Pediatric Insights

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In This Issue

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UPMC CHILDREN'S HOSPITAL OF PITTSBURGH

Understanding the Role of Oxidative Stress in Sickle Cell Disease

Sickle cell disease (SCD) is a group of related blood disorders, each caused by a single point mutation in a single gene. That one tiny error confers upon people who inherit two copies of the gene a lifetime of episodes of pain and hospitalization and a reduced lifespan.

Deirdre Nolfi-Donegan, MD
Assistant Professor of Pediatrics
University of Pittsburgh School of Medicine

Cheryl A. Hillery, MD
Professor of Pediatrics
University of Pittsburgh School of Medicine

SCD is the most common genetic disease not only in the United States but also in the world. An estimated 1 in 500 African Americans have the disease, while about 1 in 12 carry the autosomal recessive mutation. Nor is it found only in people of African ancestry — the causative mutation is also common in countries ranging from South and Central America to Mediterranean Europe, Middle East, and India. Worldwide, about 250 million people carry the gene responsible for SCD and other hemoglobin diseases.

The major cause of pain, suffering, and death in SCD is tissue injury and inflammation caused by repeated vaso-occlusion that results in progressive organ damage. Much remains unknown about exactly how sickled red cells injure the blood vessels and how this leads to the blood-vessel and organ damage observed in patients.

It is known that the causative mutation leaves the body's hemoglobin prone to sticking together after delivering its oxygen payload from the red blood cells to the tissues. The resulting hemoglobin crystals can break through the cells' membrane, killing them and spilling the free hemoglobin into the bloodstream.

"Hemoglobin is very damaging when it's not contained within the protected environment of an intact red cell," says **Deirdre Nolfi-Donegan, MD**, assistant professor of pediatrics at the University of Pittsburgh School of Medicine and physician in the Division of Pediatric Hematology/Oncology at UPMC Children's Hospital of Pittsburgh. "It can release large amounts of reactive oxygen species, which can damage nearby tissues. This is why we and others in the scientific community think that redox — the complementary processes of oxidation and reduction — is a key driver of much of the damage that occurs at both the cellular and organ levels in SCD."

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Sickle Cell Disease *Continued from Page 1*

The substantial oxidative stress created within red blood cells and, eventually, other organs in SCD has recently emerged as a major area of research interest in the field. "In the last five years, we've really moved forward in our understanding of redox signaling as a primary driver of SCD," says **Cheryl A. Hillery, MD**, professor of Pediatrics at the University of Pittsburgh School of Medicine. Dr. Hillery also is the clinical director of Hematology and director of the Comprehensive Pediatric Sickle Cell Program in the Division of Pediatric Hematology/Oncology at UPMC Children's.

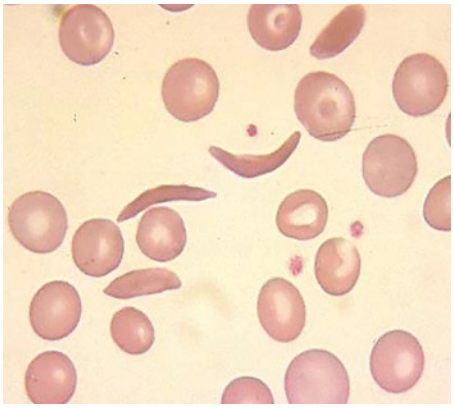
Despite recent advances in the field, most patients with SCD still die in middle age, says Dr. Hillery. The disease can be cured by bone-marrow transplantation, but this requires a matched donor, and it is rare — even within families — for a matched donor to be available. While recent progress has been made in gene therapy for SCD, says Dr. Hillery, a cure for everyone is not yet at hand. Because of this, research into oxidative stress in the disease remains highly relevant.

Dr. Hillery and Dr. Nolfi-Donegan were recently invited to write a comprehensive review of redox biology in SCD. The paper was published in a *Current Opinion in Physiology* themed issue on redox regulation in June 2019.

The two researchers have long-standing interests in redox biology. Dr. Hillery, a clinician and bench scientist, began her research career studying molecules involved in platelet adhesion. "Then it was discovered that red cells in SCD are sticky. I put my knowledge into red-cell adhesion, and then I just fell in love with research on SCD," she says.

Prior to joining UPMC in 2015, Dr. Hillery was on the faculty at the Medical College of Wisconsin, where work in her lab showed that, in a mouse model of SCD, the omega-3 fatty acids found in fish oil — which are potent antioxidants — could improve the flexibility of red blood cells.

