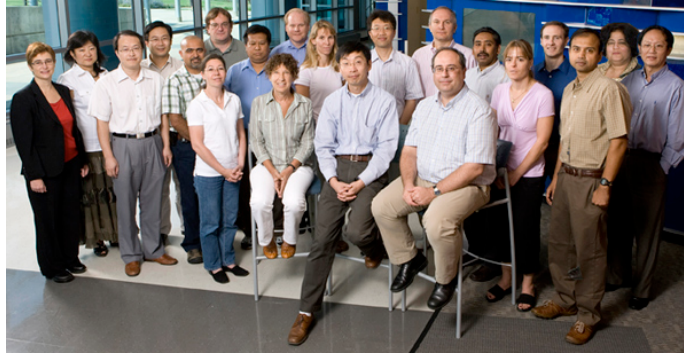


## Experimental Hematology and Cancer Biology

### Division Photo



First Row: Marie-Dominique Filippi, Nancy Ratner, Yi Zheng, Jose Cancelas; Second Row: Ashish Kumar, Ruhikanta Meetei, Susanne Wells, Gang Huang, Mohammad Azam, Elke Grassman, Biplab DasGupta; Third Row: Fukun Guo; Fourth Row: Theodosia Kalfa, Dao Pan, Jianqiang Wu, Paul Andreassen, Timothy Cripe, Lee Grimes, James Mulloy, Punam Malik, Qishen Pang

Not Pictured: Hartmut Geiger, Lionel Chow, Rachid Drissi, Stella Davies, Ajay Perumbeti, Han vanderLoo

### Division Data Summary

#### Research and Training Details

Number of Faculty	19
Number of Joint Appointment Faculty	12
Number of Research Fellows	22
Number of Research Students	15
Number of Support Personnel	64
Direct Annual Grant Support	\$6,332,861
Peer Reviewed Publications	58

### Significant Publications

**Guo F, Cancelas JA, Hildeman D, Williams DA, Zheng Y. Rac GTPase isoforms Rac1 and Rac2 play a redundant and crucial role in T-cell development. (2008) Blood, 112(5): 1767-75.**

Rac GTPases have been implicated in the regulation of diverse functions in various blood cell lineages, but their role in T-cell development is not well understood. We have carried out conditional gene targeting to achieve hematopoietic stem cell (HSC)- or T-cell lineage-specific deletion of Rac1 or Rac1/Rac2 by crossbreeding the Mx-Cre or Lck-Cre transgenic mice with *Rac1<sup>loxp/loxp</sup>* or *Rac1<sup>loxp/loxp</sup>;Rac2<sup>-/-</sup>* mice. We found that (1) HSC deletion of both Rac1 and Rac2 inhibited production of common lymphoid progenitors (CLPs) in bone marrow and suppressed T-cell development in thymus and peripheral organs, whereas deletion of Rac1 moderately affected CLP production and T-cell development. (2) T cell-specific deletion of Rac1 did not affect T-cell development, whereas deletion of both Rac1 and Rac2 reduced immature CD4+CD8+ and mature CD4+ populations in thymus as well as CD4+ and CD8+ populations in spleen. (3) The developmental defects of Rac1/Rac2 knockout T cells were associated with proliferation, survival, adhesion, and migration defects. (4) Rac1/Rac2 deletion suppressed T-cell receptor-mediated proliferation, IL-2 production, and Akt activation in thymocytes. Thus, Rac1 and Rac2 have unique roles in CLP production and share a redundant but essential role in later stages of T-cell development by regulating survival and proliferation signals.

**Patel N, Gonsalves CS, Yang M, Malik P, Kalra VK. Placenta growth factor induces 5-lipoxygenase-activating protein to increase leukotriene formation in sickle cell disease. (2009) Blood, 113(5): 1129-38.**

Individuals with sickle cell disease (SCD) have increased inflammation, a high incidence of airway hyperreactivity

(AH), and increased circulating leukotrienes (LT). We show that expression of 5-lipoxygenase and 5-lipoxygenase activating protein (FLAP), key catalytic molecules in the LT pathway, were significantly increased in peripheral blood mononuclear cells (MNCs) in patients with SCD, compared with healthy controls. Placenta growth factor (PIGF), elaborated from erythroid cells, activated MNC and THP-1 monocytic cells to induce LT production. PIGF-mediated increased FLAP mRNA expression occurred via activation of phosphoinositide-3 (PI-3) kinase, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, and hypoxia inducible factor-1 (HIF-1). HIF-1 small interfering RNA (siRNA) reduced PIGF-induced FLAP expression. FLAP promoter-driven luciferase constructs demonstrated that PIGF-mediated luciferase induction was abrogated upon mutation of HIF-1 response element (HRE), but not the nuclear factor- $\kappa$ B (NF- $\kappa$ B) site in the FLAP promoter; a finding confirmed by chromatin immunoprecipitation (ChIP) analysis. PIGF also increased HIF-1 binding to the HRE in the FLAP promoter. Therefore, it is likely that the intrinsically elevated levels of PIGF in SCD subjects contribute to increased LT, which in turn, mediate both inflammation and AH. Herein, we identify a mechanism of increased LT in SCD and show HIF-1 as a hypoxia-independent target of PIGF. These studies provide new avenues to ameliorate these complications.

**Singh TR, Singh R, Mahmood Ali A, Busygina V, Raynard S, Fan Q, Du C, Andreassen PR, Sung P, Meetei AR. BLAP18/RMI2, a novel OB-fold-containing protein, is an essential component of the Bloom helicase-double Holliday junction dissolvosome. (2008) *Genes Dev*, 22(20): 2856-68.**

Bloom Syndrome is an autosomal recessive cancer-prone disorder caused by mutations in the *BLM* gene. *BLM* encodes a DNA helicase of the RECQ family, and associates with Topo III $\alpha$  and BLAP75/RMI1 (BLAP for BLM-associated polypeptide/RecQ-mediated genome instability) to form the BTB (BLM–Topo III $\alpha$ –BLAP75/RMI1) complex. This complex can resolve the double Holliday junction (dHJ), a DNA intermediate generated during homologous recombination, to yield noncrossover recombinants exclusively. This attribute of the BTB complex likely serves to prevent chromosomal aberrations and rearrangements. Here we report the isolation and characterization of a novel member of the BTB complex termed BLAP18/RMI2. BLAP18/RMI2 contains a putative OB-fold domain, and several lines of evidence suggest that it is essential for BTB complex function. First, the majority of BLAP18/RMI2 exists in complex with Topo III $\alpha$  and BLAP75/RMI1. Second, depletion of BLAP18/RMI2 results in the destabilization of the BTB complex. Third, BLAP18/RMI2-depleted cells show spontaneous chromosomal breaks and are sensitive to methyl methanesulfonate treatment. Fourth, BLAP18/RMI2 is required to target BLM to chromatin and for the assembly of BLM foci upon hydroxyurea treatment. Finally, BLAP18/RMI2 stimulates the dHJ resolution capability of the BTB complex. Together, these results establish BLAP18/RMI2 as an essential member of the BTB dHJ dissolvosome that is required for the maintenance of a stable genome.

