MCW Administrative and Regulatory Burden Committee

- Created by Dr. Ann Nattinger, Dean of Research
- Lead by Dr. Joe Thulin and Dr. Cecilia Hillard
- Committee is charged with - Increasing research efficiency by reducing burden
  1. Identify areas of burden for PIs and staff
  2. Evaluate federal regulations tied to areas of burden
  3. Determine if requirements are grounded in federal regulations or MCW requirements and what can be modified or done away with

- Applies to animal and human related research
MCW Administrative and Regulatory Burden Committee

- **In person**
  - Need to meet before March 29th
  - Administrative Assistant: Allison Stachowiak astachowiak@mcw.edu

- **Via email (tcassini@mcw.edu)**
  - What entity the burden comes from (IACUC, IRB, G&C, etc.).
  - What burden exists
  - How it impacts you as a researcher
Surgery Research Conference

Colorectal Surgery Research Update
March 14, 2018
Research GRANTS

NASA’s Human Research Program and the NASA Space Biology Program
John Baker, PhD
**Pediatric Congenital Cardiac Surgery**
“Defining the relationship between simulated weightlessness and space radiation on cardiovascular disease, and the effectiveness of a countermeasure”

Children’s Research Institute’s Pilot Grant Awardees
PI: Kirk Pritchard, PhD
**Pediatric Surgery Division**
Co-I: Joohyun Kim, MD, PhD & Michael Zimmerman, MD
**Transplant Surgery Division**
“Role of MPO in Liver Ischemia and Reperfusion Injury in Transplantation”
This RFA seeks to support collaborative, faculty-initiated research that aligns with MCW’s nine strategic research priority areas and exhibits strong changemaking potential. Full-time or full-professional effort MCW faculty members within the School of Medicine are eligible to apply, and requests should not exceed a total of $200,000 over two years. Approximately five meritorious awards will be granted. Selected applicants will be invited to submit full proposals, with funded projects beginning on January 1, 2019.

***Please contact Krissa Packard if you are considering applying for this funding opportunity***
Medical College of Wisconsin, Department of Surgery
We Care Fund for Medical Innovation and Research
2018 Faculty Seed Grants

Eligibility

$150,000 Grant
• Full time faculty member in the Department of Surgery
• Interdisciplinary collaboration with another division, department or center at MCW

$50,000 Grant
• Assistant & Associate Professors

Overview

The mission of the We Care Fund is to use contributions made available by the philanthropic community to support Department of Surgery faculty demonstrate the importance of innovation and discovery to advance science and clinical care of patients.

Key Dates

RFA
Budget Review:
eBridge application to GCO:
Emailed We Care:
Scientific Committee Review:
Award Notifications:
Anticipated Start Date:

February 12, 2018
April 11, 2018
April 18, 2018
April 25, 2018
June 21, 2018
July 16, 2018
September 1, 2018
MARCH

Publications

Cardiothoracic Surgery

“Comparison of Outcomes and Costs Associated With Aspirin+/– Clopidogrel After Coronary Artery Bypass Grafting.” *American Journal of Cardiology* (Hossein G. Almassi)

Pediatric Surgery

“Role of intestinal Hsp70 in barrier maintenance: contribution of milk to the induction of Hsp70.2.” *Pediatric Surgery International* (David M. Gourlay)


“Nogo-B receptor promotes epithelial-mesenchymal transition in non-small cell lung cancer cells through the Ras/ERK/Snail1 pathway.” *Cancer Letters* (Xiaoyu Qi & Qing Robert Miao)

“Medical and Surgical Management of Pediatric Ulcerative Colitis.” *Medical and Surgical Management of Pediatric Ulcerative Colitis* (Thomas T. Sato) [Review]

“Pediatric and Congenital Colorectal Diseases in the Adult Patient.” *Clinics in Colon & Rectal Surgery* (David M. Gourlay)

“Healthcare Utilization and Comorbidities Associated with Anorectal Malformations in the United States.” *Journal of Pediatrics* (Casey Calkins)

Congenital Heart Surgery


General Surgery


“Improved immediate postoperative pain following laparoscopic inguinal herniorrhaphy using self-adhering mesh.” *Surgical Endoscopy* (Daniel G. Davila, Melissa C. Helm, Irene S. Pourladian, Matthew J. Frelich, Andrew S. Kastenmeier, Jon C. Gould & Matthew I. Goldblatt)

Vascular Surgery


Colorectal Surgery

“Elevated Venous Thromboembolism Risk Following Colectomy for IBD Is Equal to Those for Colorectal Cancer for Ninety Days After Surgery.” *Diseases of the Colon & Rectum* (Fadwa Ali, Carrie Y. Peterson, Kirk A. Ludwig & Timothy J. Ridolfi)
Women’s Cardiovascular Health: Part 2  March 17th 4:00pm

We will focus on how women can improve their bone health, the gender differences which exist around medication use, and how women can achieve healthy weight loss.

