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An Update From the Division of Hematology/Oncology

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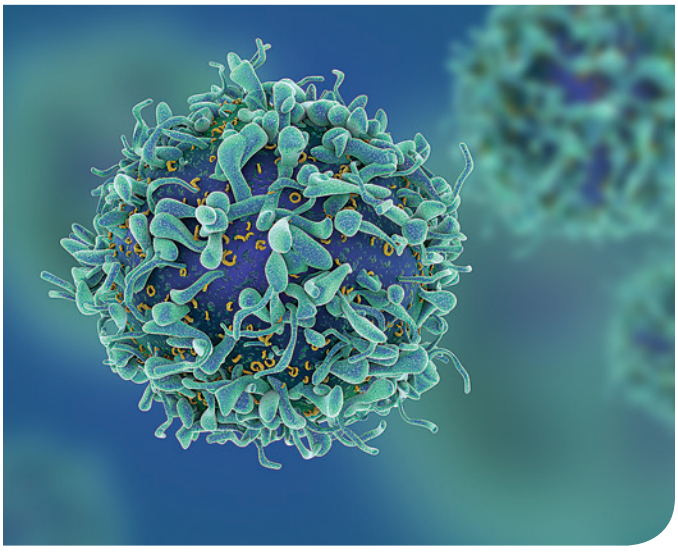
BEST CHILDREN'S HOSPITALS U.S.News & WORLD REPORT HONOR ROLL 2016-17

Fighting Graft-Versus-Host Disease After Blood and Bone Marrow Transplants

Craig A. Byersdorfer, MD, PhD, is a pediatric hematologist/oncologist in the Division of Blood and Marrow Transplantation and Cellular Therapies, with a research focus on posttransplant complications, specifically graft-versus-host disease (GVHD) and the role that T cells play in driving this condition.

In December 2016, Dr. Byersdorfer was awarded a prestigious American Society of Hematology (ASH) Scholar Award to pursue his research into posttransplant complications. The $150,000 award will be distributed over three years and will allow Dr. Byersdorfer and members of his lab to continue investigations into the mechanisms by which GVHD propagates, as well as letting them identify potential interventions to eliminate or mitigate this all-too-common complication of blood and marrow transplantation (BMT).



"Graft-versus-host disease affects 30 to 50 percent of transplant patients and has been an intractable problem for decades. We even know that GVHD is a T-cell driven phenomenon. If we are able to modulate T-cell metabolism in a way that shuts down the most active cells driving the condition, or identify ways to eliminate them altogether, we will make BMT a safer and more effective therapy for individuals with otherwise incurable diseases," says Dr. Byersdorfer.

Researching T-cell Metabolism in GVHD

Dr. Byersdorfer's work leading up to his ASH Scholar Award has focused on gaining a better understanding of in vivo T-cell metabolism and the role of particular metabolic proteins on the development of both effector and regulatory T cells. In ongoing research, Dr. Byersdorfer has found that metabolic proteins previously thought to be involved in effector T-cell responses may also play a fundamental role in the generation of regulatory T cells. "In the last 12 to 15 months, my lab has become more and more interested in the role of metabolic pathways in controlling the generation and expansion of regulatory T-cell populations."

Dr. Byersdorfer and his research colleagues use an animal model of GVHD to study T-cell metabolism in vivo and have published seminal findings related to this work.[1-3]

Prior to these published studies, the expectation was that activated T cells would use glucose for energy production. To a degree, this was true. However, Dr. Byersdorfer's team found that T cells activated during GVHD also converted their metabolism to burn more fatty acids. In fact, GVHD-activated T cells began to metabolize fat to such a degree that they became dependent upon it for survival.

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Ewing Sarcoma and the Mechanisms of Metastasis

The survival rate of recurrent and metastatic Ewing sarcoma is dismally low, a painful fact to those trying to cure it. **Kelly M. Bailey, MD, PhD**, has her sights set on drastically improving the odds for those young individuals affected by it.

