2014 Research Annual Report

Experimental Hematology

Cincinnati Children's

Division Summary

RESEARCH AND TRAINING DETAILS

Number of Faculty	**25**
Number of Joint Appointment Faculty	**15**
Number of Research Fellows	**33**
Number of Research Students	**18**
Number of Support Personnel	**82**
Direct Annual Grant Support	**$8,832,677**
Direct Annual Industry Support	**$190,451**
Peer Reviewed Publications	**74**

CLINICAL ACTIVITIES AND TRAINING

Division Photo

Row 1: MD Filippi, N Ratner
Row 2: E Boscolo, M Xin, P Malik, M Azam, K Komurov
Row 3: S Wells, F Guo, R Waclaw, R Meetei, J Mulloy, D Starczynowski, N Nassar
Row 4: C Lutzko, Q Pang, B Mizukawa, R Lu, G Huang, B Seibel, J Cancelas, Y Zheng, D Reynaud
Row 5: H Vanderloo, J Degen, M Flick

Research Highlights

Yi Zheng, PhD
Discovery of Cdc42 as a central controller of intestinal epithelial cell polarity and a relationship in a childhood gut disease.

We reported in *Gastroenterology* that Cdc42 coordinates cell polarity, migration, proliferation and differentiation of the small intestinal epithelium, defect of which may be causal for microvilli inversion disease.

Yi Zheng, PhD
RhoA regulates hematopoietic stem cell lineage definition.

We reported in *J Exp Med* that RhoA GTPase Controls Mitosis and Programmed Necrosis of Hematopoietic Progenitors.

Paul Andreassen, PhD
We reported in *Oncogene* that the RAD51 paralog, RAD51C, which is both a FA and BRCA protein, directly binds the WD40 domain of PALB2, like BRCA2 and RAD51. Thus, our study yields new insight into the function of RAD51 paralogs and suggests that PALB2 acts in HR by coordinating a complex of effector proteins.

Jose Cancelas, MD, PhD
We reported in *Nat Commun* the role of Klf5 in bone marrow homing of hematopoietic stem cells through a

novel mechanism of regulation of Rab GTPase-mediated integrin activation. The study provides a novel target for intervention and a better understanding of the molecular mechanisms that control stem cell homing.

Jose Cancelas, MD, PhD
We validated the use of an additive solution for platelet storage in humans as published in *Transfusion 2013*.

Jose Cancelas, MD, PhD
We collaborated with Dr. Horwitz to unveil the mechanism of ELANE mutations in severe congenital neutropenia modeled with induced pluripotent stem cells.

Jay Degen, PhD
Factor XII and deep vein thrombosis.

Together with Dr. Matthew Flick and researchers at UNC, Chapel Hill, we reported in the *Journal of Clinical Investigation* that the genetic elimination of the fibrin-stabilizing transglutaminase, factor XIII, diminishes the red blood cell content and dramatically decreases the overall mass of venous thrombi formed in vivo. The finding has potential implications for patients at risk of deep vein thrombosis (DVT) and life-threatening pulmonary embolism. These studies infer that pharmacologic interventions at the level of factor fXIII could be a novel and effective prophylactic strategy in DVT, a condition that affects ~500,000 people in the United States every year.

Jay Degen, PhD
Hemostatic factors and bone disease

Collaborative studies with Dr. Matthew Flick and investigators at Vanderbilt University revealed that fibrin deposition and plasmin-mediated fibrin clearance were powerful determinants inflammatory osteoporosis. One inference of this work is that anticoagulants could be useful tools in supporting bone heath and optimal bone repair. These studies were reported in *Arthritis Rheumatology*.

Jay Degen, PhD
Fibrinolytic proteases and joint disease

For the first time, a specific molecular determinant was identified that controls the differential development of joint disease in either proximal or distal joints. Studies lead by Dr. Matthew Flick revealed that the fibrinolytic protease, plasmin, can simultaneously drive and ameliorate arthritis pathogenesis in distinct anatomic locations in the same subject. This work done together with Drs. Jay Degen and Sherry Thornton were published in *Arthritis Rheumatology*.

Hartmut Geiger, PhD
Molecular Switch in Stem cell aging and hematopoietic stem cell rejuvenation.

We reported in *Nature* an unexpected shift from canonical to non-canonical Wnt signalling due to elevated expression of Wnt5a in aged HSCs that causes stem cell ageing. Wnt5a treatment of young HSCs induces ageing associated stem cell apolarity and an ageing-like myeloid-lymphoid differentiation skewing via activating the small RhoGTPase Cdc42. Conversely, Wnt5a haploinsufficiency attenuates HSC ageing, while stem cell intrinsic reduction of Wnt5a expression results in functionally rejuvenated aged HSCs. In summary our data demonstrate a critical, but reversible role for stem cell intrinsic non-canonical Wnt5a signalling in HSC ageing.

Marie-Dominique Filippi, PhD
Role of Rap1b in neutrophil migration and lung inflammation

We reported in *the Journal of Experimental Medicine* a novel signaling network that limits neutrophil migration into tissues and limits neutrophil-mediated lung inflammation. We show that Rap1b activity is critically important to limit neutrophil activation during inflammation. It limits excessive Akt phosphorylation in neutrophils and the ability of these cells to exploit an unusual route of migration across the endothelial barrier, ie directly through endothelial cells. As a result, Rap1b limits the extent of neutrophil-mediated lung inflammation and susceptibility to endotoxin shock. This study identifies a novel inhibitory pathway of neutrophil migration and inflammation, and provides critical new information on an ill-defined route of neutrophil migration. This is significant since there are very few identified inhibitors of inflammation; this could have broad impact for targeting excessive inflammatory reactions.

Marie-Dominique Filippi, PhD
Role of ATF3 in innate immunity. le of ATF3 in innate immunity.

We reported in *Blood* the dichotomous role of the activating transcription factor 3 (*ATF3*) gene, a key component of Toll-like receptor signaling, in neutrophilic responses. It negatively controls chemokine production from the lung tissue in order to limit neutrophil recruitment during inflammation. On the other, it is a positive regulator of neutrophil migration via Tiam2-dependent focal complex formation.

Marie-Dominique Filippi, PhD
Role of p190-B RhoGAP in the formation of a functional hematopoietic stem cell niche

We reported in *Leukemia* the critical role of p190-B, a negative regulator of Rho activity, in the formation of a functional mesenchymal-derived niche for normal hematopoiesis. p190-B is critical for balancing the lineage fate differentiation of mesenchymal stem cell toward osteoblasts versus adipocytes in order to organize a functional mesenchymal/hematopoietic niche during development. The study is important for our fundamental understanding of hematopoiesis. Since hematopoietic microenvironment dysfunctions are associated with bone marrow failure or cancer, our study has broad implication for hematopoietic disorders and regenerative medicine.

Matthew Flick, PhD
Plasminogen as a joint specific molecular determinant of arthritis

Our group illustrated that the fibrinolytic protease, plasmin, can simultaneously drive and ameliorate arthritis pathogenesis in distinct anatomic locations in the same subject. This work, done in collaboration with Drs. Jay Degen and Sherry Thornton and published in the journal *Arthritis and Rheumatology,* represents the first specific molecular determinant mediating the differential development of joint disease in either proximal or distal joints.

Matthew Flick, PhD
The fibrinogen-plasminogen axis drives inflammation-mediated osteoporosis.

Collaborative studies between Dr. Matthew Flick, Dr. Jay Degen, and investigators at Vanderbilt University revealed that persistent fibrin deposition secondary to the loss of plasmin-mediated fibrin clearance promotes inflammatory osteoporosis. These studies, published in *Arthritis and Rheumatology*, suggest that anticoagulants could be useful tools in supporting bone heath and optimal bone repair.

Matthew Flick, PhD
Factor XIII and deep vein thrombosis

Collaborative studies between Dr. Matthew Flick, Dr. Jay Degen and researchers at UNC, Chapel Hill and

reported in the *Journal of Clinical Investigation* indicate that the genetic elimination of the fibrin-stabilizing transglutaminase, factor XIII, dramatically diminishes the red blood cell content and the overall mass of venous thrombi. These studies infer that pharmacologic interventions at the level of factor fXIII could be a novel and effective prophylactic strategy in DVT, a condition that affects ~500,000 people in the United States every year.

Mathew Flick, PhD
The coagulation protease thrombin drives colitis-associated cancer

Collaborative studies between Drs. Matthew Flick, Eric Mullins, and Joe Palumbo in the CBDI along with Dr. Kris Steinbrecher in GI demonstrated that thrombin-mediated procoagulant function promotes colon cancer tumorigenesis. The studies were published in *Cancer Research*.

Fukun Guo, PhD
The Guo lab studies the role of mTOR in hematopoiesis.

Fukun Guo, PhD
The Guo lab studies the role of Cdc42 and RhoA in T cell activation and differentiation

Fukun Guo, PhD
The Guo lab studies mTOR as a potential therapeutic target in T lymphocytic leukemia

Kakajan Komurov, PhD
Exploring the feasibility of re-activating oncogenic proteotoxicity for cancer therapy

Using an integrated approach, we found a clinically significant vulnerability of HER2+ breast cancers, where they get addicted to the ER-associated degradation pathway for survival. Targeting this pathway specifically kills HER2+ breast cancers. The manuscript for this research is currently in revision in a major journal.

