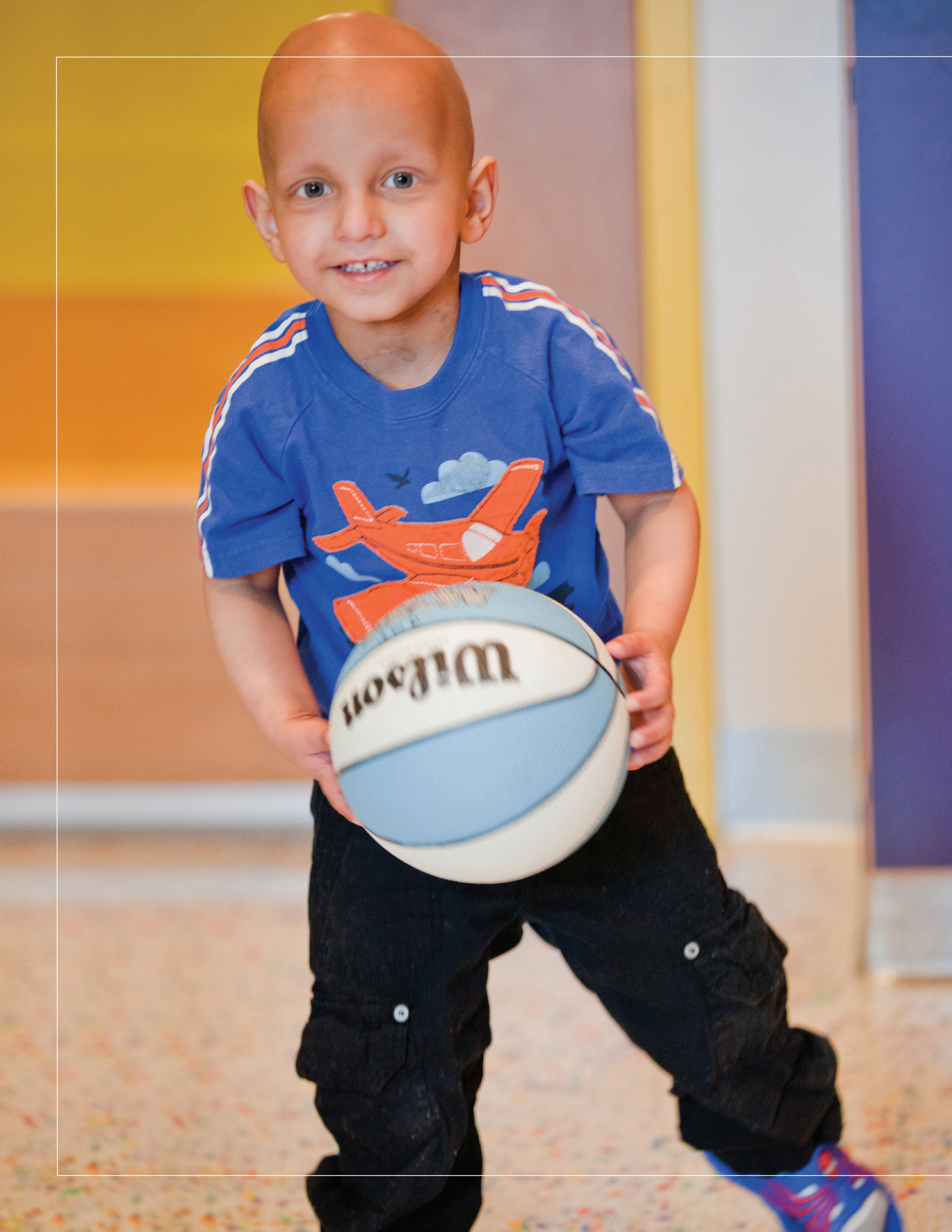
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DIVISION OF
BLOOD AND MARROW TRANSPLANTATION AND CELLULAR THERAPIES

Mission

The clinical mission of the Division of Blood and Marrow Transplantation and Cellular Therapies (BMT&CT) is to design and test disease-specific, biologically rational, novel, reduced-toxicity transplantation regimens for patients with high-risk leukemia or lymphoma and for those afflicted with life-threatening inherited conditions that can lead to bone marrow failure, immune deficiency, autoimmune diseases, and neurodegenerative conditions. Less-intense chemotherapy is combined with risk-tailored and pharmacologically personalized immunosuppression. Post-transplant cell therapy is offered to decrease disease recurrence and reduce infectious complications with the overarching goals to improve quality of life and disease-free survival after cord blood or bone marrow transplantation.