**Williams JP, Wu J, Johansson G, Rizvi TA, Miller SC, Geiger H, Malik P, Li W, Mukoyama Y, Cancelas JA, Ratner N. Nf1 mutation expands an EGFR-dependent peripheral nerve progenitor that confers neurofibroma tumorigenic potential. (2008) *Cell Stem Cell* 3, (6): 658-69.**

Defining growth factor requirements for progenitors facilitates their characterization and amplification. We characterize a peripheral nervous system embryonic dorsal root ganglion progenitor population using in vitro clonal sphere-formation assays. Cells differentiate into glial cells, smooth muscle/fibroblast (SM/Fb)-like cells, and neurons. Genetic and pharmacologic tools revealed that sphere formation requires signaling from the EGFR tyrosine kinase. *Nf1* loss of function amplifies this progenitor pool, which becomes hypersensitive to growth factors and confers tumorigenesis. *DhhCre;Nf1<sup>fl/fl</sup>* mouse neurofibromas contain a progenitor population with similar growth requirements, potential, and marker expression. In humans, *NF1* mutation predisposes to benign neurofibromas, incurable peripheral nerve tumors. Prospective identification of human EGFR+;P75+ neurofibroma cells enriched EGF-dependent sphere-forming cells. Neurofibroma spheres contain glial-like progenitors that differentiate into neurons and SM/Fb-like cells in vitro and form benign neurofibroma-like lesions in nude mice. We suggest that expansion of an EGFR-expressing early glial progenitor contributes to neurofibroma formation.

**Zhou Y, Du W, Koretsky T, Bagby GC, Pang Q. TAT-mediated intracellular delivery of NPM-derived peptide induces apoptosis in leukemic cells and suppresses leukemogenesis in mice. (2008). *Blood*, 112(6): 2474-83.**

Nucleophosmin (NPM) is frequently overexpressed in leukemias and other tumors. NPM has been reported to suppress oncogene-induced senescence and apoptosis and may represent a therapeutic target for cancer. We fused a NPM-derived peptide to the HIV-TAT (TAT-NPM C) and found that the fusion peptide inhibited proliferation and induced apoptotic death of primary fibroblasts and preleukemic stem cells. TAT-NPM C down-regulated several NF- $\kappa$ B-controlled survival and inflammatory proteins and suppressed NF- $\kappa$ B-driven reporter gene activities. Using an inflammation-associated leukemia model, we demonstrate that TAT-NPM C induced proliferative suppression and apoptosis of preleukemic stem cells and significantly delayed leukemic development in mice. Mechanistically, TAT-NPM C associated with wild-type NPM proteins and formed complexes with endogenous NPM and p65 at promoters of several antiapoptotic and inflammatory genes and abrogated their transactivation by NF- $\kappa$ B in leukemic cells. Thus, TAT-delivered NPM peptide may provide a novel therapy for inflammation-associated tumors that require NF- $\kappa$ B signaling for survival.

## Division Highlights

Yi Zheng, PhD

We have revealed an essential role of Rac1/Rac2 GTPases in T-cell development by regulating unique cell cycle and survival pathways (Guo et al., Blood 2008).

#### **Paul Andreassen, PhD**

The Andreassen lab has shown that monoubiquitinated FANCD2 is required for homologous recombination at telomeres in a subset of cancer cells (Fan et al. 2009 Nucleic Acids Res.)

#### **Christopher Baum, MD**

In a prospective study involving ~ 100 patients with acute leukemia, the baum lab has identified neurotrophin receptor expression as a novel prognostic marker (Li et al., Blood 2009).

In a murine model, the Baum lab demonstrated that cell-intrinsic factors play a major role in the risk of insertional leukemia induction by gene vectors (Kustikova et al., Mol Ther 2009).

Together with two colleagues (Dr. Ute Modlich and Sabine Knoess), Baum lab has obtained a prestigious award of the German Research Foundation (DFG) for research to replace, reduce and refine animal experiments (50000 € Ursula M. Haendel animal protection award 2009).

#### **Jose Cancelas, MD, PhD**

Demonstration that mastocytosis in a murine model of chronic eosinophilic leukemia/mastocytosis induced by expression of the fusion gene FIP1L1/PDGFRa depends on SCF/c-kit signaling and subsequent synergistic activation of Akt. This manuscript is a result of a very successful collaboration with the Division of Allergy/Immunology of CCHMC (Dr. M. Rothenberg). (Yamada et al, Blood. 2008).

#### **Marie-Dominique Filippi, PhD**

We have identified and characterized a critical signaling module regulating blood neutrophil migration - the mechanisms and essential features of neutrophil polarity regulation by Cdc42.

#### **Hartmut Geiger, PhD**

Demonstration of phenotypes of aged hematopoietic stem cells in vivo, particularly the "hyperactivity" in terms of moving on the bone marrow niche (Blood 2009).

#### **Elke Grassman, PhD**

We have provided certification testing for a clinical vector and completed mouse safety studies to support and IND for use in a multi-institutional gene transfer trial for the treatment of severe combined Immunodeficiency (X-SCID). Data from the mouse safety studies was presented at the ASGT's 12th annual meeting, May27-30, 2008 in San Diego, CA in an oral abstract session.

We have developed high complexity assays to support production development of lentiviral vector products.

We have initiated mouse safety studies for a gene transfer trial for sickle cell anemia.

#### **Fukun Guo, PhD**

Discovered a unique role of the Rho GTPase Cdc42 in regulating B-cell development and activation, specifically in modulating pre-pro-B cell survival and cell cycle progression in the bone marrow and spleen (Guo F, et al. Blood, 2009, in press).

#### **Punam Malik, MD**

We identified the mechanism of reduction in titers from lentivirus vectors carrying chromatin insulator elements in the 3' LTR. (*Molecular Therapy* 2009).

