PEDIATRIC
INSIGHTS

WINTER 2022 • An Update From the Division of Pediatric Hematology/Oncology

Premedicating ALL Patients Prior to PEG-Asparaginase Therapy Shows Efficacy and Cost-Effectiveness

Acute lymphoblastic leukemia (ALL) is the most common form of cancer affecting children and adolescents.

ALL accounts for roughly 25% of malignancies diagnosed during childhood. While this disease demonstrates a high success rate for cure in younger patients, older adults diagnosed with ALL demonstrate a worse prognosis.

Treatment of ALL in pediatric patients often involves the use of asparaginase or its long-acting formulation pegylated (PEG)-asparaginase. PEG-asparaginase is a highly effective chemotherapy but carries with it the potential for toxicities and severe allergic reactions in some patients.

Substitutions for PEG-asparaginase have been possible in the past with the recently discontinued agent Erwinia, and now with a new recombinant version from the same manufacturer, Jazz Pharmaceuticals, called Rylaze, with comparable efficacy. Erwinia had to be administered more frequently with a baseline higher treatment cost and subsequent higher costs due to increased dosing requirements. Erwinia also was in limited supply globally while it was still being manufactured.

UPMC Children's Hospital of Pittsburgh Division of Pediatric Hematology/Oncology researcher **Meghan McCormick, MD, MS**, led a recent study examining the use of premedication prior to administration of PEG-asparaginase in pediatric ALL patients as a way to prevent allergic response. The group investigated cost-effectiveness of this approach versus the substitute Erwinia therapy.

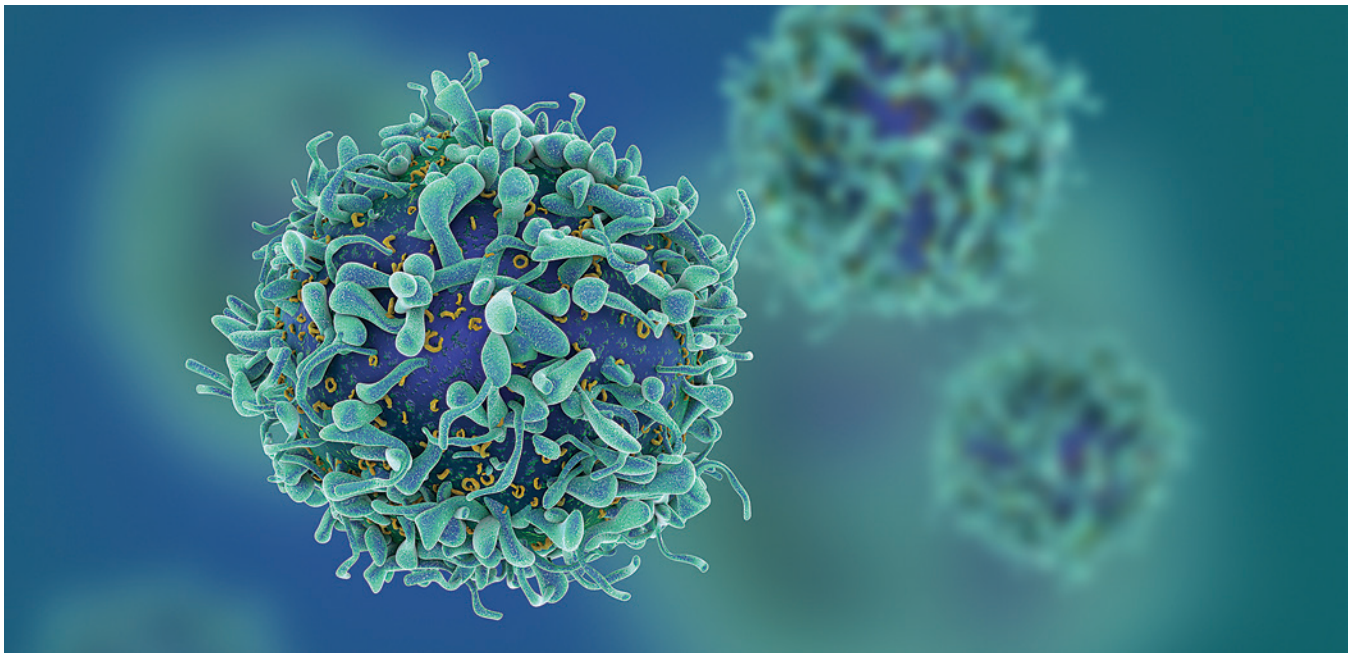
Dr. McCormick and her colleagues' study was published in March in the journal *Pediatric Blood & Cancer.*

Dr. McCormick's team modeled several treatment scenarios using the premedication with PEG-asparaginase approach versus Erwinia in patient cohorts diagnosed with standard risk and high-risk ALL. Premedicating patients before PEG-asparaginase therapy has been shown to be effective in

Continued on Page 8

In this issue

UPMC | CHILDREN'S HOSPITAL OF PITTSBURGH



New Research Shows Beneficial Role of Deleting AMPK in Graft-Versus-Host Disease

Graft-versus-host disease (GVHD) continues to be a troubling complication of allogeneic stem cell transplantation (alloSCT), carrying with it the potential for numerous morbidities and a significant risk of overall mortality. Post-transplant treatment options for GVHD remain limited to steroid therapy or nonspecific immunosuppression. Notably, steroid therapy carries risks of its own, and individuals with treatment-resistant GVHD have exceptionally high mortality rates.

