Research Report 2020

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Blood Research Institute

B cells (B) via interactions with T cells are driven to produce antibodies that facilitate the clearance of viruses (v) and bacteria (bac) that cause disease. The cover was created by Savannah Neu, a graduate student in the Dittel laboratory, and was the cover of the Journal of Molecular Biology, Vol. 433, Issue 1.

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Blood Research Institute

Message from Interim Executive Vice President Roy L. Silverstein, MD

On July 1, 2020 I stepped in as the interim EVP for Research and Director of the Versiti Blood Research Institute (VBRI) to fill the enormous shoes of Dr. Gil White. As Dr. White transitions towards retirement, he is focusing his efforts on COVID-19 research, development work with the Versiti BRI Foundation, and mentoring all of us at the VBRI. 2020 was a year like no other in the history of the research mission of Versiti. All our lives were upended by the SARS-COV2 pandemic, and the researchers at Versiti were not exempt. To protect the safety of our investigators, staff, and community, laboratory and clinical research programs went into a near "hibernation" state beginning in mid-March. Only "essential" research or COVID-related research could continue, and this only on a very limited scale. By mid-summer, as personal protective equipment (PPE) became more available and case rates fell, a careful, slow, phased re-opening began, paying very close attention to CDC and local guidelines. This scaled back research effort reduced access to our laboratories and limited our ability to carry out clinical research through the spring of 2021. Nevertheless, our researchers stayed busy and productive, mostly working from home analyzing data, writing papers and grants, planning new studies, and in many cases pivoting their research programs to directly address the pandemic. Not surprisingly, research grant revenues and expenditures were down a bit in 2020 compared to 2019, but we expect this to rebound in 2021.

The pivot of research to COVID-19 was truly remarkable and clearly demonstrated the Versiti core values of innovation and collaboration. Gil White, Shawn Jobe, Renren Wen, Weiguo Cui, Demin Wang, Matt Riese, Subra Malarkannan, Versiti MSI Transfusion Medicine specialists, and others initiated new collaborations among themselves and with hematologists, infectious disease specialists, and intensivists at Froedtert Hospital and Medical College of Wisconsin (MCW) to develop clinical research protocols testing the efficacy of Covid Convalescent Plasma in treating hospitalized patients with COVID-19. These protocols included collection and banking of patient plasma and blood cells which proved to be valuable tools to study the immunologic responses to infection and potential mechanisms underlying the tendency of COVID-19 patients to develop dangerous blood clots. The team obtained new peer-reviewed funding through the Advancing a Healthier Wisconsin Endowment at MCW and submitted several NIH grants to continue the work. Karin Hoffmeister received supplemental funding on her NIH grants to study glycobiology-related mechanisms of COVID-19 infection, and Lisa Baumann-Kreuziger obtained new NIH funding through "operation warp speed" to lead multi-institution, randomized controlled clinical trials to

test efficacy of anti-coagulation therapy in COVID-19 patients.

2020 was a year of transition for the VBRI in many other aspects. We had several important retirements announced, including Dick Aster's. His 50 years of leadership and scientific accomplishments are unparalleled in American Medicine and his legacy at Versiti will be long lasting. Jack Gorski retired in November after many years of scientific leadership and innovation in immunology research that led to major advances in bone marrow and solid organ transplantation. Tom Abshire announced his retirement as Director of the MSI after 10 incredibly productive years of service. Josh Field was named interim MSI Director upon Tom's retirement. Josh is world renowned for his leadership in developing innovative clinical care models and clinical research programs for adults with sickle cell disease. Versiti established a new endowment, the Versiti Endowed Chair for Clinical Research, to support Josh in these efforts, the first ever endowment to support the clinical research mission at Versiti. Drs. Aster, Abshire and Gorski have all been named Emeritus Senior Investigators and we will continue to call on them for advice and mentoring. MSI and BRI investigators, Shawn Jobe and Matt Karafin, left Versiti in 2020 to pursue exciting opportunities at other academic medical centers, Shawn at Michigan State and Matt at University of North Carolina. We will miss them both but are proud that they have moved into leadership roles at outstanding institutions. After many years of administrative leadership, Tina Koplinski left the BRI at the end of 2020.

Sadly, we experienced the premature and unexpected passing of Matt Riese in December after a brief illness. More will be said about Dr. Riese's career and scientific accomplishments later in this report, but he was a brilliant physician scientist whose warmth and generosity had a great impact at Froedtert and MCW, where he practiced medical oncology, and at VBRI where he was a valued colleague, collaborator, and mentor, as well as a rising star in the fields of immune-oncology and CAR-T cell therapeutics. His untimely loss is being felt throughout the Versiti and MCW family.

Although many of our favorite scientific events, including the Aster, Mosseson, Fredrick and Zeigler visiting lectureships and the Annual Immunology Symposium were cancelled this year, we were able to switch to virtual platforms later in the year to resume weekly research-in-progress seminars by students and fellows, monthly seminars by our faculty, and a limited series of seminars by outside scientists. The Scientific Advisory Board convened in a virtual format in November and reviewed the Immunology program. We missed the social aspects of the visit and the chance to connect in person with the Board, but the visit went well and accomplished the goals of this important annual scientific review. Overall, there was high enthusiasm for this group of investigators. In their summary comments, the Board noted the many high impact publications from the immunology group and recognized the value of sustained VBRIF support for highly innovative scientists, such as Bonnie Dittel, who are undertaking high risk/high reward research. They also called out the value of providing support to investigators as they transition from early to mid-career. This advice was prescient, as Versiti committed later in the year to establish a new endowment for supporting the research mission. The Versiti Endowed Chair for Discovery Research was awarded to Weiguo Cui in the immunology program specifically to address this need.

We were excited to welcome three new investigators to the VBRI in 2020. Brian Branchford is a pediatric hematologist and physician scientist who joined MSI and VBRI in June, after completing training at University of Colorado, Anschutz. Brian has a prestigious NIH K08 Career Development Award and will be participating in clinical care and clinical research programs in the Comprehensive Center for Bleeding Disorders at Versiti as well as developing a research program focused on genomics, platelet biology and coagulation under the mentorship of Peter Newman. Ze Zheng is a PhD investigator recruited in partnership with the Department of Medicine at MCW. She comes to us from Columbia University in New York and is developing a research program focused on blood coagulation, fibrinolysis, and lipoprotein metabolism. Her innovative research has already led to highly competitive career development grants from ASH and AHA and pilot grant awards from MCW and the National Hemophilia Foundation. Yiliang Chen is a PhD

investigator also recruited in partnership with MCW. He trained in my laboratory and has established a productive independent laboratory focused on innate immunity and macrophage metabolism as they relate to vascular disease. His collaborative work with me and Weiguo Cui led to a multi-PI NIH R01 grant application in June.

Individual accomplishments during the year were numerous. Bonnie Dittel was awarded a highly competitive R01 grant from the NIH Director's Fund for High Risk/High Reward Research based on her discovery of a novel subset of B cells that play a role in autoimmunity. Jieqing Zhu renewed his NIH R01 grant and received a new R01, based on his elegant structural biology approaches to understanding blood cell function. Karen-Sue Carlson obtained an NIH R03 grant to complement her K08 career development award focused on the roles of the bone marrow microenvironment in regulating blood cell formation. Karen also played a key leadership role in 2020 as Chair of the BRI COVID-19 "return to work" task force. Alan Mast received a new multi-PI R01 with an investigator at University of Wisconsin to study abnormal blood coagulation, and Sid Rao is a co-investigator on 2 new NIH grants with collaborators at MCW. Our faculty hold many national and international leadership positions, including service on NIH Study Sections (Dittel, Hoffmeister, Rao), editorial boards of prestigious journals (Falet, Silverstein, P. Newman, Hoffmeister, Malarkannan), and committees for leading professional societies, such as ASH and ISTH (P. Newman, Baumann-Kreuziger, Chrzanowska, Flood, Malec, Mast, Silverstein). Peter Newman filed a patent for his work developing "designer" red blood cells via gene editing and stem cell technologies.

Mentorship is highly valued at Versiti and we are proud of the efforts of our faculty to support the career development of their students and postdoctoral fellows. In 2020 we had 18 postdocs and 28 graduate students in training at the BRI. Weiguo Cui had a particularly notable year in this regard, with Gang Xin moving on to an independent tenure track faculty position at Ohio State University, Ryan Zander obtaining a highly competitive K99/R00 career development award from NIH, and Moujtaba Kasmani obtaining an F30 fellowship from NIH to support his PhD training. Tyce Kearl, a fellow in Subra Malarkannan's lab obtained a faculty appointment at MCW in pediatric oncology and the cell processing lab in the Cancer Center.

None of the successes of the VBRI could have occurred without the active participation and engagement of the many talented scientific and administrative support staff that work every day to keep the train on the tracks. The grants and contracts team led by Greg Wendling, finance team led by Dan Plinska, HR support provided by Amanda Heath, research core team led by Bill Cashdollar, facilities team led by Bill Elmore, and the administrative assistants are simply the best in class. I personally owe a huge debt of gratitude to Tina Koplinski (Director of Research Administration), Peter Newman (VP for Research), Bill Cashdollar, Gil White, Tom Abshire, and my colleagues on the Versiti Executive Leadership Team – particularly CEO Chris Miskel, CFO Tony Watkins, and Chief of Human Resources Jim Weidner – for providing guidance, support, and institutional knowledge during my transition to the interim leadership role at VBRI. Lastly, I thank Shana Maker and Marcia Iverson for their behind-the-scenes efforts to put this annual research report together.

Roy L. Silverstein, MD
Interim Director, Blood Research Institute
Linda and John Mellowes Professor and Chair,
Department of Medicine
Medical College of Wisconsin

Research By The Numbers – 2020

12
New NIH Awards

$24.2 Million
New NIH Awards

$958+ Thousand
Royalty Income

$16 Million
Research Revenues

4
Patents Applied for/Granted

43
Investigators

$470+ Thousand
Average Funding per Investigator

3
New Diagnostic Tests Developed

13
Core Labs

Transfusion Medicine

Transfusion Medicine research has a long history at Versiti, 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, immunologic aspects of blood transfusion, 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
Faculty, Harvard 1964-1970
Started at Versiti: 1970

Research Interests

Immune destruction of red blood cells, white blood cells, and platelets is a major cause of morbidity and mortality. Dr. Aster's work is aimed at understanding the causes of blood cell destruction by autoantibodies, drug-induced antibodies, and antibodies triggered 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. Other work concerns the mechanism whereby transfusion of incompatible blood cells induces auto-antibodies capable of causing thrombocytopenia or hemolytic anemia. Findings made in these and related studies are defining new methods for antibody detection to improve diagnosis and treatment in patients with immune blood cell destruction and improved understanding of the molecular basis for these conditions.

Awards, Honors and Service

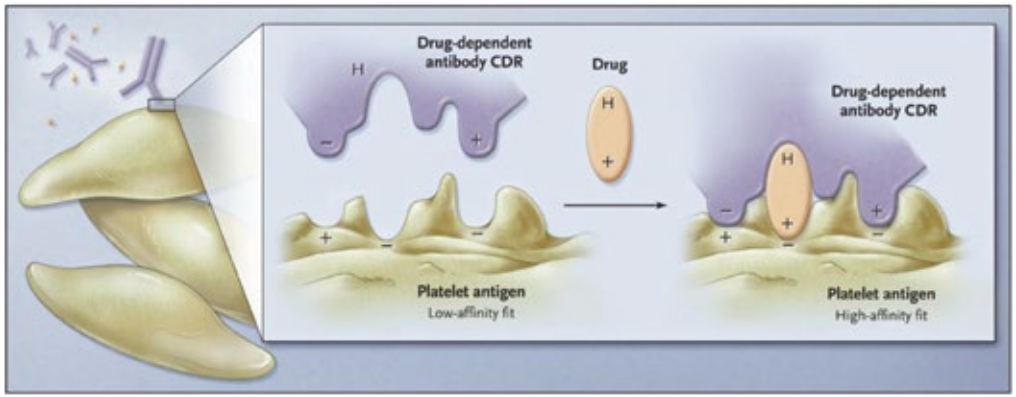
- Founder: GTI Diagnostics (subsidiary of VBRIF)
- Karl Landsteiner Award, American Association of Blood Banks (AABB)
- Henry Stratton Medal for translational research, American Society of Hematology
- Distinguished Service Award, Medical College of Wisconsin (MCW)
- Wallace Coulter Award for career achievement, American Society of Hematology, 2019
- Reviewer for the journals Blood, New England Journal of Medicine, Lancet, Nature, Science Translational Medicine and Transfusion
- Grant reviewer (Transfusion Medicine), Center for Scientific Review, National Institutes of Health

Funding

RO1-HL-13629-47 National Heart Lung and Blood Institute.

Publications

1. Bougie DW, Sutton J, Aster RH. Recapitulation of posttransfusion purpura by cross-strain platelet immunization in mice. Blood Adv. 2020 Jan 28;4(2):287-295. PMID: 31968077
2. Samuelson Bannow BT, Warad D, Jones C, Pechauer S, Curtis BR, Bougie DW, Sharma R, Grill D, Redman M, Khalighi PR, Leger R, Pruthi RK, Chen D, Sabath D, Aster RH, Garcia D, Padmanabhan A. A prospective, blinded study of a PF4-dependent assay for HIT diagnosis. Blood. 2020 Sep 8:blood.2020008195. doi: 10.1182/blood.2020008195. Online ahead of print. PMID: 32898858
3. Moore J, Baer MR, Grover BE, Aster RH, Millstein LS. Moxifloxacin-Induced Thrombocytopenia Mediated by Moxifloxacin-Dependent IgM and IgG Antiplatelet Antibodies: A Case Report. Cureus. 2020 Sep 17;12(9):e10507. doi: 10.7759/cureus.10507. PMID: 33094048



Proposed mechanism by which a sensitizing drug reacts with antibody an enhances its reaction with an epitope on a platelet glycoprotein.

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

Brian Curtis, PhD, D(ABMLI), MT(ASCP) SBB
Director, Platelet & Neutrophil Immunology Lab, Versiti
Senior Director, Diagnostic Hematology
Senior Investigator, Blood Research Institute, Versiti
Assistant Adjunct Professor, Clinical and Translational Science Institute, Medical College of Wisconsin
PhD, University of Wisconsin-Milwaukee
Started at Versiti: 1991

Research Interests

Antibodies specific for antigens carried on blood platelets and white blood cells (neutrophils) cause thrombocytopenia (low platelet count) 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 Versiti 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 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 and prevention of FNAIT.

Awards, Honors and Service

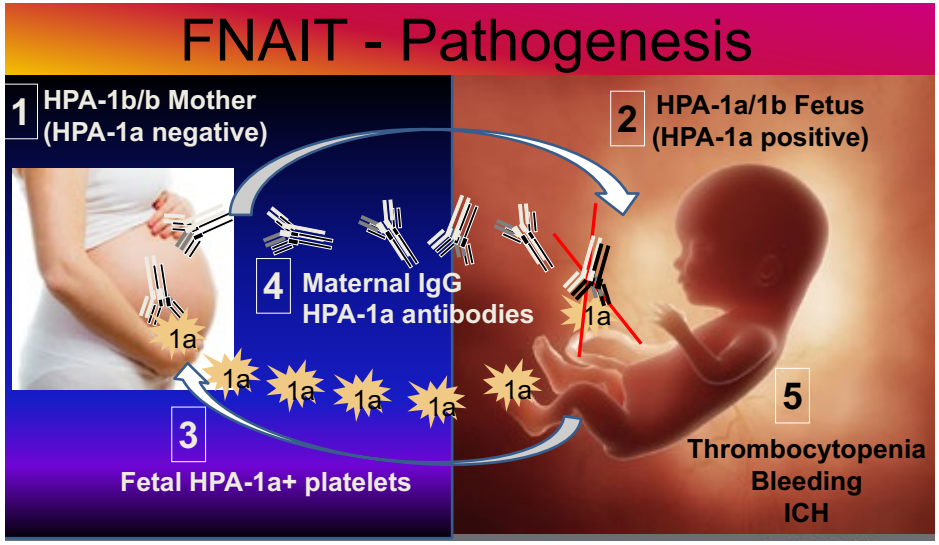
- Member, Editorial Board, Transfusion since 2011
- Member, ISBT International Granulocyte Immunobiology Steering Committee since 2014
- Co-chair, ISBT Platelet Immunobiology Working Party, Quality Subcommittee since 2018
- Member, Editorial Board, Annals of Blood since 2020
- Lecturer, National Institutes of Health Clinical Center, Department of Transfusion Medicine, SBB Technology Program Bethesda, MD since 2020

Funding

"Designer Blood Cells Using CRISPR-Cas 9 Gene Editing." Versiti Moonshot Fund, Versiti (PI).

Publications

1. Kjær M, Geisen C, Akkök ÇA, Wikman A, Sachs U, Bussel JB, Nielsen K, Walles K, Curtis BR, Vidarsson G, Järås K, Skogen B. Strategies to develop a prophylaxis for the prevention of HPA-1a immunization and fetal and neonatal alloimmune thrombocytopenia. Transfus Apher Sci. 2020 Feb;59(1):102712. Review. PMID: 31948915
2. Schmidt AE, Sahai T, Refaai MA, Sullivan M, Curtis BR. Severe Platelet Transfusion Refractoriness in Association with Antibodies Against CD36. Lab Med. 2020 Sep 1;51(5):540-544 PMID: 31925433
3. Narayanan P, Curtis BR, Shen L, Schneider E, Tami JA, Paz S, Burel SA, Tai LJ, Machemer T, Kwoh TJ, Xia S, Shattil SJ, Witztum JL, Engelhardt JA, Henry SP, Monia BP, Hughes SG. Underlying Immune Disorder May Predispose Some Transthyretin Amyloidosis Subjects to Inotersen-Mediated Thrombocytopenia. Nucleic Acid Ther. 2020 Apr;30(2):94-103. PMID: 32043907



Gregory Denomme, PhD

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

Research Interests

Dr. Denomme is Senior Director of Versiti's Immunohematology and Transfusion Service Laboratory, a division of Versiti 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 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 Service

- Petteway-Shepherd Award, North Carolina Association of Blood Bankers
- Working Party member, Red Blood Cell Immunogenetics and Blood Group Terminology
- International Society for Blood Transfusion
- Editorial Board Member, International Journal of Clinical Transfusion Medicine
- Editorial Board Member, Transfusion

Funding

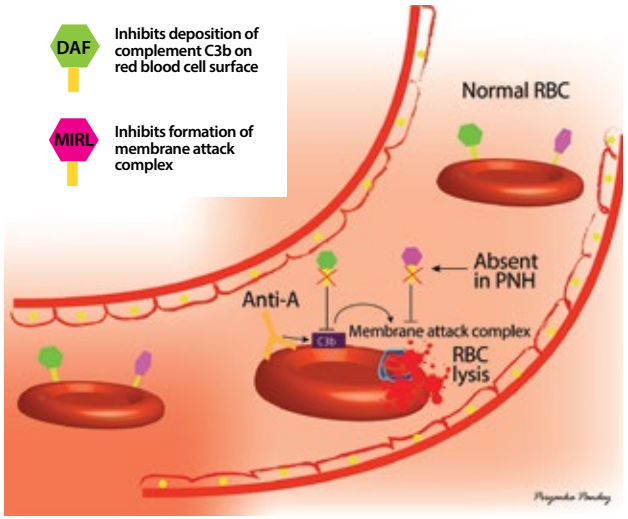
Designer blood cells: CRISPR/cas9 alteration of red blood cell and platelet antigens. G. Denomme (Principal Investigator) B. Curtis, P. Newman (Senior Investigator). Versiti Strategic Funding 2019.

