Significant Accomplishments

Experimental Hematology and Cancer Biology

NEW APPROACH TARGETING NF1

Neurofibromatosis type 1 (NF1) patients develop benign neurofibromas and malignant peripheral nerve sheath tumors that remain incurable. A group led by Nancy Ratner, PhD, found that NF1 mutation causes sustained ERK activation in these tumors. They showed that an MEK inhibitor reduces aberrantly proliferating tumor cells, shrinks neurofibromas in mice, and prolongs survival of mice implanted with human cancer cells. This study, reported in the Journal of Clinical Investigation, demonstrates that deregulated ERK signaling is critical for the growth of NF1 peripheral nerve tumors and provides a strong rationale for future clinical trials.

PASSING THROUGH THE BLOOD-BRAIN BARRIER

Dao Pan, PhD, and colleagues discovered a non-invasive procedure to deliver large-molecule therapeutic agents across the blood-brain barrier to treat neurological disorders. Findings were published online in February 2013 in PNAS. To realize the potential of large molecular weight substances to treat neurological disorders, they fused a receptor-binding peptide from apolipoprotein E with a potentially therapeutic protein that can be transcytosed into the central nervous system in a mouse model of a lysosomal storage disorder with central nervous system defects. They demonstrated the therapeutic potential of this approach by correcting brain glycosaminoglycan and β-hexosaminidase in the mice.

STEM CELL REGENERATION MECHANISM
Krüppel-like factor 5 regulates pluripotent stem cell self-renewal. In a work published in *Nature Communication*, Jose Cancelas Perez, MD, PhD, and colleagues reported that Krüppel-like factor 5-deficient hematopoietic stem cells and progenitors fail to engraft after transplantation. They supplied evidence that Krüppel-like factor 5 is indispensable for adhesion, homing, lodging and retention of hematopoietic stem cells and progenitors in the bone marrow through Rab5-dependent regulation of β1/β2 integrins.

**CHEMICALS TARGETING G-PROTEIN COUPLED RECEPTOR SIGNALING**

The G-protein-mediated Rho GTPase signaling axis has been implicated in human pathophysiology and is a potential therapeutic target. Yi Zheng, PhD, and colleagues reported in *PNAS*, the rational design and identification of a family of small molecule inhibitors specifically targeting Rho activators to benefit cancer stem cell therapy. Their work presents a new drug design strategy for dual inhibition of an enzyme-substrate pair that leads to enhanced efficacy and specificity of a targeted therapy.

**Hematology**

**WARE NAMED DIVISION DIRECTOR**

After a thorough search process, the Hematology Faculty and Search Committee selected Russell Ware, MD, PhD, as the new Division Director. Ware comes to Cincinnati Children’s from Baylor College of Medicine in Houston. He obtained his MD and PhD degrees from Duke University, and completed his fellowship in Pediatric Hematology/Oncology at Duke. He has been involved in clinical and translational hematology research projects for more than 25 years, with a primary interest in sickle cell disease. Ware has substantial personal experience with directing patient-oriented research, and currently runs an NIH-funded project to investigate genetic modifiers of sickle cell disease. Ware also is the national principal investigator for several NIH-funded multi-center sickle cell clinical trials, including the Stroke With Transfusions Changing to Hydroxyurea (SWiTCH), TCD With Transfusions Changing to Hydroxyurea (TWiTCH) and Sparing Conversion to Abnormal TCD Elevations (SCATE) studies. Most recently he has moved his research efforts into the international arena, starting SCD pilot screening programs in Angola, Uganda and other regions of Africa. He has published more than 225 peer-reviewed articles and has personally trained dozens of students and fellows. Ware will lead the Division of Hematology with overall goals of expanding its research portfolio, growing clinical expertise, and developing national and international prominence.

**Oncology**

**NO. 1 PEDIATRIC CANCER PROGRAM IN THE NATION**

The Oncology Division has had a very successful year, culminated by being named the top pediatric cancer program in the country by *US News and World Report*. This honor reflects successful team science, team process improvement and team clinical care initiatives that are fundamental to the Division. Key associated advances included successful bench-to-bedside implementation of faculty-led, investigator-initiated clinical trials using targeted small molecules for relapsed leukemia, brain tumors, advanced sarcomas and liver/renal tumors. These initiatives all involved close integration of translational oncology efforts between Oncology, Experimental Hematology, Blood/Marrow Transplant, Pathology, Clinical Pharmacology, and Biomedical Informatics.