We generated a novel human gamma-globin gene vector for genetic correction of sickle cell anemia in a humanized sickle mouse model and identified critical determinants for successful correction. (*Blood* 2009).

We assessed the genotoxic potential of gene therapy vectors for hemoglobinopathies (*Molecular Therapy* 2009).

We showed that placenta growth factor augments endothelin-1 and endothelin-B receptor expression via hypoxia-inducible factor, linking erythropoiesis, pulmonary hypertension and inflammation in sickle cell disease. (*Blood* 2008).

We also showed that placenta growth factor induces 5-lipoxygenase-activating protein expression via hypoxia-inducible factor-1 $\alpha$  to increase leukotriene formation in sickle cell disease. (*Blood* 2009).

#### **Ruhikanta Meetei, PhD**

Discovery of a new component of BTB complex called BLAP18/RMI2 and implication of its role in a cancer-predisposing condition called Bloom's Syndrome (Gene & Dev 2008).

Discovery that one FA patient (EUFA867) with biallelic mutations in FANCM also carries biallelic mutations in FANCA

(Blood 2009).

### Dao Pan, PhD

Lysosomal enzyme in red project: We are the first to demonstrate that erythroid cells, transduced with a tissue-specific lentiviral vector, can produce and release a lysosomal enzyme efficiently and continuously at supra-physiological levels in the circulation, and can also achieve phenotypic correction in peripheral organs and the CNS of mouse model with Hurler syndrome (manuscript submitted).

KCC profiling project—in collaboration with Dr. Joiner: the changes of expression from three KCl cotransporter genes and with different splicing isoforms were studied during human and murine erythroid differentiation, suggesting the KCC3a is dominant in human red blood cells (manuscript in preparation).

### Qishen Pang, PhD

**Role of FANCA in HSC/P cell migration and homing** – We recently demonstrated a cell-autonomous defect of HSC/P cells from FA-A patients in homing and identified a failure of the hematopoietic supportive capacity of FA-A stromal cells. A manuscript based on this work was published in *Blood*.

**Functional interaction between FA and p53 pathways in oxidative and oncogenic stress responses** – We studied the function of FA proteins in oxidative DNA damage and oncogenic stress response and found that BM cells from *Fanca*<sup>-/-</sup> and *Fancc*<sup>-/-</sup> mice elicited a p53-dependent growth arrest and DNA damage response to oxidative and oncogenic stress. We published these results in *Cancer Res*.

**Identification B activator during FA leukemogenesis of NPM as a NF- $\kappa$ B-driven reporter gene activities. Akinflammatory proteins and suppressed NF- $\kappa$ B** manuscript based on this work was published in *Blood*

### Nancy Ratner, PhD

A discovery that expansion of an EGFR-expressing early glial progenitor contributes to neurofibroma formation. It provides new insights to therapeutic strategies targeting this tumor initiating cell population (Cell Stem Cell 2009)

### Jianqiang Wu, PhD

Role of EGFR in neurofibroma development in Neurofibromatosis type 1 (Williams, Wu et al, Cell Stem Cell. 2008, 3(6):658-69.)

Preclinical therapeutic trials of RAD001 and BEZ-235 on a neurofibroma mouse model

## Division Collaboration

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### Collaboration with Developmental Biology

#### Collaborating Faculty: C.-Y. Kuan; K. Campbell

Rac1 deficiency in the forebrain results in neural progenitor reduction and microcephaly. Dev. Biol. 325(1):162-70. (2009)

### Collaboration with Hematology/Oncology

#### Collaborating Faculty: Frank Smith

Defective adhesion, migration and homing are associated with altered Cdc42 activity in cells from Fanconi anemia patients. Blood 112(5):1683.

### Collaboration with Immunobiology

#### Collaborating Faculty: D. Hildeman

Rac1 and Rac2, play redundant and critical role in T-cell development. Blood 112(5):1767-75.

### Collaboration with UC Cancer Cell Biology

#### Collaborating Faculty: Erik Knudsen

(2009) RB/p107/130 pocket proteins: Protein dynamics and interactions with target gene promoters. J. Biol. Chem. doi:10.1074/jbc.M808740200.

### Collaboration with Allergy/Immunology

#### Collaborating Faculty:

Analysis of the signaling mechanisms responsible for FIP1L/PDGFR $\alpha$ -induced chronic eosinophilic leukemia and mastocytosis.

### Collaboration with Pulmonary

#### Collaborating Faculty: Tim LeCras

Tim Le Cras supports the Geiger lab in better understanding the role of EGFR signaling in hematopoiesis.

### Collaboration with UC

**Collaborating Faculty: Peter Stambrook**

We work together with the Stambrook lab to understand DNA repair pathways in hematopoietic stem cells.

**Collaboration with UC**

**Collaborating Faculty: Anil Mennon**

In experiments with the Menon lab we determine the influence of the mother on the epigenetic make-up of hematopoietic stem cell during development.

**Collaboration with Hematology/Oncology; Boston Children's Hospital; Institute of Child Health in London; Necker Hospital**

**Collaborating Faculty: Lisa Filipovich; David Williams; Adrian Thrasher; Alan Fisher**

which will be sites conducting the Phase I X-SCID gene transfer trial and using the clinical vector produced at CCHMC, translational cores.

**Collaboration with Immunobiology**

**Collaborating Faculty: David Hildeman; Lee Grimes**

They have performed some assays.

**Collaboration with Hematology/Oncology**

**Collaborating Faculty: Clint Joiner; Karen Kalinyak; Eric Mullins; Susanne Wells**

Sickle Cell Research

**Collaboration with Developmental Biology**

**Collaborating Faculty: Jay Degen; James Wells**

Sickle Cell Research

**Collaboration with Immunobiology**

**Collaborating Faculty: Marsha Wills-Karp**

Sickle Cell Research

**Collaboration with Pulmonary Medicine**

**Collaborating Faculty: William Hardie; Gary McPhail; Carolyn Kerckmar**

Sickle Cell Research

**Collaboration with Cardiology**

**Collaborating Faculty: Bill Gottliebson; Janaka Wansapura; Woody Benson; Jeffrey Towbin**

Sickle Cell Research

**Collaboration with Genetics**

**Collaborating Faculty: William Nichols**

Sickle Cell Research

**Collaboration with UC**

**Collaborating Faculty: Robet Franco; George Atweh; Rupak Bannerjee**

Role of Placenta growth factor in sickle acute chest syndrome

**Collaboration with Immunobiology**

**Collaborating Faculty: Lee Grimes**

Mouse modeling of human T-ALL

**Collaboration with Molecular Immunology**

**Collaborating Faculty: Claire Chougnnet; Julio Aliberti**

Characterization of a new xenograft model that greatly potentiates human T-cell development from human CD34+ cells. May prove useful for HIV research, graft vs host disease, analysis of in vivo human T-cell development and modeling human T-cell leukemia.