Kakajan Komurov, PhD
Integrated drug discovery pipeline

We are developing an integrated drug discovery pipeline to facilitate the discovery of novel drugs targeting the oncogenic stress pathways in cancers. A preliminary run of this pipeline to discover novel inhibitors of the p97/VCP ATPase, an important target we have identified in breast cancers (see previous), has resulted in a preliminary high rate of true hits. We are pursuing several new drug candidates, and further refining our computational approach.

Kakajan Komurov, PhD
Global mis-splicing programs in cancers

We have recently discovered a highly significant pattern of global mRNA splicing in most human cancers. This pattern, which we termed Short Isoform Program (SIP), defines a novel subclass of cancers with distinct molecular and clinical characteristics. This project is also currently ongoing.

Qing Richard Lu, PhD
Medulloblastoma origins and treatment, and identify GNAS as a novel tumor suppressor in medulloblastomas.

We reported in *Nature Medicine* 2014 that G protein alpha (GNAS) functions as a prognostic marker potent tumor suppressor gene in Sonic Hedghog (SHH) driven medulloblastoma (MB) and that GNAS could be used as a prognostic biomarker for SHH subgroup MBs. We also identified that combinatorial treatment with cAMP raising agents and SHH receptor antagonists can effectively inhibit tumor growth.

Qing Richard Lu, PhD
Generation of transgenic mouse expressing the membrane-anchored GFP (mEGFP) in myelinating cells

We reported in *Genesis* 2014 that we generated a novel transgenic mouse line to allow direct visualization of membrane architecture of myelinating cells. This new transgenic mouse line will be a useful tool to monitor myelin membrane formation and assembly during development and repair in response to injuries.

Carolyn Lutzko, PhD
The Lutzko lab studies the development and translation of gene therapy for sickle cell anemia.

The Lutzko lab studies the development of induced pluripotent stem cell models of blood diseases to study cell biology of disease, develop and test drugs or therapeutics and correct the genetic defects.

Punam Malik, MD
The Malik lab has begun a clinical trial for gene therapy for sickle cell disease.

Punam Malik, MD
The Malik lab has begun working on gene therapy for HLH with Drs. Jordan and Risma

The Malik lab has begun a clinical trial for sickle nephropathy.

Ruhikanta Meetei, PhD
Role and regulation of (BTR) complex (BLM-Topo III α-RMI1-RMI2) in Bloom Syndrome.

We reported in *JBC, a* Monopolar spindle 1 (MPS1) protein-dependent phosphorylation of RecQ-mediated genome instability protein 2 (RMI2) at serine 112 is essential for BLM-Topo III α-RMI1-RMI2 (BTR) protein complex function upon spindle assembly checkpoint (SAC) activation during mitosis. Overall, this study suggests that the phosphorylation of the BTR complex is essential to maintain a stable genome.

James Mulloy, PhD
The Mulloy lab defined the role that the tumor suppressor RUNX1 plays in MLL-fusion AML.

James Mulloy, PhD
The Mulloy lab established an improved approach to xenografting human cells in immunodeficient mice.

Dao Pan, PhD
Innovative therapy for lysosomal storage diseases

We reported in *PNAS (2014)* that megakaryocyte/platelet lineage is capable of generating and storing a fully functional lysosomal enzyme and leads to highly efficient, continuous, and versatile (discretely or membrane-protected) transport/distribution of enzyme into the circulation and major diseased organs. This study provides proof-of-concept of megakaryocyte/platelet as a depot for efficient production, protected delivery and effective distribution of lysosomal enzymes.

Dao Pan, PhD
Treatment for neuronopathic Gaucher Disease

We have generated key data that led to a reward of NIH R01 application on Oct. 2013.

Qishen Pang, PhD
Targeting the FA pathway in sensitizing leukemia to chemotherapy

The study demonstrates that the mTOR kinase inhibitor pp242 enhances anti-tumor activity of conventional

chemo-drugs *in vitro* and *in vivo* by suppressing FANCD2 and consequently augmenting DNA damage leading to apoptosis. The finding suggests that inhibition of the FA pathway coupled with chemo-therapy may be beneficial for cancer treatment. We published these studies in *Leukemia*.

Qishen Pang, PhD
Modeling graft-versus-host disease in FA mice

We reported in *Blood* that deletion of *Fanca* or *Fancd2* dysregulates the suppressive activity of regulatory T cells (Tregs), shown functionally as exacerbation of graft-versus-host disease (GVHD) in mice**.** This study may contribute mechanistically to clinical immune deficiency in FA patients.

Nancy Ratner, PhD
Targeting the Blood Brain Barrier

We reported in *Cell Reports* that Ras activation in brain oligodendrocytes induces nitric oxide-driven defects in myelin and leak in the high resistance vessels comprising the blood brain barrier. This is important as it identifies a new cell type that be modulated to open the BBB, and identifies a signaling pathway that may be effective as a therapy in Rasopathy patients, who have brain RAS pathway mutations.

Nancy Ratner, PhD
NIH Career Merit Award

Jacob K. Javits Neuroscience Investigator Award, NIH-NINDS, 2014 (NIH Merit Award)

Nancy Ratner, PhD
Identification of therapies for Neurofibromatosis

We published In a series of papers, most with Dr. David Largaespada (Minnesota), identifying targetable pathways in nerve sarcoma, MPNST. Published in Nature Genetics, Cancer Discovery, Oncogene, Oncotarget and Am. J. Pathology the papers demonstrate the importance of MEK and PI3K signaling and a point of crosstalk between the two pathways, and some efficacy of a drug combination targeting both.

Damien Reynaud, PhD
Young investigator award, Conquer Cancer Now Foundation two years, $60,000 Direct/year

Title: Systemic Metabolic Disorders and Leukemic Clonal Dominance.

Goals:

- establish the effect of obesity on leukemia initiation and progression
- probe how the pro-inflammatory activity of the obese adipose tissue contributes to disease development.

Daniel Starczynowski, PhD
Targeting innate immune signaling in MDS

We reported in *Cancer Cell* that IRAK1 is a druggable target in MDS. Small molecule inhibitors of IRAK1 eliminated the MDS clone in vitro and in vivo. The study provides evidence that the innate immune pathway is important for sustaining the MDS clone.

Daniel Starczynowski, PhD
Xenograft model of MDS

We reported in *Leukemia* that a MDS patient-derived cell line could engraft into immune-compromised mice.

The study provides a mouse model to evaluate novel therapies for MDS.

Johannes Van der Loo, BA, MS, PhD
We completed manufacturing of three (3) lots of lentiviral vector for the treatment of Sickle Cell Anemia in a phase I trial to be opened at Cincinnati Children's Hospital (PI: Malik)

Johannes Van der Loo, BA, MS, PhD
We were successful in the development of methods for GMP production of a Foamy Viral vector expressing human CD18 for the treatment of Leukocyte Adhesion Deficiency (Sponsor: A. Larochelle, NIH, clinical sites NIH and Cincinnati Children's)

Johannes Van der Loo, BA, MS, PhD
Appointed member of the Editorial Board of *Molecular Therapy – Methods & Clinical Development*

Johannes Van der Loo, BA, MS, PhD
Awarded through the CCTST Institutional Clinical and Translational Science Award, NIH/NCRR Grant Number 8UL1TR000077-04

Ronald Waclaw, PhD
Role of the protein tyrosine phosphatase Shp2 in oligodendrocyte development.

We reported in the *Journal of Neuroscience*, the RASopathy gene, Shp2 is crucial for oligodendrocyte progenitor cell development in the telencephalon.

Specifically, we found that expressing a Noonan Syndrome Rasopathy mutation results in increased oligodendrocyte progenitor cells and also abnormal myelination in the white matter regions.

Jianqiang Wu, MD, MS
Early neurofibroma formation and pre-clinical therapeutic testing

We reported in *Oncogene* that overexpression of EGFR in neurofibroma causes malignant transformation due to Stat3 activation.

We showed Stat3 contributes to neurofibroma initiation and maintenance

Mei Xin, PhD
Investigates the role of the Hippo signaling pathway in cardiovascular development and disease

We have established the lab, and generated genetically modified mouse models to delete and overexpress the Hippo pathway mediater Yap1 in a tissue specific manner.

Significant Publications

Dai M, Han J, El-Amouri SS, Brady RO, Pan D. Platelets are efficient and protective depots for storage, distribution, and delivery of lysosomal enzyme in mice with Hurler syndrome. *Proc Natl Acad Sci U S A.* 2014 Feb 18;111(7):2680-85.

Use of megakaryocytes/platelets for transgene expression may take advantage of their rapid turnover and protective storage in platelets and reduce the risk of activating oncogenes in hematopoietic stem and progenitor cells. Dao lab provided a proof of concept that cells from megakaryocytic lineage and platelets are capable of generating and storing fully functional lysosomal enzymes and can also lead to efficient delivery of both the enzymes released into the circulation and those protected within platelets/microparticles. The study opens a door for use of the megakaryocytes/platelets as a depot for efficient production, delivery, and effective

tissue distribution of lysosomal enzymes.

Goyama S, Schibler J, Cunningham L, Zhang Y, Rao Y, Nishimoto N, Nakagawa M, Olsson A, Wunderlich M, Link KA, Mizukawa B, Grimes HL, Kurokawa M, Liu PP, **Huang G**, **Mulloy JC**. Transcription factor RUNX1 promotes survival of acute myeloid leukemia cells. *J Clin Invest.* 2013 Sep 3;123(9):3876-88.