**Division Publications**


Erythrocyte NADPH oxidase activity modulated by Rac GTPases, PKC, and plasma cytokines 
contributes to oxidative stress in sickle cell disease. 

44. Gow KW, Bamhart DC, Hamilton TE, Kandel JJ, Chen MK, Ferrer FA, Price MR, Mullen EA, Geller JL, 
Gracias EJ, Rosen N, Khanna G, Naranjo A, Ritchey ML, Grundy PE, Dome JS, Ehrlich PF. 
Primary nephrectomy and intraoperative tumor spill: report from the Children's Oncology Group (COG) 
renal tumors committee. 

45. Goyama S, Mulloy JC. 
Making healthy stem cells: the new role of TPO. 

Rac1 controls Schwann cell myelination through 
cAMP and NF2/merlin. 

47. Gutmann DH, Parada LF, Silva AJ, Ratner N. 
Neurofibromatosis type 1: modeling CNS dysfunction. 

Fischer A, Mahlaoui N, Nichols KE, Grunebaum E, Al Zahrani D, Roifman CM, Boelens J, Davies EG, 
Cavazzana-Calvo M, Notarangelo L, Gaspar HB. 
Outcome of hematopoietic stem cell transplantation for 
adenosine deaminase-deficient severe combined immunodeficiency. 
Blood. 2012; 120:3615-24; quiz 3626.

The NF2 tumor suppressor regulates microtubule-based vesicle trafficking via a novel Rac, MLK and p38(SAPK) 
pathway. 

DG, Maekawa T. 
Cyclic AMP responsive element binding proteins are involved in 'emergency' 
granulopoiesis through the upregulation of CCAAT/enhancer binding protein beta. 

51. Horwitz MS, Corey SJ, Grimes HL, Tidwell T. 
ELANE mutations in cyclic and severe congenital 
neutropenia: genetics and pathophysiology. 

52. Hoskins EE, Morreale RJ, Werner SP, Higginbotham JM, Laimins LA, Lambert PF, Brown DR, Gillison ML, 
Nuovo GJ, Witte DP, Kim MO, Davies SM, Mehta PA, Butsch Kovacic M, Wikenheiser-Brokamp KA, 
Wells SI. 
The fanconi anemia pathway limits human papillomavirus replication. 

Pharmacotherapeutic management of pediatric gliomas: current and upcoming strategies. 

54. Hummel TR, Miles L, Mangano FT, Jones BV, Geller JL. 
Clinical heterogeneity of desmoplastic infantile ganglioglioma: a case series and literature review. 

55. Ishikawa ET, Cancelas JA. 
Lack of communication rusts and ages stem cells. 

N. 
MEK inhibition exhibits efficacy in human and mouse neurofibromatosis tumors. 


86. Myers KC, Lawrence J, Marsh RA, Davies SM, Jodele S. High-dose methylprednisolone for veno-


139. Zhang MJ, Dawies SM, Camitta BM, Logan B, Tiedemann K, Eapen M, Thiel EL. Comparison of outcomes after HLA-matched sibling and unrelated donor transplantation for children with high-


Grants, Contracts, and Industry Agreements

Experimental Hematology

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<th>Grant and Contract Awards</th>
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<td>Analysis of Staphylococcus Aureus Host Interactions</td>
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<td>FILIPPI, M</td>
<td>Regulation of Neutrophil Migration and Polarity</td>
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<td>Mechanisms Linking the Hemostatic Protease Thrombin to Arthritic Disease</td>
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<td>GEIGER, H</td>
<td>Activated Protein C for Treatment of Radiation Combined Injury</td>
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<td>Molecular Mechanisms and Therapies for Radiation-Induced Myelodysplastic Syndrome</td>
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<td>Suppressing a Tumor Suppressor RUNX1: A Novel Approach to Treat Pediatric Acute Leukemia</td>
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<td>Regulation of Intracellular Trafficking in NF2</td>
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<td>Targeting Metabolic Vulnerabilities of ERBB2-Driven Breast Cancer</td>
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<td>Identification of Drug Development Pathway for Improving Prognosis of Pediatric Leukemia</td>
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<td>Genetic Therapy for CNS Manifestations in MPS I via BBB-Targeted Protein Delivery</td>
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Training Programs in Cancer Therapeutics
National Institutes of Health(University of Cincinnati)
T32 CA 117846 09/14/12-08/31/14 $48,435