The Byersdorfer Laboratory in the Division of Blood and Marrow Transplantation and Cellular Therapies (BMT-CT) at UPMC Children's Hospital of Pittsburgh, led by associate professor of pediatrics **Craig A. Byersdorfer, MD, PhD**, is focused on studying the basic science of GVHD — its mechanistic properties — and through that work, identifying potential targets for novel therapies.

"Stem cell transplantation is and continues to be a promising therapy for otherwise incurable diseases. But we must figure out a way to either eliminate the possibility of GVHD — which would be a tremendous accomplishment — or develop treatment options that can safely ameliorate the condition if it occurs," says Dr. Byersdorfer.

In July, Dr. Byersdorfer and colleagues published findings from their latest study[1] on the role of AMPK in GVHD in the journal *JCI Insight.*

AMPK is an enzyme that functions as a cellular energy sensor and regulates specific metabolic pathways within activated cells. In T cells, AMPK activity is upregulated because of the level and duration of allogeneic stimulation post-transplant.

Key Study Findings

Dr. Byersdorfer's study produced several notable findings that he and his team plan to investigate further as they piece together the mechanistic properties of AMPK and its role in T cell-driven GVHD, including whether AMPK can serve as a viable target for therapeutic intervention or modulation.

Using a knockout mouse model in which the gene coding for AMPK is deleted in donor T cells, Dr. Byersdorfer's team found that not only was the severity of GVHD suppressed to 40% of healthy controls, but that beneficial graft-versus-leukemia responses and reconstitution of the immune system post-transplant remained intact. Furthermore, these beneficial effects were maintained over a range of T cell doses.

Continued on Page 6

Beyond the LPPS: Determining Eligibility for Pediatric Cancer Clinical Trials Requires a Reassessment

A recent multicenter study published in the journal *Cancer* (online ahead of print) calls into question the validity of pediatric oncology providers' use of the Lansky Play-Performance Scale (LPPS) as an eligibility requirement for inclusion of children in cancer clinical trials.

The lead and corresponding author of the study was **Scott H. Maurer, MD.** Dr. Maurer is an associate professor of pediatrics at the University of Pittsburgh School of Medicine in the Division of Pediatric Hematology/Oncology and Department of Pediatrics. Dr. Maurer serves as Director of the Palliative Medicine and Supportive Care Program at UPMC Children's Hospital of Pittsburgh.

This study is the first of its kind to critically assess clinician-reported LPPS scores as a functional measure of patient status. While the LPPS has existed for decades, it was never designed for or validated for use by clinicians for the kind of widespread use it now occupies in the field, including its use as a criteria for clinical trial eligibility.

In an accompanying editorial authored by Angela Steineck MD, MS, and Abby R. Rosenberg, MD, MS, MA, they point out that Dr. Maurer and colleagues' study is the first published analysis of a measure of pediatric functional status used as an indicator of one's eligibility to safely participate in a clinical trial.

Key Findings

Dr. Maurer and colleagues' assessment of the use of LPPS by clinicians as a determinant of clinical trial eligibility revealed that this is a flawed approach. The team found that parent or caregiver assessments using the LPPS measure deviated significantly from clinician's assessment.

Furthermore, the study also found that both caregiver and clinician LPPS scoring poorly correlated with the child's self-report as measured by the Pediatric Patient-Reported Outcomes Measurement Information System® (PROMIS).

What this means, in general, is that children, caregivers, and clinicians differ significantly in their perceptions and reporting of the child's functional status, and these differences are sustained over various timepoints in therapy.

"Our findings show that we as clinicians, who are ultimately responsible for whether or not an individual patient can participate in a clinical trial, need to reassess our approach to evaluating and determining patient functional status and thus their ability to participate in trials. As we point out in our discussion, how clinician use of LPPS stacks up against parent use of LPPS and patient-reported outcomes measures is discordant. This discordance undoubtedly contributes to patients being excluded from trials who are good candidates and vice versa. This is an issue of access, potential efficacious outcomes, and safety," says Dr. Maurer. "Moving forward, we need to study how to best incorporate recently validated tools for patient, parent, and clinician report of a child's clinical status when determining what it means to be eligible for a clinical trial. In the meantime, clinical trialists and pediatric oncologists should be aware that parent and child perspectives should be included when considering the appropriateness of offering a clinical trial."

