Experimental Hematology

Division Details

RESEARCH AND TRAINING DETAILS	
Faculty	**26**
Joint Appointment Faculty	**14**
Research Fellows and Post Docs	**28**
Research Graduate Students	**22**
Total Annual Grant Award Dollars	**$13,265,497**
Total Annual Industry Award Dollars	**$1,438,232**
Total Publications	**80**

Row 1: E Boscolo, D Pan, T Kalfa, M Nasimuzzaman, A Kumar, M Azam

Row 2: N Nassar, R Waclaw, R Meetei, R Drissi, J Cancelas, F Guo, Y Zheng

Row 3: Q Pang, R Lu, M Flick, P Andreassen, S Witting, D Reynaud

Research Highlights

Discovery of a potential therapeutic target of severe congenital neutropenia

Drs. Jose Cancelas Perez, MD, PhD, and Carolyn Lutzko, PhD, led a team of Cancer and Blood Diseases Institue (CBDI) investigators tackling a long standing question on how severe congenital neutropenia (SCN) may come arise. An article on this is featured in *The Journal of Clinical Investigation*. SCN is often associated with inherited heterozygous point mutations in ELANE, which encodes neutrophil elastase (NE). However, a lack of appropriate models to recapitulate SCN has substantially hampered the understanding of the genetic etiology and pathobiology of this disease. To this end, we generated both normal and SCN patient-derived induced pluripotent stem cells (iPSCs), and performed genome editing and differentiation protocols that recapitulate the major features of granulopoiesis. Pathogenesis of ELANE point mutations was the result of promyelocyte death and differentiation arrest, and associated with NE mislocalization and activation of the unfolded protein response/ER stress (UPR/ER stress). Similarly, high-dose G-CSF (or downstream signaling through AKT/BCL2) rescues the dysgranulopoietic defect in SCN patient-derived iPSCs through C/EBPβ-dependent emergency granulopoiesis. In contrast, sivelestat, an NE-specific small-molecule inhibitor, corrected dysgranulopoiesis by restoring normal intracellular NE localization in primary granules; ameliorating UPR/ER stress; increasing expression of CEBPA, but not CEBPB; and promoting promyelocyte survival and differentiation. Their data suggest that SCN disease pathogenesis includes NE mislocalization, which in turn triggers dysfunctional survival signaling and UPR/ER stress. This paradigm has the potential to be clinically exploited to achieve therapeutic responses using lower doses of G-CSF combined with targeting to correct NE mislocalization.

Novel epigenetic regulation of oligodendrocyte and astrocyte fate switch

Dr. Quing Lu, PhD, and collaborators defined, and reported in *Developmental Cell*, a novel mechanism of oligodendrocyte and astrocyte lineage determination by Hdac3 interaction with p300 histone acetyltransferase. Establishment, and maintenance, of central nervous system glial cell identity ensures proper brain development and function, yet the epigenetic mechanisms underlying glial fate control

remain poorly understood. They found that the histone deacetylase Hdac3 controls oligodendrocyte-specification gene Olig2 expression and functions as a molecular switch for oligodendrocyte and astrocyte lineage determination. Hdac3 ablation leads to a significant increase of astrocytes with a concomitant loss of oligodendrocytes. Lineage tracing indicates that the ectopic astrocytes originate from oligodendrocyte progenitors. Genome-wide occupancy analysis reveals that Hdac3 interacts with p300 to activate oligodendroglial lineage-specific genes, while suppressing astroglial differentiation genes including NFIA. Furthermore, we find that Hdac3 modulates the acetylation state of Stat3 and competes with Stat3 for p300 binding to antagonize astrogliogenesis. Their studies suggest that Hdac3 cooperates with p300 to prime and maintain oligodendrocyte identity while inhibiting NFIA and Stat3-mediated astrogliogenesis, and thereby regulates phenotypic commitment at the point of oligodendrocyte-astrocytic fate decision.