**Collaboration with Human Genetics**

**Collaborating Faculty: Xiaoyang Qi**

Lead compound testing of a patented, proprietary anti-cancer compound in human leukemia xenograft models.

**Collaboration with Developmental Biology**

**Collaborating Faculty: Jim Wells**

Mechanistic dissection of the activation of B-catenin in AML1-ETO-expressing cells

**Collaboration with Hematology/Oncology**

**Collaborating Faculty: Clinton Joiner**

to study the expression of ion transporter (KCC) during erythropoiesis and potential therapeutic effect by

manipulation of KCC using shRNA approach on Sickle Cell Diseases.

#### **Collaboration with UC**

##### **Collaborating Faculty: Robert Franco**

to study the expression of ion transporter (KCC) during erythropoiesis and potential therapeutic effect by manipulation of KCC using shRNA approach on Sickle Cell Diseases.

#### **Collaboration with Hematology/Oncology**

##### **Collaborating Faculty: Theodosia Kalfa**

to provide expertise on real-time RT-qPCR in her project studying RAC expression during erythropoiesis, and to use her expertise in our project studying red cell-specific expression of lysosomal enzyme.

#### **Collaboration with Developmental Biology**

##### **Collaborating Faculty: Alex Kuan**

to provide expertise/work on lentiviral vector construction and LV-mediated gene transfer into isolated neuronal cells for his project; and on large-molecule delivery across brain-blood-barrier (BBB) using his expertise in brain pathology.

#### **Collaboration with UC**

##### **Collaborating Faculty: David Hui**

for his expertise on LDL receptor superfamily and apoE metabolism to study large-molecule delivery across BBB.

#### **Collaboration with UC**

##### **Collaborating Faculty: Keith Crutcher**

who provide his expertise on neuroanatomy and toxicity in our project on large-molecule delivery across BBB.

#### **Collaboration with Ohio State University**

##### **Collaborating Faculty: Greg Lesinski; William Carson**

to provide expertise/work on shRNA lentiviral vector construction and LV-mediated gene transfer into primary cells in their project studying the function and regulation of STAT5 in immune system.

#### **Collaboration with Human Genetics**

##### **Collaborating Faculty: Ying Sun; Greg Grabowski**

to collaborate on CNS abnormality in murine MPS models.

#### **Collaboration with Biomedical Informatics**

##### **Collaborating Faculty: Bruce Aronow**

Miller, S.J., Jessen, W.J., Mehta, T., Hardiman, A., Sites, E., Kaiser, S., Jegga, A., Li, H., Upadhyaya, M. . . , Giovannini, M., Muir, D., Wallace, M.R., Lopez, E., Serra, E., Lazaro, C., Stemmer-Rachamimov, A., Page, G., Aronow, B.J. and **Ratner**, N. Integrative genomic analyses show altered Schwann cell development in Neurofibromatosis tumors and implicate *SOX9* as an addicting oncogene

#### **Collaboration with Hematology/Oncology**

##### **Collaborating Faculty: John Perentesis; Tim Cripe**

Johansson, G., Mahller, Y., Collins, M.H., Kim, M-O., Nobukuni, T., Perentesis, J.P.,Cripe, T.P., Lane, H.A., Kozma, S., Thomas, G., **Ratner**, N. (2008) Effective *In Vivo* Targeting of the mTOR Pathway in Malignant Peripheral Nerve Sheath Tumor, *Mol. Cancer Therapeutics*, 7(5):1237-45.

#### **Collaboration with UC/GRI**

##### **Collaborating Faculty: George Thomas; Sara Kozma; William Seibel**

Johansson, G., Mahller, Y., Collins, M.H., Kim, M-O., Nobukuni, T., Perentesis, J.P.,Cripe, T.P., Lane, H.A., Kozma, S., Thomas, G., **Ratner**, N. (2008) Effective *In Vivo* Targeting of the mTOR Pathway in Malignant Peripheral Nerve Sheath Tumor, *Mol. Cancer Therapeutics*, 7(5):1237-45.

#### **Collaboration with Developmental Biology**

##### **Collaborating Faculty: Brian Gebelein**

MPNST Gene Project

#### **Collaboration with Radiology**

##### **Collaborating Faculty: Diana Lindquist; Scott Dunn**

Magnetic resonance image (MRI) monitors neurofibroma development in a neurofibroma mouse model.

#### **Collaboration with Molecular Immunology**

##### **Collaborating Faculty: Chris Karp**

Modification of cystic fibrosis lung disease severity by polymorphisms in genes regulating neutrophil function. *Nature* 2009

## Collaboration with Blood Bone Marrow Transplantation

### Collaborating Faculty: A. Filipovich

Metarhizium Anisoplia in a patient with hypohydrotic ectodermal dysplasia and immune deficiency. Pediatric Infection Disease Journal 2008

## Faculty Members

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**Yi Zheng, PhD**, Professor ; *Division Director; Endowed Chair; Program Leader*

**Research Interests:** Signaling Program

**Paul Andreassen, PhD**, Assistant Professor

**Research Interests:** Leukemia Biology

**Mohammed Azam, PhD**, Research Assistant Professor

**Research Interests:** Cancer Pathology

**Jose Cancelas, MD, PhD**, Associate Professor ; *Program Leader*

**Research Interests:** Stem Cell Program

**Marie-Dominique Filippi, PhD**, Research Assistant Professor

**Research Interests:** Stem Cell Program

**Hartmut Geiger, PhD**, Research Associate Professor

**Research Interests:** Stem Cell Program

**Elke Grassman, PhD**, Assistant Professor ; *Director, TTDSL*

**Fukun Guo, PhD**, Research Instructor

**Research Interests:** Signaling Program

**Gang Huang, PhD**, Research Assistant Professor

**Research Interests:** Cancer Pathology

**Punam Malik, MD**, Associate Professor ; *Program Leader; Director of Cores*

**Research Interests:** Molecular and Gene Therapy Program

**Ruhikanta Meetei, PhD**, Assistant Professor

**Research Interests:** Signaling Program

**James Mulloy, PhD**, Research Associate Professor

**Research Interests:** Leukemia Biology Program

**Dao Pan, PhD**, Research Assistant Professor

**Research Interests:** Molecular and Gene Therapy Program

**Qishen Pang, PhD**, Associate Professor

**Research Interests:** Signaling Program

**Nancy Ratner, PhD**, Professor ; *Program Leader; Endowed Chair*

**Research Interests:** Cancer Biology Program

**Lilith Reeves, MS**, Field Service Associate Professor ; *Director*

**Research Interests:** Translational Cores

**Tilat Aziz Rizvi, PhD**, Research Assistant Professor

**Research Interests:** Cancer Biology Program

**Johannes van der Loo, PhD**, Field Service Assistant Professor

**Research Interests:** Vector Production

**Jianqiang Wu, MD**, Research Instructor ; *Cancer Biology*

## Joint Appointment Faculty Members

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**Christopher Baum, MD**, Adjunct Associate Professor

