Research Publication Series

August 2019

MEDICAL COLLEGE OF WISCONSIN

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About the Research Publication Series:

The Medical College of Wisconsin is a major national research center and the second-largest research institution in Wisconsin. Basic science, clinical, and translational researchers thrive in the unique setting of an academic medical center. The innovative work of our scientists leads to groundbreaking discovery that impacts healthcare and saves lives. The Research Publication Series is a sampling of recent publications by faculty, staff, and student investigators.

MCW Collaborative Highlights, indicated with the puzzle piece icon, call out articles that are produced by multidisciplinary teams. These articles represent collaborative efforts between researchers from different departments, centers, divisions, or fields of study.

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Publication Stats: August 2019

Publication Type	July Total
Articles	55
Editorial Material	4
Reviews	8
Total	**67**

Publications in Top Quartile Journals
36 out of 67 (53.7%)

Total Publications Fiscal Year to Date:
1,712

Publication stats are pulled by the MCW Libraries for the previous month using the Science Citation Index and Social Sciences Citation Index. For inclusion, one or more authors must be institutionally affiliated with MCW. Letters and abstracts are excluded from the data. The MCW Fiscal Year runs from July 1 – June 30.

Research Publication Series:

August 2019

Staley Brod, MD
"Myelinating Proteins in MS Are Linked to Volumetric Brain MRI Changes"

Nita Salzman, MD, PhD
"Microbiome Signatures Associated with Steatohepatitis and Moderate to Severe Fibrosis in Children With Nonalcoholic Fatty Liver Disease"

Michael J. Burke, MD
"Replacing cyclophosphamide/cytarabine/mercaptopurine with cyclophosphamide/etoposide during consolidation/delayed intensification does not improve outcome for pediatric B-cell acute lymphoblastic leukemia: a report from the COG"

Shao-Min Shi, MD
"Modified V-Y Turndown Flap Augmentation for Quadriceps Tendon Rupture Following Total Knee Arthroplasty: A Retrospective Study"

Rana Higgins, MD, FACS, FASMBS
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"Sortase-Dependent Proteins Promote Gastrointestinal Colonization by Enterococci"

Garrett K. Berger, PharmD
"Outcomes in different age groups with primary Ewing sarcoma of the spine: a systematic review of the literature"

Lynn W. Sun, MD, PhD
"Assessment of Consistency Between Peer-Reviewed Publications and Clinical Trial Registries"

Cover Image from "Rete Testis Invasion Is Consistent With Pathologic Stage T1 in Germ Cell Tumors"

Staley Brod, MD
Professor
Director, Division of MS/Neuro-Immunology
Diplomate, American Board of Internal Medicine
Diplomate, American Board of Psychiatry and Neurology
Department of Neurology
Medical College of Wisconsin

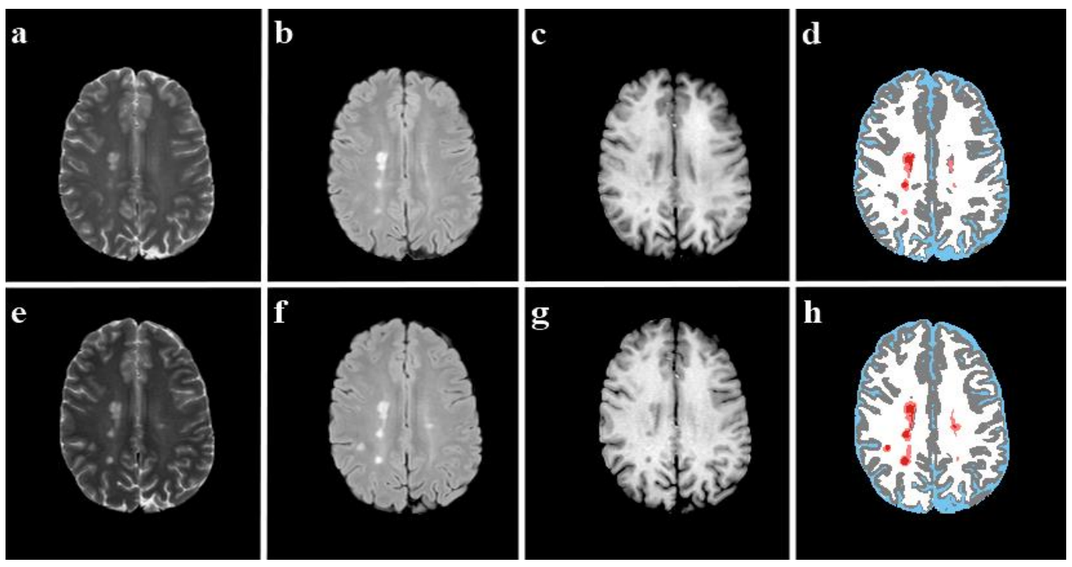
I have been a Professor of Neurology and the Director of the Division of Neuro-immunology at MCW since 2016. My research interests include animal models of auto-immune disease, immunomodulation, oral administration of type 1 interferons and ACTH in multiple sclerosis (MS) and insulin dependent diabetes mellitus (type 1 diabetes). The research in my laboratory is directed at understanding the underlying immune abnormalities of human auto-immune disease. Current studies are directed at understanding the mechanism of inflammation in the MS animal models using novel proteins and determining which cells are responsible for its suppression. We are working to understand the relationship of Volumetric Brain MR changes and Myelinating Proteins in MS in humans.