Discovery of a new molecular pathway of airway hyperresponsiveness in sickle cell disease

Dr. Punam Malik, MD, led a team of collaborators who determined, and reported in *The Journal of Clinical Investigations*, the placenta growth factor pathway as a key augmenting component in airway hyperresponsiveness and asthma. Airway hyperresponsiveness (AHR) affects 55%-77% of children with sickle cell disease (SCD) and occurs even in the absence of asthma. While asthma increases SCD morbidity and mortality, the mechanisms underlying the high AHR prevalence in a hemoglobinopathy remain unknown. In allergen-exposed mice, loss of Plgf dampened AHR, reduced inflammation and eosinophilia, and decreased expression of the Th2 cytokine IL-13 and the leukotriene-synthesizing enzymes 5-lipoxygenase and leukotriene-C4-synthase. Plgf-/- mice treated with leukotrienes phenocopied the WT response to allergen exposure; conversely, anti-PlGF Ab administration in WT animals blunted the AHR. Notably, Th2-mediated STAT6 activation further increased PlGF expression from lung epithelium, eosinophils, and macrophages, creating a PlGF/leukotriene/Th2-response positive feedback loop. Similarly, they found that the Th2 response in asthma patients associates with increased expression of PlGF and its downstream genes in respiratory epithelial cells. In an SCD mouse model, they observed increased AHR and higher leukotriene levels abrogated by anti-PlGF Ab or the 5-lipoxygenase inhibitor zileuton. Their findings indicate that PlGF exacerbates AHR and uniquely links the leukotriene and Th2 pathways in asthma, and suggest that zileuton and anti-PlGF Ab could be promising therapies to reduce pulmonary morbidity in SCD.

Significant Publications

Wu J, Keng VW**, Patmore DM, Kendall JJ, Patel AV, Jousma E, Jessen WJ**, **Choi K**, Tschida BR, Silverstein KA, Fan D, Schwartz EB, Fuchs JR, Zou Y, Kim MO, Dombi E, Levy DE, **Huang G**, **Cancelas JA**, Stemmer-Rachamimov AO, Spinner RJ, Largaespada DA, **Ratner N**. **Insertional Mutagenesis Identifies a STAT3/Arid1b/beta-catenin Pathway Driving Neurofibroma Initiation**. *Cell Rep*. 2016 Mar 1;14(8):1979-90.

To identify genes and signaling pathways that initiate Neurofibromatosis type 1 (NF1) neurofibromas, we used unbiased insertional mutagenesis screening, mouse models, and molecular analyses. We mapped an Nf1-Stat3-Arid1b/β-catenin pathway that becomes active in the context of Nf1 loss. Genetic deletion of Stat3 in Schwann cell progenitors (SCPs) and Schwann cells (SCs) prevents neurofibroma formation, decreasing SCP self-renewal and β-catenin activity. β-catenin expression rescues effects of Stat3 loss in SCPs. Importantly, P-STAT3 and β-catenin expression correlate in human neurofibromas. Mechanistically, P-Stat3 represses Gsk3β and the SWI/SNF gene Arid1b to increase β-catenin. Knockdown of Arid1b or Gsk3β in Stat3(fl/fl);Nf1(fl/fl);DhhCre SCPs rescues neurofibroma formation after in vivo transplantation. Stat3 represses Arid1b through histone modification in a Brg1-dependent manner, indicating that epigenetic modification plays a role in early tumorigenesis. Our data map a neural tumorigenesis pathway and support testing JAK/STAT and Wnt/β-catenin pathway inhibitors in neurofibroma therapeutic trials.

Arumugam PI, **Mullins ES**, Shanmukhappa SK, Monia BP, **Loberg A**, Shaw MA, **Rizvi T**, Wansapura J, **Degen JL**, **Malik P**. **Genetic diminution of circulating prothrombin ameliorates multiorgan pathologies in sickle cell disease mice**. *Blood*. 2015 Oct 8;126(15):1844-55.