Hanover Medical School

Gene Therapy

**Tim Cripe, MD, PhD**, Associate Professor

Hematology/Oncology

Musculoskeletal Tumor, Translational Research Trials

**Timothy Crombleholme, MD**, Professor

Surgery

Molecular Fetal Therapy

**Stella Davies, MB, BS, PhD, MRCP**, Professor

Hematology/Oncology

Blood and Marrow Transplantation, Leukemia Biology

**Rachid Drissi, PhD**, Research Assistant Professor

Hematology/Oncology

Oncology

**Leighton Grimes, PhD**, Research Associate Professor

Immunobiology  
Cancer Pathology

**Clinton Joiner, MD, PhD**, Professor

Hematology/Oncology  
Sickle Cell

**Theodosia Kalfa, MD, PhD**, Assistant Professor

Hematology/Oncology  
Red Blood Cells and Sickle Cells

**Joe Palumbo, MD**, Research Associate Professor

Hematology/Oncology  
Hematology

**Janos Sumegi, MD, PhD**, Professor

Hematology/Oncology  
Immune Deficiency and Histiocytosis

**Susanne Wells, PhD**, Assistant Professor

Hematology/Oncology  
Cancer Biology

**David Williams, MD**, Adjunct Professor

Children's Hospital Boston  
Stem Cell Biology

## Trainees

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- **Zsuzsanna Adam, PhD**, 2006, University of Debrecen, Hungary
- **Shirin Akhter, PhD**, 2003, University of Windsor, Windsor Canada
- **Abdulla Mahmood Ali, PhD**, 2004, Indian Institute of Science, India
- **Paritha Arumugan, PhD**, University of Madras, Chennai, TamilNadu, India
- **Suchitra Basu, PhD**, 2008, University of Toledo
- **Emily Bosco, PhD**, 2006, University of Cincinnati
- **Fu-Sheng Chou, MD**, 2004, OSU
- **Eric Dickerson**, ,
- **Changhu Du, MD, PhD**, 2004, Guangzhou Institute of Respiratory Disease, Guangzhou Medical School, China
- **Wei Du, MD, PhD**, 2007, Graduate School of Medicine, Tohoku University, Japan
- **Marthe-Sandrine Eiyomo Mwa Mpollo, Msc**, University of Toronto
- **Satyam Eleswarapu, PhD, MS, DVM**, 2009, Blacksburg
- **Qiang Fan, PhD**, 2002, SUNY at Stony Brook
- **Yuxin Feng, PhD**, 2007, BioChain Institute
- **Gabriel Ghiaur**, ,
- **Brittany Goetz**, ,
- **Daniel Gonzalez-Nieto, PhD**, 2003, Hospital Ramon & Cajal, Madrid, Spain
- **Matthew Grogg, PhD**, 2006, University of Dayton
- **Li Guo, PhD**, 2007, Institute of Neuroscience, Chinese Academy of Sciences, Shanghai, China
- **Marnie Hall, PhD**, 2005, University of Cincinnati, College of Medicine
- **Tomoyasu Higashimoto, PhD**, 2006, University of Southern California
- **Adrienne Hontz, PhD**, 2008, The University of Kansas Medical Center
- **Walter Jessen, PhD**, 2004,
- **Gunnar Johanson, MS**, 2002, Umea Universitet, Sweden
- **Edwin Jousma, Msc**, 2003, University of Amsterdam, the Netherlands
- **Nathan Kolasinki**, ,
- **Jie Li, PhD**, Academy of Sciences, China
- **Kevin Link, PhD**, 2007, University of Cincinnati
- **Anuj Mankad, PhD**, 2006, Oregon Health and Science University, Portland, Oregon
- **Filippo Marchioni, PhD**, 2005, University of Bologna
- **Debra Mayes, PhD**, 2006, University of Arkansas for Medical Sciences
- **Jaime Melendez, PhD**, 2001, University of Chile
- **Kyle Mitts, BS**, 2009, Xavier University



- **Richard Morreale, PhD**, 2007, University of California
- **Whitney Nordheim**, ,
- **Deanna Patmore, BS**, 2007, Voorhees College
- **Melissa Rawe**, , University of Cincinnati
- **Amitava Sengupta, PhD**, 2008, Jadavpur University/Saha Institute of Nuclear Physics Kolkata, India
- **Xun Shang, PhD**, 2004, National University of Singapore
- **Thiyam Singh, PhD**, 2003, University of Maryland at Baltimore
- **Nisha Sipes, MS**, 2004, University of Cincinnati
- **Nambirajan Sundaram, PhD**, 2008,
- **Fabrizia Urbinati, PhD**, 2005, University of Modena, Italy
- **Shiv Viswanathan, PhD**, 2003, University of Cincinnati
- **Daren Wang, PhD**, 2004, Akita University Medical School, University of China Medical School, China
- **Junping Wei, MD**, 2004, Hebei Medical University School of Medicine,
- **Jon Williams, BS**, 2001, Muskingum College
- **Yang Mingyan**, ,
- **Zhao Xinghui**, ,

## Significant Accomplishments

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### Overview

Division of Experimental Hematology and Cancer Biology continues the tradition to publish high quality papers and to win grant supports in 2008-2009. The following projects, encompassing multiple programs and disciplines in the division, represent some of the highlights.

