Drs. Amanda Kong & Andreas Beyer present: We Care Award Update: *Mitochondrial Telomerase as Regulator of Mitochondrial Damage and Secondary Messengers in Chemotherapy Induced Microvascular Dysfunction*

**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 Tracy Wang, MD, MPH!

MCW Cancer Center Pilot Grant Recipient

Molecular Testing to Direct Extent of Initial Thyroid Surgery
Good Luck **Joshua Hunt, PhD**!

Chosen by the internal selection committee of MCW to be one of two early career faculty members to apply for the **2019 Moore Inventor Fellows Award**

*Feasibility of a Multi-Institutional Validation Study of the ITSS*

Sponsored by the [American Association for the Surgery of Trauma Multi-institution Trials Committee](https://www.aast.org).
Congratulations **Tammy Kindel**, MD, PhD!

NIH: National Heart, Lung, & Blood Institute:K08 Recipient

*The Role of GLP-1 in cardiac recovery after bariatric surgery in obesity-induced heart failure*
Drs. **Kirk Pritchard** & Stephen Naylor

Celebrating new licensing agreement for their company **ReNeuroGen, LLC**

“A novel tripeptide that inhibits myeloperoxidase production of toxic oxygen radicals.”

The drug has been shown to dramatically decrease, and speed recovery from, brain injury in trials in mice.
The We Care Fund for Medical Innovation and Research
Committee is requesting applications for seed funding for Department of Surgery faculty. Two grants will be awarded: one grant for up to $100,000 and one grant for up to $150,000, both distributed over two years.

Key Dates
- Request for Applications (RFA) Release Date: **Thursday, February 7, 2019**
- Department of Surgery Budget Assistance (Mary Halverson and Karen Larson): No Later Than – **Wednesday, March 27, 2019**
- Proposal submitted in eBridge (same as sponsor deadline): No Later Than – 5:00 pm, Monday, April 8, 2019
- Scientific Review Committee Meeting: **Thursday, June 6, 2019**
- Recommended for Funding Notifications: No Later Than – Monday, July 8, 2019
- Anticipated Start Date: **Sunday, September 1, 2019**
2019 Clinical Research Scholars Program

- Full time junior faculty
- Pursuing careers in academic medicine
- Independent investigators
- 20% protected research time

Applications are due by April 5, 2019
Program begins on September 10, 2019
March 5th Clinical Research POWER LUNCH: Budget Development for Clinical Trials

Symposium objectives:

• Increase understanding clinical trial budgets
• Understand the different methods for staff time in the clinical trial budget
• Offer tips to justify your budget to sponsor

11:45am: Lunch
12-1pm: Presentation in Alumni Center
1-2pm: DOS Q&A in HUB A1015

Lunch will be provided for those who RSVP by Feb 19. The event is open to all faculty and staff. We encourage any staff in a clinical research environment to attend.

1.0 AMA PRA Category 1 Credit.
Publications

January 2019

Pediatric Surgery
Sema3E/PlexinD1 signaling inhibits postischemic angiogenesis by regulating endothelial DLL4 and filopodia formation in a rat model of ischemic stroke. *FASEB Journal*.
(Zhou YF, Chen AQ, Wu JH, Mao L, Xia YP, Jin HJ, He QW, Miao QR, Yue ZY, Liu XL, Huang M, Li YN, Hu B)

Research
Disruption of FOXP3-EZH2 Interaction Represents a Pathobiological Mechanism in Intestinal Inflammation. *Cellular and Molecular Gastroenterology and Hepatology*.

Vascular Surgery

Trauma & Acute Care Surgery
(Eddine SBZ, Boyle KA, Dodgion CM, Davis CS, Webb TP, Juern JS, Millia DJ, Carver TW, Beckman MA, Codner PA, Trevino C, de Moya MA)

Surgical Oncology

Elective Regional Therapy Treatment for Hepatic Adenoma. *Annals of Surgical Oncology*.
(Silva JP, Klooster B, Tsai S, Christians KK, Clarke CN, Mogal H, Clark Gamblin T)

(Robbins JR, Schmid RK, Hammad AY, Gamblin TC, Erickson BA)

