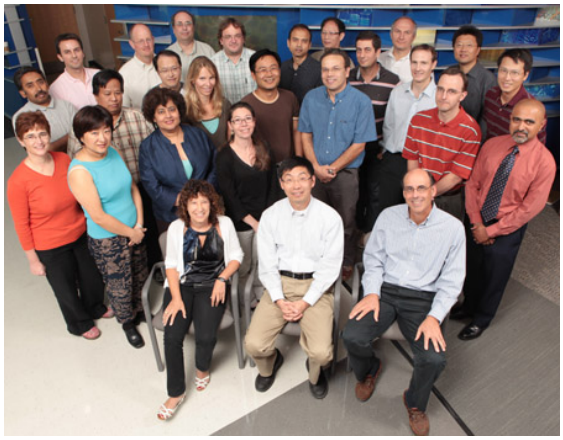
Experimental Hematology and Cancer Biology

Division Data Summary

Research and Training Details

Number of Faculty	**23**
Number of Joint Appointment Faculty	**16**
Number of Research Fellows	**24**
Number of Research Students	**16**
Number of Support Personnel	**76**
Direct Annual Grant Support	**$9,116,728**
Direct Annual Industry Support	**$39,935**
Peer Reviewed Publications	**70**

Division Photo



Row 1: N Ratner, Y Zheng, J Degen
Row 2: D Pan, P Malik, MD Filippi, R Drissi, R Waclaw, A Kumar
Row 3: T Kalfa, R Meetei, S Wells, J Wu, J Mulloy, L Chow
Row 4: M Azam, F Guo, B DasGupta, N Nassar, G Huang
Row 5: D Starczynowski, M Flick, J Cancelas, P Andreassen, Q Pang, L Grimes

Significant Publications

Flick MJ, Chauhan AK, Frederick M, Talmage KE, Kombrinck KW, Miller W, Mullins ES, Palumbo JS, Zheng X, Esmon NL, Esmon CT, Thornton S, Becker A, Pelc LA, Di Cera E, Wagner DD, Degen JL. **The development of inflammatory joint disease is attenuated in mice expressing the anticoagulant prothrombin mutant W215A/E217A**. *Blood*. 117(23):6326-37. Jun 9, 2011.

Thrombin is a positive mediator of thrombus formation through the proteolytic activation of protease-activated receptors (PARs), fibrinogen, factor XI (fXI), and other substrates, and a negative regulator through activation of protein C, a natural anticoagulant with anti-inflammatory/cytoprotective properties. Protease-engineering studies have established that 2 active-site substitutions, W215A and E217A (fII(WE)), result in dramatically reduced catalytic efficiency with procoagulant substrates while largely preserving thrombomodulin (TM)-dependent protein C activation. To explore the hypothesis that a prothrombin variant favoring antithrombotic pathways would be compatible with development but limit inflammatory processes in vivo, we generated mice carrying the fII(WE) mutations within the endogenous prothrombin gene. Unlike fII-null embryos, fII(WE/WE) mice uniformly developed to term. Nevertheless, these mice ultimately succumbed to spontaneous bleeding events shortly after birth. Heterozygous fII(WT/WE) mice were viable and fertile despite a shift toward an antithrombotic phenotype exemplified by prolonged tail-bleeding times and times-to-occlusion after $FeCl_3$ vessel injury. More interestingly, prothrombin(WE) expression significantly ameliorated the development of inflammatory joint disease in mice challenged with collagen-induced arthritis (CIA). The administration of active recombinant thrombin(WE) also suppressed the development of CIA in wild-type mice. These studies provide a proof-of-principle that pro/thrombin variants engineered with altered substrate specificity may offer

therapeutic opportunities for limiting inflammatory disease processes.

Sengupta A, Arnett J, Dunn S, Williams DA, Cancelas JA. **Rac2 GTPase deficiency depletes BCR-ABL+ leukemic stem cells and progenitors in vivo**. *Blood*. 116(1):81-4. Jul 8, 2010.

Chronic myelogenous leukemia (CML) is a clonal myeloproliferative disease (MPD) initiated by p210-BCR-ABL-mediated transformation of hematopoietic stem cells (HSCs). Inhibition of the ABL kinase alone is not sufficient to eradicate leukemic stem cells (LSCs). We have previously shown that the deficiency of Rac2 GTPase signaling, but not Rac1, in p210-BCR-ABL-transduced hematopoietic cells prolonged survival of mice with MPD. Here we demonstrate that absence of Rac2 GTPase prolongs survival of HSC-initiated, inducible Scl/p210-BCR-ABL (Scl/p210) binary transgenic mice, it induces apoptosis, and, unlike in normal HSC and progenitor (HSC/P), impairs LSC and progenitor (LSC/P) proliferation in vivo. As a result, Rac2 deficiency causes functional exhaustion of the LSC pool in vivo. This defect is not due to impaired interaction with the hematopoietic microenvironment as reflected by its unaltered adhesion, migration, and homing to recipient organs. In summary, Rac2 deficiency exhausts the LSC pool in vivo through impairment of oncogene-induced proliferation and survival signals.

Hummel TR, Jessen WJ, Miller SJ, Kluwe L, Mautner VF, Wallace MR, Lázaro C, Page GP, Worley PF, Aronow BJ, Schorry EK, Ratner N. **Gene expression analysis identifies potential biomarkers of neurofibromatosis type 1 including adrenomedullin**. *Clin Cancer Res*. 16(20):5048-57. Oct 15, 2010.

