2013 Research Annual Report

Hematology

Division Details

Division Data Summary

RESEARCH AND TRAINING DETAILS	
Number of Faculty	8
Number of Joint Appointment Faculty	2
Number of Research Fellows	3
Number of Support Personnel	39
Direct Annual Grant Support	$1,187,614
Direct Annual Industry Support	$191,120
Peer Reviewed Publications	13

CLINICAL ACTIVITIES AND TRAINING	
Number of Clinical Staff	5
Number of Clinical Fellows	3
Number of Other Students	2
Inpatient Encounters	1,480
Outpatient Encounters	3,877

Division Photo

Row 1: E Mullins, C Tarango
Row 2: R Gruppo, K Kalinyak, P Malik, T Kalfa
Row 3: R Ware, J Palumbo, L Shook, C Quinn

Significant Publications

George A, Pushkaran S, Konstantinidis DG, Koochaki S, Malik P, Mohandes N, Zheng Y, Joiner CH, **Kalfa TA**. **Erythrocyte NADPH oxidase activity modulated by Rac GTPases, PKC, and plasma cytokines contributes to oxidative stress in sickle cell disease**. *Blood.* 2013; 121: 2099-107.

It was demonstrated that NADPH oxidase is a source of reactive oxygen species (ROS) in human sickle cell red blood cells (RBC) and that the activation of NADPH oxidase is mediated through Ca2+-regulated protein kinase C and Rac GTPase signaling. Moreover, evidence was presented the RBC NADPH oxidase activity can be induced by plasma inflammatory cytokines. This work suggests a novel pathogenic mechanism in sickle cell disease (SCD), namely that systemic inflammation and enzymatically derived ROS within the sickle erythrocyte act in a positive-feedback loop to contribute to acute and chronic organ damage of SCD, and opens possibilities for targeted therapy.

Quinn CT, McKinstry RC, Dowling MM, Ball WS, Kraut MA, Casella JF, Diamini N, Ichord RN, Jordan LC, Kirkham FJ, Noetzel MJ, Roach ES, Strouse JJ, Kwiatkowski JL, Hirtz D, DeBaun MR. **Acute silent cerbral ischemic events in children with sickle cell anemia**. *JAMA Neurol*. 2013; 70:58-65.

Children with sickle cell anemia are at high risk of brain injury, including stroke and silent cerebral infarction. This manuscript describes a common and previously unrecognized form of brain injury in children with sickle cell anemia, which we call an acute silent cerebral ischemic event (ASCIE). We show that asymptomatic children with sickle cell anemia experience cerebral ischemia far more frequently than previously recognized. We conclude that the brain in sickle cell anemia is at constant threat of ischemic injury.

McCavit TL, Xuan L, Zhang S, Flores G, **Quinn CT**. **National trends in incidence rates of hospitalization for**

stroke in children with sickle cell disease. *Pediatr Blood Cancer*. 2013; 60:823-7.

Transcranial Doppler ultrasonography (TCD) can identify children with sickle cell anemia at highest risk of stroke. The stroke prevention in sickle cell anemia trial (STOP) demonstrated the efficacy of primary stroke prevention using TCD to direct the initiation of chronic transfusion therapy. We aimed to determine the effectiveness of primary stroke prevention in the entire U.S. population. We found that the annual incidence of stroke in children with sickle cell anemia in the U.S. decreased 45% in the 10 years after publication of the STOP trial results. The remaining burden of stroke indicates that there are ongoing challenges to the effective implementation of primary stroke prevention across the nation.

Soucie JM, De Staercke C, Monahan PE, Recht M, Chitlur MB,**Gruppo R**, Hooper WC, Kessler C, Kulkarni R, Manco-Johnson MJ, Powell J, Pyle M, Riske B, Sabio H, Trimble S, the USHTCN. **Evidence for the transmission of parvovirus B19 in patients with bleeding disorders treated with plasma-derived factor concentrates in the era of nucleic acid test screening**. *Transfusion*. 2013; 53:1217-1225.