The division's translational research mission focuses on developing new cellular therapy programs and testing the use of bone marrow transplantation following solid organ transplantation to establish immunity, extend organ survival, and achieve eventual tolerance. Some patients come to Pittsburgh as their last hope after being too sick to be treated anywhere else.

The division's laboratory-based research mission focuses on elucidating mechanisms of alloreactivity (the biological principle driving graft-versus-host disease [GVHD] and rejection) and mechanisms essential for successful tolerance. These studies will help design new and better drugs and immunotherapy interventions.

FACULTY

Paul Szabolcs, MD
Professor of Pediatrics
and Immunology
Chief, Division of BMT&CT
Program Director, BMT&CT
Medical Director, Blood and Marrow
Processing Laboratory

Jessie Barnum, MD
Assistant Professor of Pediatrics

Craig Byersdorfer, MD, PhD
Assistant Professor of Pediatrics
and Immunology

Beth Carella, MD
Assistant Professor of Pediatrics

Xiaohua Chen, PhD
Research Assistant Professor
of Pediatrics

Randy Windreich, MD
Assistant Professor of Pediatrics
Director, BMT&CT Fellowship
Training Program
Director, Pediatric Hematology/
Oncology/BMT&CT
Outpatient Clinic

OVERVIEW OF DIVISION

The Division of BMT&CT was established in July 2011 upon the arrival of Division Chief Paul Szabolcs from Duke University. Prior to that, it was called the Blood and Marrow Transplantation (BMT) Program, operated as a part of the Pediatric Hematology/Oncology Division, and averaged 20–24 transplants a year.

In 2017, the BMT&CT division had five faculty physicians with clinical activities. Since the arrival in August 2014 of Craig Byersdorfer, a clinician-scientist, all clinical transplant services have been provided by members of the BMT&CT division. The division is poised to perform 40–50 transplants per year over the next two to three years and to open novel clinical protocols that will primarily recruit patients from out of state.

The division is the only center in the world with the ability to successfully engraft children suffering from sickle cell disease, thalassemia, and many other disorders with a reduced-intensity regimen paired with a single-unit, human leukocyte antigen (HLA)-mismatched cord blood graft (ClinicalTrials: NCT01962415). A CliniMACS® device has been successfully implemented since 2012 to support novel clinical trials with T-cell-depleted autologous transplantation for Crohn's disease and T-cell-depleted HLA-mismatched allogeneic bone marrow transplantation, all approved by the U.S. Food and Drug Administration as an Investigational New Drug (IND).

The division is the only center in the world to offer tandem lung and bone marrow transplantation for pediatric and adult patients with immune deficiencies who have progressed to pulmonary failure by recovering organ and marrow from the same deceased HLA-mismatched unrelated donor. This programmatic effort is supported by the National Institute of Allergy and Infectious Diseases (NIAID) in the National Institutes of Health (NIH). Mechanistic laboratory studies will analyze acquisition of mucosal immunity and tolerance. Ongoing collaborations with University of Pittsburgh investigators and UPMC clinicians will extend this concept toward new indications with disease-specific protocols opening in fiscal year 2018.

CLINICAL ACTIVITIES

During the academic year of 2017, the division performed 38 transplants. Most transplant grafts were procured from unrelated allogeneic donors, with unrelated cord blood (UCB) grafts being most common. By 2016, the use of unrelated bone marrow grafts had exceeded the use of HLA-matched sibling marrow transplantation. Autologous mobilized stem cell rescue is performed for children with high-risk neuroblastoma and brain tumors. Haploidentical transplants were performed by both *in vitro* T-cell depletion and by post-transplant cyclophosphamide administration. With all possible transplant modalities on site, the division can find a suitable donor for any patient who may benefit from hematopoietic stem cell transplantation (HSCT).

One of the division's signature protocols (ClinicalTrials: NCT01962415) has attracted patients from two dozen states, ranging from Florida to Alaska. Patients with about 20 unique genetic diagnoses are enrolled on this reduced-intensity conditioning (RIC) trial. Diagnoses range from sickle cell disease, thalassemia, osteopetrosis, Krabbe disease, metachromatic leukodystrophy, to many primary immune deficiency syndromes such as BLS and X-linked inhibitor of apoptosis

deficiency. Day 100 non-relapse mortality has remained exceptionally low; there have been no deaths during this most vulnerable transplant period. With more than three dozen patients enrolled so far, one-year event-free survival exceeds 90% in the unrelated cord blood transplant setting, exceeding the results of centers of excellence worldwide. In 2016, the division opened an institutional prospective trial for children and young adults afflicted with high-risk acute myeloid leukemia (AML), employing RIC and myeloablative conditioning for HSCT in AML/myelodysplastic syndromes (ClinicalTrials: NCT02626715). To bridge the temporary post-transplant immune-deficient state, the division has performed therapeutic T-cell infusions with adenovirus hexon-specific interferon gamma-captured cells under IND/Institutional Review Board (IRB)-approved treatment plans. These will pave the way for new protocols that will open in 2018 and take advantage of a new CliniMACS® Prodigy device and conceptual advances.