"Myelinating Proteins in MS Are Linked to Volumetric Brain MRI Changes"

Brod SA, Lincoln JA, Nelson F. *Journal of Neuroimaging*. 2019;29(3):400-405.

There is evidence of a relationship between pro-myelinating proteins and clinical MS activity during clinical relapse or recovery from clinical relapses. We examined the linkage between pro-myelinating biomarkers and volumetric changes in multiple sclerosis (MS) subjects during serial magnetic resonance (MR) imaging. We enrolled 13 MS subjects with active brain MRI scans not on disease modifying therapies (DMTs). Subjects underwent baseline MRI, serum and CSF sampling. Qualitative changes; new/resolving Gd, new/enlarging/diminishing T2 and T1 hypointense lesions were compared to baseline in subsequent MRI scans, and volumetric analysis was calculated. Analysis of biomarkers on serial CSF samples was performed only in subjects with qualitative (and quantitative) changes on MRI. The study was performed at a MS Center of Excellence academic medical center. There was increased CSF N-CAM during increased qualitative T1 activity. A positive correlation between CSF and serum N-CAM and T1 lesion volume was observed. A negative correlation between serum BDNF and BPH (T1 vol/T2 vol + T1 vol) was observed. Increased N-CAM levels may be related to repair or re-myelination following injury to the brain as shown by increased T1 volumes. Our data suggest an early kind of blood signaling that induces release of peripheral BDNF levels.

Figure 1. Longitudinal MRI-AP Processing Showing Qualitative Change in MS Lesions.



Panels a-d show an example of single-time point and & panels e-h longitudinal registration and semi-automated MRI Automated Processing (MRI-AP) tissue segmentation. The MRI-AP standard output includes T2 (panel a & e), Fluid Attenuated Inversion Recovery (FLAIR) (panel b & f), pre-contrast T1 (panel c & g) and expert-validated MRI-AP segmentation (d & h). Panels d & h show final tissue segmentation of CSF (light blue), cortical and deep gray matter (light gray), white matter (white), T2-hyperintense lesion (salmon) and T1-hypointense lesion (dark red). Qualitative changes in T2 and T1 lesions are clearly visible on longitudinally segmented images.

Nita Salzman, MD, PhD
Professor
Division of Gastroenterology
Department of Pediatrics
Medical College of Wisconsin

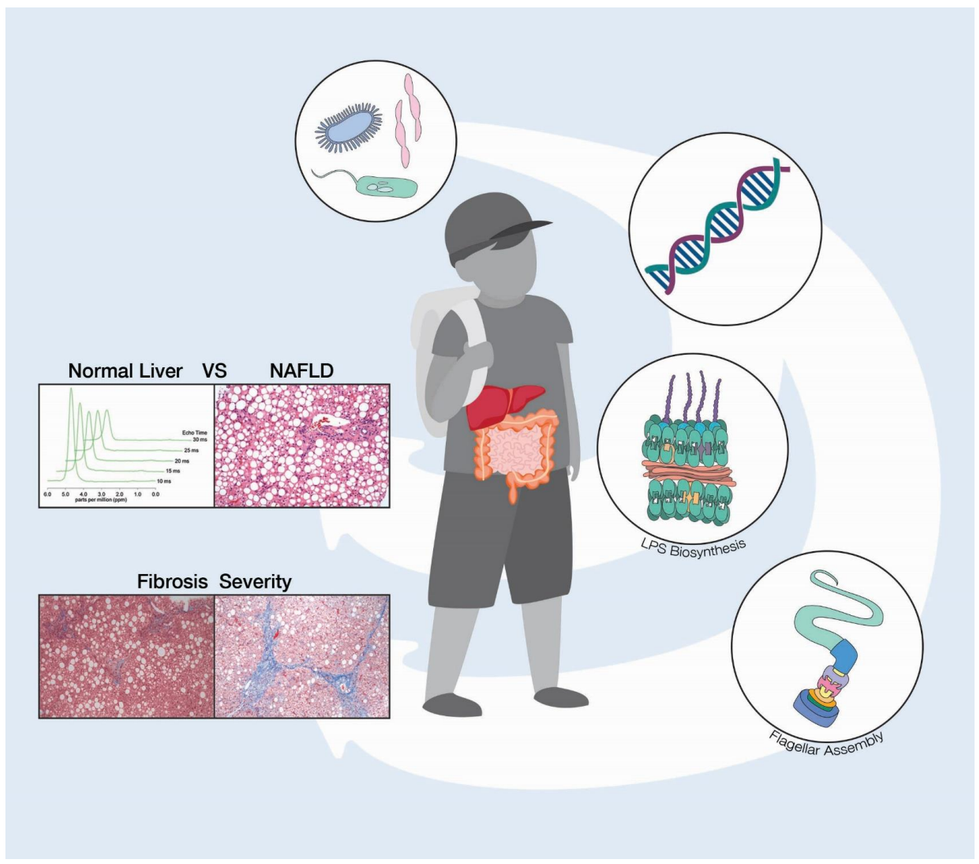
I am a Professor of Pediatrics, Microbiology and Immunology, Associate Director of the Medical Scientist Training Program, co-leader of the Immunology, Inflammation and Infection research unit of the Children's Research Institute, and Director of the MCW Center for Microbiome Research. My laboratory has a dual focus on both basic and translational research, including the role of the intestinal microbiome in human health and disease, and also focusing on interactions between the mucosal innate immune system, enteric pathogens, and the microbiome.