Effect of Donor Race-Matching on Overall Survival for African American Patients Undergoing Liver Transplantation for Hepatocellular Carcinoma. *Journal of the American College of Surgeons*.
(Silva JP, Maurina MN, Tsai S, Christians K, Clarke CN, Mogal H, Saeian K, Gamblin TC)
“The Word on Medicine: where Knowledge is changing life”

February 23rd at 4:00 pm

We have a special replay of "The Word On Medicine" radio program focused on Prostate Cancer with medical experts and patients discussing the diagnosis and treatment

Dr. Kenneth Jacobsohn
Dr. William Hall
Dr. Scott Johnson
Jessica Motl PA-C
Next Month:

Division of Congenital Heart Surgery: Research Updates

March 13th 2019
Conference Room M
5:00-6:00pm

Viktor Hraska, MD
Surgery Research Conference

Amanda L. Kong, MD, MS & Andreas Beyer PhD
February 13, 2019
Breast Cancer Treatment and Cardiac Failure

- Scope of the problem
- Different drugs, different risks
- Patient cases
- Current research findings
Significance

• Breast Cancer
  • Most commonly diagnosed cancer in women
  • Second leading cancer cause of death (after lung cancer)
  • More than 3.5 million breast cancer survivors in the US
    • Surgery, radiation, chemotherapy, anti-endocrine therapy
• Treatment related cardiotoxicity
  • No standard guidelines for monitoring
  • No standard definition of cardiotoxicity
    • \( \geq 10\% \) drop in LVEF, symptomatic or asymptomatic?
    • Any drop in LVEF
    • Heart failure, etc…

Monitoring

• 2-D echo
  • Monitors LVEF
  • Low baseline EF 50-55% and asymptomatic drop increases risk of heart failure
  • Limitation: poor detection of subclinical myocardial injury

• Cardiac MRI
  • Gold standard for systolic and diastolic cardiac function
  • Direct imaging of myocardium
  • Limitation: high cost, limited availability
Cardiovascular Toxicity

• Chemotherapy
  • Anthracyclines (ie: doxorubicin)
    • Dose dependent
    • Early or late onset (1 year cut off)
    • Most incidents peak at one year post-treatment
    • Late onset incidence not truly known, no good data
    • Irreversible cardiomyocyte damage

• Monoclonal antibodies
  • HER2 (human epidermal growth factor receptor) treatments
    • Reversible cardiomyocyte damage
Anthracyclines

- Used in the adjuvant treatment of breast cancer for >25 years
- Early Breast Cancer Trialists’ Collaborative Group demonstrated superiority to CMF in meta-analysis in 2005
  - 6 months of anthracycline based chemotherapy → reduce the annual cancer death rate by 38% for women <50 at diagnosis and 20% for ages 50-69
  - Irrespective of use of tamoxifen, ER status, node status, other tumor characteristics
- Optimal dose around 60mg/m² for doxorubicin and 100mg/m² for epirubicin
  - CHF associated with cumulative dose
  - Risk of CHF increased with concomitant administration of other cytotoxic drugs (ie: cyclophosphamide)
  - Limiting cumulative dose to 240 to 360 mg/m² of doxorubicin has reduced incidence of CHF to 1.6-2.1%
    - Cardiac failure may not occur until much later

Early Breast Cancer Trialists Collaborative Lancet 365: 2005
Gianni et al. JCO 27: 2009
Anthracyclines

- Type I chemotherapy-related cardiac dysfunction (CRCD)
  - Initiated just after the earliest exposure to the drug
  - Threshold level of damage results in cell death
- Anthracyclines
  - Lead to structural cardiomyocyte alterations and cell death
    - ? Mediated by reactive oxygen species
  - Type I damage diagnosed by reduced LVEF
    - Increases heart’s vulnerability to later cardiac stress
Targeted Therapy

• Trastuzumab
  • Monoclonal antibody designed to block HER2
  • Addition to chemotherapy results in a reduction of breast cancer recurrence by 50% and mortality by 33%
• Type II CRCD
  • Reversible
  • Asymptomatic LVEF drops that recover after cessation of the drug although LVEF decline can continue
  • NSABP B-31 → asymptomatic decrease in LVEF in 14% patients requiring cessation
Cases
Case 1  KB

- 45 year old female
  - PMH: cardiac ablation for SVT in 2014
  - PSH: cholecystectomy
  - FHx: adopted
  - Works as a college pastor, very physically active

- Physical exam: unremarkable
Work-up

- **4/15/16 screening mammogram**
  - New extensive calcifications and focal asymmetry throughout the RIGHT breast, highly suspicious for multicentric carcinoma.

