A clinical research oversight committee chaired by a senior faculty member, Dr. Glenn Bubley, oversees all aspects of the functioning of the CCTO.

Mentorship Committee

In order to ensure that faculty members are realizing their professional goals, the senior faculty have developed a mentorship committee chaired by Dr. Cannistra. This group is composed of four faculty members who are assigned junior faculty with whom they meet at regular intervals to discuss progress and challenges. The mentors then meet with the Division Chief bi-monthly to discuss progress and suggest guidance in order to ensure success. This committee provides the opportunity for idea generation, problem solving and constructive suggestions that are the essential ingredients of a successful career.

Honors and Awards

Elena Levantini, PhD – Received the 2011-2014 FAMRI Clinical Innovator Award.

John Frangioni, MD, PhD – Promoted to Professor of Medicine and Professor of Radiology.

David McDermott, MD – Elected Chairman of the Cytokine Working Group and received the Team Science Award from the Cytokine Working Group for 2010.

Patient Spotlight

Erin McCabe — *It's been nearly six years since I received my second bone marrow transplant from my brother. Looking back, the thing I appreciated the most as a patient was the management of care and how it was a team format where I never felt like I was going to be forgotten about, and how doctors and nurses worked together. I appreciated the small nurse-to-patient ratio and the time they took to communicate with me about what was going on, always with a personal touch. They really became part of our family.*

Selected Publications

Zhou X Z, Huang P, Lee TH, Shi R, Lu G, Bronson R, Lu KP. The telomerase inhibitor PinX1 is a major haploinsufficent tumor suppressor essential for chromosome stability in mice. *J Clin Invest* 2011; 121:1266-82.

Scully R. The spindle-assembly checkpoint, aneuploidy, and gastrointestinal cancer. *N Engl J Med* 2010; 363:2665-6.

Tung, N. Clinical outcome of triple negative breast cancer in BRCA1 mutation carriers and noncarriers. *Cancer* 2011; 117:3093-100.

Choi HS, Ashitate Y, Lee JH, Kim SH, Matsui A, Insin N, Bawendi MG, Semmler-Behnke M, Frangioni JV, Tsuda A. Rapid translocation of nanoparticles from the lung airspaces to the body. *Nat Biotechnol* 2010; 28:1300-3.

Konstantinopoulos PA, Spentzos D, Fountzilas E, Francoeur N, Sanisetty S, Grammatikos AP, Hecht JL, Cannistra SA. Keap1 mutations and Nrf2 pathway activation in epithelial ovarian cancer. *Cancer Res* 2011; 71:5081-9.

Panka, DJ, Sullivan RJ, Mier JW. An inexpensive, specific and highly sensitive protocol to detect the BrafV600E mutation in melanoma tumor biopsies and blood. *Melanoma Res* 2010; 20:401-7.

Wong ET, Gautam S, Malchow C, Lun M, Pan E, Brem S. Bevacizumab for recurrent glioblastoma multiforme: a meta-analysis. *J Natl Compr Canc Netw* 2011; 9:403-7.