Sickle cell disease (SCD) results in vascular occlusions, chronic hemolytic anemia, and cumulative organ damage. A conspicuous feature of SCD is chronic inflammation and coagulation system activation. Thrombin (factor IIa [FIIa]) is both a central protease in hemostasis and a key modifier of inflammatory processes. To explore the hypothesis that reduced prothrombin (factor II [FII]) levels in SCD will limit vaso-occlusion, vasculopathy, and inflammation, we used two strategies to suppress FII in SCD mice. Weekly

administration of FII antisense oligonucleotide "gapmer" to Berkeley SCD mice to selectively reduce circulating FII levels to ~10% of normal for 15 weeks significantly diminished early mortality. More comprehensive, long-term comparative studies done used mice with genetic diminution of circulating FII. Here, we tracked cohorts of FII(lox/-) mice (constitutively carrying ~10% normal FII) and FII(WT) mice in parallel for a year following the imposition of SCD via hematopoietic stem cell transplantation. This genetically imposed suppression of FII levels resulted in an impressive reduction in inflammation (reduction in leukocytosis, thrombocytosis, and circulating interleukin-6 levels), reduced endothelial cell dysfunction (reduced endothelial activation and circulating soluble vascular cell adhesion molecule), and a significant improvement in SCD-associated end-organ damage (nephropathy, pulmonary hypertension, pulmonary inflammation, liver function, inflammatory infiltration, and microinfarctions). Notably, the study achieved all of these benefits with a relatively modest 1.25-fold increase in prothrombin times, and in the absence of hemorrhagic complications. Taken together, these data establish that prothrombin is a powerful modifier of SCD-induced end-organ damage, and present a novel therapeutic target to ameliorate SCD pathologies.

Prasad JM, Gorkun OV, Raghu H, Thornton S, **Mullins ES**, **Palumbo JS**, Ko YP, Hook M, David T, Coughlin SR, **Degen JL**, **Flick MJ**. **Mice expressing a mutant form of fibrinogen that cannot support fibrin formation exhibit compromised antimicrobial host defense**. *Blood*. 2015 Oct 22;126(17):2047-58.

Fibrin(ogen) is central to hemostasis and thrombosis and also contributes to multiple physiologic and pathologic processes beyond coagulation. However, the precise contribution of soluble fibrinogen vs. insoluble fibrin matrices to vascular integrity, tissue repair, inflammation, and disease was undefined and unapproachable. To establish the means to distinguish fibrinogen- and fibrin-dependent processes in vivo, researchers generated Fib(AEK) mice that carry normal levels of circulating fibrinogen but lack the capacity for fibrin polymer formation due to a germ-line mutation in the Aα chain thrombin cleavage site. Homozygous Fib(AEK) mice developed to term and exhibited postnatal survival superior to that of fibrinogen-deficient mice. Unlike fibrinogen-deficient mice, platelet-rich plasma from Fib(AEK) mice supported normal platelet aggregation in vitro, highlighting that fibrinogen(AEK) retains the functional capacity to support interactions with platelets. Thrombin failed to release fibrinopeptide-A from fibrinogen(AEK) and failed to induce polymer formation with Fib(AEK) plasma or purified fibrinogen(AEK) in 37°C mixtures regardless of incubation time. Fib(AEK) mice displayed both an absence of fibrin polymer formation following liver injury, as assessed by electron microscopy, and a failure to generate stable occlusive thrombi following FeCl3 injury of carotid arteries. Fib(AEK) mice exhibited a profound impediment in Staphylococcus aureus clearance following intraperitoneal infection similar to fibrinogen-deficient mice, yet Fib(AEK) mice displayed a significant infection dose-dependent survival advantage over fibrinogen-deficient mice following peritonitis challenge. Collectively, these findings establish for the first time that fibrin polymer is the molecular form critical for antimicrobial mechanisms while simultaneously highlighting biologically meaningful contributions and functions of the soluble molecule.

