

Research Report 2017



BLOODCENTER
of WISCONSIN™

PART OF VERSITI

Blood Research Institute

A Message from Executive Vice President Gilbert White, II, MD, Chief Scientific Officer



Jackie Fredrick, who led the organization as CEO for 15 years through the economic downturn of 2008 and the repercussions the downturn had throughout the healthcare industry and the NIH, retired as planned in 2017 and we welcomed Chris Miskel, our sixth CEO, who comes from the finance and innovation areas of Eli Lilly & Co and Baxter Healthcare/Baxalta/Shire.

2017 was another strong year for research. Grant revenues for the year were \$15.2 M, a record for us and exceeded our 2017 budget by \$1 M. New NIH R-type grants or competitive renewals were obtained by **Dick Aster** (years 46-49), **Sid Rao**, **Karin Hoffmeister**, **Hardy Weiler** (2 grants), **Bonnie Dittel**, **Bin Ren**, and **Dan Bougie**. New K-type awards went to **Matt Karafin** and **Anand Padmanabhan**. Altogether, there were 16 new NIH grants in 2017 that totaled \$8.2 M. BloodCenter also was part of a \$44 M award that went jointly to Marshfield Clinic, UW-Madison, Medical College of Wisconsin, and Versiti. The grant, titled "All of US-Wisconsin," is part of President Obama's Precision Medicine Initiative (PMI) and, together with these other partner institutions, we will enroll 100,000 of the million volunteers in the PMI. **Gil White** is the site lead for BCW/Versiti. In addition, **Dick Aster** received our seventh Bridge Award from the American Society of Hematology, more than ASH has awarded to any other institution in the country. **Weiguo Cui** received the first R. Douglas Ziegler Innovation Award and the Versiti Moonshot Award for his work related to a new immunotherapy approach to the treatment of bladder cancer, which he has termed ReACT.

Industry sponsored research grants totaled \$0.25 M or 2% of our annual revenues.

Bin Ren from Roy Silverstein's laboratory joined the faculty as Assistant Investigator. Bin's research focuses on angiogenesis, especially that in the tumor microenvironment, and so expands our expertise in the vascular biology area. **Alex Minella** left to take a position at Amgen Corporation as Medical Director in the Medical Sciences Division, Early Development in Hematology/Oncology. Alex contributed much in his three years at the BRI as a scientist and a mentor. **Rachel Bercovitz** also left to take a faculty position as Associate Professor of Pediatrics at the Northwestern University's Feinberg School of Medicine in Chicago. **Weiguo Cui** and **Hervé Falet** were promoted to Investigator. **Josh Field** was named Chief of the Section of Non-Malignant Hematology at MCW.

High on the list of accomplishments for the year were two for-profit start-up companies, two new patents and two new tests for our Diagnostic Labs. In our history, we have only had one start-up before this year: GTI, Inc, which was sold in 2008. One of the new start-ups was based on **Weiguo Cui's** ReACT technology and is by **Biomotiv** in Cleveland, Ohio. The second start-up is based on **Anand Padmanabhan's** PEA-HIT discovery which forms the basis for a more facile and accurate new test for Heparin-induced Thrombocytopenia. **Retham**, a company formed by Anand, has licensed the technology. The patents were

Continued: A Message from Executive Vice President Gilbert White, II, MD, Chief Scientific Officer

to **Bonnie Dittel**, for her discovery with Harvard scientists of gelsolin as a possible therapeutic for MS, and to **Anand Padmanabhan** for his PEA-HIT test.

We had numerous individual accomplishments during the year. We celebrated **Marcia Iverson's** 40th year and **Trudy Holyst's** 25th year with the organization. **Karin Hoffmeister** and **Marijke van den Berg** gave 2 of the 7 total plenary talks at the biennial ISTH meeting in Berlin. **Hardy Weiler** gave a State-of-the-Art lecture at the same meeting. **Alan Mast** was elected Chair of the next Hemostasis Gordon Conference to be held in the summer of 2018. **Tom Abshire** received the Joan Cox Gill Award for Service, and **Gil White** received the Lifetime Achievement Award, both from the Hemostasis and Thrombosis Research Society. **Dick Aster** received the T. Michael Bolger award from the Milwaukee Regional Research Forum for his contributions to research. **Laura Savatski**, Technology Transfer Officer for BCW, was elected to the Board of Directors for the Association of University Technology Managers (AUTM). **Debra Newman, Alan Mast, Karin Hoffmeister, Magda Chrzanowska, Roy Silverstein** and **Bob Montgomery** continue to serve on NIH review panels. **Andrea Brown** and **Michael Frohna** served on the planning committee for the 2017 annual Association of Independent Research Institutes (AIRI) Conference. Three students, Panida Lertkiatmongkol from **Peter Newman's** lab, Steven Blinka from **Sid Rao's** lab, and Lan Luo from PLA Medical School in China and **Demin Wang's** lab completed their PhD degree in 2017.

One of the goals for research for 2017 was to integrate into the other communities now served by Versiti. The **Heartland Charitable Fund** continued to provide support for a joint research project between Sid Rao and John Crispino in the Cancer Center at Northwestern University School of Medicine. Connections between the

BRI and the **Van Andel Institute (VAI)** in Grand Rapids, MI were established leading to an opportunity for Diagnostic Laboratories to develop a new test for an early pancreatic cancer marker. VAI scientists also were connected with the Pancreatic Cancer group at MCW. Interactions with the **Indiana Hemophilia and Thrombophilia Center (IHTC)** were developed on three fronts: clinical research collaborations in hemophilia, a pharmacy opportunity at IHTC and St. Vincent's Hospital, and work with Diagnostic Labs.

The 15th Annual **Aster Lecture** was delivered on June 5th by Dr. Lawrence "Skip" Brass, Professor of Medicine and Pharmacology at the University of Pennsylvania and Chair of our Scientific Advisory Board. His talk was titled *Why Bleeding Stops: A Deep Dive into Systems Biology*. The 16th Annual **Mosesson Lecture** was delivered on October 5th by Dr. Evan Sadler, Professor in the Department of Medicine at Washington University at St. Louis. Dr. Sadler is a Professor in the Department of Medicine at the Washington University School of Medicine and former Howard Hughes Medical Institute Investigator and former ASH President. His talk was on "Von Willebrand Factor, ADAMTS13, and Thrombotic Microangiopathies." The 1st Annual **Jacqueline Fredrick Lecture**, titled "Using Atomic Level Structural Data to Inform the Design of Integrin b3 Family Therapeutics," was given on October 6th by Dr. Barry Collier, Professor of Medicine at the Rockefeller University and CEO of the Rockefeller Hospital. The 1st Annual **R. Douglas Ziegler Innovation Lecture** was given by Dr. Jonathan Stamler, Director of the highly innovative Harrington Discovery Institute at Case Western Reserve University, on November 9th. His talk was titled "Advancing Red Cell Dependent Vasodilation into Medicines." Dr. Stamler's visit also included a luncheon with Versiti Executives and a reception that included local high school teachers. All four lectures were outstanding and examples

of cutting-edge science and translation.

The 11th Annual **Center for Human Immunology Symposium** was held October 25th at the Blood Research Institute. The symposium featured renowned speakers from Stanford University, Memorial Sloan Kettering Cancer Center, the University of Pennsylvania, the University of Iowa, and MIT. This year's meeting was hosted by **Weiguo Cui, Bonnie Dittel, and Matt Riese**.

The **Scientific Advisory Board** reviewed part of the Vascular Biology program in October. Overall, there was considerable enthusiasm for this remarkably productive group of investigators. In their summary comments, the Board stressed the importance of supporting existing investigators, succession planning for senior investigators, strategic planning for research, and transition to Versiti.

At years' end, there were 42 trainees in the BRI. All of our T32 Training Grant positions were filled in 2017: Ryan Zander in **Weiguo Cui's** lab, Alyssa Moroi in **Peter Newman's** lab, Nate Schloemer in **Subra Malarkannan's** lab, and Sreemanti Basu in **Hardy Weiler's** lab. Gang Xin in **Weiguo Cui's** lab was the 2017 Doolittle Fellow and Anna Strzepa in **Bonnie Dittel's** lab was the Gallagher Fellow. Seven new graduate students (Yao Chen and Achia Khatun in **Weiguo Cui's** lab, Wen Zhu in **Demin Wang's** lab, Nathan Eaton in **Hervé Falet's** lab, Puja Agrawal and Katelyn Heimbruch in **Sid Rao's** lab, and Luke Christiansen in **Nan Zhu's** lab) selected the BRI as their place to train.



Gilbert C White, II, MD
Chief Scientific Officer

Research By The Numbers – 2017



16
New NIH
Grants



\$44 Million
Joint Precision
Medicine
Initiatives



2
Patents
Approved



\$15.2
Million
Research
Revenues



\$37.2
Million
New
Applications



2
New Diagnostic
Tests Developed



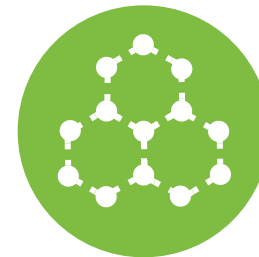
\$584
Thousand
Average
Funding per
investigator




2
Start-Up
Companies
Formed



33
Investigators



13
Core Labs



Transfusion Medicine

Transfusion Medicine research has a long history at BloodCenter, reflecting its basic mission to provide a safe and effective supply of blood products for patients who require transfusion.

Effective transfusion therapy requires knowledge of the biology and physiology of blood, satisfactory methods for collecting and storing blood cells with maximum preservation of function, and an understanding of the many diseases in which transfusion of blood components can be beneficial.

Research conducted by the Transfusion Medicine group addresses each of these areas. Investigators in the Transfusion Medicine Program study basic biology and clinical implications of a range of transfusion-related issues.

Richard H. Aster, MD

CEO Emeritus and Senior Investigator, Blood Research Institute
Professor, Department of Medicine, Medical College of Wisconsin (MCW)
MD, University of Michigan 1957
Hematology, Harvard University 1965
Faculty, Harvard 1964-1970
Employed at BloodCenter of Wisconsin: 1970



diagnosis and treatment in patients with antibody-induced blood cell destruction.

Awards, Honors and Memberships

- Founder: GTI Diagnostics (subsidiary of BCRF)
- Co-founder, BloodCenter Research Foundation
- Co-founder, Great Lakes Hemophilia Association
- Co-founder, Blood Centers of America (BCA)
- Karl Landsteiner and Emily Cooley Awards, American Association of Blood Banks (AABB)
- Bernard Fantus Lifetime Achievement Award (AABB)
- Distinguished Service Award, Medical College of Wisconsin (MCW)

- Tom Zuck Lifetime Achievement Award, America's Blood Centers (ABC)
- T Michael Bolger Award for Distinguished Service (MCW)

Funding

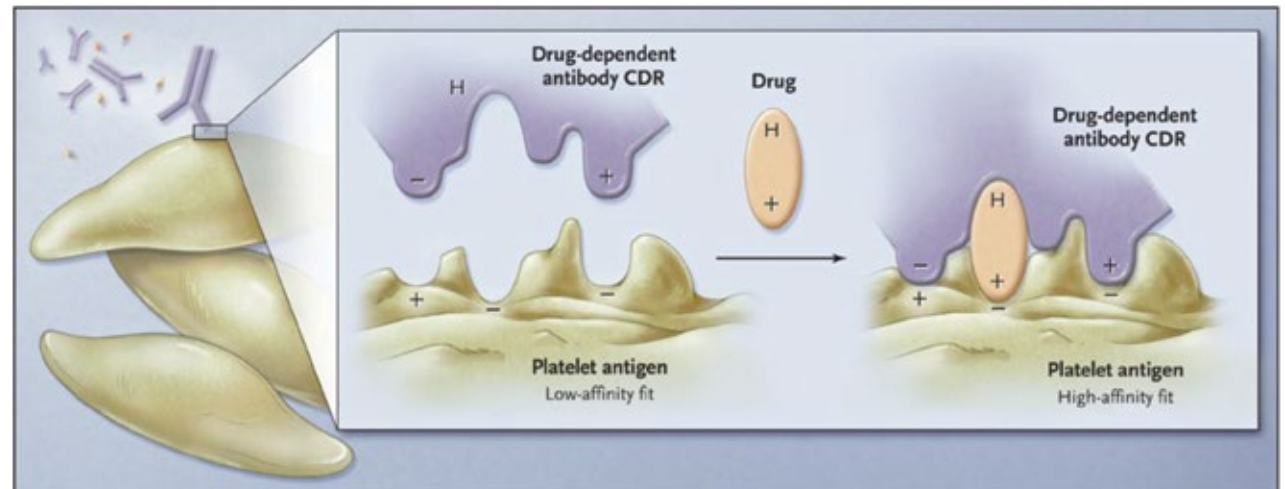
R01-HL-13629-47 National Heart Lung and Blood Institute. 1969-2020

Publications

1. Jones CG, Pechauer SM, Curtis BR, Bougie DW, Irani MS, Dhakal B, Pierce B, Aster RH, Padmanabhan A. A Platelet Factor 4-Dependent Platelet Activation Assay Facilitates Early Detection of Pathogenic Heparin-Induced Thrombocytopenia Antibodies. *Chest*. 2017 Oct;152(4):e77-e80. PMID: 2899155

Research Interests

Immune destruction of red blood cells, white blood cells, and platelets is a major cause of morbidity and mortality in patients. Dr. Aster's work is aimed at understanding the causes of blood cell destruction by autoantibodies, drug-induced antibodies, and antibodies induced by blood transfusion or exposure to fetal blood cells during pregnancy. Recent studies in his laboratory have shown that metabolites generated in the body following exposure to various drugs can induce antibodies that cause platelet destruction and bleeding and provide new insights into the cause of "idiosyncratic" drug-sensitivity reactions. Findings made in these and related studies are defining new methods for antibody detection to improve



Rachel Bercovitz, MD, MS

Associate Medical Director, Assistant Investigator, Blood Research Institute, BloodCenter of Wisconsin
Assistant Professor of Pathology and Pediatrics, Medical College of Wisconsin
MD, University of Illinois College of Medicine, 2005
Employed at BloodCenter of Wisconsin: 2012



Research Interests

Dr. Bercovitz joined the Medical Sciences Institute (MSI) faculty in August 2012. Her primary research interest is in understanding the role platelet defects (both qualitative and quantitative) play in bleeding issues in pediatric patients and developing diagnostic tools and therapeutic protocols that will minimize bleeding risk as well as exposure to blood transfusions. She is engaged in a collaborative study between the Blood Research Institute and the Herma Heart Center and Department of Pediatrics of Children's Hospital of Wisconsin to define bleeding risks and effectiveness of platelet transfusions in children undergoing cardiac surgery.

Awards, Honors and Memberships

- Member, American Academy of Pediatrics
- Member, American Heart Association
- Member, Hemostasis and Thrombosis Research Society

Funding

"Platelet dysfunction and transfusion requirements in pediatric patients on cardiopulmonary bypass"

Hemostasis and Thrombosis Research Society Mentored Research Award \$150,000 (PI) 7/1/2016 – 9/30/2017

"Innovative Diagnosis, Evaluation, and Assessment of Hemostasis" Clinical and Translational Sciences Institute

of Southeastern Wisconsin (CTSI) Pilot Award \$50,000 (PI)
4/01/2016 – 3/31/2018

Brian Curtis, PhD, D(ABMLI), MT(ASCP) SBB, Investigator



Research Interests

Antibodies specific for antigens carried on blood platelets and white blood cells (neutrophils) cause thrombocytopenia and neutropenia (low neutrophil count) in various immune disorders and can be difficult to identify. Work in Dr. Curtis' laboratory has led to improved methods for detecting such antibodies and to new understanding of the blood disorders in which they are involved. Dr. Curtis serves as Director of the Platelet and Neutrophil Immunology Reference Laboratory of BloodCenter of Wisconsin and applies his research findings to improve the effectiveness with which this laboratory enhances medical care for patients referred for diagnostic testing. One particular area of expertise for

Director, Platelet & Neutrophil Immunology Lab, BloodCenter of Wisconsin
Senior Director, Versiti Product Development and Clinical Lab, BloodCenter of Wisconsin
Investigator, Blood Research Institute, BloodCenter of Wisconsin
Assistant Adjunct Professor, Clinical and Translational Science Institute, Medical College of Wisconsin
PhD, University of Wisconsin-Milwaukee, 2010
Employed at BloodCenter of Wisconsin: 1991

the lab is in diagnosis of Fetal and Neonatal Alloimmune Thrombocytopenia (FNAIT), a disorder in which a pregnant mother can make antibodies that destroy her child's platelets. Recent work in the Curtis lab has allowed for improved diagnosis of FNAIT.

Awards, Honors and Memberships

- Member, American Society of Clinical Pathologists (ASCP)
- Member, American Association of Blood Banks (AABB)
- Member, American Society of Hematology (ASH)
- Member, International Society of Blood Transfusion (ISBT)
- Member, International Society of Thrombosis & Hemostasis (ISTH)
- Diplomat, American Board of Medical Laboratory Immunology (ABMLI)
- Member, Editorial Board, Transfusion

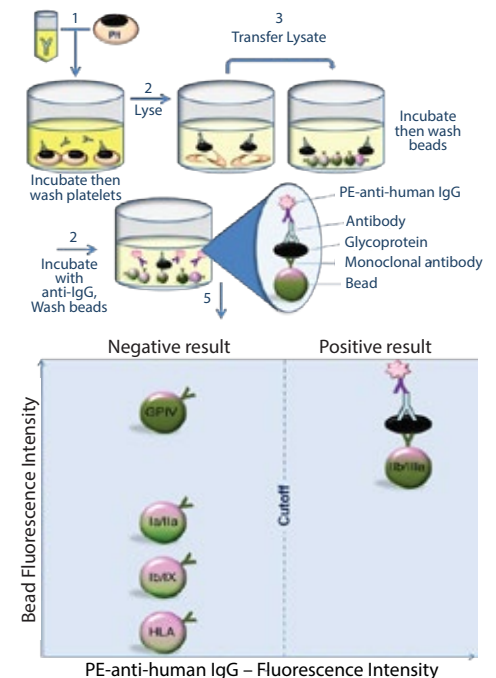
Funding

"Development of a New and Improved Diagnostic Assay for Antibody Detection in Patients with Suspected Heparin-Induced Thrombocytopenia (HIT)". Strategic Investment Fund, BloodCenter of Wisconsin (Co-PI).

Publications

1. Curtis BR. Non-chemotherapy drug-induced neutropenia: key points to manage the challenges. Hematology Am Soc Hematol Educ Program. 2017 Dec 8;2017(1):187-193. Review. PMID: 29222255

2. Krista Metzner, Julie Bauer, Heather Ponzi, Allison Ujcich, Brian R. Curtis. Detection and identification of platelet antibodies using a sensitive multiplex assay system - Platelet Antibody Bead Array (PABA). Transfusion 2017; Jul;57(7):1724-1733.
3. Mia J. Sullivan, Randy Kuhlmann, Julie Peterson, Brian R. Curtis. A new low frequency alloantigen (Domb) located on platelet glycoprotein IIIa as a cause of maternal sensitization leading to neonatal alloimmune thrombocytopenia. Transfusion 2017; Jul;57(7):1847-1848.



Gregory Denomme, PhD

Senior Director of Immunohematology and Innovation, Versiti: BloodCenter of Wisconsin
Senior Investigator, Blood Research Institute, BloodCenter of Wisconsin
PhD, Microbiology and Immunology, University of Western Ontario, 1993
Employed at BloodCenter of Wisconsin: 2009



Research Interests

Dr. Denomme is Director of BloodCenter's Immunohematology and Transfusion Service Laboratory, a division of BCW Clinical Laboratories. He is an immunology and immunohematology-trained scientist with interests in the immune response to red cell antigens, the expression of blood groups, and bench-to-bedside studies in immunohematology. His work integrates the immunogenetics with transfusion medicine to explore the genetic basis of blood group expression and the functional polymorphisms underlying the pathology of immune-mediated red cell hemolysis.