"Microbiome Signatures Associated with Steatohepatitis and Moderate to Severe Fibrosis in Children With Nonalcoholic Fatty Liver Disease"

Schwimmer JB, Johnson JS, Angeles JE, et al. *Gastroenterology*. 2019 in press.

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease in American children. Factors explaining disease development and severity are poorly characterized. Evidence suggests the intestinal microbiome may influence NAFLD pathogenesis. We evaluated the fecal microbiome of children with NAFLD, and age and Body Mass Index (BMI)-matched control children without NAFLD, characterizing bacterial composition and functional capacity that discriminate between cases and controls and those associated with greater disease severity. We found intestinal microbial dysbiosis was associated with disease development and severity. NAFLD and its severity were associated with greater abundance of genes encoding inflammatory bacterial products. This could be used for predictive models of disease, suggesting alterations to intestinal microbiome may contribute to pathogenesis of NAFLD and be used as markers of disease or severity.

Proposed *Gastroenterology* Issue Cover Art



Michael J. Burke, MD

Associate Professor
Director, Leukemia & Lymphoma Program
Co-Director, Developmental Therapeutics Program
Children's Hospital of Wisconsin
Medical College of Wisconsin

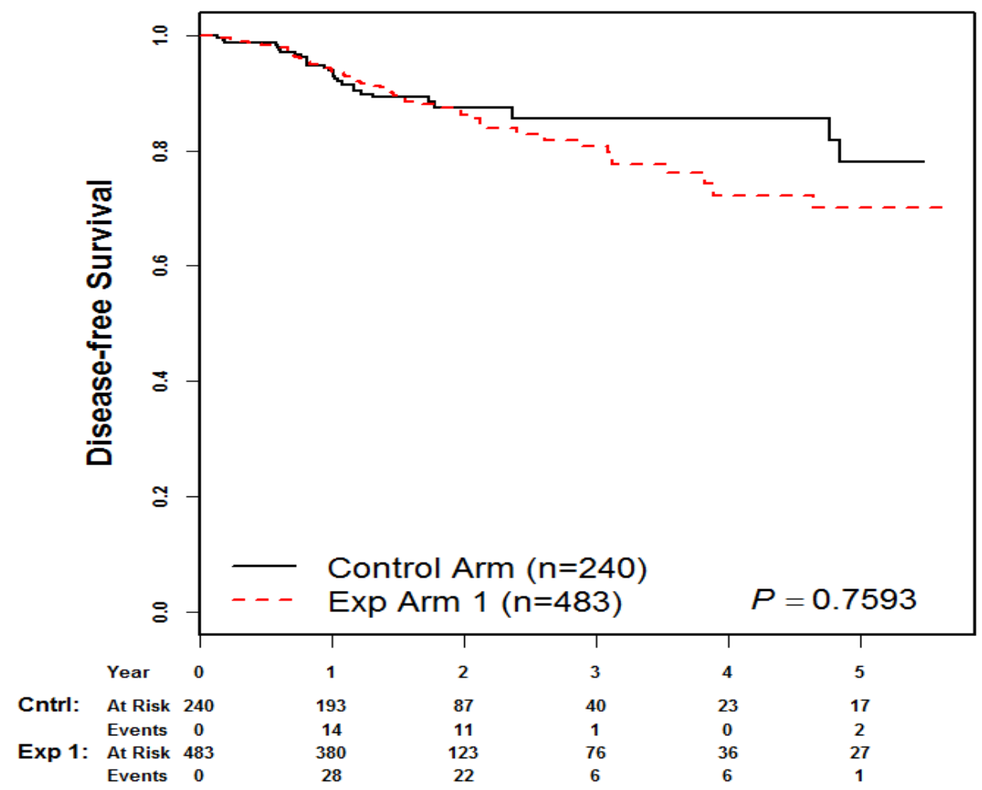
I am an Associate Professor in the Department of Pediatrics, Division of Hematology/Oncology/Bone Marrow Transplantation. I direct the Leukemia & Lymphoma Program at Children's Hospital of Wisconsin and have developed early phase and upfront clinical trials in acute leukemia that have opened locally as well as nationally through consortiums such as the Children's Oncology Group and the Therapeutic Advances in Childhood Leukemia & Lymphoma (TACL). My research interests have primarily focused on the development of early phase clinical trials investigating novel agents and/or combination therapies for relapsed/refractory leukemia. Specifically, I have been investigating epigenetic modifying therapies in acute leukemia which led to the development of the first multi-agent epigenetic trial in pediatric ALL that was completed in TACL.