Varney ME, **Niederkorn M**, Konno H, Matsumura T, Gohda J, Yoshida N, Akiyama T, **Christie S**, **Fang J**, Miller D, Jerez A, Karsan A, Maciejewski JP, **Meetei RA**, Inoue J, **Starczynowski DT**. **Loss of Tifab, a del(5q) MDS gene, alters hematopoiesis through derepression of Toll-like receptor-TRAF6 signaling**. *J Exp Med*. 2015 Oct 19;212(11):1967-85.

TRAF-interacting protein with forkhead-associated domain B (TIFAB) is a haploinsufficient gene in del(5q) myelodysplastic syndrome (MDS). Deletion of Tifab results in progressive bone marrow (BM) and blood defects, including skewed hematopoietic stem/progenitor cell (HSPC) proportions and altered myeloid differentiation. A subset of mice transplanted with Tifab knockout (KO) HSPCs develop a BM failure with neutrophil dysplasia and cytopenia. In competitive transplants, Tifab KO HSPCs are out-competed by wild-type (WT) cells, suggesting a cell-intrinsic defect. Gene expression analysis of Tifab KO HSPCs identified dysregulation of immune-related signatures, and hypersensitivity to TLR4 stimulation. TIFAB forms a complex with TRAF6, a mediator of immune signaling, and reduces TRAF6 protein stability by a lysosome-dependent mechanism. In contrast, TIFAB loss increases TRAF6 protein and the dynamic range of TLR4 signaling, contributing to ineffective hematopoiesis. Moreover, combined deletion of TIFAB and miR-146a, two genes associated with del(5q) MDS/AML, results in a cooperative increase in TRAF6 expression and hematopoietic dysfunction. Re-expression of TIFAB in del(5q) MDS/AML cells results in attenuated TLR4 signaling and reduced viability. These findings underscore the importance of efficient regulation of innate immune/TRAF6 signaling within HSPCs by TIFAB, and its cooperation with miR-146a as it relates to the pathogenesis of hematopoietic malignancies, such as del(5q) MDS/AML.

He D, Marie C, **Zhao C**, Kim B, **Wang J**, **Deng Y**, Clavairoly A, Frah M, **Wang H**, **He X**, Hmidan H, Jones BV, Witte D, Zalc B, Zhou X, Choo DI, Martin DM, Parras C, **Lu QR** . **Chd7 cooperates with Sox10 and regulates the onset of CNS myelination and remyelination**. *Nat Neurosci*. 2016 May;19(5):678-89.

Mutations in CHD7, encoding ATP-dependent chromodomain helicase DNA-binding protein 7, in CHARGE syndrome lead to multiple congenital anomalies, including craniofacial malformations, neurological dysfunction and growth delay. Mechanisms underlying the CNS phenotypes remain poorly understood. We found that Chd7 is a direct transcriptional target of oligodendrogenesis-promoting factors Olig2 and Smarca4/Brg1 and required for proper onset of CNS myelination and remyelination. Genome-occupancy analyses in mice, coupled with transcriptome profiling, revealed that Chd7 interacted with Sox10 and targeted the enhancers of key myelinogenic genes. These analyses identified previously unknown Chd7 targets, including bone formation regulators Osterix (also known as Sp7) and Creb3l2, which are also critical for oligodendrocyte maturation. Thus, Chd7 coordinates with Sox10 to regulate the initiation of myelinogenesis and acts as a molecular nexus of regulatory networks that account for the development of a seemingly diverse array of lineages, including oligodendrocytes and osteoblasts, pointing to previously uncharacterized Chd7 functions in white matter pathogenesis in CHARGE syndrome.

Division Publications

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2. Adams G, Rosenfeldt L, Frederick M, Miller W, Waltz D, Kombrinck K, McElhinney K, Flick M, Monia B, Revenko A. **Colon Cancer Growth and Dissemination Relies Upon Thrombin, Stromal Par-1, and Fibrinogen.** *Cancer Res*. 2015; 75:4235-43.