Dr. Hillery was recruited to UPMC to direct the Comprehensive Pediatric Sickle Cell Program and build a strong clinical and translational program in benign hematology at the



University of Pittsburgh and UPMC Children's. She has cared for both children and adults with SCD for over 25 years.

Dr. Nolfi-Donegan came to sickle cell research as a fellow at UPMC, after finishing her medical residency at Cohen Children's Medical Center in New York. "I'm interested in platelets, like Dr. Hillery, and there is a lot of platelet dysregulation and pathology in SCD," she says.

Hypothesizing that a better understanding of basic redox biology in SCD could lead to the development of more effective therapies, Dr. Hillery and Dr. Nolfi-Donegan have been partnering with researchers in the University of Pittsburgh's Vascular Medicine Institute (VMI) and in particular with Sruti Shiva, PhD, who studies redox reactions in mitochondria.

"We are trying to determine what redox reactions are significant in SCD," says Dr. Nolfi-Donegan. "Should we be focusing on mitochondrial redox reactions? Should we be looking at these reactions in red blood cells? Or between hemoglobin and the endothelium? Is there a specific type of redox reaction that's the 'smoking gun' for many of the problems that patients with SCD develop? These are the kinds of questions we hope to answer."

The three researchers originally came together around their shared interest in a molecule called HMGB1, an inflammatory marker that, depending on its redox status, may activate platelets, says Dr. Nolfi-Donegan.

"My lab was the first to show that HMGB1 is elevated at baseline in SCD, and that it rises further during acute crises in SCD," says Dr. Hillery. "We're now looking at how it activates and injures the endothelium, and Dr. Nolfi-Donegan is investigating its effects on platelets."

In collaboration with Dr. Hillery and Dr. Shiva, Dr. Nolfi-Donegan recently submitted a grant application to explore the role of mitochondrial redox reactions in SCD.

"We want to explore how mitochondrial dysfunction in SCD may drive abnormal platelet activation, which could potentially lead to unwanted clot formation," says Dr. Nolfi-Donegan. "How do you get from a hemoglobin molecule that has escaped the red cells to platelet activation, and to reactive oxygen species that are possibly driving that platelet activation? There are a lot of dots to connect."

The UPMC clinical team provides the most advanced care available to both children and adults with SCD, says Dr. Hillery. "We have one of the best adult sickle cell clinical research teams in the world," she says. The level of expertise available at UPMC to treat adults with sickle cell disease is rare, she says, as until recently most people with the disease died in childhood.

The UPMC sickle cell team also is very involved in clinical research. Several medications recently approved to treat SCD have some antioxidant properties, says Dr. Hillery, though their effect on reducing sickle cell pain crises has been modest. Drugs that more specifically target oxidative stress in the disease are needed, she says.

A clinical trial is now underway at UPMC, which will test a medication that reduces the amount of mitochondrial reactive oxygen species in all cells, including red cells and platelets. "Eventually, the aim would be to see if this translates into a reduction in platelet activation, lowers levels of red blood cell destruction (hemolysis), and decreases vascular dysfunction in subjects with SCD," says Dr. Nolfi-Donegan.

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Exploring Sedation Practices in Pediatric Patients with Acute Lymphoblastic Leukemia

Five-year survival rates for children diagnosed with pediatric acute lymphoblastic leukemia (ALL) now exceed 90%. An estimated 20% to 40% of survivors, however, develop neurocognitive late effects. These can be very subtle changes in learning, including effects on executive function, working memory, processing speed, and visual-motor abilities. Specialized testing with a neuropsychologist helps to identify these needs.

"Interest in the risk of neurocognitive deficits for children treated for ALL with contemporary treatment regimens has tended to focus on the effects of chemotherapy directed to the central nervous system," says **Jean M. Tersak, MD**, a hematologist/oncologist at UPMC Children's Hospital of Pittsburgh, principal investigator with the Children's Oncology Group (COG), and professor of pediatrics at the University of Pittsburgh School of Medicine, who studies late effects, quality of life, and neurocognitive outcomes in survivors of childhood cancer.

Given the excellent survival rate in this population, it is important to consider other factors that may contribute to some patients' observed neurocognitive changes. One such factor is the use of repeated sedation for lumbar puncture procedures in patients with ALL.