Plexiform neurofibromas (pNF) are Schwann cell tumors found in a third of individuals with neurofibromatosis type 1 (NF1). pNF can undergo transformation to malignant peripheral nerve sheath tumors (MPNST). There are no identified serum biomarkers of pNF tumor burden or transformation to MPNST. Serum biomarkers would be useful to verify NF1 diagnosis, monitor tumor burden, and/or detect transformation. We used microarray gene expression analysis to define 92 genes that encode putative secreted proteins in neurofibroma Schwann cells, neurofibromas, and MPNST. We validated differential expression by quantitative reverse transcription-PCR, Western blotting, and ELISA assays in cell conditioned medium and control and NF1 patient sera. Of 13 candidate genes evaluated, only adrenomedullin (ADM) was confirmed as differentially expressed and elevated in serum of NF1 patients. ADM protein concentrati on was further elevated in serum of a small sampling of NF1 patients with MPNST. MPNST cell conditioned medium, containing ADM and hepatocyte growth factor, stimulated MPNST migration and endothelial cell proliferation. Thus, microarray analysis identifies potential serum biomarkers for disease, and ADM is a serum biomarker of NF1. ADM serum levels do not seem to correlate with the presence of pNFs but may be a biomarker of transformation to MPNST.

Chou FS, Wunderlich M, Griesinger A, Mulloy JC. **N-Ras(G12D) induces features of stepwise transformation in preleukemic human umbilical cord blood cultures expressing the AML1-ETO fusion gene**. *Blood*. 117(7):2237-40. Feb 17, 2011.

AML1-ETO (AE) is a fusion product of t(8;21) observed in 40% French-American-British M2 type of acute myeloid leukemia (AML). Clinical data suggest that Ras mutation is a frequent cooperating event in t(8;21) AML. Whether constitutively active Ras promotes leukemogenesis on the t(8;21) background has not been demonstrated experimentally. Here, we retrovirally expressed N-Ras(G12D) in AE-expressing human hematopoietic cells to investigate cooperativity. The AE/N-Ras(G12D) cultures were cytokine-independent, enriched for CD34 positivity, and possessed increased colony-forming and replating abilities. N-Ras(G12D) expression led to Bcl-2 up-regulation and reduced apoptosis. Ectopic Bcl-2 expression also resulted in enhanced colony-forming and replating abilities but was insufficient to sustain cytokine independence. AE/N-Ras(G12D) cells were more sensitive to Bcl-2 inhibition with ABT-737 than parent AE cells. Enhanced engraftment of AE/N-Ras(G12D) cells was observed on intrafemoral injection into immunodeficient mice, presumably because of improved survival in the bone marrow microenvironment. N-Ras(G12D) promotes

progression toward transformation in AE-expressing cells, partially through up-regulating Bcl-2.

Sengupta A, Duran A, Ishikawa E, Florian MC, Dunn SK, Ficker AM, Leitges M, Geiger H, Diaz-Meco M, Moscat J, Cancelas JA. **Atypical protein kinase C (aPKCzeta and aPKClambda) is dispensable for mammalian hematopoietic stem cell activity and blood formation**. *Proc Natl Acad Sci U S A*. 108(24):9957-62. Jun 14, 2011.

The stem-cell pool is maintained by a balance between symmetric and asymmetric division of stem cells. The facultative use of symmetric and asymmetric cell division is thought to be orchestrated by a polarity complex consisting of partitioning-defective proteins Par3 and Par6, and atypical protein kinase C (aPKCζ and aPKCλ), which regulates planar symmetry of dividing stem cells. In this report by Dr. Jose Cancelas' group, it is shown that in contrast to accepted paradigms, polarization and activity of adult hematopoietic stem cell (HSC) do not depend on either aPKCζ or aPKCλ or both. Mice, having deleted aPKCζ and aPKCλ, have normal hematopoiesis, including normal HSC self-renewal, engraftment, differentiation, and interaction with the bone marrow microenvironment. In addition, aPKCζ- and aPKCλ-deficient HSCs elicited a normal pattern of hematopoietic recovery secondary to myeloablative stress. Thus, contrary to the hypothesis of a unique, evolutionary conserved aPKCζ/λ-directed cell polarity signaling mechanism in HSC fate determination, this study unambiguously demonstrates that atypical protein kinase Cs are dispensable for HSC fate determination.

Division Highlights

Yi Zheng

The Zheng lab has published the first RhoA knockout mouse model and discovered an essential role of RhoA GTPase in regulating cell mitosis. This work is leading to a series of studies of RhoA physiologic and pathological functions in mammals. (Melendez J, Stengel K, Zhou X, Chauhan BK, Debidda M, Andreassen P, Lang RA, Zheng Y. **RhoA GTPase is dispensable for actomyosin regulation but is essential for mitosis in primary mouse embryonic fibroblasts**. *J. Biol. Chem.* 286(17):15132-7. 2011.)

Paul Andreassen

1. The Andreassen lab published a paper (F. Zhang et al. *Chromosoma*. 110:1637-1649. 2010.) which demonstrated that FANCJ acts in parallel with monoubiquitinated FANCD2, rather than strictly downstream as previously believed. Further, FANCJ promotes chromatin access of monoubiquitinated FANCD2.

2. The Andreassen lab collaborated with the group of Satoshi Namekawa in the Division of Reproductive Sciences at CCHMC. This work on DNA damage response proteins in silencing of the sex chromosomes in male germ cells was published in Genes & Development (Y. Ichijima et al. **MDC1 directs chromosome-wide silencing of the sex chromosomes in male germ cells**. *Genes Dev*. 25:959-971. May, 2011.).

Jose Cancelas

1. We demonstrate that a new protocol of pathogen inactivation using the alkylant S-303 provides a reasonable safety level for stored red cell viability in vivo (Cancelas JA et al. **Stored red blood cell viability is maintained after treatment with a second-generation S-303 pathogen inactivation process**. *Transfusion*. May 13, 2011.)
2. We demonstrate that prion filtration as a novel system for pathogen inactivation provides a reasonable safety level for stored red cell viability and immunogenicity in vivo (Cancelas JA et al. **Infusion of P-Capt prion-filtered red blood cell products demonstrate acceptable in vivo viability and no evidence of neoantigen formation**. *Transfusion*. Oct, 2011.)

3. We demonstrate that riboflavin and UV light may be used in stored, but not long-term stored, whole blood products (Cancelas JA et al. **In vivo viability of stored red blood cells derived from riboflavin plus ultraviolet light-treated whole blood**. *Transfusion*. 51(7):1460-8. Jul, 2011.).

