Division Data Summary

**Research and Training Details**

<table>
<thead>
<tr>
<th>Details</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Faculty</td>
<td>20</td>
</tr>
<tr>
<td>Number of Joint Appointment Faculty</td>
<td>4</td>
</tr>
<tr>
<td>Number of Research Fellows</td>
<td>5</td>
</tr>
<tr>
<td>Number of Research Students</td>
<td>4</td>
</tr>
<tr>
<td>Number of Support Personnel</td>
<td>87</td>
</tr>
<tr>
<td>Direct Annual Grant Support</td>
<td>$2,320,582</td>
</tr>
<tr>
<td>Direct Annual Industry Support</td>
<td>$61,221</td>
</tr>
<tr>
<td>Peer Reviewed Publications</td>
<td>35</td>
</tr>
</tbody>
</table>

**Clinical Activities and Training**

<table>
<thead>
<tr>
<th>Details</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Clinical Staff</td>
<td>2</td>
</tr>
<tr>
<td>Number of Clinical Fellows</td>
<td>6</td>
</tr>
<tr>
<td>Number of Other Students</td>
<td>14</td>
</tr>
<tr>
<td>Inpatient Encounters</td>
<td>8,575</td>
</tr>
<tr>
<td>Outpatient Encounters</td>
<td>6,814</td>
</tr>
</tbody>
</table>

**Significant Publications**


Mutations in the PTEN, TP53, and RB1 pathways are obligate events in the pathogenesis of human glioblastomas. We induced various combinations of deletions in these tumor suppressors in astrocytes and neural precursors in mature mice, resulting in astrocytomas ranging from grade III to grade IV (glioblastoma). There was selection for mutation of multiple genes within a pathway, shown by somatic amplifications of genes in the PI3K or Rb pathway in tumors in which Pten or Rb deletion was an initiating event. Despite multiple mutations within PI3K and Rb pathways, elevated Mapk activation was not consistent. Gene expression profiling revealed striking similarities to subclasses of human diffuse astrocytoma. Astrocytomas were found within and outside of proliferative niches in the adult brain.


The purpose of this study was to determine the maximum-tolerated dose (MTD), dose-limiting toxicities (DLT), and pharmacokinetics of vorinostat administered as a single agent and in combination 13-cis retinoic acid (13cRA) in children with refractory solid tumors; to evaluate the tolerability of the solid tumor MTD in children with refractory leukemias; and to characterize the pharmacokinetics of a vorinostat suspension in children. Vorinostat was administered orally daily starting at 180 mg/m(2)/d with escalations planned in 30%
increments. Pharmacokinetic studies were performed with the initial dose. Acetyl-histone (H3) accumulation was assessed by Western blotting of peripheral blood mononuclear cells (PBMC). Sixty-four patients were enrolled on this multipart trial. In patients with solid tumors, the MTD was 230 mg/m\(^2/d\) with dose-limiting neutropenia, thrombocytopenia, and hypokalemia at 300 mg/m\(^2/d\). DLTs observed with the combination of 13cRA and vorinostat included thrombocytopenia, neutropenia, anorexia, and hypertriglyceridemia, resulting in a MTD of vorinostat 180 mg/m\(^2/d\) 4 times per week and 13cRA 80 mg/m\(^2/d\) dose twice per day, days 1 through 14 every 28 days. Wide interpatient variability was noted in vorinostat disposition, with area under the concentration-time curves at 230 mg/m\(^2/d\) for the capsule (range, 1,415 to 9,291 ng/mL x hr) and oral suspension (range, 1,186 to 4,780 ng/mL x hr). Significant accumulation of acetylated H3 histone in PBMC was observed after administration of vorinostat, particularly at higher doses. One patient with neuroblastoma experienced a complete response to the combination. In children with recurrent solid tumors, vorinostat is well-tolerated at 230 mg/m\(^2/d\), with a modest dose reduction being required when combining vorinostat with 13cRA. Drug disposition is similar to that observed in adults.


Plexiform neurofibromas (pNF) are Schwann cell tumors found in a third of individuals with neurofibromatosis type 1 (NF1). pNF can undergo transformation to malignant peripheral nerve sheath tumors (MPNST). There are no identified serum biomarkers of pNF tumor burden or transformation to MPNST. Serum biomarkers would be useful to verify NF1 diagnosis, monitor tumor burden, and/or detect transformation. We used microarray gene expression analysis to define 92 genes that encode putative secreted proteins in neurofibroma Schwann cells, neurofibromas, and MPNST. We validated differential expression by quantitative reverse transcription-PCR, Western blotting, and ELISA assays in cell conditioned medium and control and NF1 patient sera. Of 13 candidate genes evaluated, only adrenomedullin (ADM) was confirmed as differentially expressed and elevated in serum of NF1 patients. ADM protein concentration was further elevated in serum of a small sampling of NF1 patients with MPNST. MPNST cell conditioned medium, containing ADM and hepatocyte growth factor, stimulated MPNST migration and endothelial cell proliferation. Thus, microarray analysis identifies potential serum biomarkers for disease, and ADM is a serum biomarker of NF1. ADM serum levels do not seem to correlate with the presence of pNFs but may be a biomarker of transformation to MPNST.