To learn more about pediatric oncologists' sedation practices in patients with ALL, Dr. Tersak and her colleagues conducted an electronic survey of individuals in leadership roles at 103 COG member institutions. The study, published in February 2020 in *Pediatric Blood & Cancer,* is the first to quantify the prevalence of sedation of ALL patients in COG institutions, which treat more than 90% of all the children and adolescents diagnosed with cancer each year in the United States.

Developing Brain

Studies in animal models suggest that sedation and general anesthesia may harm the developing brain. Data from human studies are scant, making this an under-represented area of investigation. Since 2017, the U.S. Food and Drug Administration (FDA) has required drug manufacturers to include a warning on the labels of anesthetic and sedative agents indicating that repeated or lengthy use of these agents in children aged under three years or in women in the third trimester of pregnancy "may affect the development of children's brains."

"Children undergoing treatment for ALL are sedated or anesthetized numerous times," says Dr. Tersak. "They are sedated when undergoing magnetic resonance imaging (MRI) or computed tomography (CT) scans, biopsies, bone marrow aspirations, or port placement. However, the most frequent reason for sedation is lumbar puncture. Over two to three years of treatment, a child with ALL probably undergoes about 30 lumbar punctures."

Advantages and Risks

The researchers received responses from 64 institutions of the 103 institutions surveyed (62%). These institutions reported seeing a total of about 2,018 new ALL diagnoses annually (mean per institution 31.5, range 3–110). Across all responding institutions, more than 95% of children with ALL were sedated when receiving lumbar punctures.

The most commonly used forms of sedation — reported by more than 85% of all responding institutions — were propofol alone (reported by 36 institutions, or 56%) or propofol in conjunction with midazolam, an opioid, or both (reported by 20 institutions, or 31%). Three institutions (5%) reported using midazolam and an opioid without propofol. Others reported using ketamine alone, ketamine and propofol, ketamine/midazolam or fentanyl/midazolam, or general anesthesia.

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Sedation Practices in Pediatric Patients with ALL *Continued from Page 3*

"We already have evidence that methotrexate — a mainstay modality in ALL treatment — may have neurotoxic effects, particularly in younger children," says Dr. Tersak. Repeated exposure to sedation may add to the existing neurocognitive risks associated with methotrexate."

Unanswered Questions

More research is needed to compare the long-term effects of different sedating agents, particularly in younger children who are repeatedly exposed to these agents, indicates Dr. Tersak.

"Are there critical age periods when children are most vulnerable to the adverse effects of sedation exposure? Do all sedating agents impact the developing brain equally? Is it possible to deliver agents at the same time as the sedation to protect the brain? Are there effective alternatives to sedation, such as the use of relaxation or distraction techniques?" she says. "We do not currently know the answers to these questions."

The dramatic improvement in survival rates for childhood ALL has resulted in a large population of survivors. This presents an opportunity to begin to study such questions as outlined above. A better understanding of sedation practices in children with ALL provides a foundation to build upon, to investigate which methods are the safest, including the potential long-term neurocognitive outcomes.

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Further Reading

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UPMC Children's Pediatric Cancer Researcher Awarded V Foundation Grant for Hepatoblastoma Research

UPMC Children's Hospital of Pittsburgh researcher **Edward V. Prochownik, MD, PhD**, was awarded a 2020 Connor's Cure (WWE) grant from the V Foundation.

Dr. Prochownik is director of oncology research at UPMC Children's, the Paul C. Gaffney Professor of Pediatrics, and professor of molecular genetics and biochemistry at the University of Pittsburgh School of Medicine. His research interests are focused on the c-Myc oncoprotein — its molecular inhibitors and regulation, function and pharmacologic regulation, and the impact of its expression on cellular metabolism. Dr. Prochownik also is interested in the molecular causes of hepatoblastoma, the most common liver cancer in children.

Dr. Prochownik's 2020 Connor's Cure grant will support a new research project titled "Patient-Derived NFE2L2/NRF2 Mutations Promote Aggressive Forms of Hepatoblastoma."

Study Details

Hepatoblastoma (HB) is the most common pediatric liver cancer. Although usually highly curable, HB tumors with certain features are quite lethal and associated with less than 20% survival. About 80% of HBs harbor acquired mutations in a protein known as b-catenin and show abnormal regulation of another protein (YAP) that cooperates with b-catenin mutants during tumorigenesis.

