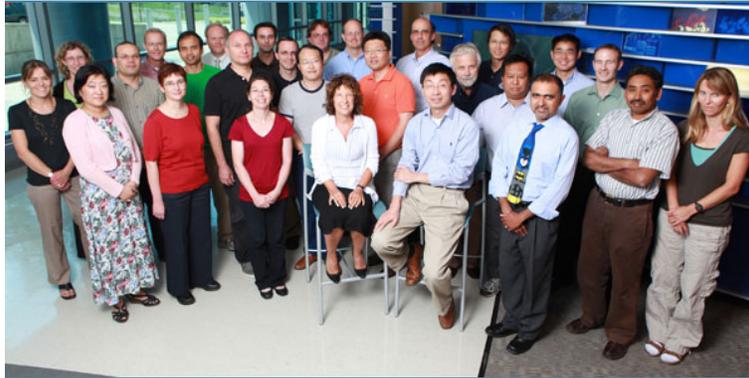


Division Photo



First Row: M. Filippi, N. Ratner, Y. Zheng, A. Kumar; Second Row: D. Pan, T. Kalfa, L. Grimes, F. Guo, G. Huang, J. Sumegi, R. Meetei, J. Mulloy, M. Azam, S. Wells; Third Row: E. Grassman, R. Drissi, B. DasGupta, R. Waclaw, M. Flick, J. Degen, L. Chow, B. Mizukawa; Fourth Row: C. Lutzko, H. vanderLoo, T. Cripe, D. Starczykowski, P. Andreassen

Division Data Summary

Research and Training Details

Number of Faculty	15
Number of Joint Appointment Faculty	15
Number of Research Fellows	29
Number of Research Students	22
Number of Support Personnel	53
Direct Annual Grant Support	\$7,912,394
Peer Reviewed Publications	66

Significant Publications

James C. Mulloy, Jose A. Cancelas, Marie-Dominique Filippi, Theodosia A. Kalfa, Fukun Guo, and Yi Zheng. (2010) Rho GTPases in hematopoiesis and hemopathies. Blood 115:936-47

This review is a timely summary of an important and fast progressing field and also is an objective review of a major research area in EHCBS over the past decade. Rho family GTPases are intracellular signaling proteins regulating multiple pathways involved in cell actomyosin organization, adhesion and proliferation. Our knowledge of their cellular functions came mostly from previous biochemical studies using mutant overexpression approaches in various clonal cell lines. Recent progress in understanding Rho GTPase functions in blood cell development and regulation by gene targeting of individual Rho GTPases in mice has allowed a genetic understanding of their physiologic roles in hematopoietic progenitors and mature lineages. In particular, mouse gene targeting studies have provided convincing evidence that individual members of the Rho GTPase family are essential regulators of cell type-specific functions and stimuli-specific pathways in regulating hematopoietic stem cell interaction with bone marrow niche, erythropoiesis and red blood cell actin dynamics, phagocyte migration and killing, and T- and B-cell maturation. In addition, deregulation of Rho GTPase family members has been associated with multiple human hematologic diseases such as neutrophil dysfunction, leukemia, and Fanconi anemia, raising the possibility that Rho GTPases and downstream signaling pathways are of therapeutic value. In this review, recent genetic studies of Rho GTPases in hematopoiesis and several blood lineages and the implications of Rho GTPase signaling in hematologic

malignancies, immune pathology and anemia, were discussed in-depth.

Wang D, Zhang W, Kalfa TA, Grabowski G, Davies S, Malik P, Pan D. (2009) Reprogramming erythroid cells for lysosomal enzyme production leads to visceral and CNS cross-correction in mice with Hurler syndrome. Proc Natl Acad Sci U S A. 106(47):19958-63. PMID: 19903883 [PubMed - indexed for MEDLINE]

Restricting transgene expression to maturing erythroid cells can reduce the risk for activating oncogenes in hematopoietic stem cells (HSCs) and their progeny, yet take advantage of their robust protein synthesis machinery for high-level protein production. This study sought to evaluate the feasibility and efficacy of reprogramming erythroid cells for production of a lysosomal enzyme, alpha-L-iduronidase (IDUA). An erythroid-specific hybrid promoter provided inducible IDUA expression and release during in vitro erythroid differentiation in murine erythroleukemia cells, resulting in phenotypical cross-correction in an enzyme-deficient lymphoblastoid cell line derived from patients with mucopolysaccharidosis type I (MPS I). Stable and higher than normal plasma IDUA levels were achieved in vivo in primary and secondary MPS I chimeras for at least 9 months after transplantation of HSCs transduced with the erythroid-specific IDUA-containing lentiviral vector (LV). Moreover, long-term metabolic correction was demonstrated by normalized urinary glycosaminoglycan accumulation in all treated MPS I mice. Complete normalization of tissue pathology was observed in heart, liver, and spleen. Notably, neurological function and brain pathology were significantly improved in MPS I mice by erythroid-derived, higher than normal peripheral IDUA protein. These data demonstrate that late-stage erythroid cells, transduced with a tissue-specific LV, can deliver a lysosomal enzyme continuously at supraphysiological levels to the bloodstream and can correct the disease phenotype in both viscera and CNS of MPS I mice. This approach provides a paradigm for the utilization of RBC precursors as a depot for efficient and potentially safer systemic delivery of nonsecreted proteins by ex vivo HSC gene transfer.