References

Maurer SH, Hinds PS, Reeve BB, Mack JW, McFatrich M, Lin L, Withycombe JS, Jacobs SS, Baker JN, Castellino SM, Freyer DR. Patients, Caregivers, and Clinicians Differ in Performance Status Ratings: Implications for Pediatric Cancer Clinical Trials. *Cancer.* 2021; 0:1-7. Epub Ahead of Print.

Steineck A, Rosenberg AR. Why Performance Status? A Case for Alternative Functional Assessments in Pediatric Oncology Clinical Trials. *Cancer.* 2021; Editorial.

Continued on Page 4

Clinical Trial Update:

Results From Phase 1 Entinostat Study

Andrew J. Bukowinski, MD, MS, from the Division of Pediatric Hematology/Oncology at UPMC Children's Hospital of Pittsburgh was the principal investigator and lead author on a phase 1 study evaluating the use of entinostat to treat recurrent or refractory solid cancers in children and adolescents. The study was published in the journal *Pediatric Blood & Cancer*.

Dr. Bukowinski serves as Director of the Oncology Developmental Therapeutics Program at UPMC Children's, one of 13 sites selected to participate in the Children's Oncology Group (COG) Pediatric Early Phase Clinical Trials Network (PEP-CTN).

The new trial, for which additional details can be found on ClinicalTrials.gov under identifier ADVL1513, was designed to elucidate the pharmacokinetics, pharmacodynamics, and maximum tolerated dose of entinostat in children with refractory and recurrent solid tumors.

Entinostat is a class I histone deacetylase (HDAC) inhibitor that has been studied in a wide variety of solid tumors in adults.

This was the first trial of entinostat in pediatric cancer patients.

Study Results — Overview

21 patients were recruited for participation in the study. The median age of participants was 14 years.

Study participants were given either 3 or 4 mg/m^2 once per week for a total of four doses over a 28-day period in a rolling six-dose escalation.

There were no dose limiting toxicities in any patients during the first two cycles of the study at either the 3 or 4 mg level. All but one of the patients experienced progression of their disease during their second dose cycle and before all cycles could be administered.

Based on these findings, the 4 mg/m^2 dose will be the dose recommended for further study in phase 2 trials.

References

Bukowinski A, Chang B, Reid JM, Liu X, Minard CG, Trepel JB, Lee M-J, Fox E, Weigel BJ. A Phase 1 Study of Entinostat in Children and Adolescents With Recurrent or Refractory Solid Tumors, Including CNS Tumors: Trial ADVL1513, Pediatric Early Phase-Clinical Trial Network (PEP-CTN). *Pediatr Blood Canc.* 2021; 68(4): e28892.

ClinicalTrials.gov Identifier: NCT027880804. Entinostat in Treating Pediatric Patients With Recurrent or Refractory Solid Tumors. Principal Investigator: Andrew Bukowinski; COG Phase 1 Consortium.

Beyond the LPPS *Continued from Page 3*

Further Reading

Hinds PS, Weaver MS, Withycombe JS, Baker JN, Jacobs SS, Mack JW, Maurer SH, McFatrich M, Pinheiro LC, Reeve BB, Wang J. Subjective Toxicity Profiles of Children in Treatment for Cancer: A New Guide to Supportive Care? *J Pain Symptom Manage.* 2021; 61(6): 1188-1195.

Mack JW, McFatrich M, Withycombe JS, Maurer SH, Jacobs SS, Lin L, Lucas NR, Baker JN, Mann CM, Sung L, Tomlinson D, Hinds PS, Reeve BB. Agreement Between Child Self-Report and Caregiver-Proxy Report for Symptoms and Functioning of Children Undergoing Cancer Treatment. *JAMA Pediatr.* 2020 Nov 1; 174(11):e202861.

McFatrich M, Brondon J, Lucas NR, Hinds PS, Maurer SH, Mack JW, Freyer DR, Jacobs SS, Baker JN, Mowbray C, Wang M, Castellino SM, Barz Leahy A, Reeve BB. Mapping Child and Adolescent Self-Reported Symptom Data to Clinician-Reported Adverse Event Grading to Improve Pediatric Oncology Care and Research. *Cancer.* 2020 Jan 1; 126(1): 140-147.

New Study to Probe the Mechanisms of Platelet Activation by Hemolysis in Sickle Cell Disease

Deirdre Nolfi-Donegan, MD, assistant professor of pediatrics in the Division of Pediatric Hematology/Oncology at UPMC Children's Hospital of Pittsburgh, was the recipient of a 2021 Hemostasis and Thrombosis Research Society (HTRS) Mentored Research Award.

Dr. Nolfi-Donegan's research project, "Pathologic Platelet Activation in Sickle Cell Disease," will investigate the mechanisms driving platelet activation in the context of hemolysis and oxidative stress that lead to thrombosis in sickle cell disease (SCD).