Dr. Bailey joined Children's Hospital of Pittsburgh of UPMC's Division of Pediatric Hematology/Oncology in October 2016 after completing her residency and fellowship at the University of Michigan Medical School in Ann Arbor. Dr. Bailey's research is focused on Ewing sarcoma and its metastatic pathways, and how micro-environmental stresses can affect both primary and metastatic disease states and progression.

Determining why certain individuals' cancers behave more aggressively is of primary importance for Dr. Bailey, given the fact that relapsed and refractory cases are exceptionally difficult to treat successfully. Dr. Bailey's research efforts were recently boosted when she was awarded a 2016 Young Investigator Grant from Alex's Lemonade Stand Foundation. The three-year, $150,000 award will fund Dr. Bailey's research project, titled *Micro-environmental Regulators of Ewing's Sarcoma Metastasis.* "I'm incredibly honored to have received this award. Metastatic Ewing sarcoma is such a profoundly difficult disease to treat. If we can identify environmental factors surrounding the tumor that make some Ewing sarcomas more prone to metastasize, we could make great strides toward improving outcomes for our patients," says Dr. Bailey.

Certain stresses placed on a tumor may cause it to act more aggressively.

How Micro-Environmental Stresses May Contribute to Metastatic Disease

Certain stresses placed on a tumor may cause it to act more aggressively. This is the thrust of Dr. Bailey's research into why some Ewing sarcomas metastasize and others do not. Her past research and continuing investigations are examining how exposure to chemotherapy, hypoxia, nutrient deprivation, and other factors may conspire to promote an environment in which tumor cells become more mobile and prone to metastasis. "My goal is to understand the micro-environment surrounding the tumor, how current therapies can alter this environment, and how these external influences affect tumor growth and spread," says Dr. Bailey.

Not all Ewing sarcoma patients develop metastatic or refractory disease, and so there may be tumor- or patient-specific factors that lead to this devastating outcome. Dr. Bailey will be researching several possible factors that may play a role in metastatic Ewing sarcoma. Deprivation of oxygen and nutrients to primary tumors may be one reason they begin to exhibit invasive characteristics. It may be a survival strategy of the tumor cells when faced with chemotherapeutic or other environmental stresses. Dr. Bailey explains, "I want to look at the way sub-cytotoxic chemotherapy doses — doses that affect the cells but do not kill them — change the way sarcoma cells behave." And since chemotherapy is a systemic approach, it may be changing the micro-environment of the lungs, which is one of the most common sites of metastasis for Ewing sarcoma.

Another avenue of research will focus on the Wnt pathway. Ewing sarcoma cells have varying levels of responsiveness to Wnt. Wnt's are proteins that are abundant in the bone micro-environment, the primary site of Ewing sarcoma development. Wnt-responsive cells are, generally speaking, more aggressive than non-Wnt-responsive cells. The Wnt pathway may be another way forward in better understanding how metastatic disease occurs and how to intervene to stop it.

"We still don't have the tools to predict which patients are at high risk of metastatic disease, but I'm hopeful that my research will move our field further in that direction." •

Reading Resources

For more information about Dr. Bailey's recent grant award, visit Alexslemonade.org. For more background on her research, please see the following paper:

Bailey KM, Airik M, Krook MA, Pederson EA, Lawlor ER. Micro-environmental Stress Induces Src-Dependent Activation of Invadopodia and Cell Migration in Ewing Sarcoma. *Neoplasia*. 2016; 18(8): 480-488.

Characterizing the Molecular and Genetic Nature of Tumors

As a new recruit to the Division of Pediatric Hematology/Oncology, **Wen-I (Wendy) Chang, MD**, assistant professor of Pediatrics at the University of Pittsburgh School of Medicine, is filling a niche in the program with her research into the molecular characteristics of tumors and the application of this knowledge for targeted therapies and interventions.