RUNX1 is generally considered a tumor suppressor in myeloid neoplasms. Inactivating RUNX1 mutations have frequently been found in patients with myelodysplastic syndrome and cytogenetically normal acute myeloid leukemia. However, no somatic RUNX1 alteration was found in AMLs with leukemogenic fusion proteins, raising the possibility that RUNX1 could actually promote the growth of the leukemia cells. The studies by the Mulloy lab unveiled an unexpected prosurvival role for RUNX1 in myeloid leukemogenesis. Inhibiting RUNX1 activity rather than enhancing it could be a promising therapeutic strategy for AMLs with leukemogenic fusion proteins.

Mayes DA, Rizvi TA, Titus-Mitchell H, Oberst R, Ciraolo GM, Vorhees CV, Robinson AP, Miller SD, **Cancelas JA**, Stemmer-Rachamimov AO, Ratner N. Nf1 loss and Ras hyperactivation in oligodendrocytes induce NOS-driven defects in myelin and vasculature. *Cell Rep.* 2013 Sep 26;4(6):1197-212.

Patients with neurofibromatosis type 1 and Costello syndrome have behavioral deficits. In NF1 patients, these may correlate with white matter enlargement and aberrant myelin. The Ratner lab modeled these features by inducing Nf1 loss or HRas hyperactivation in mouse oligodendrocytes. They found that Nf1/Ras regulates oligodendrocyte NOS and that dysregulated NO signaling in oligodendrocytes can alter the surrounding vasculature. The data suggest that antioxidants may improve some behavioral deficits in Rasopathy patients.

Rhyasen GW, Bolanos L, Fang J, Jerez A, Wunderlich M, Rigolino C, Mathews L, Ferrer M, Southall N, Guha R, Keller J, Thomas C, Beverly LJ, Cortelezzi A, Oliva EN, Cuzzola M, Maciejewski JP, **Mulloy JC**, **Starczynowski DT**. Targeting IRAK1 as a therapeutic approach for myelodysplastic syndrome. *Cancer cell.* Jul 8 2013;24(1):90-104.

Myelodysplastic syndromes arise from a defective hematopoietic stem/progenitor cell. Consequently, there is an urgent need to develop targeted therapies capable of eliminating the MDS-initiating clones. The Starczynowski lab identified that IRAK1, an immune-modulating kinase, is overexpressed and hyperactivated in MDSs. Suppression of IRAK1 is detrimental to MDS cells, and combined IRAK1 and BCL2 inhibitors more effectively eliminated MDS clones, implicating IRAK1 as a drugable target in MDSs.

Zhou X, Florian MC, Arumugam P, Chen X, **Cancelas JA**, Lang R, Malik P, Geiger H, **Zheng Y**. RhoA GTPase controls cytokinesis and programmed necrosis of hematopoietic progenitors. *J Exp Med.* 2013 Oct 21;210(11):2371-85.

Hematopoietic progenitor cells are central to hematopoiesis as they provide large numbers of lineage-defined blood cells necessary to sustain blood homeostasis. The small GTPase RhoA is an intracellular molecular switch that integrates cytokine, chemokine, and adhesion signals to coordinate multiple context-dependent cellular processes. By using a RhoA conditional knockout mouse model, the Zheng lab we showed that RhoA deficiency causes a multilineage hematopoietic failure that is associated with defective multipotent HPCs, indicating that RhoA is a critical and specific regulator of multipotent HPCs during cytokinesis and thus essential for multilineage hematopoiesis.

Division Publications

1. Araten DJ, Krejci O, Ditata K, Wunderlich M, Sanders KJ, Zamechek L, Mulloy JC. **The rate of spontaneous mutations in human myeloid cells**. *Mutat Res*. 2013; 749:49-57.
2. Beverly LJ, Starczynowski DT. **IRAK1: oncotarget in MDS and AML**. *Oncotarget*. 2014; 5:1699-700.

3. Boespflug ND, Kumar S, McAlees JW, Phelan JD, Grimes HL, Hoebe K, Hai T, Filippi MD, Karp CL. **ATF3 is a novel regulator of mouse neutrophil migration**. *Blood*. 2014; 123:2084-93.
4. Broering TJ, Alavattam KG, Sadreyev RI, Ichijima Y, Kato Y, Hasegawa K, Camerini-Otero RD, Lee JT, Andreassen PR, Namekawa SH. **BRCA1 establishes DNA damage signaling and pericentric heterochromatin of the X chromosome in male meiosis**. *J Cell Biol*. 2014; 205:663-75.
5. Chandrakasan S, Malik P. **Gene therapy for hemoglobinopathies: the state of the field and the future**. *Hematol Oncol Clin North Am*. 2014; 28:199-216.
6. Chen P, Price C, Li Z, Li Y, Cao D, Wiley A, He C, Gurbuxani S, Kunjamma RB, Huang H, Jiang X, Arnovitz S, Xu M, Hong GM, Elkahloun AG, Neilly MB, Wunderlich M, Larson RA, Le Beau MM, Mulloy JC, Liu PP, Rowley JD, Chen J. **miR-9 is an essential oncogenic microRNA specifically overexpressed in mixed lineage leukemia-rearranged leukemia**. *Proc Natl Acad Sci U S A*. 2013; 110:11511-6.
7. Cui R, Gale RP, Zhu G, Xu Z, Qin T, Zhang Y, Huang G, Li B, Fang L, Zhang H, Pan L, Hu N, Qu S, Xiao Z. **Serum iron metabolism and erythropoiesis in patients with myelodysplastic syndrome not receiving RBC transfusions**. *Leuk Res*. 2014; 38:545-50.
8. Dai M, Han J, El-Amouri SS, Brady RO, Pan D. **Platelets are efficient and protective depots for storage, distribution, and delivery of lysosomal enzyme in mice with Hurler syndrome**. *Proc Natl Acad Sci U S A*. 2014; 111:2680-5.
9. Davalos D, Baeten KM, Whitney MA, Mullins ES, Friedman B, Olson ES, Ryu JK, Smirnoff DS, Petersen MA, Bedard C, Degen JL, Tsien RY, Akassoglou K. **Early detection of thrombin activity in neuroinflammatory disease**. *Ann Neurol*. 2014; 75:303-8.
10. Du W, Amarachintha S, Sipple J, Schick J, Steinbrecher K, Pang Q. **Inflammation-mediated notch signaling skews fanconi anemia hematopoietic stem cell differentiation**. *J Immunol*. 2013; 191:2806-17.
11. Du W, Erden O, Pang Q. **TNF-alpha signaling in Fanconi anemia**. *Blood Cells Mol Dis*. 2014; 52:2-11.
12. Du W, Erden O, Wilson A, Sipple JM, Schick J, Mehta P, Myers KC, Steinbrecher KA, Davies SM, Pang Q. **Deletion of Fanca or Fancd2 dysregulates Treg in mice**. *Blood*. 2014; 123:1938-47.
13. Ehrman LA, Mu X, Waclaw RR, Yoshida Y, Vorhees CV, Klein WH, Campbell K. **The LIM homeobox gene Isl1 is required for the correct development of the striatonigral pathway in the mouse**. *Proc Natl Acad Sci U S A*. 2013; 110:E4026-35.
14. Ehrman LA, Nardini D, Ehrman S, Rizvi TA, Gulick J, Krenz M, Dasgupta B, Robbins J, Ratner N, Nakafuku M, Waclaw RR. **The protein tyrosine phosphatase Shp2 is required for the generation of oligodendrocyte progenitor cells and myelination in the mouse telencephalon**. *J Neurosci*. 2014; 34:3767-78.
15. Filippi MD. **New regulatory role for SRF in neutrophils**. *Blood*. 2014; 123:2903-4.
16. Florian MC, Nattamai KJ, Dorr K, Marka G, Uberle B, Vas V, Eckl C, Andra I, Schiemann M, Oostendorp RA, Scharffetter-Kochanek K, Kestler HA, Zheng Y, Geiger H. **A canonical to non-canonical Wnt signalling switch in haematopoietic stem-cell ageing**. *Nature*. 2013; 503:392-6.
17. Geiger H. **HSC senescence upon irradiation**. *Blood*. 2014; 123:3060-1.
18. Geiger H, Denkinger M, Schirmbeck R. **Hematopoietic stem cell aging**. *Curr Opin Immunol*. 2014; 29C:86-92.
19. Geiger H, Zheng Y. **Cdc42 and aging of hematopoietic stem cells**. *Curr Opin Hematol*. 2013; 20:295-300.
20. Goyama S, Mulloy JC. **NF-kappaB: a coordinator for epigenetic regulation by MLL**. *Cancer Cell*. 2013; 24:401-2.
21. Goyama S, Schibler J, Cunningham L, Zhang Y, Rao Y, Nishimoto N, Nakagawa M, Olsson A, Wunderlich M, Link KA, Mizukawa B, Grimes HL, Kurokawa M, Liu PP, Huang G, Mulloy JC. **Transcription factor RUNX1 promotes survival of acute myeloid leukemia cells**. *J Clin Invest*. 2013; 123:3876-88.

