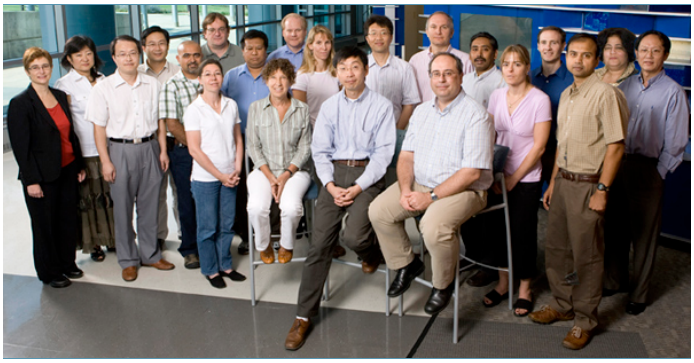
Experimental Hematology and Cancer Biology

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 *Rac1loxp/loxp* or *Rac1loxp/loxp;Rac2–/–* 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 (PlGF), elaborated from erythroid cells, activated MNC and THP-1 monocytic cells to induce LT production. PlGF-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 PlGF-induced FLAP expression. FLAP promoter-driven luciferase constructs demonstrated that PlGF-mediated luciferase induction was abrogated upon mutation of HIF-1 response element (HRE), but not the nuclear factor- B (NF- B) site in the FLAP promoter; a finding confirmed by chromatin immunoprecipitation (ChIP) analysis. PlGF also increased HIF-1 binding to the HRE in the FLAP promoter. Therefore, it is likely that the intrinsically elevated levels of PlGF 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 PlGF. 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 dissolvasome. (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 IIIα and BLAP75/RMI1 (BLAP for BLM-associated polypeptide/RecQ-mediated genome instability) to form the BTB (BLM–Topo IIIα–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 IIIa 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 dissolvasome 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, Mukouyama Y, Cancelas JA, Ratner N. Nf1 mutation expands an EGFR-dependent peripheral nerve progenitor that confers neurofibroma tumorigenic potential. (2008) Cell Stem Cell3, (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;Nf1fl/fl* 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-B–controlled survival and inflammatory proteins and suppressed NF- 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- B in leu-kemic cells. Thus, TAT-delivered NPM peptide may provide a novel therapy for inflammation-associated tumors that require NF-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-1α 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-/-* and *Fancc-/-* 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 leukemogenesiskof NPM as a NF-– We showed B-controlled survival andkthat a NPM antagonist down-regulated several NF- B-driven reporter gene activities. Akinflammatory proteins and suppressed NF- 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

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 thre signaling mechanisms responsible for FIP1L/PDGFRa-induced chronic eosinophilic leukemia nad 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 Kercsmar
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 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 Hematology/Oncology
Collaborating Faculty: Clinton Jointer
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

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, Gangzhou Medical School, China
- **Wei Du, MD, PhD,** 2007, Graduate School of Medicine, Tohoku University, Japan
- **Marthe-Sandrine Eiymo 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
- **Adrianne 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 Amsterdan, 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, Heibei Medical University School of Medicine,
- **Jon Williams, BS,** 2001, Muskingum College
- **Yang Mingyan, ,**
- **Zhao Xinghui, ,**

Significant Accomplishments

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 IIIα 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

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.
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Grants, Contracts, and Industry Agreements

Grant and Contract Awards — Annual Direct / Project Period Direct

ANDREASSEN, P

FANCD2 Monobiquitination 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 Mylogenous 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

LINK, K

Targeting the FLT3 Signaling in MLL-AF9 Leukemia
Hope Street Kids
07/01/08 - 06/30/10 $40,000 / $80,000

MALIK, P

Cincinnati Comprehensive Sickle Cell Center - Project 5
National Institites 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

MAYES, D

NF1 and Ras Activation in Oligodendrocyte Progenitor Cell Development and Lyelination
National Multiple Sclerosis Society
FG 1762A1 07/01/08 - 06/30/11 $45,976 / $143,300

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

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

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

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

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
Current Year Direct	**654,943**

Funded Collaborative Efforts

Ratner, N

Cincinnati NF1 Preclniical Testing Center
The Children's Tumor Foundation
Cripe, Timothy — 06/01/09 - 05/31/11 — 10 %

Cancelas, J

Transcriptional Control of Respiratory Epithelial Progenitor Cells
National Institutes of Health
Whitsett, Jeffery — 08/28/07 - 06/30/11 — 10 %

Pan, D

Cincinnati Comprehensive Sickle Cell Center
National Institutes of Health
Joiner, Clinton — 06/15/08 - 03/31/12 — 15 %

Total 6,332,861