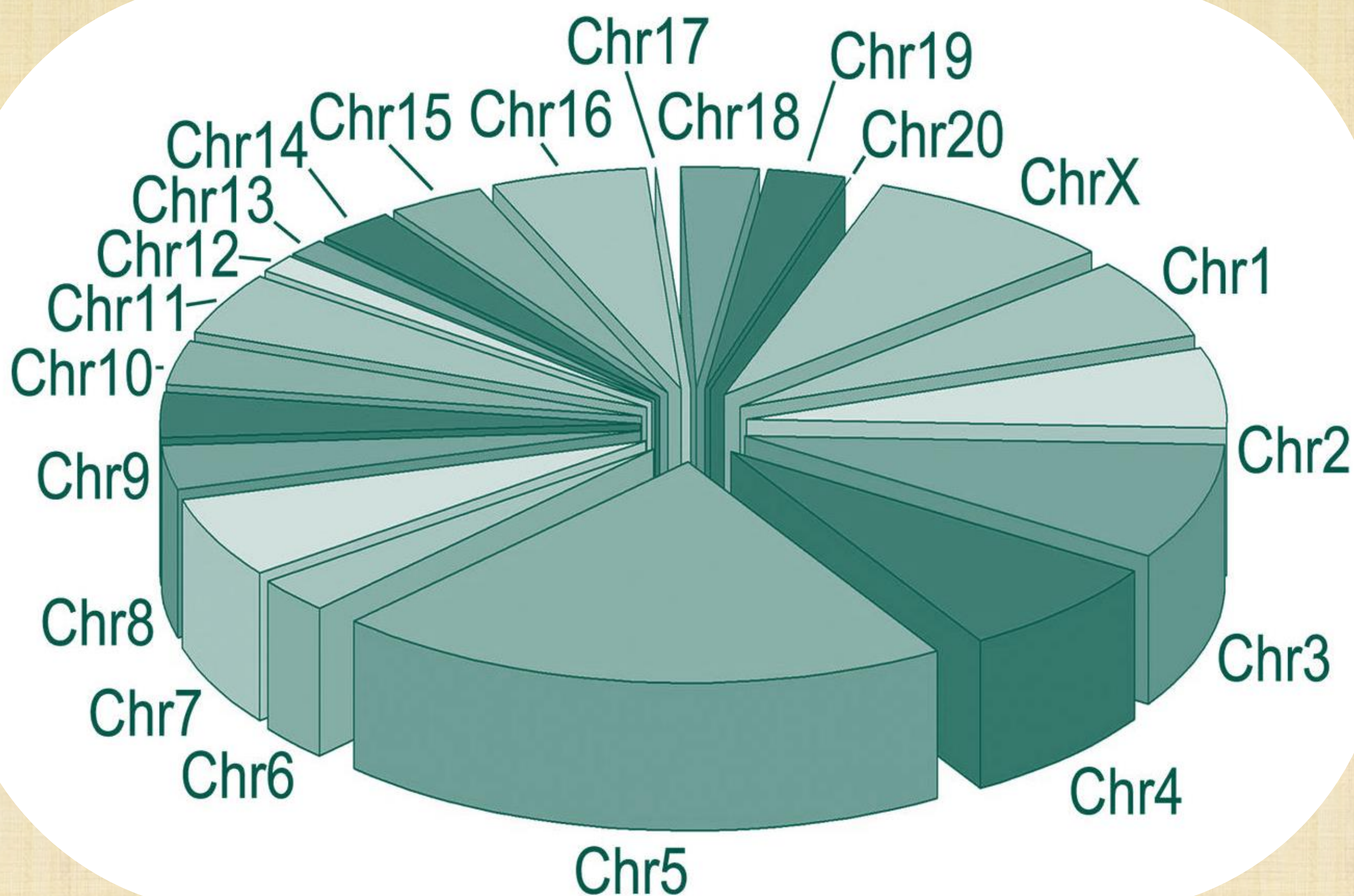


Research Publication Series

September 2019



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: Fiscal Year 2019 Totals

Publication Type	FY19 Total
Articles	1,406
Editorial Material	134
Reviews	177
Total	1,723

