Future Directions & Opportunities for Cancer-related Research Collaborations
CTSI – Cancer Center Workshop

Academic & Research Disciplines

- Medicine
- Biomedical Informatics
- Rehabilitation
- Psychology
- Economics
- Nursing
- Dentistry
- Public Health
- Computer Science
- Business
- Physical Therapy
- Exercise Science
- Biomedical Engineering
- Genetics
- Physics
- Chemistry
- Mechanical Engineering
- Psychiatry
Ming You, MD, PhD

- Dr. You received his medical degree from Peking University College of Medicine and his Ph.D. in Pathology from Medical College of Ohio
- He is the Joseph F. Heil Jr. Professor in Molecular Oncogenesis
- Dr. You is Professor of Pharmacology and Toxicology, Senior Associate Dean for Cancer Research, Education and Clinical Care and Director of the MCW Cancer Center
- Dr. You’s primary research interests are in the area of Genetics and Chemoprevention of Lung Cancer
Overview of the MCW Cancer Center
Cancer is the TOP STRATEGIC PRIORITY of The Medical College of Wisconsin (MCW) because of its devastating effect on so many.

Our VISION: To become an NCI-designated Cancer Center as characterized by scientific excellence and the capability of integrating diverse MCW research programs to focus on the problem of cancer.

Research Cures Cancer!
Location

[Map of Wisconsin showing cities such as Madison, Green Bay, Eau Claire, Appleton, Sheboygan, and MCW.]
Why NCI-designation is Important

- Improves patient treatment, care, and prevention of cancer
- Attracts the best and brightest physicians and scientists to our region
- Brings more National Cancer Institute dollars to the region
- Promote scientific collaborations among the researchers in our region
- Lets industry know that we are ripe for a high tech environment and for economic development
NCI-Essential Characteristics

- Cancer Focus
- Institutional Commitment
- Organizational Capabilities
- Facilities
- Center Director
- Interdisciplinary Coordination and Collaboration
Growth Expected in MCW Cancer-related Research (total cost) in the Next 5 Years

**NCI Funding Goals**

<table>
<thead>
<tr>
<th>Year</th>
<th>NCI</th>
<th>Other NIH</th>
<th>Other CR</th>
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<tbody>
<tr>
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<td>10</td>
<td>7</td>
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</tr>
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<td>2012</td>
<td>15</td>
<td>10</td>
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<td>2013</td>
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<td>2014</td>
<td>25</td>
<td>20</td>
<td>4</td>
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<tr>
<td>2015</td>
<td>30</td>
<td>25</td>
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</table>
Marcio Malogolowkin, MD, Assoc. Dir. of Pediatric Oncology

MACC Fund Chair – Pediatric Oncology Research

Increase interaction of physician and laboratory scientists to further our understanding of disease and to provide unique therapy options for children and young adults with cancer

- Increase preclinical and translational capabilities for pediatric cancers
- Increase early phase clinical trials
- Increase NIH/NCI funding
- Support training programs for pediatric cancer investigators
Shared Resources

- Biostatistics and Informatics Core – John P. Klein, PhD
- Clinical Trials Office – James P. Thomas, MD, PhD
- Tissue Procurement Core – Saul Suster, MD
- Immunological Monitoring Core – Jeffrey Woodliff, PhD, and Carolyn Taylor, PhD
- Small Animal Imaging Core – Jim Joers, PhD and Kimberly Pechman, PhD
- Bioenergetics Core – Balaraman Kalyanaraman, PhD
- Observational Methods – Tina Yen, MD, MPH
- Genomics Core – Howard Jacob, PhD
Faculty Disease Committees

- Breast Cancer
- Genitourinary Cancers
- Endocrine Cancers
- Colorectal Cancers
- Liver, Pancreas and Bile Duct Cancers
- Blood and Lymph Node Cancers
- Bone Marrow Transplant
- Brain and Spine Tumors
- Bone and Connective Tissue Cancers
- Head and Neck Cancers
- Skin Cancers
- Lung Cancers
- Gynecologic Cancers
- Pediatric Cancers

Faculty Disease Leaders

- Co-leaders selected from relative disciplines
  - e.g. surgery, med onc and rad onc
- Identified by the respective department and division leaders in conjunction with Cancer Center Leadership
Clinical Care at Froedtert Hospital