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4. Amarachintha S, Sertorio M, Wilson A, Li X, Pang Q. **Fanconi Anemia Mesenchymal Stromal Cells-Derived Glycerophospholipids Skew Hematopoietic Stem Cell Differentiation through Toll-Like Receptor Signaling.** *Stem Cells*. 2015; 33:3382-96.

5. Arumugam PI, Mullins ES, Shanmukhappa SK, Monia BP, Loberg A, Shaw MA, Rizvi T, Wansapura J, Degen JL, Malik P. **Genetic Diminution of Circulating Prothrombin Ameliorates Multiorgan Pathologies in Sickle Cell Disease Mice.** *Blood*. 2015; 126:1844-55.

6. Barry D, Xu K, Meadows S, Zheng Y, Norden P, Davis G, Cleaver O. **Cdc42 Is Required for Cytoskeletal Support of Endothelial Cell Adhesion During Blood Vessel Formation in Mice.** *Development*. 2015; 142:3058.

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8. Bick G, Zhang F, Meetei AR, Andreassen PR. **Coordination of the Recruitment of the Fancd2 and Palb2 Fanconi Anemia Proteins by an Ubiquitin Signaling Network.** *Chromosoma*. 2016:1-14.

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14. Du W, Amarachintha S, Erden O, Wilson A, Meetei AR, Andreassen PR, Namekawa SH, Pang Q. **Fancb Deficiency Impairs Hematopoietic Stem Cell Function.** *Sci Rep*. 2015; 5:18127.

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Grants, Contracts, and Industry Agreements

Annual Grant Award Dollars

Investigator	Title	Sponsor	ID	Dates	Amount
Mark Althoff	Scribble in Hematopoietic Stem Cell Activity	National Institutes of Health	F31 HL132468	4/1/2016 - 3/31/2019	$36,036
Laura Barreyro, PHD	Environmental Carcinogenesis and Mutagenesis Training Grant	National Institutes of Health (University of Cincinnati)	T32 ES007250	9/30/2015 - 9/29/2018	$48,192
Elisa Boscolo, PHD	Venous Malformations (VM): A Murine Model to Identify Therapies to Target Aberrant Venous Development	National Institutes of Health	R01 HL117952	8/7/2014 - 4/30/2018	$351,000
Jose Cancelas-Perez	Validation of a Rationally Designed Guanine Nucleotide Exchange Factor Inhibitor in Lymphoblastic Leukemia	Wm Lawrence & Blanche Hughes Foundation (USC Parker Institute for)	Cancelas, Jose, WLBH	1/1/2014 - 12/31/2016	$70,000
Jose Cancelas-Perez;Carolyn M Lutzko	G-CSF in Human Severe Congenital Neutropenia	National Institutes of Health	R01 GM110628	7/1/2015 - 6/30/2019	$308,100
Jose Cancelas-Perez	Development of a Method to Store Refrigerted Platelets for Human Transfusion	National Institutes of Health (Cleveland Clin Lerner Col of Med of CWRU)	U54 HL119810	8/1/2015 - 7/31/2016	$195,000
Kyung Hee Chang	Angiotensin in Stem Cell Recruitment and Mobilization	National Blood Foundation	Change, Kyung, NBF	7/1/2014 - 6/30/2016	$37,500
Chris Richard Evelyn, PHD	Environmental Carcinogenesis and Mutagenesis Training Grant	National Institutes of Health (University of Cincinnati)	T32 ES007250	11/19/2015 - 11/18/2016	$52,116
Jing Fang	Mechanisms linking p62/SQSTM1 to the Evolution of Myelodyplastic Syndrome	Aplastic Anemia & MDS International Fdn	Fang, Jing, AAMDS	7/1/2015 - 4/17/2016	$30,000
Marie-Dominique Filippi, PHD	Hypoxia and Potassium Channel Activity in T Lymphocytes	National Institutes of Health (University of Cincinnati)	R01 CA095286	7/1/2015 - 6/30/2018	$9,185
Marie-Dominique Filippi, PHD	Molecular Regulation of Neutrophil Transcellular Migration	National Institutes of Health	R01 GM112792	7/1/2015 - 6/30/2019	$308,100
Marie-Dominique Filippi, PHD	Regulation of Hematopoietic Stem Cell	National Institutes of Health	R01 DK102890	7/1/2015 - 6/30/2020	$426,291