Manufacturing processes of plasma-derived clotting factor concentrates widely used for the treatment of hemophilia A or B utilize a variety of viral inactivation steps to prevent viral transmission. Since 2000, B19V nucleic acid test (NAT) screening of plasma pools has been implemented to further decrease the viral burden in these products. To assess the impact of NAT screening on B19V seroprevalence study. Patients exposed to plasma-derived concentrates after the initiation of NAT screening were 1.7 times more likely to have antibodies to B19V than patients unexposed to plasma-derived products. These results are consistent with continued B19 transmission despite newer viral attenuation processes. The signifance is that more effective viral inactivation and detection processes are needed to protect users of plasma-derived products from infection with B19V or other new or emerging viruses.

Division Publications

1. Crosby LE, Barach I, McGrady ME, Kalinyak KA, Eastin AR, Mitchell MJ. **Integrating interactive web-based technology to assess adherence and clinical outcomes in pediatric sickle cell disease**. *Anemia*. 2012; 2012:492428.
2. Dowling MM, Quinn CT, Plumb P, Rogers ZR, Rollins NK, Koral K, Buchanan GR. **Acute silent cerebral ischemia and infarction during acute anemia in children with and without sickle cell disease**. *Blood*. 2012; 120:3891-7.
3. Flick MJ, Du X, Prasad JM, Raghu H, Palumbo JS, Smeds E, Höök M, Degen JL. **Genetic elimination of the binding motif on fibrinogen for the S. aureus virulence factor ClfA improves host survival in septicemia**. *Blood*. 2013; 121:1783-94.
4. George A, Pushkaran S, Konstantinidis DG, Koochaki S, Malik P, Mohandas N, Zheng Y, Joiner CH, Kalfa TA. **Erythrocyte NADPH oxidase activity modulated by Rac GTPases, PKC, and plasma cytokines contributes to oxidative stress in sickle cell disease**. *Blood*. 2013; 121:2099-107.
5. McCavit TL, Xuan L, Zhang S, Flores G, Quinn CT. **National trends in incidence rates of hospitalization for stroke in children with sickle cell disease**. *Pediatr Blood Cancer*. 2013; 60:823-7.
6. Niu H, Chen X, Gruppo RA, Li D, Wang Y, Zhang L, Wang K, Chai W, Sun Y, Ding Z, Gartner TK, Liu J. **Integrin αIIb-mediated PI3K/Akt activation in platelets**. *PLoS One*. 2012; 7:e47356.
7. Quinn CT, Dowling MM. **Cerebral tissue hemoglobin saturation in children with sickle cell disease**. *Pediatr Blood Cancer*. 2012; 59:881-7.
8. Quinn CT, McKinstry RC, Dowling MM, Ball WS, Kraut MA, Casella JF, Dlamini N, Ichord RN, Jordan LC, Kirkham FJ, Noetzel MJ, Roach ES, Strouse JJ, Kwiatkowski JL, Hirtz D, DeBaun MR. **Acute silent cerebral ischemic events in children with sickle cell anemia**. *JAMA Neurol*. 2013; 70:58-65.

9. Quinn CT, Packman CH. **Hemolytic anemias**. In: KR McCrae, DP Steensma, eds. *American Society of Hematology Self-Assessment Program (ASH-SAP)*. Washington, D.C.: American Society of Hematology (ASH); 2013.
10. Soucie JM, De Staercke C, Monahan PE, Recht M, Chitlur MB, Gruppo R, Hooper WC, Kessler C, Kulkarni R, Manco-Johnson MJ, Powell J, Pyle M, Riske B, Sabio H, Trimble S, the USHTCN. **Evidence for the transmission of parvovirus B19 in patients with bleeding disorders treated with plasma-derived factor concentrates in the era of nucleic acid test screening**. *Transfusion*. 2013; 53:1217-1225.
11. Soucie JM, Monahan PE, Kulkarni R, De Staercke C, Recht M, Chitlur MB, Gruppo R, Hooper WC, Kessler C, Manco-Johnson MJ, Powell J, Pyle M, Riske B, Sabio H, Trimble S. **Evidence for the continued transmission of parvovirus B19 in patients with bleeding disorders treated with plasma-derived factor concentrates**. *Transfusion*. 2013; 53:1143-4.
12. Spar DS, Anderson JB, Palumbo JS, Kukreja KU, Czosek RJ. **Symptomatic upper-extremity deep venous thrombosis after pacemaker placement in a pediatric patient: how to treat?**. *Pediatr Cardiol*. 2013; 34:1275-9.
13. Trachtenberg FL, Mednick L, Kwiatkowski JL, Neufeld EJ, Haines D, Pakbaz Z, Thompson AA, Quinn CT, Grady R, Sobota A, Olivieri N, Horne R, Yamashita R, Thalassemia Clinical Research N. **Beliefs about chelation among thalassemia patients**. *Health Qual Life Outcomes*. 2012; 10:148.