Dr. Nolfi-Donegan's investigation will focus on mitochondrial bioenergetics, platelet function, and in vivo thrombus formation. Specifically, she will examine how high mobility group box 1 (HMGB1), a protein released from activated immune cells and necrotic tissues whose level is increased in patients with sickle cell disease, interacts with free hemoglobin to promote platelet mitochondrial reactive oxygen species (ROS) production and platelet activation. This work will contribute novel findings that may lead to new and improved preventive strategies or therapies that guard against thrombo-inflammatory complications in individuals with sickle cell disease. Dr. Nolfi-Donegan's research may also be applicable to other hemolytic diseases in which thrombus formation is a key factor, such as paroxysmal nocturnal hemoglobinuria and unstable hemoglobinopathies.

Dr. Nolfi-Donegan is mentored in her research by Division colleague Cheryl A. Hillery, MD, professor of pediatrics, clinical director of Hematology, and director of the Comprehensive Pediatric Sickle Cell Program at UPMC Children's, and Sruti Shiva, PhD, professor in the Department of Pharmacology and Chemical Biology and co-director of the Center for Metabolism and Mitochondrial Medicine at the University of Pittsburgh.

Hepatoblastoma Research Update

A research team from the laboratory of **Edward Prochownik, MD, PhD**, in the Division of Pediatric Hematology/Oncology at UPMC Children's Hospital of Pittsburgh has uncovered how mutations in a gene known as NFE2L2/NRF2, in combination with ß-catenin and YAP mutations drive the genesis of highly aggressive forms of hepatoblastoma, the most common liver malignancy in children.

The study also identified a key group of 22 genes that are deregulated in all forms of hepatoblastoma and whose expression was altered by any combination of ß-catenin, YAP, and NFE2L2/NRF2. The expression levels of a 10 gene subset of these genes was able to predict with a high degree of accuracy those patients who were less likely to survive.

Aggressive hepatoblastoma in pediatric patients is very difficult to treat and demonstrates poor survival. The findings of this study represent a significant advancement toward elucidating the molecular mechanisms driving tumor progression. Evaluation of these deregulated gene sets could inform the development of new approaches for targeting features of aggressive disease.

The study[1] was published in March in the journal *Cellular and Molecular Gastroenterology and Hepatology.* Huabo Wang, PhD, was the lead author of the paper. Edward V. Prochownik, MD, PhD, the Paul C. Gaffney Professor of Pediatrics and professor of microbiology and Molecular Genetics, was the senior author of the study.

An editorial on the study's findings and the potential clinical impact was also published in March from Nikolai A. Timchenko, PhD, from Cincinnati Children's Hospital Medical Center.[2]

References

[1] Wang H, Lu J, Mandel JA, Zhang W, Schwalbe M, Gorka J, Liu Y, Marburger B, Wang J, Ranganathan S, Prochownik EV. Patient-Derived Mutant Forms of NFE2L2/NRF2 Drive Aggressive Murine Hepatoblastomas. *Cell Mol Gastroenterol Hepatol.* 2021; 12: 199-228.

[2] Timchenko NA. Help for Sick Kids: New Insights Into Hepatoblastoma. Editorial. Cell Mol *Gastroenterol Hepatol.* 26 March 2021.

Graft-Versus-Host Disease *Continued from Page 2*

Data from the study also indicate that when AMPK is deleted, the number of effector T cells decreased early in the post-transplant process. However, important metabolic (fatty acid oxidation) and intrinsic cellular activities, including autophagy and mammalian target of rapamycin (mTOR) signaling, were unaffected.

Furthermore, the study team uncovered that AMPK activity within the first 72 hours is critical in regards to subsequent GVHD initiation. As most clinical incidences of GVHD are noticed between day 20 and 60 post-transplant, it is likely that subclinical activity is already happening at the cellular level long before it can be detected through histologic or other laboratory testing.

"It appears that AMPK activity is absolutely critical in donor T cells during the first 72-96 hours post-transplant, for reasons that are not entirely clear. Some of our future studies will delve further into understanding how and why this is the case. We suspect that this initial post-transplant period will be crucial in managing GVHD in the future," says Dr. Byersdorfer.

Testing the Hypothesis in the Face of Immunosuppression

Since stem cell transplant patients all receive some form of immunosuppression as part of their therapeutic regimen, Dr. Byersdorfer and his team ran separate experiments on their models in the face of an immunosuppression agent, in this case, tacrolimus. T cells from immunosuppressed models continued to show the same strong increase in AMPK activity that was seen in non-immunosuppressed T cell populations. Importantly, these data suggest that inhibition or genetic deletion of AMPK would still be beneficial to patients on current regimens of post-transplant immunosuppression.