Publications

1. Pandey P, Anani WQ, Pugh T, Gottschall JL, Denomme GA. Complement activating ABO anti-A IgM/IgG act synergistically to cause erythrophagocytosis: implications among minor ABO incompatible transfusions. J Transl Med. 2020 May 28;18(1):216. PMID: 32466782
2. Denomme GA, Anani WQ. ABO titers: harmonization and identifying clinically relevant ABO antibodies. Transfusion. 2020 Mar;60(3):441-443. PMID: 32128831
3. Srivastava K, Albasri J, Alsuhaibani OM, Aljasem HA, Bueno MU, Antonacci T, Branch DR, Denomme GA, Flegel WA. SCAR: The high-prevalence antigen 013.008 in the Scianna blood group system. Transfusion. 2020 Oct 24. doi: 10.1111/trf.16152. Online ahead of print. PMID: 33098316

Antibody mediated lysis of PNH red blood cell clone

(Pandey et al. Blood Advances 2017)



Hervé Falet, PhD

Investigator, Blood Research Institute, Versiti
Assistant Professor, Medical College of Wisconsin
PhD, Paris Descartes University, 1997
Postdoctoral fellowship, Brigham and Women's Hospital and Harvard Medical School, 2001
Started at Versiti: 2016

Research Interests

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

Blood platelets respond to external stimuli by rapidly changing shape and recruiting other platelets. Platelets circulate in blood at a concentration of 150,000-450,000/µl that is maintained by a fine balance between production and clearance. 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 by bone marrow 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 Versiti Blood Research Institute, Dr. Falet 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 Service

- Member, Scientific Committee on Megakaryocytes and Platelets, American Society of Hematology 2019-2022

Funding

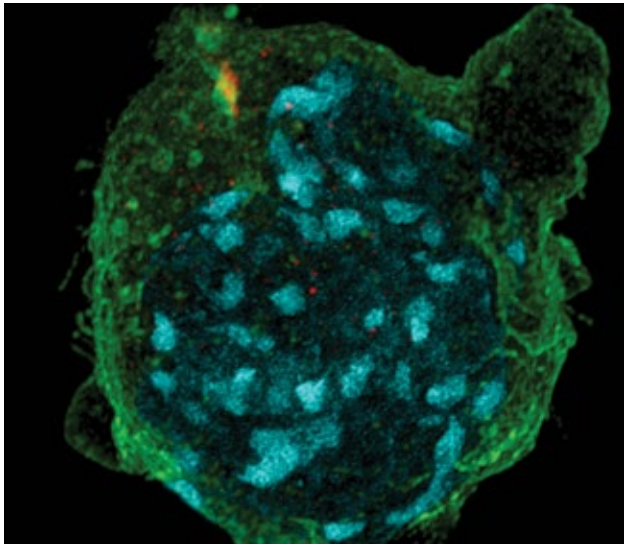
National Institutes of Health R01 HL126743, "Endocytosis in Platelet and Megakaryocyte Biology"

Publications

1. Eaton N, Drew C, Wieser J, Munday AD, Falet H. Dynamin 2 is required for GPVI signaling and platelet hemostatic function in mice. Haematologica. 2020 May;105(5):1414-1423. PMID: 31296575

2. Unsworth AJ, Bye AP, Sage T, Gaspar RS, Eaton N, Drew C, Stainer A, Kriek N, Volberding PJ, Hutchinson JL, Riley R, Jones S, Mundell SJ, Cui W, Falet H, Gibbins JM. Anti-platelet properties of Pim kinase inhibition is mediated through disruption of thromboxane A2 receptor signalling. Haematologica. 2020 May 28:haematol.2019.223529. doi: 10.3324/haematol.2019.223529. Online ahead of print. PMID: 32467143

Structured Illumination Microscopy of PACSIN2 (red), CD41 (green), and DAPI (blue) in midstage mouse megakaryocyte.



Joshua Field, MD, MS

Senior Medical Director, Versiti
Senior Investigator, Blood Research Institute, Versiti
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
Started at Versiti: 2010

Research Interests

Dr. Field is concerned with clinical aspects and optimization of treatment for adults with sickle cell disease (SCD).

Awards, Honors and Service

- American Society of Hematology: Committee on Quality, Washington, DC, 2016-2020

Funding

"A Randomized, Placebo-controlled, Phase 2 Study to Evaluate the Safety and Pharmacodynamics of Once-daily Oral IW-1701 in Patients with Stable Sickle Cell Disease," Cyclerion Pharmaceuticals, Inc., Principal Investigator, 06/01/2018 – present.

"Investigating the Role of the Microbiome and Inflammation in Acute and Chronic Pain in Patients with Sickle Cell Disease," NIH/NHLBI – R01, Co-Investigator, 09/01/2018 – 08/31/2023

"A Phase 3, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Study of Fostamatinib Disodium in the Treatment of Warm Antibody Autoimmune Hemolytic Anemia," Rigel Pharmaceuticals, Inc., Principal Investigator, 06/01/2019 – Present

"The Inflammatory Index as a Biomarker for Pain in Patients with Sickle Cell Disease," MCW/NINDS – R61, Co-Investigator, 02/01/2020 – 07/31/2022

"MACC/EPPIC-Net as a Hub for the HEAL Initiative EPPIC-Net," 1U24NS115679-01, Co-investigator, 09/18/2019 – 03/31/2024

"SHP655 (rADAMTS13): A Phase 1/2 randomized, double-blind, placebo-controlled, multicenter, ascending dose, safety and PK/PD study of SHP655 (rADAMTS13) in sickle cell disease at baseline health and during acute vaso-occlusive crisis," Baxalta US Inc./ Shire, Principal Investigator, 02/01/2020 – End of study

Publications

1. Karafin MS, Simpson P, Field JJ. Chronic Pain Does Not Impact Baseline Circulating Cytokine Levels in Adults with Sickle Cell Disease. Acta Haematol. 2020 May 13:1-6. PMID: 32403100
2. Field JJ, Kassim A, Brandow A, Embury SH, Matsui N, Wilkerson K, Bryant V, Zhang L, Simpson P, DeBaun MR. Phase 2 trial of montelukast for prevention of pain in sickle cell disease. Blood Adv. 2020 Mar 24;4(6):1159-1165. PMID: 32208487
3. Chou ST, Alsawas M, Fasano RM, Field JJ, Hendrickson JE, Howard J, Kameka M, Kwiatkowski JL, Pirenne F, Shi PA, Stowell SR, Thein SL, Westhoff CM, Wong TE, Akl EA. American Society of Hematology 2020 guidelines for sickle cell disease: transfusion support. Blood Adv. 2020 Jan 28;4(2):327-355. PMID: 31985807

Porscha

Porscha Burks was diagnosed with sickle cell disease when she was 4 years old. As she got older, the painful episodes caused by the disease became more frequent and difficult to recover from. In 2011, Porscha met Versiti's Joshua Field, MD, at the Adult Sickle Cell Clinic, where she now receives regular blood transfusions every four weeks that help manage her pain.

Investigators at Versiti Blood Research Institute are on the forefront of blood health advances for sickle cell disease (SCD). Versiti conducts a variety of clinical research in SCD, and Senior Investigator Joshua Field, MD, regularly treats patients at the Adult Sickle Cell Clinic in Milwaukee, Wisconsin.

Jerome Gottschall, MD

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

Research Interests

Dr. Gottschall is a Co-Principal Investigator on the Recipient Epidemiology and Donor Evaluation Study-IV-Pediatrics (REDS IV-P) sponsored by the National Heart Lung and Blood Institute in which Versiti is one of several participating organizations. REDS IV-P includes studies on blood safety, blood availability, and other transfusion-related studies. REDS IV-P utilizes large donor, component and recipient databases to help answer important transfusion-related questions. REDS IV-P is mainly focused on transfusion issues in pediatric patients. Dr. Gottschall also is concerned with the clinical aspects of immune hemolytic anemia and in the status of iron levels in repeat blood donors. An avid athlete, Dr. Gottschall says sports have taught him three critical skills that he uses in his medical work and throughout his life: discipline; persistence; and setting goals.

Awards, Honors and Service

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

Publications

1. Gottschall J, Wu Y, Triulzi D, Kleinman S, Strauss R, Zimrin AB, McClure C, Tan S, Bialkowski W, Murphy E, Ness P; NHLBI Recipient Epidemiology and Donor Evaluation (REDS-III) Study. The epidemiology of platelet transfusions: an analysis of platelet use at 12 US hospitals. Transfusion. 2020 Jan;60(1):46-53. PMID: 31850522
2. Hauser RG, Esserman D, Karafin MS, Tan S, Balbuena-Merle R, Spencer BR, Roubinian NH, Wu Y, Triulzi DJ, Kleinman S, Gottschall JL, Hendrickson JE, Tormey CA; (for the NHLBI Recipient Epidemiology and Donor Evaluation Study-III (REDS-III)). The evanescence and persistence of RBC alloantibodies in blood donors. Transfusion. 2020 Apr;60(4):831-839. PMID: 32061102
3. Townsend M, Kamel H, Van Buren N, Wiersum-Osselton J, Rosa-Bray M, Gottschall J, Rajbhandary S. Development and validation of donor adverse reaction severity grading tool: enhancing objective grade assignment to donor adverse events. Transfusion. 2020 Jun;60(6):1231-1242. PMID: 32452048

Matthew Karafin, MD

Medical Director, Medical Sciences Institute, Versiti
Associate Investigator, Blood Research Institute, Versiti
Associate 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
MS, Medical College of Wisconsin, Milwaukee, WI, 2015
Started at Versiti: 2012

Research Interests

Dr. Karafin's research interests include the use of red cell transfusion for patients with sickle cell disease, etiology and prevention of red cell alloimmunization, 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 Service

- Member, American Society for Apheresis (ASFA): Chair, Education Committee
- Member, American Association of Blood Banks (AABB): Chair, Molecular Testing Accreditation Program Unit Committee
- Member, College of American Pathologists (CAP)
- Member, American Society for Clinical Pathology (ASCP)
- Member, Alpha Omega Alpha (AOA)

Funding

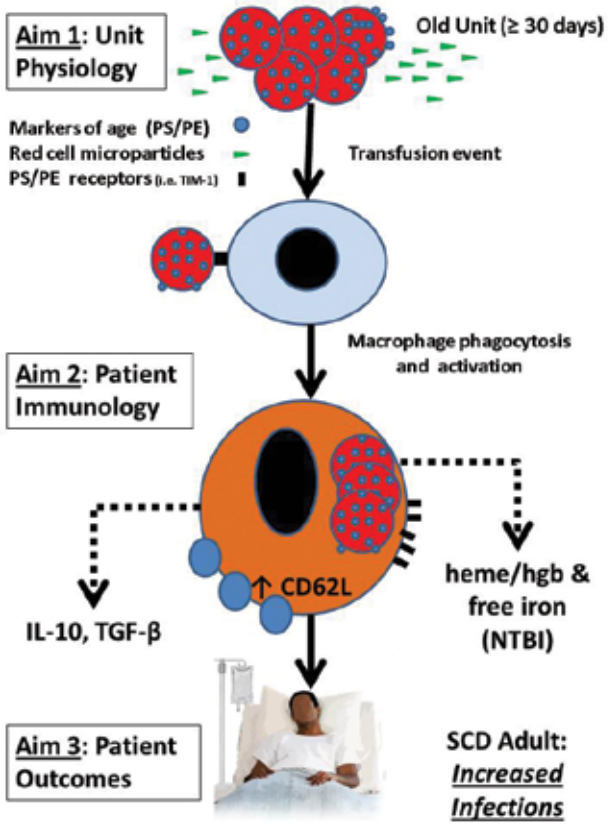
HHSN26819HB00003R (Mast) 04/01/2019 – 03/31/2026 NIH/NHLBI $1,000,038 "Recipient Epidemiology and Donor Evaluation Study-IV-Pediatric (REDS-IV-P)" (Co-I)

1R01HL148151-01 (MPI: Spitalnik, D'Alessandro, Karafin, Zimring) 09/25/2019 – 08/31/2023 NIH/NHLBI $173,014 (Versiti) "The Impact of Oxidative Stress on Erythocyte Biology" (Co-PD/PI)

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. Karafin MS, Simpson P, Field JJ. Chronic Pain Does Not Impact Baseline Circulating Cytokine Levels in Adults with Sickle Cell Disease. Acta Haematol. 2020 May 13:1-6. PMID: 32403100
2. Karafin MS, Hendrickson JE, Kim HC, Kuliya-Gwarzo A, Pagano MB, Perumbeti A, Shi PA, Tanhehco YC, Webb J, Wong E, Eichbaum Q. Red cell exchange for patients with sickle cell disease: an international survey of current practices. Transfusion. 2020 Jul;60(7):1424-1433 PMID: 32583456
3. Hauser RG, Esserman D, Karafin MS, Tan S, Balbuena-Merle R, Spencer BR, Roubinian NH, Wu Y, Triulzi DJ, Kleinman S, Gottschall JL, Hendrickson JE, Tormey CA; (for the NHLBI Recipient Epidemiology and Donor Evaluation Study-III (REDS-III)). The evanescence and persistence of RBC alloantibodies in blood donors. Transfusion. 2020 Apr;60(4):831-839. PMID: 32061102



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 Versiti and other institutions to understand the role that sugars play in biology.

Karin Hoffmeister, MD

Hauske Family Endowed Chair in Glycobiology
Senior Investigator, Blood Research Institute, Versiti
Professor of Biochemistry, Medical College of Wisconsin
Director of Translational Glycomics Center
MD, Technical University of Aachen, Aachen, Germany, 1993
Doctor of Medicine, Doctoral Research Program, Technical University of Aachen, 1995
Started at Versiti: 2016

Research Interests

Dr. Hoffmeister investigates how glycans regulate hematopoiesis and end-effector blood cells. 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 and the bone marrow niche environment. 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. Dr. Hoffmeister's 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 Service

- Member, Hemostasis and Thrombosis Study Section
- Member, Transfusion Medicine Study Section, special panel
- Member, American Society of Hematology
- Editorial Board, Blood Advances
- Editorial Board, Journal of Thrombosis and Hemostasis

Funding

RO1 HL089224-10 "Carbohydrate Mediated Platelet Clearance"

3R01 HL089224 14S1 "Carbohydrate Mediated Platelet Clearance"

R01 HL089224-04 "VWF- Mechanisms of Regulation"

K12 HL141954-01 "Glycans in Blood Hematopoiesis and Disease"

1P01 HL151333 01A1 "Molecular and Clinical Glycobiology of the Bone Marrow Environment"

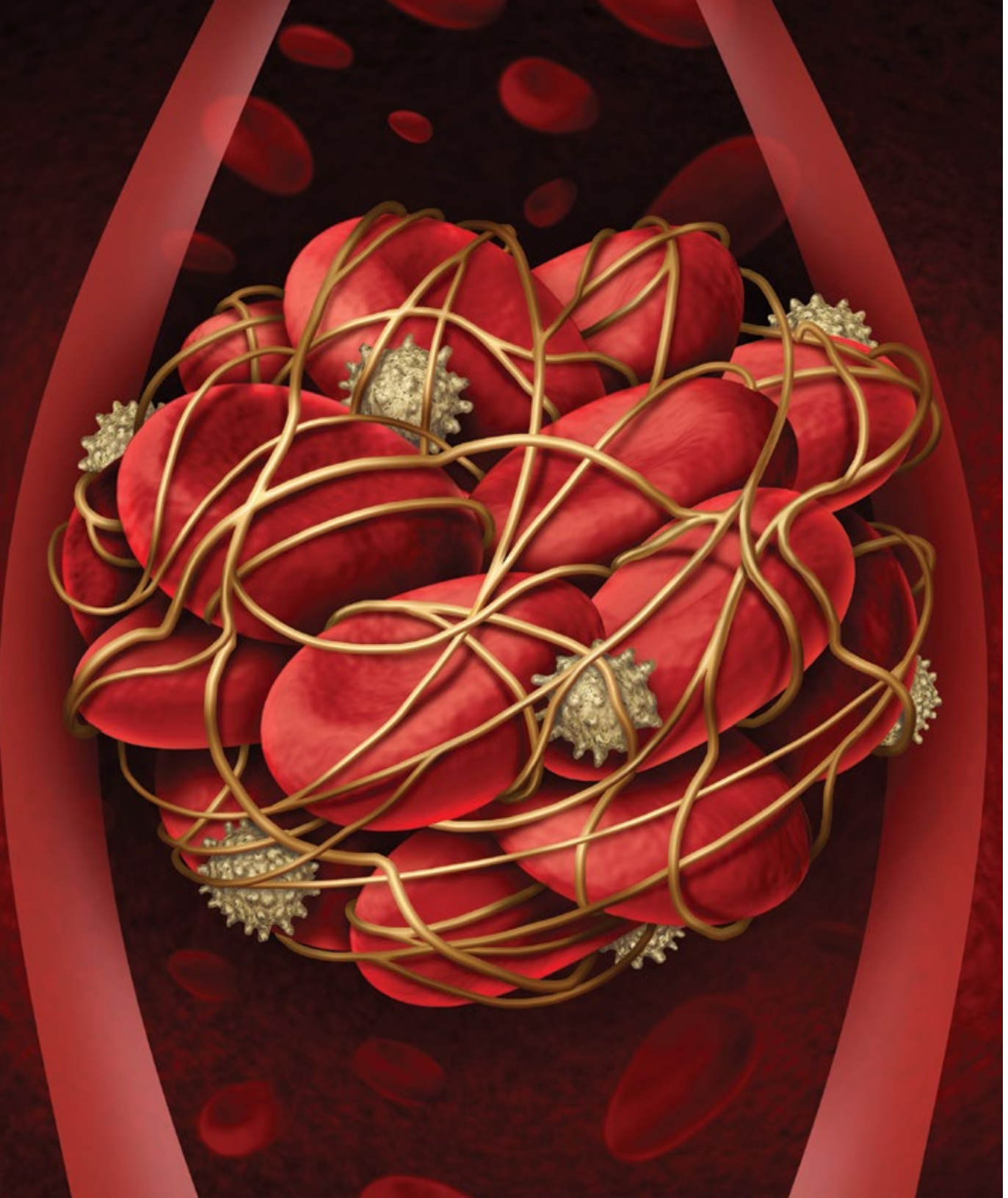
R01 AI140736 03S1 (Lau, PI), Hoffmeister Co-PI, "ST6GAL-1 Sialyltransferase in Inflammation"

Versiti Moonshot Funding Hoffmeister PI - ITP

Versiti Moonshot Funding Hoffmeister PI – Hemolysin Project

Publications

1. Giannini S, Lee-Sundlov MM, Rivadeneyra L, Di Buduo CA, Burns R, Lau JT, Falet H, Balduini A, Hoffmeister KM. β4GALT1 controls β1 integrin function to govern thrombopoiesis and hematopoietic stem cell homeostasis. Nat Commun. 2020 Jan 17;11(1):356. PMID: 31953383
2. Lee-Sundlov MM, Stowell SR, Hoffmeister KM. Multi-faceted Role of Glycosylation in Transfusion Medicine, Platelets and Red Blood Cells. J Thromb Haemost. 2020 Jul;18(7):1535-1547. PMID: 32350996
3. Anani WQ, Ashwood HE, Schmidt A, Burns RT, Denomme GA, Hoffmeister KM. Predictive modeling of complex ABO glycan phenotypes by lectin microarrays. Blood Adv. 2020 Aug 25;4(16):3960-3970. PMID: 32822483
4. DeHelian DJ, Gupta S, Wu J, Thorsheim CL, Estevez B, Cooper M, Litts K, Lee-Sundlov MM, Hoffmeister K, Poncz M, Ma P, Brass LF. RGS10 and RGS18 differentially limit platelet activation, promote platelet production, and prolong platelet survival. Blood. 2020 Oct 8;136(15):1773-1782. PMID: 32542378
5. Di Buduo CA, Giannini S, Abbonante V, Rosti V, Hoffmeister K, Balduini A. Increased β4GALT1 expression associates with platelet surface galactosylation and thrombopoietin plasma levels in MPNs. Blood. 2020 Nov 25:blood.2020007265. doi: 10.1182/ blood.2020007265. Online ahead of print. PMID: 33238000



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, Versiti
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/Oncology, University of Colorado Health Science Center, 1985-88
Started at Versiti: 2009

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 recently completed a study funded by the NIH entitled "Comparative Effectiveness in the Diagnosis of VWD" which focused on new diagnoses of VWD and how to better define this bleeding disorder from a clinical, laboratory and molecular basis. Currently, he is Other Significant Contributor/Key Personnel for the Administrative Core A (Clinical Acquisition Core) for Dr. Robert Montgomery's PPG; "Zimmerman Program on the Biology of VWD"

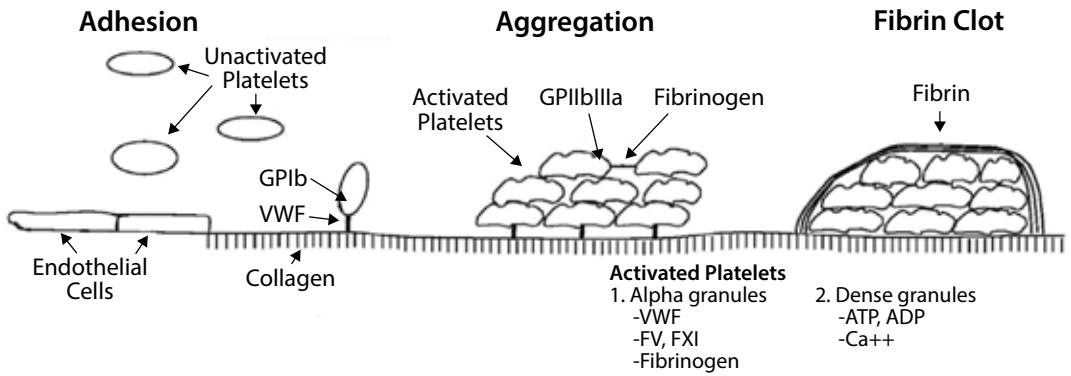
Awards, Honors, and Service

- Distinguished Emeritus Member, American Society of Hematology (ASH) and Member, International Society of Thrombosis and Haemostasis (ISTH)
- Past President, Hemostasis and Thrombosis Research Society (HTRS)
- Past ASH Committee on Training
- Past Chair, American Thrombosis and Hemostasis Network (ATHN)
- Past Co-Chair, SSC Scientific Subcommittee on VWF, ISTH
- Best Doctors in America 2009-2018
- Clinical Translational Sciences Institute (CTSI) SE WI KL2 and Pilot Grant Review Committees
- CTSI of SE WI Board of Directors
- Versiti Blood Research Institute NIH T32 Training Grant Steering Committee
- Executive Steering Committee, Kids-DOTT 1 R01HL130048 (R01/U01)
- Co-Chair, Hematology Focused Fellowship Steering Committee; Committee on Training, ASH

Publications

1. Gill JC, Conley SF, Johnson VP, Christopherson PA, Haberichter SL, Diaz CD, Strong TC, Zhang J, Simpson P, Abshire TC, Montgomery RR, Flood VH. Low VWF levels in children and lack of association with bleeding in children undergoing tonsillectomy. Blood Adv. 2020 Jan 14;4(1):100-105. PMID: 31905240
2. DiGiandomenico S, Christopherson PA, Haberichter SL, Abshire TC, Montgomery RR, Flood VH, and the Zimmerman Program Investigators. Laboratory variability in the diagnosis of type 2 VWD variants. J Thromb Haemost. 2020 Nov 10. doi:10.1111/jth.15129. [Epub ahead of print] PMID: 33049112

Platelet-Vessel Interaction



Lisa Baumann-Kreuziger, MD, MS

Medical Director, Medical Sciences Institute; Associate Investigator, Blood Research Institute, Versiti
Associate Professor of Medicine, Division of Hematology/Oncology, Medical College of Wisconsin
MD, University of Wisconsin School of Medicine and Public Health, 2006
Started at Versiti: 2013

Research Interests

Venous thromboembolism occurs in more than a half million Americans every year. Anticoagulation after venous thromboembolism (VTE) can prevent recurrence but is associated with a risk of bleeding. Dr. Baumann-Kreuziger has developed a research network of >100 clinical researchers called the Venous thromboEmbolism Network US (VENUS). Versiti has supported the development of a coordinating center to allow clinical research in VTE to be performed faster, answer important questions, and help patients with VTE. Since March 2020, her research has focused on coronavirus-19 (COVID-19), anticoagulation, and thrombosis. Dr. Baumann Kreuziger has been involved in the American Society of Hematology Frequently Asked Questions, the NIH COVID-19 Guideline panel, and the Accelerating COVID-19 Therapeutic Interventions and Vaccines-4 Antithrombotic trials. Lastly, Dr. Baumann Kreuziger is involved with the Recipient Epidemiology and Donor Evaluation-III study.