Dr. Chang comes to Children's Hospital of Pittsburgh of UPMC after having completed her medical degree, internship, residency, and postdoctoral research in molecular genetics at Columbia University, in addition to a pediatric hematology/oncology fellowship while at Johns Hopkins University and the National Cancer Institute.

While new to Children's Hospital, Dr. Chang has a number of goals for her future research, collaborations, and clinical practice. First, and perhaps foremost, is Dr. Chang's work in the molecular characterization of solid tumors. "I am an oncologist who sees all types of tumors, and I'm also a hematologist with a special interest in benign hematologic diseases. I very much am interested in being a broad provider, however, I was trained as a sarcoma specialist, and this is where I will be focusing most of my research efforts in the future," explains Dr. Chang. Past research by Dr. Chang has led to a better understanding of the genetic makeup of Ewing sarcoma tumors and the factors at play in relapsed and refractory solid tumors, and she plans to continue this line of research now that she is at Children's.

In addition, Dr. Chang has an interest and specialty in molecular genetics, and how innate or germ-line mutations that individuals carry can lead to a predisposition to developing cancer. "If we can understand how these mutations work, we may be able to use very targeted, first-line therapies to treat certain types of sarcoma, targeting specific cancer cells while avoiding systemic cytotoxic chemotherapy and its side effects," says Dr. Chang.

Collaborative Ideas

One specific program that Dr. Chang is working to get off the ground in collaboration with **Kelly Bailey, MD, PhD**, as well as surgical teams, the Department of Pathology, and initiatives ongoing at the Center for Genomics and the Institute of Precision Medicine under the direction of Adrian Lee, PhD, is a pediatric oncology tumor bank. "Our goal is to be able to get tissue samples from the surgeons in the operating room for study, and to work with Pathology to freeze and save these samples for future genetic sequencing or for use in animal model studies," says Dr. Chang. Applications of this kind of tumor bank for Dr. Chang include a more precise characterization of an individual's tumor that could allow for the use of precision therapies to target specific aspects of a tumor.

Another collaborative effort Dr. Chang is seeking to start up is a cancer predisposition clinic, where families who have an inherited risk of cancer can be counseled on various aspects related to their underlying genetic makeup and how these could affect their decision making in the future. "Once we are able to get the tumor bank up and running, and we start to sequence tumors, we can offer screening and sequencing services to these individuals to try and figure out what is running through the family's genetic makeup that's causing cancer," says Dr. Chang. For example, individuals with a TP53 mutation that leads to Li-Fraumeni syndrome could potentially pass on the mutation to their children, and this would predispose these children to a higher chance of developing sarcomas and breast cancer. "By identifying such characteristics, we can better counsel patients and their families."

Precision Therapy Is the Future of Cancer Treatment

For Dr. Chang, it all comes down to understanding the individual makeup of a person's disease, what characteristics make it unique, and how to use those characteristics to develop and deliver precisely targeted therapies to achieve the best possible outcomes. "I'm very much a translational researcher, and being able to develop targeted therapies and get them into patients is the ultimate goal. To be able to do the bench-to-bedside transition, and then to be able to characterize a patient's tumor and give them genetic counseling is where our field is evolving." •

Reading Resources

Below are selected publications highlighting some of Dr. Chang's research and investigative interests prior to arriving at Children's Hospital.

Chang W, et al. MultiDimensional ClinOmics for Precision Therapy of Children and Adolescent Young Adults with Relapsed and Refractory Cancer: A Report from the Center for Cancer Research. *Clin Cancer Res.* 2016; 22(15): 3810-3820.

Chang W, et al. Founder Fukutin Mutation Causes Walker-Warburg Syndrome in Four Ashkenazi Jewish Families. *Prenat Diagn.* 2009; 29(6): 560-569.

Blood and Bone Marrow Transplants Continued from Page 1

"If we are able to inhibit the metabolic adaptations that occur in these T cells, for example by limiting the increase in fat oxidation, there's a good chance we will reduce the incidence and/or severity of GVHD," says Dr. Byersdorfer.