Osteosarcoma survivors have received significant chemotherapy and have undergone substantial surgeries. The authors assessed the long-term outcomes (at 20 years) of 733 5-year survivors of childhood osteosarcoma diagnosed from 1970 to 1986 to provide a comprehensive evaluation of medical and psychosocial outcomes for survivors enrolled in the Childhood Cancer Survivor Study (CCSS). Outcomes evaluated included overall survival, second malignant neoplasms (SMNs), recurrent osteosarcoma, chronic health conditions, health status (general and mental health and functional limitations), and psychosocial factors. Outcomes of osteosarcoma survivors were compared with general-population statistics, other CCSS survivors, and CCSS siblings. The overall survival of children diagnosed with osteosarcoma who survived 5 years at 20 years from original diagnosis was 88.6% (95% confidence interval [CI], 86.6%-90.5%). The cumulative incidence of SMNs at 25 years was 5.4%, with a standardized incidence ratio of 4.79 (95% CI, 3.54-6.33; P<.01). Overall, 86.9% of osteosarcoma survivors experienced at least 1 chronic medical condition, and >50% experienced >/=2 conditions. Compared with survivors of other cancers, osteosarcoma survivors
did not differ in their reported general health status (odds ratio [OR], 0.9; 95% CI, 0.7-1.2), but were more likely to report an adverse health status in at least 1 domain (OR, 1.9; 95% CI, 1.6-2.2), with activity limitations (29.1%) being the most common. Childhood osteosarcoma survivors in this cohort did relatively well, considering their extensive treatment, but are at risk of experiencing chronic medical conditions and adverse health status. Survivors warrant life-long follow-up.


Studies in embryonic development have guided successful efforts to direct the differentiation of human embryonic and induced pluripotent stem cells (PSCs) into specific organ cell types in vitro. For example, human PSCs have been differentiated into monolayer cultures of liver hepatocytes and pancreatic endocrine cells that have therapeutic efficacy in animal models of liver disease and diabetes, respectively. However, the generation of complex three-dimensional organ tissues in vitro remains a major challenge for translational studies. Here we establish a robust and efficient process to direct the differentiation of human PSCs into intestinal tissue in vitro using a temporal series of growth factor manipulations to mimic embryonic intestinal development. This involved activin-induced definitive endoderm formation, FGF/Wnt-induced posterior endoderm patterning, hindgut specification and morphogenesis, and a pro-intestinal culture system to promote intestinal growth, morphogenesis and cytodifferentiation. The resulting three-dimensional intestinal 'organoids' consisted of a polarized, columnar epithelium that was patterned into villus-like structures and crypt-like proliferative zones that expressed intestinal stem cell markers. The epithelium contained functional enterocytes, as well as goblet, Paneth and enteroendocrine cells. Using this culture system as a model to study human intestinal development, we identified that the combined activity of WNT3A and FGF4 is required for hindgut specification whereas FGF4 alone is sufficient to promote hindgut morphogenesis. Our data indicate that human intestinal stem cells form de novo during development. We also determined that NEUROG3, a pro-endocrine transcription factor that is mutated in enteric anendocrinosis, is both necessary and sufficient for human enteroendocrine cell development in vitro. PSC-derived human intestinal tissue should allow for unprecedented studies of human intestinal development and disease.
Surgical services for oncology patients; Children's Oncology Group clinical research activities

UC Department of Radiation Oncology » J. Breneman; R. Lavigne
  Radiation oncology clinical services for oncology patients; Children's Oncology Group clinical research activities

Human Genetics » L. Bao; T. Smolarek
  Genetic services for oncology patients; Children's Oncology Group clinical research activities

Pathology » D. Witte; M. Collins; J. Yin; J. Mo; R. McMasters; L. Miles
  Pathology services for oncology patients; Children's Oncology Group clinical research activities

Behavioral Medicine and Clinical Psychology » D. Drotar; A. Pai
  Adherence research; "Promoting Treatment Adherence in Adolescent Leukemia" (NIH)

Radiology » M. Gelfand; A. Towbin
  Nuclear medicine services for oncology patients; Children's Oncology Group clinical research activities

Endocrinology » S. Rose; M. Rutter
  Endocrinology services for oncology patients; Children's Oncology Group and other clinical research activities

Physical Medicine and Rehabilitation » D. Pruitt
  Rehabilitation services for oncology patients; Children's Oncology Group and other clinical research activities

Biomedical Informatics; Human Genetics; Developmental and Behavioral Pediatrics; Biostatistics and Epidemiology » B. Aronow; T. Smolarek; D. Schonfeld; M. Kim
  Down syndrome leukemia research: etiology and risk factors, pharmacogenetics of therapy and outcomes (J. Perentesis)

Pathology; Radiology; Surgical Services » M. Gelfand; S. Sharp; A. Towbin; J. Yin; T. Maugins
  Clinical services for neuroblastoma patients; clinical research related to neuroblastoma (J. Perentesis, B. Weiss)

University of Cincinnati Drug Discovery Center » R. Papoian
  Pediatric leukemia, solid tumor, and brain tumor drug discovery screening (J. Perentesis, B. Weiss, M. Absalon, M. O'Brien)

Neurosurgery; Pathology; Radiology » T. Maugins; J. Yin; M. Gelfand; S. Sharp
  Neuroblastoma Program: (B. Weiss, R. Nagarajan)