<table>
<thead>
<tr>
<th></th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>Mean</th>
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<tr>
<td>Total New Cancer Patients per year</td>
<td>3106</td>
<td>3395</td>
<td>3403</td>
<td>3806</td>
<td>3,428</td>
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<tr>
<td>Solid Tumor per year</td>
<td>2609</td>
<td>2840</td>
<td>2886</td>
<td>3208</td>
<td>2,886</td>
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<td>Hematologic/Lymphatic per year</td>
<td>563</td>
<td>505</td>
<td>470</td>
<td>556</td>
<td>499</td>
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<tr>
<td>Other/Ill defined per year</td>
<td>34</td>
<td>50</td>
<td>47</td>
<td>42</td>
<td>43</td>
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<tr>
<td>Adult Transplants per year</td>
<td>118</td>
<td>144</td>
<td>140</td>
<td>154</td>
<td>139</td>
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</table>

Froedtert/MCW New Adult Cancer Patients

- 2008: 3106
- 2009: 3395
- 2010: 3403
- 2011: 3806

Mean: 3,428
### Average Number of New Patients per Year (2008-2010)

- **28%** Transplants
- **18%** Solid CNS
- **15%** Solid Non-CNS
- **20%** Liquid
- **19%** Benign / Other

### Composition of Patient Population

<table>
<thead>
<tr>
<th>Category</th>
<th>Percentage</th>
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</thead>
<tbody>
<tr>
<td>Transplants</td>
<td>28%</td>
</tr>
<tr>
<td>Solid CNS</td>
<td>18%</td>
</tr>
<tr>
<td>Solid Non-CNS</td>
<td>15%</td>
</tr>
<tr>
<td>Liquid</td>
<td>20%</td>
</tr>
<tr>
<td>Benign / Other</td>
<td>19%</td>
</tr>
</tbody>
</table>

### New Patient Volume is Constant

<table>
<thead>
<tr>
<th>Category</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total New Patients Per Year</td>
<td>232</td>
</tr>
<tr>
<td>Transplants</td>
<td>42</td>
</tr>
<tr>
<td>Solid Tumor CNS</td>
<td>34</td>
</tr>
<tr>
<td>Solid Tumor Non-CNS</td>
<td>66</td>
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<tr>
<td>Liquid</td>
<td>44</td>
</tr>
<tr>
<td>Benign / Other</td>
<td>46</td>
</tr>
</tbody>
</table>
MCW Tissue Bank

FUNCTIONS:

• To serve as the core facility at MCW for the prospective banking of specimens
• To serve as a link and “honest broker” between the banked specimens and the Clinical Data Warehouse (currently being developed by MCW Bioinformatics)
• To obtain informed consent from patients for the banking of specimens for research
• To facilitate research development and collaboration among researchers on campus
• To serve as a tissue/pathology core for future institutional core grants (PPG, SPORE, etc)
• To ensure uniform processing and handling of research specimens and the integrity and quality of the samples banked for research

MCW TISSUE BANK:

Location: Dynacare Lab Building, lower level, L-50 (next to Histology Lab)
Tissue Bank Manager: Mary Rau
Director of Tissue Procurement: Dr. Jian Huang
Director of Tissue Bank: Saul Suster, M.D.
The mitochondria-targeted antioxidant Mito-CP enhances the effects of 2-deoxy-D-glucose (2-DG), and kills MCF-7 breast cancer cells but not MCF-10A mammary epithelial cells.
Cancer cells make abnormally high amounts of the protein called SmgGDS.

Cancer cells grow more slowly when we stop the cells from making SmgGDS.

Therapeutic approaches to control SmgGDS and other newly identified molecules that promote cancer are being developed in collaboration with Cancer Center members and with scientific colleagues worldwide.
CXCL12 Treatment Inhibits Metastasis in a Preclinical Mouse Model

Drury et al., PNAS, 2011
Cancer Prevention Opportunities
When To Do Animal Studies

PHASE III Prevention Trials XXXX
Animal Experiments XXXXXXXXXXXXXXXXXXXXXXXXXXXXX
For men and women in the US, younger than 85 years, death rates from heart disease have dropped markedly since 1975, while overall death rates from cancer have shown relatively little change.
Research Example: Cancer Chemoprevention

Use of Black Raspberry Powder to Prevent Cancer

Freeze-dried powder
plays a central role in cancer care & research.