"Replacing cyclophosphamide/cytarabine/mercaptopurine with cyclophosphamide/etoposide during consolidation/delayed intensification does not improve outcome for pediatric B-cell acute lymphoblastic leukemia: a report from the COG"

Burke MJ, Salzer WL, Devidas M, et al. *Haematologica*. 2019;104(5):986-992.

Approximately 90% of patients with pediatric B-cell acute lymphoblastic leukemia (B-ALL) are cured. However, some patients remain at very high risk (VHR) of relapse. AALL1131 aimed to determine if the substitution with cyclophosphamide/etoposide (Experimental Arm 1) would improve disease-free survival (DFS) of pediatric patients with VHR B-ALL compared to standard therapy (Control Arm). Patients 1-30 years of age with newly diagnosed VHR B-ALL were randomized post-induction to Control Arm or Experimental Arm 1 during Part 2 of Consolidation and Delayed Intensification. 4-year DFS rates were 85.5 +6.8% (Control Arm) versus 72.3 +6.3% (Experimental Arm 1) (p-value = 0.76). There were no significant differences in Grade 3/4 adverse events. Substitution of this therapy for VHR B-ALL patients on Children's Oncology Group AALL1131 randomized to cyclophosphamide/etoposide did not improve DFS.

Figure 1.
Outcomes based on information in the database at Dec. 31, 2017 with additional follow-up; Four-year disease-free survival rates were 85.5±6.8% in the control arm (Contr) versus 72.3±6.3% in experimental arm 1 (Exp 1) (P=0.76).



Shao-Min Shi, MD
Distinguished Professor
Department of Orthopaedic Surgery
Medical College of Wisconsin

I am an Assistant Professor and Distinguished Professor working in the Department of Orthopedic Surgery. I completed my Hand Surgery Fellowship in Grand Rapids, Michigan and studied under a hand surgery Scholarship at the Christine M. Kleinert Institute for Hand and Microsurgery in Louisville, Kentucky. My clinical and research interests include hand and microsurgery and free tissue transfer coverage, particularly for complicated lower extremity injuries. My research specialty is about quadriceps tendon rupture following total knee arthroplasty (TKA).

"Modified V-Y Turndown Flap Augmentation for Quadriceps Tendon Rupture Following Total Knee Arthroplasty: A Retrospective Study"

Shi SM, Shi GG, Laurent EM, Ninomiya JT. *The Journal of Bone and Joint Surgery. American Volume*. 2019;101(11):1010-1015.

Quadriceps tendon rupture following TKA is an infrequent but potentially devastating adverse event. Although uncommon, the long-term sequelae of this injury can result in permanent inability to walk. Despite the severity of this injury, there is no single accepted treatment, with various surgical methods producing mixed results. Therefore, the purpose of this study was to assess the efficacy of a modified V-Y turndown flap as a viable alternative method of treatment for this injury. Twenty-four quadriceps tendon ruptures in 23 patients who underwent TKA with use of a modified V-Y turndown. Following the repair procedure, patients had significant ($p<0.0001$) improvements in mean Knee score 88.7 and mean strength 4.80 and all able to walk without assistive devise. The modified V-Y quadriceps tendon turndown flap was a reliable alternative treatment for achieving restoration of the extensor mechanism after complete quadriceps tendon rupture following TKA.

Fig. 1. The triangular flap of the quadriceps tendon is designed.