Dr. Lohr
Dr. Neuner
Dr. Shaker
Dr. Lalonde
Sara Arndt NP
Dr. Gosset
Dr. Lor
Dr. Groden
Dr. Findling
Dr. Higgins
Amy Kulwicki RD

Prostate Cancer (Urology)  April 14th, 2018 3:00pm
Next Month:

Cardiothoracic Surgery Research Update
Paul Pearson, MD, PhD, Professor and Division Chief, Cardiothoracic Surgery

Intro to REDCap
Mark Oium
Biomedical Informatics Software Engineer

Wednesday, April 11
5:00-6:00 pm
Location: HUB A1015/A1035

***Please note the location change***
Colorectal Surgery Research Update

March 14, 2018
Division of Research Conference
Introductions

Division of Colorectal Surgery

Kirk A. Ludwig MD

Mary Otterson MD

Carrie Y. Peterson MD

Timothy J. Ridolfi MD
Research Focus

Improving surgical care and recovery for colorectal patients:

- Rectal Cancer
  - Low anterior resection syndrome
  - Better imaging
  - Reduced leak rates after a low anastomosis

Enhanced Recovery
- BRIDGE study
- IV acetaminophen
- Alvimopan

Clinical Experience and Questions
Rectal Cancer

40000 new cases of rectal cancer yearly in the United States

Goals of therapy:
Curative Resection
Restore Function
Maintain Quality of Life

Low anterior resection with total mesorectal excision is usually the treatment of choice
Low Anterior Resection
Low Anterior Resection – Functional Results

A low anterior resection undeniably alters a patient's bowel function.

Patients describe:
- Frequency
- Urgency
- Incontinence
- Clustering

Up to 90% of patients experience these symptoms. A 1-2 year period of adaptation is typically observed.
Low Anterior Resection – Functional Results

Low Anterior Resection Syndrome and Quality of Life: an International Multicenter Study

Therese Juul, Ph.D.¹ • Madelene Ahlberg, M.H.Sc.² • Sebastiano Biondo, Ph.D.³
Eloy Espin, Ph.D.⁴ • Luis Miguel Jimenez, M.D.⁴ • Klaus E. Matzel, Ph.D.⁵
Gabriella Jansson Palmer, Ph.D.² • Anna Sauermann, M.D.⁵ • Loris Trenti, M.D.³
Wei Zhang, M.D.⁵ • Søren Laurberg, D.M.Sc.¹ • Peter Christensen, D.M.Sc.¹

796 pts treated with LAR for rectal cancer
LAR Syndrome Score and EORTC QLQ-C30
at least 16 months post operation
50-90% of LAR patients experience bowel dysfunction
Concluded: Those with severe LARS had significantly worse QoL in 7 of 8 domains compared to those without or minor LARS

Dis Colon Rectum 2014; 57: 585–591
Low Anterior Resection Syndrome

Is removing the rectal reservoir really the cause?

Studies that attempt to document the physiologic changes after low anterior resection are a bit inconsistent, except with regards to the neorectal compliance issue.

Observation that after complete mobilization and division of bowel there are very strong contractions within the mobilized colon that do not propagate.
Low Anterior Resection Syndrome

Sympathetic nerves are divided during ligation of the inferior mesenteric artery

Parasympathetic nerves are divided during pelvic mobilization

This leaves the neo-rectum under the control of the intrinsic nervous system
Rectal Cancer Related Projects

1. Causes of Low Anterior Resection Syndrome
2. Evaluation of Rectal Cancer with 7T MRI and Novel 3.5T Sequences
3. Lifebond Surgical Sealant Study
Animal Model

Colon Transit

<table>
<thead>
<tr>
<th>Post Operative Day</th>
<th>Geometric Center</th>
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<tbody>
<tr>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>7</td>
<td>7</td>
</tr>
</tbody>
</table>

