

Bone Marrow Transplantation and Immune Deficiency



Division Data Summary

Research and Training Details

| | |
|-------------------------------------|-----------|
| Number of Faculty | 12 |
| Number of Joint Appointment Faculty | 4 |
| Number of Research Fellows | 1 |
| Number of Research Students | 1 |
| Number of Support Personnel | 54 |
| Direct Annual Grant Support | \$917,385 |
| Direct Annual Industry Support | \$8,624 |
| Peer Reviewed Publications | 39 |

Clinical Activities and Training

| | |
|----------------------------|-------|
| Number of Clinical Staff | 4 |
| Number of Clinical Fellows | 4 |
| Inpatient Encounters | 9,133 |
| Outpatient Encounters | 3,816 |

Division Photo



Left to Right: R Marsh, K Myers, S Jodele, A Kumar, M Jordan, A Filipovich, S Davies, M Grimley, P Mehta, S Joshi

Significant Publications

Laskin BL, Goebel J, **Davies SM**, Khoury JC, Bleesing JJ, **Mehta PA**, **Filipovich AH**, Paff ZN, Lawrence JM, Yin HJ, Pinkard SL, **Jodele S**. **Early clinical indicators of transplant-associated thrombotic microangiopathy in pediatric neuroblastoma patients undergoing auto-SCT.** *Bone Marrow Transplant.* 46:682-9, 2011.

Marsh RA, Madden L, Kitchen BJ, Mody R, McClimon B, Jordan MB, Bleesing JJ, Zhang K, **Filipovich AH**. **XIAP deficiency: a unique primary immunodeficiency best classified as X-linked familial hemophagocytic lymphohistiocytosis and not as X-linked lymphoproliferative disease.** *Blood.* 116:1079-82. 2010.

Marsh RA, Vaughn G, Kim MO, Li D, **Jodele S**, Joshi S, **Mehta PA**, Davies SM, **Jordan MB**, Bleesing JJ, **Filipovich AH**. **Reduced-intensity conditioning significantly improves survival of patients with hemophagocytic lymphohistiocytosis undergoing allogeneic hematopoietic cell transplantation.** *Blood.* 116:5824-31. 2010.

Smith AR, Majhail NS, MacMillan ML, DeFor TE, **Jodele S**, Lehmann LE, Krance R, **Davies SM**. **Hematopoietic cell transplantation comorbidity index predicts transplantation outcomes in pediatric patients.** *Blood.* 117:2728-34. 2011.

Division Collaboration

Immunobiology » L. Grimes

MEIS1 and MLL-fusion leukemia: Research project investigating the role of MEIS1 in MLL-fusion leukemia using transgenic mice. (A. Kumar)

Experimental Hematology and Cancer Biology » J. Mulloy

Animal models of human leukemia: Research project aimed at developing xenograft mouse models of human leukemia using primary patient derived material. (A. Kumar)

Experimental Hematology and Cancer Biology » J. Mulloy; J. Cancelas

The molecular origin of monosomy 7 in very young children. Translational research project exploring the

causes of monosomy 7. (P. Mehta, SM Davies)

Experimental Hematology and Cancer Biology » N. Ratner

MEIS1 and MPNSTs: Research project aimed at understanding the role of MEIS1 in malignant peripheral nerve sheath tumors (MPNST). (A. Kumar)

Nephrology; Biostatistics & Epidemiology » J. Goebel; B. Dixon; P. Devarajan; J. Khoury

A Prospective Analysis of Clinical and Biochemical Markers for Pediatric Stem Cell Transplant-Associated Thrombotic Microangiopathy. Study open and more than half the needed patients enrolled. Preliminary data generated and grant applications submitted. (J. Bleesing, SM. Davies, A. Filipovich, R. Harris, S. Jodele, M. Jordan, S. Joshi, A. Kumar, R. Marsh, P. Mehta)

Critical Care; Radiology; Nephrology » H. Wong; S. Poynter; W. Ball; J. Leach; J. Goebel; M. Mitsnefes