Human Genetics; Neurology; Clinical Pharmacology; Radiology; Neurosurgery; Ophthalmology; Orthopaedic Surgery; Physical Medicine and Rehabilitation; Pathology » E. Schorry; R. Hopkin; A. Vinks; A. Towbin; S. Sharp; M. Gelfand; M. Sutton; M. Collins; D. Pruitt; C. West; A. Crawford; K. Crone
  Multidisciplinary clinical services for patients with neurofibromatosis; clinical research related to neurofibromatosis, including national clinical trial of mTOR inhibition to treat NF1-related plexiform neurofibromas (B. Weiss, J. Perentesis, T. Hummel)

Experimental Hematology and Cancer Biology; Pathology; University of Cincinnati Department of Cancer and Cell Biology; University of Minnesota » N. Ratner; M. Collins; G. Thomas; S. Kozma; D. Largaespada
  Cincinnati Center of Neurofibromatosis Research (P50) (J. Perentesis, T. Cripe)

Pathology » L. Miles
ACNS0822: a randomized phase II/III study of suberoylanilide hydroxamic acid (SAHA) (IND# 71976) and local irradiation or temozolomide and local irradiation or arsenic trioxide and local irradiation followed by maintenance bevacizumab (IND# 7921) and irinotecan in children with newly diagnosed high-grade glioma (M. Fouladi, R. Drissi)

**Human Genetics** » X. Qi
Testing SapC nanoparticle for anti-glioma activity in vivo (L. Chow)

**Pathology** » L. Miles
Characterization of murine brain tumors and collection of pediatric glioma samples (L. Chow)

**Obstetrics and Gynecology** » L. Ayensu-Coker
Fertility Consultation Service for oncology patients (K. Burns)

**Obstetrics and Gynecology; Christ Hospital** » L. Ayensu-Coker; S. Lindheim
Cincinnati chapter of the Oncofertility Consortium

**UC Department of Cancer and Cell Biology Proteomics Core** » K. Greis
Phosphoproteomic analysis of glioblastoma (B. DasGupta)

**UC Drug Discovery Center** » R. Papoian
Small molecule inhibition of AMP kinase (B. DasGupta)

**Developmental Biology** » K. Campbell
Understanding the role of AMP kinase in mammalian forebrain development (B. DasGupta)

**Pathology** » K. Setchell
Analysis of metabolites and nucleotides in the developing brain (B. DasGupta)

**Imaging Research Center** » D. Lindquist
Proton and phosphorus MRS to examine brain metabolites in the postnatal brain (B. DasGupta)

**University of Minnesota** » M. Georgieff; I. Tack; R. Rao
Proton spectroscopy detection of metabolic intermediates during early postnatal brain development (B. DasGupta)

**University of Minnesota** » M. Georgieff; I. Tack; R. Rao
Detection of glycolysis and TCA cycle intermediates from subregions of the developing mouse brain by LC-MS (B. DasGupta)

**University of Leuven, Belgium** » K. Norga
Understanding AMPK-dependence of AICAR and metformin action in the fly brain (B. DasGupta)

**Mayo Clinic** » S. Giri
Examining AMPK-dependence of metformin action in mice (B. DasGupta)

**Neurology; Ophthalmology; Radiology** » D. Rose; C. West; J. Leach
Visual pathway research for children with retinal or optic pathway tumors (J. Geller)

**Ophthalmology** » J. Augsburger
A pilot study of intravenous topotecan and vincristine in combination with subconjunctival carboplatin for patients with a history of bilateral retinoblastoma and refractory/recurrent intraocular disease (IND# 104,942) (J. Geller)

**Human Genetics; Pathology; Surgical Services** » N. Leslie; A. Gupta; G. Tiao
Screening children affected by hepatoblastoma for familial adenomatous polyposis (FAP) and a retrospective review of clinical and pathology features of children with hepatoblastoma with or without FAP (J. Geller)
Pathology; Pediatric and Adolescent Gynecology » R. McMasters; L. Ayensu-Coker
Management of ovarian sex-cord stromal tumors (J. Geller)

Human Genetics » N. Leslie
Pediatric Hereditary Cancer Predisposition Clinic (J. Geller)

Surgical Services; Gastroenterology, Hepatology, and Nutrition; Radiology; Pathology » G. Tiao; J. Nathan; M. Leonis; A. Towbin; K. Kukreja; A. Gupta; K. Bove; J. Yin
Liver Tumor Research Group (J. Geller)

Surgical Services; Gastroenterology, Hepatology and Nutrition; Developmental Biology; Radiology; Pathology » J. Nathan; M. Alonso; F. Ryckman; G. Tiao; M. Leonis; J. Bucuvalas; K. Campbell; A. Towbin; K. Kukreja; K. Bove; A. Gupta
Liver transplantation clinical services and clinical research activities for hepatoblastoma patients (J. Geller)

Nephrology; UC Division of Hematology/Oncology » J. Bissler; M. Czyz-Krzeska; O. Rixe; G. Thomas
UC/CCHMC Renal Tumor Working Group (J. Geller)

Infectious Diseases; Investigational Pharmacy; Radiology; Crusade Labs » B. Connelly; M. Cloughessy; D. Lagory; J. Racadio; A. Towbin; M. Brown; J. Connor
Phase I trial of HSV1716 (T. Cripe)

Infectious Diseases; Investigational Pharmacy; Radiology; Experimental Hematology and Cancer Biology; Jennerex Biotherapeutics » B. Connelly; M. Cloughessy; D. Lagory; J. Racadio; A. Towbin; H. van der Loo; D. Kirn
Phase I trial of JX-594 (T. Cripe)