Five to 10% of HBs also contain mutations in the protein NFE2L2, which normally protects against certain types of DNA damage. Dr. Prochownik's laboratory has modeled HB in mice by co-expressing mutants of b-catenin and YAP, termed D(90) and YAPS127A, respectively. In preliminary studies, either one of two patient-associated NFE2L2 mutants markedly accelerated tumor creation by D(90) + YAPS127A. Unexpectedly, both also were found to be oncogenic in their own right when co-expressed with either D(90) or YAPS127A. Thus, any two members of the D(90) + YAPS127A + NFE2L2 triad causes tumor growth.

This proposal will investigate how each pair-wise combination of D(90) + YAPS127A + NFE2L2 mutants alter various tumor characteristics to optimize growth. The study also will identify the small number of key genes that underlie HB generation and thus represent the most important subset. This has previously been an impossible task because the gene expression differences between livers and tumors are so large. However, identifying the common genes that are deregulated by each pair-wise combination of factors should facilitate this. This research will, therefore, identify the most critical molecular changes that cause HB. Dr. Prochownik's research is translationally relevant because knowing the identities of the key genes that underlie transformation may uncover novel therapeutic targets.

A New Target for Poor-Prognosis Non-Hodgkin Lymphoma

As scientists improve their understanding of the signaling pathways that cancer cells depend on to grow and survive, new potential strategies for treatments can emerge. Sometimes an unexpected discovery leads researchers in the direction of a completely new target.

Linda M. McAllister-Lucas, MD, PhD
Chief, Division of Pediatric Hematology/Oncology, UPMC Children's Hospital of Pittsburgh

Jing Cheng, MD, PhD
Research Assistant Professor McAllister-Lucas Laboratory

Such was the case for researchers in the laboratory of **Linda M. McAllister-Lucas, MD, PhD**, at UPMC Children's Hospital of Pittsburgh, who have identified a potential new treatment target for a subtype of non-Hodgkin lymphoma (NHL) that currently has a poor prognosis.

Survival for most patients with NHL has increased greatly over the last few decades, following the introduction of the targeted therapy rituximab. But for patients with a type of NHL called ABC–diffuse large B-cell lymphoma (ABC–DLBCL), three-year progression-free survival has remained at about 40%, compared with 75% for patients with other NHL subtypes.

Most ABC–DLBCL lymphomas are dependent for growth and survival on a cell-signaling pathway called the canonical NF-κB pathway. Much recent research has focused on a protein in this pathway called MALT1.

"We know that MALT1 plays a role in normal lymphocyte function but also in the genesis of lymphoma," says **Jing Cheng, MD, PhD**, a research assistant professor in the McAllister-Lucas Laboratory, who led the new work.

In laboratory studies, blocking MALT1 function can kill or slow the growth of ABC–DLBCL cells. Because the protein also appears to help drive the growth of other, rarer NHL subtypes, blocking MALT1 may kill or slow growth in them as well.

"MALT1 is required for the growth and survival of multiple lymphoma subtypes in addition to ABC–DLBCL, such as mantle-cell lymphoma and peripheral T-cell lymphoma," says Dr. Cheng. "So MALT1 has emerged as a promising pharmaceutical target."

Dr. McAllister-Lucas and her team have been working for years to tease out the many functions of MALT1 in lymphoma cells. Several years ago, they were contacted by colleagues at Michigan State University who study a family of proteins called the G-coupled protein receptor kinases. The Michigan team had just discovered that once such protein, G protein-coupled receptor kinase 2 (GRK2), can bind to MALT1.

"Our colleagues are experts on GRK2, but they had no idea about MALT1," says Dr. Cheng. "So, they contacted us."

That call led to a years-long collaboration that also drew in participants from the University of California, San Francisco, as well as universities in Belgium and Switzerland. The results from the work, published in February 2020 in the *Journal of Clinical Investigation*, suggest that manipulating GRK2 may be a new way to shut down MALT1 activity in the lymphomas that depend on it.

Uncovering Two Functions for One Protein

In the new research, Dr. Cheng and her colleagues confirmed that GRK2 binds to MALT1 and determined the exact region of MALT1 where this interaction takes place. When bound to MALT1, GRK2 inhibited downstream signaling in the NF-κB pathway.

Importantly, the team found that GRK2 binding inhibits two different functions of MALT1. Normally, MALT1 can serve as both a scaffold and a protease. As a scaffold, it physically brings other proteins in the NF-κB pathway together so they can interact. As a protease, it cleaves other proteins that would otherwise interfere with NF-κB pathway signaling.