RESEARCH AND OTHER SCHOLARLY ACTIVITIES

Paul Szabolcs, MD

RESEARCH

Paul Szabolcs is a physician-scientist whose clinical and research interests are focused on the biology of donor-derived cellular immunity and modulating alloreactivity in recipients of allogeneic hematopoietic cell transplantation (HCT). The overall goal of his efforts is to develop novel diagnostic and therapeutic approaches to accurately diagnose, predict, and therapeutically accelerate post-transplant immune reconstitution without increasing GVHD. He has developed a research program to elucidate mechanisms essential for successful tolerance. These studies will help to develop novel immunotherapy interventions. He continues to focus on unrelated cord blood transplantation (UCBT) as the dominant clinical scenario and laboratory model. His work has continued to influence the global field of transplantation medicine, especially the translational science of HLA-mismatched bone marrow transplantation as it is applied in tandem with solid organ transplantation.

LABORATORY-BASED RESEARCH

Graft Engineering and Immunotherapy After UCBT. The Szabolcs lab studies HCT recipient and donor pairs to analyze the development of protective immunity and to modulate T-cell responses toward amplifying leukemia-reactive T cells. Szabolcs and Xiaohua Chen study active mechanisms responsible for development of tolerance in HLA-mismatched cord blood recipients. This research aims at developing innovative immunomodulatory strategies relevant to multiple disease categories.

Immune Reconstitution After Cord Blood Transplant. Szabolcs and Chen perform correlative studies of T-cell immune reconstitution in ongoing clinical trials utilizing UCBT to identify the predictors of clinical outcomes. Since late 2012, the research has increasingly focused on elucidating mechanisms of tolerance in mixed chimerism and understanding the role of regulatory T cells in those with tolerance and those without, namely those suffering from GVHD.

Paul Szabolcs, MD
Division Chief, Blood and Marrow Transplantation and Cellular Therapies

CLINICAL RESEARCH

Reduced-Intensity UCBT for Children With Rare Metabolic and Primary Immune Deficiency (PID) Disorders. Children with PID syndromes, even those who may have significant comorbidities, can be cured with reduced-toxicity regimens. The CHP BMT&CT medical team works closely with collaborating services, in particular the Program for the Study of Neurodevelopment in Rare Disorders (NDRD) at CHP and Medical Genetics, to identify those who may benefit from HCT. The team offers a novel RIC regimen (ClinicalTrials: NCT01962415) that is testing the hypothesis that it can reduce/eliminate transplant-related mortality and achieve superior neurocognitive outcomes compared to traditional myeloablative conditioning for a wide variety of inherited metabolic disorders, including but not limited to Krabbe disease, metachromatic leukodystrophy, and mucopolysaccharidosis syndromes.

In fiscal year 2017, Szabolcs focused on a new UPMC initiative called the Immune Transplant and Therapy Center (ITTC), where novel auto-transplant protocols will be developed for autoimmune disorders such as inflammatory bowel disease and scleroderma. With Beth Carella, MD, Szabolcs continues to design allogeneic transplant protocols

to address HLA-matched donor availability in sickle cell disease by offering HLA-mismatched unrelated donor and/or haploidentical transplantation in children and adults. Barnum's virus-specific T-cell therapy protocol will play a critical support role in this initiative.

Autologous Stem Cell Transplantation With CD34-Selected Peripheral Blood Stem Cells (PBSCs) in Pediatric and Young Adult Patients With Severe Crohn's Disease and Other Autoimmune Disorders (ClinicalTrials: NCT0692939). This study continues to evaluate the safety and efficacy of high-dose immunotherapy followed by infusion of autologous CD34-selected PBSCs in pediatric and young adult patients who are refractory to all other treatment modalities.