Lionel Chow

Chow lab studies High-Grade Astrocytoma (HGA) and Oligodendroglioma (ODG), which are very aggressive brain tumors in adults and children. We use a combination of novel mouse models and human tumor studies to elucidate the biology of these tumors in order to develop and test effective treatments for this disease. Studies with genetically-engineered mouse models that develop HGA and ODG spontaneously to explore the molecular signals and cooperating mutations that drive tumor growth. We recently described our studies on some of these models (Chow LM et al. **Cooperativity within and among Pten, p53, and Rb pathways induces high-grade astrocytoma in adult brain**. *Cancer Cell.* 19(3):305-16. 2011.).

Jay Degen

Thrombin-mediated proteolysis is central to the control of hemostasis and thrombosis, but it is increasingly understood that prothrombin and multiple thrombin substrates play a pivotal role in embryonic development, tissue repair, malignancy, and inflammation. In collaborative studies done with Dr. Matthew Flick (Flick et al. **The development of inflammatory joint disease is attenuated in mice expressing the anticoagulant prothrombin mutant W215A/E217A**. *Blood.* 117(23): 6326-6337. 2011.), we examined for the first time the in vivo consequences of the expression of a re-engineered form of prothrombin, termed prothrombin^{WE}, with substrate specificity favoring the activation of protein C (a protease with known anticoagulant and anti-inflammatory properties). The expression of prothrombin^{WE} was found to significantly limit the development of inflammatory joint disease in mice challenged with collagen-induced arthritis (CIA). Furthermore, the administration of exogenous active recombinant thrombin^{WE} also suppressed the development of arthritis in wild-type mice. These studies provide a proof-of-principle that pro/thrombin variants engineered with altered substrate specificity may offer therapeutic opportunities for limiting inflammatory disease processes.

Marie Dominique-Filippi

The overarching goal of my research program is to understand the molecular regulation of hematopoietic cell functions. Specifically, we have been investigating the role of cell shape and cytoskeleton reorganization in modulating hematopoietic stem cell self renewal and engraftment, and neutrophil migration and trafficking. We have identified a new role for p190-B-RhoGAP as a regulator of hematopoietic stem cell self renewal and cell fate decision during cell division. Furthermore, we are now showing that p190-B may do so by fine tuning cytoskeleton/microtubule reorganization as well as epigenetic regulation of gene expression. Other research project is to dissect the process of cell migration in neutrophils. We recently showed that Cdc42 unexpectedly uses aMb2 integrin signaling for efficient directed migration. We have now dissected this mechanism in more detail and have uncovered a novel mechanism of neutrophil migration involving WASp, Lipid raft formation, CD11b and microtubules. (manuscript in preparation)

Matthew Flick

1. We have demonstrated that introduction of a (pro)thrombin variant termed fII W215A/E217A either genetically or pharmacologically can limit the development of arthritis in mice. This work is presented in a manuscript in the journal *Blood* in June of 2011 and was highlighted in an “Inside Blood” commentary. (Flick MJ, Chauhan AK, Frederick M, Talmage KE, Kombrinck KW, Miller W, Mullins ES, Palumbo JS, Zheng X, Esmon NL, Esmon CT, Thornton S, Becker A, Pelc LA, Di Cera E, Wagner DD, Degen JL. **The**

development of inflammatory joint disease is attenuated in mice expressing the anticoagulant prothrombin mutant W215A/E217A. *Blood.* 117(23):6326-6337. 2011.)

2. Progress has been made demonstrating that the coagulation factor fibrinogen promotes *S. aureus* virulence by supporting pathogen adherence via the bacterial receptor Clumping Factor A. A formal collaboration with Dr. Magnus Hook at the Texas A&M Health Science Center has developed in association with this work and new funding (NIH R01 AI020662 Consortium Agreement) has been obtained.

Hartmut Geiger

The Geiger lab published in 2010 on a the finding that the Epidermal-Growth-Factor Receptor regulates mobilization of hematopoietic stem cells from bone marrow into peripheral blood and that pharmacological inhibition of EGFR signaling by the drug Erlotinib enhances granulocyte-colony-stimulating factor induced mobilization of stem cells.

(Ryan MA, NattamaiKJ, Xing E, Schleimer, Daria D, Sengupta A, Köhler A, Liu W, Gunzer M, Jansen M, Ratner N, Le Cras TD, Waterstrat A, Van Zant G, Cancelas JA, Zheng Y, Geiger H. **Pharmacological inhibition of EGFR signaling enhances G-CSF induced hematopoietic stem cell mobilization**. *Nat. Med*. *16* (10). 1141-6. 2010.)

Fukun Guo

We have studied the role of Cdc42 in T cell development and function and revealed an essential function of Cdc42 mediating IL7 signaling and T cell homeostasis (Guo F, et al. **Coordination of IL-7 receptor and T-cell receptor signaling by cell-division cycle 42 in T-cell homeostasis**. *PNAS*. 107(43):18505-10. 2010; Guo F, et al. **Distinct roles of Cdc-42 in thymopoiesis and effector and memory T cell differentiation**. *PLoS One.* 6(3):e18002. 2011.)

Carolyn Lutzko

1. Development of human induced pluripotent stem cells (iPSC) from human peripheral blood.

2. Development of clinical lentiviral transduction conditions for human CD34+ cells.

Ruhikanta Meetei

Mutations in BLM, a RecQ-like helicase, are linked to the autosomal recessive cancer-prone disorder Bloom's syndrome. BLM associates with topoisomerase (Topo) IIIα, RMI1, and RMI2 to form the BLM complex that is essential for genome stability. Here we report the crystal structures of multiple domains of RMI1-RMI2, providing direct confirmation of the existence of three oligonucleotide/oligosaccharide binding (OB)-folds in RMI1-RMI2. Our structural and biochemical analyses revealed an unexpected insertion motif in RMI1N-OB, which is important for stimulating the dHJ dissolution. We also revealed the structural basis of the interaction between RMI1C-OB and RMI2-OB and demonstrated the functional importance of the RMI1-RMI2 interaction in genome stability maintenance. (Wang F, Yang Y, Singh TR, Busygina V, Guo R, Wan K, Wang W, Sung P, Meetei AR, Lei M. **Crystal structures of RMI1 and RMI2, two OB-fold regulatory subunits of the BLM complex**. *Structure*. 18(9):1159-70. Sep 8, 2010.)