Punam Malik, MD	Self-renewal by GTPase Activating Protein Signaling				
Jonathan Fletcher	Cytokine Signaling in Neurofibroma Development	National Institutes of Health	F30 NS096796	3/1/2016 - 2/28/2018	$40,176
Matthew Flick, PHD	Novel Anti-fibrotic Mechanisms in Chemical-induced Liver Injury	National Institutes of Health (Michigan State University)	R01 ES017537	8/1/2015 - 6/30/2020	$35,058
Hartmut Geiger, PHD	Novel t-MDS Predisposing Genes and Pathways	Edward P. Evans Foundation	BSR2015	9/1/2015 - 8/31/2016	$200,000
Hartmut Geiger, PHD	Molecular Mechanisms and Therapies for Radiation-Induced Myelodysplastic Syndrome (MDS)	University of Kentucky	UKRF-Hartmut	4/1/2012 - 9/30/2015	$100,000
FuKun Guo, PHD	Novel Signaling Function of Cdc42 GTPase In Vivo	National Institutes of Health	R01 GM108661	5/1/2014 - 2/28/2018	$273,000
FuKun Guo, PHD	Novel Therapeutics of Targeting mTOR Pathway in T-cell Leukemia	National Institutes of Health	R21 CA198358	7/10/2015 - 6/30/2017	$373,230
Cindy LF Hochstetler	Unraveling the Mystery of How Bad Homes and Bad Cells can lead to Leukemia Development and Relapse	Cancer Free Kids	wong, cindy, cfk	7/1/2015 - 6/30/2016	$15,000
Kakajan Komurov, PHD	Modeling and Targeting the Hexosamine Pathway in Drug Resistance	Susan G Komen for the Cure	CCR13263034	8/1/2013 - 7/31/2016	$150,000
Kakajan Komurov, PHD	Exploiting Proteotoxic Stress in Therapy-refractory HER2+ Breast Cancers	National Institutes of Health	R01 CA193549	5/1/2015 - 4/30/2020	$356,850
Qing Richard Lu, PHD	Histone Deacetylase Control of CNS Myelination and Remyelination	National Multiple Sclerosis Society	Lu, Qing, NMSS	4/1/2015 - 3/31/2018	$249,975
Qing Richard Lu, PHD	A Novel Therapeutic Approach for Medulloblastoma Treatment	University of Cincinnati	M16	12/1/2015 - 11/30/2016	$50,000
Qing Richard Lu, PHD	The Establishment of Schwann Cell Polarity and the Initiation of Myelination	National Institutes of Health (The Univ of California, San Francisco)	R01 NS062796	5/1/2014 - 4/30/2019	$122,850
Qing Richard Lu, PHD	Molecular Mechanisms of Oligodendrocyte Differentiation and Myelination	National Institutes of Health	R01 NS072427	9/20/2015 - 8/31/2020	$466,702