Future Studies and Clinical Implications

While AMPK's mechanism of action with respect to GVHD pathogenesis, maintenance, and severity is not fully understood, it may still prove to be a viable target in modulating disease severity. Due to AMPK's involvement in multiple cell types throughout the body, systemic inhibition of AMPK is unlikely to be a viable therapeutic strategy. However, there are potential alternatives that Dr. Byersdorfer and his team are considering.

Stem cell transplant therapies, by their very nature, involve a period of time between when cells are harvested from the donor and when they are transplanted into the new host. This creates a window in which to target potentially pathogenic T cells ex vivo prior to patient administration. In this case, modulatory approaches to suppress AMPK activity, such as pharmacologic inhibition of AMPK or genetic deletion of the AMPK gene using CRISPR-mediated technologies, could be undertaken between donor cell collection and subsequent recipient administration.

"Our lab is actively pursuing this line of research as part of our ongoing investigations on the role of AMPK in T cells," says Dr. Byersdorfer. "We are intrigued by the possibility of modifying or targeting donor cells prior to transplantation as a means to reduce or prevent GVHD."

Reference

[1] Monlish DA, Beezhold KJ, Chiaranunt P, Paz K, Moore NJ, Dobbs AK, Brown RA, Ozolek JA, Blazar BR, Byersdorfer CA. Deletion of AMPK Minimizes Graft-Versus-Host Disease Through an Early Impact on Effector Donor T Cells. *JCI Insight.* 2021 July 22; 6(14): 143811. Epub ahead of print.

Further Reading

Braverman EL, Waltz G, Byersdorfer CA. Immunometabolism in Haematopoietic Stem Cell Transplantation and Adoptive Cellular Therapies. *Curr Opin Hematol.* 2020 Nov; 27(6): 353-359. Review.

Brown RA, Byersdorfer CA. Metabolic Pathways in Alloreactive T Cells. *Front Immunol.* 2020 Jul 24; 11: 1517. Review.

Glick GD, Rossignol R, Lyssiotis CA, Wahl D, Lesch C, Sanchez B, Liu X, Hao LY, Taylor C, Hurd A, Ferrara JL, Tkachev V, Byersdorfer CA, Boros L, Opipari AW. Anaplerotic Metabolism of Alloreactive T Cells Provides a Metabolic Approach to Treat Graft-Versus-Host Disease. *J Pharmacol Exp Ther.* 2014 Nov; 351(2):2 98-307.

Byersdorfer CA, Tkachev V, Opipari AW, Goodell S, Swanson J, Sandquist S, Glick GD, Ferrara JL. Effector T Cells Require Fatty Acid Metabolism During Murine Graft-Versus-Host Disease. *Blood.* 2013 Oct 31; 122(18): 3230-3237.

Determining the Prevalence, Incidence, and Risk for Thrombotic Microangiopathy After Hematopoietic Stem Cell Transplantation

A retrospective study published in May in the *Journal of Personalized Medicine* analyzed data on hematopoietic stem cell transplant (HSCT) from 42 institutions that are part of the Pediatric Health Information System network between the years 2000-2012. The study sought to better understand the prevalence, incidence, and risk factors for developing the post-transplant complication thrombotic microangiopathy (TMA).

Leading the study were UPMC Children's Hospital of Pittsburgh Division of Pediatric Hematology/Oncology fellow and first author **Archana Ramgopal, DO**, (left) and director of pediatric sickle cell research, **Ramasubramanian Kalpatthi, MD**, senior author (right). Joining Drs. Ramgopal and Kalpatthi were Shiva Sridar, and Jignesh Dalal, MD, from Case Western Reserve Rainbow Babies Children's Hospital.

TMA is a severe complication experienced by some patients after HCST. There is uncertainty surrounding the prevalence and incidence of this disorder, who may be at greatest risk for developing the condition, and which patient cohorts have an increased risk of mortality. Coupled with the current lack of consensus on diagnostic criteria, there is an incomplete understanding of the molecular and cellular mechanisms driving thrombotic microangiopathy in HSCT patients.

Study Highlights

Dr. Ramgopal and Dr. Kalpatthi's study examined data from 12,369 cases of HSCT in children, adolescents, and young adults under the age of 21 at the time of transplantation. They identified 93 cases of TMA, representing 0.8% of the total cohort. Within the cluster of TMA cases, they observed a mortality rate of 30%.

In their analysis, TMA was more often associated with allogeneic HSCT and peripheral blood stem cell transplant cases. Additionally, the diagnosis of cytomegalovirus (CMV) infection, herpesvirus 6 (HHV-6), graft-versus-host disease (GVHD), and fungal infection was associated with higher rates of TMA.

Of these associative factors for TMA, only HHV-6 was found to be a risk factor for both acquiring TMA and for higher rate of mortality.

Other associated complications identified in the patient cohort include hypertension and renal failure.

An important contribution to the understanding of TMA from this study is the association of various infections to increased rates of the disorder, a component not fully appreciated prior to this analysis.