James Mulloy

In FY2011 the Mulloy lab published in *Leukemia* on a new mouse model that represents the “next generation” mouse for use in leukemia xenografting. This mouse has been licensed to Jackson Labs and is being released to the research community in July 2011. The Mulloy lab is currently using this model in

chemotherapy studies in an effort to understand chemoresistance and relapse, especially in AML. In other work published in *Blood*, the lab has used a cooperating oncogene, activated N-ras, to promote progression of AML1-ETO pre-leukemia. One long-term goal of the Mulloy lab is to have various common cytogenetically-defined leukemia models functional in the human stem cell model system, to complement studies that are done using murine genetic approaches. These recent studies bring this goal closer to fruition.

Nicolas Nassar

Our research is focused on understanding at the molecular level the cycling of Ras. Our goal is to design small molecule modulators of oncogenic Ras in cancer.

Qishen Pang

Studies of the cytoplasmic function of FANCA and FANCC proteins – The finding suggest cytoplasmic function of FANCA and FANCC in leukemogenesis. We published this work in *J. Biol. Chem*.

Identification of IL-3Ra as a cell surface marker for leukemia-initiating cells (LICs) in FA AML patients - We found that interleukin-3 receptor a (IL-3Ra) is a promising candidate as an LIC-specific antigen for FA AML, which may serve a valuable therapeutic target. We published the work in *Blood*.

Nancy Ratner

1. Wood M, Rawe M, Johansson G, Pang S, Soderquist RS, Patel AV, Nelson S, Seibel W, Ratner N, Sanchez Y. **Discovery of a small molecule targeting IRA2 deletion in budding yeast and neurofibromin loss in malignant peripheral nerve sheath tumor cells**. *Mol Cancer Ther*. Sep, 2011.

To identify new therapeutic approaches targeting neurofibromatosis, we screened the University of Cincinnati small molecule library in NF1+/+ and NF1-/- MPNST sarcoma cell lines and in budding yeast lacking the NF1 homologue IRA2 (ira2Δ). Using this novel model system approach to identify and validate target pathways for cancer cells in which NF1 loss drives tumor formation, here we describe UC1, a small molecule that targets NF1-/- cell lines and ira2Δ budding yeast and identify a possible target pathway for NF1-associated MPNST.

2. Wu J, Dombi E, Jousma E, Scott Dunn R, Lindquist D, Schnell BM, Kim MO, Kim A, Widemann BC, Cripe TP, Ratner N. **Preclincial testing of Sorafenib and RAD001 in the Nf(flox/flox);DhhCre mouse model of plexiform neurofibroma using magnetic resonance imaging**. *Pediatr Blood Cancer*. Feb 11, 2011.

We used magnetic resonance imaging (MRI) in collaboration with the Imaging Resource Center to monitor neurofibroma development in the Nf1(flox/flox); DhhCre mouse model of GEM grade I neurofibroma. The data demonstrate that volumetric MRI analysis can be used to monitor the therapeutic effect in the preclinical neurofibroma drug screening, mimicking current human clinical testing, and suggest that Sorafenib might have clinical activity in some neurofibromas.

Daniel Starczynowski

1. Identified a novel regulatory mechanism of TRAF6 protein stability by autophagy:

Jing Fang, Lyndsey Bolanos, Garrett Rhyasen, Carmen Rigolino, Agostino Cortelezzi, Esther N. Oliva, Mariella Cuzzola, Daniel Starczynowski, manuscript in preparation

2. Identified a novel gene, IRAK1, that is important in the maintenance of Myelodysplastic syndrome:

Garrett Rhyasen, Lyndsey Bolanos, Jing Fang, Carmen Rigolino, Agostino Cortelezzi, Esther N. Oliva,

Mariella Cuzzola, Daniel Starczynowski, manuscript in preparation

Han vanderLoo

The Vector Production Facility manufactured 631 vector products and brought in $440K in revenue from GMP manufacturing and $103K in revenue from manufacturing of research-grade products. A total of 133 visitors toured the Translational Cores Facility.

Ronald Waclaw

We are currently writing two manuscripts describing the effect of Shp2 (PTPN11) mutations on brain development, specifically in the development of myelinating oligodendrocytes and the development of cortical projection neurons. These findings are significant because Shp2 is mutated in the RAS related disorders, Noonan and LEOPARD syndrome. Patients in both of these syndromes exhibit neurocognitive defects. We hope to understand the neurodevelopmental abnormalities that occur when Shp2 mutations are expressed and that this will provide evidence towards the developmental basis of the behavioral phenotypes.

Jianqiang Wu

Neurofibroma preclinical therapeutic trials: Preclincial testing of Sorafenib and RAD001 in the Nf(flox/flox); DhhCre mouse model of plexiform neurofibroma using magnetic resonance imaging. (Wu J, Dombi E, Jousma E, Scott Dunn R, Lindquist D, Schnell BM, Kim MO, Kim A, Widemann BC, Cripe TP, Ratner N. **Preclincial testing of Sorafenib and RAD001 in the Nf(flox/flox) ;DhhCre mouse model of plexiform neurofibroma using magnetic resonance imaging**. *Pediatric Blood and Cancer.* In press, 2011.)

Division Collaboration

Immunobiology » Lee Grimes; David Hildeman; Jochen Mattner; Marsha Wills-Karp; Fred Finkelman

Studying the role of Cdc42 in T and B lymphocyte development and function. (Guo F, Zhang S, Tripathi P, Mattner J, Phelan J, Sproles A, Mo J, Wills-Karp M, Grimes HL, Hildeman D, Zheng Y. **Distinct roles of Cdc42 in thymopoiesis and effector and memory T cell differentiation**. *PLoS One6.* e18002. 2011.)