Singh TR, Saro D, Ali AM, Zheng XF, Du CH, Killen MW, Sachpatzidis A, Wahengbam K, Pierce AJ, Xiong Y, Sung P, Meetei AR. (2010) MHF1-MHF2, a histone-fold-containing protein complex, participates in the Fanconi anemia pathway via FANCM. Mol Cell. 37(6):879-86. PMID: 20347429

FANCM is a Fanconi anemia nuclear core complex protein required for the functional integrity of the FANCD2-BRCA1 pathway of DNA damage response and repair. Here we report the isolation and characterization of two histone-fold-containing FANCM-associated proteins, MHF1 and MHF2. We show that suppression of MHF1 expression results in (1) destabilization of FANCM and MHF2, (2) impairment of DNA damage-induced monoubiquitination and foci formation of FANCD2, (3) defective chromatin localization of FA nuclear core complex proteins, (4) elevated MMC-induced chromosome aberrations, and (5) sensitivity to MMC and camptothecin. We also provide biochemical evidence that MHF1 and MHF2 assemble into a heterodimer that binds DNA and enhances the DNA branch migration activity of FANCM. These findings reveal critical roles of the MHF1-MHF2 dimer in DNA damage repair and genome maintenance through FANCM.

Li J, Du W, Maynard S, Andreassen PR, Pang Q. (2010) Oxidative stress-specific interaction between FANCD2 and FOXO3a. Blood. 2010 Feb 25;115(8):1545-8

The molecular pathway by which Fanconi anemia (FA) proteins function in oxidative stress response has not been defined. Here we report the functional interaction of the FA protein Fanconi anemia complementation group D2 (FANCD2) and the forkhead transcription factor forkhead box O 3a (FOXO3a). FOXO3a colocalized with FANCD2 foci in response to oxidative stress. The FANCD2-FOXO3a complex was not detected in cells deficient for the FA core complex component FANCA but could be restored in corrected cells. Consistent with this, a nonmonoubiquitinated FANCD2 mutant failed to bind FOXO3a. Although both mitomycin C and ionizing radiation induced FANCD2 monoubiquitination, neither could induce the association of FANCD2 and FOXO3a. Overexpression of FOXO3a reduced abnormal accumulation of reactive oxygen species, enhanced cellular resistance to oxidative stress, and increased antioxidant gene expression in corrected but not mutant FA-D2 cells. The novel oxidative stress response pathway identified in this study, in which FANCD2 and FOXO3a converge, probably contributes to cellular antioxidant defense.

Xu H, Eleswarapu S, Geiger H, Szczur K, Daria D, Zheng Y, Settleman J, Srour EF, Williams DA, Filippi MD. (2009) Loss of the Rho GTPase activating protein p190-B enhances hematopoietic stem cell engraftment potential. Blood. 114(17):3557-66. Epub 2009 Aug 27. PMID: 19713466

Hematopoietic stem cell (HSC) engraftment is a multistep process involving HSC homing to bone marrow, self-renewal, proliferation, and differentiation to mature blood cells. Here, we show that loss of p190-B RhoGTPase activating protein, a negative regulator of Rho GTPases, results in enhanced long-term engraftment during serial transplantation. This effect is associated with maintenance of functional HSC-enriched cells. Furthermore, loss of p190-B led to marked improvement of HSC in vivo repopulation capacity during ex vivo culture without altering proliferation and multilineage differentiation of HSC and progeny. Transcriptional analysis revealed that p190-B deficiency represses the up-regulation of p16(Ink4a) in HSCs in primary and secondary transplantation recipients, providing a possible mechanism of p190-B-mediated HSC functions. Our study defines p190-B as a critical transducer element of HSC self-renewal activity and long-term engraftment, thus suggesting that p190-B is a target

for HSC-based therapies requiring maintenance of engraftment phenotype.

Division Highlights

Yi Zheng, PhD

The Zheng lab reported a novel discovery that genetic or pharmacological targeting of Rac1, a member of the Rho family small GTPases, is beneficial in suppressing loss of contact inhibition initiated by *Nf2*-deficiency and lymphomagenesis induced by the loss of p53 in the journals *Oncogene* and *Blood*, respectively.

Paul Andreassen, PhD

The Andreassen group published a collaborative paper with Jun-ichi Nakayama's lab in Kobe, Japan [T. Hayakawa et al. (2010) *Journal of Cell Science* 123:1124-1130] that found a novel connection between a Fanconi anemia protein involved in DNA repair and a protein that plays a critical role in chromatin remodeling.