Awards, Honors and Service

- American Society of Hematology Thrombophilia Guideline panel
- American College of Chest Physicians Antithrombotic Therapy for VTE Disease Guideline Panel Member
- NIH COVID-19 Guideline Panel

Funding

"Coagulopathy of COVID-19: A Pragmatic Randomized Controlled Trial of Therapeutic Anticoagulation versus Standard Care as a Rapid Response to the COVID-19 Pandemic (RAPID COVID COAG)" Investigator-initiated trial of anticoagulation in patients with COVID-19. The award allowed Versiti to be the United States Coordinating Center for the RAPID trial. International Network of VENous Thromboembolism Clinical Research Networks (INVENT-VTE) (Co-I/Site-PI/US Coordinating Center PI) 9/2020 – present

"ACTIV-4 Inpatient Platform" Versiti is the coordinating center for the RAPID network of 12 hospitals for the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) Inpatient trial investigating an approach aimed at preventing clotting events and improving outcomes in hospitalized COVID-19 patients. We are responsible for site initiation, study start-up, regulatory submission, and site payment. ACTIV public-private partnership (Research Director for the Coordinating Center)

"Recipient Epidemiology and Donor Evaluation Study III" (REDS III), Contract NIH/NHLBI: HHSN268201100003I (PI: Mast) 03/15/2011 – 03/14/2020.

Publications

1. Rosovsky RP, Sanfilippo KM, Wang TF, Rajan SK, Shah S, Martin KA, Ni Áinle F, Huisman M, Hunt BJ, Khan SR, Kevane B, Lee AYY, McLintok C, Baumann Kreuziger L. Anticoagulation Practice Patterns in COVID-19: A Global Survey. Res Pract Thromb Haemost. 2020 Jul 9;4(6):969-83. PMID: 32838111
2. Kreuziger LB, Edgren G, Hauser RG, Zaccaro D, Kiss J, Westlake M, Brambilla D, Mast AE. Red Blood Transfusion Does Not Increase Risk of Venous or Arterial Thrombosis.Am J Hematol. 2020 Oct 29. doi: 10.1002/ajh.26038. [Epub ahead of print] PMID: 33119918
3. Aberg J, Adimora A, Baker J, Baumann Kreuziger L, et al. Information on COVID-19 Treatment, Prevention, and Research. National Institutes of Health. https://www.covid19treatmentguidelines.nih.gov/. 2020.

Brian Branchford, MD

Associate Medical Director, Medical Sciences Institute, Versiti
Associate Investigator, Blood Research Institute, Versiti
Assistant Professor, Pediatric Hematology/Oncology/Bone Marrow Transplant,
Medical College of Wisconsin
MD, University of Wisconsin-Madison School of Medicine and Public Health, 2005
Pediatric Fellowship, University of Colorado School of Medicine and Children's Hospital Colorado, 2012
Started at Versiti: 2020

Research Interests

Thromboinflammation, platelet activation signaling, murine thrombosis models, hospital-acquired venous thromboembolism (risk factors and prevention strategies).

Awards, Honors and Service

- American Society of Hematology: Translational Research Training in Hematology 2010-2011
- National Institutes of Health Loan Repayment Program: 2011-2020
- American Society of Hematology Abstract Achievement Award: 2011, 2012, 2015
- Director of the Board, Hemostasis and Thrombosis Research Society: 2017-2020
- Member, International Society of Thrombosis and Haemostasis, Scientific and Standardization Committee (Pediatric and Neonatal Hemostasis and Thrombosis)
- Working Group for Pediatric Hospital-Acquired Venous Thromboembolism Prevention/Risk Scores: 2014-2020
- Member, Clinical Genome Resource Hemostasis/ Thrombosis Clinical Domain
- Working Group for Platelet Disorders: 2019-2020
- Member, Executive Committee (US Representative) International Pediatric Thrombosis Network
- Member, American Society of Hematology

Funding

NIH K08 Mentored Research Award (K08 HL146941-01): The role of inflammation in platelet activation and thrombosis (PI)

Publications

1. Loi M, Branchford B, Kim J, Self C, Nuss R. COVID-19 anticoagulation recommendations in children. Pediatr Blood Cancer. 2020 Sep;67(9):e28485. doi: 10.1002/pbc.28485. PMID: 32558124
2. Park I, Johnson LK, Cox A, Branchford BR, Di Paola J, Bublil EM, Majtan T. Hypermethioninemia leads to fatal bleeding and increased mortality in a Transgenic I278T Mouse Model of Homocystinuria. 2020 Jul 24;8(8):244. doi: 10.3390/biomedicines8080244.PMID: 32722248.
3. Mahajerin A, Jaffray J, Branchford B, Stillings A, Krava E, Young G, Goldenberg NA, Faustino EVS. Comparative validation study of risk assessment models for pediatric hospital-acquired venous thromboembolism. J Thromb Haemost. 2020 Mar;18(3):633-641. PMID: 31808292

Juliana Perez Botero, MD

Medical Director Molecular Oncology and Genetics Laboratory, Versiti Diagnostic Labs
Associate Investigator, Blood Research Institute, Versiti
Assistant Professor of Medicine, Division of Hematology/Oncology, Medical College of Wisconsin
MD, Universidad de los Andes, Bogotá, Colombia 2010
Started at Versiti: 2017

Research Interests

Inherited disorders affecting the components of the blood, blood vessel and immune system are a heterogenous group of rare conditions with overlapping clinical manifestations. Establishing an accurate and timely diagnosis of these conditions is challenging, not only because of their specific clinical characteristics, but the lack of familiarity in clinicians approaching these patients due to their very low incidence.

Dr. Perez Botero's research interest is the development of clinical laboratory assays that more effectively diagnose and predict the clinical course of patients with inherited and acquired non-malignant hematologic conditions, in particular, platelet disorders. One of the main goals of her research is to create systems that provide clinically meaningful and actionable recommendations that enhance the scope of practice of general clinicians, as well as making access to genetic data, and its correlation with clinical phenotypes, widely available.

Awards, Honors and Service

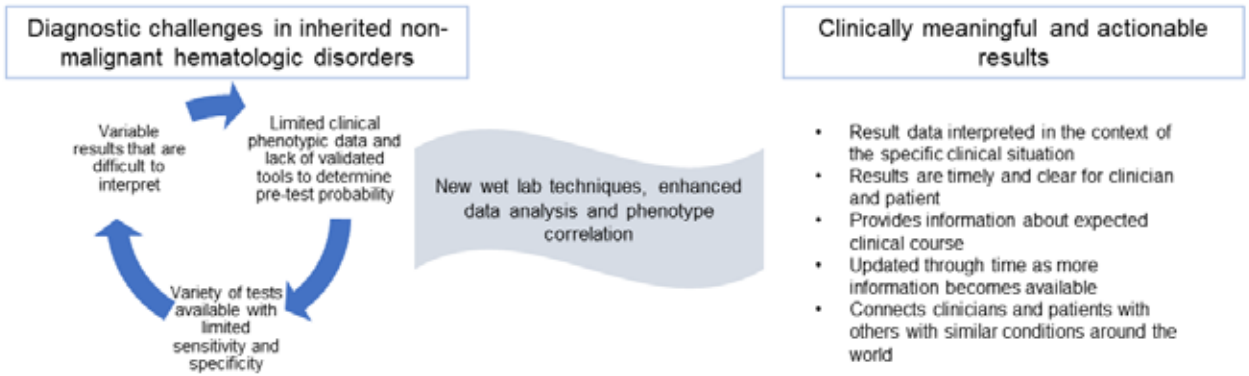
- Member, Platelet Disorders Expert Panel, part of ClinGen (Clinical Genome Resource) since 2018
- Member, Hemostasis and Thrombosis Gene Curation Expert Panel, part of ClinGen (Clinical Genome Resource) since 2019

Funding

"Clinical glycomics for the development of a novel ITP diagnostic test," Versiti Moonshot Fund, Versiti (Co-PI)

Publications

1. Botero JP, Lee K, Branchford BR, et al. Glanzmann thrombasthenia: genetic basis and clinical correlates. Haematologica. 2020 Apr;105(4):888-894. PMID: 32139434
2. McBane R, Wysokinski WE, Le-Rademacher JG, Zemla T, Ashrani A, Tafur A, Perepu U, Anderson D, Gandabolu K, Perez Botero J, Leon-Ferre RA, Henkin S, Lenz CJ, Houghton DE, Vishnu P, Loprinzi CL. Apixaban and Dalteparin in Active Malignancy Associated Venous Thromboembolism: The ADAM VTE Trial. (2019). J Thromb Haemost. 2020 Feb;18(2):411-421.



Yiliang Chen, PhD

Assistant Investigator, Blood Research Institute, Versiti
Assistant Professor, Medical College of Wisconsin
PhD, University of Toledo, 2009
Started at Versiti: 2020

Research Interests

Dr. Chen is interested in a chronic inflammatory disease called atherosclerosis, which is the leading cause of death in the developed countries. Atherosclerosis is characterized by atherosclerotic plaques in the medium and large arteries and the major components of the plaques are lipid-laden innate immune cells called macrophages. Using a variety of genetically modified mice as in vivo animal models together with in vitro cell culture models and many biochemical techniques, the Chen lab studies the molecular mechanisms underlying the pro-atherogenic functions of the macrophages.

The Chen lab also uses novel state-of-the-art technologies some of which include single cell RNA sequencing, high resolution confocal microscopy, Seahorse extracellular flux metabolic assays and gas chromatography and mass spectrometry (GC-MS) to explore cell expression networks that are linked to immune activation and metabolic status.

Awards, Honors and Service

- Member of the American Heart Association
- Editorial Board Member, Frontiers in Cardiovascular Medicine

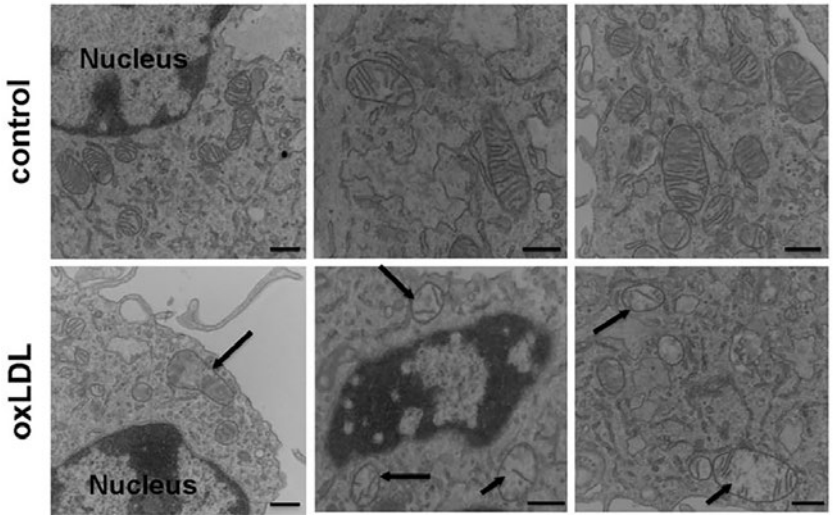
Funding

Scientist Development Grant, American Heart Association

Startup funding, Medical College of Wisconsin

Publications

1. Zhang J, Li X, Yu H, Larre I, Dube P, Kennedy DJ, Tang WHW, Westfall K, Pierre SV, Xie Z, Chen Y. Regulation of Na/K-ATPase expression by cholesterol: isoform specificity and the molecular mechanism. Am J Physiol Cell Physiol. 2020 Dec 1;319(6):C1107-C1119. PMID: 32997514
2. Wang X, Cai L, Xie JX, Cui X, Zhang J, Wang J, Chen Y, Larre I, Shapiro JI, Pierre SV, Wu D, Zhu G-Z, Xie Z. A caveolin binding motif in Na/K-ATPase is required for stem cell differentiation and organogenesis in mammals and C. elegans. Sci Adv. 2020 May 27;6(22):eaaw5851. PMID: 32537485
3. Sodhi K, Denvir J, Liu J, Sanabria JR, Chen Y, Silverstein R, Xie Z, Abraham NG, Shapiro JI. Oxidant-Induced Alterations in the Adipocyte Transcriptome: Role of the Na,K-ATPase Oxidant Amplification Loop. Int J Mol Sci. 2020 Aug;21(16): 5923. PMID: 32824688



"Macrophage mitochondria networks" as assessed by confocal microscopy. Oxidized LDL (oxLDL) significantly alters the mitochondria phenotype and leads to metabolic switch, which facilitates chronic inflammation during atherosclerosis. (Circulation Research, 2019)

Magdalena Chrzanowska, PhD, FAHA

Investigator, Blood Research Institute, Versiti
Associate 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
Started at Versiti: 2005

Research Interests

The complications of cardiovascular disease remain major killers of the American population. The maintenance of normal cardiovascular function is critically dependent on vascular endothelial cells (ECs) that line blood vessels. ECs perform many critical functions, such as preventing leakage of blood cells and plasma from the circulation, preventing inappropriate blood clotting, and regulating selective transfer of cells and substances into and out of blood vessels. Importantly, ECs respond to blood flow and inflammatory signals in their environment by secreting active substances to maintain normal organ function and correct blood pressure.

Dr. Chrzanowska's research is focused on understanding molecular mechanisms underlying EC functions, and the role of a protein, designated Rap1, in regulating these functions. Her recent research revealed new mechanisms through which ECs respond to the flow of blood and inflammatory signals and how defects in these mechanisms contribute to atherosclerosis in an in vivo disease model. These are the first necessary steps in developing new strategies to prevent the progression of atherosclerosis. Importantly, Dr. Chrzanowska's studies identified potential novel therapeutic targets for treatment of cardiovascular disease.

Awards, Honors and Service

- American Heart Association, ATVB Council – 2020 AHA Scientific Sessions Programming Committee
- NIH Vascular Cell and Molecular Biology Study Section – 2015-2019, ad hoc 2020
- Frontiers in Cardiovascular Medicine, Lipidology – Associate Editor
- Frontiers in Cardiovascular Medicine, Atherosclerosis and Vascular Medicine – Review Editor
- North American Vascular Biology Organization, Membership Committee

Funding

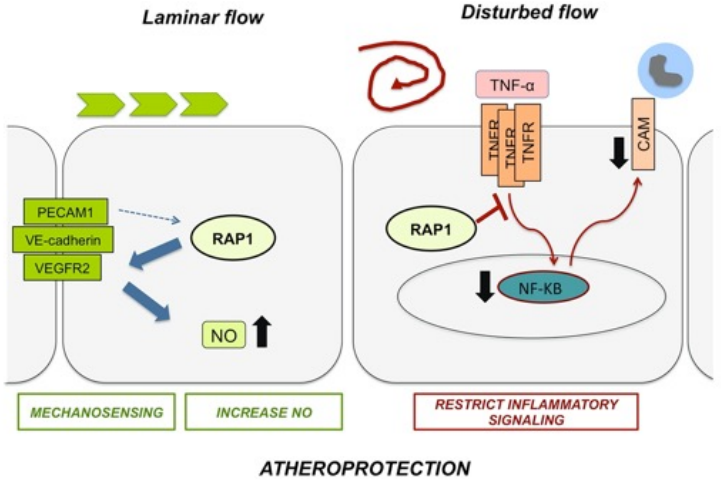
NIH/NHLB R01 - HL111582-07 Chrzanowska-Wodnicka, M, (PI) 4/16/12 - 6/30/20 "Rap1 in endothelial homeostasis"

Publications

1. Kosuru R, Chrzanowska M. Integration of Rap1 and Calcium Signaling. Int J Mol Sci. 2020 Feb 27;21(5). Review. PMID: 32120817

2. Singh B, Kosuru R, Lakshmikanthan S, Sorci -Thomas M, Sparapani R, Vasquez-Vivar J, Zhang DX, Chrzanowska M. Endothelial Rap1 (Ras-association proximate 1) restricts inflammatory signaling to protect from the progression of atherosclerosis. Arterioscler Thromb Vasc Biol. 2020 Dec 3; doi: 10.1161/ATVBAHA.120.315401 [Epub ahead of print] PMID: 33267664.

Via discrete mechanisms, endothelial Rap1 protects from atherosclerosis in the presence and absence of laminar flow. In response to laminar flow, Rap1 promotes nitric oxide (NO) release via its mechanosensing function. In the absence of laminar flow, or in the presence of disturbed flow, Rap1 restricts transcription factor NF-κB activation and proinflammatory gene expression in endothelium.



Veronica H. Flood, MD

Associate Professor of Pediatrics, Division of Hematology/Oncology, Medical College of Wisconsin
Associate Medical Director, Comprehensive Center for Bleeding Disorders, Medical Sciences Institute
Associate Investigator, Blood Research Institute, Versiti
MD, Tufts University School of Medicine, 1999
Started at Versiti: 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.

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 Service

- Standing member, NIH Study Section, National Heart, Lung, and Blood Institute, Mentored Patient-Oriented Research review panel
- Chair, Mentored Research Award Committee, Hemostasis and Thrombosis Research Society
- Clinical Chair, Von Willebrand Disease Management Guideline Panel, ASH/ISTH/NHF/WFH

Funding

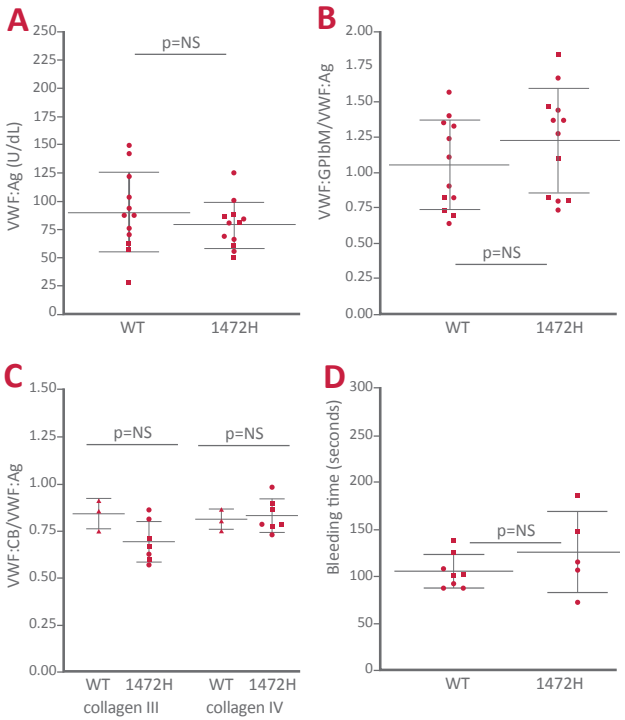
R01 HL126810 "Mechanism of Type 4 Collagen Interactions with Von Willebrand Factor" (PI)

Publications

1. *Lohmeier HK, Slobodianuk TL, Kanaji S, Haberichter SL, Montgomery RR, Flood VH Von Willebrand Factor Variant D1472H Has No Effect in Mice with Humanized VWF-Platelet Interactions. Blood Advances 4(7):4065-4068, 2020.
2. Gill JC, Conley SF, Johnson VP, Christopherson PA, Haberichter SL, Diaz CD, Strong TC, Zhang J, Simpson P, Abshire TC, Montgomery RR, Flood VH. Low VWF Levels in Children and Lack of Association with Bleeding in Children Undergoing Tonsillectomy. Blood Advances 4(1):100-105, 2020.
3. Flood VH, Slobodianuk TL, Keesler D, Lohmeier HK, Fahs S, Zhang L, Simpson P, Montgomery RR. Von Willebrand Factor Binding to Myosin Assists in Coagulation. Blood Advances 4(1):174-180, 2020.