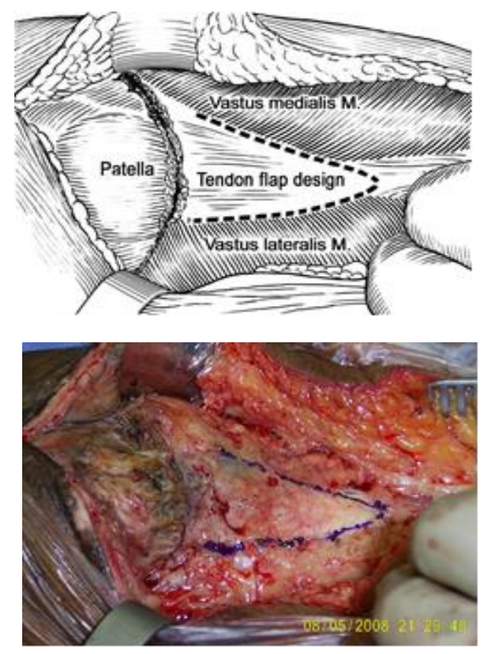
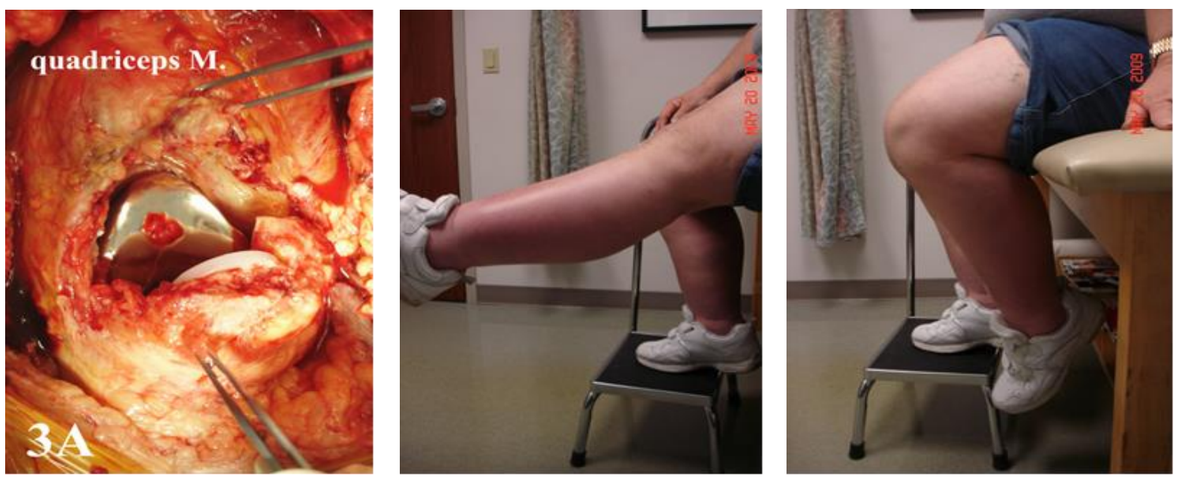
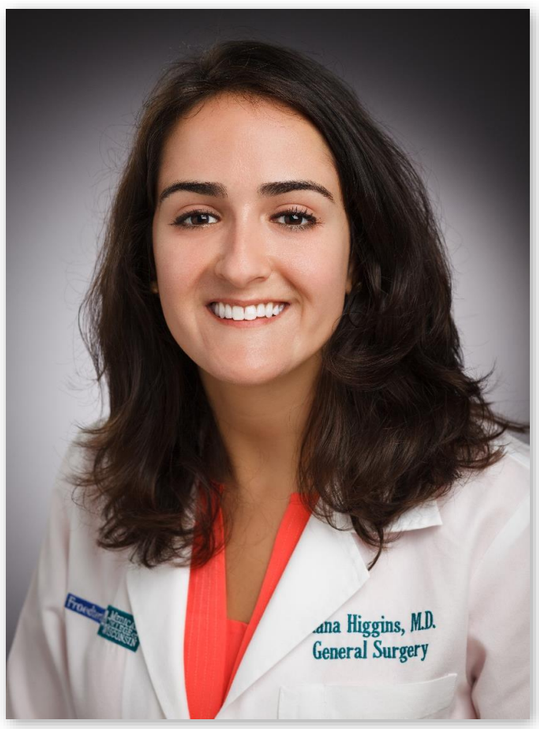


Table 1. Preoperative and postoperative Knee Society knee score, extensor lag, range of motion, and extensor strength.

	Preoperative	Postoperative	P Value
Knee Society knee score	44.5 (25-70)	88.7 (45-95)	<0.0001
Knee Society function score	45.6 (30-70)	87.5 (65-95)	<0.0001
Extensor lag (°)	42.8 (20-80)	2.3 (0-35)	<0.0001
Range of motion (°)	69.4 (40-100)	109.8 (75-125)	<0.0001
Extension strength (1-5)	2.5 (1-3)	4.8 (3-5)	<0.0001

Fig. 3. A 65-yr-old patient who underwent total knee arthroplasty and lateral retinacular release. The quadriceps tendon ruptured with patellar instability 2 months after the patient fell. The patient had a modified V-Y turndown flap to repair the tendon and followed up at 24 months. The patient regained full range of motion and quadriceps muscle power was excellent.