Publications in Top Quartile Journals
1,163 out of 1,723 (67.5%)

Total Publications:
1,723

Publication stats are pulled by the MCW Libraries 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:

September 2019

Andrew D. Spearman, MD

“Arteriovenous fistula creation for hypoxia after single ventricle palliation: A single-institution experience and literature review” 

Kristen Klement, MD

“Discussion of preoperative mammography in women undergoing reduction mammoplasty” 

Nicholas Gannon, MD

“Pathologic necrosis following neoadjuvant radiotherapy or chemoradiotherapy is prognostic of poor survival in soft tissue sarcoma” 

Gang Cheng, PhD

“Targeting lonidamine to mitochondria mitigates lung tumorigenesis and brain metastasis” 

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“Proline residues in scavenger receptor-BI's C-terminal region support efficient cholesterol transport” 

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NEW FEATURE: MCW Interdisciplinary Collaborative Research Network

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Cover Image from “Identification of a Rat Mammary Tumor Risk Locus That Is Syntenic with the Commonly Amplified 8q12.1 and 8q22.1 Regions in Human Breast Cancer Patients”



Andrew D. Spearman, MD

Assistant Professor
Division of Cardiology
Department of Pediatrics
Medical College of Wisconsin

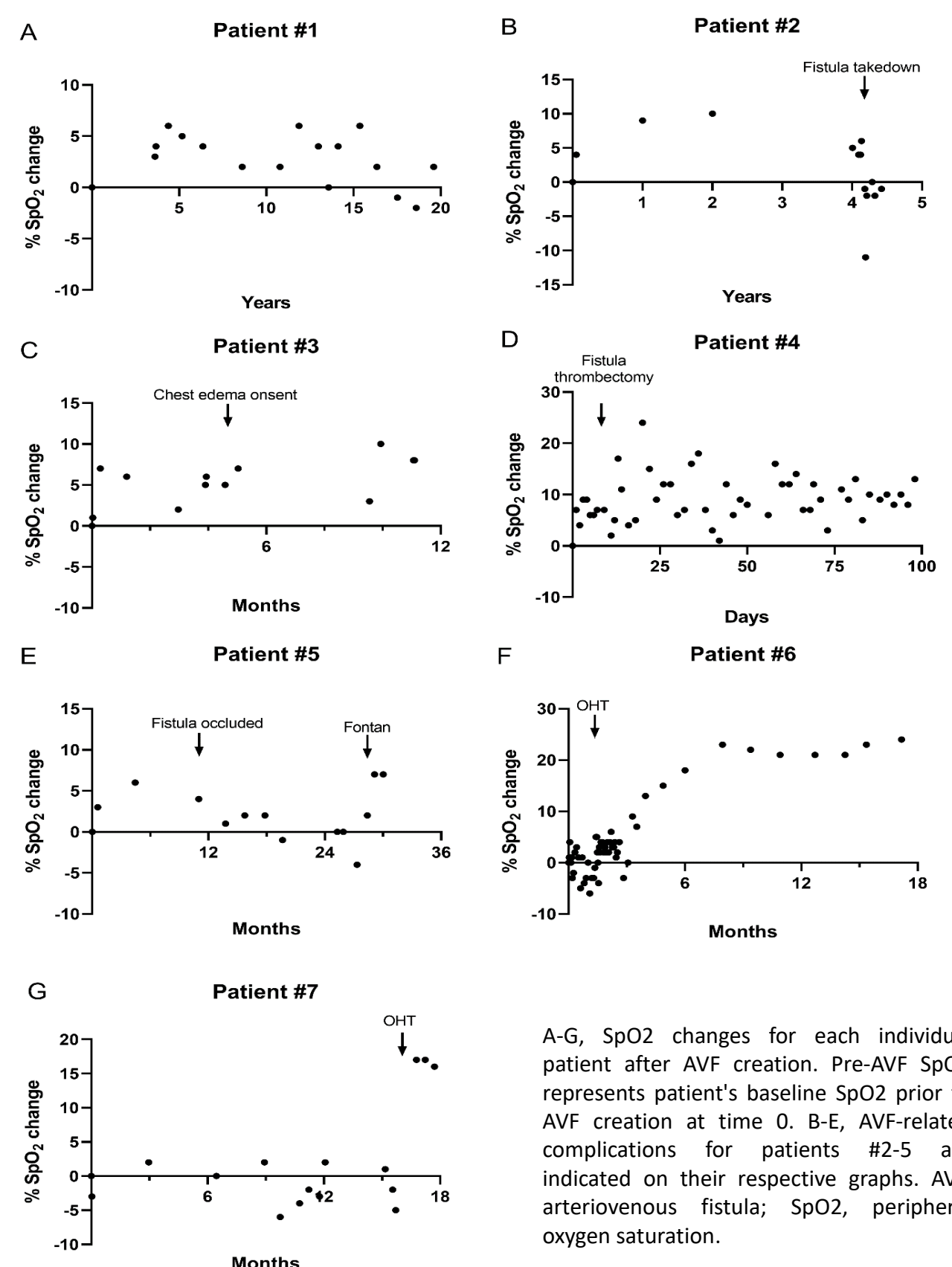
I am a pediatric cardiologist in the Herma Heart Institute at Children's Hospital of Wisconsin and Assistant Professor in the Division of Pediatric Cardiology at MCW. I am a physician-scientist in-training with research interests in the pulmonary microvasculature. I'm interested in applying basic science and translational research approaches to improve medical care for patients with congenital heart disease (CHD). I am specifically interested in the pathophysiology of pulmonary arteriovenous malformations (PAVMs). PAVMs are abnormal vascular connections in the lungs between arteries and veins. PAVMs form frequently in children after surgical palliation for single ventricle CHD. There are currently no effective medical therapies to treat CHD-associated PAVMs. The only curative treatment is heart transplantation.