Figure below: 1472H mice display normal VWF. Panel A shows normal VWF expression. Panel B shows normal platelet GPIbα binding. Panel C shows normal collagen binding with types III and IV collagen. Panel D shows no difference in tail bleeding times.

Squares represent male mice and circles represent female mice. Triangles represent mice for whom gender was not known.



Kenneth Friedman, MD

Senior Medical Director Hemostasis Reference Lab, Diagnostic Labs, Versiti
Investigator, Blood Research Institute, Versiti
Professor of Internal Medicine and Pathology, Medical College of Wisconsin
MD, SUNY Upstate Medical University, Syracuse, NY 1980
Started at Versiti: 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 because 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 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 Service

- Medical Director, Hemophilia Outreach Center, Green Bay, WI
- Medical Director of the Apheresis Center for the NMDP site in Milwauke

Publications

1. Irani MS, Sanchez F, Friedman K. Caplacizumab for treatment of thrombotic thrombocytopenic purpura in a patient with anaphylaxis to fresh-frozen plasma. Transfusion. 2020 Aug;60(8):1666-1668. PMID: 32358818
2. MacQuarrie KL, Williams O, Friedman KD, Bercovitz RS. Compound heterozygous protein C variants undetectable by common laboratory testing causing purpura fulminans after the neonatal period. Am J Hematol. 2020 Dec;95(12):1616-1621.PMID: 32833261

Alan

At 5 years old, Alan was diagnosed with hemophilia. Doctors did not expect him to live much longer than 40 years. He was eventually introduced to Versiti's Comprehensive Center for Bleeding Disorders (CCBD) and has been able to persevere past hemophilia. Now Alan is in his 80's, living a happy and healthy life with his wife Evelyn.

"I wouldn't be alive today without the CCBD."

Sandra Haberichter, PhD

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

- Member, American Society of Hematology 2020
- Chair, ISTH SSC scientific committee on von Willebrand Factor 2020
- Member, International Society on Thrombosis and Haemostasis 2020
- Guideline panel member, ASH ISTH NHF WFH Guidelines on Diagnosis of VWD

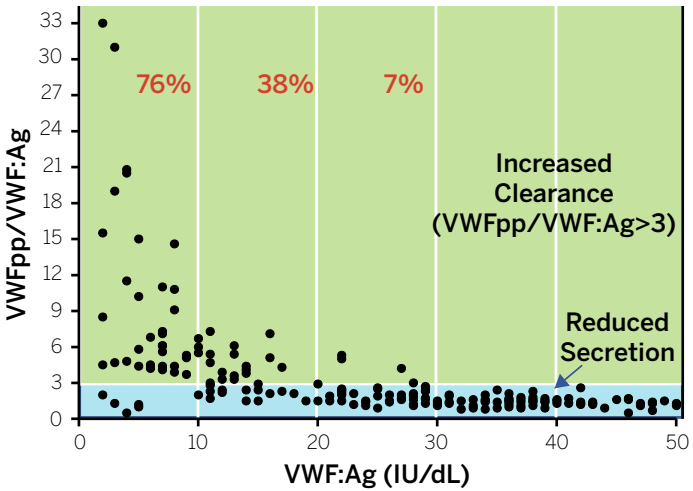
Funding

R01 HL136430 "VWF- Mechanisms of Regulation"

P01 HL144457 Project 2 – "Molecular Impact of Carbohydrates on VWF Biology"

Publications

1. Kalot MA, Al-Khatib M, Connell NT, Flood V, Brignardello-Petersen R, James P, Mustafa RA, VWD Working Group (Haberichter S, et al). An international survey to inform priorities for new guidelines on von Willebrand disease. Haemophilia. 2020 Jan;26(1):106-116. PMID: 31769905
2. Gill JC, Conley SF, Johnson VP, Christopherson P, Haberichter SL, Diaz CD, Strong TC, Zhang J, Simpson PM, Abshire TC, Montgomery RR, Flood VH. Low VWF Levels in Children and Lack of Association with Bleeding in Children Undergoing Tonsillectomy. Blood Advances. 2020 Jan 14;4(1):100–105. PMID:31905240.
3. Lohmeier HK, Slobodianuk TL, Kanaji S, Haberichter SL, Montgomery RR, Flood VH. von Willebrand Factor Variant D1472H Has No Effect in Mice with Humanized VWF-Platelet Interactions. Blood Adv. 2020 Sep 8;4(17):4065-4068. PMID: 32870970



Increased VWF clearance is 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

Associate Investigator, Medical Sciences Institute/Blood Research Institute, Versiti
Associate Professor, Department of Pediatrics and Medicine, Medical College of Wisconsin
PhD, Medical College of Wisconsin, 1998
MD, Medical College of Wisconsin, 1999
Started at Versiti: 2013

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 from these studies are 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 procoagulant platelets might work to prevent bleeding in patients with severe hemophilia.

Awards, Honors and Service

- 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. Darling TK, Schenk MP, Zhou CC, Maloba FM, Mimche PN, Gibbins JM, Jobe SM, Lamb TJ. Platelet α-granules contribute to organ-specific pathologies in a mouse model of severe malaria. Blood Adv. 2020 Jan 14;4(1):1-8. PMID: 31891656
2. Jobe S. A dastardly, deadly duo in stroke. Blood. 2020 Feb 6;135(6):395-396. PMID: 32027749

Yan-Qing Ma, PhD

Investigator, Blood Research Institute, Versiti
PhD, Chinese Academy of Sciences, 2004
Started at Versiti: 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 αIIb/β3 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 αIIb/β3 during platelet activation. A particular goal is to define how kindlin-3, a key integrin activator in platelets, coordinates with 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, the most common pathology of cardiovascular disease.

Awards, Honors and Service

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

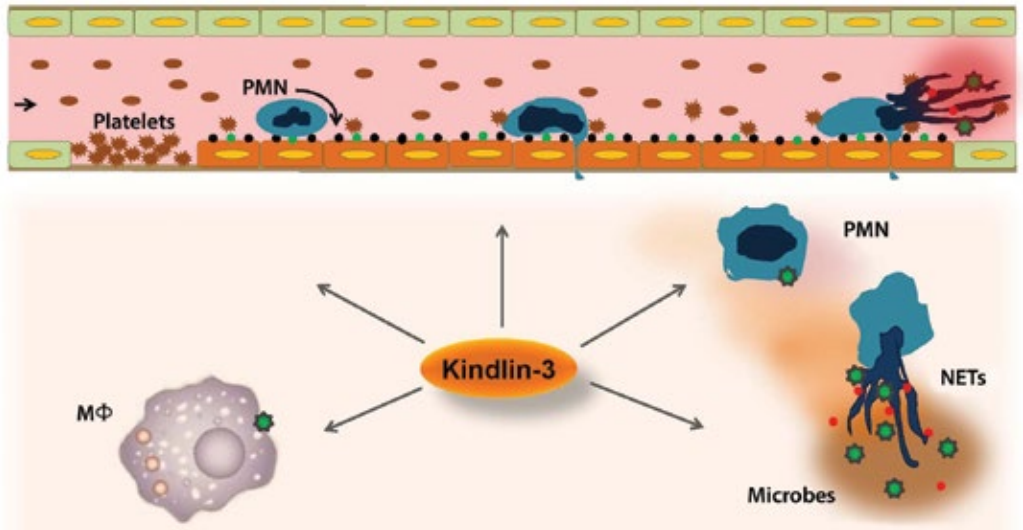
Funding

R01 HL131654 "Kindlin-3 Signaling in Blood Cells"

Publications

1. Sun J, Xiao D, Ni Y, Zhang T, Cao Z, Xu Z, Nguyen H, Zhang J, White GC, Ding J, Ma YQ#, Xu Z#. Structure basis of the FERM domain of kindlin-3 in supporting integrin αIIbβ3 activation in platelets. Blood Adv. 2020 Jul 14; 4(13):3128-3135.

Kindlin-3 signaling in platelets and leukocytes



Lynn Malec, MD, MSc

Medical Director, Comprehensive Center for Bleeding Disorders, Medical Sciences Institute
Associate Investigator, Blood Research Institute, Versiti
Associate Professor of Medicine, Division of Hematology/Oncology, Medical College of Wisconsin
MD, UW Madison School of Medicine and Public Health, 2006
MSc, University of Pittsburgh, Institute for Clinical Research Education, 2014
Started at Versiti: 2016

Research Interests

Dr. Lynn Malec developed an interest in hemostasis during her Internal Medicine and Pediatrics residency at the University of Pittsburgh. This interest flourished during her fellowship in Pediatric Hematology/Oncology at Children's Hospital of Pittsburgh during which time she gained 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 joined the Versiti BRI/MSI in 2016 and currently serves as the Medical Director of the Comprehensive Center for Bleeding Disorders where she leads the team's patient care and clinical research efforts. 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 (rFVIIIFc) has in immune tolerance induction and is conducting a multi-site observational study to evaluate the efficacy and safety of rFVIIIFc for ITI. She has fostered ties with basic scientists at the Blood Research Institute including Drs. Shi and Cui to evaluate the immunologic mechanisms of inhibitor resolution. Additionally, during the COVID-19 pandemic she became interested in the hematologic complications of Multisystem Inflammatory Syndrome in Children (MIS-C) and has led efforts to better understand risks of thrombosis in these patients and anticoagulation prevention strategies.

Awards, Honors and Service

- Fredrick Clinical Research Scholar: Awarded this two-year position at Versiti Blood Research Institute to pursue clinical research in hemostasis, 2020
- ITI School in Hemophilia; selected from a pool of international applicants to attend a faculty-driven, hemophilia inhibitor-focused training academy highlighting the latest knowledge and current challenges of immune tolerance induction (ITI) treatment in an era of new potential therapeutic options. Malmo, Sweden, 2020
- "Notable Hero in Health Care"; selected by BizTimes Milwaukee for work on the Children's Wisconsin Multisystem Inflammatory in Children (MIS-C) Committee, 2020
- Treasurer, Hemostasis and Thrombosis Research Society, 2018-present
- Learning Action Network Member, Foundation for Women and Girls with Bleeding Disorders 2014-present.

Funding

Bioverativ Investigator Initiated Funding Program "Hemophilia Inhibitor Response to Eloctate" 2016-2021 (Principal Investigator) $74,000

Publications

1. Ebbert PT, Xavier F, Malec LM, Seaman CD, Ragni MV. Observational study of recombinant factor VIII-Fc, rFVIIIFc, in hemophilia A. Thromb Res. 2020 Nov;195:51-54. doi: 10.1016/j.thromres.2020.07.004. Epub 2020 Jul 5. PMID: 32653601.
2. Malec LM, Cheng D, Witmer CM, White G, Jaffray J, Kouides PA, Haley K, Sidonio R, Recht M, Ragni MV. The Impact of Extended Half-Life Factor Concentrates on Prophylaxis for Severe Hemophilia in The United States Am J Hematol. Aug 2020;10.1002/ajh.25844. doi:10.1002/ajh.25844
3. Malec LM, Croteau SE, Callaghan M, Sidonio R. Spontaneous Bleeding and Poor Bleeding Response with Extended Half-life Factor IX Products: A Survey of Select US Hemophilia Treatment Centers. Haemophilia May 2020, doi:10.2222/hae.13943

Alan Mast, MD, PhD

Senior Investigator, Blood Research Institute, Versiti
Medical Director, Medical Services, Versiti
Walter A. Schroeder Endowed Chair for Blood Research
Associate Professor, Departments of Pathology and of Cell Biology, Neurobiology and Anatomy (CBNA), Medical College of Wisconsin
MD, Duke University, 1991
PhD, Duke University, 1991
Started at Versiti: 2003

Research Interests

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.

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 and how blood coagulation proteins modulate vascular development (See Figure).

Awards, Honors and Service

- Associate Editor, Journal of Thrombosis and Haemostasis
- Member, American Society of Hematology Committee for Scientific Affairs
- Co-Chair, American Society of Hematology Working Group on Innovations in Clinical Trials
- Member, Diversity, Equity and Inclusion Committee, International Society of Thrombosis and Haemostasis

Funding

REDS-IV-P - Contract: 7N92019D00035 (PI: Mast)

TFPI R01 - 5R01HL068835-14 (PI: Mast)

Novo Nordisk Research Grant (PI: Mast)

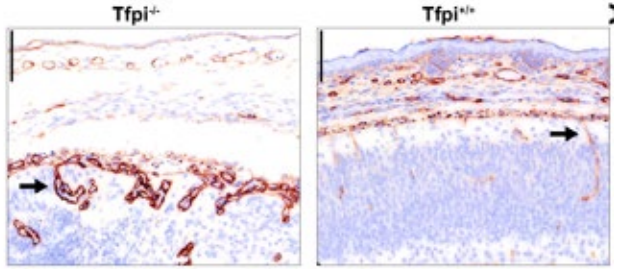
Placental Biology R01 - R01HD99638-02 (PI: Soares)

CDC COVID-19 Seroprevalence Study - 75D30120C08170 (PI: Simmons/Stone)

Publications

1. Mast AE, Langer JC, Guo Y, Bialkowski W, Spencer BR, Lee T-H, Kiss J, Cable RG, Brambilla D, Busch MP, Page GP. Genetic and behavioral modification of hemoglobin and iron status among first-time and high-intensity blood donors. Transfusion. 2020 Apr;60(4):747-758. PMID: 32163187
2. Mast AE, Szabo A, Stone M, Cable RG, Spencer BR, Kiss JE: The benefits of iron supplementation following blood donation vary with baseline iron status. Am J Hematol. 2020 Jul;95(7):784-791. PMID : 32243609
3. Maroney SA, Westrick RJ, Cleuren AC, Martinez ND, Siebert AE, Zoff M, Ginsburg D, Weiler H, Mast AE: Tissue factor pathway inhibitor is required for cerebrovascular development in mice. Blood. 2020 Jul 31; doi: 10.1182/blood.2020006054. PMID: 32735640

Pictures of the brains of embryonic mice that are either normal (Tfpi+/+) or that lack TFPI (Tfpi-/-). The arrows highlight a normal vessel growing into the Tfpi+/+ brain and the disoriented, abnormal blood vessels growing into the Tfpi-/- brain.



Robert R. Montgomery, MD

Senior Investigator, Blood Research Institute, Versiti
Attending Physician, Children's Hospital Wisconsin
Professor of Pediatric Hematology and Populations Health – Epidemiology,
Medical College of Wisconsin
Research Member, Hematologic Malignancy and Translation Science Institute, MCW
MD, University of Pittsburgh School of Medicine
Pediatric Hematology Fellowship, U of Colorado Medical School, Denver
Molecular Immunology Fellowship, Scripps Research Institute, La Jolla
Started at Versiti: 1980

Research Interests

Dr. Montgomery's research laboratory is studying von Willebrand Disease (VWD), where the VWF protein is abnormal or reduced, and Hemophilia, where the factor VIII (FVIII) is reduced or absent. Interestingly these two proteins have 2 different genes but once synthesized, the FVIII binds to VWF until it is dissociated at the site of vascular bleeding. The R01 grant and manuscript 3 listed below address this critical interaction and why it is important. The Program Project Grant (PPG) addresses the discovery of new functional abnormalities in VWF and we create animal models that study the biology in living mouse and rat models that have been genetically engineered to function as human diseases and how they should be treated. After studying more than 1200 individuals with VWD, as many as 30% don't have a gene abnormality, so we are doing whole-genome sequencing to find additional genes that affect synthesis, function, and clearance. Basic research has made discoveries that are then *transferred to Versiti's Diagnostic Lab* so that patients can be correctly studied and treated. These include a new VWF functional assay (VWF:GPIbM), Antibodies and Inhibitors of VWF function(VWF-Ab), and specific assay of VWF binding to type IV collagen (VWF:CB4B).

Awards, Honors and Service

- National Hemophilia Foundation (a) Medical and Scientific Advisory Committee member, (b) Chair, Review of Baxter-Shire-Takeda Fellowships, (c) Judith Graham Poole Review Group, (d) Career Development Award Review Group
- Hemostasis and Thrombosis Research Society (a) Executive Secretary (end March 2020) (b) Review Committee, Mentored Research Awards
- Novo Nordisk, Access to Insight Award Review Committee
- NIH, U54 External Annual Advisory Committee
- NIH/NGF/ISTH/WFH, VWD Guidelines Committee
- Great Lakes Hemophilia Foundation (a) Board Member and (b) Finance Committee Member

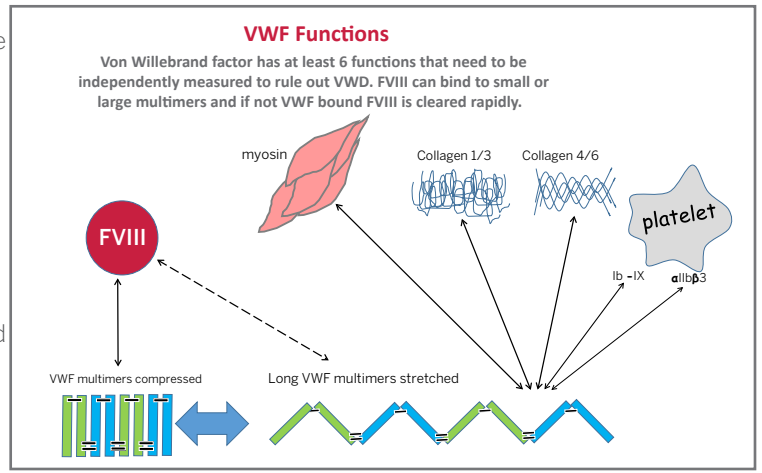
Funding

P01 HL144457 "Zimmerman Program on the Biology of VWD" National Heart, Lung, and Blood Institute; Program Director: R.R. Montgomery; 2019 – 2024.

R01 HL139847 "Molecular Interactions of FVIII and VWF" National Heart, Lung and Blood Institute/National Institutes of Health; Principal Investigator, R.R. Montgomery; 2018 – 2022.

Publications

1. Garcia J, Flood VH, Haberichter SL, Fahs SA, Mattson JG, Geurts AM, Zogg M, Weiler H, Shi Q, Montgomery RR. A rat model of severe VWD by elimination of the VWF gene using CRISPR/Cas9. Res Pract Thromb Haemost. 2019 Dec 29;4(1):64-71. doi: 10.1002/rth2.12280. eCollection 2020 Jan. PMID: 31989086
2. Flood VH, Slobodianuk TL, Keesler D, Lohmeier HK, Fahs S, Zhang L, Simpson P, Montgomery RR. von Willebrand factor binding to myosin assists in coagulation. Blood Adv. 2020 Jan 14;4(1):174-180. PMID: 31935285
3. Shi Q, Mattson JG, Fahs SA, Geurts AM, Weiler H, Montgomery RR. The severe spontaneous bleeding phenotype in a novel hemophilia A rat model is rescued by platelet FVIII expression. Blood Adv. 2020 Jan 14;4(1):55-65. PMID: 31899798).



Debra Newman, PhD

Senior Investigator, Blood Research Institute, Versiti
Professor, Department of Pharmacology & Toxicology and of Microbiology and Molecular Biology, Medical College of Wisconsin
PhD, Biology, Marquette University, 1989
Started at Versiti: 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. Dr. Newman's research has recently focused on the contributions of platelet abnormalities to excessive bleeding in the fetal and neonatal periods when excessive bleeding can have life-long developmental consequences. Newborns who undergo surgery for congenital heart defects experience very severe bleeding. Dr. Newman's lab recently demonstrated that decreases in platelet count and function occur normally during heart surgery but can be corrected with platelet transfusion so that they will not complicate bleeding in newborn heart surgery patients. This research justifies administration of the right number of platelets at the right time to effectively control bleeding in this at-risk population. Deletion of segment 11.2 on the q arm of one copy of chromosome 22 gives rise to 22q11.2 Deletion Syndrome (22q11.2DS), which is commonly found in patients with congenital heart defects. One the many genes that are deleted in 22q11.2DS is GPIBB, which encodes a component of an important platelet receptor (GPIb-IX-V). Dr. Newman's lab demonstrated that loss of one copy of GPIBB is not associated with increased bleeding. This finding indicates that patients with 22q11.2DS who must undergo surgery for congenital heart defects are not at increased risk for severe bleeding because of loss of one copy of GPIBB. Dr. Newman's lab also studies Fetal/Neonatal Alloimmune Thrombocytopenia (FNAIT), which is a disorder that arises when a pregnant person's immune system recognizes a developing baby's platelets as foreign and clears them from the baby's circulation. Dr. Newman is currently working in collaboration with several investigators at Versiti to investigate *who* is at highest risk for development of FNAIT, *what* causes the most severe forms of the disease, *when* and *where* during pregnancy the immune response to a baby's platelets develops, and *why* the mechanisms that normally ensure tolerance of fetal differences by the parent fail in FNAIT. This research is urgently needed to predict who will deliver babies with severe FNAIT so that they can be treated to prevent the most severe forms of the disease. Ultimately, however, we aim to prevent this deleterious immune response from developing in the first place.

A major focus of research in Dr. Newman's 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. Dr. Newman has discovered that PECAM-1 works with another potent T cell suppressor, Transforming Growth Factor ß (TGFß), to inhibit T cell anti-tumor responses. Her 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 TGFß work together to inhibit T cell responses. This research will help improve T cell-based therapies for treatment of cancer and autoimmune disease.