PET  
(Positron Emission Tomography)

CT  
(x-ray Computed Tomography)

MRI  
(Magnetic Resonance Imaging)

Truly Transformative Power Lies Ahead !!!
Elimination of Leukemia in a Transplant Patient by the Immune System
A New Initiative in Personalized Cancer Treatment

Haber, Gray, Baselga Cell 2011
BCR-ABL Imatinib
100% Chronic myeloid leukemia

HER2 Trastuzumab
20-30% Invasive ductal carcinoma

EGFR Erlotinib/ Gefitinib
20% Lung adenocarcinomas

BRAF V600E Vemurafenib
50-60% Melanoma

ALK Crizotinib
3-5% Lung adenocarcinoma

A. John Iafrate, 2010
CML Mortality Has Declined in the United States, and the Annual Incidence Is Unchanged

Lung Cancer Whole Genome Sequencing at MCW Cancer Center
Filter 1: not present in both individuals

Filter 2: present in dbSNP

Filter 3: present in 1000 genomes or 200 exomes

Filter 4: non-coding and synonymous variants

Filter 5: homozygous variants

Filter 6: predicted to be tolerated

Filter 7: LOD score

Filter 8: allele frequency

Patient 122
56868 variants
34912 variants
4555 variants
4018 variants
234 variants
88 heterozygous SNPs
12 heterozygous indels

Patient 167
56440 variants
4555 variants
4018 variants
234 variants
17 heterozygous SNPs
1 heterozygous indel

Family 504
$100 million institutional commitment over 10 years (09/01/2010 – 08/31/2020)

$50 million capital fundraising campaign for MCW Cancer Center
(09/01/2010 – 08/31/2015)

$5 million from FH to support of MCW Cancer Clinical Trial Office

$5 million from AHW to support MCW Tissue Bank
# Cancer-related Faculty Recruitments

<table>
<thead>
<tr>
<th>Name</th>
<th>Title</th>
<th>Institution</th>
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<tbody>
<tr>
<td>Ming You, MD, PhD</td>
<td>Professor</td>
<td>Washington University</td>
</tr>
<tr>
<td>Marshall Anderson, PhD</td>
<td>Professor</td>
<td>University of Cincinnati</td>
</tr>
<tr>
<td>Michael Bishop, MD, FACP</td>
<td>Professor</td>
<td>National Institutes of Health</td>
</tr>
<tr>
<td>Matthew Budde, PhD</td>
<td>Professor</td>
<td>National Institutes of Health</td>
</tr>
<tr>
<td>Thomas Clark Gamblin, MD</td>
<td>Associate Professor</td>
<td>University of Pittsburgh</td>
</tr>
<tr>
<td>Jian Huang, MD</td>
<td>Assistant Professor</td>
<td>Baylor College of Medicine</td>
</tr>
<tr>
<td>Michael James, PhD</td>
<td>Assistant Professor</td>
<td>Washington University</td>
</tr>
<tr>
<td>David Johnstone, MD</td>
<td>Professor</td>
<td>Dartmouth Hitchcock Medical Center</td>
</tr>
<tr>
<td>Pengyuan Liu, PhD</td>
<td>Associate Professor</td>
<td>Washington University</td>
</tr>
<tr>
<td>Yan Lu, PhD</td>
<td>Assistant Professor</td>
<td>Washington University</td>
</tr>
<tr>
<td>Alexander Craig Mackinnon, Jr., MD, PhD</td>
<td>Assistant Professor</td>
<td>University of Chicago/NorthShore</td>
</tr>
<tr>
<td>Marcio Malogolowkin, MD</td>
<td>Professor</td>
<td>Assoc. Dir. of Pediatric Oncology</td>
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<tr>
<td>Tugan Lufti Muftuler, PhD</td>
<td>Assistant Professor</td>
<td>University of California-Irvine</td>
</tr>
<tr>
<td>Roy Silverstein, MD</td>
<td>Chairman and Professor</td>
<td>Cleveland Clinic</td>
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<tr>
<td>Gary Stoner, PhD</td>
<td>Professor</td>
<td>The Ohio State University</td>
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<tr>
<td>James Thomas, MD, PhD</td>
<td>Professor</td>
<td>The Ohio State University</td>
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<tr>
<td>Jay Tichelaar, PhD</td>
<td>Assistant Professor</td>
<td>Washington University</td>
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<tr>
<td>Susan Tsai, MD</td>
<td>Assistant Professor</td>
<td>Johns Hopkins Hospital</td>
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<tr>
<td>Haris Vikis, PhD</td>
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<td>Washington University</td>
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<tr>
<td>Liang Wang, MD, PhD</td>
<td>Associate Professor</td>
<td>Mayo Clinic College of Medicine</td>
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<tr>
<td>Li-Shu Wang, PhD</td>
<td>Assistant Professor</td>
<td>The Ohio State University</td>
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<tr>
<td>Donghai Xiong, PhD</td>
<td>Assistant Professor</td>
<td>Washington University</td>
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Pending Recruitments