PRES working group: To identify patients at risk for PRES, outline uniform evaluation and therapy guidelines. (S. Jodele, SM Davies)

Nephrology » J. Goebel; BL Laskin

Jodele S Davies SM, Lawrence J, Mehta PA, Bleesing JJ, Filipovich AH, Marsh RA. **Blood, and Not Urine, BK Viral Load Predicts Renal Outcome in Children with Hemorrhagic Cystitis following Hematopoietic Stem Cell Transplantation.** *Biol Blood Marrow Transplant.* 2011

Nephrology » J. Goebel; BL Laskin

Small vessels, big trouble in the kidneys and beyond: hematopoietic stem cell transplantation-associated thrombotic microangiopathy. (S Jodele, SM Davies).

Critical Care » R. Chima; D. Wheeler

BMT-PICU risk score index working group: To determine outcome predictors for BMT patients that are treated in PICU. To validate BMT-PICU risk score at CCHMC and later at collaborating institutions. (S Jodele, SM Davies)

Critical Care » R. Chima; D. Wheeler

Paper describing excellent outcomes for children admitted to PICU post-transplant admitted to PICU. (S Jodele, SM Davies)

Surgery; Gastroenterology » J. Nathan; G. Tiao; M. Alonzo; N. Yazigi ; S. Kocoschis

Incidence of acute and chronic graft versus host disease and donor T-cell chimerism after small bowel or combined organ transplantation. In press in the Journal of Pediatric Surgery.

Surgery ; Dermatology » R. Azizkhan ; A. Lucky

Preparation of a stem cell transplant protocol for children with epidermolysis bullosa. (S Jodele and SM Davies).

Genetics; Pathology » T. Smoralek; S. Zimmerman ; R. McMasters

Myers K, Davies SM, Harris RE, Mehta PA. **The clinical phenotype of children with Fanconi anemia caused by biallelic FANCD1/BRCA2 mutations.** *Pediatr Blood Cancer.* 2011.

Faculty Members

Stella Davies, MBBS, PhD, MRCP, Professor

Jacob G. Schmidlapp Endowed Chair; Director, Bone Marrow Transplantation and Immune Deficiency Executive Co-Director, Cancer and Blood Diseases Institute Director, Division of Bone Marrow Transplantation and Immune Deficiency

Research Interests Blood and Marrow Transplant, Fanconi anemia and other marrow failure disorders, Pharmacogenetics and Pharmacokinetics, Survivorship Research, and BMT for Children with Leukemia.

Jacob Bleesing, MD, PhD, Associate Professor

Research Interests Clinical Investigation of Primary Immunodeficiency Disorders, with emphasis on disorders of immunodysregulation and B-cell disorders

Alexandra Filipovich, MD, Professor

Ralph J. Stolle Chair in Clinical Immunology
Director, Immunodeficiency and
Medical Director, Diagnostic Laboratory

Research Interests Histiocytic disorders, primary immune deficiency disorders and Immunoreconstitution
Following Pediatric Stem Cell Transplantation

Michael Grimley, MD, Associate Professor

Research Interests Bone marrow transplantation for children with malignant and non-malignant disorders
and treatment of chronic GVHD.

Richard Harris, MD, Professor

Research Interests Transplantation for children with bone marrow failure syndromes and aplastic anemia

Sonata Jodele, MD, Assistant Professor

Research Interests Phase I clinical trials; stem cell transplantation; high risk pediatric
malignancies; childhood neuroblastoma, Ewing's sarcoma, renal complications of transplantation.

Sarita Joshi, MD, Assistant Professor

Research Interests Management of Diamond-Blackfan anemia, transplantation for hemoglobinopathies, and
autologous transplantation for malignancy.

Ashish Kumar, MD, PhD, Assistant Professor

Research Interests Etiology of childhood leukemia, transplantation of children with malignancy and primary
immune deficiencies.

Rebecca Marsh, MD, Assistant Professor

Research Interests Pathogenesis of HLH with XIAP deficiency, diagnostic laboratory assays, improving
outcomes of allogeneic BMT in primary immune deficiencies, use of reduced intensity conditioning regimens.