Awards, Honors and Service

- Member, Program Project Grant Review Parent Committee, National Heart, Lung & Blood Institute, National Institutes of Health, 2017 – present
- Member, Planning Committee, International Society on Thrombosis & Haemostasis 2021 Annual Meeting, 2019 – present

Funding

NIH R35- HL139937 (Co-Investigator)

Publications

1. Zhi H, Kanaji T, Fu G, Newman DK, Newman PJ. Generation of PECAM-1 (CD31) conditional knockout mice. Genesis. 2020 Feb;58(2):e23346. PMID: 31729819
2. Zwifelhofer NMJ, Bercovitz RS, Cole R, Yan K, Simpson PM, Moroi A, Newman PJ, Niebler RA, Scott JP, Stuth EAD, Woods RK, Benson DW, Newman DK. Platelet Function Changes during Neonatal Cardiopulmonary Bypass Surgery: Mechanistic Basis and Lack of Correlation with Excessive Bleeding. Thromb Haemost. 2020 Jan;120(1):94-106. PMID: 31752040

Peter Newman, PhD

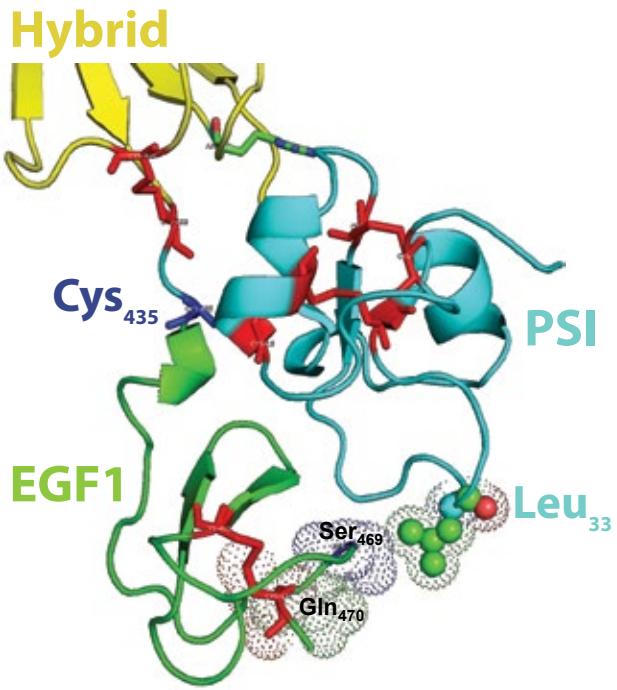
Jacquelyn Fredrick Endowed Chair for Foundational Research
Vice President for Research, Versiti Blood Center of Wisconsin
Associate Director, Blood Research Institute, Versiti
Professor, Department of Pharmacology and of
Cell Biology, Neurobiology and Anatomy, Medical College of Wisconsin
PhD, St. Louis University, 1983
Started at Versiti: 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, the generation of antigenically-distinct megakaryocytes and platelets from induced pluripotent stem cells, and examining the pathophysiology of neonatal alloimmune thrombocytopenia using a newly developed humanized mouse model - all funded by a seven-year, $7M R35 grant from the 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 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 Service

- R35 Outstanding Investigator Award, NIH National Heart, Lung, and Blood Institute 2018-25



- Chair, NIH Program Project Review Committee 2020-21
- Editor, Arteriosclerosis, Thrombosis and Vascular Biology (Journal of the American Heart Association) 2012-2020
- Chair, BloodWorks Northwest Scientific Advisory Board 2012-present

Funding

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

Publications

1. Zhi H, Kanaji T, Fu G, Newman DK, Newman PJ. Generation of PECAM-1 (CD31) conditional knockout mice. Genesis. 2020 Feb;58(2):e23346. PMID: 31729819
2. Zwifelhofer NMJ, Bercovitz RS, Cole R, Yan K, Simpson PM, Moroi A, Newman PJ, Niebler RA, Scott JP, Stuth EAD, Woods RK, Benson DW, Newman DK. Platelet Function Changes during Neonatal Cardiopulmonary Bypass Surgery: Mechanistic Basis and Lack of Correlation with Excessive Bleeding. Thromb Haemost. 2020 Jan;120(1):94-106. PMID: 31752040

Ruchika Sharma, MD

Associate Medical Director, Platelet Neutrophil Immunology laboratory, Hemostasis Laboratory, Versiti
Assistant Investigator, Blood Research Institute, Versiti
Assistant Professor of Pediatrics, Division of Hematology/Oncology, Medical College of Wisconsin
MD, Maulana Azad Medical College, University of Dehli, 2008
Fellowships in Pediatric Hematology/Oncology, 2012-15 and Pediatric Hemostasis-Thrombosis, Nationwide Children's Hospital, The Ohio State University
Started at Versiti: 2016

Research Interests

Dr. Sharma's professional and research interests center around novel diagnostic approaches to non-malignant hematology in underserved or challenging patient populations. Dr. Sharma specializes in the diagnosis and treatment of a variety of disorders of thrombosis and hemostasis in pediatrics and young adults. A developing area of interest for her is multidisciplinary approach to the management of young women with hematological disorders. Dr. Sharma also provides medical oversight to the Platelet Neutrophil Immunology Diagnostic Laboratory at Versiti Blood Center of Wisconsin.

Dr. Sharma completed her Medical School in Maulana Azad Medical College/University of Delhi, India. She went to University of Toledo for her internship and pediatric residency and completed fellowships in Pediatric Hematology/ Oncology/ Bone Marrow transplantation and Hemostasis-Thrombosis at Nationwide Children's Hospital/ The Ohio State University. During her fellowship she conducted basic research in animal models of thrombosis (blood clotting) in nephrotic syndrome, a major kidney disease in children. She continues to study hemostatic disorders in young women.

Awards, Honors and Service

- Young Investigator Travel Award for THSNA 2020\

Funding

Startup funding, Medical College of Wisconsin

Publications

1. Samuelson Bannow B, Warad DM, Jones CG, Pechauer SM, Curtis BR, Bougie DW, Sharma R, Grill DE, Redman MW, Khalighi PR, Leger RR, Pruthi RK, Chen D, Sabath DE, Aster RH, Garcia DA, Padmanabhan A. Platelet Factor 4-dependent platelet activation assay for the diagnosis of Heparin-induced Thrombocytopenia: Results of a prospective, blinded multi-center diagnostic study. Blood. 2020 Sep 8; doi: 10.1182/blood.2020008195. [Epub ahead of print] PMID: 32898858.
2. Jacobson-Kelly AE, Sharma R, Powers JM. (2020) Iron Deficiency Anemia. In: Srivaths L (eds) Hematology in the Adolescent Female. Springer, Cham. doi:10.1007/978-3-030-48446-0_17

Qizhen Shi, MD, PhD

Senior Investigator, Blood Research Institute, Versiti
Professor of Pediatric Hematology, Medical College of Wisconsin
MD, Fujian Medical University, Fuzhou, China, 1990
PhD, Fujian Medical University, Fuzhou, China, 1998
Hematology Fellowship, Medical College of Wisconsin 2000 – 2006
Started at Versiti: 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 even 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 inhibitors. Furthermore, platelet gene therapy can induce profound antigen-specific peripheral immune tolerance. Currently, Dr. Shi is exploring a safe non-genotoxic preconditioning for platelet gene therapy. 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 may aid the design of more effective protocols to prevent inhibitor development and to induce immune tolerance in patients with hemophilia A.

Awards, Honors and Service

- Reviewer and Co-Chair, Small Business Special Emphasis Panel (SEP), NIH/NHLBI, 3/2020 and 11/2020.
- Reviewer, Children's Research Institute Pilot Innovative Research grant, 10/2020.
- Editorial board member, Molecular Therapy Methods and Clinical Development (Mol Ther – Meth & Clin Dev) 2017-present

Funding

R01 HL102035 "Platelet Derived FVIII Gene Therapy of Hemophilia A." Role: PI

NHF Bridge Award "Investigation of VWF as an immunomodulator of the immunogenic response towards FVIII." Role: PI

1R01 HL142791A. "Phase I clinical trial testing Feasibility of hematopoietic stem cell gene therapy using platelet FVIII to safely improve hemostasis for severe hemophilia A with inhibitory antibodies to FVIII." Role: Co-I

Publications

1. Shi Q, Mattson GJ, Fahs SA, Guerts AM, Weiler H, Montgomery RR. The severe spontaneous bleeding phenotype in a novel hemophilia A rat model with an inversion mutation is rescued by platelet-targeted FVIII expression. Blood Adv. 2020 Jan 14;4(1):55-65. PMID: 31899798
2. Shi Q, Carman CV, Chen Y, Sage PT, Xue F, Liang XM, and Gilbert GE. Unexpected enhancement of FVIII immunogenicity by endothelial expression in lentivirus-transduced and transgenic mice. Blood Adv. 2020 May 26;4(10):2272-2285. PMID: 32453842
3. Cai Y and Shi Q. Platelet-targeted FVIII gene therapy restores hemostasis and induces immune tolerance for hemophilia A. Front. Immunol. 2020 Jun 12;11:964. PMID: 32595633

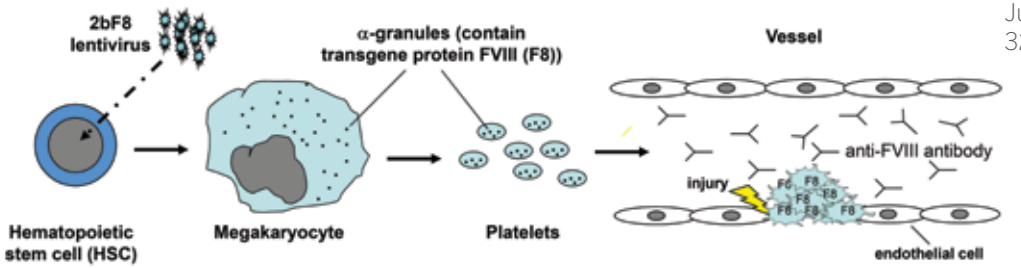


Fig. 1 Graphical summary of platelet-targeted gene therapy.

Roy Silverstein, MD

Senior Investigator and Interim Director, Blood Research Institute, Versiti
John and Linda Mellowes Professor and Chair
Department of Medicine, Medical College of Wisconsin
MD, Emory University School of Medicine, 1979
Clinical Training in Medicine & Hematology/Oncology, Weill Medical College of Cornell University, 1985
Started at Versiti: 2011

Research Interests

Research by Dr. Silverstein's group concerns basic mechanisms underlying common vascular diseases, especially thrombosis and atherosclerosis, with particular emphasis on the role of a cellular receptor designated CD36 expressed on platelets, macrophages, fat cells and other tissues. CD36 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 state associated with these conditions as well as in accumulation of cholesterol in blood vessel walls, leading to atherosclerosis. Recent work in the Silverstein lab has demonstrated that CD36 triggers very specific signaling pathways inside cells that promote these maladaptive responses. 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 Service

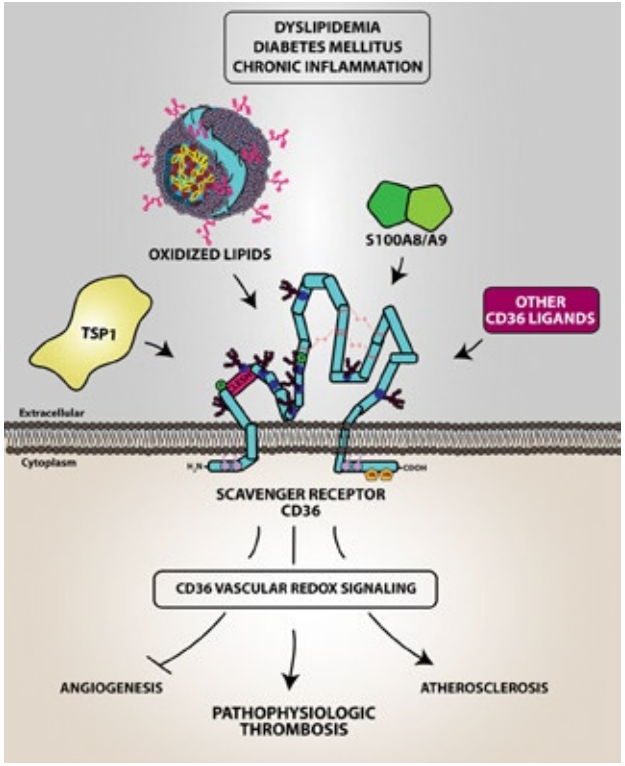
- President, American Society of Hematology 2019
- Chair, Medical College Physicians Board, 2018-2020
- Member, Clinical Executive Committee, Froedtert and Medical College of Wisconsin
- 26th William Maloney Lecture, Brigham and Women's Hospital Harvard Medical School
- Editorial Boards: J. Clinical Investigation and J. Experimental Medicine

Funding

R01 HL142152: "ERK5 and CD36 link oxidative stress to platelet dysfunction and ischemic injury"

Publications

1. Yang M, Li E, Harberg V, Chen E, Yue H, Ferreira RB, Wynia-Smith SL, Carroll KS, Zielonka J, Flaumenhaft R, Silverstein RL*, Smith BC*. Cysteine Sulfenylation by CD36 Signaling Promotes Arterial Thrombosis in Dyslipidemia. Blood Advances. 2020 Sep 22;4(18):4494-4507. PMID: 32946569. *equal contribution
2. Schill RL, Knaack DA, Powers HR, Chen Y, Yang M, Schill DJ, Silverstein RL, Sahoo D. Modification of HDL by reactive aldehydes alters select cardioprotective functions of HDL in macrophages. FEBS J. 2020 Feb;287(4)695-707. PMID: 31386799.
3. Sodhi K, Denvir J, Liu J, Sanabria JR, Chen Y, Silverstein R, Xie ZJ, Abraham NG, Shapiro JI. Oxidant-Induced Alterations in the Adipocyte Transcriptome: Role of the Na,K-ATPase Oxidant Amplification Loop. Int J Mol Sci. 2020 Aug 18;21(16): 5923. PMID: 32824688.



Hartmut Weiler, PhD

Ziegler Family Chair for Research, Senior Investigator, Blood Research Institute, Versiti
Associate Professor, Department of Physiology, Medical College of Wisconsin
Director, Transgenic Core Facility, Medical College of Wisconsin / Blood Research Institute
Dr.rer.nat., Technische Hochschule Darmstadt Germany, 1989
Started at Versiti: 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 2020, 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. In the latter work, Dr. Weiler and his lab utilized the so-called Endothelial-TRAPapproach to characterize the in vivo translatome of endothelial cells in a variety of organs (see below). 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 Versiti Blood Research Institute. The facility provides a wide range of genome editing services facilitating the generation of genetically altered rodents serving as models for human disease.

Funding

"Zimmerman Program on the Biology of VWD" NHLBI – 1P01HL144457

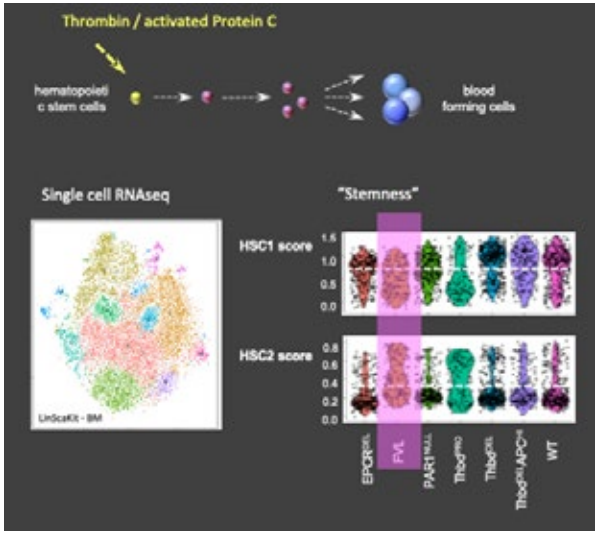
"Serpin Regulation of Coagulation Proteases" – NHLBI – R01HL062565

"Protein C Pathway Mitigation of Radiation-Induced Vascular Dysfunction" – NIAID – U01AI133561

Figure: During infections, the blood coagulation mechanism is activated, resulting in the formation of thrombin and activated protein C. These proteases modify how hematopoietic stem cells rapidly give rise to innate immune cells (granulates, monocytes) that help fending off the infectious pathogens. Naturally occurring mutations such as the Leiden polymorphism in the gene for coagulation factor V enhance the production of thrombin and activated protein C, and thereby the function of hematopoietic stem cells. Biocomputational single-cell analysis of gene activity (scRNAseq) in bone marrow stem and progenitor cells (left graphic: stem cells in purple; each dot represents the entire transcriptome of one single cell) reveals drastically reduced "stemness" of pluripotent stem cells (HSC1) and erythroid/platelet-biased stem cells (HSC2).

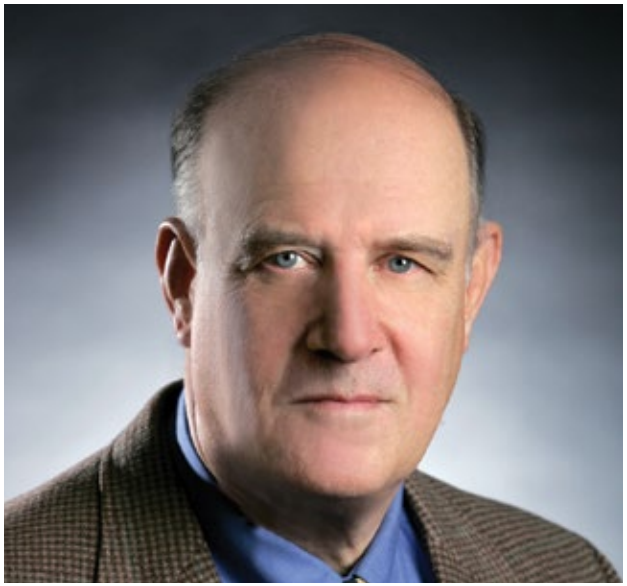
Publications

1. Maroney SA, Westrick R, Cleuren A, Martinez ND, Siebert AE, Zogg M, Ginsburg D, Weiler H, Mast AE. Tissue factor pathway inhibitor is required for cerebrovascular development in mice. Blood. 2020 Jul 31; doi: 10.1182/blood.2020006054. [Epub ahead of print] PMID: 32735640
2. Shi Q, Mattson JG, Fahs SA, Geurts AM, Weiler H, Montgomery RR. The severe spontaneous bleeding phenotype in a novel hemophilia A rat model is rescued by platelet FVIII expression. Blood Adv. 2020 Jan 14;4(1):55-65. PMID: 31899798
3. Saffarzadeh M, Grunz K, Nguyen TS, Lee YK, Kitano M, Danckwardt S, Santos CD, Weiler H, Reyda S, Ruf W. Macrophage Protease-Activated Receptor 2 Regulates Fetal Liver Erythropoiesis in Mice. Blood Adv. 2020 Nov 24;4(22):5810-5824. PMID: 33232477



Gilbert White, II, MD

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



Research Interests

Work by Dr. White's group has been broadly aimed at understanding signaling pathways involved in the hemostatic responses by blood platelets. Recent focus was on a small G 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. The ability of Rap 1b to bi-directionally modulate platelet function makes it a potentially interesting therapeutic reostat for anti-platelet therapy in the treatment of heart attacks and strokes.

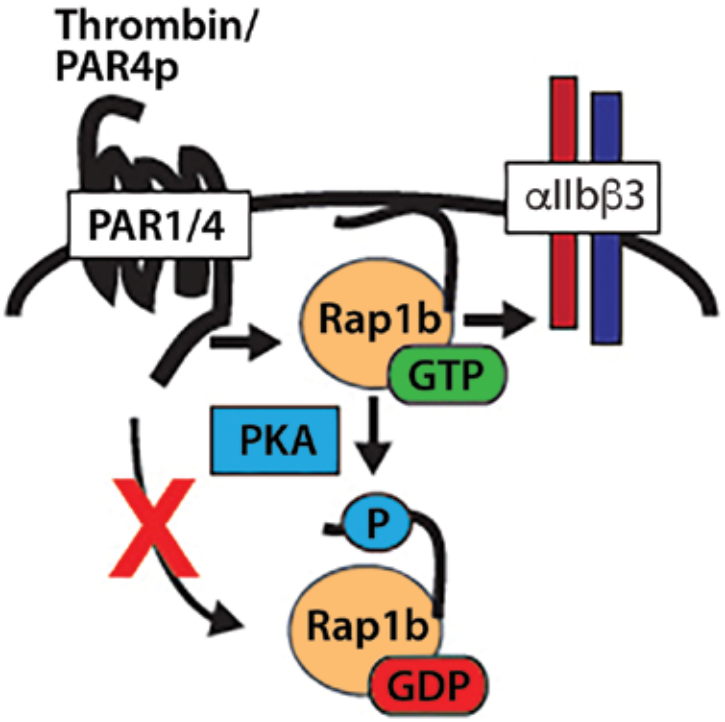
Awards, Honors and Service

- Sol Sherry Lecture, American Heart Association
- Board of Directors, Great Lakes Hemophilia Foundation
- Chair, American Society of Hematology (ASH) Bridge Grant Review Program
- Member, International Society of Thrombosis and Hemostasis (ISTH) Awards & Honors Committee
- Editorial Board, Haemophilia
- Co-Editor, 6th edition of Thrombosis and Hemostasis

Funding

UL1 TR001435 Clinical and Translational Science Institute, NCATS

T32 GM080202 "Medical Scientist Training Program", NIGMS



Ze Zheng, MBBS, PhD

Assistant Investigator, Blood Research Institute, Versiti
Assistant Professor, Division of Endocrinology and Molecular Medicine, Department of Medicine, Medical College of Wisconsin (MCW)
MBBS, Clinical Medicine, Jiamusi University, 2008
PhD, Molecular Biology and Genetics, Wayne State University, 2015
Postdoctoral Research Fellow, Columbia University, 2020

Research Interests

Our laboratory studies the interactions between metabolism and blood clot lysis. Fibrinolysis, the primary mechanism that dissolves a blood clot, is initiated by a serine protease tissue-type plasminogen activator (tPA). Our previous study discussed a novel source and regulation of endogenous basal plasma tPA derived from hepatocytes, which is important for fibrinolysis when a vessel injury occurs. The tPA activity is inhibited primarily by the serpin plasminogen activator inhibitor 1 (PAI-1). A balance between tPA and PAI-1 in plasma is essential for preventing excessive clotting. Our recent study revealed the mechanism of how hepatocytes sense metabolic stresses and imbalance the production of tPA and PAI-1, influencing the degree of impaired fibrinolysis in obesity. The goal of our laboratory is to understand the role of hepatocyte-derived tPA and basal fibrinolysis in hemostasis, and to develop diagnostic/ preventive/ therapeutic strategies that can be used to combat atherosclerosis, thrombosis, and bleeding disorders.