VARNEY, M

Environmental Carcinogenesis and Mutagenesis
National Institutes of Health(University of Cincinnati)
T32 ES 007250 05/01/12-04/30/14 $6,894

WU, J

STAT3 in Neurofibroma Tumorigenesis and Therapy
Department of Defense Army
W81XWH1110259 07/01/11-06/30/14 $132,862

Exploring the Plexiform Neurofibroma Interactone
Neurofibromatosis Therapeutic Acceleration Program(John Hopkins University)
05/15/13-05/14/15 $292,910

ZHENG, Y

Cincinnati Center for Excellence in Molecular Hematology
National Institutes of Health
P30 DK 090971 07/01/10-06/30/13 $505,315

Zheng, Y Admin Core $91,497
Grabowski, G Genomics and Genetic Core $63,001
Cancelas, J Cell Analysis and Sorting Core $65,112
Malik, P Translational Core $163,824
Mulloy, J Xenotransplant and Transgenic Core $68,765
Zheng, Y Summer Students $30,370

Pharmacological Rejuvenation of Aged Hematopoietic Stem Cells
National Institutes of Health(P2D Bioscience)
R34 AG 042986 08/15/12-07/31/13 $84,870

Rac GTPase-Specific Small Molecular Inhibitors
National Institutes of Health
R01 CA 141341 03/24/09-01/31/14 $151,943

Training Program in Pediatric Hematologic and Oncologic Diseases
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Current Year Direct $7,783,205

Industry Contracts

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<td>Seattle Genetics</td>
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GRASSMAN, E

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Current Year Direct Receipts $274,014

Total $8,057,219

Hematology

Grant and Contract Awards

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**Current Year Direct** $1,187,614

**Industry Contracts**

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## Oncology

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<td><strong>CHLON, T</strong></td>
<td><strong>Pelotonia Fellowship Program</strong></td>
<td>Ohio State University Comprehensive Cancer</td>
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<td>03/01/13-02/28/15</td>
<td>$39,264</td>
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<td><strong>CHOW, L</strong></td>
<td><strong>Micro-RNA Expression in Pediatric High-Grade Glioma</strong></td>
<td>Childhood Brain Tumor Foundation</td>
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<td>09/01/11-08/31/13</td>
<td>$22,727</td>
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<td><strong>Molecular Targeting of High-Grade Astrocytoma</strong></td>
<td>The Sontag Foundation</td>
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<td>10/01/11-09/30/15</td>
<td>$130,435</td>
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<td><strong>Molecular Targeting of Pediatric High-Grade Glioma</strong></td>
<td>St. Baldrick's Foundation</td>
<td></td>
<td>07/01/11-06/30/14</td>
<td>$110,000</td>
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<td><strong>CRIPE, T</strong></td>
<td><strong>Neurofibromatosis Preclinical Consortium Center Award</strong></td>
<td>The Children's Tumor Foundation</td>
<td>2011-05-003</td>
<td>07/01/11-06/30/13</td>
<td>$204,545</td>
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<td><strong>DASGUPTA, B</strong></td>
<td><strong>Regulation of Forebrain Neurogenesis by the Energy Sensor AMP Kinase</strong></td>
<td>National Institutes of Health</td>
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## Current Year Direct Receipts

<table>
<thead>
<tr>
<th>Description</th>
<th>Amount</th>
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<tr>
<td>Total</td>
<td>$1,378,734</td>
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<tr>
<td><strong>Grant and Contract Awards</strong></td>
<td>$191,120</td>
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DORRIS, K

Molecular Epidemiology in Children’s Environmental Health Training Program
National Institutes of Health (University of Cincinnati)
T32 ES 010957 10/01/12-06/30/13 $40,635

DRISSI, R

Telomerase as a Marker and Therapeutic Target for Pediatric High-Grade Glioma
Team Connor Childhood Cancer Foundation
TCCCF 01/01/13-12/31/13 $60,000

FOULADI, M

Children’s Oncology Group Chair
National Institutes of Health (Children’s Hospital of Philadelphia)
U10 CA 098543 04/13/12-02/28/14 $11,550

The Pediatric Brain Tumor Consortium
National Institutes of Health (St. Jude Children’s Hospital)
U01 CA 08155 04/01/11-03/31/14 $44,115

Establishment of an International Diffuse Intrinsic Pontine Glioma (DIPG) Registry
The Cure Starts Now Foundation
01/01/12-05/31/14 $231,092