SIG S10: Flow Cytometry Sorter Equipment (Cancelas)

Guo F, Hildeman D, Tripathi P, Velu CS, Grimes HL, Zheng Y. **Coordination of IL-7 receptor and T-cell receptor signaling by cell-division cycle 42 in T-cell homeostasis**. *Proc Natl Acad Sci U S A.* 107(43):18505-10. 2010.

The nature of the collaboration is the role of Cdc42 in acute lung inflammation, examination of lung respiratory function. (Filippi)

Molecular Immunology » Claire Chougnet; Julio Aliberti

The nature of the collaboration is the 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. (Mulloy).

Bone Marrow Transplantation and Immunodeficiency » Ashish Kumar

The nature of the collaboration is the role of Meis1 in MLL leukemia (Mulloy).

Pathology » Gang Huang; Lili Miles

The nature of the collaboration is the role of Runx1 in AML (Mulloy) and the characterization of murine brain tumors and collection of pediatric glioma samples (Chow).

Reproductive Sciences » Satoshi Namekawa

This work on DNA damage response proteins in silencing of the sex chromosomes in male germ cells was published in Genes & Development (Y. Ichijima et al. **MDC1 directs chromosome-wide silencing of the sex chromosomes in male germ cells**. *Genes Dev*. 25(9):959-971. 2011.). (Andreassen)

Environmental Health; Biomedical Engineering » Jarek Meller

In collaboration with Jared Meller, we are screening in silico a library of chemicals for small compounds that bind to oncogenic Ras. (Nassar)

Human Genetics; Hematology » Mehdi Keddache; Clint Joiner

Collaboration in this field with Dr. Clint Joiner (Hematology) and Dr. Mehdi Keddache and Dr. Kejian Zhang from (Human Genetics) continues and we have now an IRB-approved protocol a study to identify the genetic mutation(s) in genes encoding red blood cell (RBC) membrane proteins responsible for erythrocyte cytoskeleton defects in patients with non-immune hemolytic anemia that is not due to hemoglobin or erythrocyte enzyme disorder. The goal is to further understand the pathogenesis of this group of diseases and obtain information on the interaction of the erythrocyte cytoskeleton proteins with each other. (Hammill M, Risinger MA, Joiner CH, Keddache M, Kalfa TA. **Compound heterozygosity for two novel mutations in the erythrocyte protein 4.2 gene causing spherocytosis in a Caucasian patient**. *Br.J.Haematol*. 152(6):780-3. Mar, 2011.)

Human Genetics » Xiaoyang Qi; Elizabeth Schorry

The nature of the collaboration is testing SapC nanoparticle for anti-glioma activity in vivo (Chow).

Dr. Schorry and I do not have a grant together, but she runs the Nf1 clinic and we published a manuscript together in 2010 based on co-mentorship of a fellow. She helps us obtain human tissue and is an internal advisor for our NF Center. (Hummel TR, Jessen W, Miller SC, Kluwe L, Mautner V, Wallace MR, Lazaro C, Page GP, Worley P, Aronow B, Schorry E, Ratner N. **Gene expression analysis identifies potential biomarkers of neurofibromatosis type 1 including adrenomedullin**. *Clin Cancer Res.* 16, 5048-5057. 2010.)

Hematology » Joseph Palumbo; Erik Mullins

Flick MJ, Chauhan AK, Frederick M, Talmage KE, Kombrinck KW, Miller WM, Mullins ES, Palumbo JS, Zheng X, Esmon NL, Esmon CT, Thornton S, Becker A, Pelc LA, Di Cera E, Wagner DD, Degen JL. **The development of inflammatory joint disease is attenuated in mice expressing the anticoagulant prothrombin mutant W215A/E217A**. *Blood.* 117: 6326-6337. 2011. (Degen)

Project: The role of thrombomodulin in tumor cell metastasis. Manuscript: Horowitz NA, Blevins EA, Miller WM, Perry AR, Talmage KE, Mullins ES, Flick MJ, Queiroz KCS, Shi K, Spek CA, Conway EM, Monia BP, Weiler H, Degen JL, Palumbo JS. **Thrombomodulin is a determinant of metastasis through a mechanism linked to the thrombin binding domain but not the lectin-like domain**. *Blood*. In press, 2011. (Flick)

Akunuru S, Palumbo J, Zhan Z, Zhai QJ, Zheng Y. **Rac1 targeting suppresses human non-small cell lung adenocarcinoma cancer stem cell activity**. *PLoS One.* 6(2):e16951. Feb 9, 2011.(Zheng)

Oncology » Lionel Chow; Timothy Cripe; John Perentesis

The nature of the collaboration is studying the role of Foxm1 in a genetic model of high-grade astrocytoma. (Waclaw)

R21 CA133663: Virotherapy for Neuroblastoma Stem Cells. Use of targeted therapy with oncolytic

herpesviruses in neuroblastoma stem cells. (Cancelas)

We are co-investigators on a P50 award "Cincinnati Center for NF Research." In addition, Dr. Cripe and I work closely on NF Preclinical Therapuetuics through a grant from the Children's Tumor Foundation. (Ratner)

Pulmonary Biology » Vladimir Kalinichenko; Jeffrey Whitsett; Anne Perl

The nature of the collaboration is studying the transcription factor Foxm1 in the development of forebrain neurons. (Waclaw)

The nature of the collaboration is the differentiation of human pluripotent stem cells into respiratory lineages; Development of flow cytometry tools to identify respiratory progenitors. Development of flow cytometry tools to identify and quantify epithelial lineages during lung injury repair (Lutzko)

Rheumatology; Human Genetics » Sherry Thornton; Xiaoyang Qi

Project: SapC-DOPS Agents: Imaging and therapeutics in Arthritis. A CTSA grant awarded to Drs. Thornton, Qi and Flick was used to support this work, and a NIH R21 application was submitted to extend support for this project. (Flick)