Pediatric General and Thoracic Surgery; Immunobiology; Molecular Immunology; Pulmonary Medicine; Bioceros » J. Frischer; D. Hildeman; S. Divanovic; E. Janssen; L. Boon
Proangiogenic inflammatory response to oncolytic HSV injection in preclinical models (T. Cripe)

Immunobiology; Molecular Immunology » D. Hildeman; E. Janssen
Role of dendritic cells is sensing oncolytic HSVs in cancer (T. Cripe)

Pathology; The Ohio State University; University of Pittsburgh » M. Collins; A. Chiocca; B. Kaur; J. Gloriosos; W. Goins
Receptor-mediated resistance to oncolytic HSV in neuroblastoma (T. Cripe)

The Ohio State University » A. Chiocca; B. Kaur
Oncolytic HSV enhanced by chondroitinase transgene expression (T. Cripe)

Experimental Hematology and Cancer Biology; Biostatistics and Epidemiology; Radiology; Washington University in St. Louis; Harvard University; University of California, San Francisco; House Research Institute; National Institutes of Health » N. Ratner; J. Wu; M. Kim; D. Lindquist; D. Gutmann; K. Cichowski; K. Shannon; M. Giovannini; A. McClatchey; E. Dombi
Children's Tumor Foundation Neurofibromatosis Preclinical Consortium (T. Cripe)

University of Bologna, Italy » I. Orienti
A novel carbon-based polymer micelle as cancer therapy (T. Cripe)

University of New South Wales, Australia » P. Gunning
Preclinical antitumor efficacy of novel tropomyosin isoform inhibitors (T. Cripe)

General and Thoracic Surgery; Biomedical Informatics » T. Crombleholme; B. Aronow
Development of a midkine-regulated oncolytic Herpes virus (T. Cripe)
Experimental Hematology and Cancer Biology; Pathology » N. Ratner; J. Cancelas; M. Collins

EYA4 in MPNST (T. Cripe)

Immunobiology » D. Hildeman

Regulatory T cells in oncolytic HSV virotherapy (T. Cripe)

Surgical Services; Otolaryngology; Dermatology; Radiology; Pathology; Cardiology; Gastroenterology, Hepatology and Nutrition; Urology; Endocrinology; Orthopaedics; Neurology; Pulmonary Medicine; Ophthalmology; Pain Management and Palliative Care; Human Genetics » R. Azizkhan; A. Dasgupta; R. Elluru; A. Lucky; M. Patel; T. Abruzzo; W. Ball; A Zbojiewicz; K. Crone; A. Gupta; P. Eghtesday; K. Goldchneider; R. Hirsch; R. Hopkin; A. Kaul; P. Reddy; M. Rutter; J. Sorger; M. Sutton; R. Wood; K. Yakuboff; J. Taylor; M. Yang; M. Seid

Hemangioma and Vascular Malformation Center, clinical services and clinical research, including a clinical trial of rapamycin for complicated vascular anomalies, a vascular tumor registry, and a vascular anomaly tissue repository (D. Adams, A. Hammill)

Gastroenterology, Hepatology and Nutrition; Radiology; Nephrology; Cardiology; Pathology » N. Yazigi; A. Brody; J. Goebel; R. Spicer; K. Uzark; D. Witte

Post-Transplant Lymphoproliferative Disease Working Group (M. Absalon)

Faculty Members

John Perentesis, MD, FAAP, Professor
   Deb Kleisinger Endowed Chair of Novel Cancer Treatments
   Executive Co-Director, Cancer and Blood Diseases Institute
   Director, Division of Oncology
   Director, Leukemia/Lymphoma Program
   Cincinnati Children’s Principal Investigator, Children’s Oncology Group (COG)
   Cincinnati Children’s Principal Investigator, National Cancer Institute Pediatric Phase I Consortium
   Research Interests New anticancer drug development; molecular oncogenesis and pharmacogenetics in high risk leukemia, lymphoma and pediatric cancers

Michael Absalon, MD, PhD, Assistant Professor
   Director, Medical Education Program
   Associate Director, Leukemia/Lymphoma Program
   Research Interests New therapeutics; relapsed leukemia and lymphoma, post-transplant lymphoproliferative disease, T-cell lymphoma

Denise M. Adams, MD, Professor
   Medical Director, Comprehensive Hemangiomas and Vascular Malformation Clinic
   Director, Hematology/Oncology Fellowship Program
   Research Interests Angiogenesis, endothelial cell proliferation, vascular anomalies, mTOR inhibition as a therapeutic approach to complex vascular anomalies

Karen Burns, MD, Assistant Professor
   Clinical Director, Cancer Survivor Center
   Research Interests Childhood cancer survival; fertility preservation and outcomes; adolescent and young adult outcomes and quality of life

Lionel Chow, MD, Assistant Professor
   Research Interests Molecular genetics of pediatric high-grade glioma, animal models of brain tumors, translational therapeutics for gliomas

Timothy Cripe, MD, PhD, Professor
Research Director, Musculoskeletal Tumor Program  
Co-Medical Director, Office for Clinical and Translational Research  
Director of Pilot and Collaborative Studies, Center for Clinical and Translational Science and Training

**Research Interests** Mechanistic, preclinical, and clinical studies of oncolytic virotherapy, antiangiogenesis, and signal transduction inhibitors for sarcomas, neuroblastoma and other pediatric solid tumors

