Surgery Research Conference

2018-2019 Research Residents &

Dr. Gamblin’s We Care Award Updates

October 10th, 2018

ACCME Accreditation Statement: The Medical College of Wisconsin is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. AMA Credit Designation Statement: The Medical College of Wisconsin designates this live activity for a maximum of 1.0 AMA PRA Category 1 Credit™. Physicians should claim only the credit commensurate with the extent of their participation in the activity. Hours of Participation for Allied Health Care Professionals: The Medical College of Wisconsin designates this activity for up to 1.0 hours of participation for continuing education for allied health professionals.
Research Highlights
Congratulations!

Thomas W. Carver, MD
Associate Professor
Division of
Trauma and Acute Care Surgery

Recipient of the
MCP

Excellence in Professionalism Award
2018 MCW Research Day
Poster Session Honorable Mentions

Jacqueline Blank, MD
Colorectal Surgery

Auricular Neurostimulation for NonPharmacologic Post-Operative Pain Control: A Randomized Controlled Trial

Kimberly Somers, PA-C
Pediatric Surgery

Splitting Hairs and Challenging Guidelines: Defining the Role of Perioperative Antibiotics in Pediatric Appendicitis Patients
The Department of Surgery presents:

2018 Fall Research Symposium Winners

- Michael Cain, MD
  Mentored by David Joyce, MD, Cardiothoracic Surgery
  Surgical Outcomes of Minimally Invasive vs. Sternotomy Approaches to Single-Vessel Coronary Artery Bypass Grafting: A Study from The Society of Thoracic Surgeons National Database

- Katherine Hu, MD
  Mentored by Timothy Ridolfi, MD, Colorectal Surgery
  Factors Predicting Unplanned 30-day Readmissions in Surgical Patients

- Hailey Hayes
  Mentored by Tammy Lyn Kindel, MD, PhD, General Surgery
  Sleeve Gastrectomy in Obese Wistar Rats Improves Diastolic Function Independent of Weight Loss

- Ronald Schocke
  Mentored by Chris Davis, MD, Trauma and Acute Care Surgery
  Feasibility and Impact of Stop the Bleed Training of an Entire Medical School Class
MCW Cardiovascular Center Research Retreat

SAVE the DATE

Accepted Abstracts
• Michael Cain, MD
• Nathan Smith, MD
• Courtney Goulet
  (winner of the Women in Science student awards)

Friday, October 19th, 8 am – 4 pm - Harley Davidson Museum
MCW Office of Research Professionalism Week Program:

Who has been a Magnanimous Mentor to you?

- Spent hours polishing your grant application.
- Sat down with you for an hour to walk through a spreadsheet.
- Helped you develop an excellent lecture.
- Took a few minutes to walk you to the cafeteria on your first day.
- Offered constructive feedback on a manuscript or paper.
- Supported your application for an award, committee or professional society.
- Is a mentor-by-example: leading a committee, volunteering for a good cause or recognizing someone else who helped them.

Recognize a Mentor today!

Sept 17-Oct 19, 2019
SAVE the DATE!

MEDICAL COLLEGE OF WISCONSIN
DEPARTMENT OF SURGERY
BREAST CARE 101: WHAT YOU NEED TO KNOW

FRIDAY, NOVEMBER 9, 2018

Four Points by Sheraton
Milwaukee North Shore
8900 North Kildeer Court
Brown Deer, WI 53209
SAVE the DATE!

Tips for Successful Scholarly Publishing Event

November 13, 2018
12:00-1:00pm

Register Here

Melanie Masserant, Account Development Manager, Springer Nature

Michael McCrea, PhD, ABPP-CN, Professor of Neurosurgery and Neurology; Eminent Scholar; Co-Director of the Center for Neurotrauma Research; Director of Brain Injury Research

Hershel Raff, PhD, Professor, Medicine, Physiology and Surgery, MCW Medical School; Professor, MCW Pharmacy School; Director, Endocrine Research Laboratory, Aurora St. Luke's Medical Center, Aurora Research Institute

Carol Williams, PhD, Professor of Pharmacology & Toxicology; Kathleen M. Duffey Fogarty Eminent Scholar in Breast Cancer Research; Co-Director, Cancer Biology Program, MCW Cancer Center
Surgical Oncology

**Adjuvant and Neoadjuvant Therapy, Treatment for Advanced Disease, and Genetic Considerations for Adrenocortical Carcinoma: An Update from the SSO Endocrine and Head and Neck Disease Site Working Group.**

*Annals of Vascular Surgery*
(Dickson PV, Kim L, Yen TWF, Yang A, Grubbs EG Patel D, Solorzano CC)

Trauma and Acute Critical Care

**Ultrasound Training in Surgical Critical Care Fellowship: A Survey of Program Directors.**

*Journal of Surgical Education.*
(Carver, TW)