Rana Higgins, MD, FACS, FASMBS
Assistant Professor
Division of Minimally Invasive and Bariatric Surgery
Department of Surgery
Medical College of Wisconsin

I am an Assistant Professor of Surgery in the Division of Minimally Invasive General and Bariatric Surgery. Within this, I specialize in foregut, hernia, bariatric and robotic surgery. My research specialty focuses on clinical quality outcomes and surgical education within the field of minimally invasive general surgery.

"The Pros and Cons of Partial Versus Total Fundoplication for Gastroesophageal Reflux Disease"

Higgins RM, Gould JC. *Journal of Laproendoscopic & Advanced Surgical Techniques*. 17 May 2019, 10.1089/lap.2019.0297.

Laparoscopic Nissen fundoplication is currently the most commonly performed procedure for GERD. In patients with inefficient esophageal motility, a partial fundoplication such as a Toupet 270-degree posterior fundoplication is often recommended. There is controversy as it relates to the necessity of this tailored approach to fundoplication. There is also debate when it comes to the suitability and even the superiority of a partial compared to a full fundoplication. There are numerous randomized controlled trials and meta-analyses of these trials to guide the debate. From the evidence, it would appear that a full and a partial fundoplication are associated with similar GERD-related outcomes and that a partial fundoplication is associated with fewer side effects such as bloating and dysphagia.

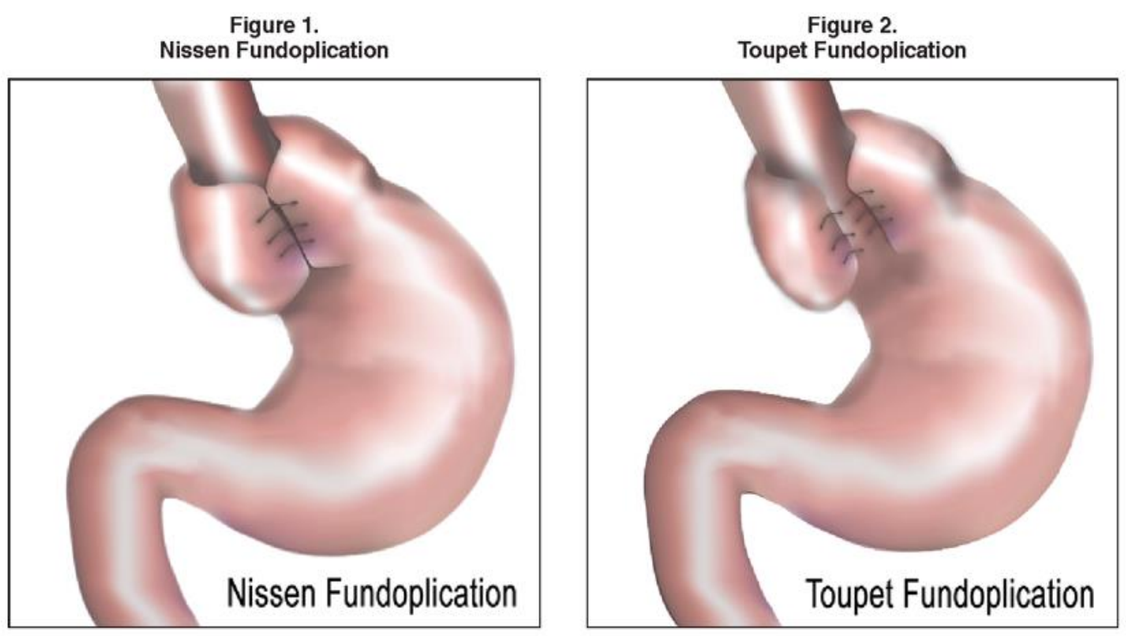


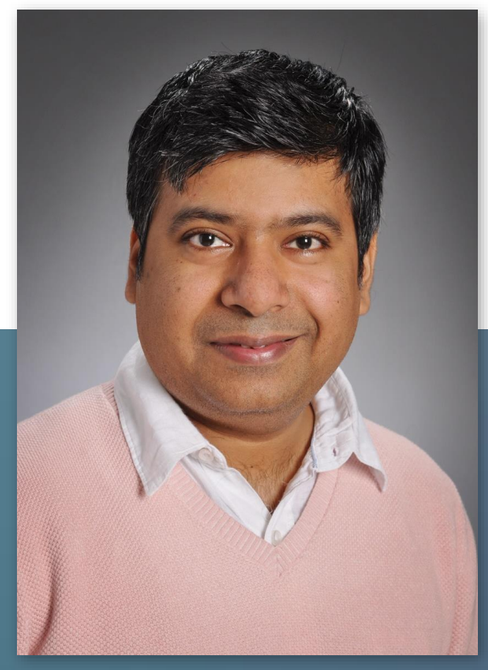
Figure from Halbert KL. Nissen vs. toupet fundoplication in the treatment of gastroesophageal reflux disease. *Pediatric nursing.* 2011.37(4):171-174.