- CCB Recruitment
  - Hyeongnam Jeong, PhD, University of Southern California
- MCC Recruitment
  - Laura Kresty, PhD, University of Miami
- Joan A. Van Deuren Endowed Chair for Breast Cancer Research
  - George Somlo
- MACC Fund Chair
- Associate Director of Clinical Operations
- Associate Director of Basic Sciences
  - Michael Wargovich, PhD
- Associate Director of Prevention & Control
Organizational Capabilities

- Planning and Advisory Committees (ISAB, SLC & ESAB)
- Membership Review Process
- Research Development Awards (seed grants)
Membership Update

- Applications Received: 224

- Members
  - Research: 141
  - Clinical: 58
  - Affiliate: 25

<table>
<thead>
<tr>
<th>Total</th>
<th>Program</th>
<th>Research</th>
<th>Clinical</th>
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<td>42</td>
<td>CCB</td>
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<td>TBI</td>
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<td>31</td>
<td>CI</td>
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<td>29</td>
<td>PCPS</td>
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<td>55</td>
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<td>25</td>
<td>Affiliates</td>
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<tr>
<td>224</td>
<td>TOTAL</td>
<td>141</td>
<td>58</td>
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</table>
Facilities

- Sixth floor of MACC Fund building
- Third and fourth floors of TBRC building
- Departmental space for cancer faculty
- Clinical Cancer Center of FH
- Children's hospital
Center Director

• To lead the cancer research and advancing cancer treatment at MCW
• To recruit the best and brightest faculty in cancer research
• To ensure cancer focus and to grow cancer research funding
• To develop multidisciplinary cancer research and care
• To increase translational cancer research and clinical trials
Interdisciplinary Coordination

• Engaged and integrated leadership
• Targeted recruitment
• Shared resources (CTO, tissue banks, imaging, and genomics)
• Large grant (SPORE and PPG) planning seed grants
• Regular program and cancer center – wide meetings
• Multidisciplinary oncology clinical programs
• Collaborations with CTSI members
Areas for Growth

• Program Development Needs
  – Capital Campaign
  – Institutional Commitment

• Recruitment Efforts
  – NCI funded investigators
  – Fill in scientific expertise in growth areas

• Clinical Trials Office
  – Novel investigator initiated clinical trials

• Shared Resources identified and implemented
  – Collaboration with Clinical and Translational Science Institute (CTSI)
  – Includes 5 area institutions to extend scientific resources
Updates/Future of MCW Cancer Center

- AHW Full Program Funding
- Cores funded in Programs
- Establish the External Scientific Advisory Board
- Cancer Center Support Grant Submission Timeline
- Recruitment
Cancer Center Support Grant Timeline

2012
- Jan/Feb - Full Funding
- Feb/May - ISAB Retreats
- Draft of Program Write-ups
- Late Fall - 1st ESAB Meeting

2013
- Summer - Executive Review ESAB
- Finish Recruiting
- Full Draft of CCSG
- Fall - Endorsement of ESAB

2014
- CCSG Submission
Define the molecular mechanisms that promote malignancy, which is characterized by the uncontrolled proliferation, invasion, and metastasis of cancer cells.

Develop novel therapeutic agents and approaches to diagnose and treat cancer, while limiting toxicity in normal cells.
The Cancer Cell Biology program will

- bring together investigators from multiple institutions and disciplines to collaborate in innovative studies of cancer cell biology
- support new and ongoing studies in cancer cell biology led by investigators conducting basic, clinical, applied, and translational research
- provide access to advanced technical resources and equipment that facilitate cancer research
The Cancer Cell Biology program will

• build a comprehensive understanding of the molecular mechanisms that cause cancer

• develop more effective approaches to treat cancer
Cancer Cell Biology Program Goals

• Establish an interactive community of researchers investigating the mechanisms that regulate the survival, proliferation, invasion, and metastasis of cancer cells.

• Identify and validate new therapeutic targets that can be used for better detection and treatment of cancer.

• Test new approaches to sensitize cancer cells to chemotherapy and radiotherapy while diminishing the toxic side effects of these therapies in normal cells.
Identify and optimize small molecular weight agents that selectively inhibit the malignant characteristics of cancer cells without harming normal cells.

Develop animal models to test mechanisms of cancer development and progression, and to test the efficacies of new cancer treatments.