The fact that GRK2 could inhibit both MALT1 functions was surprising and exciting, says Dr. Cheng. "All the MALT1 inhibitors developed so far only target the protease activity of MALT1, not the scaffold," she says. "If we could develop an inhibitor that targets both these functions of MALT1, it might be more potent in treating MALT1-dependent lymphoma."

The researchers also examined survival in people with ABC–DCBCL in relation to GRK2 levels in their tumors. They found that both progression-free and overall survival were significantly worse for patients with the lowest GRK2 levels (bottom 25%) compared with those whose tumors had the highest levels of the protein (top 25%). GRK2 levels did not affect survival in patients with non-MALT1–dependent subtypes of lymphoma.

In follow-up studies, knocking down GRK2 in ABC–DLBCL cells led to more aggressive tumor growth in mice implanted with those cells.

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Hyundai Young Investigator Grant Awarded to Lisa Maurer, MD, PhD

Lisa Maurer, MD, PhD, is the recipient of a Hyundai Hope on Wheels Young Investigator Award. Dr. Maurer's research award will help to further her work exploring immune regulation in non-Hodgkin lymphoma.

Non-Hodgkin lymphoma (NHL) is a relatively uncommon form of cancer in children and adolescents under the age of 20. In a subset of children with NHL, the cancer occurs as a result of an underlying genetic cancer predisposition syndrome. There are several genetic syndromes that result in an inability to properly repair damaged DNA and are associated with a risk of developing lymphoma. For example, children with Ataxia-telangiectasia carry a mutation in a protein called ATM, and this mutation causes damaged DNA to accumulate in cells. Children with Ataxia-telangiectasia have an increased risk of multiple cancers, including NHL. NHL that occurs as the result of a genetic syndrome, such as Ataxia-telangiectasia, is especially difficult to cure.

Dr. Maurer's research will investigate why lymphomas in children with genetic syndromes affecting DNA damage repair are difficult to treat by examining how the immune system interacts with lymphoma cells with damaged DNA and to identify potential new therapeutic targets and treatment options.

The first aim of Dr. Maurer's research will examine how DNA damage induced by chemotherapy can change the immune system's response to NHL, while the second aim of the study will examine how DNA damage caused by a loss of the ATM protein affects the immune system's response to non-Hodgkin lymphoma.

More About Dr. Maurer

Lisa Maurer, MD, PhD, is a pediatric oncologist with an interest in pediatric leukemia and lymphoma. She also is a physician-scientist in the Lucas/McAllister Lab in the Rangos Research Center at UPMC Children's Hospital of Pittsburgh. Currently, Dr. Maurer's research focus is on the role of GRK2 in inhibition of the MALT1 proto-oncoprotein in lymphomagenesis. She earned her medical degree and doctorate from the University of Wisconsin School of Medicine and Public Health, and then completed her residency at the University of California San Francisco. Dr. Maurer's fellowship in pediatric hematology/oncology was completed at UPMC Children's Hospital of Pittsburgh.

Non-Hodgkin Lymphoma *Continued from Page 5*

"We know that ABC–DLBCL requires active MALT1 for its growth and survival," says Dr. McAllister-Lucas, chief of the Division of Pediatric Hematology/Oncology at UPMC Children's and a professor of pediatrics at the University of Pittsburgh School of Medicine. "The results of this study identify GRK2 as a binding partner and negative modulator of MALT1.

"To our knowledge, GRK2 is the first protein that has been shown to inhibit both the scaffolding and protease activities of MALT1," she says. "These findings strongly suggest that GRK2 has a tumor suppressor role in ABC–DLBCL."

Next Steps Toward Treatment

The research team considered the possibility that mutations or deletions in the GRK2 gene may account for the low levels of the protein in diffuse large B-cell lymphoma. However, they found only one example of such a mutation in six published data sets, comprising more than 300 patients.

"We're now exploring whether other molecular mechanisms could be responsible for downregulation of GRK2 in diffuse large B-cell lymphoma — for example, epigenetic alterations or microRNA regulation," says Dr. Cheng. "More work is needed in these areas before GRK2 itself could be considered a druggable target."

The McAllister-Lucas Laboratory also is collaborating on structural studies of GRK2–MALT1 protein interactions. In addition, they are working with the Chen Drug Discovery Laboratory of the University of Pittsburgh, led by Bill Chen, PhD, to identify small molecules that could potentially mimic GRK2 in its role as a dual-function MALT1 inhibitor.