Tandem Solid Organ Transplant and T-Cell-Depleted BMT. This new treatment modality was developed to transplant in stages two organs, both procured from a partially HLA-matched cadaveric donor. The therapy addresses the unmet need to offer meaningful and high-quality life to children and young adults who have pulmonary or other end organ failure and severe immune deficiency. Szabolcs was the sponsored investigator for this protocol; collaborators came from the Thomas E. Starzl Transplant Institute, Mellon Institute, University of Pittsburgh Cancer Center, and Children's Hospital of Pittsburgh. The team continued to enroll patients on a protocol titled "Sequential Cadaveric Lung and Bone Marrow Transplant for Primary Immune Deficiency Diseases" (ClinicalTrials: NCT01852370). One patient received a lung transplant for IL-7R null severe combined immunodeficiency in September 2015 and received the bone marrow transplant from the same cadaveric donor in January 2016. She was the first patient in the world to engraft with one of eight high-resolution HLA-matched cadaveric bone marrow, and she successfully weaned off immunosuppression in May 2017. This is also the first case of engraftment and immune reconstitution with a bone marrow graft prepared from vertebral bodies. Adult and pediatric patients with no other life-saving alternatives have come from as far as Texas and Rhode Island to enroll on this research protocol. This work was supported by NIAID/NIH R34 and UO1 grants to Szabolcs as communicating co–principal investigator (PI).

Cadaveric Donor Lung and Bone Marrow Transplantation in Immunodeficiency Diseases. 1U01AI125050-01: NIH/NIAID, 07/06/16-06/30/21. For patients with PID who develop the complication of end-stage lung disease, neither BMT nor lung transplantation are therapeutic options. This is the first clinical trial to evaluate the safety and efficacy of a *combined-tandem* strategy for lung transplant followed by BMT to correct the defective immune system, using the same organ donor. The lab performs tests to determine whether BMT restores the ability to fight infection and allows acceptance of the lungs, which would permit eventual withdrawal of all immunosuppression medications in these unique, combined transplant recipients. Ancillary mechanistic studies will test for global and mucosal immune competence, and others will test for mechanisms of tolerance. Szabolcs is the communicating PI. John McDyer, MD, UPMC Adult Lung Transplantation, is co-PI. Multiple investigators have joined this translational research proposal from Children's Hospital of Pittsburgh (Geoff Kurland, MD, Marian Michaels, MD, and Jay Kolls, MD, PhD), Presbyterian Hospital of UPMC, and the University of Pittsburgh Department of Immunology (Fadi Lakkis, MD, and Dario Vignali, PhD).

MAJOR LECTURESHIPS AND SEMINARS

- "Studies on Alloreactivity and Tolerance After Peripheral Blood and Cord Blood Transplantation: Is There a Tipping Point?" University of Pittsburgh Cancer Institute, Cancer Immunology Program Seminars, Pittsburgh, Pa., April 2016
- "Lung Transplantation in Tandem with Bone Marrow Transplantation from Partially HLA-Matched Deceased Donors: Clinical and Mechanistic Studies," 2016 STI Scientific Retreat, Pittsburgh, Pa., November 2016
- "Reduced-Intensity Transplantation Is Effective for Multiple Genetic Diseases: The Pittsburgh Protocol," Dubai-Arab Medical Congress, 2017
- "Reduced-Intensity Unrelated Donor Transplantation for Non-Malignant Diseases: A Journey Toward Combined Organ and Marrow Transplantation," hematology grand rounds, UPMC Shadyside Hospital, University of Pittsburgh Cancer Institute, Pittsburgh, Pa., March 2017
- "Mechanisms of Tolerance Following HLA-Mismatched Cord Blood Grafts: A Journey Toward Tandem Cadaveric Organ + Marrow Transplantation," grand rounds, Memorial Sloan Kettering Cancer Center, New York, N.Y., June 2017
- "Mechanisms of Tolerance Following HLA-Mismatched Cord Blood Grafts: A Journey Toward Tandem Cadaveric + Organ Marrow Transplantation," Children's Hospital of Pittsburgh of UPMC Molecular Medicine Research Seminar, June 2017

EDITORIAL BOARDS

- *Cytotherapy*
- *Blood Research*
- *American Journal of Transplantation*

PROFESSIONAL AFFILIATIONS/SOCIETY MEMBERSHIPS

- American Society of Hematology
- American Society for Blood and Marrow Transplantation
- Center for International Blood and Marrow Transplant Research (CIBMTR)
- American Association of Immunologists
- Society for Pediatric Research Clinical Immunology Society
- Federation of Clinical Immunology Society
- UPCI
- Fellow, American Academy of Pediatrics
- International Society for Cellular Therapy

Jessie Barnum, MD

RESEARCH

Haploidentical Viral-Specific T Lymphocytes to Treat Persistent Reactivation or Infection With Adenovirus, Cytomegalovirus, and Epstein-Barr Virus After HCT or Solid Organ Transplantation. Jessie Barnum focuses on improving available therapy for patients with serious and often life-threatening viral infections after BMT. Available antivirals are quite toxic and often ineffective. She continues toward an institutional investigator-initiated protocol of T-cell immunotherapy for adenovirus, cytomegalovirus, and Epstein-Barr virus.