Dr. Ramgopal and Dr. Kalpatthi's analysis identifies additional risk scenarios for the disease that clinicians and transplantation protocols should be cognizant of, and it sets the stage for further analysis and follow-up investigations to better understand the risks for developing TMA and the potential for therapeutic interventions.

Reference

Ramgopal A, Sridar S, Dalal J, Kalpatthi R. Thrombotic Microangiopathy: Multi-Institutional Review of Pediatric Patients Who Underwent HSCT. *J Pers Med.* 2021 May 25; 11(6): 467.

UPMC Children's Oncology Researchers Discover and Treat First Known Case of AML in Pediatric Patient With ALPS-FAS

A clinical team from the Division of Pediatric Hematology/Oncology at UPMC Children's Hospital of Pittsburgh published their experience in diagnosing and successfully treating the first known case of acute myeloid leukemia and mast cell proliferation in a pediatric patient with autoimmune lymphoproliferative syndrome (ALPS).

The case report was published in the journal *Pediatric Blood Cancer.*

Former pediatric resident **Naomi Gunawardena, MD**, was the first author of the study. She was joined in the case report by **Meghan McCormick, MD, MS**, and senior author **A. Kim Ritchey, MD**, from the Pediatric Hematology/Oncology Division at UPMC Children's. Collaborating on the case report was former Department of Pathology faculty **Yen-Chun Liu, MD, PhD**.

Case Highlights

The patient was initially diagnosed with ALPS-FAS at the age of 8 months. At age 14, the patient developed AML, which rapidly responded to chemotherapy with no evidence of minimal residual disease after the first cycle. After initiation of chemotherapy, he was also found to have mast cell proliferation, which persisted after five rounds of therapy.

Ultimately, the patient underwent an allogeneic hematopoietic stem cell transplantation (allo-HCST) as it was felt that the potential benefit of the transplant outweighed the risks associated with the approach in this particular patient.

Since the patient's allo-HCST, he has remained in remission from both the AML and mast cell proliferation for more than 24 months.

Reference

Gundawardena N, McCormick M, Liu Y-C, Ritchey AK. Successful Treatment of Acute Myeloid Leukemia and Mast Cell Proliferation in a Patient With Autoimmune Lymphoproliferative Syndrome. *Pediatr Blood Cancer.* 2021 Aug; 68(8): e29012.

PEG-Asparaginase Therapy *Continued from Page 1*

dampening the incidence or severity of allergic reactions, which subsequently require discontinuation of the therapy and a change to a different modality. In fact, the Division of Pediatric Hematology/Oncology at UPMC Children's has routinely used premedication prior to all doses of PEG-asparaginase.

However, it was unclear whether or not premedication and PEG-asparaginase therapy was a more cost-effective approach to treatment, in comparison to Erwinia.

"It is more advantageous for patients and families, in a number of ways, if we can administer premedications in order to keep them on PEG-asparaginase, and to avoid any treatment toxicities that would necessitate discontinuation and a change in therapy to the more laborious approach inherent with Erwina," says Dr. McCormick. "Our modeling shows premedication has the potential to reduce therapy conversions, and it can be done cost-effectively using existing, readily available treatment options and strategies that combine therapeutics with vigilant patient monitoring."

Modeling from the study points to the use of premedication combined with patient monitoring as the more cost-effective approach in both standard risk and high-risk patients, with a corresponding 8% and 7% reduction in therapy conversions, respectively, when compared to using monitoring only with no premedication.

Reference

McCormick M, Lapinski J, Friehling E, Smith K. Premedication Prior to PEG-Asparaginase Is Cost-Effective in Pediatric Patients With Acute Lymphoblastic Leukemia. *Pediatr Blood Cancer.* 16 April 2021; E29051. Epub ahead of print.

Erica Braverman, MD, Awarded Hyundai Hope on Wheels® Young Investigator Grant

Erica Braverman, MD, Instructor of Pediatrics in the Division of Pediatric Hematology/Oncology at UPMC Children's Hospital of Pittsburgh, was awarded a 2021 Hyundai Hope on Wheels® Young Investigator Grant.

The two-year, $200,000 grant will support Dr. Braverman's research proposal to investigate how upregulation of the AMP-activated protein kinase (AMPK) pathway in chimeric antigen receptor (CAR) T cells may lead to improved, more durable responses for leukemia and other cancers.

Dr. Braverman's research interests focus on cancer immunotherapy, specifically areas of investigation related to improving T cell function and metabolic fitness to better fight and destroy cancer cells.

Preliminary studies by Dr. Braverman have shown that upregulation of the AMPK pathway in T cells can make them more metabolically efficient. AMPK is an enzyme that functions as a cellular energy sensor and regulates specific metabolic pathways within activated cells, in the metabolism of T cells, and in general, promotes and enhances metabolic fitness to support T cell function and survival.