The Pediatric Brain Tumor Consortium - Per Patient
National Institutes of Health (St. Jude Children’s Hospital)
U01 CA 08155 04/01/11-03/31/14 $9,259

GELLER, J

Epigenetic and Clinical Impact of SMARCB1 Loss in Cancer
National Institutes of Health (Children’s Memorial Hospital)
R21 CA 166790 07/01/2012-06/30/2014 $9,273

MOREIRA RIDSDAL, D

The Role of CDC42 in MLL-AF9 Induced AML Xenograft Model
American Society of Hematology
06/01/13-05/31/14 $5,000

O’BRIEN, M

Molecular Targeting of Chemotherapy-Resistant Pediatric Acute Myeloid Leukemia
Hyundai Hope on Wheels
O’Brien-HOW 12/01/12-11/30/13 $75,000

PERENTESIS, J
Children's Oncology Group Chair - Millennium  
National Institutes of Health (Children's Hospital of Philadelphia)  
03/01/12-02/28/17  
$10,395

Children's Oncology Group Chair - Workload Intensity  
National Institutes of Health (Children's Hospital of Philadelphia)  
U10 CA 098543  
03/01/12-02/28/17  
$27,791

Children's Oncology Group Phase I / Pilot Consortium  
National Institutes of Health (National Childhood Cancer Foundation)  
U01 CA 097452  
09/01/06-07/31/15  
$22,525

COG Supplemental Reimbursement  
St. Baldrick's Foundation (Children's Hospital of Philadelphia)  
03/01/12-02/18/17  
$39,193

Pediatric Phase I - Pilot Consortium (per case)  
National Institutes of Health (Children's Hospital of Philadelphia)  
UM1CA097452  
07/24/12-05/31/15  
$46,010

Pediatric Phase I Scientific Leadership  
National Institutes of Health (Children's Hospital of Philadelphia)  
UM1CA097452  
09/26/12-07/31/15  
$11,501

Children's Oncology Group Phase I / Pilot Consortium - per patient  
National Institutes of Health (Children's Hospital of Philadelphia)  
U01 CA 097452  
09/01/06-07/31/12  
$125,705

PHILLIPS, C  

Genetic Model of Cytarabine Sensitivity in Children with AML  
American Association for Cancer Research  
07/01/12-06/30/14  
$50,000

PRIVETTE, L  

Cincinnati Interdisciplinary Women's Health Research Career Training Grant  
National Institutes of Health (University of Cincinnati)  
K12 HD 051953  
07/01/12-06/30/14  
$79,933

Defining the Role of the DEK Oncagene in Breast Cancer Stem Cell Tumorigenicity Ad Pre-Clinical Testing of Therapeutic DEK Targeting Strategies  
Ride Cincinnati Foundation  
RCF  
04/01/13-03/31/14  
$40,000

ROMICK-ROSENDALE, L  

Environmental Carcinogenesis and Mutagenesis  
National Institutes of Health (University of Cincinnati)  
T32 ES 007250  
09/01/12-06/30/13  
$41,170

WEISS, B
Phase I Trial of the MEK 1 Inhibitor AZX6244 with Plexiform
Children's Tumor Foundation (Children's Hospital of Philadelphia)
02/01/12-01/31/14 $37,182

Children's Oncology Group Chair - Workload Intensity
National Institutes of Health (Children's Hospital of Philadelphia)
U10 CA 098543 03/01/12-02/28/17 $11,550

WELLS, S

Fanconi Anemia and HPV Transformation
National Institutes of Health
R01 CA 102357 09/28/09-08/31/14 $191,834

Role and Regulation of the Human DEK Proto-Oncogene
National Institutes of Health
R01 CA 116316 09/05/12-06/30/17 $174,318

Targeting the Ron-DEK Signaling Axis in Breast Cancer
Department of Defense
W81XWH-12-1-0194 09/01/12-08/31/14 $125,000

WILLIAMS, J

ETV2 Role in Tumor-Induced Lymphangiogenesis, A Putative Therapeutic Target
St. Baldrick's Foundation
07/01/12-06/30/14 $69,659

Current Year Direct $2,610,576

Industry Contracts

FOUALDI, M
Genetech, Inc $19,250

GELLER, J
Bayer Healthcare, Inc $73,615

WAGNER, L
Sarcoma Alliance for Res through Collaboration $2,887

WEISS, B
Children's Hospital Los Angeles $12,890

Current Year Direct Receipts $108,642

Total $2,719,218