**Exploring the gold-standard: Evidence for a two-factor model of the Clinician Administered PTSD Scale for the DSM-5.**

*Psychological Trauma: Theory, Research, Practice and Policy*
(Hunt JC, Chesney SA, Jorgensen TD, Schumann NR, deRoon-Cassini TA)

Pediatric Congenital Cardiac Surgery

**360-Degree Cone Reconstruction for Ebstein's Anomaly.**

*Annals of Thoracic Surgery*
(Mitchell ME, Hraska V, Kouretas PC)

**Monocusp valve placement in children with tetralogy of Fallot undergoing repair with transannular patch: A functioning pulmonary valve does not improve immediate postsurgical outcomes.**

Congenital Heart Disease
(Singh NM, Loomba RS, Gudausky TM, Mitchell ME)

Vascular Surgery

**Sex-dependent outcomes following elective endovascular aortic repair.**

*Journal of Surgical Research*

General Surgery

**Mesh Selection in Abdominal Wall Reconstruction**

*Plastic & Reconstructive Surgery*
(Lak KL & Goldblatt MI)
Cardiothoracic Surgery

Long-term Results of Stereotactic Body Radiation Therapy in Medically Inoperable Stage I Non-Small Cell Lung Cancer.
JAMA Oncology
(Timmerman RD, Hu C, Michalski JM, Bradley JC, Galvin J, Johnstone DW, Choy H)

Atrial Fibrillation Should Guide Prophylactic Tricuspid Procedures During Left Ventricular Assist Device Implantation.
ASAIO Journal
(Anwer LA, Tchantchaleishvili V, Poddi S, Daly RC, Joyce LD, Kushwaha SS, Topilsky Y, Stulak JM, Maltas S)

Resident versus attending surgeon graft patency and clinical outcomes in on- versus off-pump coronary artery bypass surgery
Journal of Thoracic & Cardiovascular Surgery

Expanding the use of bilateral internal thoracic artery: Yes! We can.
Journal of Thoracic & Cardiovascular Surgery
(Saran N, Locker C, Joyce DL)

Pediatric Surgery

Nogo-B receptor increases the resistance to tamoxifen in estrogen receptor-positive breast cancer cells.
Breast Cancer Research

Meconium-stained amniotic fluid as a predictor of poor outcomes in gastroschisis.
Journal of Pediatric Surgery
(Koehler SM, Loichinger M, Peterson E, Christensen M, Szabo A, Wagner AJ)

Bioprosthetic pulmonary valve endocarditis: Incidence, risk factors, and clinical outcomes.
Congenital Heart Disease

Ovarian masses in the child and adolescent: An American Pediatric Surgical Association Outcomes and Evidence-Based Practice Committee systematic review.
Journal of Pediatric Surgery
“The Word on Medicine: where Knowledge is changing life”

Everything You Need to Know About the Flu
Saturday, October 13th 3pm

REPLAY: Breast Cancer: Dr. Amanda Kong, Chief of Breast Surgery, Division of Surgical Oncology in the Department of Surgery, Devoted to breast cancer in honor of Breast Cancer Awareness month. Learn more (PDF)
Saturday, October 13th 5pm
Future presentations/speakers?

- Budget
- IRB Submissions
- Overview of MCW Grants
- Grant Writing
- NIH Submission Guidelines
- Research Mentoring
- Biostatistics
- Office of Technology

Click here to submit your idea!
Vascular Surgery Research Update

Gary Seabrook, MD

November 14, 2018
Conference Room M
5:00-6:00pm
(1) Tumor Centric Approach: Surgical Therapy Paramount

Supportive Care to enhance delivery of treatment and improve Quality of life

(2) Treatment Centric Approach: Multimodality Therapy is Key

(3) Patient Centric Approach: Choosing Appropriate Therapies

Targeted therapies

Germline Testing
Somatic Mutations in Pancreatic Cancer

**Background:** Frequently tumors are sent for commercial genetic testing, but it is unclear what clinical value is gained from this.

**Hypothesis:** Genetic testing does not identify actionable targets that are currently amendable to targeted therapies.

**Project Aims:**
1. Quantitate actionable mutations from commercial testing using a 560-580 gene panel
2. Examine whether identified mutations were associated with a change in clinical care
3. Determine whether tumor sequencing cost effective? (Lindsay Bliss)
Background: Neoadjuvant therapy has become increasingly utilized in patients with pancreatic cancer. Many patients receive dose reductions or treatment breaks secondary to toxicity.

Hypothesis: Treatment breaks and dose reduction negatively impact patient survival.