“Role of Conserved Histidine and Serine in the HCXXXXXRS Motif of Human Dual-Specificity Phosphatase 5”

Gupta A, Brahmbhatt J, Syrlybaeva R, et al. *Journal of Chemical Information and Modeling*. 2019;59(4):1563-1574.

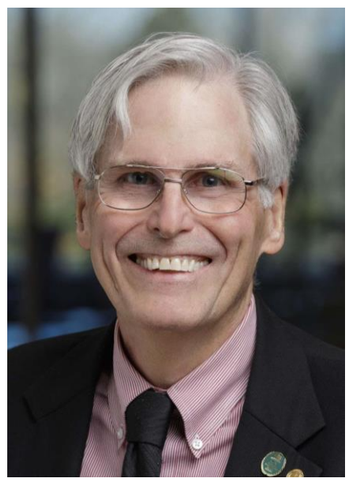
Dual specificity protein phosphatase 5 (DUSP5) is a critical regulator of immune response and cellular inflammation. In this study, we utilized computational modeling to identify and predict the importance of two conserved amino acid residues H262 and S270, in the DUSP5 catalytic site. We generated DUSP5 mutant proteins carrying specific mutations H262F and S270A in the phosphatase domain. We observed altered enzymatic activity for both mutants with a synthetic (pNPP) and physiological substrate (pERK), when compared to wildtype DUSP5 protein. This strategy could facilitate generation of small molecules that will therapeutically manipulate DUSP5 activity to regulate immune response and inflammation.

Ankan Gupta, PhD
Postdoctoral Fellow
Department of Pediatrics



L. Adrienne Allen, DVM, CPIA
Animal Research Liaison
Office of Research

Julian Lombard, PhD
Professor
Department of Physiology



“High salt diet impairs cerebral blood flow regulation via salt-induced angiotensin II suppression”

Allen LA, Schmidt JR, Thompson CT, Carlson BE, Beard DA, Lombard JH. *Microcirculation*. 2019;26(3):e12518.

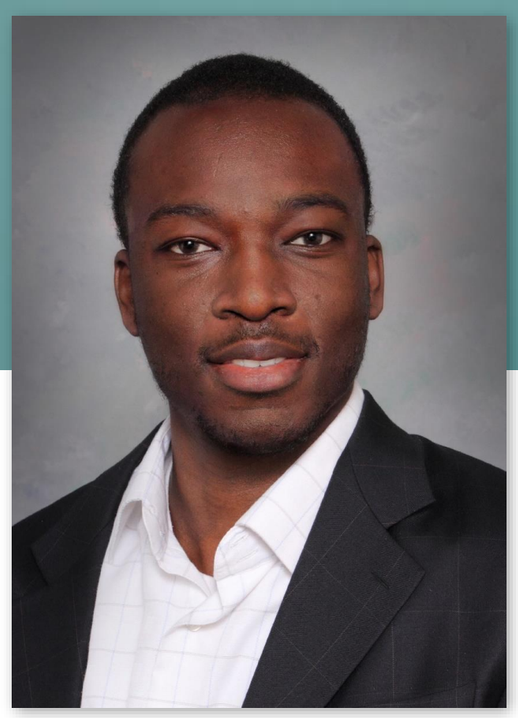
This study sought to determine whether salt-induced angiotensin II suppression impairs cerebral blood flow (CBF) autoregulation. CBF was evaluated via laser-Doppler flowmetry during hemorrhage-induced reductions in arterial pressure. Autoregulatory responses in rats fed high salt (4% NaCl) vs low salt (0.4%NaCl) diet were analyzed using linear regression analysis, model-free analysis, and a mechanistic theoretical model of blood flow through cerebral arterioles. Short-term (3 days) and chronic (4 weeks) high salt diet impaired CBF autoregulation. Prevention of salt-induced angiotensin II suppression by chronic low dose ANG II infusion restored CBF autoregulation in rats fed short-term high salt diet.

“Rete Testis Invasion Is Consistent With Pathologic Stage T1 in Germ Cell Tumors”

Farooq A, Jorda M, Whittington E, et al. *American Journal of Clinical Pathology.* 2019;151(5):479-485.