If the population of over-activated cells that are driving GVHD can be identified through their metabolic properties, it may be possible to eliminate them early in the transplantation process. Alternatively, with the increasing use of cellular therapies and genetic reprogramming, one might even envision disabling metabolic pathways in T cells prior to transplantation, thereby stopping fatty acid oxidation in a select group of cells before it even starts. These ideas are at the heart of Dr. Byersdorfer's future research based upon his current and provocative findings in an animal model of a very real human disease. •

References

More information about Dr. Byersdorfer's recent research into T cells and T-cell metabolism can be found in these published papers:

1. Byersdorfer CA. The Role of Fatty Acid Oxidation in the Metabolic Reprogramming of Activated T cells. *Front Immunol.* 2014; 5:641.
2. Byersdorfer CA, et al. Effector T cells Require Fatty Acid Metabolism During Murine Graft-Versus-Host Disease. *Blood.* 2013; 122(18): 3230-3237.
3. Chiaranunt P, Ferrara JL, Byersdorfer CA. Rethinking the Paradigm: How Comparative Studies on Fatty Acid Oxidation Inform Our Understanding of T cell Metabolism. *Mol Immunol.* 2015; 68(2 Pt C): 564-574.

ABOUT THE DIVISION: PEDIATRIC HEMATOLOGY/ONCOLOGY

Under the leadership of **Linda M. McAllister-Lucas, MD, PhD**, division chief, and associate professor of Pediatrics at the University of Pittsburgh School of Medicine, Children's Hospital of Pittsburgh of UPMC's Division of Pediatric Hematology/Oncology boasts the largest and most comprehensive care center in western Pennsylvania, eastern Ohio, and northern West Virginia for pediatric and young adult patients with all forms of cancer and disorders of the blood. The division is part of UPMC CancerCenter and the University of Pittsburgh Cancer Institute.

Clinical Programs and Services

- Adolescent and Young Adult Oncology
- Ewing Sarcoma
- Hemophilia
- Hemostasis and Thrombosis
- Leukemia
- Sickle Cell Disease
- Neuro-Oncology
- Survivorship Clinic
- Mario Lemieux Lymphoma Center for Children and Young Adults

Research and Clinical Trials

Investigators within the division are conducting important and ground-breaking research and clinical trials in pursuit of the pathways of tumorigenesis, metastatic disease, and innovative therapies for a full range of oncological conditions. •

Breaking New Ground in Transplantation Medicine

Paul Szabolcs, MD, chief of the Division of Blood and Marrow Transplantation and Cellular Therapies, recently secured a new NIH UO1 award in support of the first clinical trial in the world to study the feasibility and efficacy of tandem lung and bone marrow transplantation where the deceased lung donor-derived immune system will provide immunity.

The five-year grant, titled *Cadaveric Donor Lung and Bone Marrow Transplantation in Immunodeficiency Diseases,* was funded for just under $5 million to support a first-in-humans clinical trial and a series of mechanistic laboratory studies. It is poised to determine whether children and adults with end-stage lung disease as a result of a primary immunodeficiency syndrome can be cured by bone marrow transplantation with resolution of the underlying immunodeficiency, and offer long-term survival by receiving a pair of healthy lungs. Significantly, the lungs and bone marrow will be recovered from the same cadaveric, unrelated donor despite multiple mismatches across HLA barriers. The study has several aims, including whether or not long-term immunosuppressive therapies can be withdrawn as a consequence of bone marrow transplant-mediated tolerance.