**Biplab Dasgupta, PhD,** Assistant Professor  
**Research Interests** Brain development, energy metabolism, brain cancer

**Rachid Drissi, MD,** Assistant Professor  
**Research Interests** Replicative senescence, telomere disruption signaling to DNA damage pathways

**Maryam Fouladi, MD, FRCP,** Professor  
**Medical Director, Neuro-Oncology Program**  
**Cincinnati Children's Principal Investigator, Collaborative Ependymoma Research Network (CERN)**  
**Research Interests** Novel drug development for the treatment of children with recurrent or poor prognosis brain tumors

**James I. Geller, MD,** Associate Professor  
**Medical Director, Kidney and Liver Tumors Program**  
**Co-Medical Director, Retinoblastoma Program**  
**Research Interests** Developmental therapeutics for pediatric solid tumors, especially liver and kidney tumors and retinoblastoma

**Adrienne Hammill, MD,** Assistant Professor  
**Research Interests** New approaches to the assessment and treatment of hemangiomas and vascular malformations

**Trent Hummel, MD,** Instructor  
**Research Interests** New therapeutics in neuro-oncology; diffuse intrinsic pontine glioma, neurofibromatosis type 1 and 2 related tumors, biomarker development

**Beatrice Lampkin, MD,** Professor Emerita  
**Research Interests** Blood and bone marrow morphology and the significance thereof in relationship to patients' case histories

**Benjamin Mizukawa, MD,** Instructor  
**Research Interests** Pediatric leukemia and lymphoma; role of small Rho GTPases in leukemogenesis and leukemic stem cell biology and their potential as therapeutic targets in acute myeloid leukemia

**Rajaram Nagarajan, MD,** Assistant Professor  
**Outpatient and Inpatient Clinical Director**  
**Director of Cancer Control and Outcomes Research, Cancer Survivor Center**  
**Research Interests** Bone tumors; functional and quality of life outcomes following cancer therapy

**Maureen O'Brien, MD,** Assistant Professor  
**Associate Director, Leukemia/Lymphoma Program**  
**Research Interests** High-risk acute lymphoblastic leukemia; novel therapies for relapsed leukemia and lymphoma; complications of leukemia therapy

**Christine Phillips, MD,** Instructor  
**Research Interests** Developmental therapeutics for acute myeloid leukemia; pharmacogenomics of cytarabine and other chemotherapeutic agents

**Lars Wagner, MD,** Associate Professor  
**Medical Director, Musculoskeletal Tumor Program**
**Cincinnati Children’s Principal Investigator, Sarcoma Alliance for Research Through Collaboration (SARC)**

**Research Interests** Developmental therapeutics for neuroblastoma, sarcomas, and brain tumors

**Brian D. Weiss, MD**, Associate Professor  
Associate Director for Safety and Compliance, Cancer and Blood Diseases Institute  
Medical Director, Neuroblastoma Program  
Cincinnati Children’s Principal Investigator, New Approaches to Neuroblastoma Therapy Consortium (NANT)

**Research Interests** Targeted agents for neurofibromatosis type 1-related malignancies (including plexiform neurofibromas, optic pathway gliomas, and juvenile myelomonocytic leukemia); chemotherapy safety

**Susanne Wells, MD**, Associate Professor  
Director, Epithelial Carcinogenesis and Stem Cell Program

**Research Interests** Epithelial malignancies, human papillomavirus biology and new targets of the HPV E6/E7 oncogenes, the role of epithelial stem cells in carcinogenesis

**Joint Appointment Faculty Members**

**Mi-Ok Kim, PhD**, Associate Professor  
Center for Epidemiology and Biostatistics

**Ahna Pai, PhD**, Assistant Professor  
Adherence Psychology

**Saulius Sumanas, PhD**, Assistant Professor  
Developmental Biology

**Mary Sutton, MD**, Associate Professor  
Neurology

**Clinical Staff Members**

- Carina Braeutigam, MD
- Vasudha Narayanaswamy, MD

**Trainees**

- Michael Bishop, MD, PL-V, Children's Mercy Hospital, Kansas City
- Kathleen Dorris, MD, PL-VI, Children's Memorial Hospital, Northwestern University
- Sarah Fitzgerald, MD, PL-VI, Rainbow Babies & Children's Hospital/University of Cleveland
- Dawn Pinchasik, MD, PL-IV, Children's Hospital of Pittsburgh
- Jennifer Pope, MD, PL-VI, Medical College of Wisconsin
- Jennifer Williams, MD, PL-IV, T.C. Thompson Children's Hospital/University of Tennessee

**Significant Accomplishments**

**Study of Sirolimus for Complex Vascular Anomalies**

Complex vascular malformations can be difficult to treat with surgery and cause disfigurement, chronic pain and organ dysfunction with significant morbidity and mortality. Oncologist Denise Adams, MD, medical director of the Hemangioma and Vascular Malformation Center (HVMC), has developed an investigator-initiated phase 2 study to assess the safety and efficacy of the mTOR inhibitor sirolimus. This study, supported by an FDA Orphan Products Grant, represents the first prospective clinical trial of a new medical
therapy for these conditions. Adams is an internationally recognized authority on vascular anomalies, and the HVMC is an internationally recognized referral center and a model of collaboration among the Cancer and Blood Diseases Institute, the Department of Surgery and the Division of Developmental Biology. Adams has also helped to lead development of a robust and growing interdisciplinary working group on vascular biology whose research is guiding the development of future clinical trials.