Parinda Mehta, MD, Assistant Professor

Research Interests Blood and Marrow Transplant, Fanconi anemia and other failure disorders,
Pharmacogenetics and Pharmacokinetics

Kasiani Myers, MD, Instructor

Research Interests Blood and Marrow Transplant, Fanconi anemia and other marrow failure disorders,
longitudinal studies of hematopoiesis

Janos Sumegi, MD, PhD, Professor

Research Interests Lymphoproliferative disease, Hemphagocytic Lymphohisstiocytosis, Usher syndrome,
etiology of childhood sarcomas.

Joint Appointment Faculty Members

Mark Johnson, MD, Assistant Professor

Child Psychiatry

Research Interests Psychiatric support of bone marrow transplant patients

Michael Jordan, MD, Assistant Professor

Immunobiology

Research Interests Regulation of the immune response; immunotherapy of cancer, animal models of
hemophagocytic disorders.

Mi-Ok Kim, PhD, Associate Professor

Biostatistics & Epidemiology

Ahna Pai, PhD, Assistant Professor

Adherence Psychology in children receiving bone marrow transplantation

Clinical Staff Members

- Ernest Lawhorn, MD
- Olive Eckstein, MD
- Anna Pesok, MD
- Gregory Wallace, DO

Trainees

- Hilary Haines, MD, PL-VII, University of Alabama
- Omar Niss, MD, PL-IV, University of Nebraska Medical Center/Creighton University
- Chu Ri Shin, MD, PL-VII, Virginia Commonwealth University
- Jordan Wright, MD, PL-IV, University of Alabama

Significant Accomplishments

Treatment of HLH

Our Bone Marrow Transplant Program is a leader in diagnosis and treatment of HLH, with children travelling to Cincinnati from across the US and other nations for therapy. This year Rebecca Marsh, MD, and Lisa Filipovich, MD, published data in the journal *Blood* about the outcomes of two transplant strategies and identified reduced intensity transplantation as the optimal approach.

Fanconi Anemia Comprehensive Care Clinic

The Fanconi Anemia Comprehensive Care Clinic continues to expand. We offer life-long care to more than 150 children and adults with this rare disorder. Most children with Fanconi anemia eventually develop marrow failure and require transplantation. We have completed an important study of endocrinological abnormalities in this population, led by Susan Rose, MD, Division of Endocrinology. We also have explored the mechanism of endocrinopathy in a mouse model study lead by Qishen Pang, PhD, Division of Experimental Hematology. This study showed that oxidant stress causes tissue damage in Fanconi anemia. Parinda Mehta, MD, has used these data to develop a novel clinical trial using an anti-oxidant food supplement.

Prospective proteomic study of TMA

Transplant associated thrombotic microangiopathy (TMA) is a severe complication of transplantation, commonly leading to organ failure and death. Sonata Jodele, MD, in collaboration with the Division of Nephrology, has launched a study of proteomic biomarkers of TMA, identifying possible markers that can predict occurrence of the disorder 10 to 14 days before clinical presentation. We expect these data to generate new treatment options for this disorder.

Intensive care and bone marrow transplant

Bone marrow transplant is associated with significant morbidity and mortality, and a significant proportion of children will require intensive care. We have collaborated with Ranjit Chima, MD, and Derek Wheeler, MD, FAAP, to analyze intensive care outcomes in this high-risk population. The data show that 82 percent of children admitted after stem cell transplant survive and leave the ICU. These outstanding results were presented at the annual meeting of the American Society of Bone Marrow Transplant and the Society for Critical Care Medicine.