Awards, Honors and Service

- Co-Chair, Fibrinolysis SSC Subcommittee, International Society on Thrombosis and Haemostasis, 2020-2024
- Committee Member, Ethics Committee, International Society on Thrombosis and Haemostasis, 2018-2022
- Committee Member, Task Force on PhD Careers, American Society of Hematology, 2019-2021
- Review Committee Member, Study Section for Hematology Opportunities for the Next Generation of Research Scientists (HONORS) Award, American Society of Hematology, 2019-2021

Funding

ASH Scholar Award, American Society of Hematology, 2019-2022

AHA Career Development Award, American Heart Association, 2019-2022

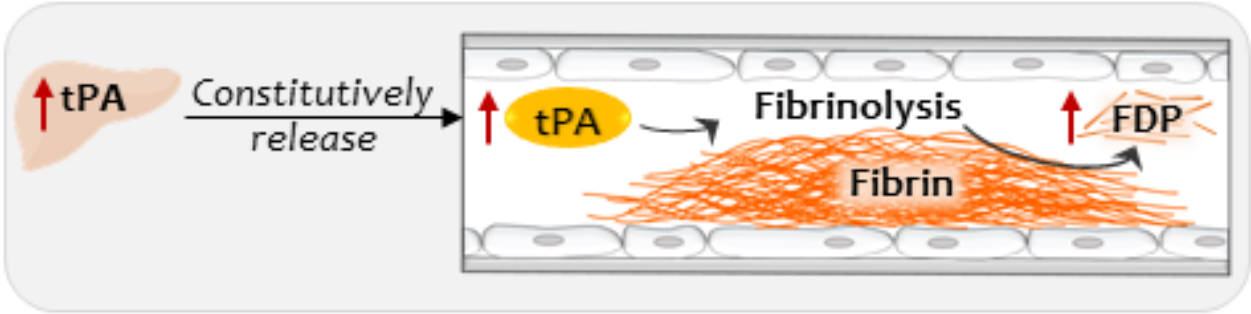
COVID-19 Rapid Response Grant, Cullen Run Foundation, MCW Cardiovascular Center, 2020-2021

NHF Career Development Award, National Hemophilia Foundation, 2021-2023

Start-up Fund, Advancing a Healthier Wisconsin Endowment, Medical College of Wisconsin and Versiti Blood Research Institute

Publications

1. Zheng Z#, Nakamura K, Gershbaum S, Thomas S, Bessler M, Schrope B, Krikhely A, Liu RM, Ozcan L, López JA, Tabas I#: Interacting Pathways of PAI-1 and tPA Gene Regulation in Hepatocytes Influence Impaired Fibrinolysis Severity in Obesity. 2020 Aug 3. J Clin Invest. [#co-corresponding authors].
2. Zheng Z#, Nayak L, Wang W, Yurdagul A Jr, Wang X, Cai B, Lapping S, Ozcan L, Ramakrishnan R, Pestell RG, Jain MK, Tabas I#. An ATF6-tPA pathway in hepatocytes contributes to systemic fibrinolysis and is repressed by DACH1. Blood. 2019. #Corresponding authors
3. Zheng Z*, Kim H*, Qiu Y, Chen X, Mendez R, Dandekar A, Zhang X, Zhang C, Liu AC, Yin L, Lin JD, Walker PD, Kapatos G, Zhang K. CREBH Couples Circadian Clock with Hepatic Lipid Metabolism. Diabetes. 2016. *Equal contributors



Jieqing Zhu, PhD

Investigator, Blood Research Institute, Versiti
Associate 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
Started at Versiti: 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 or antibody 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 how integrin beta subunit becomes extended during activation and how the transmembrane domain contributes to integrin structural changes, which provide new information of developing next-generation integrin inhibitors that restrain integrin conformational activation.

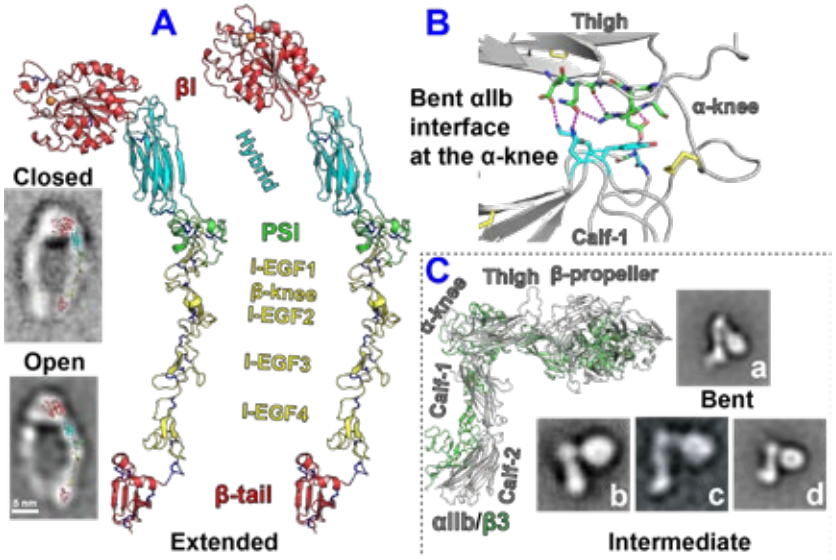
Awards, Honors and Service

- Member, American Society of Hematology (ASH) 2020
- Member, American Society for Biochemistry and Molecular Biology (ASBMB) 2020
- Editorial Boards: Scientific Reports

Funding

R01 HL131836 "Structural Transition of Cellular Integrins and Applications Thereof"

R01 GM137143 "Structural Mechanisms Underlying the Activity Regulation of the Receptor-like Protein Tyrosine Phosphatase, CD148/PTPRJ"



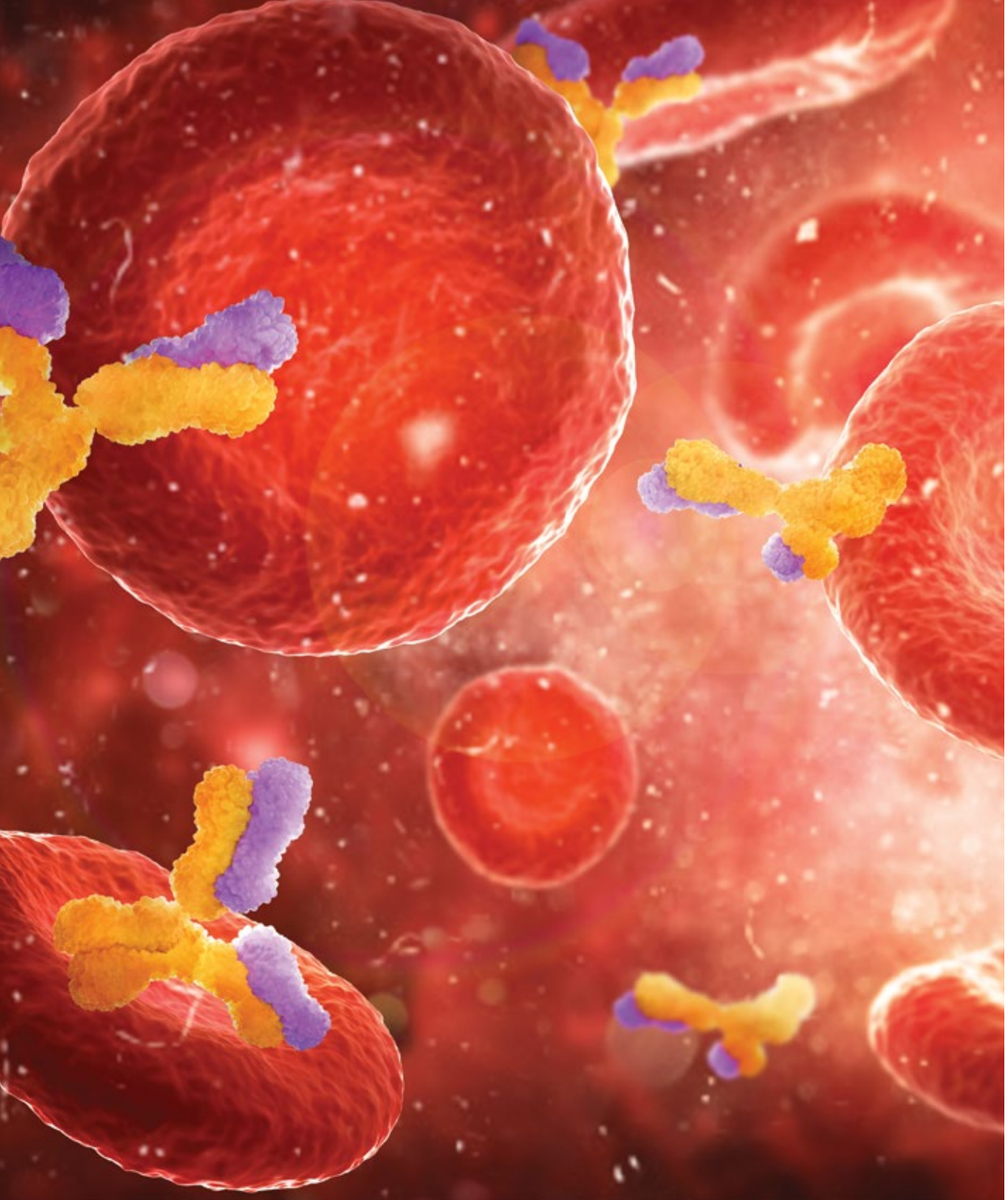
Publications

1. Majewski MW, Gandhi DM, Holyst T, Wang Z, Hernandez I, Rosas R Jr, Zhu J, Weiler H, Dockendorff C. Synthesis and initial pharmacology of dual-targeting ligands for putative complexes of integrin αVβ3 and PAR2. RSC Med Chem. 2020 Jul 9;11(8):940-949. PMID: 33479689
2. Hozwarth ST, Bayat B, Zhu J, Phuangtham R, Fischer L, Boeckelmann D, Röder L, Berghöfer H, Schmidt S, Bein G, Santoso S. Naturally occurring point mutation Cys460Trp located in the I-EGF-1 domain of integrin β3 alters the binding of some anti-HPA-1a antibodies. Transfusion. 2020 Sep;60(9):2097-2107. PMID: PMID: 32770549

COVID-19

In the wake of the COVID-19 pandemic, Versiti Blood Research Institute investigators immediately shifted their research focus to understanding the deadly virus. To aid in these efforts, Versiti was awarded several grants to apply to research related to COVID-19 convalescent plasma and to better understand why some COVID patients develop blood clots. "We are working with the National Institutes of Health's Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) partnership as they develop three master protocols for evaluating the effectiveness of blood thinners to prevent blood clots and worsening of organ damage due to COVID-19," said Associate Investigator and Medical Director of Hematology Lisa Baumann Kreuziger, MD, MS.

"These studies involve patients with COVID-19 at diagnosis, hospitalization and discharge from the hospital."



Immunology

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

Versiti 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.

Matthew Anderson, MD, PhD

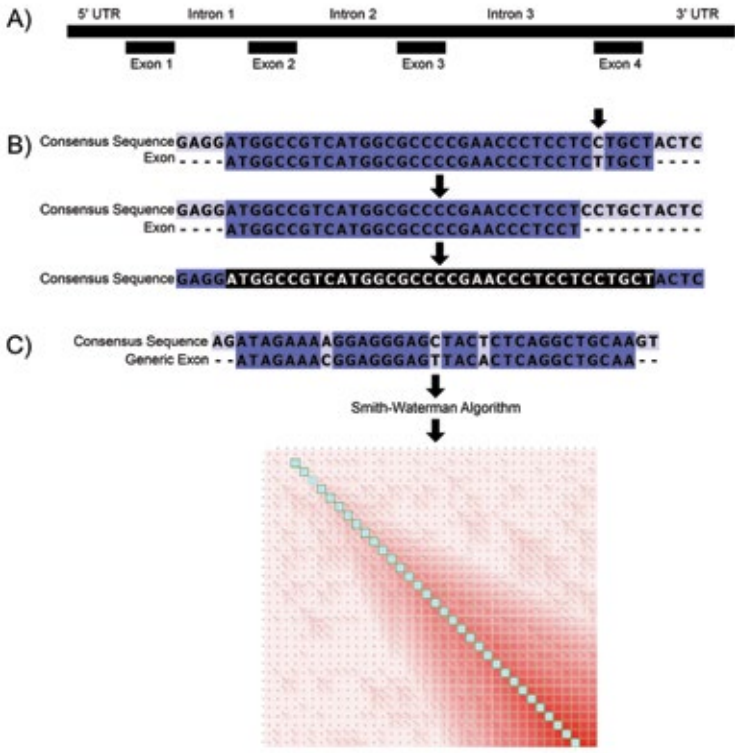
Vice President and Medical Director, Diagnostic Laboratories
Associate Investigator, Blood Research Institute, Versiti
Assistant Professor, Pathology, Medical College of Wisconsin
MD, Medical College of Wisconsin, 2006
PhD, Medical College of Wisconsin, 2004
Started at Versiti: 2013

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. Dr. Anderson's group has recently reported a novel bioinformatics approach (see figure) to directly compare HLA gene sequences from hematopoietic transplant donor and recipients, demonstrating that transplant pairs highly matched at a genetic level show improved transplant outcome. 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 Service

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



Publications

1. Cushman-Vokoun AM, Voelkerding KV, Fung MK, Nowak JA, Thorson JA, Duncan HL, Kalicanin T, Anderson MW, Yohe S. A Primer on CAR-T Therapy: What Does It Mean for Pathologists?: A Summary Guidance From the College of American Pathologists CAR-T Workgroup. Arch Pathol Lab Med. 2020 Nov 25. doi: 10.5858/arpa.2019-0632-CP. Online ahead of print. PMID: 33237994

Weiguo Cui, MD, PhD

Investigator, Blood Research Institute, Versiti
Associate Professor, Department of Microbiology and Immunology, Medical College of Wisconsin
MD/PhD, Tianjin Medical University, China, 2004
Dept. of Immunobiology, Yale University School of Medicine, 2012
Started at Versiti: 2012

Research Interests

T cell exhaustion is a crucial problem to fight off viral infection and cancer. Dr. Cui's studies are aimed at improving the understanding of how T cells become functionally exhausted in the face of viruses such as HIV and cancer. His current work is focused on the study of transcriptional and metabolic changes that take place in antigen-specific T cells during infection and cancer. An immediate goal is to identify specific factors that can reverse T cell exhaustion. Findings made will improve basic understanding of the immune response and have implications for the treatment and prevention of infectious diseases and cancer.

Awards, Honors and Service

- Dr. Gilbert C. White, II Endowed Junior Faculty Chair
- Outstanding Graduate School Educator
- Ad hoc reviewer for TTT, NIAID SEP for P01, and ZRG1 F07 U 20 L: Fellowships: Immunology

Funding

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

HDTRA11710052 (Co-I) 01/01/2018-08/20/2020 DTRA via ioGenetics "Comparative Computational Modeling of Immune Responses to Vaccines"

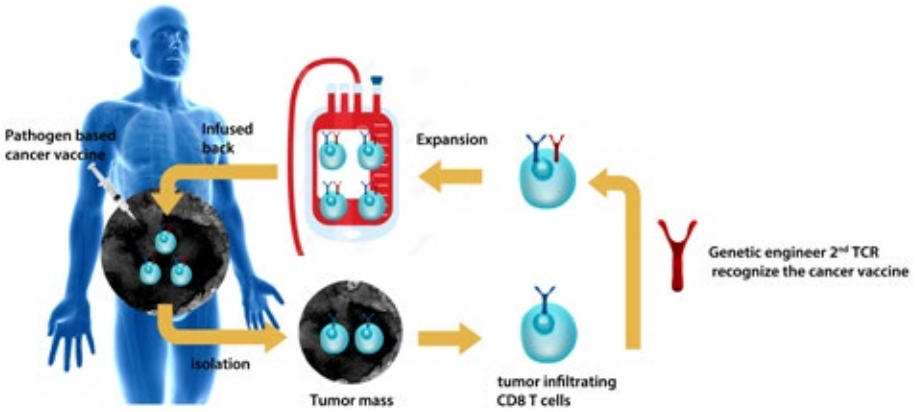
RSG-17-186-01 (PI) 01/01/18–12/31/21 American Cancer Society "Harnessing BATF-boosted Anti-tumor CD8 T cells in Cancer Immunotherapy"

MCW Cancer Center (MPI) "BCG boosted Adoptive Cell Transfer Immunotherapy to Treat Bladder Cancer"

TORFP E02 (Co-I) 08/04/19–02/03/22 NIH/NCI "Chemoprevention with Aerosolized Let-7 micro RNA in Mouse Models of Non-small Cell Lung Cancer"

1R01DK121747-01 (Co-I) 08/22/19–05/31/23 NIH/NIDDK "Shaping Diabetogenic T Cells by IL-27 in Type I Diabetes"

1R01AI148403 (PI) 09/01/19–08/31/24 NIH/NIAID "Phenotypic, Functional and Transcriptional Heterogeneity in T Cell Exhaustion"



Publications

1. Xin G, Khatun A, Topchyan P, Zander R, Volberding PJ, Chen Y, Shen J, Fu C, Jiang A, See WA, Cui W. Pathogen-Boosted Adoptive Cell Transfer Therapy Induces Endogenous Antitumor Immunity through Antigen Spreading. Cancer Immunol Res. 2020 Jan;8(1):7-18. PMID: 31719059
2. Unsworth AJ, Bye AP, Sage T, Gaspar RS, Eaton N, Drew C, Stainer A, Kriek N, Volberding PJ, Hutchinson JL, Riley R, Jones S, Mundell SJ, Cui W, Falet H, Gibbins JM. Anti-platelet properties of Pim kinase inhibition is mediated through disruption of thromboxane A2 receptor signalling. Haematologica. 2020 May 28:haematol.2019.223529. doi: 10.3324/haematol.2019.223529. Online ahead of print. PMID: 32467143
3. Fu C, Peng P, Loschko J, Feng L, Pham P, Cui W, Lee KP, Krug AB, Jiang A. Plasmacytoid dendritic cells cross-prime naive CD8 T cells by transferring antigen to conventional dendritic cells through exosomes. Proc Natl Acad Sci U S A. 2020 Sep 22;117(38):23730-23741. PMID: 32879009

Bonnie Dittel, PhD

Senior Investigator, Blood Research Institute, Versiti
Professor, Department of Microbiology and Immunology, Medical College of Wisconsin
PhD, University of Minnesota
Postdoctoral Training, Yale University
Started at Versiti: 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. In recent studies we have identified a new subset of B lymphocytes (BDL) that induce the proliferation of a critical subset of T lymphocytes designated T regulatory cells (Treg) via GITRL that are essential for controlling autoimmunity. Knowledge regarding the biological role of BDL is being leveraged to develop an adoptive cell therapy for the treatment of autoimmunity. Dr. Dittel also is investigating how immune cells propagate disease by studying the mechanisms whereby they induce neuronal damage. Findings made are expected to suggest new approaches for treating MS and other immune disorders affecting the nervous system.