22. Guo F, Li J, Du W, Zhang S, O'Connor M, Thomas G, Kozma S, Zingarelli B, Pang Q, Zheng Y. **mTOR regulates DNA damage response through NF-kappaB-mediated FANCD2 pathway in hematopoietic cells**. *Leukemia*. 2013; 27:2040-6.
23. Guo F, Li J, Zhang S, Du W, Amarachintha S, Sipple J, Phelan J, Grimes HL, Zheng Y, Pang Q. **mTOR kinase inhibitor sensitizes T-cell lymphoblastic leukemia for chemotherapy-induced DNA damage via suppressing FANCD2 expression**. *Leukemia*. 2014; 28:203-6.
24. Guo F, Zhang S, Grogg M, Cancelas JA, Varney ME, Starczynowski DT, Du W, Yang JQ, Liu W, Thomas G, Kozma S, Pang Q, Zheng Y. **Mouse gene targeting reveals an essential role of mTOR in hematopoietic stem cell engraftment and hematopoiesis**. *Haematologica*. 2013; 98:1353-8.
25. Guo L, Lee AA, Rizvi TA, Ratner N, Kirschner LS. **The protein kinase A regulatory subunit R1A (Prkar1a) plays critical roles in peripheral nerve development**. *J Neurosci*. 2013; 33:17967-75.
26. Guo L, Moon C, Zheng Y, Ratner N. **Cdc42 regulates Schwann cell radial sorting and myelin sheath folding through NF2/merlin-dependent and independent signaling**. *Glia*. 2013; 61:1906-21.
27. Huang H, Jiang X, Li Z, Li Y, Song CX, He C, Sun M, Chen P, Gurbuxani S, Wang J, Hong GM, Elkahloun AG, Arnovitz S, Wang J, Szulwach K, Lin L, Street C, Wunderlich M, Dawlaty M, Neilly MB, Jaenisch R, Yang FC, Mulloy JC, Jin P, Liu PP, Rowley JD, Xu M, He C, Chen J. **TET1 plays an essential oncogenic role in MLL-rearranged leukemia**. *Proc Natl Acad Sci U S A*. 2013; 110:11994-9.
28. Kalfa TA, Zheng Y. **Rho GTPases in erythroid maturation**. *Curr Opin Hematol*. 2014; 21:165-71.
29. Karkare S, Chhipa RR, Anderson J, Liu X, Henry H, Gasilina A, Nassar N, Roychoudhury J, Clark JP, Kumar A, Pauletti GM, Ghosh PK, Dasgupta B. **Direct inhibition of retinoblastoma phosphorylation by nimbolide causes cell-cycle arrest and suppresses glioblastoma growth**. *Clin Cancer Res*. 2014; 20:199-212.
30. Katayama K, Imai F, Campbell K, Lang RA, Zheng Y, Yoshida Y. **RhoA and Cdc42 are required in pre-migratory progenitors of the medial ganglionic eminence ventricular zone for proper cortical interneuron migration**. *Development*. 2013; 140:3139-45.
31. Kesarwani M, Huber E, Azam M. **Overcoming AC220 resistance of FLT3-ITD by SAR302503**. *Blood Cancer J*. 2013; 3:e138.
32. Kim HS, Mendiratta S, Kim J, Pecot CV, Larsen JE, Zubovych I, Seo BY, Kim J, Eskiocak B, Chung H, McMillan E, Wu S, De Brabander J, Komurov K, Toombs JE, Wei S, Peyton M, Williams N, Gazdar AF, Posner BA, Brekken RA, Sood AK, Deberardinis RJ, Roth MG, Minna JD, White MA. **Systematic identification of molecular subtype-selective vulnerabilities in non-small-cell lung cancer**. *Cell*. 2013; 155:552-66.
33. Koh CP, Wang CQ, Ng CE, Ito Y, Araki M, Tergaonkar V, Huang G, Osato M. **RUNX1 meets MLL: epigenetic regulation of hematopoiesis by two leukemia genes**. *Leukemia*. 2013; 27:1793-802.
34. Konstantinidis DG, Pushkaran S, Giger K, Manganaris S, Zheng Y, Kalfa TA. **Identification of a Murine Erythroblast Subpopulation Enriched in Enucleating Events by Multi-spectral Imaging Flow Cytometry**. *J Vis Exp*. 2014; .
35. Kumar S, Ciraolo G, Hinge A, Filippi MD. **An efficient and reproducible process for transmission electron microscopy (TEM) of rare cell populations**. *J Immunol Methods*. 2014; 404:87-90.
36. Li A, Yang Y, Gao C, Lu J, Jeong HW, Liu BH, Tang P, Yao X, Neuberg D, Huang G, Tenen DG, Chai L. **A SALL4/MLL/HOXA9 pathway in murine and human myeloid leukemogenesis**. *J Clin Invest*. 2013; 123:4195-207.
37. Li J, Pang Q. **Oxidative stress-associated protein tyrosine kinases and phosphatases in Fanconi anemia**. *Antioxid Redox Signal*. 2014; 20:2290-301.
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72. Zhou X, Zheng Y. **Cell Type-specific Signaling Function of RhoA GTPase: Lessons from Mouse Gene Targeting**. *J Biol Chem*. 2013; 288:36179-88.
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Faculty, Staff, and Trainees

Faculty Members

Yi Zheng, PhD, Professor

Leadership Co-Director, CBDI; Director, EHCB; Endowed Chair; Program Leader, Cell Signaling and Drug Discovery Program

Research Interests The physiopathological role and novel approach of therapeutic targeting of Rho GTPase and mTOR signaling networks

Paul Andreassen, PhD, Associate Professor

Research Interests Mechanistic understanding of the role of the Fanconi anemia (FA) and the breast cancer susceptibility (BRCA) networks in DNA damage responses, including checkpoint signaling and DNA repair by homologous recombination.

Elisa Boscolo, PhD, Assistant Professor

Research Interests Vascular Biology and Endothelial Tumor Biology

Jose Cancelas, MD, PhD, Professor

Leadership Program Leader, Stem Cell Program; Deputy Director, Hoxworth Blood Center (HBC); Director, Research HBC Division; Medical Director, Cellular Therapies (HBC)

Research Interests Mechanisms of stem cell activity and migration dependent on bone marrow microenvironmenew technologies for safer, more efficient blood transfusion.

Jay Degen, PhD, Professor

Leadership Program Leader, Hemostasis and Thrombosis Program

Research Interests The mechanisms linking hemostatic factors to thromboinflammatory disease processes, including sickle cell disease, neuroinflammatory disease, and sepsis.

Marie-Dominique Filippi, PhD, Associate Professor

Research Interests The role of signaling pathways in modulating hematopoietic cell fate, including migration, adhesion and self-renewal.

Matthew Flick, PhD, Assistant Professor

Leadership Director, Rheumatology P30 Animal Models of Inflammatory Disease Core

Research Interests The mechanisms by which coagulation system factors regulate the pathogenesis of arthritis, obesity, and bacterial infection.

Hartmut Geiger, PhD, Adjunct

Leadership Director, Comprehensive Mouse and Cancer Core

Research Interests Normal and abnormal adult stem cell biology, with a strong focus on hematopoiesis and aging.

Elke Grassman, PhD, HCLD, Assistant Professor

Leadership Director, Translational Trials Development and Support Laboratory

Research Interests Support Phase I/II gene transfer trials with specialized patient testing and preclinical safety studies

Fukun Guo, PhD, Assistant Professor

Research Interests Rho GTPases in T cell biology

Kakajan Komurov, PhD, Assistant Professor

Research Interests Computational and Systems Biology of Cancer

Qing Richard Lu, PhD, Professor

Leadership Scientific Director, Brain Tumor Center

Research Interests Epigenetic regulation of glial development and myelination. Molecular mechanisms of central and peripheral tumor formation

Carolyn Lutzko, PhD, Associate Professor

Leadership Director, Cell Processing Core; Co-Director, Cell Manipulations Lab; Director, Development Lab

Research Interests Dr. Lutzko's research program is focused on using stem cells to better understand and treat inherited blood disorders. One area of research is to develop induced pluripotent stem cells from patients with blood diseases. Her lab then uses these pluripotent stem cells as a renewable source for blood cells to study in the laboratory, to study disease at the cellular level, and to test potential gene and drug

therapeutics. In other studies, her lab is working with other physicians and scientists to translate cell and gene therapies for blood and other diseases from the basic lab into the clinic.

Punam Malik, MD, Professor

Leadership Marjory J. Johnson Chair of Gene and Cell Therapy; Professor of Pediatrics; Program Leader, Molecular and Gene Therapy; Director, Comprehensive Sickle Cell Program; Director, Translational Core Laboratory

Research Interests Hemoglobinopathies, Stem Cell Biology, Gene Therapy

Ruhikanta Meetei, PhD, Associate Professor

Research Interests Signaling and Drug Discovery

Shyra Miller, PhD, Assistant Professor

Research Interests Identifying and characterizing proteins comprising the FA-core and Bloom syndrome complexes which are associated with chromosome instability, highly elevated cancer incidence and hypersensitivity to a variety of genotoxic drugs.

James Mulloy, PhD, Professor

Leadership Co-Leader, Hematologic Malignancies Program; Associate Director, Hem/Onc/BMT Fellowship Program

Research Interests Dissection of the molecular pathogenesis of MLL-fusion AML and AML1-ETO-associated AML, using human xenograft models and experimentally generated human AML.

Nicolas Nassar, PhD, Associate Professor

Research Interests We combine biophysical, biochemical and cellular approaches to elucidate the structure/function relationship of signaling proteins and to inhibit them in disease.

Dao Pan, PhD, Associate Professor

Research Interests Our research focuses on combining translational and basic research on virus-mediated, in vivo and ex-vivo, gene transfer into stem cells, as well as their potential application for gene therapy of patients with inherited or acquired diseases, with the particular goal of ameliorating the central nervous system abnormalities and bone diseases.