- **Sham**
- **Denervation**
Animal Model

Saline 5-HT3 antag 5-HT4 antag

Geometric Center

Saline 5-HT3 antag 5-HT4 antag

*
Role of 5-HT

Serosa
Smooth Muscle

Smooth Muscle

Serosa

Smooth Muscle

Smooth Muscle

Extrinsic Afferent Nerve

EC cell

EC cell

Luminal Pressure

5-HT
5-HT$_3$ receptor
5-HT$_4$ receptor

IPAN
Hypothesis

- Serosa
- Smooth Muscle
  - Smooth Muscle
  - Luminal Pressure
  - 5-HT
  - 5-HT\textsubscript{3} receptor
  - 5-HT\textsubscript{4} receptor

- Mucosa
  - EC cell

- IPAN

- Smooth Muscle
  - Extrinsic Afferent Nerve
  - DRG
Upregulation of 5-HT receptors

5-HT$_3$ Mucosa

Optical Density 5-HT$_3$ / β-Actin

- Proximal
- Mid
- Distal

Sham
Denervation

* p<0.02

Colon Segment

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Upregulation of 5-HT receptors

![Graph showing optical density of 5-HT4 receptors in the colon segment.](image)

**5-HT4 Mucosa**

- **Colon Segment**
  - Proximal
  - Mid
  - Distal

- **Optical Density 5-HT4/β-actin**
  - Sham
  - Denervation

- **Significance**
  - * p<0.05
Human Study

The patients neo-rectum is biopsied 4 times

Time of surgery – proximal tissue doughnut

3 month clinic visit

6 month loop ileostomy takedown

12 month surveillance colonoscopy

Compare the changes in serotonin receptors

Funded initially though the We Care Foundation and
Subsequently through an ASCRS Career Development Award
Human

Patients enrolled 15 patients
7 have completed
8 still undergoing sample collection
Target accrual of 20 patients
5-HT study

<table>
<thead>
<tr>
<th>Sample</th>
<th>Date</th>
<th>Time, days</th>
<th>5HT3a/βActin/HC</th>
<th>5HT4/βActin/HC</th>
<th>SerT/βActin/HC</th>
</tr>
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<tr>
<td>6A</td>
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<td>0</td>
<td>8.94</td>
<td>14.38</td>
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<td>6B</td>
<td>5/25/2016</td>
<td>29</td>
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<tr>
<td>6C</td>
<td>8/30/2016</td>
<td>126</td>
<td>3.77</td>
<td>7.05</td>
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<tr>
<td>6D</td>
<td>2/15/2017</td>
<td>295</td>
<td>4.97</td>
<td>10.17</td>
<td>3.03</td>
</tr>
</tbody>
</table>
MRI study

Ultimate way to improve function following surgery would be to not remove the rectum at all.

A vast majority of rectal cancer patients receive chemotherapy and radiation before the colon is removed.

In 20-25% of cases the tumor is completely gone when the rectum is removed.

We do not have a reliable test to figure out who these people are.
7T MRI Study

MCW CIR houses one of only 20 7T MRIs capable of imaging a human

Increased magnetic strength yields higher resolution imaging
7T MRI - Hypothesis

7T MRI will accurately predict postoperative tumor depth and nodal status

Patients undergoing LAR for rectal cancer were enrolled in the trial

Following surgical excision, the specimen was suspended in a normal saline filled canister and subsequently imaged in the 7T MRI

Images were interpreted by radiologist and compared to pathologic results
7T MRI

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7T MRI of proctectomy specimens from patients with rectal adenocarcinoma

- DIVISION OF COLORECTAL SURGERY
## Preliminary Results

<table>
<thead>
<tr>
<th>Preoperative Stage</th>
<th>Pathologic Stage</th>
<th>Radiologic Stage</th>
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<tbody>
<tr>
<td>cT2 N1 M0</td>
<td>mypT3 N0 (0/26) M0</td>
<td>T2 N0 Mx</td>
</tr>
<tr>
<td>cT2 N0 M0</td>
<td>pT2 N0 (0/14) M0</td>
<td>T2/early T3 N0 Mx</td>
</tr>
<tr>
<td>cT3 N0 M0</td>
<td>pT2 N0 (0/64) M0</td>
<td>T2/early T3 N0 Mx</td>
</tr>
<tr>
<td>cT2 N1b M0</td>
<td>ypT2 N0 (0/15) M0</td>
<td>T0 N0 Mx</td>
</tr>
<tr>
<td>cT2-T3 N0 M0</td>
<td>pT2 N1b (3/23) M0</td>
<td>T1 or T2 N1b Mx</td>
</tr>
<tr>
<td>cT3 N0 M0</td>
<td>ypT4b N1a (1/14) M1b</td>
<td>T4b N1a Mx</td>
</tr>
</tbody>
</table>
Future Directions

- Patients will undergo 7T MR imaging of rectal cancer *in vivo* prior to LAR
Multidisciplinary Team

- DIVISION OF COLORECTAL SURGERY
First Human 7T MRI of Pelvis

- DIVISION OF COLORECTAL SURGERY
Acknowledgements

This research study was supported by

Colon Cancer Coalition – Get Your Rear in Gear 5K run/walk.