"If efficient, MALT1 inhibitors can be developed, adding them to combination therapy might greatly benefit patients with ABC–DLBCL and other cancer types that depend on this protein," says Dr. Cheng.

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Collaborations in Cancer Care: The Division of Blood and Marrow Transplantation and Cellular Therapies

A close collaborator with the Division of Pediatric Hematology/Oncology, The Division of Blood and Marrow Transplantation and Cellular Therapies (BMT-CT), led by **Paul Szabolcs, MD**, Division Chief and Professor of Pediatrics and Immunology at the University of Pittsburgh School of Medicine, places special emphasis on the development and use of reduced-intensity/toxicity transplant regimens for a range of non-malignant conditions that has attracted pediatric and adult patients from across the United States. Historically, these have been applied to inborn errors of immunity and inherited metabolic disorders such as mucopolysaccharidosis syndromes (MPS) and leukodystrophies.

Clinical research within the Division has led to new trial designs that recently have been approved by the U.S. Food and Drug Administration (FDA) and Institutional Review Board (IRB) of the University of Pittsburgh to bring a cure or alleviate advanced cases of certain autoimmune disorders, such as Crohn's disease (CD) and systemic sclerosis (SSc). Another exciting new protocol also received FDA and IRB approval, whereby all sickle cell disease (SCD) patients who may benefit from allogeneic transplants would be able to find partially matched healthy unrelated stem cell donors.

UPMC Children's is the only entity in the world currently performing tandem cadaveric lung and bone marrow transplantation for both pediatric and adult patients diagnosed with a primary immunodeficiency with progression to end-stage lung disease. Early favorable experience has now led to new indications that are focusing first on combined bone marrow and lung failure related to a diagnosis of idiopathic pulmonary fibrosis.

UPMC Children's is one of a small group of children's hospitals that offers CAR (chimeric antigen receptor) T-cell therapy. The BMT-CT Division uses KYMRIAH®, an FDA-approved CAR T-cell therapy for children and young adults with relapsed or refractory B-cell acute lymphoblastic leukemia.

Division News

Kelly Bailey, MD, PhD, was selected to serve as a member of the Children's Oncology Group (COG) Ewing sarcoma biology committee.

Andrew Bukowinski, MD, was appointed as director of the UPMC Pediatric Oncology Developmental Therapeutics Program and as the UPMC Children's COG Phase I Site Principal Investigator.

Erika Friehling, MD, was selected as Vice Chair of the Faculty and Professional Development Learning Community of the Association of Pediatric Program Directors (APPD).

Linda McAllister-Lucas, MD, PhD, was named to the Society for Pediatric Research (SPR) council.

A. Kim Ritchey, MD, serves as Chair of the Data and Safety Monitoring Committee (DSMC) for Children's Oncology Group (COG).

Recent Publications

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4401 Penn Ave.
Pittsburgh, PA 15224

About the Division of Pediatric Hematology/Oncology

Under the leadership of **Linda M. McAllister-Lucas, MD, PhD**, division chief and professor of Pediatrics at the University of Pittsburgh School of Medicine, UPMC Children's Hospital of Pittsburgh 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 Hillman Cancer Center and the University of Pittsburgh Cancer Institute.

Research and Clinical Trials

The Division supports an extensive research program of basic science, translational investigations, and clinical trials. This work is collectively dedicated to uncovering new insights and knowledge with respect to how and why cancers develop and spread, and to developing the next generation of therapies.

Clinical Programs and Services

- Adolescent and Young Adult Oncology
- Pediatric Solid Tumors
- Hemophilia
- Hemostasis and Thrombosis
- Leukemia
- Sickle Cell Disease
- Neuro-Oncology
- Pediatric Cancer Survivorship Clinic
- Mario Lemieux Lymphoma Center for Children and Young Adults
- Cancer Predisposition Program
- Bone Marrow Failure
- Immunocytopenias
- Melanoma
- Fertility Preservation
- Hepatoblastoma
- Histiocytosis

About UPMC Children's Hospital of Pittsburgh

Regionally, nationally, and globally, UPMC Children's Hospital of Pittsburgh 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. With generous community support, UPMC Children's Hospital has fulfilled this mission since its founding in 1890. UPMC Children's is recognized consistently for its clinical, research, educational, and advocacy-related accomplishments, including ranking 15th among children's hospitals and schools of medicine in funding for pediatric research provided by the National Institutes of Health (FY2019) and ranking on *U.S. News & World Report's* Honor Roll of America's Best Children's Hospitals (2020–21).

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