Awards, Honors and Memberships

- Member, American Association of Blood Banks (AABB)
- Board Member, International Society of Blood Transfusion, Red Cell Immunogenetics and Blood Group Terminology Workgroup
- Member, International Collaboration for Transfusion Medicine Guidelines
- Sally Frank Memorial Award, (AABB) 2017
- Kay Beattie Lectureship, Michigan Association of Blood Banks (MABB)
- Margot S Kruskall Lectureship, Harvard Medical School/ American Red Cross
- Member, International Society for Blood Transfusion
- Member, Canadian Society for Medical Laboratory Science

Funding

"Characterization of ABO Titers Among Group O and A Donors: Harmonizing and Established Protocol to Define "Low Titer" ABO Blood Products." G. Denomme (Principal Investigator) and W Anani, MD. The Foundation for America's Blood Centers (ABC). 2017 \$20,000

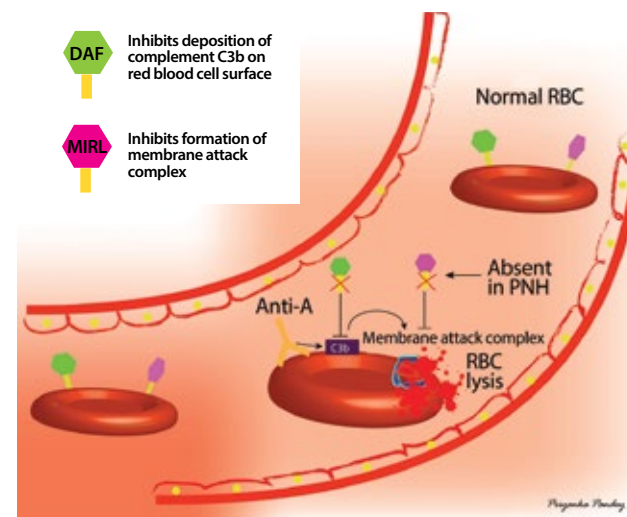
Publications

1. Anani WQ, Duffer K, Kaufman RM, Denomme GA. How do I work up pretransfusion samples containing anti-CD38? *Transfusion*. 2017 Jun; 57(6):1337-1342. PMID: 28474469
2. Anani WQ, Marchan MG, Bensing KM, Schanen M, Piefer C, Gottschall JL, Denomme GA. Practical approaches

and costs for provisioning safe transfusions during anti-CD38 therapy. *Transfusion*. 2017 Jun; 57(6):1470-1479. PMID: 28150308

3. Anani WQ, Yassai MB, Bensing KM, Denomme GA. Molecular characterization of three novel weak D type alleles with additional haplotype data on weak D Types 1.2 and 18. *Transfusion*. 2017 Apr;57(4):1092-1093 PMID: 28236294

Antibody mediated lysis of PNH red blood cell clone



Joshua Field, MD, MS

Medical Director, BloodCenter of Wisconsin
 Investigator, Blood Research Institute
 Professor of Medicine, Medical College of Wisconsin
 Medical Director, Adult Sickle Cell Disease Clinic, Froedtert Hospital
 MD, Carver College of Medicine, University of Iowa, Iowa City, IA, 2001
 Employed at BloodCenter of Wisconsin: 2010



Awards, Honors and Memberships

- Member, American Society of Hematology Guidelines on Sickle Cell Disease Committee
- Chair, Acute Pain Taxonomy Project for American Pain Society/American Association for Pain Management
- Thomas A. Smallwood Award, Froedtert Hospital, WI "In recognition of Patient Care Excellence 2017"

Funding

"A Phase 1 Open-Label, Dose-Escalation/Dose-Expansion Safety and Tolerability Study of INCB059872 in Subjects with Sickle Cell Disease" Incyte Corporation 11/01/2017 – 10/31/2019

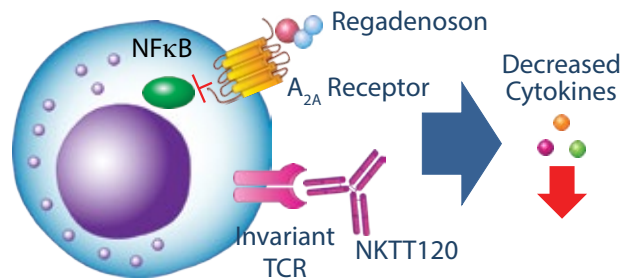
Publications

1. Field JJ. Five lessons learned about long-term pain management in adults with sickle cell disease. Hematology Am Soc Hematol Educ Program. 2017 Dec 8; 2017(1):406-411. Review. PMID: 29222285
2. Field JJ, Majerus E, Ataga KI, Vichinsky EP, Schaub R, Mashal R, Nathan DG. NNKTT120, an anti-iNKT cell monoclonal antibody, produces rapid and sustained iNKT cell depletion in adults with sickle cell disease. PLoS One. 2017 Feb 2;12(2):e0171067. doi: 10.1371/journal.pone.0171067. eCollection 2017. PMID: 28152086
3. Field JJ, Majerus E, Gordeuk VR, Gowhari M, Hoppe C, Heeney MM, Achebe M, George A, Chu H, Sheehan B, Puligandla M, Neuberg D, Lin G, Linden J, Nathan DG. Randomized phase 2 trial of regadenoson for treatment of acute vaso-occlusive crises in sickle cell disease. Blood Adv. 2017 Aug 28;1(20):1645-1649. Erratum in: Blood Adv. 2017 Oct 19;1(23):2058. PMID: 29296811

Research Interests

Dr. Field is concerned with clinical aspects and optimization of treatment for adults with sickle cell disease (SCD). He was the principal investigator on a multi-center trial to evaluate effectiveness of the adenosine_{2A} receptor agonist regadenoson, an inhibitor of inflammation that may be useful for treatment of blood vessel occlusion in SCD, as well as a trial to evaluate the cysteinyl leukotriene receptor antagonist, montelukast. Dr. Field also is examining a novel imaging modality, contrast-enhanced ultrasound, for the measurement of microvascular blood flow in patients with SCD. Preliminary results suggest that this approach can reliably measure blood flow at the capillary level and may be ideal for measuring outcomes in therapeutic trials.

Regadenoson and NKTT120 target iNKT cells



Agent	Class/mechanism	Route	Half-life	Schedule	VO approach
Regadenoson	A _{2A} R agonist/ iNKT cell inhibitor	IV	5 minutes	CIVI during VO	Treatment
NKTT120	Humanized monoclonal antibody/ iNKT cell inhibitor	IV	11 days	Undetermined (goal every 3 months)	Prevention



Tia Wilson

Tia Wilson is bravely battling sickle cell anemia. When she was just 3 years old, she suffered a stroke. She was hospitalized and began getting blood transfusions every four weeks. In 2015, Tia got a bone marrow transplant from her older brother. Now 10, Tia's health has improved, and she's hopeful that BloodCenter investigators can find better treatments – and ultimately a cure for sickle cell disease.

“My goal is to make a difference by showing families out there that we can beat this disease,” says Tia’s mom, Mickey.

Hervé Falet, PhD

Associate Investigator, Blood Research Institute, BloodCenter of Wisconsin
PhD, Paris Descartes University, 1997
Medicine, Brigham and Women's Hospital, Harvard Medical School, 2001
Employed at BloodCenter of Wisconsin: 2016



Research Interests

Dr. Hervé Falet received his master's and doctoral degrees from Paris Descartes University and completed his postdoctoral fellowship at Brigham and Women's Hospital. He joined the Blood Research Institute faculty in 2016. His primary research interests are associated with blood platelet production (thrombopoiesis) and function.

Platelets circulate in blood at a concentration of 150,000-450,000/ μ l that is maintained by a fine balance between production and clearance. At sites of vascular injury platelets respond to external stimuli by rapidly changing shape and recruiting other platelets. Deficient platelet production, due to genetic causes, secondary to cancer

therapy, or from unknown etiology, poses significant risks of mortality, mostly due to bleeding.

Blood platelets are produced in the bone marrow by megakaryocytes in a unique process that requires extensive intracellular membrane rearrangements. These include the formation of the demarcation membrane system, the surface-connected membrane extension that invaginates into the cell body and further develops to provide membranes for future platelets.

At the Blood Research Institute, Hervé investigates the roles of novel membrane binding and deforming proteins in the formation and organization of the megakaryocyte demarcation membrane system. He anticipates that his studies will yield basic information related to megakaryocyte and platelet biology, and lead to the development of new approaches to reestablish thrombopoiesis in the setting of thrombocytopenia (low platelet count).

Awards, Honors and Memberships

- Bridge Grant Award, American Society of Hematology 2017
- Bridge Grant Award, Brigham Research Institute 2017
- Member, International Society on Thrombosis and Hemostasis

Funding

R01 HL126743 "Endocytosis in Platelet and Megakaryocyte Biology"

Publications

1. Falet, H. Singling out FLI1 in Paris-Trousseau syndrome. *Blood*. 2017 Jun 29;129(26):3399-3401. PMID: 28663223
2. Sladojevic N, Oh GT, Kim HH, Beaulieu LM, Falet H, Kaminski K, Freedman JE, Liao JK. Decreased Thromboembolic Stroke but not Atherosclerosis or Vascular Remodeling in Mice with ROCK2-deficient Platelets. *Cardiovasc Res*. 2017 Sep 1;113(11):1307-1317. PMID: 28430966

Jerome Gottschall, MD

Senior Medical Director, BloodCenter of Wisconsin
Senior Investigator, Blood Research Institute, BloodCenter of Wisconsin
Professor of Pathology, Department of Pathology, Medical College of Wisconsin
MD, Ohio State University College of Medicine, 1974
Employed at BloodCenter of Wisconsin: 1979



Research Interests

Dr. Gottschall is a Co-Principal Investigator on the Recipient Epidemiology and Donor Evaluation Study-III (REDS III) sponsored by the National Heart Lung and Blood Institute in which BloodCenter is one of several participating organizations. REDS III includes studies on blood safety, blood availability, HIV transmission and other transfusion-related studies. REDS-III will utilize large donor, component and recipient databases to help answer important transfusion-related questions. Among subjects to be studied are alloimmunization (immunization against transfused blood cells), impact of blood donation on donor iron levels, benefits of red cell transfusion in the elderly, and transfusion of various blood products in

distinct clinical settings. Dr. Gottschall also is concerned with the clinical aspects of immune hemolytic anemia and in the status of iron levels in repeat blood donors. In 2015, Dr. Gottschall participated as co-author on two important articles, published in *Lancet Haematology and Transfusion*, about the importance of red cell genotyping for transfusion medicine. An avid athlete throughout his entire life, Dr. Gottschall says sports have taught him three critical life skills that he uses in his medical work and throughout his life: discipline; persistence; and setting goals.

Awards, Honors and Memberships

- Member, College of American Pathologists
- Member, American Association of Blood Banks (AABB)
- Member, American Society of Hematology

Publications

1. Anani WQ, Marchan MG, Bensing KM, Schanen M, Piefer C, Gottschall JL, Denomme GA. Practical approaches and costs for provisioning safe transfusions during anti-CD38 therapy. *Transfusion*. 2017 Jun;57(6):1470-1479. PMID: 28150308
2. Anani W, Wucinski J, Baumann Kreuziger L, Gottschall J, Karafin M. Therapeutic plasma exchange in refractory warm autoimmune hemolytic anemia. *Transfusion*. 2017 Jun;57(6):1336. PMID: 28594138
3. Cancelas JA, Gottschall JL, Rugg N, Graminske S, Schott MA, North A, Huang N, Mufti N, Erickson A, Rico S, Corash L. Red blood cell concentrates treated

with the amustaline (S-303) pathogen reduction system and stored for 35 days retain post-transfusion viability: results of a two-centre study. *Vox Sang*. 2017 Apr;112(3):210-218. PMID: 2822051

Matthew Karafin, MD

Associate Medical Director, Medical Sciences Institute, BloodCenter of Wisconsin
Junior Investigator, Blood Research Institute, BloodCenter of Wisconsin
Assistant Professor of Pathology, Medical College of Wisconsin
MD, Carver College of Medicine, University of Iowa, Iowa City, IA, 2007
Transfusion Medicine Fellowship, Johns Hopkins Hospital, 2011
Anatomical and Clinical Pathology Residency, Johns Hopkins Hospital, 2012
Employed at BloodCenter of Wisconsin: 2012



- AABB PEP Shining Star/Rising Star Award 2017
- Member, College of American Pathologists (CAP)
- Member, Alpha Omega Alpha (AOA)

Funding

Clinical & Translational Science Institute \$50,000 "The Effects of Older Red Cell Units in Adults with Sickle Cell Disease" 04-01-2017 – 03-31-2018 (PI)

HHSN268201100003I (Mast) 03/15/2011 – 03/14/2020
NIH/NHLBI \$511,520 "Recipient Epidemiology and Donor Evaluation Study III (REDS III)" (Co-I)

1K23HL136787-01A1 (Karafin) 12/15/2017 – 12/15/2022
NIH/NHLBI \$165,000 "The Effects of Older Red Cell Units in Adults with Sickle Cell Disease" (PI)

Publications

1. Anani W, Wucinski J, Baumann Kreuziger L, Gottschall J, Karafin M. Therapeutic plasma exchange in refractory warm autoimmune hemolytic anemia. *Transfusion*. 2017 Jun;57(6):1336. PMID: 28594138
2. Irani MS, Karafin MS, Ernster L. Red cell exchange to mitigate a delayed hemolytic transfusion reaction in a patient transfused with incompatible red blood cells. *J Clin Apher*. 2017 Feb;32(1):59-61. PMID: 27112240
3. Karafin MS, Bruhn R, Westlake M, Sullivan MT, Bialkowski W, Edgren G, Roubinian NH, Hauser RG, Kor DJ, Fleischmann D, Gottschall JL, Murphy EL, Triulzi DJ; National Heart, Lung, and Blood Institute Recipient Epidemiology and Donor Evaluation Study-III (REDS-III). Demographic and epidemiologic characterization of

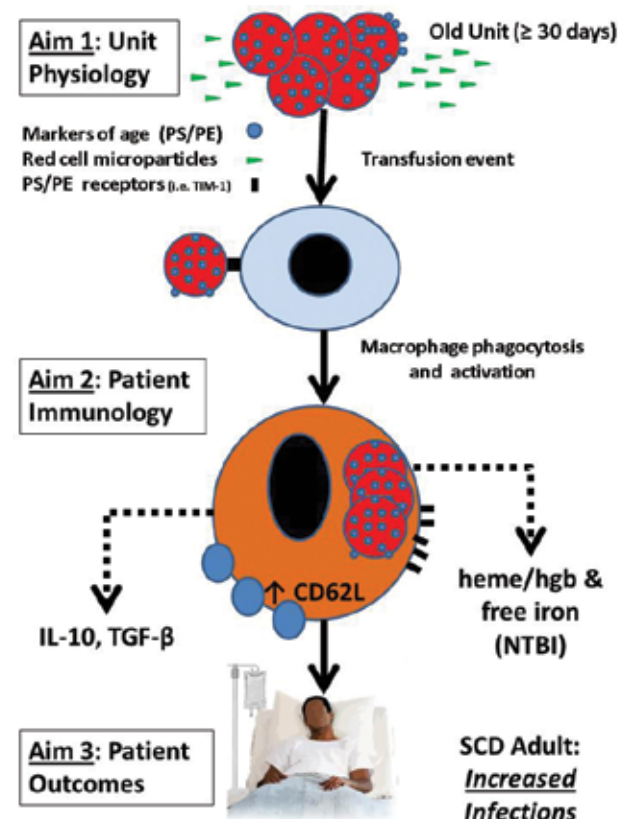
transfusion recipients from four US regions: evidence from the REDS-III recipient database. *Transfusion*. 2017 Dec;57(12):2903-2913. PMID: 29067705

Research Interests

Dr. Karafin's research interests include the use of red cell transfusion to control pain in patients with sickle cell disease, etiology and prevention of red cell alloimmunization and iron overload, benefits and risks of red cell storage for patients with sickle cell disease, benefits and risks of red cell transfusions in the elderly, and the etiology and prevention of transfusion reactions.

Awards, Honors and Memberships

- Member, American Society for Apheresis (AFSA)
- Member, American Society for Clinical Pathology (ASCP)
- Member, AABB



Anand Padmanabhan, MD, PhD,

Associate Investigator, Blood Research Institute
Medical Director, Therapeutic Services, BloodCenter of Wisconsin
Associate Professor of Pathology, Medical College of Wisconsin
MD, Thanjavur Medical College, Thanjavur, TN, India, 2000
PhD, Brown University, 2006
Employed at BloodCenter of Wisconsin: 2010



Research Interests

Heparin is widely used to prevent and treat thrombosis, but some patients given this otherwise useful anticoagulant become immunized and produce antibodies that cause thrombocytopenia (heparin-induced thrombocytopenia, HIT). The low platelet counts rarely cause bleeding but some affected individuals experience thrombosis, which can be life threatening. Dr. Padmanabhan is engaged in studies to define the properties of heparin-induced antibodies that are most likely to cause thrombosis. Findings made are expected to advance the understanding of HIT and to improve laboratory diagnosis and safety of anticoagulation with heparin.

Awards, Honors and Memberships

- Member, American Society for Apheresis (ASFA)
- Member, AABB (formerly the American Association of Blood Banks)
- Member, American Society of Hematology
- Associate Editor, Journal of Clinical Apheresis
- Member, Medical Advisory Committee, Wisconsin Donor Network (Federal designated organ Procurement Organization in Southeastern Wisconsin)

Funding

“New Approaches to Pathogenesis and Diagnosis of Heparin-Induced Thrombocytopenia/Thrombosis (HIT)”

NHLBI – K08 (PI) 04/01/2017 – 03/31/2022 \$864,000 (total for 5 years)

“Characterization of normal plasma constituents that counteract HIT antibody-mediated platelet activation: Implications for treatment of heparin-induced thrombocytopenia/thrombosis” CTSI of Southeastern Wisconsin 04/01/2017 – 03/31/2018 \$50,000 (total for 1 year) (PI)

“B cell responses in Heparin-induced thrombocytopenia” NHLBI R01 04/01/2017 – 03/31/2022 (Co-Investigator)

Publications

1. Jones CG, Pechauer SM, Curtis BR, Bougie DW, Irani MS, Dhakal B, Pierce B, Aster RH, Padmanabhan A. A Platelet Factor 4-Dependent Platelet Activation Assay Facilitates Early Detection of Pathogenic Heparin-Induced Thrombocytopenia Antibodies. *Chest*. 2017 Oct;152(4):e77-e80. PMID: 28991552
2. Padmanabhan A, Jones CG, Pechauer SM, Curtis BR, Bougie DW, Irani MS, Bryant BJ, Alperin JB, Deloughery TG, Mulvey KP, Dhakal B, Wen R, Wang D, Aster RH. IVIg for Treatment of Severe Refractory Heparin-Induced Thrombocytopenia. *Chest*. 2017 Sept 152(3):478-485. PMID: 28427966 (podcast)

Glycomics Center

The Glycomics Center, led by faculty member, Dr. Karin Hoffmeister, opened its doors in 2016 for the Blood Research Institute. Analogous to Genomics and Proteomics, Glycomics focuses on defining the structures and functions of complex carbohydrates (sugars), as found in glycoproteins, glycolipids, and glycosaminoglycans.

Complex carbohydrates are important in many physiological processes and alterations in glycosylation are associated with vast numbers of blood related and unrelated diseases and disorders. The specific focus of the Center is to harness genomic with glycomic approaches with an emphasis on exploring transcriptional and epigenetic regulatory mechanisms of carbohydrate synthesis in health and disease. The data will help to understand and predict molecular mechanisms of carbohydrate expression and recognition by proteins important in human biology and disease. The Center will bring together scientists at BloodCenter of Wisconsin and other institutions to understand the role that sugars play in biology.



Karin Hoffmeister, MD

Senior Investigator, Blood Research Institute, BloodCenter of Wisconsin
Professor of Biochemistry, Medical College of Wisconsin
Director of Translational Glycomics Center
Lecturer on Medicine, Harvard Medical School, Brigham and Women's Hospital
Associate Professor of Pediatrics, Boston Children's Hospital
MD, Technical University of Aachen, Aachen, Germany, 1993
Doctor of Medicine, Doctoral Research Program, Technical University of Aachen, 1995
Employed at BloodCenter of Wisconsin: 2016



Research Interests

Dr. Hoffmeister investigates how glycans regulate hematopoiesis and end-effector blood cells, including platelets. The general theme of Dr. Hoffmeister's research is to better understand the role of carbohydrates in hematopoietic stem cells, megakaryocytes and platelet function, survival, and interaction with other blood cells. Carbohydrate biosynthesis in nucleated cells is a highly regulated process involving several hundred glycosyltransferases. Correct glycan biosynthesis depends on the correct architecture and topology of the endoplasmic reticulum (ER) and Golgi apparatus. During maturation, differentiation and inflammation programmed remodeling of cell surface glycans

takes place by the regulated expression of specific glycosyltransferases to regulate different biological functions. Our studies expand toward defining glycosyltransferases cell-specific transcriptional regulatory mechanisms during hematopoiesis to combine phenotypic surface carbohydrate expression with genomic and epigenetic data in hematopoietic cells.

Awards, Honors and Memberships

- Member, Hemostasis and Thrombosis Study Section
- Member, Transfusion Medicine Study Section, special panel
- Member, American Society of Hematology
- Chair Megakaryocytes and Platelet Scientific Committee, ASH

Funding

R01 HL089224-10 "Carbohydrate Mediated Platelet Clearance"

P01 HL 107146-06 "Biosynthesis and Function of Lactosaminyl Glycans in Hematopoiesis"

U54 HL119145-04 "Novel Approaches for Platelet Storage B-Bic Drive"

Publications

1. Chen W, Druzak SA, Wang Y, Josephson CD, Hoffmeister KM, Ware J, Li R. Refrigeration-Induced Binding of von Willebrand Factor Facilitates Fast Clearance of Refrigerated Platelets. *Arterioscler Thromb Vasc Biol.* 2017 Dec;37(12):2271-2279. PMID: 29097365

2. Fischer K, Ohori S, Meral FC, Uehara M, Giannini S, Ichimura T, Smith RN, Jolesz FA, Guleria I, Zhang Y, White PJ, McDannold NJ, Hoffmeister K, Givertz MM, Abdi R. Testing the efficacy of Contrast Enhanced Ultrasound in detecting transplant rejection using a murine model of heart transplantation. *Am J Transplant.* 2017 May;177(4):630-640. PMID: 28009476
3. Lee-Sundlov MM, Ashline DJ, Hanneman AJ, Grozovsky R, Reinhold VN, Hoffmeister KM, Lau JT. Circulating blood and platelets supply glycosyltransferases that enable extrinsic extracellular glycosylation. *Glycobiology.* 2017 Jan;27(2):188-198. PMID: 27798070

A 3D illustration of a blood vessel with red blood cells and platelets. The vessel is shown in a cross-section, with a yellowish, textured interior. Red blood cells are depicted as red, biconcave discs, and platelets are smaller, red, disc-shaped cells. The background is a warm, orange-red gradient.