"Cancer cells can be quite good at evading detection or suppressing T cell responses, or otherwise forcing T cells into making suboptimal metabolic choices. In certain solid tumors, the microenvironment is an inhospitable, nutrient-poor, oxygen-deprived realm in which T cells are tasked with functioning. Improving how T cells respond metabolically in the face of cancers, or finding ways to boost their responsiveness in such therapies as CAR T, offer promising avenues for new therapeutics and combinatory treatment approaches," says Dr. Braverman. "Our preliminary work suggests that upregulating the AMPK pathway in human T cells is a viable approach to improving T cell metabolism in the face of cancer. We are now going to apply these findings to determine if upregulating the AMPK pathway in CAR T cells can improve therapeutic responses."

Dr. Braverman's new grant will support the creation of CAR T cells with upregulated AMPK. She will test these modified CAR T cells in a mouse model of B cell acute lymphoblastic leukemia.

"CAR T cell therapy has shown promise for some patients, but one of the limitations has been the durability of response, and this lack of durability is in part related to issues of T cell metabolism," says Dr. Braverman. "If we can improve the durability of CAR T cells, we may be able to not only improve response rates in certain leukemias, but also create a better understanding of how CAR T cell therapy may be applied to combat solid tumors, where this therapy has yet to show much efficacy."

HYUNDAI HOPE ON WHEELS
Helping Kids Fight Cancer

Additionally, Dr. Braverman will work to more fully elucidate the role of AMPK within human T cells. Her research aims to better understand which signaling pathways are being activated downstream of AMPK during T cell activation, and how the activity of these pathways affects T cell metabolism and function.

"This work has implications beyond just cancer immunotherapy and CAR T cell therapy. Understanding how to modulate the metabolic choices of immune cells has implications for virtually any disease state associated with immune dysregulation, including sepsis and auto-immune conditions. What we find could have a far-reaching impact beyond our cancer studies," says Dr. Braverman.

Recent Publications

Braverman EL, Waltz G, Byersdorfer CA. Immunometabolism in Haematopoietic Stem Cell Transplantation and Adoptive Cellular Therapies. *Curr Opin Hematol.* 2020; 27(6): 353–359.

Braverman EL, Byersdorfer CA. Increasing AMPK Activity Supports Enhanced Oxidative Metabolism, Proliferation, and In Vitro Recovery of Human CD4 T Cells [abstract]. In: *J Immunol.* 2020; 204 (1 Supplement): 240.2-240.2.

UPMC Children's Sarcoma Researcher Awarded New K08 Grant

Kelly M. Bailey, MD, PhD, a physician-scientist in the Division of Pediatric Hematology/Oncology at UPMC Children's Hospital of Pittsburgh, was awarded a National Institutes of Health K08 young investigators grant in April 2021 to further her basic science research on Ewing sarcoma.

While much is unknown about Ewing sarcoma, there is a firm understanding that great levels of heterogeneity exist among and within these tumors. Very little is presently understood about the Ewing tumor microenvironment and how various factors in that microenvironment influence anti-tumor immune response, tumor growth, and tumor metastasis. Recurrent or refractory cases of Ewing sarcoma are extraordinarily challenging to treat successfully and almost always fatal. Dr. Bailey's research program is devoted to advancing our understanding of these aspects of Ewing sarcoma biology and developing improved approaches to targeted therapies that enhance anti-tumor immunity and inhibit tumor growth and metastasis.

Dr. Bailey's new K08 grant will expand her research program's technical expertise in tumor immunology and bioinformatic analyses of Ewing sarcoma. The research projects Dr. Bailey will carry out will be focused on two inter-related and poorly understood aspects of Ewing sarcoma biology: DNA damage repair and tumor immune response. Dr. Bailey's research will evaluate the impact of DNA damage in Ewing tumor cells on tumor immunogenicity.

Recent Select Ewing Sarcoma Publications From Dr. Bailey

Hawkins AG, Julian CM, Konzen S, Treichel S, Lawlor ER, Bailey KM. Microenvironmental Factors Drive Tenascin C and Src Cooperation to Promote Invadopodia Formation in Ewing Sarcoma. *Neoplasia.* 2019 Oct; 21(10): 1063-1072.

McAuley JR, Bailey KM, Ekambaram P, Klei LR, Kang H, Hu D, Freeman TJ, Concel VJ, Hubel NE, Lee JL, Klei HB, Cheng J, Sekar P, Bridwell RE, Covic L, Lucas PC, McAllister-Lucas LM. MALT1 is a critical mediator of PAR1-driven NF-κB activation and metastasis in multiple tumor types. *Oncogene.* 2019 Dec; 38(49): 7384-7398.

Bailey KM, Julian CM, Klinghoffer AN, Bernard H, Lucas PC, McAllister-Lucas LM. EWS-FLI1 low Ewing sarcoma cells demonstrate decreased susceptibility to T-cell-mediated tumor cell apoptosis. *Oncotarget.* 2019 May 21; 10(36): 3385-3399.