Neonatology; Pulmonary Biology » Jeffrey Whitsett; Tim LeCras

R01 HL090156: Transcriptional Control of Respiratory Epithelial Progenitor Cells. Analysis of key master transcriptional regulators in the fate of epithelial and mesenchymal stem cells and progenitors in lung. The project also attempts to establish pre-clinical models of cell delivery of mesenchymal stem cells in lung disease. (Cancelas)

Ryan MA, Xing E, Schleimer D, Nattamai KJ, Daria D, Liu W, Jansen M, Ratner N, Le Cras T, Van Zant G, Cancelas J, Zheng Y, Geiger H. **Pharmacological inhibition of EGFR signaling enhances G-CSF-induced hematopoietic stem cell mobilization**. *Nature Med*. 16(10):1141-6. 2010. (Zheng)

Biostatistics » Mi-Ok Kim

We share a grant from the Children's Tumor Foundation. Dr. Kim meets with us weekly and does all statistical analysis for our Preclinical NF therapeutics. (Ratner)

Imaging Resource Center » Diana Lindquist

Dr. Lindquist oversees our mouse brain imaging and is a collaborator on a grant from the Department of Defense on brain in NF1. She also oversees our peripheral nervous system tumor MRI preclincal analysis funded by the Children's Tumor Foundation and a Bench to Bedside aware from the NIH. (Ratner)

Opthamology; Developmental Biology » Richard Lang; C. Kuan; Y. Yoshida

Dr. Lang and I just submitted a grant to the Department of Defense as co-investigators. (Ratner)

Katayama K, Melendez J, Baumann J, Leslie J, Chauhan BK, Nemkul N, Lang RA, Kuan C-Y, Zheng Y, Yoshida Y. **Loss of RhoA in neural progenitor cells causes the disruption of adherens junctions and hyperproliferation**. *Proc. Natl. Acad. Sci. USA* 108(18):7607-12. 2011. (Zheng)

Allergy and Immunology; Immunobiology » Nives Zimmerman; S. Hogan; F. Finkelman

Arumugam M, Ahrens R, Osterfeld H, Kottyan LC, Shang X, Maclennan JA, Zimmermann N, Zheng Y, Finkelman FD, Hogan SP. **Increased susceptibility of 129SvEvBrd mice to IgE-Mast cell mediated anaphylaxis**. *BMC Immunology.* 12:14. 2011. (Zheng)

Heart Institute; Molecular Cardiovascular Biology » Jeffrey Towbin; J. Molkentin

Qian L, Wythe JD, Liu J, Cartry J, Vogler G, Mohapatra B, Otway RT, Huang Y, King IN, Maillet M, Zheng Y, Crawley T, Taghli-Lamallem O, Semsarian C, Dunwoodie S, Winlaw D, Harvey RP, Fatkin D, Towbin JA, Molkentin JD, Srivastava D, Ocorr K, Bruneau BG, Bodmer R. **Tinman/Nkx2-5 acts via miR-1 and upstream of Cdc42 to regulate heart function across species**. *J Cell Biol.* 193(7):1181-96. 2011. (Zheng)

Molecular Cardiovascular Biology; Ophthalmology » J. Molkentin; Richard Lang

Xiang SY, Vanhoutte D, Del Re DP, Purcell NH, Ling H, Banerjee I, Bossuyt J, Lang RA, Zheng Y, Matkovich SJ, Miyamoto S, Molkentin JD, Dorn GW 2nd, Brown JH. **RhoA protects the mouse heart against ischemia/reperfusion injury**. *J Clin Invest.* Jul 11, 2011. (Zheng)

Ophthalmology » Richard Lang

Melendez J, Stengel K, Zhou X, Chauhan BK, Debidda M, Andreassen P, Lang RA, Zheng Y. **RhoA GTPase is dispensable for actomyosin regulation but is essential for mitosis in primary mouse embryonic fibroblasts**. *J. Biol. Chem.* 286(17):15132-7. 2011. (Zheng)

Pathology; Immunobiology » J. Mo; Marsha Wills-Karp; Lee Grimes; H. HIldeman

Guo F, Zhang S, Tripathi P, Mattner J, Phelan J, Sproles A, Mo J, Wills-Karp M, Grimes HL, Hildeman D, Zheng Y. **Distinct roles of Cdc42 in thymopoiesis and effector and memory T cell differentiation**. *PLoS One.* 6(3):e18002. Mar 24, 2011. (Zheng)

Infectious Diseases » Rhonda Cardin

The nature of the collaboration is the role of bone marrow cells in CMV latency. (Filippi)

Developmental Biology » Christopher Mayhew

The nature of the collaboration is the derivation of iPSC from human peripheral blood (Lutzko).

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Significant Accomplishments

Discovering a Target for Preventing Leukemia in Fanconi Anemia Patients

Patients with Fanconi anemia (FA) have a high risk of developing acute myeloid leukemia (AML). In a study published in *Blood* by Qishen Pang, MD, and his group, a small portion of leukemia initiating cells are responsible for leukemia progression, as identified in FA-AML patients. They found that the IL-3 receptor-α (IL-3Rα) is overexpressed on a subpopulation of progenitor cells from FA patients with AML and is a promising candidate as a leukemia-initiating cell-specific antigen for FA-AML. Xenograft studies of the leukemia-initiating cell activity of IL-3Rα-positive FA-AML cells in a “humanized” mouse model indicate that only IL-3Rα-positive cells showed significant levels of engraftment and developed leukemia in the recipient mice. Treatment of FA leukemia initiating cells with an IL-3Rα-neutralizing antibody inhibited IL-3-mediated proliferation and signaling. This study establishes that IL-3Rα is a cell-surface marker present on FA patient leukemia-initiating cells and may be a valuable therapeutic target.

Dissecting a Novel Survival Mechanism Controlling T-Cell Homeostasis

Normal T-cell biology involves carefully coordinated signaling between what are known as T-cell receptors and a protein called interluken-7 receptor (IL-7Ra). IL-7Ra is vital to the formation of white blood cells called lymphocytes, which include T-cells. Studies led by Fukun Guo, PhD, and Yi Zheng, PhD, published in *Proc. Natl. Acad. Sci., USA*, unveiled a novel process of coordinated cellular communications by a critical signaling molecule, Cdc42, that is vital to the normal development and maintenance of T cells. If the process breaks down, T cells do not fully mature. Instead they proliferate rapidly in an immature state then die off early, which could disrupt the immune system’s normal defensive functions. The work reveals novel molecular pathways affected through Cdc42’s central regulatory role in T-cell biology, and implicates Cdc42 for future diagnostic or therapeutic approaches for diseases affecting the immune system.