“Arteriovenous fistula creation for hypoxia after single ventricle palliation: A single-institution experience and literature review”

Spearman AD, Kindel SJ, Woods RK, Ginde S. *Congenital Heart Disease*. 2019.00:1-8. PMID:31368206.

Hypoxia is a common long-term morbidity for patients with single ventricle congenital heart disease (CHD). Hypoxia can worsen over time due to pulmonary arteriovenous malformations (PAVMs). An arteriovenous fistula (AVF) is occasionally surgically created in an attempt to improve oxygen saturations for patients with hypoxia due to PAVMs. The rationale for AVF creation is to increase effective pulmonary blood flow and increase hepatic factor circulation to the pulmonary vasculature. In our study, we reported our institutional experience of seven patients who underwent AVF creation from 1996 to 2017. Fig. 1 shows patient-specific oxygen saturation (SpO₂) trajectories after AVF creation. AVF creation does not universally improve SpO₂ and is prone to early complications. Our results are similar to previously published literature indicating that we lack effective therapies to treat PAVMs.

Figure 1: Patient-specific oxygen saturation trajectories after AVF creation.





Kristen Klement, MD

Assistant Professor
Department of Plastic Surgery
Medical College of Wisconsin

I am a plastic surgeon at Froedtert Hospital and Children's Hospital of Wisconsin. I attended Georgetown University School of Medicine and completed my residency in plastic surgery at MCW. I also completed a fellowship in craniofacial surgery and pediatric plastic surgery at CHW. My research interest is clinical, specifically evaluating outcomes.

“Discussion of preoperative mammography in women undergoing reduction mammoplasty”

Klement KA, Hijawi JB, Neuner J, Kelley K, Kong AL. *The Breast Journal*. 2019;25(3):439-443.

The incidental discovery of malignant or high risk lesions in breast reduction specimens may preclude the possibility of breast conserving surgery. The purpose of this study was to examine the factors associated with discussion of preoperative mammography with reduction mammoplasty patients. 638 consecutive patients were identified between January 2000 and December 2010 who underwent reduction mammoplasty. On final pathology, 8 patients (1.3%) had high-risk lesions and 2 (0.3%) demonstrated malignancy (1 DCIS, 1 invasive). Of these 10 patients, two were under the age of 40 and four had preoperative mammograms. Factors associated with mammography discussion were age ≥ 40 , White race, the presence of comorbidities, family history of breast cancer, prior breast surgery, prior breast biopsy, history of breast cancer (all $p < 0.0001$) and tobacco use ($p = 0.04$). Due to the potential risk of invasive cancer and high risk lesions in the final surgical specimen, preoperative mammography should be discussed with selected patients by plastic surgeons, particularly those who fall within national screening guidelines.