### Neurofibromatosis

Neurofibromatosis is a common autosomal dominant inherited disease symptomized by nerve tumors called neurofibromas, whose cellular origin had not been known. A team of researchers led by Dr. Nancy Ratner reported in *Cell Stem Cell* that *Nf1* gene mutation expands a peripheral nerve progenitor, which confers neurofibroma tumorigenic potential. They characterized the normal mouse peripheral nervous system embryonic dorsal root ganglion progenitor populations, and found that they require signaling from the EGFR tyrosine kinase. *Nf1* loss of function amplifies this progenitor pool, which becomes hypersensitive to growth factors and confers tumorigenesis. Mouse neurofibromas, but not normal nerve, contain a progenitor population with similar growth requirements, potential, and marker expression.

Following the mouse model studies, the team identified cells in human neurofibromas cells with progenitor properties.

This study suggests that expansion of an EGFR-expressing early glial progenitor contributes to neurofibroma formation, and provides new insights to therapeutic strategies targeting this tumor initiating cell population.

### Bloom's Syndrome

Mutations in the BLM gene give rise to Bloom's syndrome, a rare genetic disorder characterized by severe growth retardation, immunodeficiency, anemia, and reduced fertility. Importantly, Bloom's patients develop various types of cancers often at a young age. BLM encodes a DNA helicase, that associates with Topo III $\alpha$  and BLAP75/RMI1 to form a large molecular complex. This complex serves to prevent chromosomal aberrations and rearrangements. Dr. Ruhikanta Meetei and colleagues reported in *Genes & Development* the discovery of a new component of this complex called BLAP18/RMI2. This molecule represents a new protein that is important for DNA complex stabilization and checkpoint response, and is required for the maintenance of a stable genome in cells. The identification of this protein playing a critical role in Bloom's syndrome illustrates the intricacies of molecular mechanisms that ensure genomic stability and reveals new mechanism how a destabilized genome may be associated with developmental defects such as growth retardation, immunodeficiency, and infertility, as well as cancer.

## Division Publications

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1. Balcik B, Grassman E, Reeves L. [Database setup for preclinical studies of gene-modified hematopoiesis](#). *Methods Mol Biol.* 2009; 506: 467-76.
2. Geiger H, David S, Nattamai KJ, Jan V. ["Quantification of genomic mutations in murine hematopoietic cells."](#) *Methods Mol Biol.* 2009: 423-36.
3. Mahller YY, Williams JP, Baird WH, Mitton B, Grossheim J, Saeki Y, Cancelas JA, Ratner N, Cripe TP. [Neuroblastoma cell lines contain pluripotent tumor initiating cells that are susceptible to a targeted oncolytic virus](#). *PLoS ONE.* 2009; 4: e4235.
4. Nordling D, Kaiser A, Reeves L. [Release testing of retroviral vectors and gene-modified cells](#). *Methods Mol Biol.* 2009; 506: 265-79.
5. Pan D. [In situ \(in vivo\) gene transfer into murine bone marrow stem cells](#). *Methods Mol Biol.* 2009; 506: 159-69.
6. Schambach A, Swaney WP, van der Loo JC. [Design and production of retro- and lentiviral vectors for gene](#)

- [expression in hematopoietic cells](#) . *Methods Mol Biol.* 2009; 506: 191-205.
7. Schuesler T, Reeves L, Kalle C, Grassman E. [Copy number determination of genetically-modified hematopoietic stem cells](#) . *Methods Mol Biol.* 2009; 506: 281-98.
  8. von Laer D, Baum C, Protzer U. [Antiviral gene therapy](#) . *Handb Exp Pharmacol.* 2009; : 265-97.
  9. Wunderlich M, Mulloy JC. [Model systems for examining effects of leukemia-associated oncogenes in primary human CD34+ cells via retroviral transduction](#) . *Methods Mol Biol.* 2009; 538: 263-85.
  10. Fan Q, Zhang F, Barrett B, Ren K, Andreassen PR. [A role for monoubiquitinated FANCD2 at telomeres in ALT cells](#) . *Nucleic Acids Res.* 2009; 37: 1740-54.
  11. Hermann FG, Martinus H, Egelhofer M, Giroglou T, Tonn T, Roth SD, Zahn R, Schult-Dietrich P, Alexandrov A, Dietrich U, Baum C, von Laer D. [Protein scaffold and expression level determine antiviral activity of membrane-anchored antiviral peptides](#) . *Hum Gene Ther.* 2009; 20: 325-36.
  12. Modlich U, Baum C. [Preventing and exploiting the oncogenic potential of integrating gene vectors](#) . *J Clin Invest.* 2009; 119: 755-8.
  13. Zhang S, Tang Q, Xu F, Xue Y, Zhen Z, Deng Y, Liu M, Chen J, Liu S, Qiu M, Liao Z, Li Z, Luo D, Shi F, Zheng Y, Bi F. [RhoA regulates G1-S progression of gastric cancer cells by modulation of multiple INK4 family tumor suppressors](#) . *Mol Cancer Res.* 2009; 7: 570-80.
  14. Gu Y, Harley IT, Henderson LB, Aronow BJ, Vietor I, Huber LA, Harley JB, Kilpatrick JR, Langefeld CD, Williams AH, Jegga AG, Chen J, Wills-Karp M, Arshad SH, Ewart SL, Thio CL, Flick LM, Filippi MD, Grimes HL, Drumm ML, Cutting GR, Knowles MR, Karp CL. [Identification of IFRD1 as a modifier gene for cystic fibrosis lung disease](#) . *Nature.* 2009; 458: 1039-42.
  15. Andreassen PR, Ren K. [Fanconi anemia proteins, DNA interstrand crosslink repair pathways, and cancer therapy](#) . *Curr Cancer Drug Targets.* 2009; 9: 101-17.
  16. Bhatla D, Gerbing RB, Alonzo TA, Conner H, Ross JA, Meshinchi S, Zhai X, Zamzow T, Mehta PA, Geiger H, Perentesis J, Davies SM. [Cytidine deaminase genotype and toxicity of cytosine arabinoside therapy in children with acute myeloid leukemia](#) . *Br J Haematol.* 2009; 144: 388-94.
  17. Bosco EE, Mulloy JC, Zheng Y. [Rac1 GTPase: a "Rac" of all trades](#) . *Cell Mol Life Sci.* 2009; 66: 370-4.
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  20. Cornils K, Lange C, Schambach A, Brugman MH, Nowak R, Lioznov M, Baum C, Fehse B. [Stem cell marking with promotor-deprived self-inactivating retroviral vectors does not lead to induced clonal imbalance](#) . *Mol Ther.* 2009; 17: 131-43.
  21. Moreno-Carranza B, Gentsch M, Stein S, Schambach A, Santilli G, Rudolf E, Ryser MF, Haria S, Thrasher AJ, Baum C, Brenner S, Grez M. [Transgene optimization significantly improves SIN vector titers, gp91phox expression and reconstitution of superoxide production in X-CGD cells](#) . *Gene Ther.* 2009; 16: 111-8.
  22. Morris LM, Lim FY, Crombleholme TM. [Ex utero intrapartum treatment procedure: a peripartum management strategy in particularly challenging cases](#) . *J Pediatr.* 2009; 154: 126-131 e3.
  23. Morris LM, Lim FY, Livingston JC, Polzin WJ, Crombleholme TM. [High-risk fetal congenital pulmonary airway malformations have a variable response to steroids](#) . *J Pediatr Surg.* 2009; 44: 60-5.
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  26. Flevaris P, Li Z, Zhang G, Zheng Y, Liu J, Du X. [Two distinct roles of mitogen-activated protein kinases in platelets and a novel Rac1-MAPK-dependent integrin outside-in retractile signaling pathway](#) . *Blood.* 2009; 113: 893-901.
  27. Patel N, Gonsalves CS, Yang M, Malik P, Kalra VK. [Placenta growth factor induces 5-lipoxygenase-activating protein to increase leukotriene formation in sickle cell disease](#) . *Blood.* 2009; 113: 1129-38.
  28. Muller LU, Daley GQ, Williams DA. [Upping the ante: recent advances in direct reprogramming](#) . *Mol Ther.* 2009; 17: 947-53.
  29. Davies SM, Wang D, Wang T, Arora M, Ringden O, Anasetti C, Pavletic S, Casper J, Macmillan ML, Sanders J, Wall D, Kernan NA. [Recent decrease in acute graft-versus-host disease in children with leukemia receiving unrelated donor bone marrow transplants](#) . *Biol Blood Marrow Transplant.* 2009; 15: 360-6.
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  31. Wise-Draper TM, Mintz-Cole RA, Morris TA, Simpson DS, Wikenheiser-Brokamp KA, Currier MA, Cripe TP, Grosveld GC, Wells SI. [Overexpression of the cellular DEK protein promotes epithelial transformation in vitro and in](#)