Unveiling a New Pharmacologic Approach for Blood Stem Cell Harvest

A team of investigators led by Hartmut Geiger, PhD, has identified a molecular communications pathway that ultimately could lead to treatments that boost success rates for bone marrow transplants. The findings, published in *Nature Medicine*, describe the key role played by a signaling protein called granulocyte colony

stimulating factor in releasing stem cells from bone marrow into the blood circulatory system. The study further reports, based on experiments in mice, that this process can be sharply enhanced by the anti-cancer drug erlotinib. The drug inhibits a signaling pathway triggered by gene called epidermal growth factor receptor. In mice, this results in increased production of granulocyte colony stimulating factor and a five-fold increase in stem cell mobilization. These findings provide a scientific basis for enhancing the effectiveness of autologous bone marrow transplants, in which the recipient donates his or her own stem cells prior to the procedure.

Division Publications

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6. Cancelas JA. **Adhesion, migration, and homing of murine hematopoietic stem cells and progenitors**. *Methods Mol Biol*. 2011; 750:187-96.
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69. Zhang F, Fan Q, Ren K, Auerbach AD, Andreassen PR. **FANCJ/BRIP1 recruitment and regulation of FANCD2 in DNA damage responses**. *Chromosoma*. 2010; 119:637-49.
70. Zhou J, Zhu Y, Zhang G, Liu N, Sun L, Liu M, Qiu M, Luo D, Tang Q, Liao Z, Zheng Y, Bi F. **A distinct role of RhoB in gastric cancer suppression**. *Int J Cancer*. 2011; 128:1057-68.

Grants, Contracts, and Industry Agreements

Grant and Contract Awards		Annual Direct / Project Period Direct
ANDREASSEN, P		
FANCD2 Monoubiquitination in DNA Damage Responses		
National Institutes of Health		
R01 HL 085587	07/08/08-06/30/13	$225,000
CANCELAS-PEREZ, J		
Gap Junction Intercellular Communication in Bone Marrow Failure		
Department of Defense Army		
	04/01/11-10/31/12	$65,364
Rac GTPase Inhibition in Chronic Myelogenous Leukemia		
National Institutes of Health		
R01 HL 087159	04/06/09-02/28/13	$250,000
CHOI, K		
Regulation of Cellular Growth and Differentiation		
National Institutes of Health(University of Cincinnati)		
T32 CA 059268	12/06/10-04/30/11	$38,073
DEGEN, J		
Analysis of Staphylococcus Aureus Host Interactions		
National Institutes of Health(Texas A & M University)		
R01 AI 020624	09/30/10-08/31/11	$51,998

Hemostatic Factors as Determinants of Bacterial Virulence and Host Defense
National Institutes of Heath
R01 HL 085357 07/01/06-06/30/11 $242,750

Thrombin-Mediated Proteolysis in Neuroinflammatory Disease
National Institutes of Health
R01 HL 096126 08/04/09-04/30/13 $250,000

Cincinnati Rheumatic Disease Core Center (Animal Models of Arthritis/Inflammatory Disease)
National Institutes of Health
P30 AR 047363 09/01/06-06/30/11 $66,736

FENG, Y

Training Program in Cancer Therapeutics
National Institutes of Health(University of Cincinnati)
T32 CA 117846 01/01/10-08/31/11 $43,604

FILIPPI, M

Regulation of Hematopoietic Stem Cell Self Renewal
National Institutes of Health
R21 HL 104458 08/01/10-07/31/12 $150,000

Regulation of Neutrophil Migration and Polarity
National Institutes of Health
R01 HL 090676 03/01/10-02/28/15 $250,000

Small Molecule Targeting of NADPH Oxidase in Neutrophils
National Institutes of Health(Phase 2 Discovery, Inc)
R41 HL 099244 08/01/10-07/31/11 $123,728

GEIGER, H

Activated Protein C for Treatment of Radiation Combined Injury
National Institutes of Health(Blood Center of Wisconsin, Inc.)
R33 AI 080557 09/13/10-08/31/13 $80,000

GONZALEZ-NIETO, D

Connexin-43 in the Hematopoietic Stem Cell Niche
National Blood Foundation
07/01/09-06/30/11 $37,500

GRASSMAN, E

Proposed Study of Retrovirus Vector-Mediated Insertional Mutagenesis
National Institutes of Health(Battelle Memorial Institute)
N01 ES 55536 03/28/11-03/27/13 $67,503

GROGG, M

CDC42GAP in Insulin Signaling in Hepatocytes
National Institutes of Health
F32 DK 082108 09/12/08-09/11/11 $53,810

HALL, M

Targeted inhibition of EGFR as a New Drug Therapy for Acute Myeloid Leukemia
CancerFree Kids
06/01/11-05/31/12 $10,000

LAFEVER, L

Training Program in Cancer Therapeutics
National Institutes of Health (University of Cincinnati)
T32 CA 117846 09/01/10-8/31/11 $39,286

LINK, K

Environmental Carcinogenesis and Mutagenesis
National Institutes of Health(University of Cincinnati)
T32 ES 007250 09/01/10-06/30/11 $37,520

LIU, W

Personalized Medicine: Targeting Cdc42 in Acute Myeloid Leukemia
CancerFree Kids
06/01/11-05/31/12 $10,000

MALIK, P

Cincinnati Cell Characterization Core
National Institutes of Health(University of Maryland)
U01 HL 099997 09/01/10-04/30/12 $354,674

Development of Safe and Efficient Gene Therapy Strategies
National Institutes of Health(Fred Hutchinson Cancer Research Center)
R01 HL 098489 01/21/10-12/31/14 $104,312