Grants, Contracts, and Industry Agreements

Grant and Contract Awards

Annual Direct / Project Period Direct

DAVIES, S

Multicenter Pilot Trial of HSCT Lacking a Genotype Identical Donor
Fanconi Anemia Research Fund

| | | |
|---|-------------------|-----------|
| | 05/01/10-04/30/13 | \$1,920 |
| Antileukemic Effect of NK Cells in HCT for Pediatric AML | | |
| National Institutes of Health (St. Jude's Children's Research Hospital) | | |
| R01 CA 120583 | 08/01/07-06/30/12 | \$8,864 |
| Environmental Exposure: Suceptibility Alleles in a DNA Damage Response Pathway | | |
| National Institutes of Health(University of Cincinnati) | | |
| R01 ES 016625 | 12/01/08-11/30/11 | \$2,361 |
| The Children's Oncology Group Chairs Grant | | |
| National Institutes of Health(National Childhood Cancer Foundation) | | |
| U10 CA 098543 | 03/01/11-02/28/14 | \$12,831 |
| Mechanisms of RET/PTC Rearrangement in Thyriod Cancer | | |
| National Institutes of Health(University of Pittsburgh) | | |
| R01 CA 088041 | 03/01/09-02/28/12 | \$6,667 |
| Childhood Cancer Survivor Study | | |
| National Institutes of Health(St. Jude's Children's Research Hospital) | | |
| U24 CA 55727 | 12/01/05-11/30/11 | \$60,000 |
| Prediction Model for Radiation Sensitivity in Children with Cancer | | |
| National Institutes of Health | | |
| U01 CA 139275 | 07/16/09-06/30/11 | \$128,518 |

FILIPOVICH, A

Gene Therapy for SCID-X1 Using Self-Inactivating (SIN) Gammaretroviral Vector

National Institutes of Health(Children's Hospital Boston)

U01 AI 087628 09/01/10-08/31/15 \$133,693

Histiocyte Society Annual Meeting in Boston

National Institutes of Health

R13 HL 106925 02/01/11-01/31/12 \$5,000

Rare Diseases Clinical Consortia for the Rare Diseases

National Institutes of Health(The Regents of the University of California)

U54 AI 082973 09/12/09-08/31/14 \$44,978

Hypoxia and Potassium Channel Activity in T Lymphocytes

National Institutes of Health(University of Cincinnati)

R01 CA 095286 06/01/09-06/30/14 \$19,959

JORDAN, M

Hybrid Immunotherapy for Hemophagocytic Lymphohistiocytosis

Histiocytosis Association of America

01/01/11-12/31/11 \$47,500

JOSHI, S

09-SQOL Study

National Bone Marrow Donor Program

10/01/10-01/01/12 \$1,500

KUMAR, A

Novel Therapy Development for Infant Leukemia

Cancer Free Kids

07/01/10-06/30/11 \$20,000

Molecular Pathogenesis of MLL-Fusion Gene Leukemia

National Institutes of Health

K08 CA 122191 08/19/09-06/30/12 \$125,250

MARSH, R

Studies to Determine Why XIAP Deficiency Leads to HLH

Clinical Immunology Society

07/01/10-06/30/12 \$85,000

MYERS, K

Leukemogenesis, Genomic Instability and Fanconi Anemia

Bear Necessities Pediatric Cancer Foundation

07/01/10-06/30/11 \$20,000

SUMEGI, J**Epigenetic Control Of Tumorigenesis In Ewing's Sarcoma Family of Tumors**

Cancer Free Kids

07/01/10-06/30/11

\$20,000

Gene-Expression Profiling of Peripheral Blood Mononuclear Cells in Hemophagocytic Lymphohistiocytosis

Histiocytosis Association of America

12/01/10-11/30/11

\$47,500

Identification of Genes Involved in FHLH

R21 AI 076746

09/01/09-08/31/11

\$125,000

Current Year Direct**\$917,385**Industry Contracts

GRIMLEY, M

Chimerix, Inc

\$7,700

HARRIS, R

Alexion Pharmaceuticals, Inc.

\$924

Current Year Direct Receipts**\$8,624**Funded Collaborative Efforts

BLEESING, J**Cincinnati Multidisciplinary Clinical Research Center**

National Institutes of Health

Glass, D

08/18/08-07/31/13

3%

Total**\$926,009**