Project aims:
1. Assess dose intensity and duration of chemotherapy delivered to patients in the neoadjuvant setting.
2. Assess supportive care needed to administer neoadjuvant therapy.
3. Identify impact of dose reduction and treatment breaks on tumor response to neoadjuvant therapy, ability to undergo surgical resection, and overall survival.
Gemcitabine v 5FU Neoadjuvant Therapy

**Background:** The use of FOLFIRIONX has been well described for neoadjuvant therapy. Many patients receive gemcitabine based neoadjuvant therapy which has not been well described.

**Hypothesis:** Gemcitabine-based chemotherapy can be used for neoadjuvant therapy with comparable survival.

**Aims:**
1. Assess CA19-9 response to gemcitabine-based and 5-FU based neoadjuvant chemotherapy.
2. Assess ability to complete surgical resection and overall survival among patients with gemcitabine-based and 5-FU based chemotherapy.
3. Describe outcomes following neoadjuvant Gemcitabine/nab-paclitaxel compared to FOLFIRINOX.
**Area of Deprivation Index (ADI) in Pancreatic Cancer Patients**

**Background:** People from neighborhoods with high ADI have increased rates of readmissions from all causes and have higher mortality rates than those from low ADI neighborhoods. Impact of ADI on pancreatic cancer is not well studied.

**Hypothesis:** Patients from high ADI neighborhoods have poorer outcomes than those from low ADI neighborhoods.

**Aims:**
1. Assess impact of ADI on hospital readmissions.
2. Assess impact of ADI on overall survival.
3. Assess barriers to care for patients from high ADI neighborhoods.
Sarcopenia in Pancreatic Cancer Patients

**Background:** Sarcopenia has been associated with poorer postoperative outcomes in patients with pancreatic cancer. The impact of neoadjuvant therapy on sarcopenia and the impact of a prehabilitation program has not been well established.

**Hypothesis:** Increased sarcopenia is associated with poorer outcomes in patients with pancreatic cancer. Prehabilitation programs will mitigate increased sarcopenia during neoadjuvant therapy.

**Aims:**
1. Identify changes in sarcopenia throughout neoadjuvant therapy in patients who did not undergo prehabilitation program.
2. Identify impact of prehabilitation program on sarcopenia changes throughout neoadjuvant therapy.
3. Assess correlation between physical therapy assessments and measured sarcopenia.
Germline Mutations in Pancreatic Cancer

**Background:** All patients with pancreatic cancer are now recommended to undergo genetic testing evaluation.

**Hypothesis:** Germline genetic testing in pancreatic cancer patients will identify germline mutations that impact future surveillance or treatment in pancreatic cancer patients and family members.

**Aims:**

1. Describe mutations identified during germline genetic testing in patients with pancreatic cancer.
2. Describe how genetic testing in all pancreatic cancer patients was implemented at the Medical College of Wisconsin.
Katherine Hu
Research Resident (2018-2020)
Division of Colorectal Surgery

PI: Timothy Ridolfi, MD
Research Interests

• Colon and rectal surgery outcomes
• Readmissions
• Quality and safety outcomes
Projects in Progress

- Factors Predicting Unplanned Readmissions in Surgical Patients
  - PI: Carrie Peterson, MD
- Review of Rothman Index trends associated with surgical readmissions
  - PI: Carrie Peterson, MD
- Effects of Cancer Care Coordinator on Timeliness of Rectal Cancer Care
  - PI: Timothy Ridolfi, MD
- Review of single institution (VA Hospital) experience with alvimopan
  - PI: Timothy Ridolfi, MD
- Evaluating the effectiveness of pharmacologic components of ERAS protocols (ketorolac, gabapentin, ketamine, alvimopan)
  - PI: Timothy Ridolfi, MD
- Outcomes after Redo Coloanal Anastomoses
  - PI: Kirk Ludwig, MD
<table>
<thead>
<tr>
<th>Project</th>
<th>Local/Regional</th>
<th>National/Manuscript</th>
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<tbody>
<tr>
<td>Factors Predicting Unplanned Readmissions in Surgical Patients</td>
<td>- MCW Surgery Fall Research Symposium (9/14/18)</td>
<td>Submitted to 2019 Academic Surgical Congress (ASC)</td>
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<td>Review of Rothman Index trends associated with surgical readmissions</td>
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<td>American Society of Colon and Rectal Surgeons (ASCRS) Annual Meeting (06/2019)</td>
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<tr>
<td>Outcomes after redo coloanal anastomosis</td>
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<td>Diseases of the Colon and Rectum</td>
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We Care Fund for Medical Innovation and Research

- Established in 2010
- 17 projects funded to date
- $1.4 Million Funds Raised
- 100% of funds go to directly support research
We Care Update
October Research Division Meeting, T. Clark Gamblin, MD, MS, MBA
October 10, 2018
Preclinical efficacy of combined therapy with novel mitochondrial targeted and natural byproduct/glycolysis inhibitor in hepatocellular carcinoma