Thrombosis, Hemostasis & Vascular Biology

The Thrombosis, Hemostasis and Vascular Biology Program is concerned with cellular and molecular mechanisms of normal blood clotting, pathological thrombosis, and events impacting the integrity of the blood vessels that transport blood throughout our body.

Studies conducted in the laboratories of the BRI range from basic scientific investigations of blood coagulation and platelet function, to the pathophysiology, treatment, and diagnosis of bleeding and clotting disorders.

Thomas C Abshire, MD

Executive Vice President, Medical Sciences Institute and Chief Medical Officer, Versiti
Senior Investigator, Blood Research Institute
Professor of Pediatrics, Medicine and the CTSI, Medical College of Wisconsin
MD, Tulane University School of Medicine, 1979
Pediatrics, David Grant USAF Medical Center, Travis AFB, CA 1979-82
Pediatric Hematology, University of Colorado Health Science Center, 1985-88
Employed at BloodCenter of Wisconsin: 2009



Awards, Honors and Memberships

- Best Doctors in America
- Member, American Society of Hematology
- 2017 Joan Cox Gill Award for Outstanding Service to the HTRS (HTRS Service Award) April 2017

Funding

5R01HL112614-05 Montgomery/Abshire (Multiple PIs)
12/14/2013 – 11/30/2018 NIH/NHLBI "Comparative Effectiveness in the Diagnosis of VWD"

Publications

1. Kulkarni R, Presley RJ, Lusher JM, Shapiro AD, Gill JC, Manco-Johnson M, Koerper MA, Abshire TC, DiMichele D, Hoots WK, Mathew P, Nugent DJ, Geraghty S, Evatt BL,

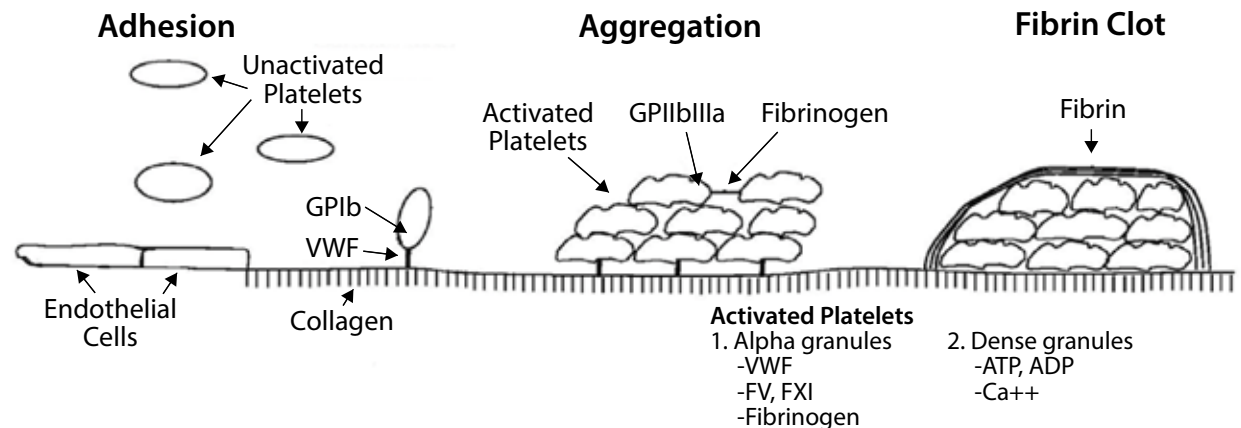
Soucie JM. Complications of haemophilia in babies (first two years of life): a report from the Centers for Disease Control and Prevention Universal Data Collection System. *Haemophilia*. 2017 Mar;23(2):207-214. PMID: 27813214

2. Miller CH, Boylan B, Shapiro AD, Lentz SR, Wicklund BM, (Abshire TC, Gill JC); Hemophilia Inhibitor Research Study Investigators. Limit of detection and threshold for positivity of the Centers for Disease Control and Prevention assay for factor VIII inhibitors. *J Thromb Haemost*. 2017 Oct;15(10):1971-1976. PMID: 28795528

Research Interests

One of Dr. Abshire's major research interests involves conducting clinical trials in patients with bleeding and thrombotic disorders with the aim of defining disease characteristics and evaluating new approaches to treatment. A recent focus is the evaluation of mild bleeding conditions in both children and adults, particularly those affected by von Willebrand Disease (vWD). With Robert Montgomery, MD, Dr. Abshire and a team of investigators from 12 centers across North America have just finished the fourth year of a study funded by the NIH entitled "Comparative Effectiveness in the Diagnosis of VWD" which is focusing on new diagnoses of vWD and how to better define this bleeding disorder from a clinical, laboratory and molecular basis.

Platelet-Vessel Interaction



Lisa Baumann Kreuziger, MD, MS

Associate Medical Director/Assistant Investigator, Blood Research Institute, BloodCenter of Wisconsin
Assistant Professor, Dept. of Medicine, Division of Hematology/Oncology, Medical College of Wisconsin
MD, University of Wisconsin School of Medicine and Public Health, 2006
Employed at BloodCenter of Wisconsin: 2013



Research Interests

Venous thromboembolism occurs in more than a half million Americans every year. Anticoagulation after venous thrombosis can prevent recurrence but is associated with a risk of bleeding. Dr. Baumann-Kreuziger aims to define the best treatment course for cancer patients with thrombosis associated with catheters and determine if a biomarker can be used to predict recurrence. Identification of a biomarker would allow anticoagulation to be individualized based on each patient's risk profile. Patients with heart failure who require implanted left ventricular assist devices (LVADs) are another group that is at high risk for bleeding and thrombotic complications. Despite use of anticoagulant

and antiplatelet medications, approximately 10% of LVAD patients will develop thrombotic complications including stroke of LVAD failure. Dr. Baumann-Kreuziger was awarded a pilot grant from the Clinical and Translational Sciences Institute to evaluate potential mechanisms of thrombosis in patients with left ventricular assist devices.

Awards, Honors and Memberships

- Top Patient Experience Recognition, Froedert Hospital 2017
- Co-founder, VENUS (Venous thromboEmbolism Network U.S.)
- Executive Committee member, INVENT (International Venous Thromboembolism Clinical Research Networks)

Funding

"Evaluating thrombi composition and persistent coagulation activation in the pathophysiology of left ventricular assist device (LVAD) thrombosis" NIH \$80,000 (PI) 7/2015 – 6/2019

"Direct Oral Anticoagulants (DOACs) versus LMWH +/- warfarin for VTE in cancer: A Randomized Effectiveness Trial (CANVAS)" Alliance Foundation (PI) 05/27/2017 – present

"Post-Thrombotic Syndrome and Predictors of Recurrence in Catheter-Related Thrombosis"

Publications

1. Anani W, Wucinski J, Baumann Kreuziger L, Gottschall J, Karafin M. Therapeutic plasma exchange in refractory warm autoimmune hemolytic anemia. *Transfusion*. 2017 Jun;57(6):1336. PMID: 28594138
2. Baumann Kreuziger L, Jaffray J, Carrier M. Epidemiology, diagnosis, prevention and treatment of catheter-related thrombosis in children and adults. *Thromb Res*. 2017 Sep;157:64-71. Review. PMID: 28710972
3. Dang G, Epperla N, Muppidi V, Sahr N, Pan A, Simpson P, Baumann Kreuziger L. Medical Management of Pump-Related Thrombosis in Patients with Continuous-Flow Left Ventricular Assist Devices: A Systematic Review and Meta-Analysis. *ASAIO J*. 2017 Jul/Aug;63(4):373-385. PMID: 27984314

Magdalena Chrzanowska, PhD, FAHA



Research Interests

Endothelial cells (EC) cover the inner surface of blood vessels and perform many critical functions, such as preventing leakage of blood cells and plasma from the circulation, preventing inappropriate blood clotting, regulating selective transfer of cells and substances into and out of blood vessels, and maintaining the correct blood pressure.

Importantly, EC can adapt their functions to their environment, by sensing blood flow and the presence of inflammatory signals.

Dr. Chrzanowska studies how a protein designated, Rap1, regulates the response of EC to changes in blood flow and inflammation. Her work helps understand the processes

Investigator, Blood Research Institute
Associate Adjunct Professor in Pharmacology and Toxicology, Medical College of Wisconsin
Research Member, Medical College of Wisconsin Cancer Center
Medical College of Wisconsin Cardiovascular Center
PhD, University of North Carolina at Chapel Hill, 1996
MSc, Jagiellonian University, Krakow, Poland, 1991
Employed at BloodCenter of Wisconsin: 2005

causing hypertension and the narrowing and hardening of the blood vessel wall in atherosclerotic disease. In 2015, Dr. Chrzanowska succeeded in obtaining the renewal of grant support from the National Institutes of Health for her work.

The complications of cardiovascular disease remain major killers of the American population. The maintenance of normal cardiovascular function is critically dependent on vascular endothelium – cells that line blood vessels. Our research is focused on understanding molecular mechanisms underlying critical endothelial cell functions, such as preventing blood leakage, selective transfer of cells and substances to and from the blood stream, regulation of blood pressure, and restorative and pathogenic new blood vessel growth.

Our recent research revealed new mechanisms through which endothelial cells respond to the flow of blood and how defects in these responses contribute to atherosclerosis in an in vivo disease model. These are the first necessary steps in developing new strategies to restore endothelial function to prevent the progression of atherosclerosis. Furthermore, our studies provided novel insights into mechanisms through which endothelial cells maintain barrier under normal conditions. Importantly, our studies identified potential novel therapeutic targets for pathological vascular hyper-permeability associated with early diabetes.

Awards, Honors and Memberships

- American Heart Association, ATVB Council – 2018 AHA Scientific Sessions Programming Committee
- Affiliate Member, Clinical and Translational Science Institute of SE Wisconsin

- Member, Medical College of Wisconsin Cardiovascular Center: Atherosclerosis, Thrombosis and Vascular Biology Signature Program
- Member, Medical College of Wisconsin Cancer Center, Cancer Cell Biology Research Program
- NIH Vascular Cell and Molecular Biology Study Section

Funding

NIH/NHLB R01 - HL111582-05 Chrzanowska-Wodnicka, M, (PI) 4/16/12 - 6/30/20 "Rap1 in endothelial homeostasis"

Publications

1. Chrzanowska-Wodnicka M. Rap1 in endothelial biology. *Curr Opin Hematol.* 2017 May;24(3):248-255. PMID: 28178039
2. Maruyama T, Jiang M, Abbott A, Yu HI, Huang Q, Chrzanowska-Wodnicka M, Chen EI, Hsu W. Rap1b Is an Effector of Axin2 Regulating Crosstalk of Signaling Pathways During Skeletal Development. *J Bone Miner Res.* 2017 Sep;32(9):1816-1828. PMID: 28520221

Kenneth Friedman, MD

Medical Director Hemostasis Reference Lab, Diagnostic Labs, BloodCenter of Wisconsin
Associate Investigator Blood Research Institute, BloodCenter of Wisconsin
Assistant Medical Director Comprehensive Center for Bleeding Disorders
Associate Professor of Internal Medicine and Pathology, Medical College of Wisconsin
MD, SUNY Upstate Medical University, Syracuse, NY, 1980
Employed at BloodCenter of Wisconsin: 1997



Research Interests

Thrombotic microangiopathies are a collection of diseases characterized by formation of platelet/protein aggregates that obstruct the microcirculation, resulting in multi-organ dysfunction. Microthrombi in thrombotic thrombocytopenic purpura are rich in von Willebrand factor as a consequence of deficiency of the von Willebrand factor control enzyme ADAMTS13. Alternatively in atypical hemolytic uremic syndrome, the microthrombi are rich in fibrin as a consequence of disordered complement regulation and endothelial cell injury. The current focus of Dr. Friedman's research of thrombotic microangiopathies is the evaluation of patient plasma and genetic samples in order to identify patterns

of disease, underlying risk factors and prognostic markers. Dr. Friedman's other area of interest relates to utilization of plasma and genetic markers to better understand the mechanisms underlying the bleeding that occurs in patients with defects of von Willebrand factor.

Awards, Honors and Memberships

- Co-Director, National Marrow Donor Program – BCW Branch
- Best Doctors in America
- Medical Director of the Apheresis Center for the NMDP site in Milwaukee
- Ad hoc Reviewer, Journal of Thrombosis and Hemostasis, Blood, and American Journal of Hematology
- Reviewer, American Journal of Hematology and Haemophilia

Publications

1. Epperla N, Hemauer K, Hamadani M, Friedman KD, Kreuziger LB. Impact of treatment and outcomes for patients with posttransplant drug-associated thrombotic microangiopathy. *Transfusion*. 2017 Nov;57(11):2775-2781. PMID: 28836275
2. Fattah H, Kumar D, George JN, Massey HD, King AL, Friedman KD, Gupta G. Successful kidney transplantation in a patient with congenital thrombotic thrombocytopenic purpura (Upshaw-Schulman syndrome). *Transfusion*. 2017 Dec;57(12):3058-3062. PMID: 28940540

3. Scully M, Cataland S, Coppo P, de la Rubia J, Friedman KD, Kremer Hovinga J, Lämmle B, Matsumoto M, Pavenski K, Sadler E, Sarode R, Wu H; International Working Group for Thrombotic Thrombocytopenic Purpura. Consensus on the standardization of terminology in thrombotic thrombocytopenic purpura and related thrombotic microangiopathies. *J Thromb Haemost*. 2017 Feb;15(2):312-322. PMID: 27868334



Adelaide Yost

“We were fortunate blood was available to treat our daughter. Now, we can look forward to her future,” says Adelaide’s mom, Katie.

Thanks to BloodCenter’s innovative research, Adelaide is living a normal, healthy life. Adelaide has von Willebrand disease. At age 5, she had multiple spontaneous bleeds and received blood transfusions that helped save her life.

Veronica H. Flood, MD

Associate Professor of Pediatric Hematology, Medical College of Wisconsin
Associate Investigator, Blood Research Institute, BloodCenter of Wisconsin
MD, Tufts University School of Medicine, 1999
Employed at BloodCenter of Wisconsin: 2016

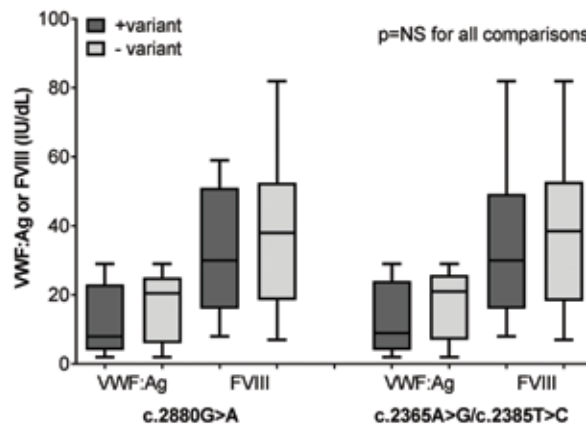


Research Interests

Dr. Flood is a pediatric hematologist and researcher at the Medical College of Wisconsin in Milwaukee. She received her medical degree from Tufts University School of Medicine, and went on to complete a residency in pediatrics at Phoenix Children's Hospital and a fellowship in pediatric hematology/oncology at Oregon Health and Science University.

She began her research career as an undergraduate studying primate genetics in the Department of Anthropology at Harvard University. Her academic career in hemostasis research includes work on the biology of von Willebrand factor (VWF). Dr. Flood is interested in how

VWF interacts with two of its main partners, platelet GPIb and collagen. Since collagen is exposed at sites of blood vessel injury, the VWF-collagen interaction is an important component of hemostasis. She also is interested in the genetics of von Willebrand disease (VWD). Through collaboration with Dr. Robert Montgomery and the Zimmerman Program for the Molecular and Clinical Biology of VWD, Dr. Flood has worked on characterizing genetic changes in VWD, with particular attention to variants that affect platelet and collagen binding. Dr. Flood has been funded by the National Heart Lung and Blood Institute since 2010, initially through a K08 award and subsequently transitioned to independent funding through an R01 grant.



Awards, Honors and Memberships

- Secretary, Hemostasis and Thrombosis Research Society
- Vice-Chair Mentored Research Award Committee Hemophilia and Thrombosis Society

Funding

R01 HL126810 "Mechanism of Type 4 Collagen Interactions with Von Willebrand Factor"

Publications

1. Doruelo AL, Haberichter SL, Christopherson PA, Boggio LN, Gupta S, Lentz SR, Shapiro AD, Montgomery RR, Flood VH. Clinical and laboratory phenotype variability in type 2M von Willebrand disease. *J Thromb Haemost*. 2017 Aug;15(8):1559-1566. PMID: 28544236
2. Sharma R, Flood VH. Advances in the diagnosis and treatment of Von Willebrand disease. *Blood*. 2017 Nov 30;130(22):2386-2391. Review. PMID: 29187375
3. Wang M, Konkle BA, Sidonio RF Jr, Flood V, Koenig C, Kulkarni R. von Willebrand disease Outreach into Integrated Care Education (VOICE): a call to action. *Haemophilia*. 2017 Jul;23(4):e370-e373. PMID: 28548287

Joan Cox Gill, MD

Senior Investigator, Blood Research Institute, BloodCenter of Wisconsin
Director, Comprehensive Center for Bleeding Disorders
Professor, Pediatrics and Medicine, Medical College of Wisconsin
MD, Medical College of Wisconsin 1976
Employed at BloodCenter of Wisconsin: 1991



guidelines in hemophilia and other bleeding disorders, and also directs several pharmaceutical contract research studies to evaluate replacement therapy products for patients with hemophilia and von Willebrand disease.

Awards and Honors

- Member, Science Committee, CDC Public Health Surveillance for Bleeding Disorders
- Best Doctors in America
- Medical Expert Panel; Federal Division of Vaccine Compensation

Publications

1. Kulkarni R, Presley RJ, Lusher JM, Shapiro AD, Gill JC, Manco-Johnson M, Koerper MA, Abshire TC, DiMichele D, Hoots WK, Mathew P, Nugent DJ, Geraghty S, Evatt BL, Soucie JM. Complications of haemophilia in babies (first two years of life): a report from the Centers for Disease Control and Prevention Universal Data Collection System. *Haemophilia*. 2017 Mar;23(2):207-214. PMID: 27813214
2. Manco-Johnson MJ, Soucie JM, Gill JC. Prophylaxis usage, bleeding rates and joint outcomes of hemophilia 1999 - 2010: a surveillance project. *Blood*. 2017 Apr 27;129(17):2368-2374. PMID: 28183693
3. Miller CH, Boylan B, Shapiro AD, Lentz SR, Wicklund BM, (Abshire TC, Gill JC); Hemophilia Inhibitor Research Study Investigators. Limit of detection and threshold for positivity of the Centers for Disease Control and Prevention assay for factor VIII inhibitors. *J Thromb Haemost*. 2017 Oct;15(10):1971-1976. PMID: 28795528

Research Interests

Dr. Gill is engaged in clinical research concerning the diagnosis and treatment of bleeding and clotting disorders in both adult and pediatric populations. She is co-investigator of a study to evaluate the ability of bleeding questionnaires to predict surgical bleeding in tonsillectomies and molar tooth extractions; co-principal investigator of a study to characterize the pharmacogenetics of the anticoagulant warfarin in pediatric patients with thrombosis; and an investigator and member of the science and advisory committees of the CDC national study of the complications of hemophilia. Dr. Gill is chair of the Great Lakes Hemophilia Foundation Regional Committee to investigate treatment

Sandra Haberichter, PhD

Investigator, Blood Research Institute, BloodCenter of Wisconsin
Director of Hemostasis Reference Laboratory, BloodCenter of Wisconsin
Associate Professor of Pediatrics, Medical College of Wisconsin
PhD, University of Wisconsin-Milwaukee, 1998
Fellowship, Blood Research Institute, BloodCenter of Wisconsin, 1998-2003
Employed at BloodCenter of Wisconsin: 1998



Research Interests

The plasma protein von Willebrand factor (VWF) plays a critical role in enabling blood platelets to interact with damaged blood vessels and stop bleeding. Genetically determined abnormalities of VWF function and synthesis cause von Willebrand Disease (VWD), a source of abnormal bleeding that affects about one percent of the general population. Dr. Haberichter's work is aimed at characterizing various genetic defects that cause VWD and defining how these defects affect the structure and function of the large, highly complex VWF molecule. Recent findings have shown that low VWF levels in patients with a sub-type of VWD, designated Type 1C, decrease VWF levels by shortening the survival of VWF in the circulation and have led to a novel laboratory assay

to diagnose this condition. Her current work is aimed at defining the molecular basis for accelerated clearance of VWF in patients with this form of VWD. Knowledge gained in these studies is expected to improve laboratory diagnosis and treatment of this common bleeding disorder.