Table 4. Pathology Results of All Patients Who Had Undergone Reduction Mammoplasty

Pathology	Number (Percentage)		
	Total N=579	< 40 yo N=333	≥ 40 yo N=246
Normal Breast	333 (57.5)	222 (66.7)	111 (45.1)
Non-proliferative Lesion	198 (34.2)	90 (27.0)	108 (43.9)
Proliferative Lesion	38 (6.6)	19 (5.7)	19 (7.7)
High Risk Lesion	8 (1.38)	2 (0.3)	6 (2.4)
Malignancy	2 (0.34)	0 (0)	2 (0.8)

Table 5. Multivariate analysis of variables predicting pre-operative discussion of mammography

Factor	Odds Ratio	95% Confidence Interval	P-Value
Age ≥ 40	12.99	8.31-20.28	<0.0001
Prior Breast Surgery	4.27	1.57-11.59	0.004
Family History of Breast Cancer	4.09	1.57-11.59	<0.0001
Prior Breast Biopsy	2.67	2.37-7.05	0.046
Personal history of Breast Cancer	12.63	3.37-47.41	0.0002

“Pathologic necrosis following neoadjuvant radiotherapy or chemoradiotherapy is prognostic of poor survival in soft tissue sarcoma”

Gannon NP, Stemm MH, King DM, Bedi M. *Journal of Cancer Research and Clinical Oncology*. 2019;456(5):1321-1330.

Neoadjuvant radiotherapy ± chemotherapy and wide local excision is an accepted management of localized soft tissue sarcomas (STS). Necrosis is prognostic for survival in osteosarcomas, but the significance for STS is undetermined. The Multidisciplinary Sarcoma Group aimed to determine if percent true necrosis, opposed to a combination of necrosis and fibrosis, leads to improved survival in extremity and trunk STS. Our data suggests necrosis may be an additional independent, prognostic variable with increased necrosis predicting a worse prognosis. Necrosis may not be a measure of treatment response and instead suggests more aggressive tumor biology as high-grade, large STS were associated with increased necrosis.

Nicholas Gannon, MD

Medical Student (graduated)
Department of Orthopaedic Surgery



Gang Cheng, PhD

Research Scientist II
Department of Biophysics

“Targeting lonidamine to mitochondria mitigates lung tumorigenesis and brain metastasis”

Cheng G, Zhang Q, Pan J, et al. *Nature Communications*. 2019;10:2205.