Qishen Pang, PhD, Professor

Research Interests Research focuses on the function of Fanconi Anemia (FA) proteins in hematopoiesis, with specific emphasis on elucidating the mechanisms by which the FA proteins regulate the hematopoietic stem cells in the context of bone marrow failure and leukemia development. These studies utilize cellular, genetic, and molecular techniques to identify and characterize critical pathways that regulate hematopoietic stem cell function.

Nancy Ratner, PhD, Professor

Leadership Beatrice C. Lampkin Endowed Chair in Cancer Biology; Co-Leader, Cancer Biology and Neural Tumors Program

Research Interests The intersection between development and inherited cancer in the peripheral nervous system; Ras signaling in cancer; NF1; NF2

Damien Reynaud, PhD, Assistant Professor

Research Interests Contribution of the metabolic environment to leukemia initiation and progression. Adipokine network associated with obesity and its role in normal and pathological hematopoiesis. Mechanism of leukemic transformation in neonates.

Daniel Starczynowski, PhD, Assistant Professor

Research Interests Molecular and cellular basis of Myelodysplastic syndromes and role of innate immune signaling in HSC function

Johannes van der Loo, BA, MS, PhD, Associate Professor

Leadership Director, Vector Production Facility; Director, Aseptic Processing Laboratories; Director, Viral Vector Core; Chair, Institutional Biosafety Committee

Research Interests Production of research grade viral vectors and development and scale-up of viral vector manufacturing for early phase clinical application in compliance with current Good Manufacturing Practices (cGMP)

Ronald Waclaw, PhD, Assistant Professor

Research Interests Molecular genetic control of cellular diversity in the forebrain. Impact of RASopathy mutations on brain development.

Jianqiang Wu, MD, MS, Assistant Professor

Research Interests Neurofibroma cell of origin; neurofibroma pre-clinical testing

Mei Xin, PhD, Assistant Professor

Research Interests The role of Hippo signaling in cardiovascular development and disease.

Joint Appointment Faculty Members

Mohammed Azam, PhD, Assistant Professor (Pathology)

Research Interests Hematology Malignancy and Drug Resistance

Lionel Chow, MD, PhD, Assistant Professor (Oncology)

Research Interests The Chow Lab studies High-Grade Gliomas which are aggressive brain tumors in adults and children with limited treatment options. Using a combination of novel and robust laboratory models coupled with the study of human tumor material, the lab's goals are to better understand the cellular origins and molecular underpinnings of these diseases in order to design and test novel therapies that will improve patient outcome.

Biplab DasGupta, PhD, Assistant Professor (Oncology)

Research Interests Our laboratory is interested in understanding the function of energy and nutrient sensing enzymes during normal brain development and in brain cancer. We use a variety of methods including in vitro culture systems, knockout and transgenic mouse models and ex vivo techniques to examine metabolic regulation in neural tissue.

Rachid Drissi, PhD, Assistant Professor (Oncology)

Research Interests Cancer Biology and Neural Tumors

Leighton Grimes, PhD, Associate Professor (Immunobiology)

Research Interests Hematology Malignancy

Gang Huang, PhD, Assistant Professor (Pathology)

Research Interests Cancer develops through a series of DNA and non-DNA related changes that progressively drive normal cells into highly malignant derivatives and the distinct mutations can cause the same cancer via their effects on the same regulatory network. The key regulators for blood cell development are DNA binding proteins and chromatin (proteins packed DNA) modification enzymes, which are often targeted by mutations or chromosomal translocations in human blood cancer. Research in Dr. Gang Huang's laboratory focuses on the DNA binding proteins and chromatin (proteins packed DNA) modification enzymes

in blood cell normal development and cancer. This research will provide new insight into the interplay between DNA binding proteins and chromatin modification enzymes in normal blood development and leukemia. It will also help to develop drugs which will benefit the future clinical treatments.

Theodosia Kalfa, MD, PhD, Assistant Professor (Hematology)
Research Interests Benign Hematology and Red Blood Cell Biology

Ashish Kumar, MD, PhD, Associate Professor (Bone Marrow Transplantation and Immune Deficiency)
Research Interests Hematological Malignancy and Therapy

Adam Lane, PhD, Instructor (Bone Marrow Transplantation and Immune Deficiency)
Research Interests Biostatistics

Benjamin Mizukawa, MD, Assistant Professor (Oncology)
Research Interests Hematological Malignancy and Signaling

Eric Mullins, MD, Assistant Professor (Hematology)
Research Interests Hemostasis and Thrombosis

Joseph Palumbo, MD, Associate Professor (Hematology)
Research Interests Hemostasis and Thrombosis

Lisa Privette Vinnedge, PhD, Instructor (Oncology)
Research Interests Advanced breast cancer (BC) has poor survival rates and is the second leading cause of cancer deaths. Mortality is a result of tumor recurrence and disease progression, which are caused by a drug-resistant BC stem cell (BCSC) population. Identifying novel molecular mechanisms is crucial for developing new treatments that may target BCSCs, a potential candidate is the frequently upregulated, chromatin remodeling protein, DEK. My work indicates that DEK (1) promotes tumor initiation and oncogenic phenotypes, (2) increases Wnt/beta-catenin pathway activity, and (3) is an estrogen receptor (ER-alpha) target gene that promotes tamoxifen drug resistance. Of importance, DEK inhibition correlates with fewer BCSC numbers, decreased overt lung metastases in murine models, and Wnt pathway inhibition. Finally, the loss of DEK enhances the cytotoxicity of the chemotherapeutic drug cisplatin. Current work focuses on the molecular functions of DEK in BCSCs and pre-clinical studies of genetic inhibition of DEK as a means to enhance therapeutic response to several classes of drugs, thus hopefully resulting in improved patient survival.

William Seibel, PhD, Assistant Professor (Oncology)
Research Interests Drug Discovery and Medicinal Chemistry

Janos Sumegi, MD, PhD, Professor (Blood and Marrow Transplantation and Immune Deficiency)
Research Interests Hematology and Gene Therapy

Susanne Wells, PhD, Associate Professor (Oncology)
Research Interests The long term goal of my research program is to identify viral and cellular modifiers of epithelial cancers, and to explore the therapeutic targeting of such modifiers for the purpose of new cancer treatments. Versatile human and murine tumor models, and my board interest in viral tumor etiology and biology form the basis for our research. In past years, we have explored translational directions which offer unique training opportunities. An emerging theme is organismal and cellular preference for certain DNA repair mechanisms, a major determinant of genome instability, cancer susceptibility and response to treatment. For instance, Fanconi Anemia (AF) patients exhibit an aberrant choice of repair in every cell of the body contributes to the susceptibility of children with FA to leukemia and solid tumors, as well as to life-threatening toxicities of chemotherapy.

Trainees

- **Shailaja Akunuru, PhD**, PGY-2, University of Cincinnati
- **Gregory Bick, BS**, PGY-5, Case Western Reserve University
- **Gasilina Anjelika,** , 2011
- **Kyung-Hee Chang, PhD**, PGY-6, University of Florida
- **Wei Du, MD, PhD**, PGY-7, Tohoku University School of Medicine, Japan
- **Marthe-Sandrine Eiymo Mwa Mpollo, Grad Student**, University of Montreal
- **Salim El-Amouri, PhD**, PGY-5, Medical University of South Carolina
- **Chris Evelyn, PhD**, 2009, University of Michigan
- **Yuxin Feng, PhD**, 2008, University of Cincinnati
- **Susuma Goyama, PhD**, PGY-5, Graduate School of Medicine, University of Tokyo
- **Paritha Arumugam, PhD**, Cincinnati Children's
- **Vikram Kohli, PhD**, PGY-5, University of Alberta
- **Leesa Sampson, PhD**, 2010, Vanderbilt University
- **Shan Lin, Grad Student**, 2010, Tsinghua University, Beijing China
- **Kevin Link, PhD**, 2007, University of Cincinnati
- **Huiqing Li, MS**, Merk
- **Xiaoyi Chen, Grad Student**, 2012, West China Medical School, Sichuan University
- **Jung-Young Park, PhD**, 2010, National Institutes of Health
- **Ami V. Patel, PhD**, PGY-5, University of Louisville
- **TingTing Zhang, PhD**, PGY-3, University of Alabama at Birmingham
- **Junqi Yang, PhD**, PGY-3, University of Cincinnati
- **Garrett Rhyasen, PhD**, GS-4, University of Victoria, Canada
- **Haley Titus-Mitchell, MS**, PGY-5, Wright State University
- **Melinda Varney, PhD**, PGY-4, Marshall University, WV
- **Inuk Zandvakili, Grad Student**, 2009, University of Western Ontario
- **Shuangmin Zhang, PhD**, PGY-4, University of Texas
- **Xuan Zhou, PhD**, 2008, Tsinghua University
- **Benjamin Mizukawa, MD**, 2008, University of Utah School of Medicine
- **Jung-Mi Lee, PhD**, PGY-1, University of Seoul, South Korea
- **Lisa Trump, PhD**, PGY-3, University of Illinois, Urbana Champaign
- **Jing Fang, MD, PhD**, PGY-4, Shanghai Second Medical University, China
- **Hongyan Zhu, PhD**, PGY-1, University of Cincinnati
- **Mei Dai, PhD**, PGY-4, Institute of Materia Medica, Chinese Academy of Sciences, PR China
- **Jing-Fen Han, PhD**, PGY-6, University of Medicine & Dentistry of New Jersey
- **Juana Serrano-Lopez, PhD**, PGY-6, University of Cordoba Argentina
- **Shanmuganathan Chandrakasan, MD**, Children's Hospital of Michigan
- **Jed Kendall, BS**, PGY-6, Brigham Young University
- **Nihal Bakeer, MD**, Cincinnati Children's
- **Preeti Tandon, PhD**, PGY-3, University of Cincinnati
- **Mathieu Sertorio, PhD**, PGY-3, University Aix-Marseille II. INSERM, France
- **Xiaoli Li, PhD**, PGY-4, Chinese Center for Disease Control and Prevention
- **Surya Amarachintha, PhD**, PGY-3, Bowling Green State University
- **Ramesh Nayak, PhD**, PGY-6, University of Texas at Tyler
- **Ashley Ficker, BS**, 2009, University of Cincinnati