Jose Cancelas, MD, PhD

Analysis of Rac GTPase activation in hematopoietic stem cell malignancies such as CML. Rac2 GTPase deficiency depletes BCR-ABL+ leukemic stem cells and progenitors in vivo. Sengupta A, Arnett J, Dunn S, Williams DA, Cancelas JA. *Blood*. 2010 Jul 8;116(1):81-4. PMID: 20407032

Marie-Dominique Filippi, PhD

The Filippi lab has reported two important findings in the journal *Blood* that the Rho GTPase negative regulator, p190B-RhoGAP, is a key regulator of hematopoietic stem cell self-renewal, and the Rho GTPase, Cdc42, controls neutrophil polarity during chemotaxis.

Hartmut Geiger, PhD

The Geiger lab published this year, among others, a manuscript describing phenotypes of aged hematopoietic stem cells in vivo, demonstrating the "hyperactivity" in terms changes in the cellular volume over time. The publication is also the first one to demonstrate 2-photon live stem cell imaging in long-bones of mice. The article in *Blood* was accompanied by a news and views description in the journal.

Fukun Guo, PhD

Guo lab has made significant stride in defining the role of Rho GTPases, particularly Cdc42, in B-cell development. (Guo F, et al. *Blood*, 2009, 114(14): 2909)

Ashish Kumar, MD, PhD

The Kumar lab has investigated the role of MEIS1 in MLL-fusion leukemia. Meis1 maintains 'stemness' in MLL-AF9 leukemia (*Blood* 2010)

Punam Malik, MD

The Malik lab has made several progresses on molecular gene therapy of sickle cell disease, including:

- a) A novel human gamma-globin gene lentivirus vector that results in genetic correction of sickle cell anemia in a humanized sickle mouse model and the critical determinants necessary for successful genetic correction.
- b) The genotoxic potential of lineage-specific lentivirus vectors carrying the beta globin locus control region as preclinical safety studies for gene therapy trial.
- c) The mechanism of reduction of lentiviral vector titers by insertion of the chicken hypersensitive site-4 insulator element and discovered that its 3' end has properties similar to the 5 insulator core, and is necessary in conjunction with the core for full insulator activity.
- d) Placenta Growth Factor, an angiogenic factor released from erythroid cells, results in induction of plasminogen activator inhibitor -1, five lipoxygenase and five lipoxygenase activator protein, and endothelin-1.

Ruhikanta Meetei, PhD

The Meetei lab published an important paper by Singh TR et al, "*MHF1-MHF2, a Histone-Fold-Containing Protein Complex, Participates in the Fanconi Anemia Pathway via FANCM*", in *Mol Cell*. 2010 Mar 26;37(6):879-86 {Highlighted in *Mol Cell*. 2010 Mar 26;37(6):749-51}. They report the isolation and characterization of two histone-fold-containing FANCM-associated proteins, MHF1 and MHF2. They also provide biochemical evidence that MHF1 and MHF2 assemble into a heterodimer that binds DNA and enhances the DNA branch migration activity of FANCM. These findings reveal critical roles of the MHF1-MHF2 dimer in DNA damage repair and genome maintenance through FANCM.

James Mulloy, PhD

This year the Mulloy lab has focused on optimizing an AML xenograft model for use in chemotherapy studies in an effort to establish a system for testing experimental compounds for efficacy against human leukemia. His lab has developed a "next generation" mouse that is superior for expansion of human leukemia samples. This manuscript has just been published online in the journal *Leukemia*. In other work, the lab continues to analyze the role of Rho proteins in acute leukemia. From preliminary data, it appears that different Rho family members play unique roles in cytogenetically distinct types of AML. These studies are proceeding with the use of murine genetic models in collaboration with Dr. Zheng as well as with human leukemia samples. The lab also continues its focus on Core Binding Factor leukemia and was involved in a paper published in *Cancer Cell* that showed the CBFb-MYH11 leukemia fusion oncoprotein has unexpected functions independent of the supposed "obligate" transcription factor partner Runx1. These studies highlight the need for a better understanding of the mechanism of action of these leukemia oncogenes to assist in identifying novel molecules

for therapeutic targeting.

Dao Pan, PhD

Pan lab's recent studies have demonstrated that late-stage erythroid cells, transduced with a tissue-specific LV, can deliver a lysosomal enzyme continuously at supraphysiological levels to the bloodstream, correct the disease phenotype in viscera organs, and can significantly improve neurological function and brain pathology (but not cure) in MPS I mice. *This work has been published on the journal Proceedings of National Academy of Sciences, and highlighted on Jan. 2010 issue of Journal of Molecular Therapy.*

Qishen Pang, PhD

Role of nucleophosmin (NPM) in FA leukemia evolution – We recently demonstrated a novel function of NPM on regulation of cell cycle progression, in which phosphorylation of NPM controls cell cycle progression at G(2)/M transition through modulation of Cdk1 and Cdc25C activities. A manuscript based on this work was published in *Carcinogenesis*.