- **4/21/16 right diagnostic mammogram**
  - Interval appearance of extensive malignant calcifications throughout the right breast for which ultrasound-guided core biopsy of the 2 most separated areas is recommended.

- **4/21/16 right ultrasound guided biopsy**
  - Ductal carcinoma in situ (DCIS), grade 3, solid type with comedo necrosis. ER+/PR+

- **4/27/16 MRI**
  - There is very extensive area of non-mass like malignant enhancement involving nearly the entire lower half of the right breast extending above the plane of the nipple both medially and laterally somewhat as well extending from nearly the nipple anteriorly to almost the chest wall.
Treatment For Breast Cancer

- 5/26/16 right total mastectomy and sentinel node biopsy
  - Microinvasive DCIS 2/3 sentinel nodes positive
- 6/10/16 for a right completion axillary dissection
  - right breast pT1micN1a(sn) Mx (ER+/PR+/HER2 non-amp, grade II IDC, 2/28 nodes+) cancer
- Adjuvant chemotherapy--AC to Taxol from end of July to December 7, 2016
  - adjuvant therapy with Adriamycin (60mg/m^2) and Cytoxan (600mg/m^2) x 4 cycles
  - 9/21/16-12/7/16: Completed Taxol (80 mg/m2) IV Day 1,8,15 q 21 days x 4 cycles
- Post-mastectomy radiation from January to February 2016
- Initiated exemestane in March 2016
Cardiac Complication

- 6/18/18 routine follow-up
  - Tachycardic to 112
  - she attributes this to nervousness/anxiety about her cancer visits.
  - Told to follow up with PCP the next day → work up normal

- 7/3/18 30 mile bike ride with friends → extremely fatigued, short of breath, went to ER.
  - Echo: EF 15-17%
  - Cardiac cath clean
  - Retrospect developed orthopnea last week of June and leg swelling
Treatment

- Started on ace inhibitor, beta blocker, diuretic → transferred cardiac care to cardio-onc team
  - Cardiac rehab started
- Cardiac MRI 7/25/18
  - 1. Moderate dilatation of the left ventricle with global hypokinesia and decreased systolic function, LVEF 24%.
  - 2. Normal right ventricular size and decreased systolic function, RVEF 39%
Recovery

- 10/4/18 EF to 36-40%
  - Left ventricle is severely enlarged in size with moderate systolic dysfunction. There is moderate global hypokinesis. There is mild (grade I) diastolic dysfunction with normal left atrial pressure.
  - Right ventricle is normal size with normal systolic function.
  - Mildly enlarged atria.
  - No significant valve disease.
  - Estimated right atrial pressure is 3 mmHg.
- 11/26/18 saw advance heart failure team
- 12/31/18 started sacubitril/valsartan for chronic heart failure
Case 2  SG

• 56 year old female
  • PMHx: HTN, hyperlipidemia, diverticulitis
  • PSHx: partial colectomy, TAH/BSO,
  • SocHx: runs family trucking business and farm
  • FHx:
    • maternal aunt- bilateral breast cancer 40s
    • Maternal cousin- breast cancer ? Age
    • Maternal aunt- ovarian cancer 82

• PE: left breast: 3 cm non-discrete mass at 9 o’clock, more like thickening, no nodes
Work up

- 10/16/15 bilateral screening mammogram
  - There are calcifications and a possible associated mass in the left breast lower inner quadrant middle depth.

- 10/29/15 left breast diagnostic mammogram and ultrasound
  - Magnification views confirm pleomorphic microcalcifications within an ill-defined mammographic mass in the 9:00 subareolar breast.
  - In the 8 to 9 o'clock subareolar breast, there is an ill-defined hypoechoic mass with acoustic shadow measuring up to 2.2 cm x 1.8 cm x 1.6 cm.