Awards, Honors and Memberships

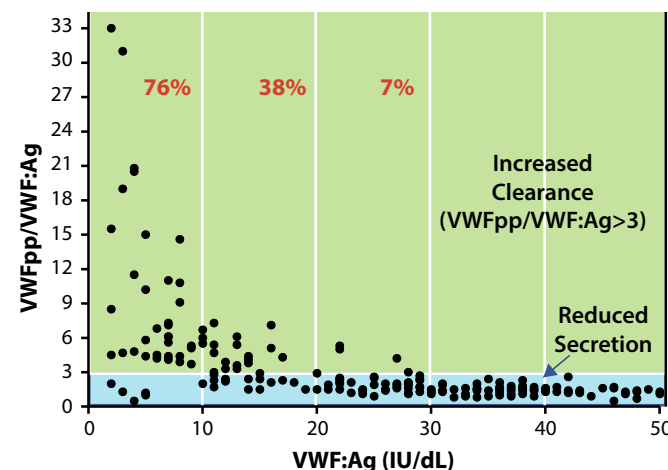
- Member, American Society of Hematology
- Chair, ISTH SSC scientific committee on von Willebrand Factor
- Member, International Society on Thrombosis and Haemostasis

Funding

P01 HL08158 "Zimmerman Program for the Molecular and Clinical Biology of VWD; Project 2: Molecular and Clinical Biology of VWF Alteration in Vitro/Vivo"

Publications

1. Doruelo AL, Haberichter SL, Christopherson PA, Boggio LN, Gupta S, Lentz SR, Shapiro AD, Montgomery RR, Flood VH. Clinical and laboratory phenotype variability in type 2M von Willebrand disease. *J Thromb Haemost.* 2017 Aug;15(8):1559-1566. PMID: 28544236
2. Jäckel S, Kiouptsi K, Lillich M, Hendrikx T, Khandagale A, Kollar B, Hörmann N, Reiss C, Subramaniam S, Wilms E, Ebner K, Brühl MV, Rausch P, Baines JF, Haberichter S, Lämmle B, Binder CJ, Jurk K, Ruggeri ZM, Massberg S, Walter U, Ruf W, Reinhardt C. Gut microbiota regulate hepatic von Willebrand factor synthesis and arterial thrombus formation via Toll-like receptor-2. *Blood.* 2017 Jul 27;130(4):542-553. PMID: 28572286



Increased VWF clearance in prevalent in moderately severe type 1 VWD.

VWFpp/VWF:Ag < 3 predicts reduced synthesis/secretion phenotype (blue).

VWFpp/VWF:Ag > 3 predicts increased plasma VWF clearance (green).

76% of subjects with VWF:Ag ≤ 10 IU/dL and 38% of subjects with VWF:Ag = 11-20 IU/dL have an increased VWF clearance phenotype (type 1C).

Shawn Jobe, MD, PhD

Medical Director, Comprehensive Center for Bleeding Disorders (CCDB)
Associate Investigator, Blood Research Institute, BloodCenter of Wisconsin
Associate Professor, Department of Pediatrics and Cell Biology, Neurobiology, and Anatomy
PhD, Medical College of Wisconsin, 1998
MD, Medical College of Wisconsin, 1999
Employed at BloodCenter of Wisconsin: 2013



expected to provide novel avenues for the treatment and prevention of thrombosis in aging-related diseases. Platelet procoagulant activity also is important in the prevention of bleeding. In other work, researchers in Dr. Jobe's lab are investigating how these procoagulant platelet events might work to prevent bleeding in patients with severe hemophilia.

Awards, Honors and Memberships

- Standing member American Heart Association Thrombosis/Hemostasis Study Section
- National Hemophilia Foundation Clinical Fellowship Advisory Board
- Member International Society on Thrombosis and Hemostasis

Publications

1. Choo HJ, Kholmukhamedov A, Zhou C, Jobe S. Inner Mitochondrial Membrane Disruption Links Apoptotic and Agonist-Initiated Phosphatidyserine Externalization in Platelets. *Arterioscler Thromb Vasc Biol.* 2017 Aug;37(8):1503-1512. PMID: 28663253
2. Kholmukhamedov A, Jobe S. Mitochondria and Platelet Cell Death. *Thromb Haemost.* 2017 Nov;117(11):2207-2208. PMID: 29044296

Research Interests

Platelets are required to stop bleeding, but inappropriate platelet adhesion and activation results in thrombosis. Dr. Jobe's group is working to understand how platelet activation is regulated. They have identified a novel platelet mitochondrial mechanism that transforms the platelet's function from proaggregatory to procoagulant. Work in Dr. Jobe's lab currently is focused on understanding how platelet mitochondrially-mediated events are regulated and how they function to regulate hemostasis and thrombosis. Changes in mitochondrial metabolism are linked closely with many diseases associated with aging including diabetes, atherosclerosis and hypertension. Insights gained through the study are

Yan-Qing Ma, PhD

Associate Investigator, Blood Research Institute, BloodCenter of Wisconsin
Assistant Professor, Dept. of Biochemistry, Medical College of Wisconsin
PhD, Chinese Academy of Sciences, 2004
Employed at BloodCenter of Wisconsin: 2011



Research Interests

Integrins comprise an extensive family of cell membrane proteins that are essential for cell-cell communication and signaling. In blood platelets, the integrin $\alpha\text{IIb}/\beta\text{3}$ undergoes complex intracellular and extracellular structural changes that enable these cells to adhere to damaged blood vessels and to each other to control bleeding. This process must be carefully regulated to enable hemostasis to be achieved without causing a clot to be propagated inappropriately. Dr. Ma's current work is aimed at understanding intracellular signaling cascades in platelets that control structural changes in integrin $\alpha\text{IIb}/\beta\text{3}$ during platelet activation. A particular goal is to define how kindlin-3, a key integrin regulator

in platelets, coordinates with upstream binding partners and creates a signaling network that regulates the platelet activation process. An important objective is to identify novel inhibitors of platelet function that can be useful for treatment and prevention of thrombosis.

Awards, Honors, and Memberships

- Member, Sigma Xi, the Scientific Research Society
- Member, American Society of Hematology
- Member, International Society on Thrombosis and Hemostasis

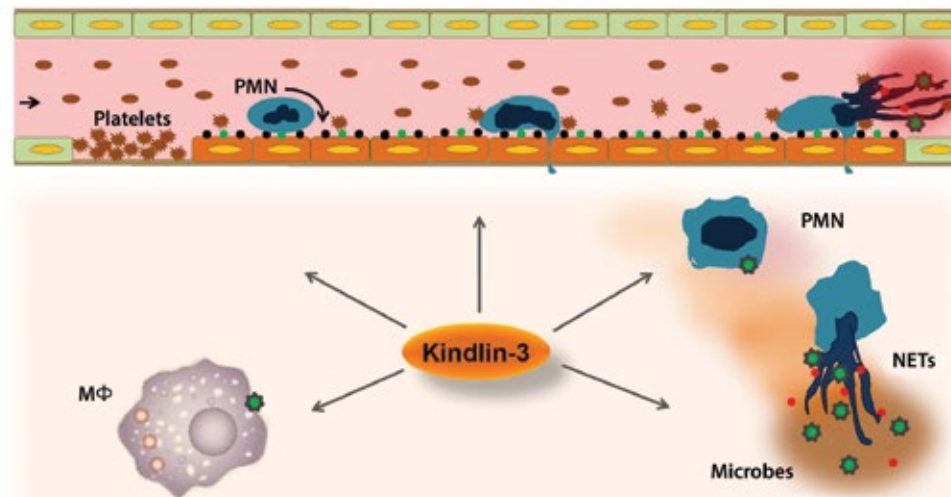
Funding

R01 HL131654 "Kindlin-3 Signaling in Blood Cells"

Publications

1. Gao J, Huang M, Lai J, Mao K, Sun P, Cao Z, Hu Y, Zhang Y, Schulte ML, Jin C, Wang J, White GC, Xu Z, Ma YQ. Kindlin supports platelet integrin $\alpha\text{IIb}\beta\text{3}$ activation by interacting with paxillin. *J Cell Sci.* 2017 Nov 1;130(21):3764-3775. PMID: 28954813

Kindlin-3 signaling in platelets and neutrophils



Lynn Malec, MD, MSc

Associate Medical Director of the Center for Comprehensive Bleeding Disorders, BloodCenter of Wisconsin MD, UW Madison School of Medicine and Public Health, 2006
Employed at BloodCenter of Wisconsin: 2016



Research Interests

Dr. Lynn Malec developed an interest in hemostasis during her Internal Medicine and Pediatrics residency at the University of Pittsburgh Medical Center (UPMC)/ Children's Hospital of Pittsburgh. This interest flourished during her fellowship in Pediatric Hematology/Oncology at Children's Hospital of Pittsburgh during which time she worked closely with Dr. Margaret Ragni to gain further expertise in the care of, and research involving, patients with congenital bleeding disorders across the age spectrum. During her fellowship, she pursued a Master's of Science in Clinical Research through the University of Pittsburgh Institute for Clinical Research Education. This

rigorous training furthered her interest in clinical research involving patients with bleeding disorders.

Dr. Malec's current research interests involve the investigation of inhibitor prevention and eradication in patients with hemophilia and the impact of prophylactic use in this patient population. She currently is investigating the role that recombinant factor VIII Fc fusion protein (rFVIII Fc) has in immune tolerance induction and is conducting a multi-site observational study to evaluate the efficacy and safety of rFVIII Fc administered every other day for ITI. Additionally, Dr. Malec recently was successful in competing for funding amongst a qualified pool of national junior investigators and has been awarded the 2016 DREAM Award through HTRS to explore the impact of extended half-life products in preventing joint bleeds and joint damage in patients with hemophilia. Dr. Malec is engaged in the care of adult and pediatric patients with disorders of hemostasis and thrombosis, as well as other benign hematologic conditions.

Awards, Honors, and Memberships

- Member, International Society on Thrombosis and Hemostasis
- Member, American Society of Pediatric Hematology and Oncology
- Member, Hemostasis and Thrombosis Research Society
- Member, American Society of Hematology
- Member, Foundation for Women and Girls with Bleeding Disorders

Funding

DREAM Award: Mentored Research Award sponsored by Hemostasis and Thrombosis Research Society (HTRS) and the American Thrombosis Hemostasis Network (ATHN) "Is Prophylaxis Putting Hemophilic Joints in the PINK: An ATHN-LINKED Observational Study into the Pink" 2017-2019 (PI) \$100,000

Publications

1. Leeper CM, Vissa M, Cooper JD, Malec LM, Gaines BA. Venous thromboembolism in pediatric trauma patients: Ten-year experience and long-term follow-up in a tertiary care center. *Pediatr Blood Cancer*. 2017 Aug;64(8). PMID: 28067012
2. Malec L, Young G. Treatment of Venous Thromboembolism in Pediatric Patients. *Front Pediatr*. 2017 Feb 28;5:26. Review. PMID: 28293549

Alan Mast, MD, PhD

Senior Investigator, Blood Research Institute, BloodCenter of Wisconsin
Medical Director, Medical Services, BloodCenter of Wisconsin
Walter A. Schroeder Endowed Chair for Blood Research
Associate Professor, Department of Pathology, Medical College of Wisconsin
Associate Professor, Department of Cell Biology, Neurobiology and Anatomy, Medical College of Wisconsin
MD, Duke University, 1991
PhD, Duke University, 1991
Employed at BloodCenter of Wisconsin: 2003



Research Interests

Blood donation removes a large amount of iron that is contained in red blood cells. Therefore, many regular blood donors become iron deficient. In his clinical research, Dr. Mast studies the effect of blood donations on iron metabolism and iron deficiency in the donor. His clinical research program has found that recovery of iron stores following blood donation takes more than six months, emphasizing the need for blood donors to take iron pills following each donation. A study found that taking 19 mg iron (the amount of iron in a typical multiple vitamin with iron) for 60 days following each donation is a simple and effective means for donors to replace iron lost during blood donation. A study of teenage blood donors, found that

teenagers are more susceptible to iron deficiency following blood donation than are adults indicating that younger donors will benefit from additional safety measures to protect them from iron depletion.

In his basic research, Dr. Mast studies a protein designated "tissue factor pathway inhibitor (TFPI)." This protein plays a critical role in preventing blood from clotting inside blood vessels. His basic research program has made several important discoveries about the molecular interactions between TFPI and blood coagulation proteins. These have led to new ideas about how bleeding and clotting disorders occur. TFPI alters bleeding severity in a disorder called hemophilia. Dr. Mast's laboratory is working to develop new pharmaceutical agents that block TFPI as a treatment for hemophilia.

Awards, Honors, and Memberships

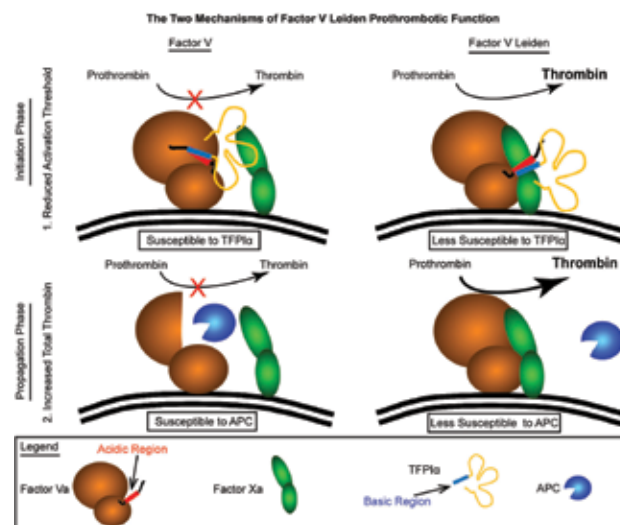
- Member, American Society of Hematology Media Experts Subcommittee
- Member, National Heart, Lung and Blood Institute Thrombosis and Hemostasis Study Section
- Member, AABB Donor Health and Safety Committee
- Member, Editorial Board: Blood Advances

Funding

REDS-IV NHLBI
TFPI R01 NHLBI
Novo Nordisk Research Grant

Publications

1. Bialkowski W, Kiss JE, Wright DJ, Cable R, Birch R, D'Andrea P, Bryant BJ, Spencer BR, Mast AE. Estimates of total body iron indicate 19 mg and 38 mg oral iron are equivalent for the mitigation of iron deficiency in individuals experiencing repeated phlebotomy. *Am J Hematol.* 2017 Sep;92(9):851-857. PMID: 28494509
2. Bloch EM, Mast AE, Josephson CD, Klein HG, Eder AF. Teenage Blood Donors: Are We Asking Too Little and Taking Too Much? *Pediatrics.* 2017 Apr;139(4). PMID: 28258073
3. Cable RG, Birch RJ, Spencer BR, Wright DJ, Bialkowski W, Kiss JE, Rios J, Bryant BJ, Mast AE. The operational implications of donor behaviors following enrollment in STRIDE (Strategies to Reduce Iron Deficiency in blood donors). *Transfusion.* 2017 Oct;57(10):2440-2448. PMID: 28703859



Robert Montgomery, MD

Senior Investigator, Blood Research Institute, BloodCenter of Wisconsin
 Attending Physician, Children's Hospital of Wisconsin
 Professor of the Clinical and Translational Science Institute, Medical College of Wisconsin
 Professor of Pediatric Hematology & Population Health – Epidemiology, MCW
 Research Member, Hematologic Malignancy & Transplantation Research Program, MCW
 MD, University of Pittsburgh Medical School, 1969
 Employed at BloodCenter of Wisconsin: 1984



response that normally blocks FVIII (this occurs in 30% of hemophilia patients). Gene therapy using this approach could be used as an alternative to using FVIII by-passing therapeutics that can sometimes run into more than \$1M/yr. No one would have predicted that gene therapy could work in these individuals. Two other projects are directed at the molecular (DNA) causes of VWD.

Awards, Honors, and Memberships

- Executive Secretary, Hemophilia (and Thrombosis) Research Society of North America
- Member, Medical and Scientific Advisory Board National Hemophilia Foundation
- Chair, Fellowship Review Program, National Hemophilia Foundation

Funding

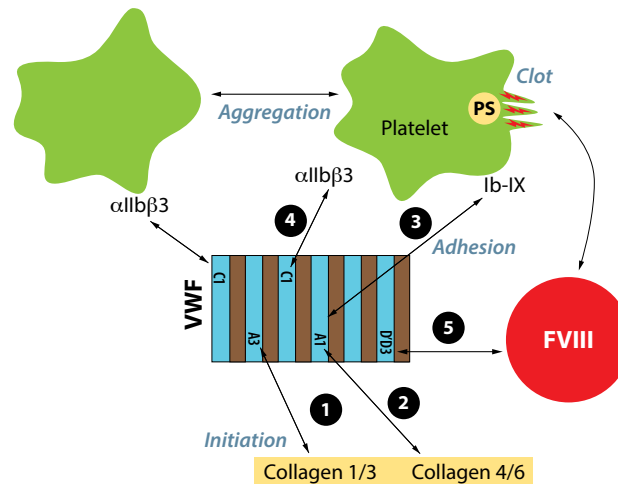
- R01 HL112614 "Comparative Effectiveness in the Diagnosis of VWD"
- P01 HL081588 "Zimmerman Program for the Molecular and Clinical Biology of VWD"
- P01 HL044612 "Molecular & Cellular Mechanisms in Transfusion Medicine: Project 5: Critical Molecular Interactions of VWF and FVIII"

Publications

1. Baumgartner CK, Mattson JG, Weiler H, Shi Q, Montgomery RR. Targeting Factor VIII expression to platelets for hemophilia A gene therapy does not induce an apparent thrombotic risk in mice. *J Thromb Haemost.* 2017 Jan;15(1):98-109. PMID: 27496751
2. Doruelo AL, Haberichter SL, Christopherson PA, Boggio LN, Gupta S, Lentz SR, Shapiro AD, Montgomery RR, Flood VH. Clinical and laboratory phenotype variability in type 2M von Willebrand disease. *J Thromb Haemost.* 2017 Aug;15(8):1559-1566. PMID: 28544236

Research Interests

Hemophilia and von Willebrand Disease (VWD) are two major hereditary bleeding disorders that our laboratory studies. The abnormal protein in hemophilia is Factor VIII (FVIII) and in VWD is von Willebrand factor (VWF). Although these are regulated by different genes, the two proteins bind together and help orchestrate the cessation of bleeding. In hemophilia we are exploring a unique form of gene therapy in which FVIII is induced to be synthesized and stored in platelets where it binds to VWF. This is not its normal site to be synthesized, but the platelet targets it to be released at the site where a blood vessel is damaged. This therapy can be effective even if the patient has begun to mount an immune



Debra Newman, PhD

Senior Investigator, Blood Research Institute, BloodCenter of Wisconsin
Associate Professor, Department of Pharmacology & Toxicology/Department of Microbiology and Molecular Biology,
Medical College of Wisconsin
PhD, Biology, Marquette 1989
Employed at BloodCenter of Wisconsin: 1989



Research Interests

Platelets are important in early wound healing, where they initially stick to damaged blood vessels and then aggregate with one another to form a platelet plug. Excessive bleeding occurs when platelet counts are low, or when platelets don't function well. Newborns who undergo heart surgery for congenital heart defects experience very severe bleeding. We want to know how much decreases in platelet count and function that occur during heart surgery contribute to severe bleeding in newborn heart surgery patients. This research will help physicians administer the right number of platelets at the right time to effectively control bleeding in this at risk population.

A major focus of research in our laboratory is Platelet Endothelial Cell Adhesion Molecule-1 (PECAM-1), which inhibits responses of many circulating blood cells, including platelets and T cells. T cells are immune cells that play an important role in clearing infections and eradicating tumors. We have recently discovered that PECAM-1 works with another potent T cell suppressor, Transforming Growth Factor β (TGF β), to inhibit T cell anti-tumor responses. Our current work is dedicated to developing a better understanding of how PECAM-1 expression is regulated in T cells and of how PECAM-1 and TGF β work together to inhibit T cell responses. This research will help us improve T cell-based therapies for treatment of cancer.

Awards, Honors, and Memberships

- Member, Program Project Grant Review Parent Committee, National Heart, Lung & Blood Institute, National Institutes of Health
- Member, ASH Scholar Award Grant Review Committee, American Society of Hematology
- Member, American Society of Hematology Committee on Scientific Affairs
- Member, Interdisciplinary Program Executive Evaluation Committee, Medical College of Wisconsin
- Ad hoc Manuscript Reviewer, Blood, American Journal of Medical Genetics, Journal of Thrombosis and Hemostasis, PLoS One

Funding

NIH R01-HL130054 (Co-Investigator)

NIH R01-HL40926 (Co-Investigator)

Publications

1. Fu G, Yu M, Chen Y, Zheng Y, Zhu W, Newman DK, Wang D, Wen R. Phospholipase Cy1 is required for pre-TCR signal transduction and pre-T cell development. Eur J Immunol. 2017 Jan;47(1):74-83. PMID: 27759161

Peter Newman, PhD

Vice President for Research, BloodCenter of Wisconsin
Associate Director/Senior Investigator, Blood Research Institute, BloodCenter of Wisconsin
Professor, Department of Pharmacology, Medical College of Wisconsin
Professor, Department of Cell Biology, Neurobiology and Anatomy, Medical College of Wisconsin
PhD, St. Louis University, 1983
Employed at BloodCenter of Wisconsin: 1983



Research Interests

Peter Newman's laboratory divides its attention between exploring the structure and function of the vascular cell adhesion and signaling receptor, PECAM-1, in platelets and endothelial cells, and the generation of antigenically-distinct megakaryocytes and platelets from induced pluripotent stem (iPS) cells - both funded by a newly-received, 7-year, \$7M Outstanding Investigator Award from the National Heart, Lung, and Blood Institute of the National Institutes of Health. Techniques range from CRISPR-mediated gene editing to protein crystallography to the development of animal models of platelet alloimmunity. Projects range from investigating the molecular basis of PECAM-1-mediated

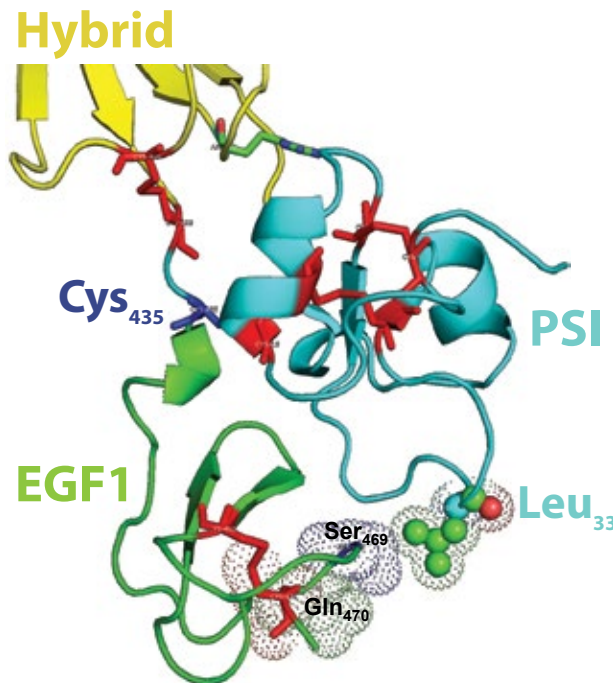
homophilic binding and the role of carbohydrate residues in this process to exploiting recent advances in CRISPR gene editing technology to generate megakaryocyte progenitor cells, megakaryocytes, and platelets from induced pluripotent stem cells to create platelet alloantigen-specific cell lines capable of long-term self-renewal, cryopreservation, and distribution.