Functional interaction between Fanconi anemia (FA) and FOXO pathways in oxidative stress responses – We showed that the FA protein FANCD2 functionally interacted with FOXO3a, which contributes to cellular antioxidant defense. We published the study in *Blood*.

Nancy Ratner, PhD

To understand biological pathways critical for common neurofibromatosis type 1 (NF1) peripheral nerve tumours an international consortium based at CCHMC used gene expression profiling. Ratner lab validated differential expression of 82 genes including the neural crest transcription factor SOX9 and its predicted targets. SOX9 expression was robust in NF and MPNST tissue sections and targeting SOX9 caused MPNST cell death. SOX9 is a biomarker of NF and MPNST, and possibly a therapeutic target in NF1.

Miller, S.J., et al. Integrative genomic analyses of neurofibromatosis tumors identify SOX9 as biomarker and survival gene (2009) *EMBO Mol. Medicine*, 1(4):236-248.

Malignant peripheral nerve sheath tumors (MPNSTs) are aggressive sarcomas without effective therapeutics. The Ratner lab used bioinformatics and identified Paired Box (PAX), Eyes Absent (EYA), Dachshund (DACH) and Six Oculis (SIX) genes, which form a regulatory interactive network in *Drosophila*, as dysregulated in human MPNST cell lines and solid tumors. Suppression of EYA4 expression caused cellular necrosis. MPNST cells expressing shEYA4 formed tiny tumors with extensive necrosis, suggesting the EYA4 pathway as a rational therapeutic target.

Miller, S.J., et al. (2009) Inhibition of Eyes Absent Homolog 4 expression induces malignant peripheral nerve sheath tumor necrosis, *Oncogene*, 29(3):368-79. PMID: PMC2809821

Jianqiang Wu, MD

Molecular mechanism of neurofibroma formation in Neurofibromatosis type 1 (NF1): Modifiers of neurofibroma number and size implicate STAT3 signaling in NF1 peripheral nerve tumorigenesis.

Division Collaboration

Collaboration with Pathology

Collaborating Faculty: Margaret Collins

Miller, S.J., et al., *Inhibition of Eyes Absent Homolog 4 expression induces malignant peripheral nerve sheath tumor necrosis*. *Oncogene*, 2010. 29(3): p. 368-79.

Collaboration with Pulmonary

Collaborating Faculty: Tim LeCras

Tim LeCras supports the Geiger Lab in better understanding the role of EGFR signaling in hematopoiesis.

Collaboration with Genetics

Collaborating Faculty: Anil Mennon

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

Collaboration with UC, Genetics

Collaborating Faculty: Peter Stambrook

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

Collaboration with Hematology/Oncology

Collaborating Faculty: Tim Cripe

Miller, S.J., et al., *Inhibition of Eyes Absent Homolog 4 expression induces malignant peripheral nerve sheath tumor necrosis*. *Oncogene*, 2010. 29(3): p. 368-79.

Collaboration with Immunobiology

Collaborating Faculty: Lee Grimes

Guo F, Velu CS, Grimes HL, and Zheng, Y. (2009) Rho GTPase Cdc42 is essential for B lymphocyte development and activation. *Blood* 114(14):2909-16.

Collaboration with Pulmonary

Collaborating Faculty: William Hardie; Matthew Ednick

The nature of the collaborations is to study the cardio-pulmonary-renal pathophysiology in sickle cell disease, develop genetic therapies for sickle cell disease and lung disorders, such as pulmonary alveolar proteinosis, and establish a comprehensive cell characterization core facility.

Collaboration with Cardiology

Collaborating Faculty: Jeff Towbin; Bill Gottliebson

The nature of the collaborations is to study the cardio-pulmonary-renal pathophysiology in sickle cell disease, develop genetic therapies for sickle cell disease and lung disorders, such as pulmonary alveolar proteinosis, and establish a comprehensive cell characterization core facility.

Collaboration with Nephrology

Collaborating Faculty: Prasad Devarajan

The nature of the collaborations is to study the cardio-pulmonary-renal pathophysiology in sickle cell disease, develop genetic therapies for sickle cell disease and lung disorders, such as pulmonary alveolar proteinosis, and establish a comprehensive cell characterization core facility.

Collaboration with Immunobiology

Collaborating Faculty: Marsha Wills-Karp; Lee Grimes

The nature of the collaborations is to study the cardio-pulmonary-renal pathophysiology in sickle cell disease, develop genetic therapies for sickle cell disease and lung disorders, such as pulmonary alveolar proteinosis, and establish a comprehensive cell characterization core facility.