Faculty, Staff, and Trainees

Faculty Members

Joseph S. Palumbo, MD, Associate Professor

Leadership Interim Director, Division of Hematology; Executive Co-Director, Cancer and Blood Diseases Institute

Research Interests Dissecting the mechanisms coupling the hemostatic and innate immune systems to cancer progression

Ralph A Gruppo, MD, Professor

Leadership Director, Hemophilia and Thrombosis Center

Research Interests Coagulation; hemophilia; thrombosis

Karen Ann Kalinyak, MD, Professor

Leadership Clinical Director, Hematology Oncology Program

Research Interests Hematology; bone marrow failure; sickle cell anemia; hemoglobinopathies

Charles Quinn, MD, Associate Professor

Leadership Director, Hematology Clinical and Translational Research

Research Interests Sickle cell disease: causes and treatment of stroke in sickle cell disease; pathophysiologic role of hemoglobin desaturation; acute sickle cell pain; survival and long-term follow-up of children with sickle cell disease

Theodosia Kalfa, MD, PhD, Assistant Professor

Research Interests Study of erythropoiesis, red blood cell structural membrane biology, and of reactive oxygen species in sickle cell disease

Eric Mullins, MD, Assistant Professor

Research Interests Interactions between hemostatic factors and the immune system in inflammatory disease; hemophilia

Cristina Tarango, MD, Assistant Professor

Research Interests Thrombosis and hemostasis, medical education

Lisa Shook, MA, CHES, Instructor

Leadership Director, Ohio Department of Health Regional Sickle Cell Newborn Screening Program

Research Interests Sickle cell disease and trait, newborn screening, transition, chronic disease self-management, health education, quality improvement outcomes

Joint Appointment Faculty Members

Punam Malik, MD, Professor (Experimental Hematology and Cancer Biology)

Ahna Pai, PhD, Associate Professor (Behavioral Medicine and Clinical Psychology)

Clinical Staff Members

Viia Anderson, MSN, CNP-PC
Margaret Kaiser, MSN, CPNP
Darice Morgan, MSN, CPNP, FNP, BC,
APN Program Lead for Hematology
Kelly Porter, MSN, CPNP
Kathy Schibler, MSN, CPNP

Trainees

Nihal Bakeer, MD, PGY-IV, Cincinnati Children's Hospital Medical Center
Shanmuganathan Chandrakasan, MD, MBBS, PGY-IV, Children's Hospital of Michigan
Satheesh Chonat, MD, PGY-IV, Michigan State University-Sparrow Hospital

Division Collaboration

Anderson Center » Devesh Dahale

Improving Hemophilia Outcomes (R. Gruppo, MD)

Nephrology; Human Genetics » Kejian Zhang, MD

Development of special assays and genetic tests that will aid in the diagnosis and management of children with atypical hemolytic syndrome (aHUS), an acute illness with high morbidity and mortality. (R. Gruppo, MD)

Experimental Hematology and Cancer Biology » Punam Malik, MD

Collaboration on studies to determine the signaling pathway that regulates ROS production in sickle RBC and assess its contribution to hemolysis, sickle nephropathy and cardiac pathology. (T. Kalfa, MD, PhD)

Experimental Hematology and Cancer Biology » Yi Zheng, PhD

Development of a high-throughput gene chip for the diagnosis of known and discovery of new genetic mutations causing hemolytic anemia due to erythrocyte cytoskeleton disorders, e.g. spherocytosis, elliptocytosis. (T. Kalfa, MD, PhD)

Human Genetics » Amber Begtrup, PhD, Mehdi Keddache, PhD, and Kejian Zhang, MD

Development of a core service, with CCTST funding, for patients with hemolytic anemias due to erythrocyte

cytoskeleton disorders, RBC enzyme deficiencies, or congenital dyserythropoietic anemias, that will offer diagnostic evaluation with ektacytometry, high-throughput gene chip analysis, and membrane protein analysis. This core will offer unique-phenotype correlation and understanding of the risk associated with splenectomy for some of these patients regarding thrombophilia and pulmonary hypertension. (T. Kalfa, MD, PhD.)