Center for Imaging Research – Daniel Soref Grant
LifeSeal Surgical Sealant

Anastomotic leaks following a colorectal anastomosis can have devastating consequences.

Leak rates have been reported as high as 20% in patients undergoing resection for rectal cancer.

LifeSeal is surgical sealant designed for staple-line reinforcement that is applied over the anastomotic line.
Study Design

Prospective, multi-center, multinational randomized, single-blind, double armed study

The primary objective is to assess the efficacy and safety of LifeSeal™ Kit as measured by the change in overall anastomotic leak rates in subjects undergoing low anterior resection with an anastomosis below 10 cm from the anal verge, over the first 17 weeks after surgery.

736 patients to be enrolled at 27 study locations
Improving Surgical Recovery

• Centered around principles of enhanced recovery
  • Less narcotics
  • Minimally invasive surgery
  • Reducing postoperative ileus

• Three central projects
  • BRIDGE study
  • IV acetaminophen meta-analysis
  • Alvimopan utilization and length of stay
BRIDGE Study

- NSS-2 BRIDGE is percutaneous auricular neurostimulation device
  - Low voltage, alternating frequency
  - Stimulates vagal afferent pathways projecting to central pain processing centers
  - Vagal stimulation can have anti-inflammatory effect systemically

- FDA approved for control of opioid withdrawal symptoms
  - 85% reduction in opioid withdrawal symptoms within 20 minutes of application
  - Animal studies indicate BRIDGE device improves pain thresholds

- Adolescents with functional GI pain had significant reduction in pain

BRIDGE Study

- RCT in postoperative patients having colorectal surgery
  - Inclusion: adult patients having small bowel, colon, or rectal resections
  - Major Exclusion: chronic narcotic or NSAID use, emergency surgery, prolonged intubation, or anticoagulation use

- Procedure
  - Device applied in AM morning of surgery
  - Device remains in place for 5 days (life of battery)
  - Anesthetic & postop care per MD
    - pain managed with PCA – no NSAIDs or regional blocks
    - Blood, saliva samples at baseline prior to application and twice daily for five days
    - VAS scores, PONV and anxiety scores daily
BRIDGE Study

• **Outcome Metrics**
  - Primary = total hospital narcotic requirement
  - Secondary = VAS scores, PONV scores, anxiety scores, serum inflammatory markers, salivary cortisol levels

• **Currently 52 patients enrolled**
  - 3 (6%) withdrew prior to study start
  - 49 participants
    - 41 (78%) completed full protocol, 8 (15%) required early termination of device
  - Power analysis indicates that 56 total patients in study, assuming 10% withdrawal rate (currently = 6%)
IV Acetaminophen in Abdominal Surgery

- Meta-analysis of use of IV acetaminophen for pain control in abdominal surgery
- Postoperative pain management relies on opioid medications
  - Contribute to postoperative ileus & dependence
- Hypothesize that IV acetaminophen more effective than other non-opioid medications for postoperative pain control & reducing narcotic use

Blank, Berger, Dux, Ali, Ludwig, Peterson. JSR, 2018. Accepted for publication.
**IV Acetaminophen in Abdominal Surgery**

- Queried four databases for keywords “acetaminophen,” “intravenous (IV),” and “postoperative”
- Inclusion: prospective, IV acetaminophen x24H, intra-abdominal surgery, comparison medication
- Primary outcome = 24H pain scores
- Secondary outcomes = 12H pain scores, 24H narcotic use
- 17 studies included
  - No study included reported LOS or return of bowel function data
IV Acetaminophen in Abdominal Surgery

- Study quality moderate, high heterogeneity
- No difference in 24H pain scores with IV acetaminophen compared to any other medication
- Open surgery with laparotomy = reduction in 24H narcotic requirement with IV acetaminophen

Blank, Berger, Dux, Ali, Ludwig, Peterson. JSR, 2018. Accepted for publication.
IV Acetaminophen in Abdominal Surgery

- Study quality moderate, high heterogeneity
- No difference in 24H pain scores with IV acetaminophen compared to any other medication
- Open surgery with laparotomy = reduction in 24H narcotic requirement with IV acetaminophen
- NSAIDs = reduction in 24H narcotic requirement better than IV acetaminophen

Blank, Berger, Dux, Ali, Ludwig, Peterson. JSR, 2018. Accepted for publication.