Collaboration with Radiology

Collaborating Faculty: Robert Fleck; Janak Wansapura

The nature of the collaborations is to study the cardio-pulmonary-renal pathophysiology in sickle cell disease, develop genetic therapies for sickle cell disease and lung disorders, such as pulmonary alveolar proteinosis, and establish a comprehensive cell characterization core facility.

Collaboration with Developmental Biology

Collaborating Faculty: James Wells; Steve Potter

The nature of the collaborations is to study the cardio-pulmonary-renal pathophysiology in sickle cell disease, develop genetic therapies for sickle cell disease and lung disorders, such as pulmonary alveolar proteinosis, and establish a comprehensive cell characterization core facility.

Collaboration with Bioinformatics

Collaborating Faculty: Bruce Aronow; Anil Jegga

The nature of the collaborations is to study the cardio-pulmonary-renal pathophysiology in sickle cell disease, develop genetic therapies for sickle cell disease and lung disorders, such as pulmonary alveolar proteinosis, and establish a comprehensive cell characterization core facility.

Collaboration with Pulmonary and Neonatology

Collaborating Faculty: Bruce Trapnell; Jeff Whitsett

The nature of the collaborations is to study the cardio-pulmonary-renal pathophysiology in sickle cell disease, develop genetic therapies for sickle cell disease and lung disorders, such as pulmonary alveolar proteinosis, and establish a comprehensive cell characterization core facility.

Collaboration with Human Genetics

Collaborating Faculty: Greg Grabowski; William Nichols

The nature of the collaborations is to study the cardio-pulmonary-renal pathophysiology in sickle cell disease, develop genetic therapies for sickle cell disease and lung disorders, such as pulmonary alveolar proteinosis, and establish a comprehensive cell characterization core facility.

Collaboration with UC - Hematology/Oncology

Collaborating Faculty: George Atweh

The nature of the collaborations is to study the cardio-pulmonary-renal pathophysiology in sickle cell disease, develop genetic therapies for sickle cell disease and lung disorders, such as pulmonary alveolar proteinosis, and establish a comprehensive cell characterization core facility.

Collaboration with UC - School of Engineering

Collaborating Faculty: Rupak Banerjee

The nature of the collaborations is to study the cardio-pulmonary-renal pathophysiology in sickle cell disease, develop genetic therapies for sickle cell disease and lung disorders, such as pulmonary alveolar proteinosis, and establish a comprehensive cell characterization core facility.

Collaboration with UC - Cardiology

Collaborating Faculty: Mohammed Ashraf

The nature of the collaborations is to study the cardio-pulmonary-renal pathophysiology in sickle cell disease, develop genetic therapies for sickle cell disease and lung disorders, such as pulmonary alveolar proteinosis, and establish a comprehensive cell characterization core facility.

Collaboration with Immunobiology

Collaborating Faculty: Lee Grimes

Mouse modeling of human T-ALL

Collaboration with Molecular Immunology

Collaborating Faculty: Claire Chougnet; 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 Department of Radiology

Collaborating Faculty: Diana Lindquist

Manuscript

Collaboration with Division of Rheumatology

Collaborating Faculty: Alexi Grom; Michael Barnes

Gene expression profiling of patients with hemophagocytic lymphohistiocytosis a collaborative work

Collaboration with Division of Allergy and Immunology

Collaborating Faculty: Marc Rothenberg

Manuscript

Collaboration with Division of Developmental Biology

Collaborating Faculty: James Wells

Manuscript

Collaboration with Division of Hepatology and Nutrition

Collaborating Faculty: Noah Shroyer

Manuscript

Collaboration with Division of Otolaryngology

Collaborating Faculty: Dr. Wilson; Dr. Patil; Dr. Casper

IRB protocol ID 2008-1331. HPV infection and associated malignancies in Fanconi Anemia patients. PI: Susanne Wells.

Collaboration with Division of Biomedical Informatics

Collaborating Faculty: Bruce Aronow

Morreale, R. J., Kahn, J. A., Butsch Kovacic, M., Hegde, R. S., Aronow, B. J., and **Wells, S. I.** 2009. Insights from the transcriptional profiling of human papillomavirus infection and associated carcinogenesis. In: Yoshida K (ed). Molecular Biology of DNA Tumor Virus Gene Products: Research Signpost, 169-196.

Collaboration with Hematology/Oncology

Collaborating Faculty: Timothy Cripe

P50 grant (Ratner, PI, Cripe Core director), Children's Tumor Foundation (Cripe PI, Ratner Co-investigator)

Collaboration with Hematology/Oncology

Collaborating Faculty: John Perentesis

P50 grant (Ratner PI, Perentesis co-investigator)

Collaboration with Biomedical Informatics

Collaborating Faculty: Bruce Aronow

Bruce Aronow DOD Program on Neurofibromatosis (Ratner, PI, Aronow Co-investigator)

Collaboration with Human Genetics

Collaborating Faculty: Elizabeth Schorry

Collaborator

Collaboration with Pathology

Collaborating Faculty: Margaret Collins

P50 grant (Ratner, PI, Collins Core-co-director)

Collaboration with Developmental Biology

Collaborating Faculty: Rashmi Hedge

Collaborator

Collaboration with Allergy/Immunology

Collaborating Faculty: Marc Rothenberg

FIP1L1/PDGFRa in chronic eosinophilic leukemia and mastocytosis

Examples:

1. FIP1L1/PDGFR alpha-associated systemic mastocytosis. Yamada Y, Cancelas JA. Int Arch Allergy Immunol. 2010;152 Suppl 1:101-5. Epub 2010 Jun 4.