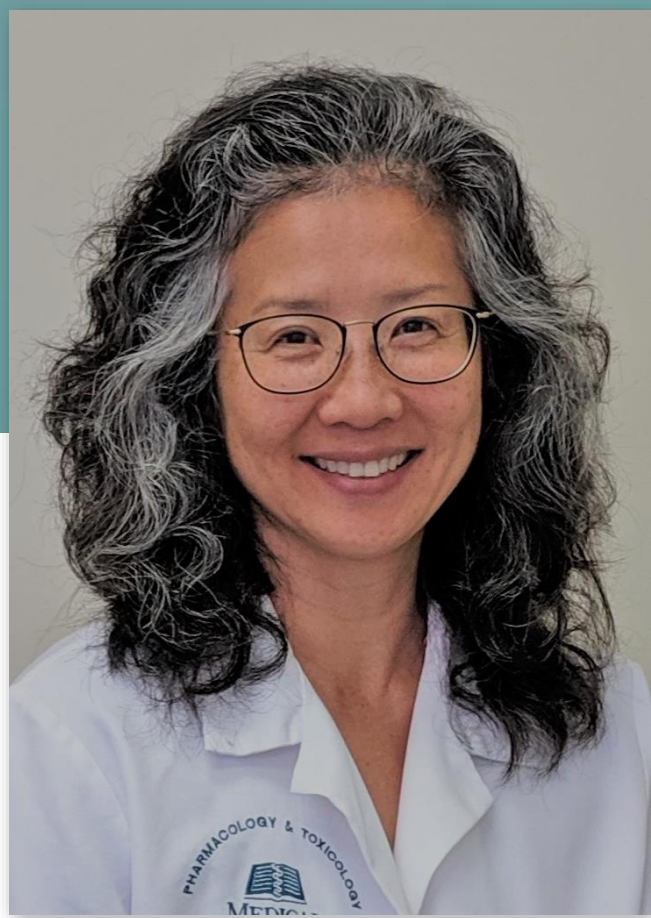
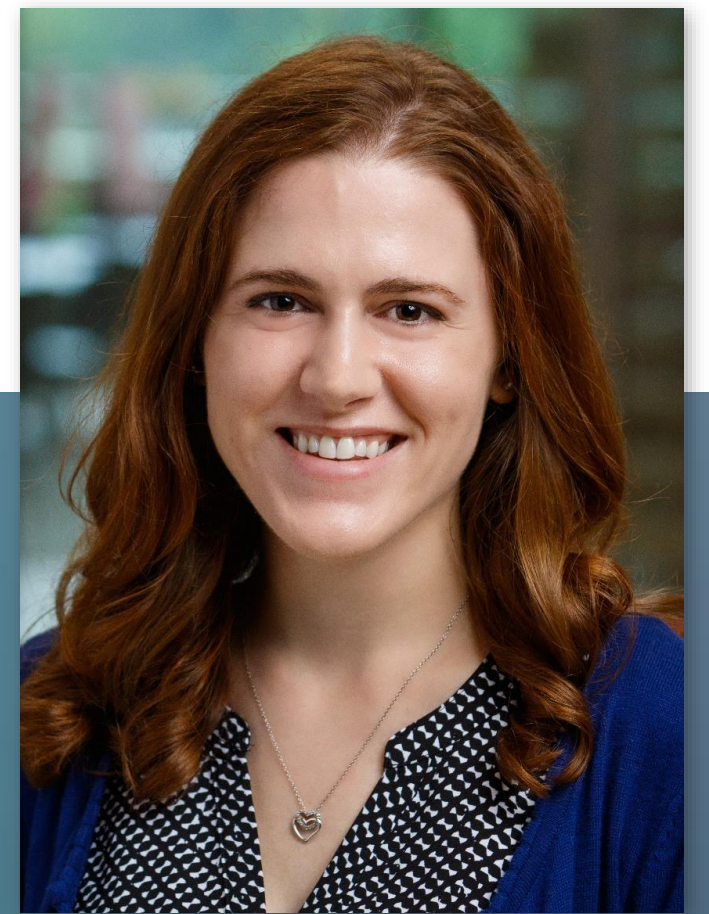
We modified lonidamine (LND) to mitochondria-targeted mito-lonidamine (Mito-LND) which is 100-fold more potent. Mito-LND, a tumor selective inhibitor of oxidative phosphorylation, inhibits mitochondrial bioenergetics in lung cancer cells and mitigates lung cancer cell viability, growth, progression, and metastasis of lung cancer xenografts in mice. Mito-LND blocks lung tumor development and brain metastasis by inhibiting mitochondrial bioenergetics, stimulating the formation of reactive oxygen species, oxidizing mitochondrial peroxiredoxin, inactivating AKT/mTOR/p70S6K signaling, and inducing autophagic cell death in lung cancer cells. Collectively, these findings show that mitochondrial targeting of LND is a promising therapeutic approach for investigating the role of autophagy in mitigating lung cancer development and brain metastasis

“Proline residues in scavenger receptor-BI's C-terminal region support efficient cholesterol transport”

Proudfoot SC, Sahoo D. *Biochemical Journal*. 2019;476(6):951-963.

High density lipoproteins (HDL) lower plasma cholesterol via reverse cholesterol transport, a process requiring the HDL receptor, scavenger receptor-BI (SR-BI). SR-BI is comprised of a large extracellular domain anchored by two transmembrane domains. It is poorly understood how SR-BI's structure contributes to its function. In this study, we analyzed a subset of proline residues within and near the C-terminal transmembrane domain that we hypothesized would support SR-BI function. Mutational analyses confirmed that loss of Pro-408 significantly impaired SR-BI expression, while loss of Pro-412, Pro-438, or Pro-459 impaired SR-BI-mediated cholesterol transport, thus highlighting the importance of proline residues for SR-BI functionality.