- [vivo](#). *Cancer Res.* 2009; 69: 1792-9.
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  42. Patel N, Gonsalves CS, Malik P, Kalra VK. [Placenta growth factor augments endothelin-1 and endothelin-B receptor expression via hypoxia-inducible factor-1  \$\alpha\$](#) . *Blood.* 2008; 112: 856-65.
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56. Newrzela S, Cornils K, Li Z, Baum C, Brugman MH, Hartmann M, Meyer J, Hartmann S, Hansmann ML, Fehse B, von Laer D. [Resistance of mature T cells to oncogene transformation](#). *Blood*. 2008; 112: 2278-86.
57. Yamada Y, Sanchez-Aguilera A, Brandt EB, McBride M, Al-Moamen NJ, Finkelman FD, Williams DA, Cancelas JA, Rothenberg ME. [FIP1L1/PDGFRalpha synergizes with SCF to induce systemic mastocytosis in a murine model of chronic eosinophilic leukemia/hypereosinophilic syndrome](#). *Blood*. 2008; 112: 2500-7.
58. Zhou Y, Du W, Koretsky T, Bagby GC, Pang Q. [TAT-mediated intracellular delivery of NPM-derived peptide induces apoptosis in leukemic cells and suppresses leukemogenesis in mice](#). *Blood*. 2008; 112: 2474-83.

## Grants, Contracts, and Industry Agreements

### Grant and Contract Awards

### Annual Direct / Project Period Direct

#### ANDREASSEN, P

##### FANCD2 Monoubiquitination in DNA Damage Responses

National Institutes of Health

R01 HL 085587

07/08/08 - 06/30/13

\$225,000 / \$1,125,000

#### BOSCO, E

##### Training Program in Cancer Therapeutics

National Institutes of Health (University of Cincinnati)

T32 CA 117846

02/01/07 - 01/31/10

\$41,796 / \$75,972

#### CANCELAS, J

##### Inhibition of Rac GTPases in the Therapy of Chronic Myelogenous Leukemia

Department of Defense - Army

W81XWH-07-1-0297

04/01/07 - 03/31/10

\$144,315 / \$450,000

##### Rac in p190-BCR/ABL Leukemia

Alex's Lemonade Stand Foundation

07/01/07 - 06/30/09

\$100,000 / \$200,000

##### Rac GTPase Inhibition in Chronic Myelogenous Leukemia

National Institutes of Health

R01 HL 087159

04/06/09 - 02/28/13

\$250,000 / \$1,000,000

#### FILIPPI, M

##### The Role of the Small GTPase RHOA in Hematopoietic Stem Cell Engraftment

American Heart Association - National

SDG0635027N

07/01/06 - 06/30/10

\$59,091 / \$236,364

#### GEIGER, H

##### Genomic Integrity and DNA-Repair Pathways in Aging

Ellison Medical Foundation

07/01/05 - 06/30/09

\$46,296 / \$185,184

##### Pathways to Mutagenesis in Vivo and in Stem Cells

National Institutes of Health (University of Cincinnati)

R01 ES 012695

08/15/06 - 06/30/11

\$2,609 / \$28,207

##### Young Stem Cell Potential in Aged Mice

National Institutes of Health

R21 DK 077762

04/01/08 - 03/31/10

\$150,000 / \$275,000

##### Activated Protein C for Treatment of Radiation Combined Injury

National Institutes of Health (Blood Center of Wisconsin, Inc.)