Outcomes of Human Adenovirus Infection and Disease in Pediatric Allogeneic Stem Cell Transplant Recipients: A Prospective, Multicenter, Observational Cohort. Barnum is a co-investigator and the BMT lead on this NIAID-funded, prospective, multicenter trial designed to study risk factors for severe adenoviral infections in stem cell transplant recipients. This protocol opened at Children's Hospital of Pittsburgh in July 2017, and it is projected to enroll 86 allogeneic transplant patients in the next five years.

Bilateral Orthotopic Lung Transplant in Tandem With CD3+ and CD19+ Cell-Depleted Bone Marrow Transplant From Partially HLA-Matched Cadaveric Donors. Barnum is a co-investigator for the Tandem Solid Organ Transplant and T-Cell-Depleted Bone Marrow Transplant protocol. This new treatment modality was developed to transplant lungs followed by bone marrow, both procured from a partially HLA-matched cadaveric donor. The therapy addresses the unmet need to offer meaningful and high quality of life for children and young adults who have significant respiratory insufficiency and severe immune deficiency. Barnum is one of two physicians fully trained to procure vertebral bodies from cadaveric donors and has performed this procedure on two occasions. She has trained other faculty in this procedure and wrote a standard operating procedure for use in the operating room.

Naïve T-Cell Depletion for Prevention of Chronic GVHD in Children and Young Adults. Barnum serves as principal investigator on this CIBMTR study, which is a multicenter, phase II, randomized, controlled trial comparing outcomes in pediatric patients receiving allogeneic HCT with either naïve T-cell-depleted peripheral blood stem cells or T-cell-replete bone marrow. This trial has progressed to the initial feasibility phase; the randomized, controlled trial will follow.

Use of Miltenyi Biotec's CliniMACS® CD34 Reagent System as a Humanitarian Use Device for Isolation of Hematopoietic Stem Cells or T-Cell Depletion in Multiple Settings. Barnum wrote this protocol to study novel graft manipulation to decrease the risk of GVHD. It was used successfully for a patient with Fanconi anemia and many comorbidities. It remains open for other patients at Children's Hospital of Pittsburgh.

Primary Immune Deficiency Treatment Consortium Protocol 6901: A Prospective Natural History Study of Diagnosis, Treatment, and Outcomes of Children With Severe Combined Immune Deficiency Disorders. Barnum serves as principal investigator on this multicenter, prospective protocol.

Primary Immune Deficiency Treatment Consortium Protocol 6903: Analysis of Patients Treated for Chronic Granulomatous Disease Since 1995. Barnum serves as co-investigator on this multicenter, prospective, retrospective, and cross-sectional protocol.

Primary Immune Deficiency Treatment Consortium Protocol 6904: Analysis of Patients Treated for Wiskott Aldrich Syndrome Since 1990. Barnum serves as co-investigator on this multicenter, prospective, retrospective, and cross-sectional protocol.

MAJOR LECTURESHIPS AND SEMINARS

- "Infectious Complications After BMT," *Association of Pediatric Hematology/Oncology Nurses* (APHON) course, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pa., September 2016, February 2017, and June 2017
- "Renal Complications After BMT," APHON course, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pa., September 2016, February 2017, and June 2017
- "Critical Illness After BMT: Respiratory Complications," Pediatric Intensive Care Unit Fellow Didactic Session, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pa., November 2016
- "Tolerance Strategies," BMT and liver transplant focus group on immune tolerance, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pa., November 2016
- "Infections in the Immunocompromised Host," Pediatric Hematology and Oncology Fellow Core Lecture Series, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pa., March 2017
- "Immune Manipulations in Transplantation," Pediatric Hematology, Oncology, Bone Marrow Transplant, and Cellular Therapies Conference, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pa., April 2017
- "Successful Engraftment, Immune Reconstitution, and Clinical Evidence of Immune Tolerance Following Cord Blood and Intestinal Transplant for Immunodeficiency and Intestinal Failure," poster presentation, Pediatric Immune Deficiency Treatment Consortium Scientific Workshop, Bethesda, Md., May 2017
- "Successful Engraftment, Immune Reconstitution, and Clinical Evidence of Immune Tolerance Following Cord Blood and Intestinal Transplant for Immunodeficiency and Intestinal Failure," oral presentation, Pediatric Immune Deficiency Treatment Consortium Educational Workshop, Bethesda, Md., May 2017
- "Successful Engraftment, Immune Reconstitution, and Prope Immune Tolerance Following Cord Blood and Intestinal Transplant for Immunodeficiency and Intestinal Failure," poster presentation, XV International Congress of the Intestinal Rehabilitation and Transplant Association, New York, N.Y., June 2017