Awards, Honors, and Memberships

- Outstanding Investigator Award, NIH National Heart, Lung, and Blood Institute 2018-25
- Distinguished Career Award, International Society of Thrombosis and Haemostasis 2013
- Guest Professor, Huazhong University of Science and Technology, China 2010
- E.F. Walton Prize, Science Foundation of Ireland 2009

Funding

2018-2025 - NIH Grant R35 HL139937 (Outstanding Investigator Award)



Qizhen Shi, MD, PhD

Investigator, Blood Research Institute, BloodCenter of Wisconsin
Associate Professor of Pediatric Hematology, Medical College of Wisconsin
MD, Fujian Medical University, Fuzhou, China, 1990
PhD, Fujian Medical University, Fuzhou, China, 1998
Molecular Hematology Fellowship, Medical College of Wisconsin 2000 – 2006
Employed at BloodCenter of Wisconsin: 2010



Research Interests

Development of inhibitory antibodies (inhibitors) against FVIII is a significant problem in the clinical care of patients with hemophilia A. One primary focus of Dr. Shi's research is to develop a gene therapy approach for the treatment of hemophilia A, including hemophilia A with inhibitors. Dr. Shi's studies have shown that engineering blood stem cells to have FVIII made and stored in platelets can solve all the problems for hemophilia A. These studies show platelet-targeted gene therapy can efficiently correct the bleeding phenotype in hemophilia A mice even in the presence of inhibitory antibodies. Furthermore, platelet gene therapy can induce immune tolerance to FVIII through CD4 T cell-mediated mechanisms. These studies are aimed at understanding why platelet-derived FVIII

can still be effective in hemophilia A even with inhibitors. In a separate line of research, Dr. Shi's team found that that FVIII's carrier protein, VWF, can modulate the antigenicity of FVIII, attenuating FVIII memory immune responses in hemophilia A mice. These studies provide important information about the impact of VWF on FVIII immune responses, which will aid the design of more effective protocols to prevent FVIII immune responses and to induce FVIII immune tolerance in patients with hemophilia A.

Awards, Honors, and Memberships

- Member, American Society of Hematology
- Member, American Society of Gene Therapy
- Member, International Society of Thrombosis and Hemostasis
- Member, North American Society on Thrombosis and Hemostasis
- Co-Chair, the Session of Future Gene and Cell Based Therapies for Hemophilia, the XXVI International Society of Thrombosis and Hemostasis (ISTH) Meeting. Berlin, Germany.
- Editorial board member, Molecular Therapy – Methods & Clinical Development
- Ad Hoc Member, Scientific Review Committee, Hemostasis/Thrombosis Study Section, NIH/NHLBI
- Member, SEP for NIH/NCI's 2017 LRP Small Business Grants study section
- Ad Hoc Reviewer, the Research Foundation - Flanders (Fonds Wetenschappelijk Onderzoek - Vlaanderen, FWO), Belgium

Funding

R01 HL102035 "Platelet Derived FVIII Gene Therapy of Hemophilia A"

Bayer Hemophilia Award "Platelet gene therapy of murine hemophilia B with pre-existing anti-FIX immunity"

Biotest Research Grant "The impact of VWF on FVIII immune response in hemophilia A with inhibitors"

Publications

1. Baumgartner CK, Mattson JG, Weiler H, Shi Q, Montgomery RR. Targeting Factor VIII expression to platelets for hemophilia A gene therapy does not induce an apparent thrombotic risk in mice. *J Thromb Haemost.* 2017 Jan;15(1):98-109. PMID: 27496751
2. Chen J, Schroeder JA, Luo X, Shi Q. The impact of von Willebrand factor on factor VIII memory immune responses. *Blood Adv.* 2017 Aug 22;1(19):1565-1574. PMID: 28920105
3. Chen Y, Luo X, Schroeder JA, Chen J, Baumgartner CK, Hu J, Shi Q. Immune tolerance induced by platelet-targeted factor VIII gene therapy in hemophilia A mice is CD4 T cell mediated. *J Thromb Haemost.* 2017 Oct;15(10):1994-2004. PMID: 28799202

Roy Silverstein, MD

Senior Investigator, Blood Research Institute, BloodCenter of Wisconsin
John and Linda Mellowes Professor and Chair, Department of Medicine, Medical College of Wisconsin
MD, Emory University School of Medicine, 1979
Affiliated with BloodCenter of Wisconsin since: 2011



state associated with these conditions as well as in accumulation of cholesterol in blood vessel walls, leading to atherosclerosis. The remarkable diversity of CD36 functions suggests that further work will have implications for treatment and/or prevention of arterial disease, thrombosis and cancer.

Awards, Honors, and Memberships

- President, Central Society for Clinical and Translational Research
- Vice President, American Society of Hematology
- Chair, AICS study section for NIH

Funding

- R01 HL111614 "Mechanistic Role of CD36 in Thrombosis"
R01 HL126645 "MRP-14, CD36 and Thrombosis"

Publications

1. Chen Y, Huang W, Yang M, Xin G, Cui W, Xie Z, Silverstein RL. Cardiotonic Steroids Stimulate Macrophage Inflammatory Responses Through a Pathway Involving CD36, TLR4, and Na/K-ATPase. *Arterioscler Thromb Vasc Biol.* 2017 Aug;37(8):1462-1469. PMID: 28619997
2. Dong L, Yuan Y, Opansky C, Chen Y, Aguilera-Barrantes I, Wu S, Yuan R, Cao Q, Chung Cheng Y, Sahoo D, Silverstein RL, Ren B. Diet-induced obesity links to ER positive breast cancer progression via LPA/PKD-1-CD36 signaling-mediated microvascular remodeling. *Oncotarget.* 2017 Apr 4;8(14):22550-22562. PMID: 28186980
3. Silverstein RL. Linking Metabolic Dysfunction to Atherosclerosis Via Activation of Macrophage CD36 Gene Transcription by Retinol Binding Protein-4. *Circulation.* 2017 Apr 4;135(14):1355-1356. PMID: 28373527

Research Interests

Research by Dr. Silverstein's group concerns basic mechanisms underlying common vascular diseases, especially thrombosis, atherosclerosis and neoplastic angiogenesis, with particular emphasis on the role of a cellular receptor designated CD36 expressed on platelets, endothelial cells, macrophages and other tissues. Recent work has shown that CD36 acts as a negative regulator of new blood vessel formation (angiogenesis), a process critical to tumor growth. CD36 also enables the recognition by platelets and macrophages of danger signals generated in the body as the result of inflammation, oxidant stress, diabetes and cancer, and may play a role in the pro-thrombotic

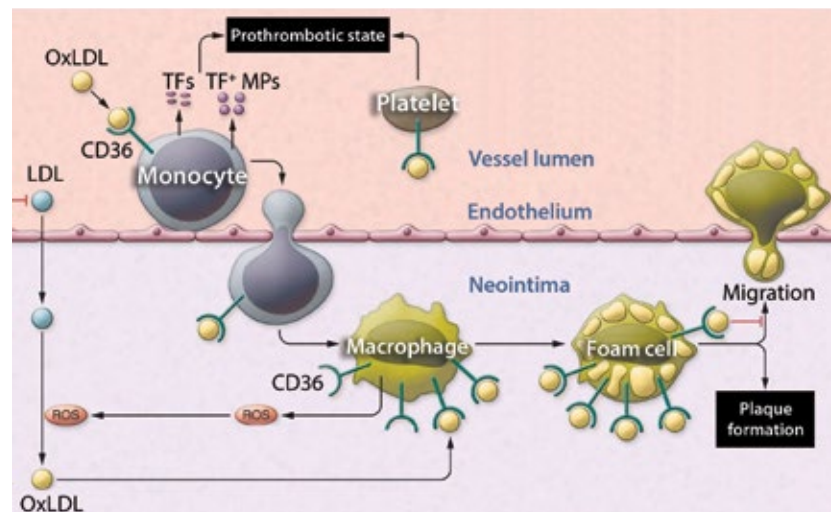


Fig 1. CD36 interactions with oxLDL on monocytes and macrophages regulates prothrombotic functions, ROS generation, foam cell formation and migration.

Hartmut Weiler, PhD

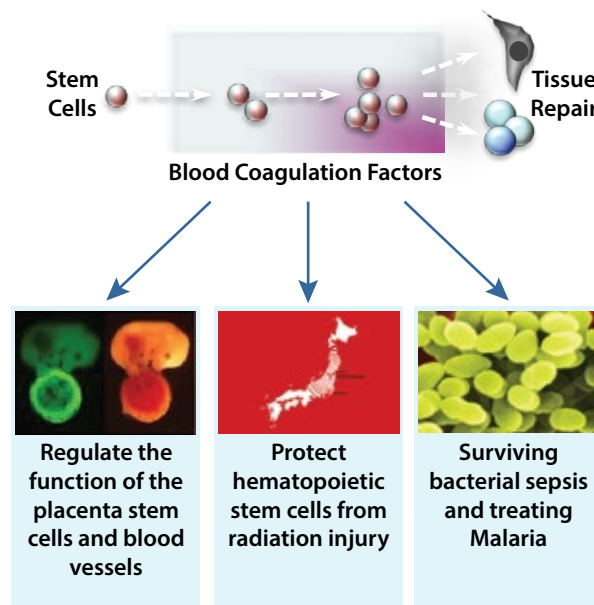
Senior Investigator, Blood Research Institute, BloodCenter of Wisconsin
Associate Professor, Department of Physiology, Medical College of Wisconsin
Director, Transgenic Core Facility, Human Molecular Genetics Center, MCW
PhD, Technische Hochschule Darmstadt, Germany, 1989
Employed at BloodCenter of Wisconsin: 1997



Research Interests

Activation of the blood clotting system serves to stop bleeding when a blood vessel is injured, but it also is a natural part of the body's response to infections, inflammation, and cancer, and plays an important role in embryonic development. In 2016, the National Institutes of Health supported work in Dr. Weiler's laboratory to develop innovative therapeutic interventions targeting blood coagulation pathways in diseases such as severe sepsis, malaria, and bone marrow failure after exposure to lethal doses of radiation. Dr. Weiler holds the Ziegler Family Chair for Research, and also directs the joint Transgenic Core Facility of the Medical College of Wisconsin (MCW) and the Blood Research Institute/ BloodCenter of Wisconsin. The facility provides a wide

Coagulation factors regulate the function of stem cells



range of genome editing services facilitating the generation of genetically altered rodents serving as models for human disease.

Awards, Honors, and Memberships

- Member, American Society of Hematology
- Member, American Heart Association
- Member, International Society on Thrombosis and Hemostasis

Funding

- “Protein C pathway function in Hematopoiesis”–NHLBI-1R01HL117132– 04/2014-03/2018 (PI) \$250,000/year
- “Regulation of Innate Immunity by Coagulation Receptors” – NHLBI-1R01 HL133348-07/2016-08/2020 (PI)–\$250,000/year
- “Coagulation Factor Signaling in Malaria”–NIH/NIAID-R01HL130678-09/2014-07/2019 Co-PI; (PI: Mosnier, L)–\$80,000/year
- “Serpins Regulation of Coagulation Proteases”–NHLBI-04/2017–06/2021 –Co-PI (PI: Rezaie) – \$68,000/year
- “Protein C Pathway Mitigation of Radiation-Induced Vascular Dysfunction”–NIAID-U01AI133561- 07/2017-06/2022 - Co-PI (Multi-PI)- 125,000/year

Publications

1. Baumgartner CK, Mattson JG, Weiler H, Shi Q, Montgomery RR. Targeting Factor VIII expression to platelets for hemophilia A gene therapy does not induce an apparent thrombotic risk in mice. *J Thromb Haemost.* 2017 Jan;15(1):98-109. PMID: 27496751
2. Kopec AK, Abrahams SR, Thornton S, Palumbo JS, Mullins ES, Divanovic S, Weiler H, Owens AP 3rd, Mackman N, Goss A, van Ryn J, Luyendyk JP, Flick MJ. Thrombin promotes diet-induced obesity through fibrin-driven inflammation. *J Clin Invest.* 2017 Aug 1;127(8):3152-3166. PMID: 28737512
3. van Mens TE, Joensen UN, Bochdanovits Z, Takizawa A, Peter J, Jørgensen N, Szecsi PB, Meijers JCM, Weiler H, Rajpert-De Meyts E, Repping S, Middeldorp S. Factor V Leiden is associated with increased sperm count. *Hum Reprod.* 2017 Nov 1;32(11):2332-2339. PMID: 28927238

Gilbert White, II, MD

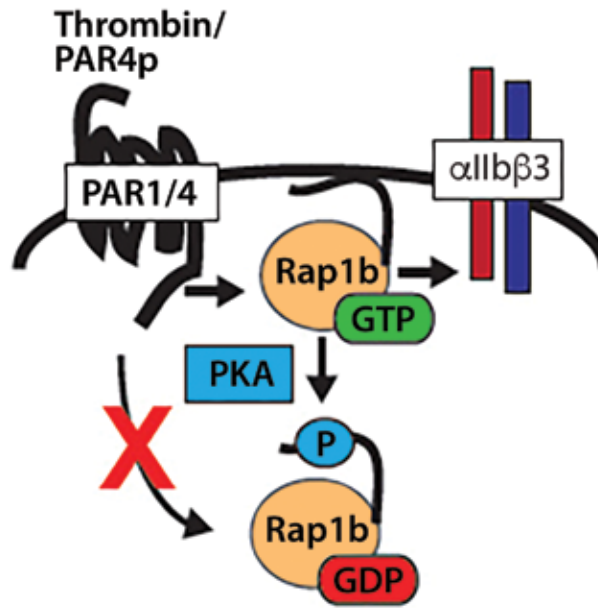
Senior Investigator/Director, Blood Research Institute, BloodCenter of Wisconsin
Richard H. and Sara E. Aster Chair for Medical Research
Professor, Dept. of Medicine, Biochemistry, and Pharmacology & Toxicology, Medical College of Wisconsin
MD, University of North Carolina, Chapel Hill, 1971
Employed at BloodCenter of Wisconsin: 2004



Research Interests

Work by Dr. White's group is aimed at understanding signaling pathways involved in the hemostatic responses by blood platelets. A longtime focus is the role of an intracellular protein, Rap 1b, which is present in high concentrations in platelets and is critical for platelet aggregation and the activation of integrins that are critical for the platelet-platelet interactions needed to form a hemostatic plug. Rap 1b also appears to be a critical target for cyclic AMP-dependent protein kinase (PKA) and phosphorylation of Rap 1b by PKA is involved in the inhibition of platelets by drugs that target the PKA pathway. Thus, Rap 1b may function as a unique and critical, bi-directional modulator of platelet activation.

Understanding how Rap 1b modulates platelet function will enable development of methods to selectively manipulate intracellular signaling pathways so as to prevent thrombosis without provoking hemorrhage in patients with impending heart attacks or strokes.



Awards, Honors, and Memberships

- Lifetime Achievement Award, Hemostasis and Thrombosis Research Society
- Board of Directors, National Hemophilia Foundation
- Board of Directors, Leukemia and Lymphoma Society
- Board of Directors, Great Lakes Hemophilia Foundation

- Board of Directors, BloodCenter Research Foundation
- Editorial Board, Haemophilia
- Board member and Chair, American Society of Hematology (ASH) Bridge Grant Review Program
- Member, International Society of Thrombosis and Hemostasis (ISTH) Awards & Honors Committee
- Member, BEE/Council Working Group to Examine PPG Funding Mechanisms

Funding

- UL1 TR001435 "Clinical and Translational Science Institute", NCATS
- UG3 OD023190 "All of US" – Wisconsin, NIH
- T32 HL07209 "Research Training in Hematology and Transfusion Medicine", NHLBI

Publications

1. Gao J, Huang M, Lai J, Mao K, Sun P, Cao Z, Hu Y, Zhang Y, Schulte ML, Jin C, Wang J, White GC, Xu Z, Ma YQ. Kindlin supports platelet integrin $\alpha IIb\beta 3$ activation by interacting with paxillin. *J Cell Sci.* 2017 Nov 1;130(21):3764-3775. PMID: 28954813
2. White GC 2nd, Blatt PM. Harold Ross Roberts, M.D.: inspirational mentor, consummate physician, superb scientist (1930-2017). *J Thromb Haemost.* 2017 Dec;15(12):2468-2470. PMID: 29152851

Jieqing Zhu, PhD

Investigator, Blood Research Institute, BloodCenter of Wisconsin
Assistant Professor, Department of Biochemistry, Medical College of Wisconsin
PhD, Institute of Microbiology, Chinese Academy of Sciences, Beijing 2003
Immune Disease Institute, Harvard Medical School, Boston 2009
Employed at BloodCenter of Wisconsin: 2011



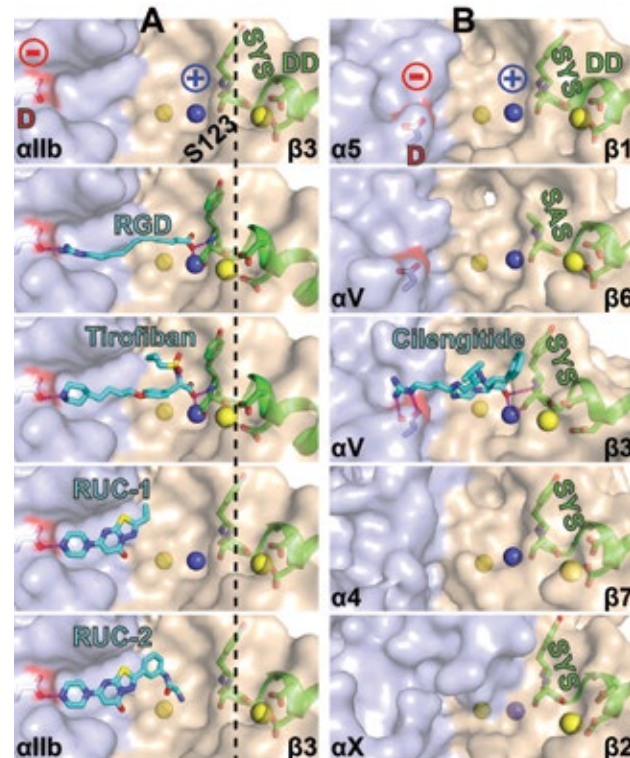
Research Interests

Membrane protein complexes designated “integrins” function as cell surface receptors to regulate cell-cell and cell-matrix interactions critical for organ development, hemostasis, antigen recognition, cellular homing to specific body sites and inflammation. Dr. Zhu is using structural biology, biochemistry and cell biology techniques to investigate how particular structural domains of integrins function in integrin activation. These studies will guide the development of small molecule inhibitors of integrin function that can be useful in the treatment and prevention of thrombosis and a range of other conditions. Recent studies have revealed the previously unappreciated function of α integrin

cytoplasmic domain in integrin activation and signaling, and the structural basis of integrin ligand-mimic inhibitors induced integrin structural changes, which provides new information of structure-based drug design.