- **Cuiping Zhang, PhD**, PGY-2, Peking Union Medical College, China
- **Swarnava Roy, PhD**, 2010, National Institutes of Health
- **Harini Raghu, PhD**, PGY-5, VIT University, Vellore, India
- **Swati Tiwari, Grad Student**, 2011, University of Delhi
- **Archana Shresta, Grad Student**, 2011, Missouri State University
- **Jeffrey Vassallo, PhD**, PGY-1, Leheigh University, BMS
- **DanYang He, BS**, Grad S, Tsing Hua University, China
- **Laiman Wu, PhD**, PGY-3, University of Edinburg, UK
- **Chuntao Zhao, PhD**, PGY-4, Oklahoma University
- **Minqing Jiang, BS**, Grad S, Shanghai Normal University
- **Fanghui Lu, BS**, Grad S, Sichuan University, China
- **Xulian He, MD**, PGY-6, Sichuan University, China
- **Alejandro Lopez-Juarez, PhD**, PGY-4, Cincinnati Children's
- **Caleb Lewis, Undergrad**, University of Cincinnati
- **Ahmad Reyes, MD**, SUNY Upstate Medical University
- **Yuan Lin, PhD**, Univesity of Rochester
- **Jordan Althoff, BS**, 2013, Murray State University
- **Hongyan Zhu, PhD**, PGY-2, University of Cincinnati
- **Taryn Surtees, BS**, 2011, Washington University in St. Louis, MO
- **Kodanda Nalapreddy, PhD**, PGY-2, Harvard
- **Khalid Kalim, PhD**, PGY-4, Deutsche Rheuma-Forschungszentrum, Germany
- **Navneet Singh, PhD**, PGY-1, University of Southern Illinois
- **Aldo Segura-Cabrera, PhD**, PGY-2, Mexico
- **Wen Chai, BS**, PGY-1, University of Minnesota
- **Rushi Patel,**
- **Bhushan Lokesh, PhD**, PGY-4, Indian Institute of Science
- **Dino Masic,**
- **Jonathan Fletcher, BS**, PGY-3, Univesity of Michigan
- **Molly Smith, BSc**, GS-1, University of Wisconsin
- **Katelyn Melgar, BSc**, MSTP-1, Bucknell University
- **Xin Duan,** , University of Cincinnati
- **Cindy Wong Ping Lun, Grad Student**, Michigan State University
- **Sachin Kumar, PhD**, PGY-3, University of New Delhi, India
- **Ashwini Hinge, PhD**, PGY-3, University of Pune, India

Division Collaboration

Katayama K, Imai F, Campbell K, Lang RA, Zheng Y, Yoshida Y. (2013) RhoA and Cdc42 are required in pre-migratory progenitors of the medial ganglionic eminence ventricular zone for proper cortical interneuron migration. *Development* 140(15):3139-45. doi: 10.1242/dev.092585. PMID:23861058. (Yi Zheng, PhD)

Developmental Biology » Yutaka Yoshida, PhD

Wan H, Liu C, Wert SE, Xu W, Liao Y, Zheng Y, Whitsett JA. (2013) CDC42 is required for structural patterning of the lung during development. *Dev Biol.* 374(1):46-57. doi: 10.1016/j.ydbio.2012.11.030. PMID:23219958. (Yi Zheng, PhD)

Perinatal Institute » Jeffrey A. Whitsett, MD

Comparisons of the function of BRCA1 and Scml2 in somatic DNA damage responses in meiosis. (Paul Andreassen, PhD)

Reproductive Sciences » Satoshi Namekawa, PhD

Paper in J Clin Invest Jan 2014. Therapeutic antagonists of microRNAs deplete leukemia-initiating cell activity. (Jose Cancelas, MD, PhD)

Developmental Biology » Brian Gebelein, PhD

Paper in Nat Commun Apr 2013. Klf5 controls bone marrow homing of stem cells and progenitors through Rab5-mediated membrane β1/β2-integrin expression. (Jose Cancelas, MD, PhD)

Immunobiology » H. Leighton (Lee) Grimes, PhD

NIH grant application. Mechanisms of Granulocyte Homeostasis. (Jose Cancelas, MD, PhD)

Immunobiology » H. Leighton (Lee) Grimes, PhD

Oral presentation at ASH Annual Meeting 2013. Myelopoiesis from induced pluripotent stem cells reveals the role of elastase activity in the pathogenesis of severe congenital neutropenia. (Jose Cancelas, MD, PhD)

Immunobiology » H. Leighton (Lee) Grimes, PhD

Paper in Blood Apr 2014. Neutropenia-associated ELANE mutations disrupting translation initiation produce novel neutrophil elastase isoforms. (Jose Cancelas, MD, PhD)

Immunobiology » H. Leighton (Lee) Grimes, PhD

Paper in J Clin Invest Jan 2014. Therapeutic antagonists of microRNAs deplete leukemia-initiating cell activity. (Jose Cancelas, MD, PhD)

Immunobiology » H. Leighton (Lee) Grimes, PhD

Oral presentation at ASH Annual Meeting 2013. Kruppel-Like-Factor 5 (Klf-5) controls hematopoietic stem cell/progenitor bone marrow homing and lodging through Rab5-mediated expression of active β1 integrin. (Jose Cancelas, MD, PhD)

Immunobiology » H. Leighton (Lee) Grimes, PhD

Poster presentation at ASH Annual Meeting 2013: Increased oxidative stress in sickle cell disease activates the renin-angiotensin-TGF-beta pathway to mediated sickle nephropathy. (Jose Cancelas, MD, PhD)

Hematology » Theodosia A. Kalfa, MD, PhD

NIH grant application. Quercetin: Novel targeted chemoprevention for Fanconi anemia patients. (Jose Cancelas, MD, PhD)

Bone Marrow Transplantation and Immune Deficiency » Parinda A. Mehta, MD

Paper in Nat Commun 2013. Klf5 controls bone marrow homing of stem cells and progenitors through Rab5-mediated membrane β1/β2-integrin expression. (Jose Cancelas, MD, PhD)

Pulmonary Biology » Jeffrey A. Whitsett, MD

Studies of molecular determinants of arthritis. (Jay Degen, PhD)

Rheumatology » Sherry L. Thornton, PhD

Role of hemostatic factors in sickle cell disease. (Jay Degen, PhD)
Hematology » Eric Mullins, MD

Role of ATF3 in neutrophil migration during lung inflammation. (Marie-Dominique Filippi, PhD)
Immunobiology » Christopher Karp, MD

The fibrinogen-plasminogen axis and arthritis pathogenesis. (Matthew Flick, PhD)
Rheumatology » Sherry L. Thornton, PhD

The coagulation protease thrombin drives colitis-associated cancer. (Matthew Flick, PhD)
Hematology » Eric Mullins, MD and Joseph S. Palumbo, MD
Gastroenterology » Eric Mullins, MD, Joseph S. Palumbo, MD, and Kris A. Steinbrecher, PhD

Publication: “mTOR regulates DNA damage response through NF-κB-mediated FANCD2 pathway in hematopoietic cells.” (Fukun Guo, PhD)

Critical Care Medicine » Basilia Zingarelli, MD, PhD

Publication: mTOR kinase inhibitor sensitizes T-cell lymphoblastic leukemia for chemotherapy-induced DNA damage via suppressing FANCD2 expression. (Fukun Guo, PhD)
Immunobiology » H. Leighton (Lee) Grimes, PhD

Testing of in vivo efficacy of targeting p97/ERAD in breast cancers.
Publication: Singh et al, In review. (Kakajan Komurov, PhD)
Oncology » Biplab Dasgupta, PhD, MS and Lisa Privette-Vinnedge, PhD

Developing Structural Equations Modeling to query complex mechanisms from cancer genomics datasets.
Publication: Lane et al, Oncogene 2013. (Kakajan Komurov, PhD)
Bone Marrow Transplantation and Immune Deficiency » Adam Lane, PhD

Development of Gene Therapy for hPAP. (Carolyn Lutzko, PhD)
Section of Neonatology, Perinatal and Pulmonary Biology » Bruce Trapnell, MS, MD

Development of markers to identify lung stem cells. (Carolyn Lutzko, PhD)
Section of Neonatology, Perinatal and Pulmonary Biology » Jeffrey A. Whitsett, MD

Development of iPSC models of cardiomyopathy. (Carolyn Lutzko, PhD)
Molecular Cardiovascular Biology » Stephanie Ware, MD, PhD

Development of iPSC models of neutropenia. (Carolyn Lutzko, PhD)
Immunobiology » H. Leighton (Lee) Grimes, PhD