Rete testis invasion by germ cell tumors is frequently concomitant with lymphovascular or spermatic cord invasion (LVI/SCI); independent implications for staging are uncertain. In our study we evaluated 171 seminomas and 178 nonseminomatous germ cell tumors (NSGCT). Rete pagetoid (ReteP) and Rete direct (ReteD) spread were more frequent in seminoma than NSGCT. In seminoma, tumor size bifurcated at >3 or < 3 cm predicted metastatic status. Tumors with ReteP or ReteD did not differ in size from those without invasions; metastatic status/relapse did not show differences. In NSGCT, ReteP/ReteD did not correlate with size, metastatic status, or relapse. Our findings support retaining AJCC pathologic T1 stage designation for rete testis invasion and pT1a/pT1b substaging of seminoma.

Ayesha Farooq, MD
Resident, PGY-4
Department of Pathology



Leou Ismael Banla, PhD
MSTP Trainee
Department of Microbiology & Immunology

“Sortase-Dependent Proteins Promote Gastrointestinal Colonization by Enterococci”

Banla LI, Pickrum AM, Hayward M, Kristich CJ, Salzman NH. *Infection and Immunity.* 2019;87(5):e00853-18.

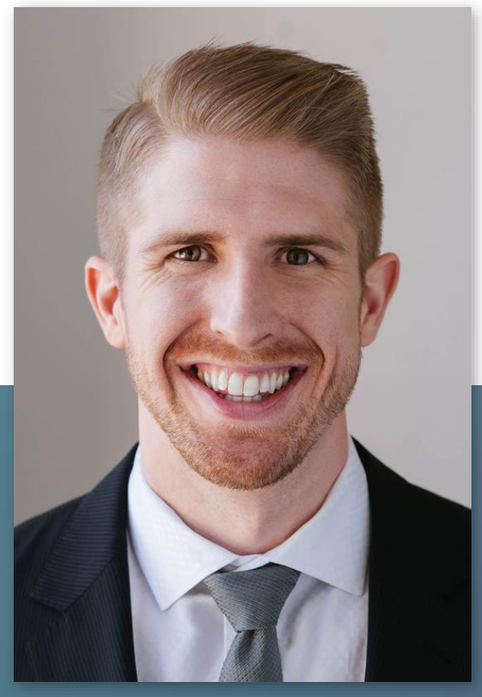
Enterococci are major agents of nosocomial infections for which gastrointestinal tract (GIT) colonization typically precedes pathogenesis. Unfortunately, the mechanisms underlying GIT colonization by these organisms are poorly characterized. Sortase-dependent proteins (SDPs) represent a subclass of surface proteins that require the enzyme SrtA for proper localization. We found that the enzymatic activity of Sortase A promotes intestinal colonization. Furthermore, deletion of SDPs with mucin-binding activity impairs intestinal colonization suggesting that SDPs promote GIT colonization by mediating mucin binding. Mucin-SDP interactions therefore represent potential targets for therapies aimed at disrupting colonization by enterococci.

“Outcomes in different age groups with primary Ewing sarcoma of the spine: a systematic review of the literature”

Berger GK, Nisson PL, James WS, Kaiser KN, Hurlbert RJ. *Journal of Neurosurgery. Spine*. 2019;316(3):H710-H721.

Ewing sarcoma is among the most prevalent of bone sarcomas in young people. Less often, it presents as a primary lesion of the spine. Primary Ewing sarcoma of the spine is a rare, debilitating disease in which the role of surgery and its impact on one’s quality of life and independence status has not been well described. This systematic review of the literature found the majority of patients experienced a favorable outcome with respect to independence status following surgery and adjunctive treatment. An increased risk of recurrence and death was also present among the adolescent age group (14–20 years).

Garrett K. Berger, PharmD
Medical Student (2021)
Vice President of Student Assembly
Department of Neurosurgery



Lynn W. Sun, MD, PhD
PGY IV Resident Physician
Department of Ophthalmology

“Assessment of Consistency Between Peer-Reviewed Publications and Clinical Trial Registries”

Sun LW, Lee DJ, Collins JA, et al. *JAMA Ophthalmology*. 2019;137(5):552-556.

Clinical trial registries are intended to increase clinical research transparency by non-selectively identifying and documenting clinical trial designs and outcomes. Inconsistencies in reported data undermine the utility of such registries. In this cross-sectional study of 106 clinical trials published in 3 ophthalmology journals in 2014, we assessed whether clinical trial registries provide meaningful information regarding recently published ophthalmic clinical trials. Corresponding registry entries were frequently missing. When present, omissions or discrepancies were often noted in trial design, results, and funding sources. These findings suggest a need for more attention to accuracy and consistency of reporting in clinical trial registries.

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