Awards, Honors, and Memberships

- Member, American Society of Hematology (ASH)
- Member, American Society for Biochemistry and Molecular Biology (ASBMB)

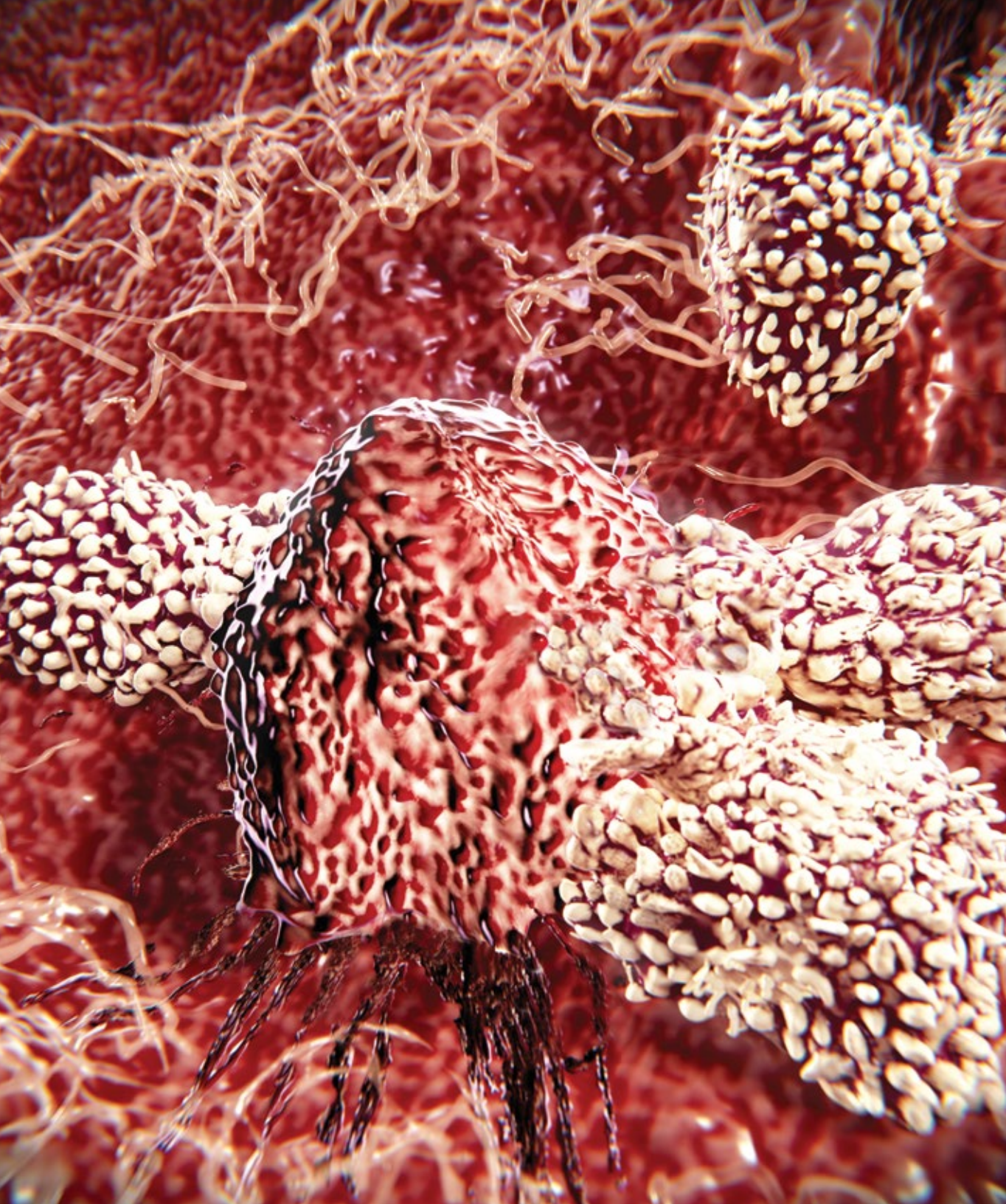


Funding

R01 HL131836 “Structural Transition of Cellular Integrins and Applications Thereof”

Publications

1. Bondu V, Wu C, Cao W, Simons PC, Gillette J, Zhu J, Erb L, Zhang XF, Buranda T. Low affinity binding in cis to P2Y2R mediates force-dependent integrin activation during hantavirus infection. *Mol Biol Cell*. 2017 Oct 15;28(21):2887-2903. PMID: 28835374
2. Cai X, Thinn AMM, Wang Z, Shan H, Zhu J. The importance of N-glycosylation on $\beta 3$ integrin ligand binding and conformational regulation. *Sci Rep*. 2017 Jul 5;7(1):4656. PMID: 28680094



Immunology

Immunobiology has been a cornerstone of research at BloodCenter of Wisconsin since 1947, going back to the early days of immunohematology. Studies by BCW investigators led to the identification of some of the first antigen systems specific to red blood cells.

BloodCenter investigators facilitated the first bone marrow transplant from an unrelated donor to successfully treat bone marrow failure (aplastic anemia) and played key roles in creation of the National Marrow Donor Program.

As knowledge of the immune system has grown, BCW's research activities in immunology have kept pace. Current research interests include fundamental aspects of the immune response as well as immunological memory, host responses to pathogens and tumors, and autoimmune responses. BCW immunologists also engage in the development of new therapies for cancer and autoimmunity.

Matthew Anderson, MD, PhD

Vice President and Medical Director, Diagnostic Laboratories
Associate Investigator, Blood Research Institute, BloodCenter of Wisconsin
Assistant Professor, Pathology, Medical College of Wisconsin
Member, Human and Molecular Genetics Center, Medical College of Wisconsin
MD, Medical College of Wisconsin, 2006
PhD, Medical College of Wisconsin, 2004
Employed at BloodCenter of Wisconsin: 2013



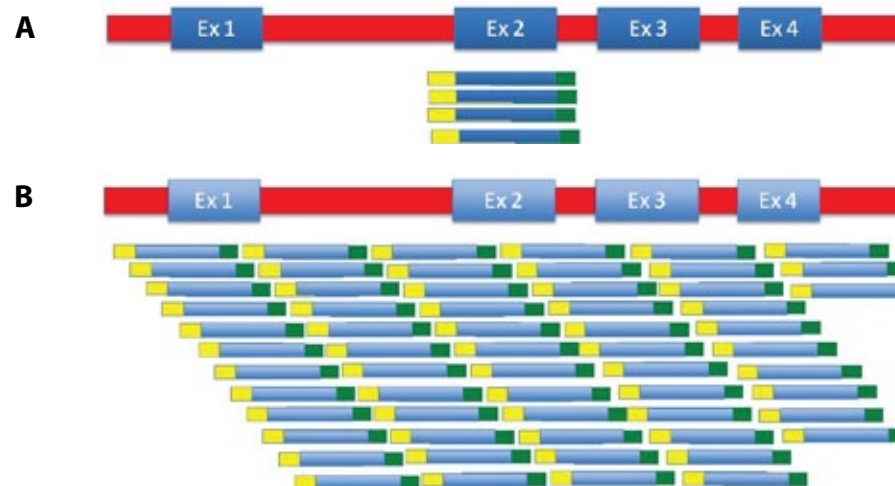
sequencing technologies can improve the accuracy of HLA genotyping by virtue of clonal template amplification and sequencing, and we currently utilize this approach for routine clinical testing. Dr. Anderson also is partnering with FMLH and CIBMTR to investigate the impact of full-gene HLA sequencing on the outcome of hematopoietic cell transplantation. In the future, he plans to develop next-generation sequencing assays to analyze other genes important for the immune response to transplants and to monitor patients for rejection.

Awards, Honors and Memberships

- Member, American Society for Histocompatibility and Immunogenetics (ASHI)
- Member, Association for Molecular Pathology
- Fellow, College of American Pathologists

Research Interests

Dr. Anderson's research interests include the use of high-throughput sequencing technologies for clinical diagnostics and biomarker discovery, with a focus on transplantation. Human leukocyte antigens (HLA) are key molecular determinants of the adaptive immune response and also control the host immune response to hematopoietic and solid-organ transplants. Clinically, the success of a transplant critically depends on a high degree of similarity between the HLA molecules of the donor and recipient. However, HLA genes are among the most polymorphic in the human genome, complicating our efforts to genotype patients using standard DNA sequencing techniques. Next-generation



Strategies for HLA genotyping

A: Standard methods for HLA genotyping typically sequence only 1-3 exons of the HLA gene (exon 2 in this example).

B: Next-generation sequencing methods utilize overlapping DNA fragments to sequence the entire HLA gene.

Weiguo Cui, MD, PhD

Associate Investigator, Blood Research Institute, BloodCenter of Wisconsin
Assistant Professor, Department of Microbiology and Molecular Genetics, Medical College of Wisconsin
MD/PHD, Tianjin Medical University, China, 2004
Dept. of Immunobiology, Yale University School of Medicine, 2012
Employed at BloodCenter of Wisconsin: 2012



Awards, Honors, and Memberships

- ASH Bridge Award 2017
- AHW Research and Education Award 2017
- D. Ziegler Innovation Award 2017
- Outstanding Graduate School Educator, Nov 2017

Funding

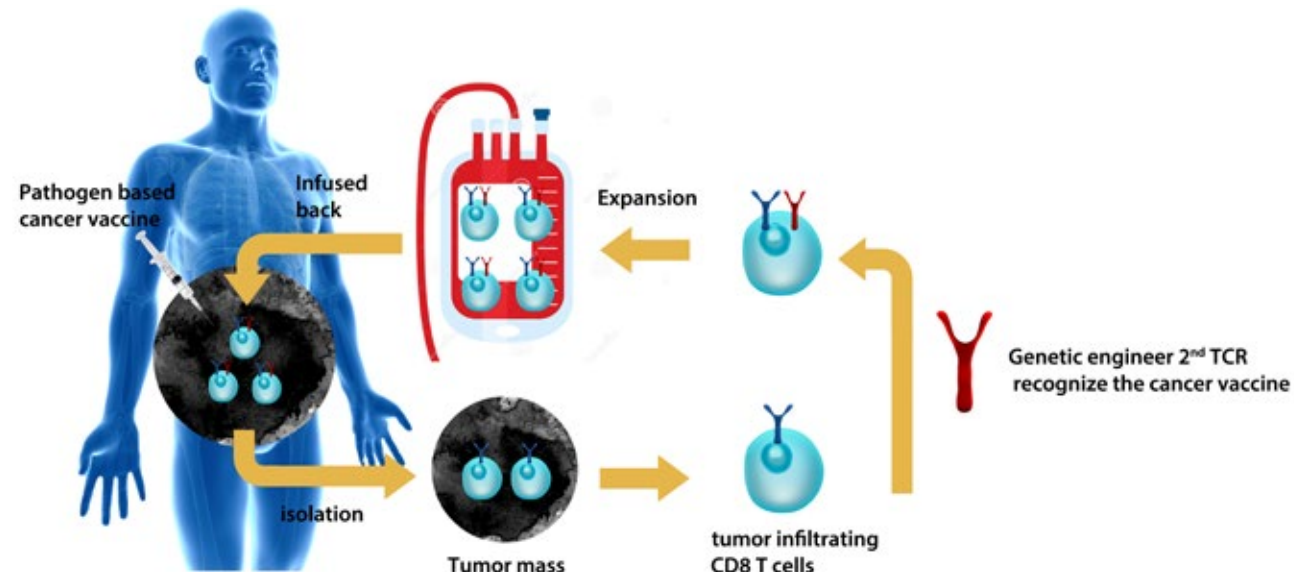
5R01AI125741-0 Cui (PI) 05/16/2016-04/30/2021 NIH/NIAID "The cellular and transcriptional control of CD8 T cell functional adaptation to chronic viruses."

Publications

1. Chen Y, Huang W, Yang M, Xin G, Cui W, Xie Z, Silverstein RL. Cardiotoxic Steroids Stimulate Macrophage Inflammatory Responses Through a Pathway Involving CD36, TLR4, and Na/K-ATPase. *Arterioscler Thromb Vasc Biol.* 2017 Aug;37(8):1462-1469. PMID: 28619997
2. Darrah EJ, Kulinski JM, Mboko WP, Xin G, Malherbe LP, Gauld SB, Cui W, Tarakanova VL. B Cell-Specific Expression of Ataxia-Telangiectasia Mutated Protein Kinase Promotes Chronic Gammaherpesvirus Infection. *J Virol.* 2017 Sep 12;91(19). PMID: 28701397.
3. Xin G, Schauder DM, Jing W, Jiang A, Joshi NS, Johnson B, Cui W. Pathogen boosted adoptive cell transfer immunotherapy to treat solid tumors. *Proc Natl Acad Sci U S A.* 2017 Jan 24;114(4):740-745. PMID: 28069963

Research Interests

Following infection, induction of a subset of lymphocytes designated memory T cells is critical for achieving protection against exposure to bacteria and viruses. Dr. Cui's studies are aimed at improving the understanding of memory T cell development. His current work is focused on the study of epigenetic changes that take place in lymphocytes during the response to an acute infection. An immediate goal is to identify specific chromosomal structures that influence T cell memory. Findings made will improve basic understanding of the immune response and have implications for the treatment and prevention of infectious diseases.



Bonnie Dittel, PhD

Senior Investigator, BloodCenter of Wisconsin, Blood Research Institute
Medical College of Wisconsin, Department of Microbiology and Immunology
PhD, University of Minnesota
Postdoctoral Training, Yale University
Employed at BloodCenter of Wisconsin: 2000



Research Interests

Autoimmunity occurs when the immune system mounts an inappropriate attack on one's own body tissues. Dr. Dittel's laboratory is concerned with immune regulation that occurs during multiple sclerosis (MS), the most prevalent autoimmune disorder affecting the central nervous system (CNS). For this work, she is utilizing a mouse model of MS designated experimental autoimmune encephalomyelitis (EAE). Current studies are aimed at understanding how key cells of the immune system (T and B lymphocytes) interact to influence the autoimmune process that causes damage to CNS tissue. Recent studies have shown that B lymphocytes influence a critical subset of T lymphocytes designated T regulatory

cells (Treg) that are essential for controlling autoimmunity. Dr. Dittel also is investigating how T lymphocytes propagate EAE by studying the mechanisms whereby they open the blood-brain-barrier and induce neuronal damage. Findings made are expected to suggest new approaches for treating MS and other immune disorders affecting the nervous system.

2. Ray A, Dittel BN. Mechanisms of Regulatory B cell Function in Autoimmune and Inflammatory Diseases beyond IL-10. *J Clin Med.* 2017 Jan 23;6(1), 12; Review. PMID: 28124981
3. Strzepa A, Pritchard KA, Dittel BN. Myeloperoxidase: A new player in autoimmunity. *Cell Immunol.* 2017 Jul;317:1-8. PMID: 28511921

Awards, Honors, and Memberships

- Outstanding graduate school educator for academic year 2016-2017 -- Medical College of Wisconsin
- Member, American Association of Immunologists
- Member, American Society for Neurochemistry
- Member, American Association for the Advancement of Scientists

Funding

1R56AI122655 - 01A1, NIAID, Mechanisms of a novel regulatory B cell subset, Principal Investigator

1R56AI129348-01A1, NIAID, B cell-mediated immune regulation, Principal Investigator

Publications

1. Klein RS, Voskuhl R, Segal BM, Dittel BN, Lane TE, Bethea JR, Carson MJ, Colton C, Rosi S, Anderson A, Piccio L, Goverman JM, Benveniste EN, Brown MA, Tiwari-Woodruff SK, Harris TH, Cross AH. Speaking out about gender imbalance in invited speakers improves diversity. *Nat Immunol.* 2017 Apr 18;18(5):475-478. No abstract available. PMID: 28418385

Jack Gorski, PhD

Senior Investigator, Blood Research Institute, BloodCenter of Wisconsin
 Assistant Professor, Microbiology and Immunology, Medical College of Wisconsin
 PhD, University of Cincinnati, 1976
 Employed at BloodCenter of Wisconsin: 1986



Research Interests

The immune response is a complicated process involving direct and indirect communication between many specialized types of cells. Dr. Gorski studies this process at a molecular level. Recent studies have provided new insights into how the immune system recognizes and generates a response against protein fragments (peptides) from germs or viruses. He is the inventor of innovative methods to characterize genetic differences between individuals that determine which protein fragments can be recognized, and how to measure the range of unique immune cells that recognize these protein fragments. Dr. Gorski currently studies how immune responses are affected by aging, how T cell responses differ between

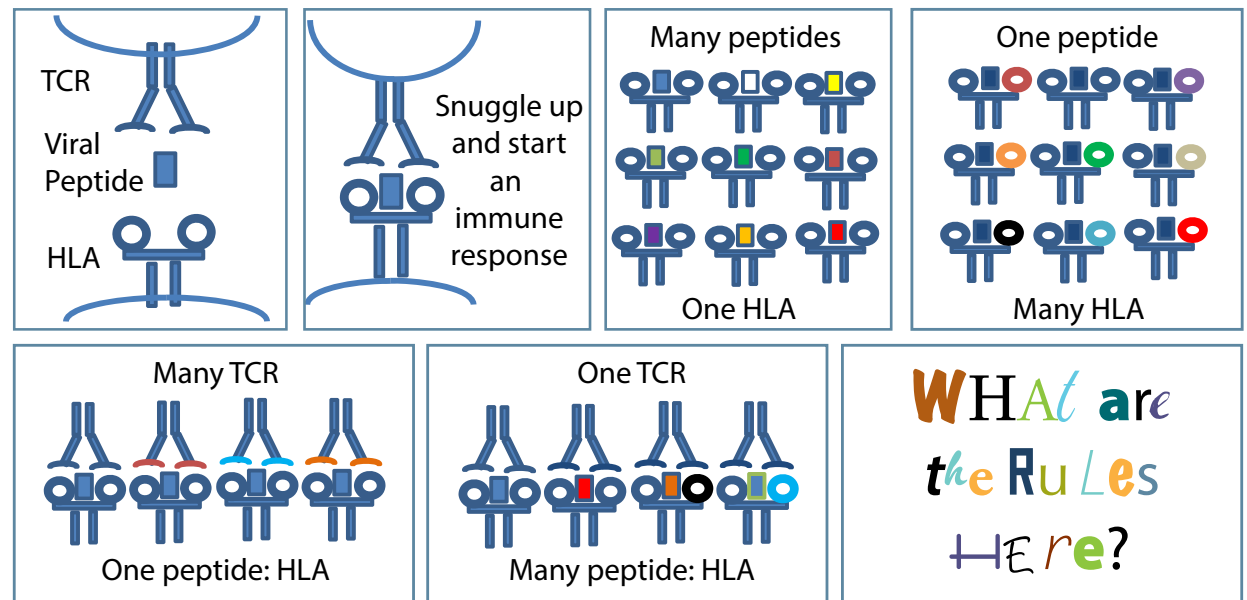
healthy children and children with an autoimmune disease, and how the spread of influenza among older persons in the US can be tracked utilizing the tools of molecular biology. Findings made in this work will advance basic understanding of the human response and its relation to autoimmunity, tissue transplantation and infectious disease.

Awards, Honors, and Memberships

- Director, Center for Human Immunology, Blood Research Institute

Publications

1. Lo CY, Strobl SL, Dunham K, Wang W, Stewart L, Misplon JA, Garcia M, Gao J, Ozawa T, Price GE, Navidad J, Gradus S, Bhattacharyya S, Viboud C, Eichelberger MC, Weiss CD, Gorski J, Epstein SL. Surveillance Study of Influenza Occurrence and Immunity in a Wisconsin Cohort During the 2009 Pandemic. *Open Forum Infect Dis.* 2017 Feb 12;4(2):ofx023. doi: 10.1093/ofid/ofx023. eCollection 2017 Spring. PMID: 28730155.
2. Yassai MB, Demos W, Gorski J. Structural and Mechanistic Implications of Rearrangement Frequencies within Human TCRBV Genes. *J Immunol.* 2017 Aug 1;199(3):1142-1152. PMID: 28659354



Subramaniam Malarkannan, PhD

Investigator Garetto Chair for Immunology and Immunotherapy, Blood Research Institute
Professor of Medicine, Divisions of Hematology/Oncology, Microbiology & Molecular Genetics, and Pediatrics,
Medical College of Wisconsin
PhD Madurai Kamaraj University, Madurai, TN, India, 1991
Employed at BloodCenter of Wisconsin: 2000



Research Interests

Natural Killer (NK) cells are a type of white blood cells that specialize in killing virus-infected and malignant cells. Due to this specialty, there is a great deal of interest in using NK cells for therapeutic purposes. Dr. Malarkannan's group studies basic, translational, and clinical aspects of NK cells. The group's studies have identified pathways that influence target cell killing and associated inflammatory changes. This work may show how these pathways can be manipulated to maximize the killing effect and minimize the adverse effects of NK cell therapy. This constitutes a new form of transfusion therapy for treatment of malignant conditions.