R21 AI 080557

07/01/08 - 06/30/10

\$40,000 / \$80,000

#### GROGG, M

##### Cdc42GAP in Insulin Signaling in Hepatocytes

National Institutes of Health

F32 DK 082108

09/12/08 - 09/11/11

\$49,646 / \$153,822

#### GUO, F

##### Genetic and Biochemical Evaluation of Rac1 GTPase Signaling Mechanism in Primary Cells

American Heart Association - Ohio

BGIA0765194B

07/01/07 - 06/30/09

\$55,000 / \$110,000

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**LINK, K****Targeting the FLT3 Signaling in MLL-AF9 Leukemia**

Hope Street Kids

07/01/08 - 06/30/10

\$40,000 / \$80,000

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**MALIK, P****Cincinnati Comprehensive Sickle Cell Center - Project 5**

National Institutes of Health

U54 HL 070871

06/15/08 - 03/31/12

\$389,734 / \$1,558,936

**CTSA: Stem Cell Research**

National Institutes of Health (University of Cincinnati)

UL1 RR 026314

04/03/09 - 03/31/14

\$27,012 / \$27,012

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**MAYES, D****NF1 and Ras Activation in Oligodendrocyte Progenitor Cell Development and Myelination**

National Multiple Sclerosis Society

FG 1762A1

07/01/08 - 06/30/11

\$45,976 / \$143,300

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**MEETEI, R****Function and Regulation FANCM in Fanconi Anemia**

National Institutes of Health

R01 HL 084082

05/01/07 - 04/30/12

\$250,000 / \$1,250,000

**Defining the Fanconi Anemia-DNA Repair Pathway by Protein Association Analysis**

Fanconi Anemia Research Foundation

10/01/07 - 09/30/09

\$75,000 / \$150,000

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**MULLOY, J****The Role of CBFb-MYH11 in Acute Myeloid Leukemia**

National Institutes of Health

R01 CA 118319

04/15/06 - 02/28/11

\$257,340 / \$887,500

**Microenvironment and Flt3 Signaling in MLL Leukemia**

Gabrielle's Angel Foundation for Cancer Research

06/01/08 - 05/31/11

\$68,182 / \$204,545

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**PAN, D****Genetic Engineering for Delivering Large Molecules Across the Blood-Brain Barrier**

University of Cincinnati Research Council

07/01/08 - 06/30/09

\$25,000 / \$25,000

**Genetic Modification for BBB-Targeted Protein Delivery**

National Institutes of Health

R01 NS 064330

09/30/08 - 08/31/13

\$218,750 / \$1,093,750

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**PANG, Q****Role of FA Protein Complexes In Hematopoiesis**

National Institutes of Health

R01 HL 076712

07/01/05 - 06/30/09

\$237,045 / \$1,000,000

**Role of Tumor Necrosis Factor in Leukemogenesis**

The Leukemia and Lymphoma Society

1013-09

07/01/08 - 06/30/13

\$103,115 / \$515,575

**Role of NPM in FA Leukemogenesis**

Fanconi Anemia Research Foundation

12/01/08 - 11/30/10

\$40,000 / \$80,000

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**RATNER, N****Mitogenic Activities In Neurofibromatosis**

National Institutes of Health

R01 NS 028840

03/22/06 - 01/31/11

\$280,467 / \$1,416,947

**Schwann Cells In Neurofibromatosis Type 2 (NF2)**

National Institutes of Health

R01 CA 118032

08/13/07 - 05/31/12

\$190,000 / \$950,000

**Cincinnati Center for Neurofibromatosis Research**

National Institutes of Health

P50 NS 057531	09/15/08 - 06/30/13	\$1,013,568 / \$5,278,047
Ratner, Nancy	Core A	297,941
Cripe, Timothy	Core B	100,525
Rizvi, Tilat	Core C	81,073
Perentesis, John	Project 1	304,308
Ratner, Nancy	Project 2	204,721

**Therapeutic Targets for Peripheral Nerve Tumors**

Department of Defense - Army

W81XWH-09-1-0135 03/01/09 - 02/28/11 \$219,843 / \$439,686

**Identification of Drug Targets for NF1**

National Institutes of Health (Dartmouth College)

R21 NS 060940 02/15/09 - 01/31/11 \$10,629 / \$21,258

**REEVES, L**

**FDA-NTP Studies of Insertional Mutagenesis**

National Institutes of Health (Battelle Memorial Institute)

HHSN29120055536 09/05/08 - 08/15/09 \$92,711 / \$132,647

**SENGUPTA, A**

**Rac GTPases and BMI-1 CML Stem Cell Niche**

Lady Tata Memorial Trust

10/01/08 - 09/30/09 \$45,717 / \$45,717

**WEI, J**

**A Novel Model of Poor Prognosis Infant Leukemia Using Primary Human Blood Stem Cells**

American Society of Hematology

07/01/07 - 12/31/08 \$50,000 / \$100,000

**ZHENG, Y**

**Cell Type and Stimulus-Specific Role of Cdc42 in Blood**

National Institutes of Health

R01 HL 085362 07/01/06 - 05/31/11 \$242,750 / \$1,221,000

**Rac of GTPases as Targets in Lymphomagenesis**

National Institutes of Health

R01 CA 125658 02/10/07 - 01/31/12 \$190,000 / \$950,000

**Training Program in Pediatric Hematologic and Oncologic Diseases**

National Institutes of Health

T32 HL 091805 09/01/08 - 08/31/13 \$151,392 / \$779,736

**Rac GTPase-Specific Small Molecule Inhibitors**

National Institutes of Health

R01 CA 141341 03/24/09 - 01/31/14 \$169,934 / \$817,982

**Rac GTPases in the Mammalian Brain Development**

National Institutes of Health

R01 NS 056435 07/01/08 - 06/30/12 \$80,000 / \$400,000

**Current Year Direct 6,332,861**

**Current Year Direct Receipts 0**

**Service Collaborations**

**Malik, P**

Proj J1 \$ 54,373

Proj NX AAV \$ 225,793

GOSH \$ 62,630

Necker \$ 66,588

Nationwide \$ 138,839

GeneDx \$ 2,723

Hoxworth (QC, CAP, CFU, CD, QC) \$ 24,309

OSU (CD, VVC)	\$ 23,959
GRI	\$ 9,578
Shriners	\$ 1,108
Harvard	\$ 1,278
Errant Gene Therapies	\$ 4,173
DanaFarber Institute	\$ 3,244
IUPUI	\$ 6,329
Biostart (proj APL)	\$ 10,000
Neogeomics	\$ 3,865
Domestic and Foreign	\$ 9,189
UC	\$ 5,505
Domestic (VVC)	\$ 1,460

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<b>Current Year Direct</b>	<b>654,943</b>
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## **Funded Collaborative Efforts**

### **Ratner, N**

#### **Cincinnati NF1 Preclinical Testing Center**

The Children's Tumor Foundation

Cripe, Timothy	06/01/09 - 05/31/11	10 %
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### **Cancelas, J**

#### **Transcriptional Control of Respiratory Epithelial Progenitor Cells**

National Institutes of Health

Whitsett, Jeffery	08/28/07 - 06/30/11	10 %
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### **Pan, D**

#### **Cincinnati Comprehensive Sickle Cell Center**

National Institutes of Health

Joiner, Clinton	06/15/08 - 03/31/12	15 %
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<b>Total</b>	<b>6,332,861</b>
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