Adolescent Medicine » Maria Britto, MD and Lori Crosby, PhD

Improving sickle cell transition of care through health information technology. (K. Kalinyak, MD)

Anderson Center »

Improving Sickle Cell Disease outcomes. Working on a standardized approach to be sure that every patient over the age of five years has a home pain management plan, and that this plan is outlined clearly in the electronic medical record. We have been able to demonstrate a significant decrease in emergency visits for uncomplicated pain. We are also working on a standardized pain management approach in the emergency department. Working on closely monitoring the timing of patients getting their first Transcranial Doppler Study to identify patients at the highest risk of having a stroke. (K. Kalinyak, MD)

Experimental Hematology and Cancer Biology » Punam Malik, MD

Collaboration on Studies involving patients with Sickle Cell Disease. Losartan Study, Zileuton Study, Placenta Growth Factor Study, Sibling Methacholine Study and Gene Therapy Study. (K. Kalinyak, MD)

Pulmonary; Radiology » Raouf Samy Amin, MD and Robert Fleck, MD

Collaboration on clinical trial exploring the role of Placenta Growth Factor in Sickle Acute Chest Syndrome. (K. Kalinyak, MD)

Pulmonary » Raouf Samy Amin, MD

Collaboration on study: Sibling Methacholine Study (K. Kalinyak, MD)

Psychology » Lori Crosby, MD

Co-Investigator of funded study entitled "Partnering with Parent Support Decision-Making Hydroxyurea in Pediatric Sickle Cell Disease. The aim of the study is to decrease parental uncertainty and increase parental support in the hydroxyurea decision-making process. (K. Kalinyak, MD)

Experimental Hematology and Cancer Biology » Jay Degen, PhD and Matthew Flick, PhD

The role of hemostasis and hemostatic factors in inflammation and immune function. (E. Mullins, MD)

Experimental Hematology and Cancer Biology » Punam Malik, MD

The role of thrombin proteolysis and fibrin deposition in sickle cell disease. (E. Mullins, MD)

Gynecology » Lesley Breech, MD

Combined hematology and gynecology clinic for young women with bleeding disorders. (E. Mullins, MD and C. Tarango, MD)

Environmental Health; University of Cincinnati, Division of Hematology/Oncology » Shuk-mei Ho, PhD and Nagla Karim, MD, PhD

Defining the role of hemostatic system components in prostate cancer pathogenesis. (J. Palumbo, MD)

Experimental Hematology and Cancer Biology » Jay Degen, PhD and Matthew Flick, PhD

Defining the role of hemostatic system components in cancer pathogenesis. (J. Palumbo, MD)

Experimental Hematology and Cancer Biology » James Mulloy, PhD

Defining the role of tissue factor, pro/thrombin and TF/thrombin mediated signaling via protease activated receptors in leukemia progression. (J. Palumbo, MD)

Gastroenterology » Kris Steinbrecher, PhD and Lee Denson, MD, PhD

Determining the role of thrombin and thrombin substrates in the pathogenesis of colitis and colitis-associated colon cancer. (J. Palumbo, MD)

Cardiology » Michael Taylor, MD, PhD and Jeffrey Towbin, MD

Clinical study of sickle cell disease-related cardiomyopathy. (C. Quinn, MD)

Nephrology » Prasad Devarajan, MD

Clinical trial of losartan in patients with sickle cell disease. (C. Quinn, MD)

Human Genetics » Sivakumaran Theru Arumugam, PhD, Amber Begtrup, PhD, Yaping Qian, PhD, and Keijan Zhang, MD

Hemoglobinopathy genetic diagnosis laboratory. (C. Quinn, MD)

Radiology » Daniel Podberesky, MD and Robert Fleck, MD

Evaluation of MRI-based methods for quantitation of hepatic iron overload in transfusion-dependent patients. (C. Quinn, MD)

Psychology » Lori Crosby, MD and Monica Mitchell, MD

Collaboration on HRSA Sickle Cell Newborn Screening program grant, including quality improvement, transition and self-management. (L. Shook)

Cardiology » David Nelson, MD, PhD, Dave Cooper, MD, Angela Lorts, MD, and David Morales, MD