**Targeted Drug Discovery and Personalized Therapies**

Despite advances in cure rates with chemotherapy, many children continue to relapse with fatal cancers or suffer severe complications from current therapies. The Division of Oncology is a national leader in the development of drugs and use of personalized genomics for better therapies for pediatric cancers.

The division is home to a leading national center for research in the development of anticancer therapies targeting tumor growth factor signaling pathways in combination with synergistic inhibition of the mTOR growth regulation pathway. Projects in tumors associated with neurofibromatosis (led by Brian Weiss, MD) and in pediatric brain tumors, sarcomas, neuroblastoma and other malignancies (led by Maryam Fouladi, MD, MSc) continue with research to identify molecular markers predictive of response. Early results of this innovative clinical translational work were presented by Fouladi at the national American Society of Clinical Oncology annual meeting. Lars Wagner, MD, is extending the team’s research in this area with his leadership of a new phase 2 clinical trial of IMC-A12 and temsirolimus (CCI-779) for children and adolescents with relapsed cancers.

A new initiative this year focuses on epigenetic therapies – specifically targeting chromatin structure and pathologic gene and micro-RNA expression to kill or “mature” malignant cells. At the 2010 American Society for Hematology national meeting, Christine Phillips, MD, presented work from the division demonstrating that complete remissions could be achieved in children with highly treatment-resistant forms of acute myeloid leukemia using decitabine. This work has provided the foundation for a new research study that Phillips is developing combining a related drug, azacytidine, with a chromatin-targeting drug, vorinostat. In parallel work, Trent Hummel, MD, is leading a phase 1 study investigating vorinostat with the conventional chemotherapy drug temozolomide for the treatment of relapsed or refractory brain or spinal tumors.

Understanding the biology of cancer stem cells and using new drugs to target these pathways are a key new area of research for the division. The laboratory of Timothy Cripe, MD, PhD, is funded to find new ways to identify and develop better therapies against neuroblastoma stem cells. James Geller, MD, is leading a phase 1 clinical trial of the small molecule c-Met inhibitor ARQ-197 in children with relapsed malignancies. Signaling through c-Met, also known as the hepatocyte growth factor, is prominent in normal stem cells but not normal tissues. However, c-Met is dysregulated in many types of human malignancies, including cancers of the kidney, liver and brain. In parallel work, Fouladi is leading a phase 1 study of the AKT inhibitor MK2206 in recurrent or refractory solid tumors and leukemias, as well as a Pediatric Brain Tumor Consortium phase 1 study of the Notch inhibitor MK0751. Notch signaling is a key regulator of viability and numbers of normal and malignant stem cells, and targeting this pathway holds particular promise for brain tumor therapy. Rachid Drissi, PhD, is leading important new research efforts to understand the role of telomerase in malignant stem cells in pediatric cancers, particularly brain tumors. He also is leading correlative biology studies for a Children’s Oncology Group study, the first national phase 1 trial of a telomerase inhibitor in children with solid tumors.

The division has recently established a new Scholar Training Program in Cancer Developmental Therapeutics
and obtained competitive funding through the Hyundai Hope on Wheels Foundation. We recruited our first scholar, Carrye Cost, MD, who will receive intensive mentoring in advanced clinical oncology, pharmacology and pharmacogenetics, cancer biology and new drug development. This program is integrated with other initiatives in drug discovery and pre-clinical drug development in partnership with the Division of Experimental Hematology and Cancer Biology and the University of Cincinnati’s Drug Discovery Center. Closely related efforts in tumor signature profiling are also under way in Division of Oncology laboratories for real-time mutational analysis of patient tumor samples so that patients with high-risk disease can be guided to the most appropriate experimental targeted therapies based on the specific signaling pathways active in their cancers.

**National Leadership in Research Consortia**

Cincinnati Children’s faculty continue to provide critical leadership in national clinical research efforts focused on pediatric cancers. John Perentesis, MD, director of the Division of Oncology, was elected to the executive committee of the Children’s Oncology Group (COG), for which he also serves as chairman of the Acute Myeloid Leukemia Relapse Committee and vice chairman of the Adolescent and Young Adult Cancer Steering Committee. In addition, he serves on the Investigational Drug Steering Committee of the National Cancer Institute’s Cancer Therapy Evaluation Program, for which he chairs the Signal Transduction Agents Task Force, and the national steering committee of the NCI-funded Pediatric Developmental Therapeutics/Phase I Consortium.

Maryam Fouladi, MD, MSc, medical director of the Neuro-Oncology Program, chairs the CNS Tumor New Agents/Relapse Committee for the Children’s Oncology Group, for which she also serves on the CNS Tumor Committee; she is a member of the national steering committee for the Collaborative Ependymoma Research Network (CERN). Brian Weiss, MD, leads a national COG pilot study of the targeted radiopharmaceutical 131I-MIBG in high-risk neuroblastoma as well as a national phase 2 study of sirolimus in neurofibromatosis type 1-related plexiform neurofibromas through the Neurofibromatosis Consortium.