Sarah C. Proudfoot, BS
Graduate Student
Department of Biochemistry

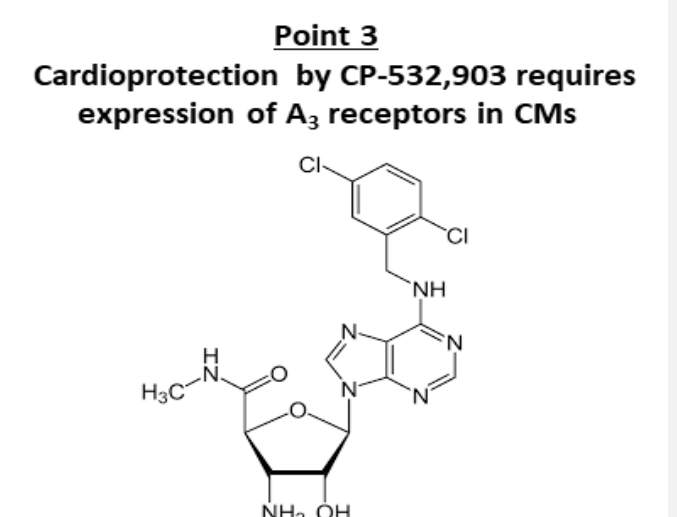
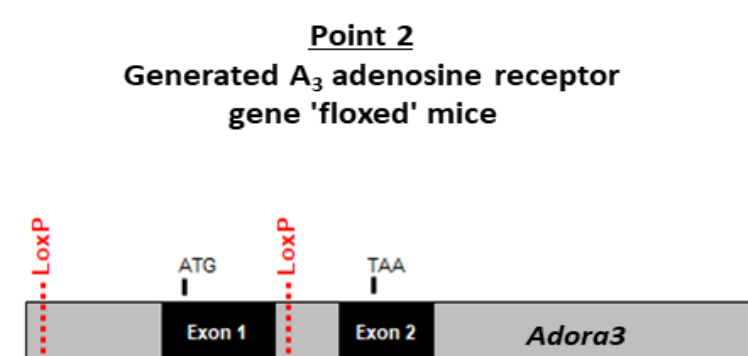
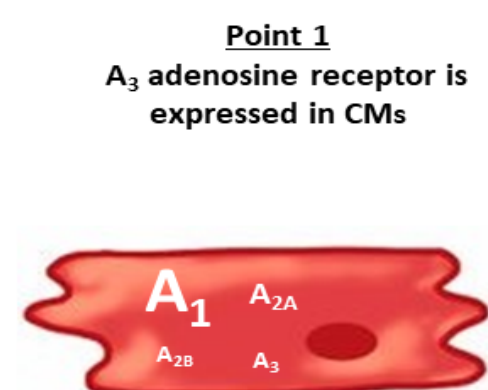


Tina C. Wan, PhD
Research Scientist
Department of Pharmacology &
Toxicology

“Ability of CP-532,903 to protect mouse hearts from ischemia/reperfusion injury is dependent on expression of A3 adenosine receptors in cardiomyocytes”

Wan TC, Tampo A, Kwok WM, Auchampach JA. *Biochemical Pharmacology*. 2019;163:21-31.

Work from this paper achieved three important goals. First, it provides evidence for expression of the A₃ adenosine receptor subtype in the myocardium. Second, we successfully prepared a genetically modified line of mice that allows for conditional depletion of the A₃ receptor in mice using the LoxP-Cre recombinase strategy. This new tool will be useful for investigators to examine the complex biology of the A₃ receptor in mice. Finally, utilizing this tool we provide new information on the mechanism of action of a new investigational drug (CP-532,903) currently being developed for treatment of organ injury, inflammatory disorders, and neuropathic pain.