Venier RE, Maurer LM, Kessler EM, Ranganathan S, McGough RL, Weiss KR, Malek MM, Meade J, Tersak JM, Bailey KM. A germline BARD1 mutation in a patient with Ewing Sarcoma: Implications for familial testing and counseling. *Pediatr Blood Cancer.* 2019 Sep; 66(9): e27824.

Bailey K, Cost C, Davis I, Glade-Bender J, Grohar P, Houghton P, Isakoff M, Stewart E, Laack N, Yustein J, Reed D, Janeway K, Gorlick R, Lessnick S, DuBois S, Hingorani P. Emerging novel agents for patients with advanced Ewing sarcoma: a report from the Children's Oncology Group (COG) New Agents for Ewing Sarcoma Task Force. F1000Res. 2019 Apr 15;8:F1000 Faculty Rev-493.

More About Dr. Bailey

Kelly M. Bailey, MD, PhD, is an assistant professor of pediatrics in the Department of Pediatrics at the University of Pittsburgh School of Medicine. Dr. Bailey is a physician-scientist in the Division of Pediatric Hematology/Oncology at UPMC Children's Hospital of Pittsburgh. She specializes in the study of pediatric bone tumors, with a specific emphasis on the immune response to pediatric sarcomas, the tumor immune microenvironment of Ewing sarcoma, and the impact of DNA damage on the immunogenicity of Ewing sarcoma.

Dr. Bailey earned her MD/PhD degrees from West Virginia University, and then completed a pediatric residency and fellowship in pediatric hematology/oncology at the University of Michigan. Other recent notable accomplishments of Dr. Bailey's are a 2020-2022 Hyundai Hope on Wheels® Young Investigator Grant, and an Alex's Lemonade Stand Young Investigator Grant in 2016 for her investigation of micro-environmental regulators of Ewing sarcoma metastasis. Dr. Bailey is one of 10 investigators that comprise the New Agents for Ewing Sarcoma Task Force of the Children's Oncology Group (COG).

Division News & Notes

Educator Award Presented to Pediatric Hematology/Oncology Faculty

Erika Friehling, MD, MS, associate professor and fellowship program director in the Division of Pediatric Hematology/Oncology at UPMC Children's Hospital of Pittsburgh, and associate vice chair of Faculty Development in the Department of Pediatrics at the University of Pittsburgh School of Medicine was recently elected to the University of Pittsburgh School of Medicine Academy of Master Educators (AME).

The AME is comprised of approximately 80 faculty members selected from the more than 2,000 faculty member UPMC system. This academy rewards excellence in education, strives to advance educational initiatives through innovation and professional development of faculty, and promotes educational scholarship. Members are nominated by faculty of the University of Pittsburgh School of Medicine and selected by the AME membership committee.

AME members are appointed to five-year terms and involved with education of medical students, graduate students, and residents across the institution.

UPMC Children's Cancer Researcher Receives Scholar Award

UPMC Children's Hospital of Pittsburgh Division of Pediatric Hematology/Oncology researcher **Kelly M. Bailey, MD, PhD**, was awarded a UPMC Hillman Cancer Center Junior Scholar Award for Meritorious Basic Cancer Research.

Dr. Bailey was recognized for her work studying the basic biology and mechanisms of DNA damage repair and the anti-tumor immune response in Ewing sarcoma.

Dr. Bailey's recognition from UPMC Hillman comes on the heels of her receiving a National Institutes of Health K08 grant in April 2021 that supports her Ewing sarcoma studies.

About the Division

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.

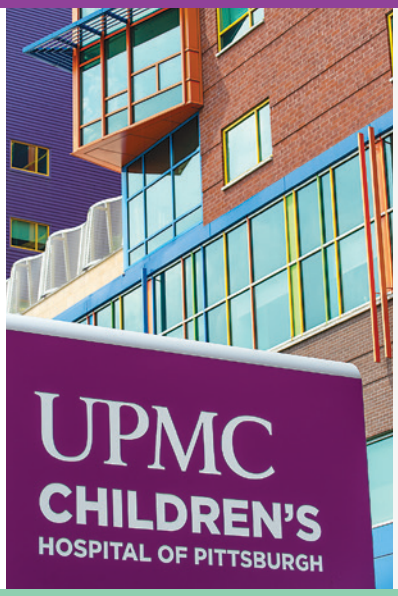
Clinical Programs and Services

- 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

UPMC | CHILDREN'S HOSPITAL OF PITTSBURGH

4401 Penn Ave.
Pittsburgh, PA 15224

Affiliated with the University of Pittsburgh School of Medicine and ranked among the nation's best children's hospitals by *U.S. News & World Report.*



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 Best Children's Hospitals (2021–22).

USNW522897 2/22 SD/MP