- DIVISION OF COLORECTAL SURGERY
Alvimopan Utilization and Length of Stay

- Peripherally acting \( \mu \)-opioid antagonist
- Shown to:
  - Accelerate recovery of GI function following abdominal surgery
  - Shorten LOS
  - Reduce POI-related morbidity without compromising opioid analgesia in ERAS settings
- More expensive drug initially
  - However, it decreases both LOS and costs of treatment
Aim of this Study

Primary Aim: Examine the relationship between alvimopan usage with LOS and cost.

Secondary Aim: Examine the relationship between IV and oral acetaminophen, IV ketamine, gabapentin, and ketorolac on LOS and cost.
Methods

• Queried the University HealthSystem Consortium (UHC) database for each hospital:
  • Performing large and small bowel surgeries (DRGs 329-334)
  • January 2015- December 2015
  • LOS & direct cost indices

• Multiple linear regression model
  • Percent drug usage among hospitals
Resident and Student Research Projects

- Pouch volvulus after IPAA (Landisch)
- Early loop ileostomy closure (Berger)
- Modified Hanley Procedure (Blank, Westein)
- Prognostic value of CT in predicting need for surgery in UC (Katbamna)
- Hand-assisted laparoscopic surgery rates (Kurtz)
- HPV and phenotype association (Foss)
- Leak rates and clinical assessment (Kream)
- Induction chemotherapy and tumor downstaging in rectal cancer (Nganzu)
- Adjuvant surgery and upstaging in rectal cancer (Berger)
- Evaluating bowel function after anal cancer treatment (Kent)
- Complete clinical response assessment with 7T MRI (Simpson)
Results

- 128 hospitals included with 46,220 cases

Median percent usages:
- Alvimopan 1.6% (0-62.6%)
- Oral Acetaminophen 41.6% (0-95.1%)
- IV Acetaminophen 30.8% (0-93.8%)
- IV Ketamine 6.7% (0-91.5%)
- Gabapentin 9.4% (0-72.5%)
- Ketorolac 36.5% (0-92.3%)
## Results

### Multivariate Analysis of Length of Stay Index

<table>
<thead>
<tr>
<th>Variables</th>
<th>Coefficient</th>
<th>SE</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
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<td>0.041</td>
<td>&lt;.0001</td>
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<tr>
<td>Percent Use:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alvimopan</td>
<td>-0.002</td>
<td>0.001</td>
<td>0.019</td>
</tr>
<tr>
<td>Tylenol Oral</td>
<td>0.000</td>
<td>0.001</td>
<td>0.783</td>
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<tr>
<td>Tylenol IV</td>
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<td>0.784</td>
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<tr>
<td>Ketamine IV</td>
<td>0.000</td>
<td>0.001</td>
<td>0.909</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>0.003</td>
<td>0.001</td>
<td>0.002</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>-0.002</td>
<td>0.001</td>
<td>0.076</td>
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</table>
## Results

<table>
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<tbody>
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<td>Intercept</td>
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<td>Percent Use:</td>
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<td>Alvimopan</td>
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<td><strong>0.006</strong></td>
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<tr>
<td>Ketorolac</td>
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<td>0.002</td>
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</table>
Conclusion

Increased usage of alvimopan is associated with decreasing LOS index following gastrointestinal surgery with no change in the cost.

Use of alvimopan in the care of patients undergoing gastrointestinal surgery should be used in ERAS protocols to reduce LOS without increasing the cost of care.

The results concerning gabapentin correlating with an increasing LOS index and an increase in direct cost index were surprising and require further investigation.
Summary and Future Possibilities

• Cancer research funding through Get Your Rear in Gear 5K Run/Walk
  • Annual event in October, proceeds to CRS Research
• Future project possibilities
  • Basic science evaluation of constipation
  • Epigenetics of rectal cancer
  • Evaluation of young rectal cancer patients
  • Anti-inflammatory effects of neurostimulation
  • Neurostimulation of chronic pain/IBS
Questions?

Thank You!
Next Month:

Cardiothoracic Surgery Research Update
Paul Pearson, MD, PhD,
Professor and Division Chief, Cardiothoracic Surgery

Wednesday, April 11
5:00-6:00 pm
Location: HUB A1015/A1035

***Please note the location change***