2. Murine model of hypereosinophilic syndromes/chronic eosinophilic leukemia. Yamada Y, Cancelas JA, Rothenberg ME. Int Arch Allergy Immunol. 2009;149 Suppl 1:102-7. Epub 2009 Jun 3.

Collaboration with Hematology/Oncology

Collaborating Faculty: Timothy Cripe

Signaling in neural cancer

1. Inhibition of Eyes Absent Homolog 4 expression induces malignant peripheral nerve sheath tumor necrosis. Miller SJ, Lan ZD, Hardiman A, Wu J, Kordich JJ, Patmore DM, Hegde RS, Cripe TP, Cancelas JA, Collins MH, Ratner N. *Oncogene*. 2010 Jan 21;29(3):368-79. Epub 2009 Nov 9. PMID: 19901965.

2. Neuroblastoma cell lines contain pluripotent tumor initiating cells that are susceptible to a targeted oncolytic virus. Mahller YY, Williams JP, Baird WH, Mitton B, Grossheim J, Saeki Y, Cancelas JA, Ratner N, Cripe TP. *PLoS One*. 2009;4(1):e4235

Collaboration with Hematology/Oncology

Collaborating Faculty: Clint Joiner

Sickle Cell Center Grants

Collaboration with UC

Collaborating Faculty: Robert Franco

Sickle Cell Center Grants

Collaboration with Division of Developmental Biology

Collaborating Faculty: Charles Vorhees; M. Williams

Behavioral Evaluation

Collaboration with Hematology/Oncology

Collaborating Faculty: Stella Davies

Expertise on BMT for lysosomal storage diseases

Collaboration with Division of Developmental Biology

Collaborating Faculty: Alex Kuan

Expertise/work on lentiviral vector construction and LV-mediated gene transfer into isolated neuronal cells; and for his expertise on immunohistochemistry analysis in CNS

Collaboration with Human Genetics

Collaborating Faculty: Greg Grabowski

Collaborate on CNS abnormality in murine MPS models, as well as Gauche disease model

Collaboration with UC

Collaborating Faculty: David Hui

Expertise on LDL receptor superfamily and apoE metabolism

Collaboration with Hematology/Oncology

Collaborating Faculty: Theodosia Kalfa

Project on RAC GTPase regulation during erythropoiesis by providing RT-qPCR assay for RAC1/2/3 for FACS sorted cells.

Collaboration with UC

Collaborating Faculty: Zhenyu Qin

Local grants and NIH R03 submission by providing assistant on lentiviral vector gene transfer in vascular cells.

Collaboration with Division of Rheumatology

Collaborating Faculty: Marsha Wills-Karp

Participate in a shared instrument grant application (MoFloXDP Sorter)

Faculty Members

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

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

- **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

Fanconi anemia

Our faculty research led to several important findings encompassing new mechanisms underlying bone marrow failure syndrome, novel approach of stem cell-based therapy, and gene therapy combating sickle cell disease. Fanconi anemia (FA) is characterized by progressive bone marrow failure, developmental defects, chromosomal abnormalities, and cellular hypersensitivity to DNA interstrand crosslink agents. FA genes and associated proteins function to resolve blocked and broken DNA replication forks. In a study published in *Molecular Cell*, a team led by Ruhikanta Meetei, PhD, identified a FANCM-associated histone-fold MHF heterodimer that promotes the remodeling of artificial replication forks and confers cellular resistance to DNA crosslinking. The discovery implicates this novel molecular complex in coordinating DNA damage response in cells.

Hurler syndrome

Another study led by Dao Pan, PhD, published in the *Proceedings of National Academy of Sciences*, reported how developing red blood cells could be used to produce lysosomal enzymes to prevent or reduced organ and central nervous system damage from the often-fatal genetic disorder Hurler syndrome. Collaborators on this study included Theodosia Kalfa, MD, PhD; bone marrow transplant director Stella Davies, MBBS, PhD, MRCP; human genetics director Greg Grabowski, MD; and Punam Malik, MD, deputy director of the comprehensive sickle cell program. The study reports that lysosomes in the cells of children with Hurler syndrome do not have a vital enzyme called IDUA, which causes their cells to accumulate too many mucopolysaccharides and leads to progressive tissue damage. In theory, a single gene insertion using a benign viral vector to prompt the cells to produce the IDUA enzyme could cure this condition. In mice receiving this treatment, the pathology of peripheral organs was completely normalized while neurological function and brain pathology were significantly improved. In addition to Hurler syndrome, this study of stem cell-based therapy has implications for treating other lysosomal storage diseases