PROFESSIONAL AFFILIATIONS/SOCIETY MEMBERSHIPS

- American Society of Bone Marrow Transplantation
- American Society of Hematology
- American Society of Pediatric Hematology/Oncology
- Transplantation Society
- Primary Immune Deficiency Treatment Consortium
- Children's Oncology Group

Craig Byersdorfer, MD, PhD

RESEARCH

Craig Byersdorfer focuses on the biology of GVHD-causing T cells following allogeneic transplantation to develop novel therapeutics to mitigate GVHD while preserving homeostatic immune reconstitution and graft-versus-leukemia effects. Specifically, Byersdorfer's research program seeks to elucidate the specific metabolic pathways that are upregulated in GVHD-causing T cells. His novel approach to disease pathogenesis continues to aim at innovative therapies. His findings on T-cell metabolism have implications extending beyond BMT to solid organ transplantation and long-term anti-leukemia responses.

LABORATORY-BASED RESEARCH

The Role of AMP-Activated Protein Kinase (AMPK) in Alloreactive T Cells. AMPK is a well-known energy sensor and is activated early in T cells during a GVHD response. Byersdorfer has shown that lack of AMPK leads to decreased rates of GVHD but preserves anti-leukemia responses. Further work has demonstrated that a lack of AMPK has consequences for both effector T cells and the generation of regulatory T cells, favoring a tolerogenic response. Future studies will utilize animal models and AMPK knockout cells to determine the mechanisms of improved GVHD in the absence of AMPK signaling.

Transcriptional Control of Fatty Acid Metabolism in Alloreactive T Cells. The Byersdorfer laboratory has previously demonstrated that GVHD-causing T cells increase their dependence on the oxidation of fat. The laboratory found that transcriptional control of fat oxidation depends on signaling through peroxisome proliferator-activated receptors (PPARs), notably PPAR-δ. His lab continues to generate PPAR-δ-deficient mice to determine its role in GVHD propagation and to define whether PPAR-δ is a potential therapeutic target for GVHD treatment.

Using Metabolic Manipulation to Improve Anti-Leukemia Responses. One of the challenges to treatment with chimeric antigen receptor (CAR) T cells for acute lymphoblastic leukemia is its frequent inability to persist *in vivo*. The Byersdorfer laboratory seeks to improve the *in vivo* persistence of CAR T cells by reprogramming their metabolism through constitutive expression of activated AMPK or PPAR-δ and thus increase anti-leukemia efficacy.

CLINICAL RESEARCH

Reprogramming Human T Cells. Having determined the metabolic pathways present in murine alloreactive T cells, the Byersdorfer laboratory has moved on to examine whether similar metabolic changes occur in human T cells during GVHD and whether their elimination mitigates GVHD. Clinical samples will be collected from human patients at the diagnosis of acute GVHD and evaluated so that the researchers can determine the metabolic pathways present. The laboratory has continued to pursue studies using gene-editing programs like CRISPR-Cas9 to eliminate metabolic proteins in human T cells and then test them in xenogeneic models of GVHD before transitioning them to clinical application.

MAJOR LECTURESHIPS AND SEMINARS

- "An Unexpected Role for AMP-Activated Protein Kinase During Graft-Versus-Host Disease," hematology/oncology/BMT seminar series, Ben Towne Cancer Center, Seattle, Wash., May 2016
- "How I Learned to Stop Worrying and Love the Bomb Biochem," keynote address, annual physician-scientist training program research symposium, University of Pittsburgh, Pittsburgh, Pa., November 2016

PROFESSIONAL AFFILIATIONS/SOCIETY MEMBERSHIPS

- American Society of Hematology
- American Society for Blood and Marrow Transplantation
- American Association of Immunologists
- Second appointment, Department of Immunology, University of Pittsburgh

HONORS

- First place, Junior Faculty Basic Science Research, annual Immuno-Oncology Young Investigators Forum, Houston, Texas, March 2016
- Hyundai Hope Scholar, May 2016
- American Society of Hematology Scholar, November 2016

Beth Carella, DO

RESEARCH

Beth Carella's clinical research focuses on expanding utilization of stem cell transplantation for patients with sickle cell disease. Collaborating with Szabolcs, she continues to develop a clinical trial to broaden opportunities for patients lacking matched sibling donors. With mismatched donors, the risk of GVHD is high; however, this protocol will use *in vitro* T-cell depletion to reduce risks. This approach will allow a larger number of severely affected patients to access a curative intervention. With an RIC regimen, the trial aims to allow for successful engraftment while reducing toxicity for this non-malignant disease. Carella is the institutional principal investigator for the BMTCTN STRIDE II protocol, which compares standard of care to myeloablative, matched transplantation for patients with sickle cell disease. She is the institutional principal investigator for the PBMTC SUP1601 protocol, which aims to identify pathogens in stem cell transplant patients with lower respiratory tract infections.