Qing Richard Lu, PHD	Chromatin Remodeling Control of CNS Myelination and Remyelination	National Institutes of Health	R01 NS075243	10/1/2013 - 3/31/2017	$341,250
Qing Richard Lu, PHD	A Novel Model of Medulloblastoma to Define Cancer Pathways and Molecular Targets	National Institutes of Health	R01 NS078092	10/1/2013 - 3/31/2017	$341,250
Qing Richard Lu, PHD	Chd7 Chromatin Remodeller Function in Myelination and Remyelination	National Multiple Sclerosis Society (Inserm Délégation Régionale Paris 6)	RG150102851	10/1/2015 - 9/30/2018	$89,360
Qing Richard Lu, PHD	Long Non-coding RNA Control of CNS Myelination and Remyelination	National Multiple Sclerosis Society	RG150705671	4/1/2016 - 3/31/2019	$232,880
Punam Malik, MD	Gene Therapy for Sickle Cell Anemia	Doris Duke Charitable Foundation	2013122	9/1/2013 - 8/31/2016	$162,000
Punam Malik, MD	PLGF-HIF1a-miR Axis in Sickle Pulmonary Hypertension	National Institutes of Health (University of Southern California)	R01 HL111372	1/1/2012 - 12/31/2016	$239,445
Punam Malik, MD Matthew Flick, PHD	Hemostatic Factors and Sickle Cell Disease	National Institutes of Health	R01 HL112603	12/1/2015 - 11/30/2016	$382,500
Punam Malik, MD	Cincinnati Cell Characterization Core	National Institutes of Health (University of Maryland (College Park))	U01 HL099997	9/1/2010 - 4/30/2017	$253,614
James Mulloy, PHD	Conferring In Vivo Metabolic Resistance to a HighIt Selective Anti-AML Agent	National Institutes of Health (University of Cincinnati)	R21 CA185370	5/1/2014 - 2/28/2016	$38,250
James Mulloy, PHD	A New Hydrogen Peroxide-Activated Agent that Selectively Targets AML Cancer Cells	University of Cincinnati	TR000077	7/1/2015 - 6/30/2016	$40,291
Nicolas Nassar, PHD	Novel Rationally Designed Ras Inhibitors for B-ALL Multi-target Therapy	The Leukemia and Lymphoma Society	607614	10/1/2013 - 9/30/2016	$200,000
Nancy Ratner, PHD	An Innovative NF1 Drug Discovery Pipeline for Preclinical Development of Novel Drugs Quickly, Safely and Effectively	The Children's Tumor Foundation (The Children's Tumor Foundation)	CTF	10/15/2015 - 6/30/2018	$75,891
Nancy Ratner, PHD	Mechanisms of Resistance to MEK Inhibition in Neurofibroma	The Children's Tumor Foundation	2015B05003	11/18/2015 - 11/18/2016	$85,000

Nancy Ratner, PHD	Neurofibroma Preclinical Therapeutics	The Children's Tumor Foundation	CTF	7/15/2013 - 7/14/2016	$351,300
Nancy Ratner, PHD	Mitogenic Activities in Neurofibromatosis	National Institutes of Health	R01 NS028840	9/15/2011 - 7/31/2017	$353,813
Nancy Ratner, PHD	Disordered Regulation of Wnt/B-catenin Signaling in MPNST Development and Maintenance	National Institutes of Health (University of Minnesota)	R01 NS086219	8/15/2014 - 6/30/2019	$274,835
Nancy Ratner, PHD	Brain Dysfunction in Neurofibromatosis	National Institutes of Health	R01 NS091037	4/1/2015 - 3/31/2020	$309,792
Nancy Ratner, PHD	Novel Combinatorial Therapies for Malignant Peripheral Nerve Sheath Tumors	National Institutes of Health	R21 NS084885	7/1/2014 - 6/30/2016	$379,455
Nancy Ratner, PHD	Ras Proteins in Nerve Tumorigensis	National Institutes of Health	R37 NS083580	4/1/2014 - 3/31/2019	$390,000
Damien Reynaud, PHD	Systemic Metabolic Disorders and Leukemic Clonal Dominance	Conquer Cancer Foundation	Reynaud, Damien, CCF	7/1/2014 - 6/30/2016	$60,000
Damien Reynaud, PHD	Investigating the Mechanisms of Leukemia Initiation in the Context of Obesity	Department of Defense Army	W81XWH1510344	9/1/2015 - 8/31/2018	$187,200
Navneet Kumar Singh, PHD	Modeling and Targeting of Oncogenic Liability in Drug-Resistant Breast Cancer	Department of Defense Army	W81XWH1610028	3/1/2016 - 2/28/2019	$186,272
Mitchell Springer, PHD	Training Program in Cancer Therapeutics	National Institutes of Health (University of Cincinnati)	T32 CA11786	8/1/2013 - 7/31/2016	$45,432
Daniel T. Starczynowski, PHD	Investigating Genetic and Molecular Determinants of Myelodysplastic Syndromes	The Leukemia and Lymphoma Society	133416	7/1/2015 - 6/30/2020	$110,001
Daniel T. Starczynowski, PHD	Defining the Role and Therapeutic Potential of TNF Recep Receptor-Associated Factor 6 in Myelodysplastic Syndromes	Gabrielle's Angel Fnd for Cancer Researc	GAFCR	6/1/2013 - 5/31/2017	$75,000
Daniel T. Starczynowski, PHD	Molecular Pathogenesis of MDS	National Institutes of Health	R01 DK102759	8/15/2014 - 5/31/2017	$233,135
Daniel T. Starczynowski, PHD	Identification and Characterization of Genes in del(5q) Myelodysplastic Syndrome	National Institutes of Health	R01 HL111103	12/1/2015 - 11/30/2016	$382,500