Awards, Honors and Service

- NIH Director's Fund Transformative Research Award
- Sigma XI, The Scientific Research Honor Society, Member
- Certificate of Appreciation, Versiti's Diversity & Inclusion Council, In honor of Women's History Month 2020
- Journal of Neuroimmunology, Editorial Board
- Brain, Behavior, and Immunity, Editorial Board
- ImmunoHorizons, Senior Editor
- NINDS, Clinical Neuroimmunology and Brain Tumors study section
- NIAID, Investigator Initiated Program Project Applications (P01), study section
- NIH, Support for Conferences and Scientific Meetings (R13), study section
- NIH, Small Business: Innovative Immunology Research, study section, Chair
- Veterans Affairs, IMMA Immunology and Dermatology Merit Review Committee Meeting
- National Multiple Sclerosis Society, Fellowship Review Committee

Funding

R01AI160244-01, NIAID, Development of a B cell therapeutic- Principal Investigator

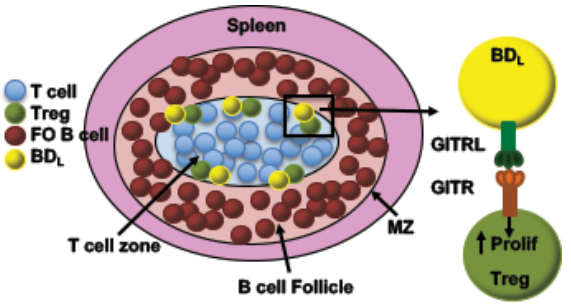
R21AI145323, NIAID, A novel human regulatory B cell subset – Principal Investigator

National Multiple Sclerosis Society - B Cell Regulation in EAE/MS – Principal Investigator

Neuroscience Research Center Imagine More, Medical College of Wisconsin Dynamics of B cell subtypes in multiple sclerosis before and after treatment- Co-investigator

Publications

1. Dittel LJ, Dittel BN, Brod SA. Ingested ACTH blocks Th17 production by inhibiting GALT IL-6. J Neurol Sci. 2020 Feb 15;409:116602. PMID: 31812846
2. Strzepa A, Gurski CJ, Dittel LJ, Szczepanik M, Pritchard KA Jr, Dittel BN. Neutrophil-Derived Myeloperoxidase Facilitates Both the Induction and Elicitation Phases of Contact Hypersensitivity. Front Immunol.. doi: 10.3389/fimmu.2020.608871. eCollection 2020. PMID: 33569056



Jack Gorski, PhD

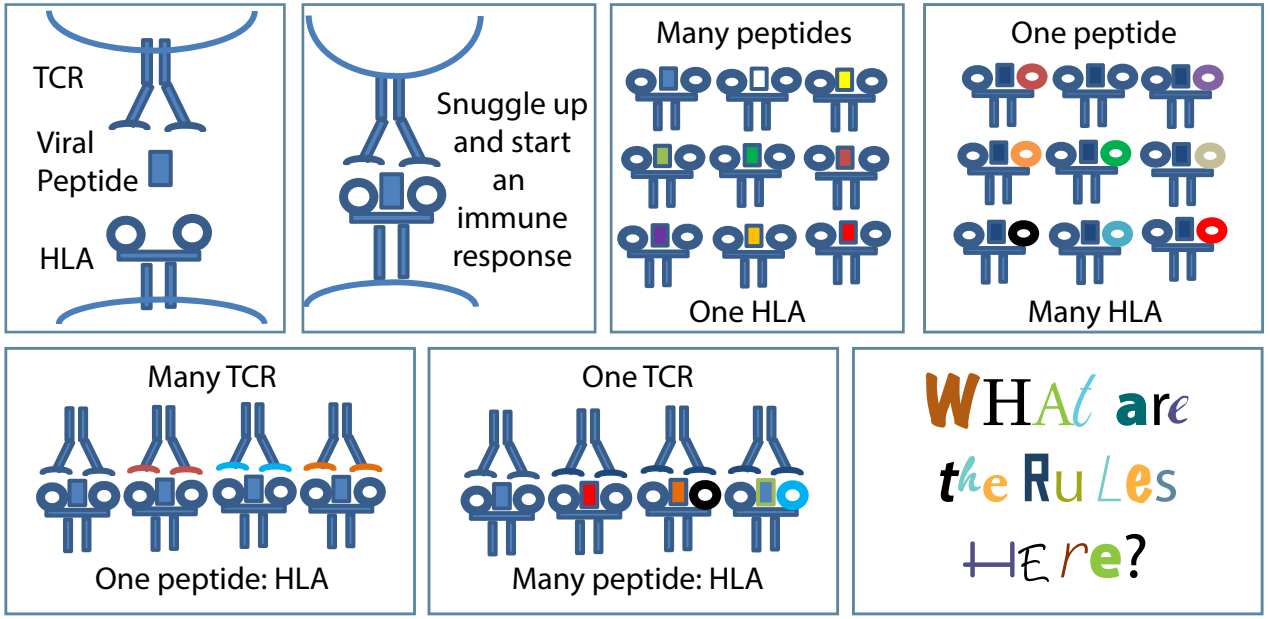
Senior Investigator, Blood Research Institute, Versiti
Assistant Professor, Microbiology and Immunology, Medical College of Wisconsin
PhD, University of Cincinnati, 1976
Started at Versiti: 1986

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. Recently he has been investigating the use of blood cells as a cellular network to identify differences in serum samples that can indicate the immune state of the person providing the serum. Finally, he is very interested in how specificity for a pathogen arises from a system whose components are not very specific. These studies will advance the basic understanding of the human response and its relation to autoimmunity, tissue transplantation and infectious disease.

Awards, Honors, and Service

- Director, Center for Human Immunology, Blood Research Institute



Subramaniam Malarkannan, PhD

Senior Investigator and Gardetto Chair for Immunology and Immunotherapy, Blood Research Institute
Professor of Medicine, Microbiology & Immunology, and Pediatrics, Medical College of Wisconsin
PhD Madurai Kamaraj University, Madurai, TN, India, 1991
Started at Versiti: 2000

Research Interests

Natural Killer (NK) cells are a type of white blood cell that specializes 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. Using single-cell sequencing, his group has determined the developmental heterogeneity of human NK cells in healthy individuals and patients with rare inherited diseases. 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 Service

- External Member, Grant Review Committee, Belgian Foundation Against Cancer, Belgium
- External Member, National Research Foundation, Government of Singapore
- Editorial Board Member, Cells, MDPI
- Guest Editor: Frontiers in Immunology, 'The Regeneration of the Functional Immune System through the Stimulation of Pluripotent Hematopoietic Stem Cells'
- Guest Editor: Cells, 'NK cell development and Functions'
- Chair, Faculty Search Committee, Immuno-Oncology Initiative, MCW Cancer Center
- Associate Editor, Frontiers in Immunology and Frontiers in Oncology
- External Member, NMRC, Government of Singapore

Funding

R38 HL143561, Stimulating access to Research in Residency (StARR).

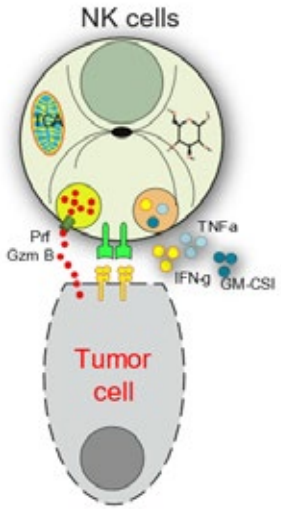
MACC Fund, "Targeting Pediatric Cancer with 'Next-Gen' CARs"

AHW, Honing inflammatory responses in cancer treatment with designer CAR-T cells.

Ann's Hope Foundation, Requirement of metabolic reprogramming in NK cells during the clearance of melanoma.

Publications

1. Yang C, Malarkannan S. Transcriptional Regulation of NK Cell Development by mTOR Complexes. Front Cell Dev Biol. 2020 Nov 10;8:566090. doi: 10.3389/fcell.2020.566090. eCollection 2020. PMID: 33240877
2. Gerbec ZJ, Hashemi E, Nanbakhsh A, Holzhauer S, Yang C, Mei A, Tsaih SW, Lemke A, Flister MJ, Riese MJ, Thakar MS, Malarkannan S. Conditional Deletion of PGC-1α Results in Energetic and Functional Defects in NK Cells. iScience. 2020 Aug 13;23(9):101454 PMID: 32858341
3. Malarkannan S. NKG7 makes a better killer. Nat Immunol. 2020 Oct;21(10):1139-1140. PMID: 32839609
4. Malarkannan S. Molecular mechanisms of FasL-mediated 'reverse-signaling. Mol Immunol. 2020 Nov;127:31-37. PMID: 32905906 Review.
5. Nanbakhsh A, Malarkannan S. Dextran Enhances the Lentiviral Transduction Efficiency of Murine and Human Primary NK Cells. Methods Mol Biol. 2020 Jan;2097:107-113. PMID: 31776922



Bill

Bill Simmons was told that he didn't have much longer to live unless he received a new heart. Thanks to the generosity of a donor, Bill is now living a healthy life with his family and advocating for organ and tissue donations.

"I've since seen a granddaughter born that I never would have seen. It saves lives and I'm the perfect example of that."

Matthew Riese, MD, PhD

(1975-2020)
Associate Professor, Department of Medicine (Division of Heme/Onc) and
Departments of Microbiology and Immunology and Surgery, Medical College of Wisconsin (MCW)
Associate Investigator, Blood Research Institute, Versiti
PhD, Medical College of Wisconsin, 2002
MD, Medical College of Wisconsin, 2004
Started at Versiti: 2012

Research Interests

The Blood Research Institute and Medical College of Wisconsin lost a valued colleague and friend with the sudden and unexpected passing of Matt Riese in 2020. Dr. Riese's lab investigated ways to improve upon existing cancer immunotherapies by targeting "off" switches inside T cells, the cells responsible for killing cancer cells. His studies incorporated both oncology and chemistry, which allowed him to blend medicine and research throughout his career.

Awards, Honors and Service

- Member, American Association for Cancer Research, 2015-current
- Member, Society for Leukocyte Biology, 2015-current
- Member, Society for Immunotherapy of Cancer, 2018-current
- Member, MCW Department of Medicine Research Committee, 2020
- Content Expert, Society for Immunotherapy in Cancer, Advances in Cancer Immunotherapy, GU Oncology, 2020
- Co-coordinator, BRI Lecture Series, 2020
- Director, BRI Technology and Transfer Office, 2020

Funding

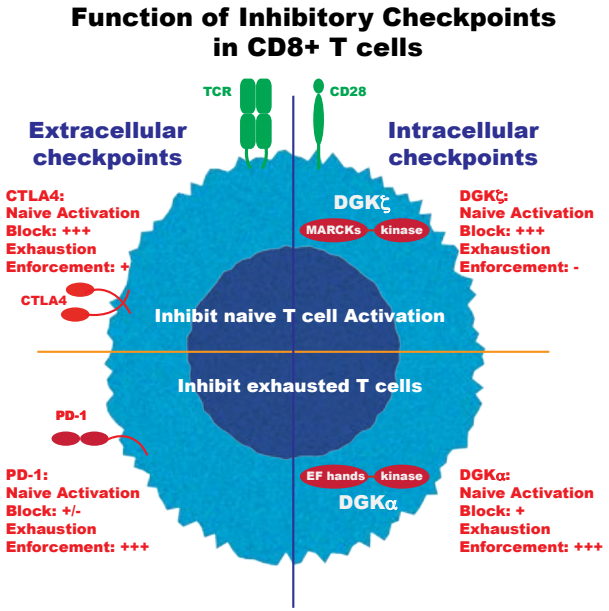
GI Innovations. 8/1/2019-7/31/2020. Evaluation of GI-101 on DGK-deficient T cells in conjunction with STING agonists (PI-Riese)

MCW Fresenius Fund. 1/1/2020-12/31/2020 (PI-Riese)

MCW Kendall Gift. 7/1/2020-6/31/2021 (PI-Riese)

Publications

1. Fong L, Hotson A, Powderly J, Sznol M, Heist RS, sChoueiri TK, George S, Hughes BG, Hellmann MD, Shepard DR, Rini BI, Kummar S, Weise AM, Riese MJ, Markman B, Emens LA, Mahadevan D, Luke JJ, Laport G, Brody JD, Hernandez-Aya L, Bonomi P, Goldman JW, Berim L, Renouf DJ, Goodwin RA, Munneke B, Ho PY, Hsieh J, McCaffery I, Kwei L, Willingham SB, Miller RA. Adenosine A2A Receptor Blockade as an Immunotherapy for Treatment-Refractory Renal Cell Cancer. Cancer Discov. 2020 Jan;10(1):40-53. PMID: 31732494
2. Wittmann D, Hall WA, Christians KK, Barnes CA, Jariwalla NR, Aldakkak M, Clarke CN, George B, Ritch PS, Riese M, Khan AH, Kulkarni N, Evans J, Erickson BA, Evans DB, Tsai S. Impact of Neoadjuvant Chemoradiation on Pathologic Response in Patients With Localized Pancreatic Cancer. Front Oncol. 2020 Apr 15;10:460. doi: 10.3389/fonc.2020.00460. eCollection 2020. PMID: 32351886
3. Yang C, Siebert JR, Burns R, Zheng Y, Mei A, Bonacci B, Wang D, Urrutia RA, Riese MJ, Rao S, Carlson KS, Thakar MS, Malarkannan S. Single-cell transcriptome reveals the novel role of T-bet in suppressing the immature NK gene signature. Elife. 2020 May 14;9:e51339. doi: 10.7554/eLife.51339. PMID: 32406817
4. George G, Schmidt L, Tolat P, Riese M, Kilari D. Salvage ipilimumab associated with a significant response in sarcomatoid renal cell carcinoma. J Immunother Cancer. 2020 Feb;8(1) pii: e000584. doi: 10.1136/jitc-2020-000584. PMID: 32114501
5. Gerbec ZJ, Hashemi E, Nanbakhsh A, Holzhauer S, Yang C, Mei A, Tsaih SW, Lemke A, Flister MJ, Riese MJ, Thakar MS, Malarkannan S. Conditional Deletion of PGC-1α Results in Energetic and Functional Defects in NK Cells. iScience. 2020 Aug 13;23(9):101454 PMID: 32858341



Demin Wang, PhD

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

Research Interests

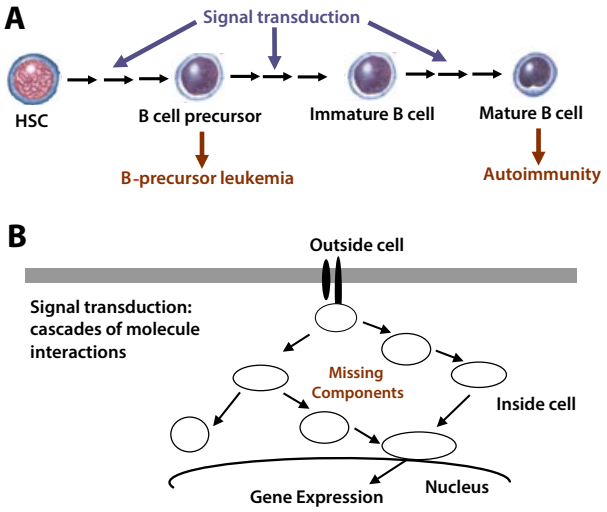
Dr. Wang is concerned with self-renewal and differentiation of cells (hematopoietic stem cells, HSCs) that give rise to blood cells and to the subset of white blood cells (B lymphocytes) that produce antibodies. His studies are designed to identify and functionally characterize signaling molecules and pathways that are critical to HSC and B cell biology. Recent studies have identified a novel and important role of the signaling molecule Kras in regulating alloreactive T cell function during acute graft-versus-host disease. These findings support Kras as a novel and effective therapeutic target for acute graft-versus-host disease. Furthermore, he studies the mechanisms underlying the production of autoantibodies causing heparin-induced thrombocytopenia and thrombosis (HIT). 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 Service

- Editorial Board, Blood, 2017-present
- Reviewer, Cellular and Molecular Immunology B (CMI-B) Study Section, NIAID, NIH, 03/2020
- Reviewer, Cellular and Molecular Immunology B (CMI-B) Study Section, NIAID, NIH, 10/2020
- Member, P01 external advisory board at University of Virginia. 2020-present

Funding

R01 AI079087 "PLCγs in B cell biology and autoimmunity"



R01 HL130724 "B cell responses in heparin-induced thrombocytopenia"

Publications

1. Xia C, Wang T, Cheng H, Dong Y, Weng Q, Sun G, Zhou P, Wang K, Liu X, Geng Y, Ma S, Hao S, Xu L, Guan Y, Du J, Du X, Li Y, Zhu X, Shi Y, Xu S, Wang D, Cheng T, Wang J. Mesenchymal stem cells suppress leukemia via macrophage-mediated functional restoration of bone marrow microenvironment. Leukemia. 2020 Sep;34(9):2375-2383. PMID: 32094463
2. Gupta S, Konradt C, Corken A, Ware J, Nieswandt B, Di Paola J, Yu M, Wang D, Nieman MT, Whiteheart SW, Brass LF. Hemostasis vs. homeostasis: Platelets are essential for preserving vascular barrier function in the absence of injury or inflammation. Proc Natl Acad Sci U S A. 2020 Sep 29;117(39):24316-24325. PMID: 32929010
3. Yang C, Siebert JR, Burns R, Zheng Y, Mei A, Bonacci B, Wang D, Urrutia RA, Riese MJ, Rao S, Carlson KS, Thakar MS, Malarkannan S. Single-cell transcriptome reveals the novel role of T-bet in suppressing the immature NK gene signature. Elife. 2020 May 14;9:e51339. doi: 10.7554/eLife.51339. PMID: 32406817
4. Li J, Zhang L, Zheng Y, Shao R, Liang Q, Yu W, Wang H, Zou W, Wang D, Xiang J, Lin A. BAD inactivation exacerbates rheumatoid arthritis pathology by promoting survival of sublining macrophages. Elife. 2020 Dec 3;9:e56309. doi: 10.7554/eLife.56309. PMID: 33270017
5. Luo L, Chen Y, Chen X, Zheng Y, Zhou V, Yu M, Burns R, Zhu W, Fu G, Felix JC, Hartley C, Damnernsawad A, Zhang J, Wen R, Drobyski WR, Gao C, Wang D. Kras-Deficient T Cells Attenuate Graft-versus-Host Disease but Retain Graft-versus-Leukemia Activity.

Renren Wen, PhD

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

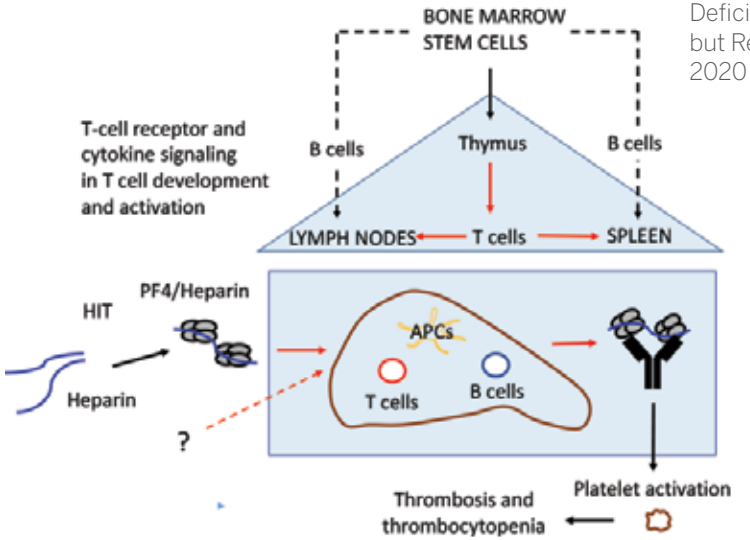
Research Interests

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. Dr. Wen's work is aimed at more fully understanding the signaling pathways that govern proper B and T cell activation and communications.

Dr. Wen's lab studies two signaling molecules that play roles in both B and T cells: phospholipase gamma, mutations of which have been associated with human autoinflammatory diseases and T cell lymphomas, and Bcl10, mutations which have been associated with human B cell lymphomas. Dr. Wen's lab also studies heparin-induced thrombocytopenia (HIT), a disease that is caused by clinical administration of heparin, which in some patients can result in limb- and life-threatening thrombosis. Dr. Wen's lab has cloned a group of antibodies that can activate platelets and contribute to the development of HIT. Her current work is focused on identifying the underlying molecular mechanisms that control the development and activation of the B cells that generate these platelet-activating antibodies, and her work will potentially lead to improved diagnosis and HIT treatment.