**Division Publications**


### Grants, Contracts, and Industry Agreements

<table>
<thead>
<tr>
<th>Grant and Contract Awards</th>
<th>Annual Direct / Project Period Direct</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ADAMS, D</strong></td>
<td></td>
</tr>
<tr>
<td>Phase II Study of Rapamycin for Complicated Vascular Anomalies</td>
<td></td>
</tr>
<tr>
<td>Food and Drug Administration</td>
<td></td>
</tr>
<tr>
<td>R01 FD 003712</td>
<td>09/25/09-07/31/13</td>
</tr>
<tr>
<td>Severity Scale and Quality of Life Instrument for Infantile Hemangiomas</td>
<td></td>
</tr>
<tr>
<td>National Institutes of Health(Indiana Univ - Purdue Univ @ Indianapolis)</td>
<td></td>
</tr>
<tr>
<td>RC1 AR 058767</td>
<td>09/29/09-08/31/11</td>
</tr>
<tr>
<td><strong>CHOW, L</strong></td>
<td></td>
</tr>
<tr>
<td>Establishment of a Pre-Clinical Model for Pediatric Glioblastoma</td>
<td></td>
</tr>
<tr>
<td>The Cure Starts Now Foundation</td>
<td></td>
</tr>
<tr>
<td>10/01/10-09/30/11</td>
<td></td>
</tr>
<tr>
<td><strong>CRIPE, T</strong></td>
<td></td>
</tr>
<tr>
<td>Phase I Study of HSV1716 in Pediatric Non-CNS Solid Tumors</td>
<td></td>
</tr>
<tr>
<td>Food and Drug Administration</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Project Title</td>
<td>Sponsor</td>
</tr>
<tr>
<td>------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Preclinical Efficacy Studies of TR100 in Pediatric Cancer</strong></td>
<td>Oncology Children's Foundation</td>
</tr>
<tr>
<td><strong>The Role of Dendritic Cells in Oncolytic Virotherapy for Rhabdomyosarcoma</strong></td>
<td>Joanna McAfee Childhood Cancer Fdn. Inc.</td>
</tr>
<tr>
<td><strong>Cincinnati NF1 Preclinical Testing Center</strong></td>
<td>The Children's Tumor Foundation</td>
</tr>
<tr>
<td><strong>Cincinnati Center for Clinical and Translational Sciences and Training (Pilot/Collaborative Studies)</strong></td>
<td>National Institutes of Health (University of Cincinnati)</td>
</tr>
<tr>
<td><strong>Cincinnati Center for Neurofibromatosis Research (Project B)</strong></td>
<td>National Institutes of Health</td>
</tr>
<tr>
<td><strong>Inhibition of Pediatric Glioma Growth by Genetic Inhibition of AMP Kinase</strong></td>
<td>CancerFree Kids Pediatric Cancer Research Alliance</td>
</tr>
<tr>
<td><strong>Molecular Epidemiology in Children's Environmental Health</strong></td>
<td>National Institutes of Health (University of Cincinnati)</td>
</tr>
<tr>
<td><strong>Telomerase: A Therapeutic Target in Pediatric Tumors</strong></td>
<td>The Cure Starts Now Foundation</td>
</tr>
<tr>
<td><strong>Correlative Biology Studies in the First Phase I Trial of a Telomerase Inhibitor in Children with Recurrent Solid Tumors</strong></td>
<td>CancerFree Kids Pediatric Cancer Research Alliance</td>
</tr>
<tr>
<td><strong>Phase I Study of MK2206, an AKT Inhibitor, in Children with Recurrent Solid Tumors or Leukemias</strong></td>
<td>CancerFree Kids Pediatric Cancer Research Alliance</td>
</tr>
<tr>
<td><strong>Children's Oncology Group Chair's Grant</strong></td>
<td>National Institutes of Health (Children's Oncology Group)</td>
</tr>
<tr>
<td><strong>CERN Clinical Trials Network-Per Patient</strong></td>
<td>Univ of Texas M.D. Anderson Cancer Center</td>
</tr>
<tr>
<td><strong>Pediatric Brain Tumor Consortium</strong></td>
<td>National Institutes of Health (St. Jude Children's Research Hospital)</td>
</tr>
<tr>
<td><strong>Pediatric Brain Tumor Consortium - per patient</strong></td>
<td>National Institutes of Health (St. Jude Children's Research Hospital)</td>
</tr>
<tr>
<td><strong>COG Phase I Agreement</strong></td>
<td>National Institutes of Health (National Childhood Cancer Foundation)</td>
</tr>
</tbody>
</table>
IRWIN, M
Developing a National Model: Cincinnati Children's School Intervention Program
The Jeff Gordon Foundation
01/01/11-12/31/11 $15,000

LEDDON, J
The Role of Dendritic Cells in Oncolytic Virotherapy
CancerFree Kids Pediatric Cancer Research Alliance
06/01/11-05/31/12 $30,000

MARMER, D
Pilot Study to Assess Minimal Residual Disease in Ewing Sarcoma
CancerFree Kids Pediatric Cancer Research Alliance
06/01/11-05/31/12 $10,000

MIZUKAWA, B
Characterization of Rac GTPases in acute myeloid leukemia (AML) and their potential as therapeutic targets
National Institutes of Health (Yale University School of Medicine)
K12 HD 000850 07/01/08-08/31/10 $17,708

ORIENTI, I
Development of RC-16 as a New Cancer Therapy
CancerFree Kids Pediatric Cancer Research Alliance
06/01/11-05/31/12 $30,000