Forming an anticoagulation team for the cardiac intensive care unit. (C. Tarango, MD and J. Palumbo, MD)

Cardiology » Dave Cooper, MD and Jason Frischer, MD

Evaluating antithrombin infusions in ECMO patients. (C. Tarango, MD and J. Palumob, MD)

Interventional Radiology » Kamlesh Kukreja, MD

Evaluating post thrombotic syndrome in patients who have received thrombolysis. (C. Tarango, MD; R. Gruppo, MD and J. Palumbo, MD)

Grants, Contracts, and Industry Agreements

Grant and Contract Awards		Annual Direct
GRUPPO, R		
Hemophilia And Thrombosis Center		
Cascade Hemophilia Consortium(Hemophilia Foundation of Michigan)		
	06/01/03-05/31/14	$110,000
Hemophilia Comprehensive Care		
Maternal and Child Health Bureau(Hemophilia Foundation of Michigan)		
H30 MC 00015	10/01/97-05/31/13	$22,000
Public Health Surveillance for the Prevention of Complications of Bleeding and Clotting Disorders		
Centers for Disease Control & Prevention(Hemophilia Foundation of Michigan)		
U27 DD 000862	10/01/97-09/29/13	$18,900
KALFA, T		
Rho GTPases in Terminal Erythroid Maturation		
National Institutes of Health		
R01 HL 116352	09/26/12-06/30/16	$250,000

TCD with Transfusions Changing to Hydroxyurea (TWiTCH)
National Institutes of Health(Baylor College of Medicine)

R01 HL 095647	03/28/11-05/15/13	$22,035

TCD with Transfusions Changing to Hydroxyurea (TWiTCH) - Per Patient
National Institutes of Health(Baylor College of Medicine)

R01 HL 095647	03/28/11-05/15/13	$12,733

KALINYAK, K

Prevention of Stroke after STOP, A Retrospective Chart Review
Medical University of South Carolina

	01/01/13-12/31/13	$4,312

MULLINS, E

Mechanisms Linking Hemostatic Factors to Neuroinflammatory Disease
National Institutes of Health

K08 HL 105672	08/22/11-07/31/16	$121,375

PALUMBO, J

Hemostatic Factors and Inflammation-Driven Colon
American Society of Hematology

	04/01/13-03/31/14	$100,000

Targeting the Clotting to Prevent Metastasis
Cancer Free Kids

	06/01/13-05/31/14	$50,000

Digestive Health Center - Pilot and Feasiblity Study
National Institutes of Health

U01 DK 062497	09/10/09-05/31/14	$47,983

QUINN, C

Hydroxyurea to Prevent CNS Complications of Sickle Cell
National Institutes of Health(The Johns Hopkins University)

R34 HL 108756	08/01/12-07/31/13	$65,000

SHOOK, L

Cincinnati Sickle Cell Newborn Screening Network
Health Resources & Services Admin

U38 MC 22218	06/01/11-05/31/15	$232,407

Sickle Cell treatment Demonstration Program
Health Resources & Services Admin(University of Cincinnati)

U1EMC0755	09/01/11-08/31/14	$7,400

Cincinnati Sickle Cell Project
Health Resources & Services Admin(Ohio Department of Health)

	07/01/98-06/30/13	$123,469
	Current Year Direct	**$1,187,614**

Industry Contracts

GRUPPO, R	
Medical College of Wisconsin	$4,716
Novo Nordisk Pharmaceuticals	$52,527
Pfizer, Inc	$8,800
Alexion Pharmaceuticals, Inc	$6,205
Bayer HealthCare Pharmaceuticals, Inc	$19,283
Bristol -Myers Squibb	$4,501
Biogen Idec Hemophilia, Inc.	$18,982
KALFA, T	
Baxter Healthcare Corp.	$2,245
KALINYAK, K	
Novartis Pharmaceuticals	$2,425
MALIK, P	
HemaQuest Pharmaceuticals, Inc	$1,080
PALUMBO, J	
Novo Nordisk Pharmaceuticals	$43,187
QUINN, C	
Adventrx Pharmaceuticals, Inc	$12,405
Eli Lilly and Company	$13,264
GlycoMimetics, Inc	$1,500
Current Year Direct Receipts	**$191,120**
Total	**$1,378,734**