Sickle cell disease

Studies on sickle cell disease pathophysiology have revealed that placenta growth factor (PlGF) induces hypoxia independent upregulation of HIF-1, a transcriptional factor from pulmonary endothelial cells and lipoxygenase and lipoxygenase activating proteins. A study led by Punam Malik, MD, and published in *Blood*, has shown that the hyperplastic erythroid cells in sickle cell disease produced elevated PlGF, which in turn promotes inflammation and airway hyper-reactivity seen in patients with sickle cell disease. Another study, in mice, has found that transferring the gamma globin gene into sickle hematopoietic stem cells using an erythroid-specific, self-inactivating lentivirus vector results in complete correction of sickle cell disease. These findings have led to a Phase I clinical trial protocol that was recently approved by the Recombinant Advisory Committee at the NIH.

Division Publications

1. :

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

FANCD2 Monoubiquitination in DNA Damage Responses

National Institutes of Health

R01 HL 085587

07/01/09 - 06/30/11

\$155,389 / \$155,389

Azam, M

Molecular and Therapeutic Analysis of Human Leukemia using Human Induced Pluripotent Stem Cells

The V Foundation

12/01/09 - 11/30/11

\$100,000 / \$200,000

Cancelas-Perez, J**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

Rac GTPase Inhibition in Chronic Myelogenous Leukemia

National Institutes of Health

R01 HL 087159 08/01/09 - 07/31/11 \$140,217 / \$140,217

Vav as a Molecular Target in Pediatric p190-BCR-ABL Acute Lymphoblastic Leukemia

Cancer Free Kids

05/01/10 - 04/30/11 \$20,000 / \$20,000

Chou, F-S**A Preclinical Trial of Targeting the Self-Renewal Pathway to Eradicate Leukemic Stem Cells**

Cancer Free Kids

05/01/10 - 04/30/11 \$40,000 / \$40,000

Feng, Y**Training Program in Cancer Therapeutics**

University of Cincinnati (National Institutes of Health)

T32 CA 117846 01/01/10 - 08/31/10 \$28,936 / \$28,936

Filippi, M-D**The Role of the Small GTPase RhoA in Hematopoietic Stem Cell Engraftment**

American Heart Association

07/01/06 - 06/30/10 \$59,091 / \$236,364

Regulation of Neutrophil Migration and Polarity

National Institutes of Health

R01 HL 090676 03/01/10 - 02/28/15 \$250,000 / \$1,250,000

Geiger, H**Pathways to Mutagenesis in Vivo and in Stem Cells**

University of Cincinnati (National Institutes of Health)

R01 ES 012695 08/15/06 - 06/30/11 \$2,609 / \$21,777

Activated Protein C for Treatment of Radiation Combined Injury

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

R21 AI 080557 07/08/08 - 06/30/10 \$30,000 / \$70,000

Gonzalez-Nieto, D**Connexin-43 in the Hematopoietic Stem Cell Niche**

National Blood Foundation

07/01/09 - 06/30/11 \$37,500 / \$75,000

Grogg, M**CDC42GAP in Insulin Signaling in Hepatocytes**

National Institutes of Health

F32 DK 082108 09/12/08 - 09/11/11 \$51,710 / \$155,166

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

Hope Street Kids

07/01/08 - 06/30/10 \$40,000 / \$80,000

Discovery Of Novel Therapeutic Targets For The Treatment of Pediatric Leukemia

Cancer Free Kids

09/1/09 - 08/31/10 \$20,000 / \$20,000

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

National Institutes of Health

U54 HL 070871	06/15/08 - 03/31/12	\$371,040 / \$1,558,936
Cincinnati Center for Clinical and Translational Sciences and Training - Stem Cell Research		
University of Cincinnati (National Institutes of Health)		
UL1 RR 026314	04/03/09 - 03/31/14	\$42,284 / \$69,296

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

National Multiple Sclerosis Society

07/01/08 - 06/30/11

\$47,771 / \$143,300

Meetei, R**Function and Regulation of FANCM in Fanconi Anemia**

National Institutes of Health

R01 HL 084082

05/01/07 - 04/30/12

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

Function and Regulation of FANCM in Fanconi Anemia

National Institutes of Health

R01 HL 084082

07/01/09 - 06/30/11

\$159,256 / \$159,256

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

National Institutes of Health

R01CA118319

04/15/06 - 02/28/11

\$174,976 / \$1,049,888

Microenvironment and Flt3 Signaling in MLL leukemia

Gabrielle's Angel Foundation for Cancer Research

06/01/08 - 05/31/11

\$68,182 / \$204,546

Next Generation DNMT-1 Depletion Therapy for Leukemia

Cleveland Clin Lerner Col of Med of CWRU (Department of Defense Army)