PERENTESIS, J
The Children's Oncology Group Chair Grant
National Institutes of Health (Children's Oncology Group)
U10 CA 098543 03/01/08-02/28/13 $30,083
The Children's Oncology Group Chair Grant - Per Patient
National Institutes of Health (Children's Oncology Group)
U10 CA 098543 03/01/08-02/28/13 $156,398
Children's Oncology Group Phase I
National Institutes of Health (Children's Oncology Group)
U01 CA 097452 08/01/02-07/31/12 $23,222
Children's Oncology Group Phase I - Per Patient
National Institutes of Health (Children's Oncology Group)
U01 CA 097452 08/01/02-07/31/12 $70,203
Children's Oncology Group New Publication Committee
National Institutes of Health (Children's Oncology Group)
U01 CA 97542 09/01/06-07/31/12 $25,363
Cincinnati Children's Hyundai Scholar in Childhood Cancer Drug Development
Hyundai Hope on Wheels
10/01/10-09/31/11 $100,000
Cincinnati Center for Neurofibromatosis Research (Project 1)
National Institutes of Health
P50 NS 057531 09/15/08-06/30/13 $296,849

POPE, J
Analysis of Antioxidant Polymorphisms in Patients with Down Syndrome and CML
St. Baldrick's Foundation
07/01/10-06/30/12 $68,209
Analysis of Antioxidant Polymorphisms in Patients with Down Syndrome and CML
Hyundai Hope on Wheels
07/01/10-06/30/11 $50,000
<table>
<thead>
<tr>
<th>Name</th>
<th>Title</th>
<th>Institution</th>
<th>Start Date</th>
<th>End Date</th>
<th>Funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRIVETTE-VINNEDGE, L</td>
<td>The Role of DEK in Breast Cancer Development and Therapy</td>
<td>National Institutes of Health</td>
<td>F32 CA 139931</td>
<td>09/15/09-09/14/11</td>
<td>$50,474</td>
</tr>
<tr>
<td>WAGNER, L</td>
<td>NAB-PACLITAXEL and SPARC in Pediatric Sarcoma</td>
<td>CancerFree Kids Pediatric Cancer Research Alliance</td>
<td>06/01/11-05/31/12</td>
<td></td>
<td>$15,000</td>
</tr>
<tr>
<td>WANG, P-Y</td>
<td>Virotherapy on Primary Neuroblastoma Cells</td>
<td>Alex's Lemonade Stand Foundation</td>
<td>07/01/10-06/30/12</td>
<td></td>
<td>$40,000</td>
</tr>
<tr>
<td>WEISS, B</td>
<td>Neurofibromatosis Consortium (STOPN - Protocol 102 mTOR)</td>
<td>Department of Defense Army(University of Alabama-Birmingham)</td>
<td>07/01/10-06/30/11</td>
<td></td>
<td>$19,373</td>
</tr>
<tr>
<td>WELLIS, S</td>
<td>Fanconi Anemia and HPV Transformation</td>
<td>Alex's Lemonade Stand Foundation</td>
<td>07/01/10-06/30/12</td>
<td></td>
<td>$40,000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alex's Lemonade Stand Foundation</td>
<td>07/01/10-06/30/12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Industry Contracts</td>
<td></td>
<td></td>
<td></td>
<td>$2,320,582</td>
<td></td>
</tr>
<tr>
<td>CRIPE, T</td>
<td>Crusade Laboratories Limited</td>
<td>$8,163</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Jennerex Biotherapeutics</td>
<td>$6,582</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FOULADI, M</td>
<td>Genetech</td>
<td>$15,400</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GELLER, J</td>
<td>ArQule, Inc</td>
<td>$1,277</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OBRIEN, M</td>
<td>Novartis Pharmaceuticals</td>
<td>$11,935</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PERENTESIS, J</td>
<td>CHLA - NANT</td>
<td>$10,795</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WAGNER, M</td>
<td>Sarcoma Alliance for Res through Collabo</td>
<td>$7,069</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current Year Direct Receipts</td>
<td></td>
<td></td>
<td></td>
<td>$61,221</td>
<td></td>
</tr>
<tr>
<td>Funded Collaborative Efforts</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRIPE, T</td>
<td>Cincinnati Center for Clinical and Translational Sciences and Training</td>
<td>National Institutes of Health</td>
<td>523x347</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Crusade Laboratories Limited</td>
<td>$8,163</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Jennerex Biotherapeutics</td>
<td>$6,582</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FOULADI, M</td>
<td>Genetech</td>
<td>$15,400</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GELLER, J</td>
<td>ArQule, Inc</td>
<td>$1,277</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OBRIEN, M</td>
<td>Novartis Pharmaceuticals</td>
<td>$11,935</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PERENTESIS, J</td>
<td>CHLA - NANT</td>
<td>$10,795</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WAGNER, M</td>
<td>Sarcoma Alliance for Res through Collabo</td>
<td>$7,069</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current Year Direct Receipts</td>
<td></td>
<td></td>
<td></td>
<td>$61,221</td>
<td></td>
</tr>
<tr>
<td>Name</td>
<td>Proposal Dates</td>
<td>Percentage</td>
<td>Funding Amount</td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------</td>
<td>-----------------------</td>
<td>------------</td>
<td>----------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heubi, J</td>
<td>04/01/09-03/31/14</td>
<td>6%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PERENTESIS, J</td>
<td>Promoting Treatment Adherence in Adolescent Leukemia</td>
<td>3%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>National Institutes of Health</td>
<td>09/28/07-07/31/12</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drotar, D</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>$2,381,803</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>