MAJOR LECTURESHIPS AND SEMINARS

- "HLA Typing, Part 1," oral presentation, Hematology/Oncology Fellow Lecture Series, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pa., February 2017
- "HLA Typing, Part 2," oral presentation, Hematology/Oncology Fellow Lecture Series, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pa., June 2017

ADVISORY COMMITTEE MEMBERSHIPS

- University of Pittsburgh IRB, June 2017

PROFESSIONAL AFFILIATIONS/SOCIETY MEMBERSHIPS

- American Society of Pediatric Hematology/Oncology
- American Society of Blood and Marrow Transplant
- American Society of Hematology
- Children's Oncology Group
- American Academy of Pediatrics

Xiaohua Chen, PhD

RESEARCH

Xiaohua Chen focuses on characteristics and corresponding biomarkers that are essential for human transplant tolerance and their potential for application in organ transplantation. She also monitors immune reconstitution in ongoing clinical protocols.

Cadaveric Donor Lung and Bone Marrow Transplantation in Immunodeficiency Diseases. As a co-investigator, Chen spearheads the tolerance and immune competence studies in the Szabolcs laboratory.

Regulatory T Cells and Tolerance in HSCT. Clonal deletion of alloreactive thymocytes is a critical and central mechanism in forming long-term tolerance; however, hyporeactivity may depend on additional peripheral mechanisms with or without immunosuppression. The degree of influence from peripheral factors is unknown. Chen's studies explore the mechanisms of long-term immune tolerance formed in allo-HSCT and their potential in organ transplantation. Both central (clonal deletion) and peripheral (anergy, Treg, Tr1) tolerance are being examined in the HLA-mismatched cord blood and deceased donor bone marrow transplant setting. She uses high-throughput digital sequencing to track clonal evolution versus deletion. She characterizes Treg cells and evaluates anergy in patients who achieve immune tolerance and those with GVHD to continue toward mapping the longitudinal evolution of immune tolerance mechanisms and plot efficacy of GVHD treatments. Evolution of Treg and alloreactive T-cell clonotypes are studied after tandem lung and bone marrow transplant.

Cellular and Molecular Monitoring of Immune Reconstitution Post-HSCT in Ongoing Clinical Protocols. This project applies reliable approaches in cellular and molecular monitoring of immune reconstitution in ongoing clinical protocols. By using multiple *fluorescence-activated cell sorting* panels, TCRb, TCRgd BCR spectratyping, and sjTREC real-time polymerase chain reaction, Chen monitors immune recovery post-HSCT.

PROFESSIONAL AFFILIATIONS/SOCIETY MEMBERSHIPS

- Collaborative Institutional Training Initiative
- American Society of Hematology
- American Association of Immunologists
- Federation of Clinical Immunology Societies

Randy Windreich, MD

RESEARCH

Randy Windreich's clinical research focuses on HSCT for acute leukemias, using drug pharmacokinetics and pharmacodynamics to individualize and optimize therapy, particularly within the pediatric BMT patient population, as well as alternative uses for hematopoietic stem cells.

A Phase II Study of Myeloablative and RIC Regimens for Children With Acute Myeloid Leukemia or Myelodysplastic Syndrome Undergoing Allogeneic HSCT. The objective of this study is to determine safety, preliminary efficacy, and event-free survival at six months in pediatric patients receiving a myeloablative or reduced-intensity preparative regimen prior to HSCT for high-risk acute myeloid leukemia and myelodysplastic syndrome. Windreich is developing an institutional protocol for a dual-arm myeloablative and reduced-intensity transplant conditioning regimen for patients with hematologic malignancies and unrelated donors, with an emphasis on acute myeloid leukemia and acute lymphoblastic leukemia. The protocol will expand eligibility for HSCT, particularly for those with serious pre-transplant comorbidities. Subject enrollment continues.