Cincinnati Comprehensive Sickle Cell Center (Project 5)
National Institutes of Health
U54 HL 070871 04/01/08-02/29/12 $247,401

Cincinnati Comprehensive Sickle Cell Center (Bench to Bedside)
National Institutes of Health
U54 HL 070871 04/01/08-02/29/12 $101,920

Cincinnati Center for Clinical and Translational Sciences and Training (Stem Cell Research)
National Institutes of Health(University of Cincinnati)
UL1 RR 026314 04/03/09-03/31/14 $42,716

MAYES, D

NF1 and Ras Activation in Oligodendrocyte Progenitor Cell Development
National Multiple Sclerosis Society
FG1762A1/1 07/01/08-06/30/11 $49,553

MEETEI, R

Function and Regulation of FANCM in Fanconi Anemia
National Institutes of Health
R01 HL 084082 05/01/07-04/30/12 $250,000

Functional and Molecular Characterization of Two New Members of the Bloom Syndrome Complex
Ohio Cancer Research Associates
07/01/10-06/30/12 $27,272

MULLOY, J

Next Generation DNMT-1 Depletion Therapy for Leukemia
Department of Defense Army(Cleveland Clinic Lerner College of Medicine of Case Western Reserve University)
09/01/09-08/31/13 $138,386

Novel Therapeutic Target in Leukemia Stem Cells
Alex's Lemonade Stand Foundation
07/01/10-06/30/12 $100,000

Rac Signaling in MLL Leukemia
The Leukemia and Lymphoma Society
07/01/10-06/30/15 $104,762

The Role of MLL-AF9 in Acute Myeloid Leukemia
National Institutes of Health
R01 CA 140518 07/14/09-06/30/11 $247,264

NASSAR, N

Structure-function Relationship of the Adenovirus Assembly and DNA Packaging
National Institutes of Heatlh

R03 AI 090309	10/01/10-04/30/12	$96,418

OLSHAVSKY, N

Regulation of Cellular Growth and Differentiation
National Institutes of Health(University of Cincinnati)

T32 CA 059268	12/06/10-12/05/11	$38,540

PAN, D

Genetic Therapy for CNS Manifestations in MPS I via BBB-Targeted Protein Delivery
National Institutes of Health

R01 NS 064330	09/30/08-08/31/13	$216,563

PANG, Q

Role of FA Proteins in Hematopoiesis
National Institutes of Health

R01 HL 076712	04/01/10-03/31/15	$250,000

Role of Tumor Necrosis Factor in Leukemogenesis
The Leukemia and Lymphoma Society

	07/01/08-06/30/13	$103,115

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	$207,217

PATEL, A

Identification and Study of Novel Genes Critical to Survival of MPNSTS
Department of Defense

	06/01/11-5/31/13	$50,000

RATNER, N

Cincinnati Center for Neurofibromatosis Research
National Institutes of Health

P50 NS 057531	09/15/08-06/30/13	$1,100,807

Ratner, N	Project A	$47,986
Cripe, T	Project B	$105,859
Rizvi, T	Project C	$81,533
Perentesis, J	Project 1	$296,849
Ratner, N	Project 2	$223,532
Ratner, N	Project 3	$276,814
Ratner, N	Bench-to-Bedside	$68,234

Cincinnati Neuro-Oncology Research Core
National Institutes of Health

P30 CA 149239	09/30/09-08/31/11	$500,000

Modelling Brain Defects in NF1
Department of Defense

	04/01/10-03/31/13	$245,405

Schwann Cells in Neurofibromatosis Type 2
National Institutes of Health

R01 CA 118032	07/01/07-06/30/12	$184,300

SENGUPTA, A

Rac GTPases and Bmi-1 in CML Stem Cell Niche
Lady Tata Memorial Trust

	10/01/10-09/30/11	$36,747

STARCZYNOWSKI, D

Regulation and Function of TIFAB in Myelodysplastic Syndrome
Department of Defense

	06/01/11-05/31/14	$126,041

WU, J

STAT3 in Neurofibroma Tumorigenesis and Therapy
Ohio State University

	08/01/10-07/31/11	$49,205

ZHENG, Y

Cincinnati Center for Excellence in Molecular Hematology
National Institutes of Health

P30 DK 090971		09/30/10-06/30/15	$476,241
Zheng, Y	Admin Core	$113,951	
Grabowski, G	Genomics and Genetics Core	$63,000	
Cancelas, J	Cell Analysis and Sorting Core	$65,112	
Malik, P	Translational Core	$165,412	
Mulloy, J	Xenotransplant and Transgenic Core	$68,766	

Model Systems for Hematologic Disorders Caused by Ribsomal Protein Deficiency
National Institutes of Health(University of Cincinnati)

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

Multi-Photon Zeiss LSM710 Laser Confocal Scanning Microscope
National Institutes of Health

S10 RR 029406	05/09/11-05/08/12	$826,609

Rac GTPases as Targets in Lymphomagenesis
National Institutes of Health

R01 CA 125658	02/10/07-01/31/12	$167,647

Rac GTPase-Specific Small Molecular Inhibitors
National Institutes of Health

R01 CA 141341	03/24/09-01/31/14	$147,624

Targeting Cdc42 in Leukemia Stem Cells
National Institutes of Health

R01 CA 150547	03/10/10-01/31/15	$186,495

Training Program in Pediatric Hematologic and Oncologic Diseases
National Institutes of Health

T32 HL 091805	09/01/08-08/31/13	$160,128

Rac GTPases in the Mammalian Brain Development
National Institutes of Health

R01 NS 056435	07/01/08-06/30/12	$79,000

Current Year Direct **$9,116,728**

Industry Contracts

MULLOY, J

Amgen, Inc.	$39,935

Current Year Direct Receipts **$39,935**

Funded Collaborative Efforts

CANCELAS, J

Transcriptional Control of Respiratory Epithelial Progenitor Cells
National Institutes of Health

Whitsett, J	08/27/07-06/30/11	10%

PAN, D

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

Total **$9,156,663**