• Introduction
• Proposed Course
• Reality
• Future Direction
Hepatocellular Carcinoma

- Most common liver malignancy
- Surgical therapies remain definitive means of treatment (resection, transplantation, ablation, TACE)
- For unresectable disease, median survival is <1 year
- Sorafenib is the only FDA approved systemic therapy - 30% response rate
- Targeting signaling pathways may be an effective approach
• Targeted treatment are needed
• Glycolysis inhibition has been an interest using novel compound Mito-CP
• Recent evidence has revealed anticancer properties of metformin
  – In house production of metformin targeted to mitochondria has shown increased efficacious than metformin alone in pancreas cancer
Xanthohumol (XN)

- Prenylated chalcone, isolated from the hop plants
- Exhibits wide range of biological effects:
  - Anti-inflammatory
  - Anti-oxidant
  - Anti-tumorigenic
- Safe and bioavailable
- Anti-proliferative effect on various cancers
Xanthahumol and Glycolysis / Potential Collaborators

• Myeloid cell luekemia-1 (Mcl-1) is an anti-apoptotic member of Bcl-2 and highly expressed in HCC
• Mcl-1 also participates in the maintenance of mitochondrial membrane stability and prevents cytochrome C release thus promoting cell survival.
• Previous work by our group has shown glycolysis inhibition and inhibition of Mcl-1 increases suppression of HCC in vitro and vivo
• Xanthohumol (XN) – down regulates Mcl-1 and is in clinical trials to test ability to prevent DNA damage and block oxidative stress

• Combining a natural product with a novel synthesized compound analog
  – Clinical Trial
  – Preliminary data for R01
DETOUR
Antiproliferative and apoptotic effects of xanthohumol in Cholangiocarcinoma

Daniel Walden¹, Selvi Kunnimalaiyaan¹, Kevin Sokolowski¹, TClark Gamblin¹ and Muthusamy Kunnimalaiyaan¹

XN treatment inhibits tumor growth in both CCLP-1 and SG-231 cells injected in a mice xenograft model.

Effects of XN on CCLP-1, SG-231, and CC-Sw-1 cellular proliferation.

Funded by We Care Fund and Jack Stein Research Fund – Bile Duct Cancer Research
Xanthohumol in HCC

Xanthohumol Inhibits Notch Signaling and Induces Apoptosis in Hepatocellular Carcinoma
S Kunnimalaiyaan, KM Sokolowski, M Balamurugan, TC Gamblin, M Kunnimalaiyaan
PLoS One 10(5) PMID 26011160

♦ Dose dependent inhibition of cellular proliferation by MTT, colony forming ability and live cell imaging
♦ Induces apoptosis
♦ Blocks Notch signaling pathway by reducing Notch activity
♦ Exogenous expression of Notch negates XN activity
Notch1 reduction induces apoptosis

**Graph:**
- **Hep3B**
  - Notch1
  - HES-1
  - survivin
  - cyclinD1
  - FL
  - PARP
  - Cl
  - GAPDH

**Luminescence (RLU):**
- Huh-7
  - Notch1sh
- Hep3B
  - Notch1sh

*Significant differences indicated.*
Proposed mechanism of XN action

Kunnimalaiyaan et al., Mol. Cancer Ther.
How Notch1 is decreased by XN?

Crosstalk between Nrf2 and Notch signaling

Notch-Nrf2 Axis: Regulation of Nrf2 Gene Expression and Cytoprotection by Notch Signaling
Wakabayashi et al., Mol. Cellular Biol. 34(2014) 653-663

Hypothesis

XN inhibits HCC cell proliferation by altering Keap1/Nrf2-Notch-Stat3 axis
CLINICAL STUDY PROTOCOL

Phase I Study of Xanthohumol in Adults With Refractory Malignancies

25 mg (8.3 mg orally tid) for 14 days followed by 7 days off

75 mg (25 mg orally tid) for 14 days followed by 7 days off

150 mg (50 mg orally tid) for 14 days followed by 7 days off

300 mg (100 mg orally tid) for 14 days followed by 7 days off
Primary Objectives

• Evaluate the safety and tolerability of multiple doses of XN administered on a daily x 14 schedule to subjects with selected incurable cancers as a single agent
• Identify a recommended dose and schedule for further study of XN on the basis of safety, pharmacokinetic (PK), and pharmacodynamics data, to be used as single agent
• Evaluate the anti-tumor activity of XN in subjects with incurable cancer as single agent
Conclusions

• HCC novel compounds are needed
• Xanthohumol appears to have antitumor effects and while combination therapy is attractive; single agent clinical data is necessary
• Clinical Phase 1 trials will go to the IRB in next couple months
• Funding of clinical trial is due to We Care Award