Daniel T. Starczynowski, PHD	Role of TRAF6 in Myelodysplastic Syndromes	National Institutes of Health	R01 HL114582	8/1/2014 - 4/30/2018	$398,308
Daniel T. Starczynowski, PHD	Chronic Innate Immune Signaling in the Pathogenesis of MDS	Edward P. Evans Foundation	Starczynowski, Dan,	7/1/2014 - 6/30/2017	$200,000
Ronald R Waclaw, PHD	Signaling Pathways Regulating Oligodendrocyte Development and Function	National Institutes of Health	R01 NS088529	4/1/2015 - 2/29/2020	$427,986
Jianqiang Wu, MD	Exploring the Plexiform Neurofibroma Interactome	Johns Hopkins School of Medicine (Neurofibromatosis Therapeutic)	JHU	5/15/2013 - 11/14/2015	$80,550
Lai Man Wu, PHD	Functional Study of Transcriptional Regulator Sip1 in Myelination and Remyelination	National Multiple Sclerosis Society	FG2045A1T	10/1/2013 - 9/30/2016	$56,657
Mei Xin, PHD	Hippo Signaling in Heart Development and Repair	National Institutes of Health	R01 HL132211	4/1/2016 - 3/31/2021	$390,000
Yi Zheng, PHD	Cincinnati Center for Excellence in Molecular Hematology	National Institutes of Health	P30 DK090971	9/30/2010 - 9/30/2016	$293,603
Yi Zheng, PHD	Targeting Cdc42 for Bone Marrow Transplant Therapies	National Institutes of Health	R01 CA193350	5/1/2015 - 4/30/2020	$356,850
Yi Zheng, PHD	Cdc42, Hematopoietic Stem Cell Polarity and Cell Fate	National Institutes of Health	R01 DK104814	12/15/2015 - 11/30/2019	$496,716
Yi Zheng, PHD Hartmut Geiger, PHD	Stem Cell Aging and Biomarker Studies	National Institutes of Health	R56 AG050650	9/15/2015 - 8/31/2016	$390,000
Yi Zheng, PHD	Novel Sensitizers for Proton Therapy in Childhood Lymphoma	Hyundai Hope on Wheels	Zheng, Yi, HHOW	9/1/2015 - 8/31/2016	$50,000
Total Annual Grant Award Dollars					**$13,265,497**

Annual Industry Award Dollars

Investigator	Industry Sponsor	Amount
Matthew Flick, PHD	Novo Nordisk Pharmaceuticals	$82,277
Dao Pan, PHD	Shire International GmbH	$1,355,955
Total Annual Industry Award Dollars		**$1,438,232**