Awards, Honors, and Memberships

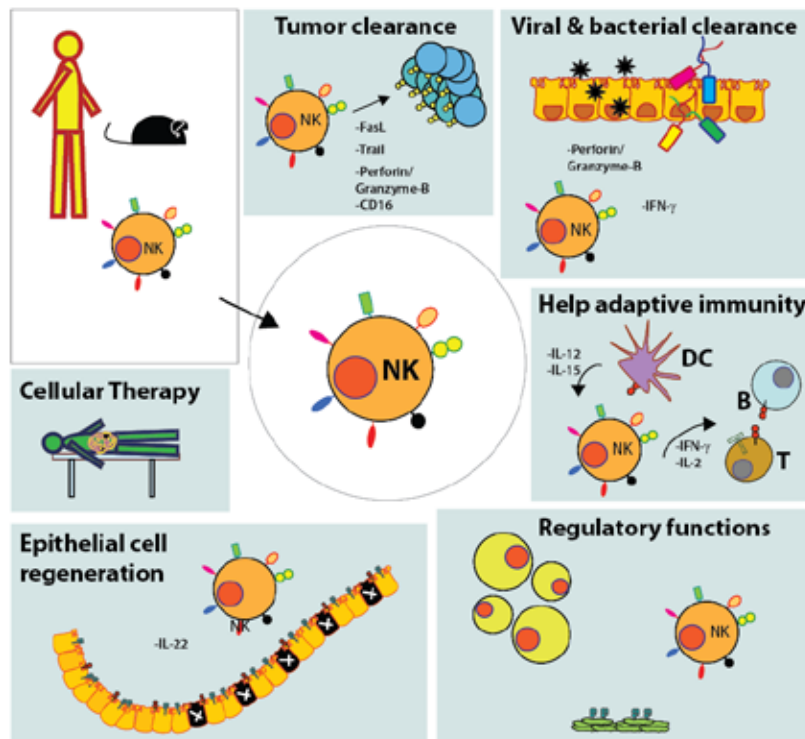
- External Reviewer, Swiss Cancer League, Bern, Switzerland
- Ad hoc Member, Innate Immunity and Inflammation Study Section, NIAID, NIH

Funding

R01 AI102893 "Molecular Mechanisms of Signaling Co-Ordination in Innate Lymphocytes"

Publications

1. Fisher JB, Peterson J, Reimer M, Stelloh C, Pulakanti K, Gerbec ZJ, Abel AM, Strouse JM, Strouse C, McNulty M, Malarkannan S, Crispino JD, Milanovich S, Rao S. The cohesin subunit Rad21 is a negative regulator of hematopoietic self-renewal through epigenetic repression of Hoxa7 and Hoxa9. *Leukemia*. 2017 Mar;31(3):712-719. PMID: 27554164
2. Li N, Xu W, Yuan Y, Ayithan N, Imai Y, Wu X, Miller H, Olson M, Feng Y, Huang YH, Jo Turk M, Hwang ST, Malarkannan S, Wang L. Immune-checkpoint protein VISTA critically regulates the IL-23/IL-17 inflammatory axis. *Sci Rep*. 2017 May 3;7(1):1485. PMID: 28469254



Matthew Riese, MD, PhD

Assistant Professor, Department of Medicine, Division of Hematology/Oncology, Medical College of Wisconsin
Associate Investigator, Blood Research Institute, Blood Center of Wisconsin
PhD, Medical College of Wisconsin, 2002
MD, Medical College of Wisconsin, 2004
Employed at BloodCenter of Wisconsin: 2012



Awards, Honors, and Memberships

- Member, American Society of Clinical Oncology
- Member, American Association for Cancer Research
- Member, Society for Leukocyte Biology

Funding

Bristol-Myers Squibb. 9/1/2016-9/1/2018. "Studies of novel compounds in mice models." (PI-Riese)

MCW Cancer Center. 11/1/2017-10/31/2018. "Optimizing Cancer Adoptive Cellular Therapies with Epigenetic Strategies." (PI-Riese, co-PI Rao).

Incyte grant 09/01/2015 – 09/01/2017 "Immune modeling of new therapeutics in mice" (PI - Riese)

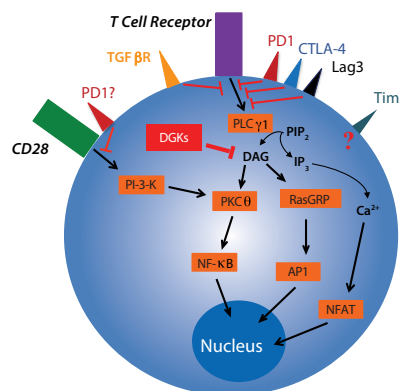
Publications

1. Frankel AE, Flaherty KT, Weiner GJ, Chen R, Azad NS, Pishvaian MJ, Thompson JA, Taylor MH, Mahadevan D, Lockhart AC, Vaishampayan UN, Berlin JD, Smith DC, Sarantopoulos J, Riese M, Saleh MN, Ahn C, Frenkel EP. Academic Cancer Center Phase I Program Development. *Oncologist*. 2017 Apr;22(4):369-374. PMID: 28314841
2. Jing W, Gershan JA, Blitzer GC, Palen K, Weber J, McOlash L, Riese M, Johnson BD. Adoptive cell therapy using PD-1+ myeloma-reactive T cells eliminates established myeloma in mice. *J Immunother Cancer*. 2017 Jun 20;5:51. PMID: 28642819
3. Jing W, Gershan JA, Holzhauer S, Weber J, Palen K, McOlash L, Pulakanti K, Wesley E, Rao S, Johnson BD, Riese MJ. T cells deficient in diacylglycerol kinase- ζ are resistant to PD-1 inhibition and help create persistent host immunity to leukemia. *Cancer Res*. 2017 Oct 15;77(20):5676-5686. PMID: 28916658

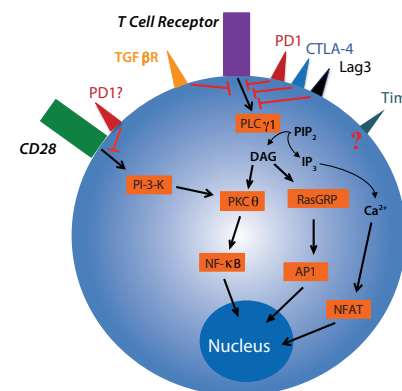
Research Interests

Immunotherapies for the treatment of malignancy have recently begun to demonstrate impressive success in achieving long-term disease control and eradication, however, the therapies work in a minority of patients. The Riese lab is investigating ways to improve upon existing cancer immunotherapies by targeting "off" switches inside T cells, the cells responsible for killing cancer cells. His studies have incorporated both oncology and chemistry and have allowed him to blend medicine and research throughout his career.

Normal T Cell



DGK-Deficient Effector T Cell



Demin Wang, PhD

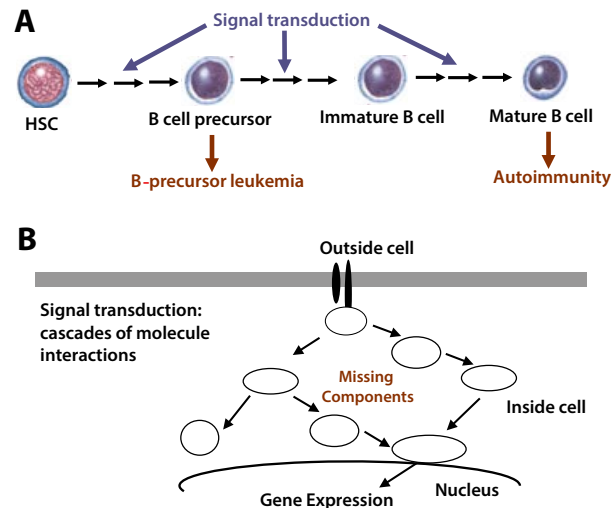
Senior Investigator, and John B. and Judith A. Gardetto Chair for Cancer Research
Blood Research Institute, BloodCenter of Wisconsin
Adjunct Faculty, Department of Microbiology and Immunology, Medical College of Wisconsin
PhD, University of Tennessee, 1995
Employed at BloodCenter of Wisconsin: 2000



Research Interests

Dr. Wang is concerned with self-renewal and differentiation of cells (hematopoietic stem cells, HSCs) that give rise to blood cells and to the subset of white blood cells (B lymphocytes) that produce antibodies. His studies are designed to identify and functionally characterize signaling molecules and pathways that are critical to HSC and B cell biology. Recent studies have identified a novel and critical signal transduction pathway that controls the development of normal early B cells and the formation of B-precursor acute lymphoblastic leukemia. These findings further our understanding of B cell development and transformation, and suggest new approaches to the treatment of leukemia. Furthermore,

recent studies have identified new mechanisms that regulate induction of tolerance in B cells, thereby limiting the possibility of autoantibody production and have led to the findings that antibodies causing heparin-induced thrombocytopenia and thrombosis (HIT) are produced by a subset of B lymphocytes designated marginal zone B cells when self-tolerance is broken. Work in these fields is expected to provide an improved understanding of autoantibody formation in human disease and suggest new approaches to prevention and treatment of autoimmunity.



Awards, Honors, and Memberships

- Editorial Board, Blood
- Member, Cellular and Molecular Immunology B Study Section, NIAID, NIH
- Workshop Chair and Speaker, International Immunology Conference: Immunity in Health and Disease, Fuzhou, China

Funding

- R01 AI079087 "PLCgs in B cell biology and autoimmunity"
- R01 HL130724 "B cell responses in heparin-induced thrombocytopenia"

Publications

1. Fu G, Yu M, Chen Y, Zheng Y, Zhu W, Newman DK, Wang D, Wen R. Phospholipase C γ 1 is required for pre-TCR signal transduction and pre-T cell development. *Eur J Immunol.* 2017 Jan;47(1):74-83. PMID: 27759161
2. Padmanabhan A, Jones CG, Pechauer SM, Curtis BR, Bougie DW, Irani MS, Bryant BJ, Alperin JB, Deloughery TG, Mulvey KP, Dhakal B, Wen R, Wang D, Aster RH. IVIg for Treatment of Severe Refractory Heparin-Induced Thrombocytopenia. *Chest.* 2017 Sept 152(3):478-485. PMID: 28427966

Renren Wen, PhD

Associate Investigator, Blood Research Institute, BloodCenter of Wisconsin
PhD, University of Tennessee Medical School, Memphis 1996
St. Jude Children's Research Hospital, Memphis 1996-2000
Employed at BloodCenter of Wisconsin: 2000



Research Interests

T and B lymphocytes are two important cell types in our adaptive immune system. Whereas B cells secrete antibodies that are essential for protection against extracellular pathogens, T cells are critical for the control of infection by intracellular pathogens, and for enabling B lymphocytes to efficiently produce antibodies. However, aberrant signaling in B and T cells can lead to abnormal development and activation of B and T cells, resulting in immune deficiency, autoimmunity, or cancer development. Dr. Wen's work is aimed at more fully understanding the molecular events, particularly in the T cell receptor and cytokine signaling pathways that govern development of T cells from their earliest

precursors to maturity and defining pathways that are critical for T cell functions. This work will potentially lead to better understanding of the molecular pathogenesis of immune deficiency, autoimmunity, or cancer development. Dr. Wen also works on heparin-induced thrombocytopenia (HIT), a serious disease that sometimes causes thrombocytopenia/thrombosis following clinical administration of heparin. It is believed that heparin complexed with a self-protein PF4 induces PF4/heparin antibodies, some of which causes HIT. Dr. Wen is trying to understand the cellular and molecular mechanisms underlying this condition. Her work on understanding the antibody in HIT at a clonal level would potentially lead to novel and improved diagnosis and HIT treatment.

Awards, Honors, and Memberships

- Member, American Society of Microbiology
- Member, American Association for the Advancement of Science

Funding

5R01 AI079087-08 Wang (PI) 06/15/2008 – 08/31/2019
NIH/NIAID "PLCγs in B Cell Biology and Autoimmunity"
Role: Co-Investigator

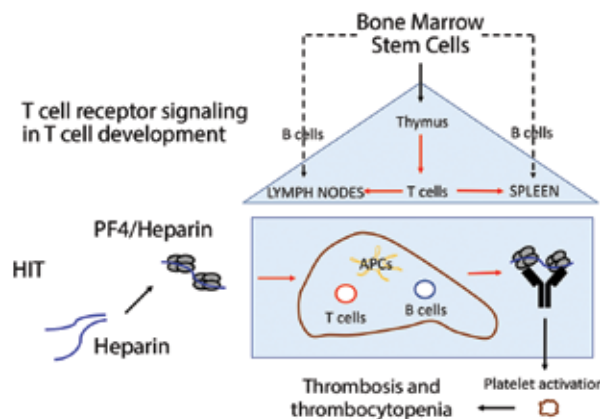
R01 HL130724 Wang (PI) 12/01/2016-11/30/2020 "B cell responses in heparin-induced thrombocytopenia" Role: Co-Investigator

Pilot Grant Wen (PI) 04/01/2017 – 03/31/2018 Clinical and Translational Science Institute "Identification of PF4/heparin-specific antibody repertoire in heparin-induced thrombocytopenia using high-throughput sequencing" Role: PI

2R01 AI083636-06 Salomon (PI) 05/08/2017-04/30/2022 "Phosphoproteomic Analysis of Feedback Networks in T Cell Signaling" Role: Co-investigator

Publications

1. Fu G, Yu M, Chen Y, Zheng Y, Zhu W, Newman DK, Wang D, Wen R. Phospholipase Cγ1 is required for pre-TCR signal transduction and pre-T cell development. *Eur J Immunol.* 2017 Jan;47(1):74-83. PMID: 27759161
2. Padmanabhan A, Jones CG, Pechauer SM, Curtis BR, Bougie DW, Irani MS, Bryant BJ, Alperin JB, Deloughery TG, Mulvey KP, Dhakal B, Wen R, Wang D, Aster RH. IVIg for Treatment of Severe Refractory Heparin-Induced Thrombocytopenia. *Chest.* 2017 Sept 152(3):478-485. PMID: 28427966



Stem Cells

Research in Stem Cell Biology and Hematopoiesis is aimed at understanding the many factors that regulate the normal process of how blood cells are formed (hematopoiesis), as well as understanding disease mechanisms that lead to abnormal hematopoiesis, which either could lead to a failure of healthy blood cell production or cause leukemia.

Studies in this area are bringing the BloodCenter into the fields of regenerative medicine, and cancer biology. These studies reflect an ongoing commitment to expanding foundational research into areas that will fundamentally improve the understanding and treatment of currently incurable blood diseases.

Housed in a new wing of the Blood Research Institute, Stem Cell Biology investigators are using cutting-edge technology to characterize molecular mechanisms involved in regulation of hematopoietic stem cells and their maturation into mature red cells, white cells and platelets.



Karen Carlson, MD PhD

Assistant Investigator, Blood Research Institute, BloodCenter of Wisconsin
Assistant Professor, Department of Internal Medicine, Division of Hematology and Oncology, Medical College of Wisconsin
MD/PhD University of Wisconsin-Madison, 2004
Hematology/Oncology Fellowship: New York Presbyterian, Weill-Cornell Medical Center, 2011
Employed at BloodCenter of Wisconsin, 2016



Research Interests

Dr. Karen-Sue Carlson is a board certified clinical hematologist. She joined the faculty at the Medical College of Wisconsin as an Assistant Professor of Medicine in the Division of Hematology and Oncology in 2013, and was appointed Assistant Investigator at the Blood Research Institute in 2016.

She maintains an active clinical focus on diseases of disordered hematopoiesis including aplastic anemia, acute and chronic leukemias, and myelodysplastic and myeloproliferative syndromes at the Medical College of Wisconsin. At the Blood Research Institute, her research focuses on extracellular matrix regulation of adult stem cell homeostasis.

Using murine models, Dr. Carlson studies how extracellular matrix (ECM), and in particular, the glycoprotein laminin- γ 1, regulate the bone marrow and gastrointestinal adult stem cell niches. She also is using 3-dimensional image reconstructions to understand how human acute myelogenous leukemia (AML) traffics through the bone marrow vascular niches during remission induction chemotherapy.

Dr. Carlson's long-term goal is to apply what she learns about the basic biology of the bone marrow extracellular matrix to develop niche-targeted therapies that will help her patients with hematopoietic diseases.

Awards, Honors, and Memberships

- Best Doctors® designation
- Member, American Society of Matrix Biology
- Member, American Society of Biochemistry and Molecular Biology
- Member, International Society of Experimental Hematology
- Member, American Society of Hematology
- Recipient of the Daniel McCarty Award for Research Excellence, awarded by the Medical College of Wisconsin's Department of Medicine

Funding

"Bone Marrow Failure in Mice Deficient for the Extracellular Matrix Component, Laminin-gamma1"
(1K08HL127187-03) -NHLBI (NIH) PI- April 1, 2015–March 31, 2020

"Acute myelogenous leukemia interface with the hematopoietic niche" MCW Cancer Center – PI – December 1, 2017–November 30, 2019

Publications

1. Kanate AS, Hari PN, Pasquini MC, Visotcky A, Ahn KW, Boyd J, Guru Murthy GS, Rizzo JD, Saber W, Drobyski W, Michaelis L, Atallah E, Carlson KS, D'Souza A, Fenske TS, Cumpston A, Bunner P, Craig M, Horowitz MM, Hamadani M. Recipient Immune Modulation with Atorvastatin for Acute Graft-versus-Host Disease Prophylaxis after Allogeneic Transplantation. *Biol Blood Marrow Transplant.* 2017 Aug;23(8):1295-1302. PMID: 28412518
2. Levin A, Kleman A, Rein L, Tarima S, Michaelis LC, Carlson KS, Hamadani M, Fenske TS, Hari P, Atallah E, Dhakal B. Early Mortality in Patients with Acute Myelogenous Leukemia Treated in Teaching versus Non-teaching Hospitals: A Large Database Analysis. *Am J Hematol.* 2017 Sep;92(9):E563-E565. PMID: 28631379
3. Thijs van Mens, Helena Liang, Sreemanti Basu, Irene Hernandez, Mark Zogg, Jennifer May, Qiuhui Yang, Mln Zhan, Rashmi Sood, Jamie Foeckler, Shawn Kalloway, Karen-Sue Carlson, and Hartmut Weiler. Variable penetrance of thrombosis in adult mice after tissue-selective and temporally controlled Thrombomodulin gene inactivation. *Blood Advances.* 2017 1:1148-1158 (10.1182).

Alex C. Minella, MD

Associate Investigator, Blood Research Institute, BloodCenter of Wisconsin
Hematology/Oncology & Cell Biology, Medical College of Wisconsin
MD, Vanderbilt University School of Medicine, 1998
Employed at BloodCenter of Wisconsin: 2014



Awards, Honors, and Memberships

- Chair, Red Cell Biology Scientific Committee, American Society of Hematology
- Editorial Board Member, Leukemia and Lymphoma
- Ad hoc service on NIH CSRS study section

Funding

R01 HL098608 "Cyclin E Regulation in Normal and Neoplastic Hematopoiesis"

Publications

1. Kesarwani AK, Ramirez O, Gupta AK, Yang X, Murthy T, Minella AC, Pillai MM. Cancer-associated SF3B1 mutants recognize otherwise inaccessible cryptic 3' splice sites within RNA secondary structures. *Oncogene*. 2017 Feb 23; 36(8):1123-1133. PMID: 27524419

Research Interests

Dr. Minella's laboratory seeks to understand how the cell division cycle is interconnected with other fundamental pathways that control cell fate and function. Current projects center on mediators of the G1-to-S-phase transition, including transcription factors, ubiquitin ligases, cyclins/cyclin-dependent kinases, and their inhibitors. One major objective is to determine how these maintain hematopoietic stem cell function, preserve normal hematopoietic differentiation programs, and restrain malignant transformation of hematopoietic progenitor cells. Another objective is to identify pathways within which the cyclin-dependent kinases have non-redundant functions in regulating protein substrates that are drivers in the molecular pathogenesis of hematopoietic diseases.

Sridhar Rao, MD, PhD

Associate Investigator, Blood Research Institute, BloodCenter of Wisconsin
MD, University of Chicago, Pritzker School of Medicine, 2001
PhD, University of Chicago, 1999
Employed at BloodCenter of Wisconsin: 2010



Research Interests

Acute Myelogenous Leukemia (AML) is a common malignancy, but despite modern chemotherapy, the majority of patients relapse. My laboratory focuses on how altered gene expression causes diseases such as cancer. The long-term goal of my laboratory is to understand how gene expression derangements can be targeted to develop less toxic, more effective chemotherapies to treat blood-derived cancer.

My laboratory focuses on Acute Myelogenous Leukemia (AML) because it represents a significant clinical challenge, with up to 50% of patients relapsing. Recent data has indicated a large number of genes (>200) can be mutated in AML, making it difficult to understand how specific,

targeted therapies can be developed. We have focused on how mutations in a specific group of genes termed the cohesin complex cause AML. Our recent work indicates that mutations in the cohesin complex promote bone marrow cells to divide abnormally, and this predisposes them to acquire additional mutations which ultimately cause leukemia. Because the cohesin mutation likely occurs early in the process, targeting these mutations could lead to new therapies. We are currently working on different targeted therapy agents already in clinical trial to determine if they could be used to treat patients with cohesin-mutated AML.