Development of anti-viral Cytotoxic T Lymphocytes. (Carolyn Lutzko, PhD)
Bone Marrow Transplantation and Immune Deficiency » Michael S. Grimley, MD

xSCID Gene Therapy. (Carolyn Lutzko, PhD)

Bone Marrow Transplantation and Immune Deficiency » Alexandra (Lisa) H. Filipovich, MD

Gene Therapy for HLH - Publication: Perforin gene transfer into hematopoietic stem cells corrects immune dysfunction in murine models of perforin deficiency. (Punam Malik, MD)

Immunology Center - Immunobiology » Michael B. Jordan, MD and Kimberly A. Risma, MD, PhD

Pulmonary Pathology in Sickle Cell Disease. (Punam Malik, MD)

Section of Neonatology, Perinatal and Pulmonary Biology » Gurjit Khurana Hershey, MD, PhD, Eric Brandt, PhD, and Timothy LeCras, PhD

Cardiac Aspects of Sickle Cell Disease. (Punam Malik, MD)

Heart Institute » Jeffrey Towbin, MD, FAAP, FACC, FAHA, Michael D. Taylor, MD, and Thomas R. Kimball, MD

Renal Aspects of SCD. (Punam Malik, MD)

Hematology » Prasad Devarajan, MD, Courtney Fitzhugh, Alex George, MD, PhD, Prasad Bodas, George Atweh, MD, Charles T. Quinn, MD, MS, Ashok Raj, Eric Kraut, and Santosh Saraf

Zileuton. (Punam Malik, MD)

Asthma Research » Sander A. Vinks, PharmD, PhD, FCP and Uwe Christians

Hematology » Karen A. Kalinyak, MD and Maa-Ohui Quarmyne, MD, PL-V

Gene Transfer and Stem Cell Maintenance. (Punam Malik, MD)

Hematology » Michael B. Jordan, MD

XSCID Gene Therapy.
Publication: New England Journal of Medicine article titled “"A Self-Inactivating γ-Retrovirus Vector for Severe Combined Immunodeficiency,"
(Punam Malik, MD)

Bone Marrow Transplantation and Immune Deficiency » Alexandra (Lisa) H. Filipovich, MD

Gene Therapy for Sickle Cell Disease. (Punam Malik, MD)

Hematology » Karen A. Kalinyak, MD, Charles T. Quinn, MD, MS, and Theodosia A. Kalfa, MD, PhD

Bone Marrow Transplantation and Immune Deficiency » Stella M. Davies, MBBS, PhD, MRCP

ROS in Sickle Cell Disease. (Punam Malik, MD)

Hematology » Theodosia A. Kalfa, MD, PhD

Xenograft Leukemia Model. (James Mulloy, PhD)

Immunobiology » H. Leighton (Lee) Grimes, PhD

Humanizing Mice. (James Mulloy, PhD)

Immunobiology » Claire A. Chougnet, PhD and Julio Aliberti, MS, PhD

Role of Meis1 in AML. (James Mulloy, PhD)
Bone Marrow Transplantation and Immunodeficiency » Ashish Kumar, MD, PhD

Role of Thrombin in AML. (James Mulloy, PhD)
Hematology » Joseph S. Palumbo, MD

Human Mast Cell Development in Humanized Immunodeficient Mice. (James Mulloy, PhD)
Immunobiology » Fred Finkelman, MD

NK cell therapy for AML. (James Mulloy, PhD)
Allergy and Immunology » Kimberly A. Risma, MD, PhD

Human Eosinophil Progenitor Cell Development in Humanized Immunodeficient Mice. (James Mulloy, PhD)
Allergy and Immunology » Patricia C. Fulkerson, MD, PhD

Human Eosinophil Cell Development in Humanized Immunodeficient Mice. (James Mulloy, PhD)
Allergy and Immunology » Nives Zimmermann, MD

Pathobiology of Monosomy 7 MDS.
(James Mulloy, PhD)
Bone Marrow Transplantation and Immune Deficiency » Parinda A. Mehta, MD

Wee1 Inhibitor in AML.
(James Mulloy, PhD)
Oncology » Maureen M. O'Brien, MD, MS

Mouse Model for XIAP.
(James Mulloy, PhD)
Bone Marrow Transplantation and Immune Deficiency » Rebecca A. Marsh, MD

Norovirus Vaccine using Humanized Mice.
(James Mulloy, PhD)
Infectious Disease » Xi Jason Jiang, PhD

AML Pathogenesis.
(James Mulloy, PhD)
Pathology » Gang Huang, PhD

Therapy for CML.
(James Mulloy, PhD)
Pathology » Mohammad Azam, PhD

Gene Therapy for Gaucher Disease leading to dual PI RO1 Award. (Dao Pan, PhD)
Human Genetics » Gregory A. Grabowski, MD

Publication “Deletion of *Fanca* or *Fancd2* dysregulates Treg in mice”. (Qishen Pang, PhD)

Bone Marrow Transplantation and Immune Deficiency » Stella M. Davies, MBBS, PhD, MRCP, Parinda A. Mehta, MD, and Kasiani C. Myers, MD

Publication “Deletion of *Fanca* or *Fancd2* dysregulates Treg in mice”. (Qishen Pang, PhD)

Gastroenterology, Hepatology and Nutrition » Kris A. Steinbrecher, PhD

Watson, A.L., Rahrmann, E.P., Moriarity, B., Choi, K., Conboy, C., Greeley, A., Halfond, A., Anderson, L., Wahl, B., Keng, V.W., Rizzardi, A., Forser, C., **Collins, M.H.**, Sarver, A., Wallace, M., Schmechel, S., **Ratner, N**., and Largaespada, D.A. (2013) Canonical Wnt/β-catenin Signaling Drives Human Schwann Cell Transformation, Progression, and Tumor Maintenance. *Cancer Discov*. Jun;3(6):674-689. (Nancy Ratner, PhD)

Pathology and Laboratory Medicine » Margaret H. Collins, MD

Rahrmann, E.P., Watson, A.L., Keng, V.W., Choi, K., Moriarity, B., Beckmann, D.A., Wolf, N., Sarver, A., **Collins, M.H**., Moertel, C.L., Wallace, M.R., Gel, B., Serra, S., **Ratner, N**., & Largaespada, D.A. (2013) Forward genetic screen for malignant peripheral nerve sheath tumor formation identifies novel genes and genetic pathways driving tumorigenesis. *Nature Genetics*, 45(7):756-66. (Nancy Ratner, PhD)

Pathology and Laboratory Medicine » Margaret H. Collins, MD

Watson, A.L., Anderson, L.K., Greeley, A.D., Keng, V.W., Rahrmann, E.P., Halfond, A.L., Powell, N.M., **Collins, M.H.**, Rizvi, T.A., Moertel, C.L., **Ratner, N**., & Largaespada, D.A. (2014) Co-Targeting the MAPK and PI3K/AKT/MTOR Pathways in Two Genetically Engineered Mouse Models of Schwann Cell Tumors Reduces Tumor Grade and Multiplicity, *Oncotarget,* 2014 Oncotarget. 2014 Mar 30;5(6):1502-14. PMID: 24681606. (Nancy Ratner, PhD)

Pathology and Laboratory Medicine » Margaret Collins

Mayes, D.A., Rizvi, T.A., Titus-Mitchell, H.,A., Oberst, R., Ciraolo, G.M., Vorhees, C.V., Robinson, A.P., Miller, S.D., Stemmer-Rachamimov, A.O., and **Ratner, N**.(2013) Nf1 loss and Ras activation in Oligodendrocytes induce NOS-driven Defects in Myelin and Vasculature *Cell Reports,* Sep 26;4(6):1197-212. (Nancy Ratner, PhD)

Neurology » Charles V. Vorhees, PhD

Grant, U.S. Army NF Program, DOD W81XWH-11-1-0057. “Cellular and Molecular Contributions to Neurofibroma Formation”, Lang, Co-PI Ratner PI. (Nancy Ratner, PhD)

Visual Systems Group » Richard A. Lang, PhD

Sharing of experiments: Subject: Consequence on diet induced obesity on hematopoietic stem and progenitor compartment. (Damien Reynaud, PhD)

Immunobiology » Senad Divanovic, PhD

Sharing of protocols/experience: inflammation and feedback inhibition of lymphopoiesis. (Damien Reynaud, PhD)

Immunobiology » Michael B. Jordan, MD

Publication: Myeloid malignancies with chromosome 5q deletion acquire a dependency on an intrachromosomal NF-kB gene network. (Daniel Starczynowski, PhD)

Center for Autoimmune Genomics and Etiology (CAGE) » Matthew T. Weirauch, PhD

Publication “The protein tyrosine phosphatase Shp2 is required for the generation of oligodendrocyte progenitor cells and myelination in the mouse telencephalon.” (Ronald Waclaw, PhD)