Awards, Honors and Service

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



Funding

R01 1R01HL148120-01 Wen (PI) 06/01/19-05/31/2023 NIH/NHLBI "Molecular Basis of the Humoral Immune Response in Heparin-Induced Thrombocytopenia" Role: PI

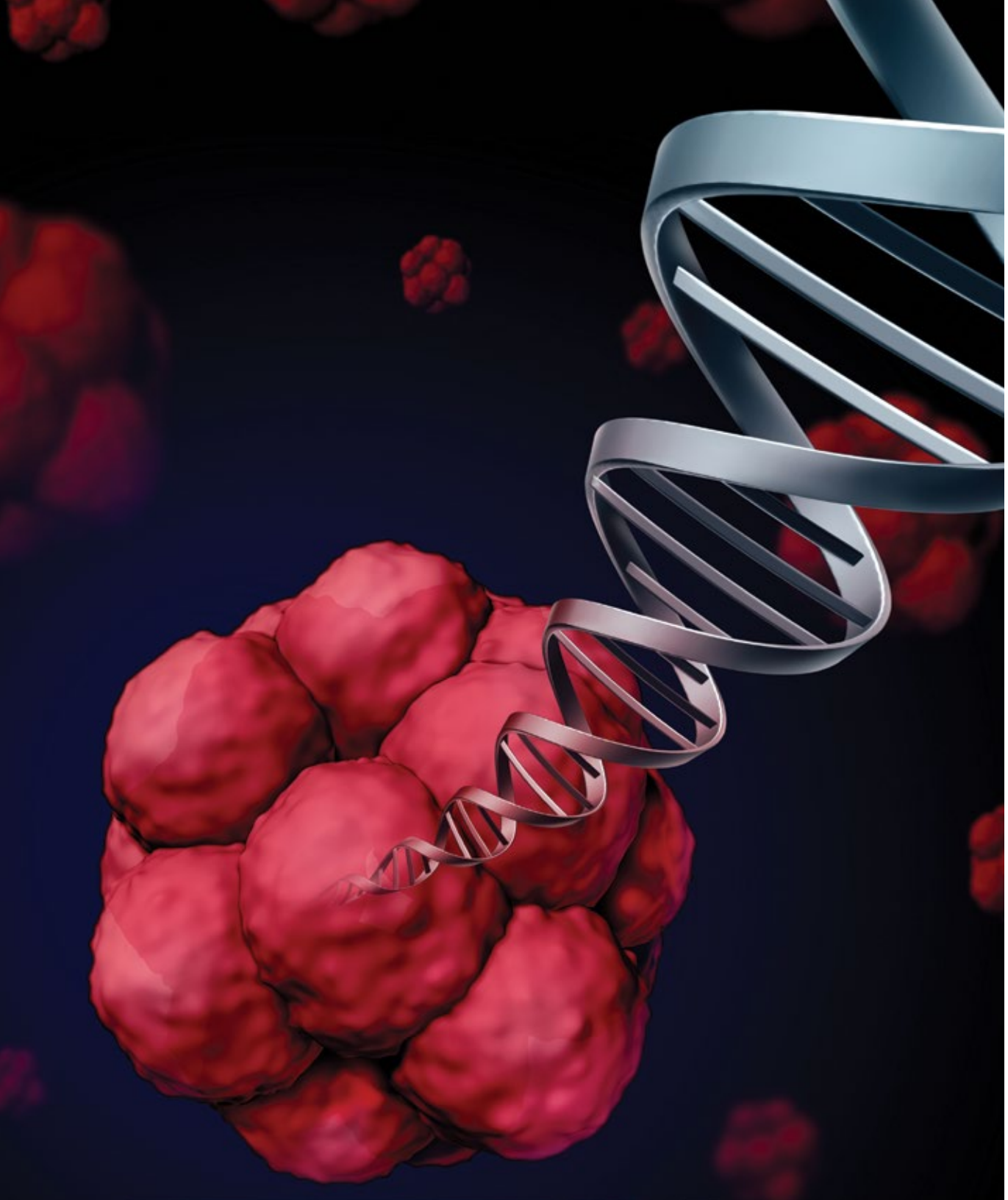
R01 HL130724 Wang (PI) 12/01/2016-11/30/2020 "B cell responses in heparin-induced thrombocytopenia" Role: Co-I

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

ACTIV-4 Mechanistic Studies "Antibody-mediated thromboinflammation in COVID-19", Role: Co-I

Publications

1. Luo L, Chen Y, Chen X, Zheng Y, Zhou V, Yu M, Burns R, Zhu W, Fu G, Felix JC, Hartley C, Damnernsawad A, Zhang J, Wen R, Drobyski WR, Gao C, Wang D. Kras-Deficient T Cells Attenuate Graft-versus-Host Disease but Retain Graft-versus-Leukemia Activity. J Immunol. 2020 Dec 15;205(12):3480-3490. PMID: 33158956



Stem Cells

Research in Stem Cell Biology and Hematopoiesis is aimed at understanding the many factors that regulate the process of how normal blood cells are formed (called 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 leukemia.

Studies in this area are bringing Versiti 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.

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

Associate Professor, Department of Internal Medicine, Division of Hematology and Oncology, Medical College of Wisconsin
Assistant Investigator, Blood Research Institute, Versiti
MD/PhD University of Wisconsin-Madison, 2004
Hematology/Oncology Fellowship: New York Presbyterian, Weill-Cornell Medical Center, 2011
Started at Versiti: 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 and Froedtert Hospital. At the Blood Research Institute, her research focuses on the bone marrow microenvironment.

Dr. Carlson studies how extracellular matrix dynamics control communication between the peripheral nervous system and the bone marrow.

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

Awards, Honors and Service

- Best Doctors designation 2018, 2019, 2020
- Associate Program Director, Hematology and Oncology Fellowship program, Medical College of Wisconsin

Funding

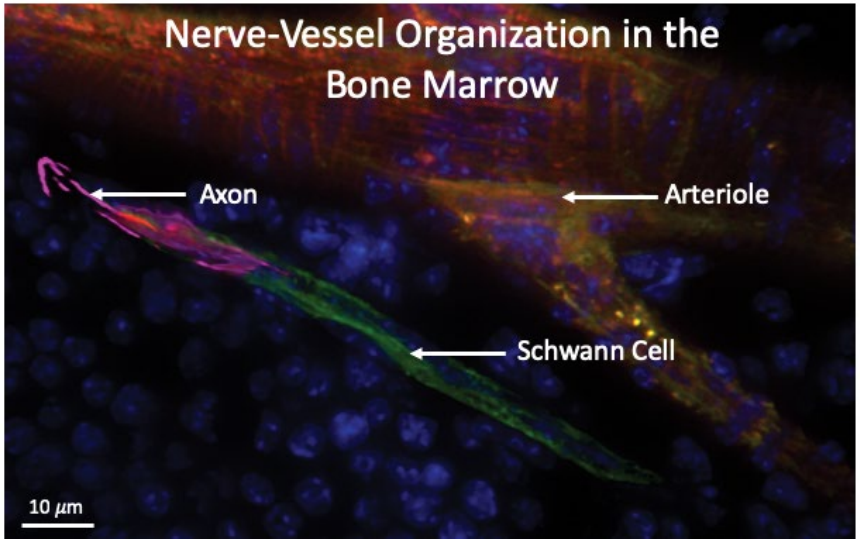
"Schwann Cell Regulation of Hematopoiesis," 1R03HL155174-01, NIH/NHLBI (12/1/2020--11/30/2022). Role: PI

"Neural Regulation of AML," Froedtert Hospital and the Scott Garrett Leukemia Research Foundation (04/01/2020 –12/31/2021). Role: PI

MCW Paulette Kroll Leukemia Research Fund, (04/01/2020 – ongoing). Role: PI

Publications

1. Basu S, Liang HPH, Hernandez I, Zogg M, Fields B, May J, Ogoti Y, Wyseure T, Mosnier LO, Burns RT, Carlson K, Weiler H. Role of Thrombomodulin expression on hematopoietic stem cells. J Thromb Haemost. 2020 Jan;18(1):123-135. PMID: 31628891
2. Guru Murthy GS, Szabo A, Michaelis L, Carlson KS, Runaas L, Abedin S, Atallah E. Improving Outcomes of Acute Promyelocytic Leukemia in the Current Era: Analysis of the SEER Database. J Natl Compr Canc Netw. 2020 Feb;18(2):169-175. PMID: 32023530.
3. Carlson KS*, Morris J, Cross LP, Rao S. "Stem Cell Biology in Bone Marrow Transplantation"; Contemporary Bone Marrow Transplantation. (Book Chapter)



John Pulikkan, PhD

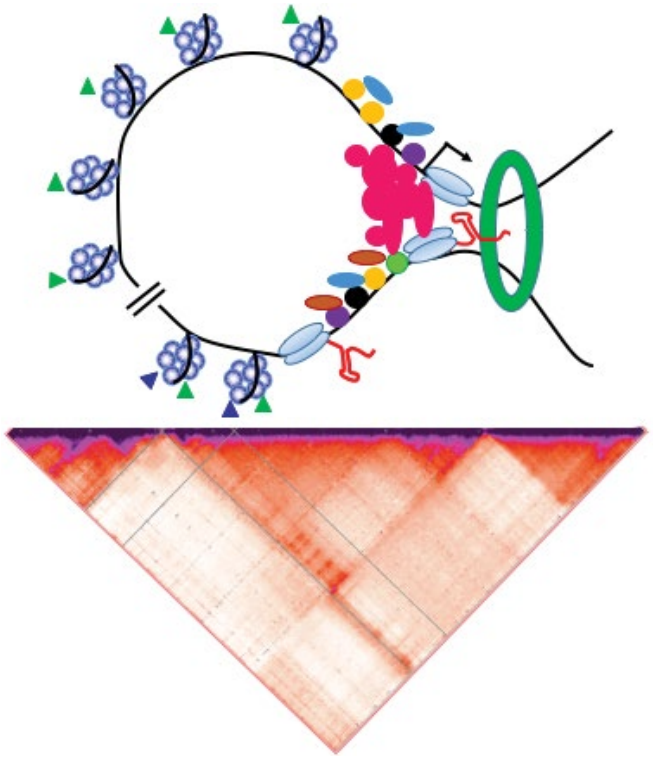
Associate Investigator, Blood Research Institute, Versiti
PhD, Ludwig Maximilians University of Munich, Munich, Germany, 2008
Postdoctoral Associate, University of Massachusetts Medical School, Worcester, MA, 2010-2018
Employed at Versiti: 2018

Research Interests

The past decade of leukemia research has indicated in a comprehensive understanding of the role of genetic and epigenetic changes in leukemogenesis. However, only recently has the three-dimensional genome architecture been implicated in leukemogenesis. While much is known about transcription factor deregulation in AML, our understanding of chromatin structure and how transcription factors regulate higher-order genome architecture is limited. Our lab is interested in understanding the interplay between transcription factors (RUNX1 and C/EBPα) and chromatin dynamics in myeloid differentiation and how this is altered in AML. Our goal is to identify and characterize novel therapeutic targets, and translate them to the clinic with academic and pharmaceutical collaborations.

Awards, Honors and Service

- Member, American Association for Cancer Research (AACR)
- Member, International Society for Stem Cell Research (ISSCR)
- Member, American Society for Hematology



Sridhar Rao, MD, PhD

Associate Investigator, Blood Research Institute, Versiti
Associate Professor of Pediatrics, Division of Hematology/Oncology, Medical College of Wisconsin
MD, University of Chicago, Pritzker School of Medicine, 2001
PhD, University of Chicago, 1999
Started at Versiti: 2010

Research Interests

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

Dr. Rao's 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. In Dr. Rao's lab, they have focused on how mutations in a specific group of genes, termed the cohesin complex, cause AML. 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. Dr. Rao is 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. He has also expanded his research interest into Ewing's Sarcoma, in which cohesin mutations have also recently been identified.

Awards, Honors and Service

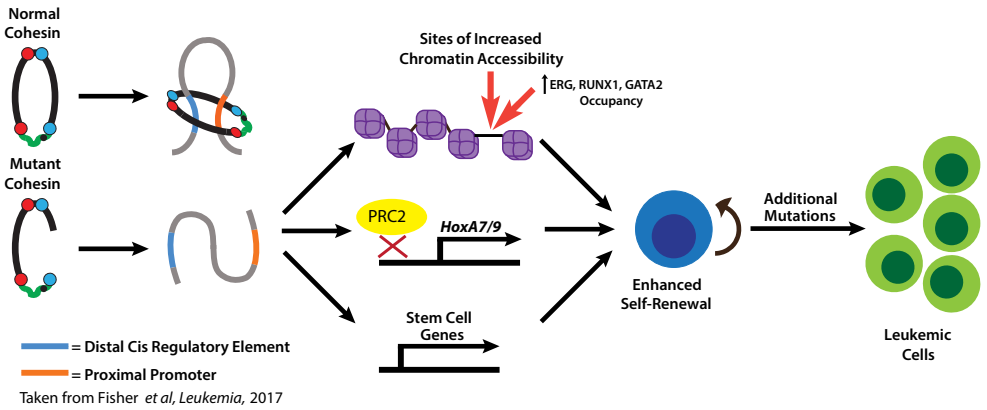
- Member, American Society of Hematology
- Member, American Association for Cancer Research
- Permanent Member, NIH CSR Standing Study Section (DEV2) 2019-2023

Funding

National Cancer Institute- R01 "Cohesin Mutations in AML"

Midwest Athletes Against Childhood Cancer (MACC Fund)

National Heart, Lung, and Blood Institute- "Genetic and Mechanisms of BP Regulation"



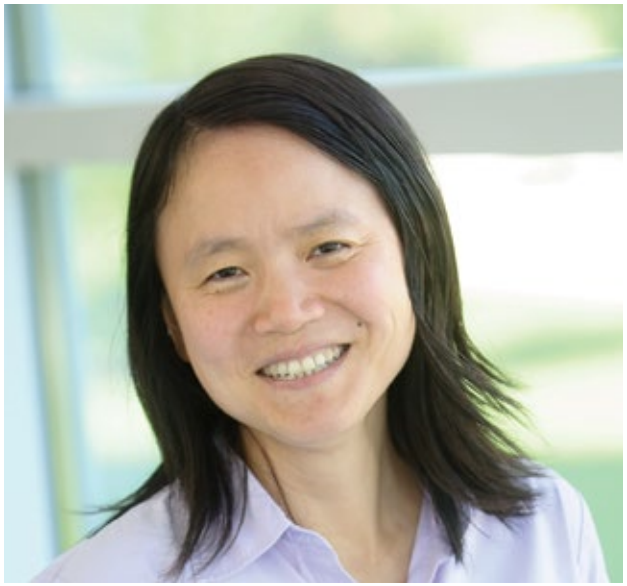
Taken from Fisher *et al, Leukemia,* 2017

Publications

1. Mishra MK, Liang EY, Geurts AM, Auer PWL, Liu P, Rao S, Greene AS, Liang M, Liu Y. Comparative and Functional Genomic Resource for Mechanistic Studies of Human Blood Pressure-Associated Single Nucleotide Polymorphisms. Hypertension. 2020 Mar;75(3):859-868 PMID: 31902252
2. Yang C, Siebert JR, Burns R, Zheng Y, Mei A, Bonacci B, Wang D, Urrutia RA, Riese MJ, Rao S, Carlson KS, Thakar MS, Malarkannan S. Single-cell transcriptome reveals the novel role of T-bet in suppressing the immature NK gene signature. Elife. 2020 May 14;9:e51339. doi: 10.7554/eLife.51339. PMID: 32406817
3. Meyer AE, Furumo Q, Stelloh C, Minella AC, Rao S. Loss of Fbxw7 triggers mammary tumorigenesis associated with E2F/c-Myc activation and Trp53 mutation. Neoplasia 2020 Nov;22(11):644-658. PMID: 33070870
4. Rao S. RUNX1 and inv(16) are frenemies in AML. Blood. 2020 Nov 19;136(21):2361-2362. PMID: 33211836

Nan Zhu, PhD

Associate Investigator, Blood Research Institute, Versiti
Assistant Professor, Cell Biology, Neurobiology and Anatomy, Medical College of Wisconsin
PhD, Boston University, Boston, MA, 2007
Started at Versiti: 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 cells (HSC) as well as leukemia stem cells (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 emerged as important players in the development of cancer as evident by recurrent mutations across a spectrum of cancers. Dr. Zhu's lab has previously screened and identified several epigenetic regulators as important for the maintenance of acute myeloid leukemia (AML). Currently, Dr. Zhu is working on elucidating their role in normal and malignant stem cell function and understanding the precise underlying molecular mechanism. Dr. Zhu has shown that one of the epigenetic regulators, JMJD1C, is important for LSC function but dispensable for HSC function, thus a potential therapeutic target. Dr. Zhu's lab is extending this finding using pre-clinical models of human AML as well as studying the molecular mechanism of how JMJD1C functions in AML. The ultimate goal of our research is to identify therapeutic targets and developed targeted therapy in AML based on knowledge gained from our research.

Funding

- NIH(NCI) R37CA229751, "The histone demethylase JMJD1C in human Acute Myeloid Leukemia"
- ASH Scholar Award, "Understanding Molecular Mechanism of JMJD1C Function in AML"

Publications

1. Lenard A, Xie HM, Pastuer T, Shank T, Libbrecht C, Kingsley M, Riedel SS, Yuan ZF, Zhu N, Neff T, Bernt KM. Epigenetic regulation of protein translation in KMT2A-rearranged AML. Exp Hematol. 2020 May;85:57-69. PMID: 32437908

Leukemia Cells

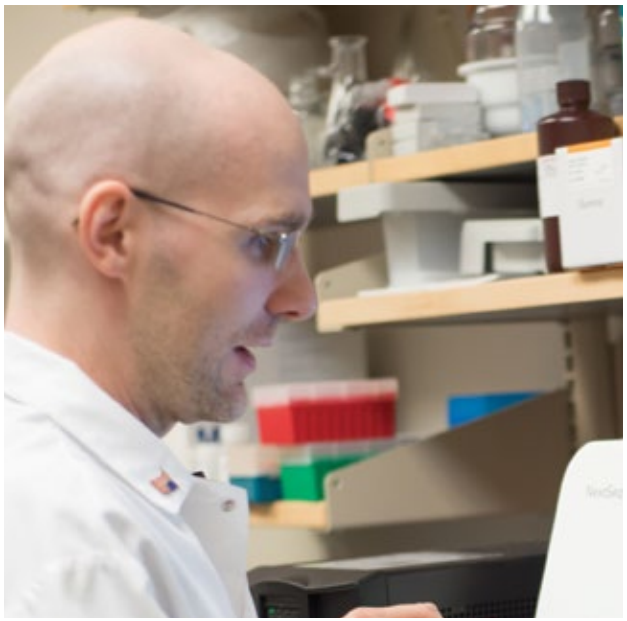
Gia

Gia Danninger is a fighter. When she was 5 years old, she was diagnosed with aplastic anemia, a rare disease that occurs when the body stops producing enough new blood cells. Doctors told her and her family that she would need a bone marrow transplant to survive.

The search took less than three weeks and in 2017, Gia underwent the bone marrow transplant and soon recovered and returned to a happy and healthy childhood. Now, Gia and her family are thankful for both blood and marrow donors that gave her – and other patients in need – a second chance at life.

"Blood and marrow donations can totally change someone's world," says, Gia's mom, Jenna.

Core Laboratories



Modern biomedical research requires access to a wide range of specialized technologies. The Versiti 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 13 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 **Single Cell Biology Cor**e features three platforms including 10x Genomics, Takara ICELL8, and Fluidigm for the molecular analysis of single cells.

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 aids investigators with protein purifications using AKTA and Agilent chromatography systems.

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

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

The **Microscopic Imaging Core** includes the confocal/multiphoton laboratory featuring an Olympus FV1000-MPEconfocal, multiphoton microscope as well as an inverted Nikon TE200, a Nikon Eclipse Ti2 inverted fluorescence microscope, a Zeiss Axioscope and a Zeiss Lumar V12 stereo microscope with fluorescence capabilities. A PhD Imaging Specialist manages the Microscopic Imaging Core.

The **Viral Vector Core** is shared between the BRI and 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 **Computational Biology Core** is led by a PhD scientist who collaborates with BRI investigators to analyze and interpret their next generation sequencing data. The Core provides not only data analysis but also integration and development of new computational methods to analyze and integrate genome wide data sets.

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 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.

Versiti Blood Research Institute Foundation

The situations that arose in 2020 affected people across the globe in so many different ways. At the Versiti Blood Research Institute (BRI), it motivated researchers who sought to understand COVID-19, and inspired them to find treatments and cures. The BRI labs went dark for a few weeks at the beginning of the pandemic, but with new precautions in place, researchers came back to their labs to continue their life-saving work. Several of the researchers turned their expertise to COVID, hoping to help with the world-wide search for a vaccine.

During this same time, the Foundation team continued with our outreach, finding creative ways to engage with our philanthropic community. I would like to thank so many of you who joined us for calls and virtual meetings.

In July, we hosted a COVID-19 Zoom, where several of our researchers talked with more than 150 attendees about the work that they are doing. At that time, so much was still unknown, and the meeting provided a great opportunity for attendees to ask questions about the research taking place.

In September, we hosted our Imagine Gala virtually. We were thrilled to have more than 170 people join us to celebrate our Inaugural Imagine Award recipient, Katie Jorgensen, our Virginia Brooks Jefferson Award recipient, Kristin Severson, and Dr. Richard Aster, who retired after more than 50 years at Versiti. The celebration of those remarkable individuals, as well as research overall helped us raise $176,000! We are incredibly grateful to all who participated.

As we look ahead to 2021, we hope you will all continue to stay safe and we look forward to seeing you in person again soon. On behalf of the researchers whose work benefits from your generosity, thank you for your support of the Versiti Blood Research Institute.

If you'd like to learn more about how you can help, please contact the Foundation office at 414-937-6799.

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 Versiti helps to identify, protect, and commercially partner discoveries to serve patient needs. Net revenues generated support further research. In 2020, four new patent applications were filed and royalty income totaled $958,226. Versiti has inked more than 50 license agreements with industry partners.

Mission Statement

The Technology Transfer Office supports Versiti'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, the Technology Transfer Office provides intellectual property, contract management, and business management administrative services for the organization. A cross functional team called the Technology Transfer Review Group provides executive oversight for this function.

Leadership 2020

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Publications 2020

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Versiti / Blood Research Institute
8733 W Watertown Plank Road
Milwaukee, WI 53226

versiti.org/BRI
Phone: 414.937.6238