Awards, Honors and Memberships

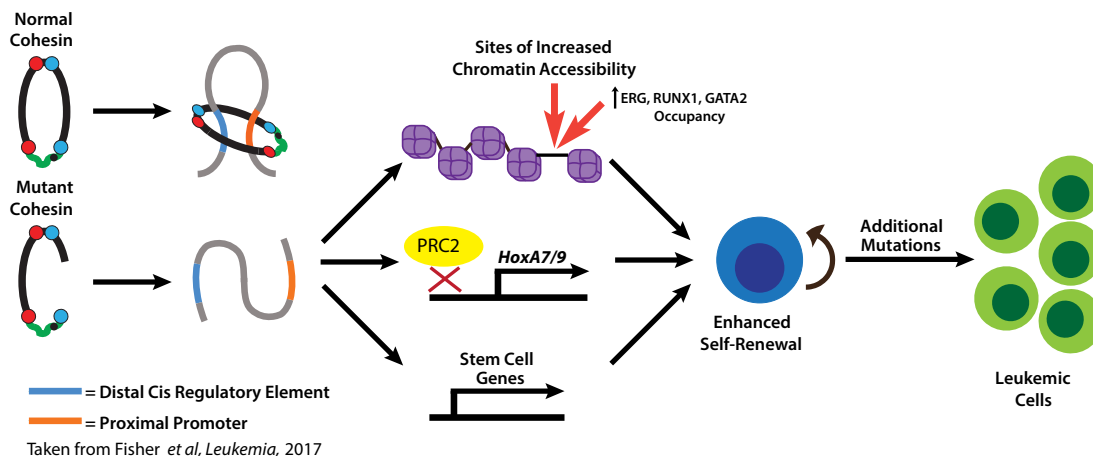
- Member, American Society of Hematology
- Member, American Society for Blood & Marrow Transplantation (ASBMT)
- Member, International Society for Stem Cell Research (ISSCR)

Funding

National Cancer Institute- R01 "Cohesin Mutations in AML"
Midwest Athletes Against Childhood Cancer (MACC Fund)

Publications

1. Blinka S, Rao S. Nanog Expression in Embryonic Stem Cells - An Ideal Model System to Dissect Enhancer Function. *Bioessays*. 2017 Dec;39(12). PMID: 28977693
2. Blinka S, Reimer MH Jr, Pulakanti K, Pinello L, Yuan GC, Rao S. Identification of Transcribed Enhancers by Genome-Wide Chromatin Immunoprecipitation Sequencing. *Methods Mol Biol*. 2017;1468:91-109. PMID: 27662872
3. Broglie L, Pommert L, Rao S, Thakar M, Phelan R, Margolis D, Talano J. Ruxolitinib for treatment of refractory hemophagocytic lymphohistiocytosis. *Blood Adv*. 2017 Aug 17;1(19):1533-1536. PMID: 29296794



Jack Zbiegien

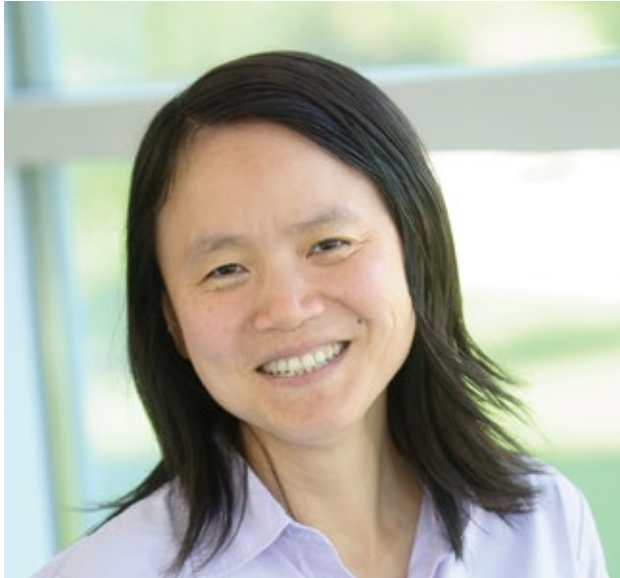
When he was 40 years old, Jack Zbiegien went to the doctor with an ear ache. It turned out to be leukemia. During his treatment, Jack received over 300 blood transfusions and a life-saving bone marrow transplant. BloodCenter has made ground-breaking discoveries to help make more life-saving bone marrow transplants possible, and its investigators work on the front lines to fight leukemia and other cancers.

“I am so thankful to have a second chance at life,” says Jack.



Nan Zhu, PhD

Associate Investigator, Blood Research Institute, BloodCenter of Wisconsin
Assistant Professor, Cell Biology, Neurobiology and Anatomy, Medical College of Wisconsin
PhD, Boston University, Boston, MA, 2007
Employed at BloodCenter of Wisconsin: 2015



Research Interests

Research in Dr. Zhu's laboratory focuses on understanding epigenetic regulation in normal and malignant hematopoiesis with emphasis on the role of such regulation in hematopoietic stem cell (HSC) as well as leukemia stem cell (LSC). Epigenetic regulation refers to changes in gene activities that are independent of the underlying gene sequences. Epigenetic regulators play an important role in normal development and differentiation. More recently, they emerge as important players in the development of cancer as evident by recurrent mutations across a spectrum of cancers. We have previously screened and identified several epigenetic regulators as important for the maintenance of

acute myeloid leukemia (AML). Currently, we are working on elucidating their role in normal and malignant stem cell function and understanding the precise underlying molecular mechanism. In 2016, our study on JMJD1C, an epigenetic regulator, demonstrated that it is important for LSC function but dispensable for HSC function, thus a potential therapeutic target. The ultimate goal of our research is to identify therapeutic targets and developed targeted therapy in AML based on knowledge gained from our research.

Awards, Honors, and Memberships

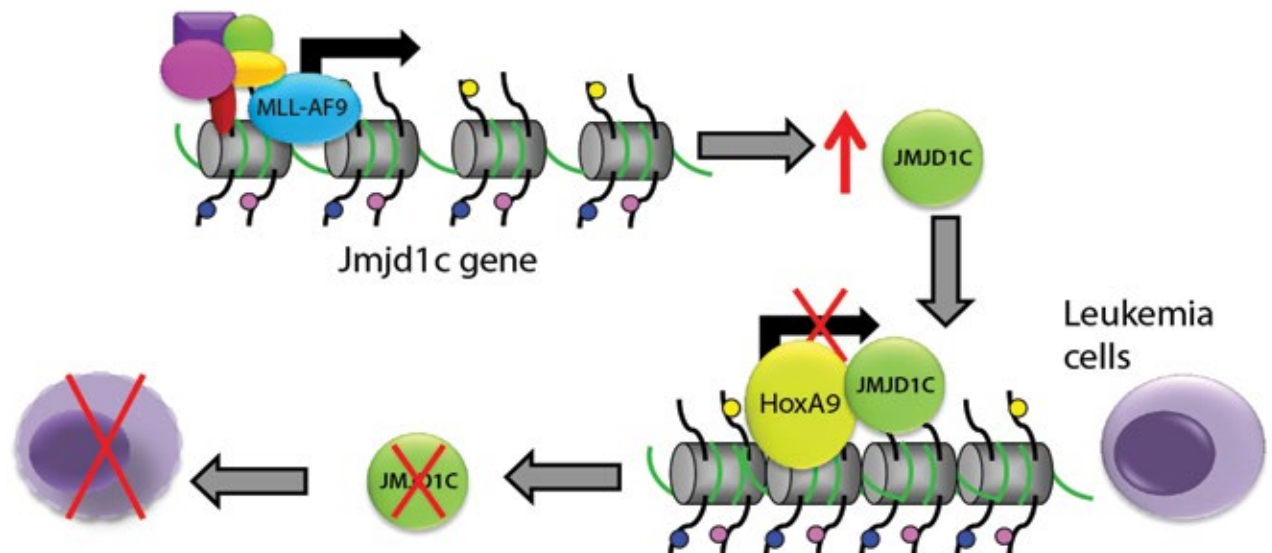
- Member, American Society for Hematology
- Howard Temin Pathway to Independence Award, NIH/NCI, 2013 - 2018

Funding

R00 CA168996 "The Role of JMJD1C in Normal and Leukemic Hematopoiesis"

Publications

1. Olp MD, Zhu N, Smith BC. Metabolically Derived Lysine Acylations and Neighboring Modifications Tune the Binding of the BET Bromodomains to Histone H4. *Biochemistry*. 2017 Oct 17;56(41):5485-5495. PMID: 28945351



Core Laboratories



Modern biomedical research requires access to a wide range of specialized technologies. The Blood Research Institute maintains cutting-edge technology platforms that give researchers from the BRI, and its affiliates on the Medical College of Wisconsin (MCW) campus, access to state-of-the-art equipment and expertise. These centralized core laboratories are a shared resource and are staffed by technical specialists that support individual research projects. Currently, the BRI is home to 11 different core laboratories.

The **Molecular Cell Biology Core** offers DNA sequencing using both capillary-based and Next-generation platforms and quantitative assays for DNA and RNA utilizing several different instrument platforms, such as a QuantStudio 6 Flex Real-time PCR system for rapid measurement of gene activity.

The **Protein Chemistry Core** synthesizes peptides using a microwave-enhanced Liberty 1 synthesizer and offers peptide purification and a variety of post-synthesis peptide modifications. The core also aids investigators with protein purifications.

The **Hybridoma Core** produces murine monoclonal antibodies for research and diagnostic purposes.

The **Flow Cytometry Core** utilizes two Becton Dickinson LSR II multicolor cytometers, a BD Accuri cytometer, a BD FACSAria high-speed cell sorter, and a FACS Melody cell sorter.

The **Microscopic Imaging Core** includes an Olympus FV1000-MPEconfocal, multiphoton microscope and an inverted Nikon TE200, a Zeiss AxioScope, and a Zeiss Lumar V12 stereo microscope with fluorescence capabilities. A PhD Imaging Specialist manages this core.

The **Biophysics Core** is equipped with a BIAcore 3000 Plasmon Resonance Spectrometer that enables scientists

to study protein-protein interactions in real time.

The **Viral Vector Core** is shared between the BRI and the MCW and specializes in vectors based on lentivirus, adenovirus and adeno-associated virus needed for research in the field of gene therapy and other experimental applications.

The **Thrombosis Core** maintains a spinning disk confocal microscope system for in vivo studies on thrombosis. This core also features an in vitro flow system designed to recapitulate the in vivo conditions of flowing blood in the vasculature (VenaFlux system from Cellix Ltd; Zeiss inverted microscope with phase contrast, fluorescence and incubation capabilities).

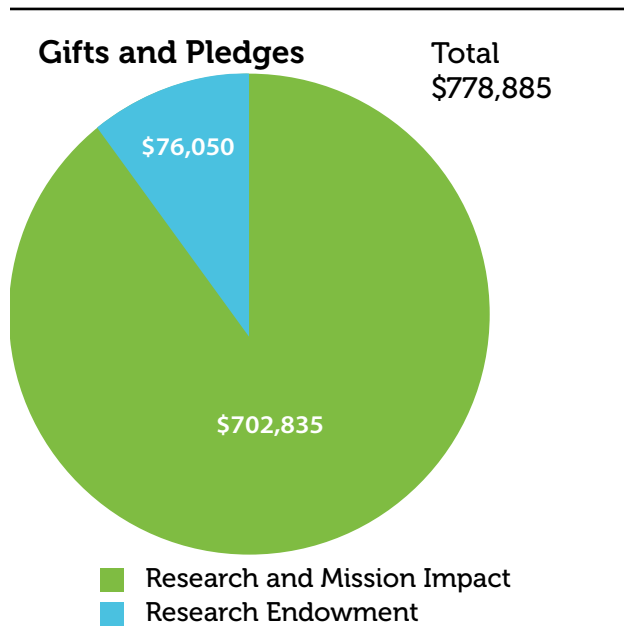
The **Histology Core** specializes in tissue preparation, cutting of fixed and frozen sections and various staining techniques. This core is staffed by a histology technician with 30 years of experience in experimental and clinical histology.

The **Gene Editing Core** is available as a resource for researchers that want to make targeted mutations in cells using recently developed CRISPR technology.

The joint **BRI/MCW Transgenic Core** aids in the generation of genetically altered animal models for the study of human disease.

The **Clinical Trials Research Office (CTRO)** supports the work of our Clinical Investigators, interfacing with the other research support services at the BRI. Services that are provided by the CTRO include, but are not limited to, clinical trial design and activation, study coordination and management, data collection, adverse event reporting, regulatory support and compliance, budgeting and contract negotiation, and financial management.

BloodCenter Research Foundation



Thank you to the more than 940 people who supported us through a charitable gift this year. We raised \$778,885 in the fight against diseases of the blood and the search for treatments and cures. These gifts, once again, have been invested in life-enhancing research, technology that accelerates new discoveries, and in helping families make important decisions about organ and tissue donations that can save another person's life.

Your gifts matter because one American dies every 40 seconds as a result of a heart disease, stroke, or other cardiovascular diseases. Additionally, one out of every four people who die today will succumb to a disease for which we are actively seeking a cure. At the Blood Research Institute, our mission is to seek treatments and cures for all diseases of the blood. And we need you to help us continue our mission.

Our highest priority is increasing our capacity to close the knowledge gap between what is known and what is yet to be discovered about diseases of the blood, to develop better medical tests, and to discover new treatments that may possibly lead to new cures. Solving society's urgent health problems is the function of foundational scientific inquiry. Science needs curiosity, serendipity, and collaboration-driven research to fill the reservoirs of knowledge that will be drawn upon for clinical application. Foundational discoveries become the bedrock on which clinical diagnosis and treatment are built.

Your Charitable Gifts to the BloodCenter Research Foundation make all this possible

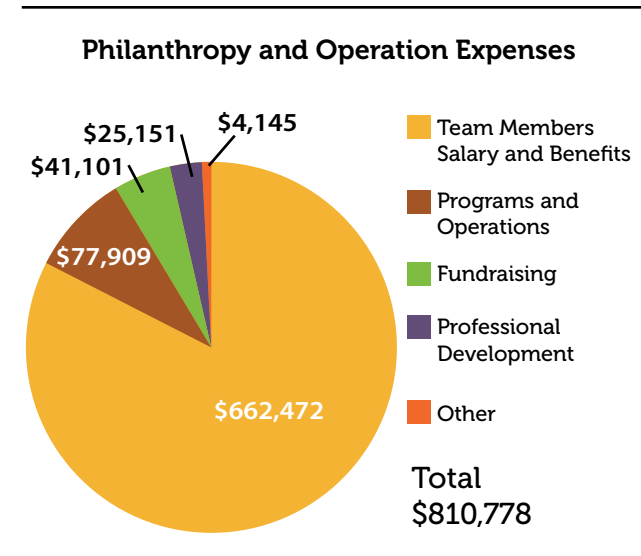
But we have more to do. Our research and physician teams work together to find answers to questions such as:

- What role do platelets have in causing heart attack and stroke?
- What causes clots to form in the deep veins of the body, such as those found in the legs, and what new treatments are required to solve this problem?
- How do cells recover from radiation and chemotherapy given during cancer treatments?
- How can we harness the power of the immune system to combat cancer?
- How can we make blood transfusions safer and more effective?

The answers to these questions and many others will lead to a better understanding of how to treat and cure diseases of the blood; leading to fewer deaths caused by heart disease, stroke, other cardiovascular diseases and cancer.

Improving Lives: Our Aspiration and Impact Areas

Our Research 2025 initiative is a long-term plan focused on closing the gap between what is known and what is still to be learned about blood diseases. During this time, we will grow and innovate more than ever before. We look ahead to this new phase with anticipation, buoyed by the success of our last 70 years. We are doing more research, establishing more partnerships and collaborations and consistently achieving more positive outcomes. Above all, we are guided by the profound impact that an integrated research program, both foundational and clinical, can have on healthcare, our clarity of purpose, and our commitment to improving lives.



Intellectual Property

Novel Approaches to Help Patients

Basic and applied biomedical research studies are aimed primarily at understanding normal and abnormal biology. This aids disease diagnosis, treatment and prevention. Research findings impact patients and patient care when companies develop products and services from new discoveries. Intellectual property and patents help to differentiate and protect these new markets. Federal guidelines encourage protection of grant-supported discoveries through patents and other mechanisms that have the potential to transform research findings into products and services that benefit the health of the public. The Technology Transfer Office of BloodCenter of Wisconsin helps to identify, protect, and commercially partner discoveries to serve patient needs. Net revenues generated support further research. In 2017, two new patents were filed, and royalty revenue totaled

approximately \$386,625. BloodCenter technologies are licensed to more than 20 companies.

Intellectual Property Revenue

Patents and licensing agreements shown below are for the years 2000-2017. Figures in chart indicate the number of individual patents filed for the year.

Mission Statement

Technology Transfer Office supports BloodCenter of Wisconsin's (BCW's) organizational mission of bringing life-saving solutions to the patient through a departmental focus on placing innovations into the hands of customers and colleagues.

Background

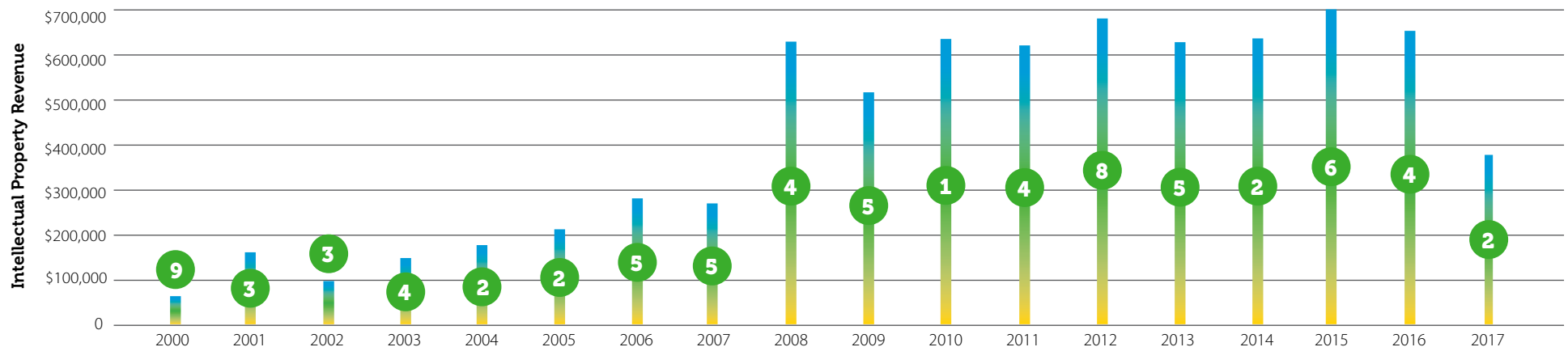
Inventor Tibor Greenwalt and colleagues discovered a white cell filtration method for blood in the 1960s. Patent activity increased in the 1980s with the discovery

of the human platelet antigen system. Currently, BCW's Technology Transfer Office provides intellectual property, contract management, and business management administrative services for the organization. A cross functional team called the Technology Transfer and Intellectual Property Review Group provides executive oversight for this function.

Performance Metrics

Metrics for the BCW are from Jan. to Dec. 2017 as compared to the Association of University Technology Managers (AUTM) 2015 survey data, the latest available. Data for the AUTM survey respondents and for the BCW are normalized for each \$10 million in total research expenditures (federal plus industry sponsored research as reported by AUTM respondents.) BCW's total research expenditures were up 39% to \$10.7 million for 2017.

PATENT APPLICATIONS FILED PER YEAR



Patents 2017



Use of Gelsolin to Treat Multiple Sclerosis and Diagnosis Neurological Disease

Researchers at Blood Research Institute led by Bonnie Dittel, PhD, and colleagues at Harvard University discovered a protein that may be of novel treatment for MS. A Chinese patent for it has been issued.

Despite significant advances in diagnosis and therapy, neurologic diseases remain a major cause of morbidity and mortality throughout the world. Neurologic diseases are common and costly. According to a recent estimate, the annual cost for treating neurologic diseases in the United States exceeds 600 billion dollars. Because the outcome of treatment depends on a proper diagnosis, it is important to have proper tests to diagnose neurologic diseases and to monitor the treatment of those diseases. Proper monitoring of treatment allows the physician to decide on the course of treatment and to advise patients and their families about the expected disease course. Thus, there also is a strong incentive to identify new improved tests and approaches to diagnose and to evaluate treatments of neurologic diseases.

Gelsolin, first discovered as an actin-binding protein involved in cell movement, has been recently implicated in a number of diseases. While the true function of plasma gelsolin is not known, clinical and animal studies have shown that depletion of plasma gelsolin by injury and inflammation is associated with poor outcomes. More recently, gelsolin was found to bind bioactive inflammatory mediators and peptides implicated in Alzheimer's disease.

Improved Heparin-Induced Thrombocytopenia (HIT) Test Receives Patent

Dr. Richard Aster; Dr. Anand Padmanabhan; Dan Bougie, Ph.D.; and research technologist Curtis Jones received a US patent in December 2017. Their patent is for an improved method to diagnose Heparin-induced Thrombocytopenia (HIT), a life-threatening disorder that develops in some patients who receive heparin, a commonly-used blood thinner.

Currently, there are two basic tests most commonly used to diagnose HIT. The first assay, Heparin/PF4-ELISA, is plagued by frequent "false" positives due to detection of other antibodies by the test in some patients without disease. While the results for this assay come in quickly, and do predict those with true disease, other patients are falsely positive. The second assay, the Serotonin Release Assay (SRA), generally considered the "gold standard" HIT test is technically highly complex and can only be performed by a few specialized laboratories. This causes delay in getting an accurate diagnosis.

A new assay developed on the basis of research findings made at BCW, the subject of this patent, is known as the Platelet Factor 4-dependent p-selectin expression assay (PEA). This assay is favorable from multiple standpoints: enhanced speed, highly accurate results, and technical simplicity so that it can be offered by a variety of laboratories, both large and small. It is hoped that this technology will greatly improve the diagnosis and treatment of this dangerous condition by providing early, accurate diagnosis thereby facilitating immediate effective therapy.

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A Brief History

For 70 years, BloodCenter of Wisconsin has been dedicated to research as a vital part of our mission. Our researchers have made numerous medical breakthroughs that have helped people in our community, across the nation, and around the world. We are extremely proud of our reputation as one of the world's premier blood research centers.

The Blood Research Institute (BRI) is home to more than 150 physicians, scientists, and technologists who work in 32 investigative laboratories. They seek knowledge that will lead to faster diagnosis, improved treatments, and ultimately cures for many diseases that threaten our communities.

The majority of our work is foundational research in the areas of:

Vascular Biology, Thrombosis, and Hemostasis

– studies of bleeding and clotting disorders, coagulation, sickle cell disease, and vascular events such as: inflammation, platelet interactions, and the integrity of the blood vessel wall

Immunobiology – studies of B cells, T cells, NK cells, autoimmunity, immune system development, and neuroimmunology

Stem Cell Biology/Hematopoiesis – studies of stem cells, the formation of blood, and malignant conditions involving blood cells

Transfusion Medicine – studies of immune diseases of the blood, transfusion therapy, and donor safety