Developmental Biology » Masato Nakafuku MD, PhD

Grants, Contracts, and Industry Agreements

Grant and Contract Awards		Annual Direct
AKUNURU, S		
Training Programs in Cancer Therapeutics		
National Institutes of Health(University of Cincinnati)		
T32 CA 117846	09/14/12-08/31/14	$42,862
CANCELAS-PEREZ, J		
Rational Design of a Vav/Rac Inhibitor as a New Therapy for High-Risk B-ALL		
The Leukemia and Lymphoma Society		
	10/01/12-09/30/15	$180,018
Validation of a Rationally Designed Guanine Nucleotide Exchange Factor Inhibitor in Lymphoblastic Leukemia		
William Lawrence & Blanche Hughes Foundation		
	01/01/14-12/31/16	$70,000
DEGEN, J		
Analysis of Staphylococcus Aureus Host Interactions		
National Institutes of Helath(Texas A&M University Health Science Center)		
R01 AI 020624	09/01/12-08/31/15	$46,736
DEGEN, J / MALIK P		
Hemostatic Factors and Sickle Cell Disease		
National Institutes of Health		
R01 HL 112603	01/01/12-11/30/16	$245,000
FILIPPI, M		
Regulation of Neutrophil Migration and Polarity		
National Institutes of Health		
R01 HL 090676	03/01/10-02/28/15	$242,550
FLICK, M		
Mechanisms Linking the Hemostatic Protease Thrombin to Arthritic Disease		
National Institutes of Health		
R01 AR 056990	08/10/09-07/31/14	$162,518
Cincinnati Rheumatic Disease Core Center (Core 2)		
National Institutes of Health		
P30 AR 047363	08/25/11-06/30/16	$45,687

GEIGER, H

Molecular Mechanisms and Therapies for Radiation-Induced Myelodysplastic Syndrome
Edward P Evans Foundation(University of Kentucky)

	04/01/12-03/31/17	$181,818

GUO, F

Novel Signaling Function of Cdc42 GTPase in vivo
National Institutes of Health

R01 GM 108661	05/01/14-02/28/18	$175,000

HENNIGAN, R

Regulation of Intracellular Trafficking in NF2
Department of Defense

W81XWH1310136	06/01/13-05/31/16	$133,290

KOMUROV, K

Modeling and Targeting the Hexosamine Pathway in Drug Resistance
Susan G Komen for the Cure

	08/01/13-07/31/16	$120,000

LU, Q

A Novel Model of Medulloblastoma to Define Cancer Pathways and Molecular Targets
National Institutes of Health

R01 NS 078092	10/01/13-03/31/17	$349,062

Chromatin Remodeling Control of CNS Myelination and Remyelination
National Institutes of Health

R01 NS 075243	10/01/13-03/31/17	$399,554

Chromatin Remodeling in Oligodendrocyte Myelination and Remyelination
National Multiple Sclerosis Society

RG4568A5T	10/01/13-03/31/14	$31,122

microRNA Control of Myelination and Remyelination in the Central Nervous System
National Multiple Sclerosis Society

RG4727A6T	10/01/13-06/30/15	$148,046

Molecular Mechanisms of Oligodendrocyte Differentiation and Myelination
National Institutes of Health

R01 NS 072427	10/01/13-08/31/15	$138,615

Identification of Novel Small Molecules for CNS Myelin Repair
National Institutes of Health(Texas A&M)

R21 NS 077215	11/01/13-06/30/15	$67,644

MALIK, P

Ameliorating Sickle Nephropathy and Pulmonary Hypertension
National Institutes of Health

R34 HL 108752 08/18/11-06/30/14 $142,800

Cincinnati Cell Characterization Core

National Institutes of Health(University of Maryland)

U01 HL 099997 09/01/10-04/30/15 $50,862

Cincinnati Cell Characterization Core (per case reimbursement)

National Institutes of Health(University of Maryland)

U01 HL 099997 05/01/11-04/30/14 $109,291

Cincinnati Center of Excellence in Hemoglobinopathies Research

National Institutes of Health

U01 HL 117709 08/15/13-05/31/18 $1,169,344

Quinn, C	Translational Research Skills Development Core	$258,435	
Kalfa, T	Research Project 1	$123,169	
Malik, P	Research Project 2	$548,319	
Quinn, C	Research Project 3	$222,743	
Kalfa, T	Summer Students	$40,542	

Gene Therapy for Sickle Cell Anemia

Doris Duke Charitable Foundation

09/01/13-08/31/16 $150,000

PLGF-H1F1a-mIRNA Axis in Sickle Pulmonary Hypertension

National Institutes of Health(University of Southern California)

R01 HL 111372 01/01/12-12/31/16 $143,001

MULLOY, J

Genotype and Phenotype of Chemoresistant AML

National Institutes of Health

R21 CA 168369 03/01/13-02/28/15 $105,488

Rac Signaling in MLL Leukemia

The Leukemia and Lymphoma Society

07/01/10-06/30/15 $104,762

LSC Mobilization and Differentiation Therapy

Hyundai Hope on Wheels

09/01/13-12/31/15 $250,000

Conferring In Vivo Metabolic Resistance to a Highly Selective Anti-AML Agent

National Institutes of Health(University of Cincinnati)

R21 CA185370 05/01/14-02/28/16 $29,928

NASSAR, N

Novel Rationally Designed Ras Inhibitors for B-ALL Multi-Target Therapy

The Leukemia and Lymphoma Society

	10/01/13-09/30/16	$180,018

PAN, D

Gaucher Disease: Treatment of Neurodegenerative Disease
National Institutes of Health

R01 NS 086134	09/01/13-05/31/18	$270,887

PANG, Q

Role of FA Proteins in Hematopoiesis
National Institutes of Health

R01 HL 076712	04/01/10-03/31/15	$242,550

Targeted Improvement in Stem Cell Therapy for Leukemia and Bone Marrow Failure Syndromes
National Institutes of Health

R01 CA 157537	02/01/11-12/31/15	$186,750

PATEL, A

Identification and Study of Novel Genes Critical to Survival of MPNST Cells
Ohio State University

	06/01/13-05/31/15	$46,092

RATNER, N

Identification of Molecular and Cellular Contributors to Neurofibroma Formation and Growth
Department of Defense

W81XWH1210133	07/01/12-06/30/15	$225,000

Identification of Neurofibroma Growth and Drug Resistance Pathways
Johns Hopkins University(Neurofibromatosis Therapeutic Acceleration Program)

	02/01/14-01/31/16	$65,902

Mitogenic Activities in Neurofibromatosis
National Institutes of Health

R01 NS 028840	09/15/11-07/31/16	$223,156

Neurofibroma Preclinical Therapeutics
The Children's Tumor Foundation

	07/15/13-07/14/16	$287,661

Ras Proteins in Nerve Tumorigenesis
National Institutes of Health

R01 NS 083580	04/01/14-03/31/19	$218,750

Regulation of GCPII for the Diagnosis and Treatment of Neurofibromas
John Hopkins University (Neurofibromatosis Therapeutic Acceleration Program)

	05/01/14-04/30/15	$33,085

SAMPSON, L

mTOR Signaling in Murine Intestinal Stem Cell and Progenitor Homeostasis
National Institutes of Health

F32 DK 097879	12/01/12-11/30/14	$55,094

SPRINGER, M

Training Programs in Cancer Therapeutics
National Institutes of Health(University of Cincinnati)
T32 CA 11786 08/01/13-07/31/15 $39,265

STARCZYNOWSKI, D

Defining the Role and Therapeutic Potential of TNF Receptor-Associated Factor 6 in Myelodysplastic Syndromes
Gabrielle's Angel Foundation for Cancer Research
06/01/13-05/31/16 $68,182

Deregulation of TIFAB in Myelodysplastic Syndrome
American Society of Hematology
07/01/11-06/30/14 $50,000

Identification and Characterization of Genes in del(5q) Myelodysplastic Syndrome
National Institutes of Health
R01 HL 111103 12/15/11-11/30/16 $245,000

TANDON, P

Characterizing the Role of Specific Ras Proteins in Neurofibroma and MPNST Formation
National Institutes of Health
F32 NS 083249 09/01/13-08/31/15 $49,214

VARNEY, M

Environmental Carcinogenesis and Mutagensis
National Institutes of Health(University of Cincinnati)
T32 ES007250 05/01/12-04/30/15 $46,092

WU, L

Functional Study of Transcriptional Regulator Sip1 in CNS Myelination and Remyelination
National Multiple Sclerosis Society
10/01/13-09/30/16 $51,642

WU, J

STAT3 in Neurofibroma Tumorigenesis and Therapy
Department of Defense Army
W81XWH1110259 07/01/11-06/30/14 $137,415

ZHENG, Y

Cincinnati Center for Excellence in Molecular Hematology
National Institutes of Health
P30 DK 090971 09/01/11-06/30/15 $456,330

A Non-Myeloablative Conditioning Regimen for Hematopoietic Stem Cell Transplant
National Institutes of Health(P2D Bioscience)

R34 HL117576	02/17/14-02/16/15	$86,732

Therapeutic Targeting of LARG-RhoA-ROCK Signaling Axis in Childhood Leukemia
Alex's Lemonade Stand Foundation

	07/01/13-06/30/15	$125,000

ZHENG, Y/ GEIGER, H

Lineage Determination and Tissue Homeostasis in the Aged Hematopoietic System
National Institutes of Health

R01 AG 040118	08/01/11-07/31/16	$212,625

ZHENG, Y / MULLOY J

Targeting Cdc42 in Leukemia Stem Cells
National Institutes of Health

R01 CA 150547	03/10/10-01/31/15	$195,237

Current Year Direct	**$8,832,677**

Industry Contracts

FLICK, M

Novo Nordisk	$115,747

GRASSMAN, E

Battelle Memorial Institute	$34,010

MULLOY, J

Amgen, Inc.	$7,261

STARCZYNOWSKI, D

Celgene Cellular Therapeutics	$33,433

Current Year Direct Receipts	**$190,451**
Total	**$9,023,128**