A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy, Safety, and Tolerability of Transendocardial Injection of Ixmyelocel-T in Subjects With Heart Failure Due to Ischemic Dilated Cardiomyopathy. This is an industry-sponsored, multicenter study through Vericel Corporation (formerly Aastrom Biosciences) (Ann Arbor, Mich.), in collaboration with the UPMC Heart and Vascular Institute at UPMC Presbyterian Hospital. The objective of this study is to assess the efficacy, safety, and tolerability of ixmyelocel-T compared to placebo (vehicle control) when administered via transendocardial catheter-based injections to subjects with end-stage heart failure due to ischemic dilated cardiomyopathy who have no reasonable revascularization options (either surgical or percutaneous interventional) likely to provide clinical benefit. Results have been published in *Lancet* (2016;387:2412-21), reporting transendocardial delivery of ixmyelocel-T in patients with heart failure and reduced ejection fraction due to ischemic dilated cardiomyopathy

resulted in a significant reduction in adjudicated clinical cardiac events and improved outcomes. An open-label extension is active for patients who had been randomly assigned to receive placebo during the study period and now have the opportunity to undergo bone marrow harvest again and receive ixmyelocel-T therapy.

A Single-Arm, Prospective Study of Remestemcel-L, Ex Vivo *Cultured Adult Mesenchymal Stromal Cells, for the Treatment of Pediatric Patients Who Have Failed to Respond to Steroid Treatment for Acute GVHD.* This is an industry-sponsored multicenter study through Mesoblast International Sarl (Switzerland). The objective of this study is to evaluate efficacy and gather additional information on safety of remestemcel-L in pediatric patients with grades B-D acute GVHD who have failed to respond to steroid treatment post-allogeneic HSCT. Subject enrollment continues.

MAJOR LECTURESHIPS AND SEMINARS

- "Blood and Marrow Transplantation Nuts and Bolts," oral presentation, Pediatric Hematology/Oncology Fellowship Conference, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pa., September 2016
- "Pediatric Hematology/Oncology and Blood and Marrow Transplantation: 2016 Updates: Transition and Growth," oral presentation, Katie Swaney Foundation board meeting, Pittsburgh, Pa., October 2016
- "Leukemias and Lymphomas," oral presentation, Pediatric Residency Conference, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pa., December 2016
- "Neuroblastoma," oral presentation, APHON Foundations and *Certified Pediatric Hematology Oncology Nurse* (CPHON) Review Course, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pa., March 2017
- "Solid Tumors," oral presentation, APHON Foundations and CPHON Review Course, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pa., March 2017
- "Pediatric Cancer: Solid Tumors," oral presentation, Pediatric Residency Conference, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pa., April 2017
- "Safety and Feasibility of Granulocyte Transfusion for High-Risk Allogeneic Stem Cell Transplant Recipients," poster presentation, American Society of Pediatric Hematology/Oncology annual meeting, Montreal, Quebec, Canada, April 2017
- "Germ Cell Tumors," oral presentation, Pediatric Hematology/Oncology Fellowship Conference, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pa., June 2017
- "Cardiac Complications During Blood and Marrow Transplantation," oral presentation, APHON Blood and Marrow Transplantation Course, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pa., June 2017

ADVISORY COMMITTEE MEMBERSHIPS

- Division of Hematology/Oncology Fellowship Oversight Committee, Children's Hospital of Pittsburgh of UPMC
- Pediatric Hematology/Oncology/BMT Outpatient Clinic Committee, Children's Hospital of Pittsburgh of UPMC
- Chemotherapy Oversight Committee, Children's Hospital of Pittsburgh of UPMC
- 9B (Oncology/BMT Inpatient Unit) Leadership Committee, Children's Hospital of Pittsburgh of UPMC
- 9B (Oncology/BMT Inpatient Unit) Infection Control Committee, Children's Hospital of Pittsburgh of UPMC
- Chemotherapy Oversight Committee, Children's Hospital of Pittsburgh of UPMC

PROFESSIONAL AFFILIATIONS/SOCIETY MEMBERSHIPS

- American Society of Pediatric Hematology/Oncology
- American Society for Blood and Marrow Transplantation
- American Society of Hematology
- Children's Oncology Group

HONORS

- Best Doctors, *Pittsburgh Magazine*, 2017

TEACHING ACTIVITIES

The faculty members in the pediatric BMT&CT division are actively involved in teaching residents and fellows. The BMT&CT Fellowship Program (Windreich, director) established an educational environment to train advanced practice fellows in BMT in 2012. Barnum and Windreich mentor pediatric fellows. Byersdorfer mentors four medical students and one undergraduate. Carella leads efforts to help design and implement the curriculum for the advanced practice providers' fellowship program.

THREE-YEAR BIBLIOGRAPHY

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Gleimer M, Li Y, Chang L, Paczesny S, Hanauer DA, Frame DG, **Byersdorfer CA**, Reddy PR, Braun TM, Choi SW. Baseline body mass index among children and adults undergoing allogeneic hematopoietic cell transplantation: Clinical characteristics and outcomes. *BMT*. 2015;50(3):402.

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