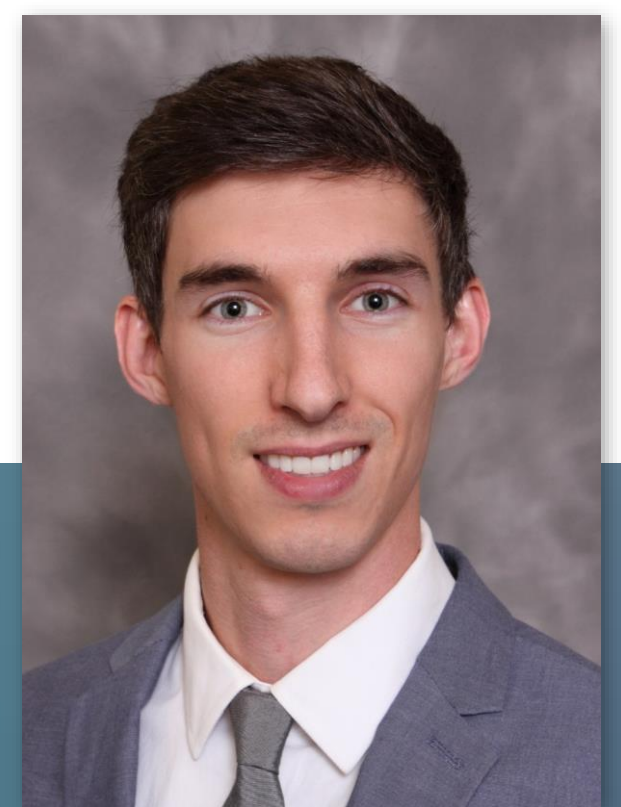
“Translating Ribosome Affinity Purification (TRAP) for RNA Isolation from Endothelial Cells In vivo”

Moran P, Guo Y, Yuan R, et al. *Journal of Visualized Experiments*. 2019;25(147).

We present an approach to purify ribosome-bound mRNA directly from vascular endothelial cells in vivo in mouse brain, lung and heart tissues. This method utilizes vascular endothelial cell (EC)-specific genetic tag of enhanced GFP (EGFP) in ribosomes in combination with RNA purification, which enables us to extract quality RNA directly in vivo in specific vascular endothelial tissues for downstream analysis such as qPCR and RNA-sequencing for gene expression and transcriptome analysis. Although our RNA yields were relatively low, our results were consistent with our previous in vitro studies, which suggests that the RNA quality is sufficient for downstream analysis.

Patrick Moran

Medical Student
Department of Medicine



Cody Plasterer

Graduate Student
Department of Physiology


“Identification of a Rat Mammary Tumor Risk Locus That Is Syntenic with the Commonly Amplified 8q12.1 and 8q22.1 Regions in Human Breast Cancer Patients”

Plasterer C, Tsaih SW, Lemke A, et al. *G3 (Bethesda)*. 2019;9(5):1739-1743.

Breast cancer risk is 31% heritable, yet the majority of the underlying risk factors remain poorly defined. Here, we used F2-linkage analysis in a rat mammary tumor model to identify a novel 11.2 Mb modifier locus of tumor incidence and burden on rat chromosome 5 (chr5: 15.4 - 26.6 Mb). Genomic and RNA sequencing analysis identified four differentially expressed candidates: TMEM68, IMPAD1, SDCBP, and RBM12. Analysis of the candidate genes in The Cancer Genome Atlas (TCGA) revealed that they fall within the commonly amplified 8q12.1 and 8q22.1 regions in human breast cancer patients and are correlated with worse overall survival.

MCW Interdisciplinary Collaborative Research Network

The ICRN project was initiated by a 2017-2018 MCW Leadership Academy team to enhance visibility of MCW investigators and promote interdisciplinary collaboration to increase funding success. The Office of Research is pleased to support this interactive, promotional opportunity for MCW investigators and centers to find collaborators on campus. The profiles linked below have been voluntarily submitted by individuals and programs seeking collaborators.




Interdisciplinary Collaborative MCW Research Network

Ke Yan, PhD

SEEKING STUDIES IN	OFFERING
<ul style="list-style-type: none">• Basic Science• Translational Research• Community	<ul style="list-style-type: none">• Study design & analyses planning• Statistical analyses & appropriate interpretation of results• Grant proposal planning & writing

Recent Publication: "The interaction of tumor cells and astrocytes promotes breast cancer brain metastases through transforming growth factor-beta2/angiopoietin-like 4 axes"

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