W81XWH-09-1-0671

09/01/09 - 08/31/13

\$133,964 / \$535,856

The Role of MLL-AF9 in Acute Myeloid Leukemia

National Institutes of Health

R01 CA 140518

07/17/09 - 06/30/11

\$247,264 / \$494,529

Pan, D**Genetic Therapy for CNS Manifestations in MPS I via BBB-targeted Protein Delivery (Supplement)**

National Institutes of Health

R01 NS 064330

09/30/08 - 08/31/13

\$238,876 / \$1,093,750

Pang, Q**Role of Tumor Necrosis Factor in Leukemogenesis**

The Leukemia and Lymphoma Society

07/01/08 - 06/30/13

\$103,115 / \$515,575

Role of Nucleophosmin in FA Leukemogenesis

Fanconi Anemia Research Fund

12/01/08 - 11/30/10

\$40,000 / \$80,000

Role of FA Proteins Complexes in Hematopoiesis

National Institutes of Health

R01 HL 076712

04/01/10 - 03/30/15

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

Role of FA Protein Complexes in Hematopoiesis

National Institutes of Health

R01 HL 076712

07/01/09 - 06/30/10

\$76,360 / \$76,360

Ratner, N**Mitogenic Activities in Neurofibromatosis**

National Institutes of Health

R01 NS 028840

03/22/06 - 01/31/11

\$285,989 / \$1,351,567

Mitogenic Activities in Neurofibromatosis

National Institutes of Health

R01 NS 028840	09/30/09 - 08/31/11	\$55,000 / \$55,000
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 of Neurofibromatosis Research		
National Institutes of Health		
P50 NS 057531	09/15/08 - 06/30/13	\$1,031,635 / \$5,254,908
Ratner, Nancy	Core A	47,823
Cripe, Timothy	Core B	105,284
Rizvi, Tilat	Core C	82,821
Perentesis, John	Project 1	296,437
Ratner, Nancy	Project 2	222,456
Ratner, Nancy	Project 3	276,814
Cincinnati Center of Neurofibromatosis Research		
National Institutes of Health		
P50 NS 057531	09/1/09 - 08/31/11	\$184,312 / \$184,312
Therapeutic Targets for Peripheral Nerve Tumors		
Department of Defense Army		
W81XWH0910135	03/01/09 - 02/28/11	\$218,353 / \$438,196
Identification of Drug Targets for NF1		
Trustees of Dartmouth College (National Institutes of Health)		
R21 NS 060940	02/15/09 - 01/31/11	\$37,918 / \$48,547
Modelling Brain Defects in NF1		
Department of Defense		
W81XWH1010116	04/01/10 - 03/31/13	\$178,305 / \$674,801
Cincinnati Neuro-Oncology Research Core		
National Institutes of Health		
P30 CA 149239	09/30/09 - 08/31/11	\$500,000 / \$1,000,000

Zheng, Y

Cell Type and Stimulus-Specific Signaling Role of CDC42		
National Institutes of Health		
R01 HL 085362	07/01/06 - 05/31/11	\$340,171 / \$1,318,421
Rac GTPases as Targets in Lymphomagenesis		
National Institutes of Health		
R01 CA 125658	02/10/07 - 01/31/12	\$190,000 / \$950,000
Rac GTPases as Targets in Lymphomagenesis		
National Institutes of Health		
R01 CA 125658	09/30/09 - 09/29/11	\$425,534 / \$425,534
Training Program in Pediatric Hematologic and Oncologic Diseases		
National Institutes of Health		
T32 HL 091805	09/01/08 - 08/31/13	\$155,724 / \$780,804
Rac GTPase-Specific Small Molecular Inhibitors		
National Institutes of Health		
R01 CA 141341	03/24/09 - 01/31/14	\$170,909 / \$818,825
Targeting CDC42 in Leukemia Stem Cells		
National Institutes of Health		
R01 CA 150547	03/10/10 - 01/31/15	\$207,500 / \$1,037,452
Model Systems for Hematologic Disorders Caused by Ribosomal Protein Deficiency		
University of Cincinnati (National Institutes of Health)		

RC1 DK 087680 09/30/09 - 07/31/11 \$7,494 / \$14,988

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 \$7,912,394

Funded Collaborative Efforts

Ratner, N

Cincinnati NF1 Preclinical Testing Center

The Children's Tumor Foundation

Cripe, T 06/01/09 - 05/31/11 10 %

Cancelas, Jose

Transcriptional Control of Respiratory Epithelial Progenitor Cells

National Institutes of Health

Whitsett, J 08/28/07 - 06/30/11 10 %

Pan, D

Cincinnati Comprehensive Sickle Cell Center

National Institutes of Health

Joiner, C 06/15/08 - 03/31/12 15 %

Total \$7,912,394