Dr. Szabolcs is the primary investigator on this UO1 grant, along with co-primary investigator John McDyer, MD, director of the Lung Transplantation Translational Research Program in the Division of Pulmonary, Allergy, and Critical Care Medicine. This study brings together a range of scientific and clinical disciplines from across UPMC and the University of Pittsburgh. If successful, this research holds significant promise for other solid organ transplant procedures where life-long immunosuppressive agents are required to combat rejection, and extended graft survival and tolerance has been out of reach. •

ABOUT THE DIVISION: BLOOD AND MARROW TRANSPLANTATION AND CELLULAR THERAPIES

The division's clinical efforts are focused on designing and testing transplant therapies for patients with leukemia, lymphoma, and other malignancies, as well as nonmalignant immune deficiencies, autoimmune conditions, and various neurodegenerative conditions.

Led by **Paul Szabolcs, MD**, division chief, and professor of Pediatrics at the University of Pittsburgh School of Medicine, the division places special emphasis on the development and use of reduced-intensity/toxicity transplant regimens for a range of conditions related to mucopolysaccharidoses, leukodystrophies, and other inherited metabolic disorders.

Clinical research within the division spans a range of autoimmune disorders, cancers of the blood, and such conditions as sickle cell disease. Crohn's disease is of particular research interest, with several ongoing phase 1 and phase 2 clinical trials investigating the efficacy of autologous stem cell transplantation in tandem with high-dose chemotherapy.

At present, the division, in collaboration with investigators and surgeons from UPMC and the University of Pittsburgh, is the only entity in the world currently performing lung and bone marrow transplantation in tandem for both pediatric and adult patients who have immunodeficiencies with progression to pulmonary failure. •

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CONTINUING MEDICAL EDUCATION

The courses below are currently available for CME credit by visiting UPMCPhysicianResources.com/Pediatrics.

The Biology of Hematopoietic Stem Cell Transplantation
Presented by: Craig A. Byersdorfer, MD, PhD

Hot Topics in Pediatric Hematology/Oncology
Presented by: A. Kim Ritchey, MD

Evidence Based Psychosocial Care in Pediatric Oncology: A Journey
Presented by: Robert Noll, PhD

Cancer Chemotherapy: The Disappointing Past, the Optimistic Present, and the Exciting Future
Presented by: Edward Prochownik, MD, PhD

RECENT PUBLICATIONS

Below are some recent publications from researchers and clinicians in the Division of Hematology/Oncology.

Coordinated Activities of Multiple Myc-dependent and Myc-independent Biosynthetic Pathways in Hepatoblastoma. Wang H, Lu J, Edmunds LR, Kulkami S, Dolezal J, Tao J, Ranganathan S, Jackson L, Fromherz M, Beer-Stolz D, Uppala R, Bharathi S, Monga SP, Goetzman ES, Prochownik EV. *J Biol Chem.* 2016; 291(51): 26241-26251.

MALT1 Protease Activation Triggers Acute Disruption of Endothelial Barrier Integrity Via CYLD Cleavage. Klei LR, Hu D, Panek R, Alfano DN, Bridwell RE, Bailey KM, Oravecz-Wilson KI, Concel VJ, Hess EM, Van Beek M, Delekta PC, Gu S, Watkins SC, Ting AT, Gough PJ, Foley KP, Bertin J, McAllister-Lucas LM, Lucas PC. *Cell Rep.* 2016; 17(1): 221-232.

Association of Pro-Inflammatory High-Density Lipoprotein Cholesterol With Clinical and Laboratory Variables in Sickle Cell Disease. Ataga KI, Hinderliter A, Brittain JE, Jones S, Xu H, Cai J, Kim S, Pritchard KA, Hillery CA. *Hematology.* 2015; 20(5): 289-296.

ABOUT CHILDREN'S HOSPITAL OF PITTSBURGH OF UPMC

Children's Hospital of Pittsburgh of UPMC is a leader in the treatment of childhood conditions and diseases, a pioneer in the development of new and improved therapies, and a top educator of the next generation of pediatricians and pediatric subspecialists.

Children's is consistently recognized for its research and clinical achievements, including ranking 10th among children's hospitals and schools of medicine (FY15) in NIH funding for pediatric research, and being named to the 2016-17 *U.S. News & World Report* Honor Roll of America's Best Children's Hospitals.