- 11/5/15 left ultrasound guided biopsy
  - IDC, grade III, ER+ (10%), PR+ (40%), HER2 2+ fish amplified (ratio 5.3), ki-67 50%

- Clinical stage II: T2N0Mx (ER+/PR+/ HER2 amplified) left breast
Treatment

- Neoadjuvant chemotherapy initiated Dec 2015
  - Completed the THP regimen x 4 cycles, dose dense AC x 4 cycles on 4/13/16.
  - Complete response on imaging

- 5/20/16 she underwent a left total mastectomy and sentinel node biopsy
  - Pathologic complete response ypT0, N0(i-)(sn).
Adjuvant Treatment

- Arimidex started June 2016
- Herceptin on hold since August 2016 secondary to decreased LVEF
- 3/3/17 left expander to implant exchange and removal of mediport
Cardiotoxicity

- 8/24/16 cardiology consultation
  - recent onset (3-4 weeks ago) dyspnea, peripheral edema, and PND/orthopnea noted shortly after receiving her last Herceptin dose (7/27/2016)
    - Start ARB, diuretic, continue beta blocker
    - Cardiac rehab

- Life impact
  - Had to cancel surgery for tissue expanders
  - decrease her work functions and childcare
Echo Findings

• 11/24/15 EF 55%
• 2/17/16 EF 62%
• 4/28/16 EF 57%
• 7/20/16 EF 52% - last dose Herceptin
  • 8/24/16 EF 37% - Herceptin on hold
• 9/28/16 EF <20%
• 11/9/16 EF 26%
• 2/28/17 EF 44%
• 5/17/17 EF 52%
• 11/22/17 EF 59%
• 4/25/18 EF 58%
• 10/24/18 EF 58%
Current Research Findings
The vascular system is like a road system
Mescher AL, Junqueira's Basic Histology
www.clinicalgate.com/physiology-of-the-cardiovascular-system/
Broken Road = hard to drive
Broken Vessels = impaired organ function

Winter South
Normal
Wisconsin Winter
Disease
Predictive Value of Coronary Flow Velocity Reserve (CFVR) (indirect assessment of coronary microvascular function)

**All Women**

- Normal CFVR > 2.32
- Decreased CFVR < 2.32

**Women without CAD** (without large vessel disease)

- Normal CFVR > 2.32
- Decreased CFVR < 2.32

p=0.003 (Log Rank)

p=0.004 (Log Rank)
Value of Conduit (FFR) vs. Microvascular (CFVR) Function in Predicting CV Outcomes (MACE)

Microvascular function drives long term outcomes more than the magnitude of conduit artery disease.

Problem:
- Neither study contained “healthy” controls
- Vascular function was only measured as function of flow velocity (indirect)

- van de Hoef et al, Circ. Cl. 2014
Clinical Problem with Microvascular Function

- While endothelial function and microvascular function is known to be a contributor of disease development including heart failure, dogma is that heart failure is a cardiac muscle/myocyte problem.

- Microvascular function is difficult to measure → can only be measured indirectly through tissue perfusion.

- Animal models do not always recapitulate human phenotypes.

- Mechanistic studies using in vivo measures in human subjects are not possible.
The Problem

Cancer

1 in 2 American men
1 in 3 American women

- Hormone receptor blockage
- Growth factor inhibition
- DNA damage induction

The Cardiovascular Disease Continuum

MCW Surgery
knowledge changing life
Anti-cancer Therapy Induced Heart Failure

Cancer Population + Chemotherapy

Problem \rightarrow cardiovascular-related death

Problem \rightarrow cardiovascular-related and/or cancer related death

Cancer free CV complication

Cancer recurs CV complication

No PROBLEM (ULTIMATE CLINICAL GOAL)
Sample Collection

- Vessels 100-200 µm in diameter obtained from otherwise discarded fresh surgical specimens.
  - Arterioles have thickness of human hair
  - Small resistance arteries and arterioles are major contributors to overall vascular resistance and blood pressure regulation
  - Clear clinical relevance of coronary microvasculature
  - Adipose (visceral) microvasculature is a good surrogate (in most cases)
Methods

- Arterioles (atrial and adipose) (~150 µM ID)
- Video microscopy to assess vascular reactivity
Methods

- Arterioles (atrial and adipose) (~150 µM ID)
- Video microscopy to assess vascular reactivity
Effect of Doxorubicin on Microvascular Function

Discarded adipose tissues from human subjects

Curves in response to flow

Diameter changes

**Adipose**

<table>
<thead>
<tr>
<th>ACh (- logM)</th>
<th>% Max. Diameter</th>
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<tbody>
<tr>
<td></td>
<td>Vehicle</td>
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<tr>
<td>9</td>
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<td>8</td>
<td>40</td>
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<tr>
<td>7</td>
<td>80</td>
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<tr>
<td>6</td>
<td>100</td>
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</table>

**Atrial**

<table>
<thead>
<tr>
<th>Pressure Gradient (cm H$_2$O)</th>
<th>% Max. Diameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Vehicle</td>
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<tr>
<td>20</td>
<td>0</td>
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<td>40</td>
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**MCW Surgery**

knowledge changing life
Effect of Doxorubicin on Microvascular Function

**Adipose FMD**

- CTRL
- Doxorubicin
- Herceptin

% Max. Diameter vs. Pressure Gradient (cm H₂O)

**Adipose ACh**

- CTRL
- Doxorubicin
- Herceptin

% Max. Diameter vs. ACh (logM)

**Graphs and Bar Chart**

- Graphs show the response of microvascular function to different treatments.
- Bar chart compares the effectiveness of different treatments.

By MCW Surgery

knowledge changing life
Immunotherapy Changes Underlying Mechanism of Microvascular Dilation

**Adipose FMD L-Name**

![Graph showing the effect of L-Name on adipose FMD](image1)

- **CTRL**
- **Herceptin**

**Adipose FMD Peg-Cat**

![Graph showing the effect of Peg-Cat on adipose FMD](image2)

- **CTRL**
- **Herceptin**

Nitric Oxide

McW Surgery

Knowledge changing life
Neoadjuvant Chemotherapy Induces Microvascular Endothelial Dysfunction

![Graph showing the effect of pressure gradient on vessel diameter with and without neoadjuvant chemotherapy.](image-url)
Trastuzumab → HER-2 → Doxorubicin

Chromosomal instability / Cell Death and Lysis

Doxorubicin → mtDNA Damage

Endothelial Dysfunction

↑ ROS
↓ ATP
Dox Increases mtDNA damage in Isolated Vessels
Initiation of mtDNA repair Prevents Dox-induced Endothelial Dysfunction

Ex-vivo treated vessels form healthy subjects
Trastuzumab

HER-2

Chromosomal instability /Cell Death and Lysis

Doxorubicin

mtDNA Damage

Endothelial Dysfunction

Primary Hit

↑ROS

↓ATP
Cell-free nucleic acids as biomarkers in cancer patients

Anti Cancer therapy

↑ cf-DNA

mtDNA

nucDNA

cf-<sub>mt</sub>DNA Decreases Endothelial NO Mediated Dilation and Elevates mtROS Production in Human Microvessels
Trastuzumab

HER-2

Chromosomal instability
/Cell Death and Lysis

Doxorubicin

mtDNA Damage

Cancer Cell

EC

Endothelial Dysfunction

Circulating DNA

EC

Inflammation

↑ROS

↓ATP
Summary ChemoTox Study

- Dox causes endothelial dysfunction in human adipose and coronary microvessels
- Breast cancer itself does not cause vascular defects
- Neoadjuvant CT causes endothelial dysfunction in human adipose vessels
- Dox Causes mtDNA damage in isolated vessels
- Initiation of mtDNA damage repair prevents Dox-induced endothelial dysfunction

What next?
- Longitudinal study (7 subjects enrolled) to evaluate effect of chemo as a causative means to induce microvascular endothelial dysfunction before onset of heart failure
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Hypertension + ATVB
Affinity Group
Cardiac Oncology pre-PPG

Tissue Sources
- MCW Pathology Tissue bank
- Department of Surgery MCW - Breast Cancer Group
The End