Establish a Bioenergetics Core Facility that will provide advanced methods to define metabolic abnormalities in cancer cells.
The program promotes advanced research in multiple areas of cancer cell biology, including

• Signal transduction mechanisms in cancer cells
• Soluble mediators in tumorigenesis, invasion, and metastasis
• Cell cycle and genomic instability in cancer cells
• Cancer cell bioenergetics and redox signaling
## Cancer Cell Biology Research Interests

### Signal Transduction Mechanisms in Cancer Cells

**Medical College of Wisconsin**

<table>
<thead>
<tr>
<th>Name</th>
<th>Research Interests</th>
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<tbody>
<tr>
<td>Magdalena Chrzanowska-Wodnicka</td>
<td>Small GTPases</td>
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<tr>
<td>Andrew Chan</td>
<td>Small GTPases, PTEN</td>
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<tr>
<td>Guan Chen</td>
<td>MAPK, p38, Small GTPases</td>
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<tr>
<td>Michael Dwinell</td>
<td>Chemokine Receptors</td>
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<td>Qing Robert Miao</td>
<td>Small GTPases, Nogo-B</td>
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<td>Kasem Nithipatikom</td>
<td>Eicosinoids, Small GTPases</td>
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<td>Jong-In Park</td>
<td>MAPK, Small GTPases</td>
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<td>Ramani Ramchandran</td>
<td>MAPK, Phosphatases</td>
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<td>Andrey Sorokin</td>
<td>Eicosinoids</td>
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<td>Carol Williams</td>
<td>Small GTPases, SmgGDS</td>
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<td>Gilbert White III</td>
<td>Small GTPases, Integrins</td>
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Cancer Cell Biology Research Interests

**Signal Transduction Mechanisms in Cancer Cells**

**University of Wisconsin-Milwaukee**

Douglas A. Steeber  
Valerica Raicu  

*L-selectin signaling*  
*FRET analysis of GPCR signaling*

**Marquette University**

Allison Abbot  

*Pathways regulated by miRNAs*

We hope to include your name and research interest
Cancer Cell Biology Research Interests

Soluble Mediators
In Tumorigenesis, Invasion, and Metastasis

Medical College of Wisconsin
Michael Dwinell  Chemokine Receptor / Ligand Functions
Samuel Hwang  Chemokine Receptor / Ligand Functions
Qing Robert Miao  Nogo-B
Sally Twining  Maspin
Brian Volkman  Chemokine Receptor / Ligand Structure

University of Wisconsin-Milwaukee
Douglas Steeber  Chemokine receptors in T cell migration

We hope to include your name and research interest
Cell Cycle and Genomic Instability in Cancer Cells

Medical College of Wisconsin:
Jonathan Bock  
Lisa Cirillo  
Vaughn Jackson  
Mark McNally  
Vera Tarakanova  
Paula Traktman

University of Wisconsin-Milwaukee
Yi-Qing Cheng  
Xiaohua Peng

We hope to include your name and research interest
Cancer Cell Biology Research Interests

**Cancer Cell Bioenergetics and Redox Signaling**

Medical College of Wisconsin

Christopher Chitambar  
Iron Regulation

Albert Girotti  
NO in Photodynamic Therapy

Neil Hogg  
Redox Biology, Bioenergetics

Joy Joseph  
Targeted Antioxidants

Balaraman Kalyanaraman  
Redox Biology, Bioenergetics

Jeannette Vasquez-Vivar  
Superoxide and eNOS

University of Wisconsin-Milwaukee

Guilherme Indig  
Mitochondria in chemotherapy

Xiaohua Peng  
Oxidative DNA damage

*We hope to include your name and research interest*
Cancer Cell Biology Research Interests

- Signal transduction mechanisms
- Soluble mediators
- Cell cycle and genomic instability
- Bioenergetics and redox signaling

- Additional areas of focus, arising from interactions with researchers from other institutions and disciplines
Many projects are identifying and validating new therapeutic targets that can be used for better detection and treatment of cancer
Identify potential targets (proteins, ROS, lipids, etc.) by detecting their abnormal expression or functions in cancer cells compared to normal cells.

Confirm that the identified targets actually contribute to malignancy, instead of being only a consequence of the malignant state.

Identify small molecular weight agents or other compounds that suppress the abnormal function or expression of the identified therapeutic target.
SmgGDS is expressed more in lung, prostate, and breast tumors compared to normal tissues.

SmgGDS is expressed more in lung, prostate, and breast tumors compared to normal tissues.

Decreasing SmgGDS diminishes the malignant features of lung, prostate, and breast cancer cells.

Tumor formation by MDA-MB-231 human breast cancer cells

- MDA-MB-231 Cells
- MDA-MB-231 cells with decreased SmgGDS expression
Establish collaborative studies to identify small molecular weight compounds that suppress SmgGDS functions or expression in cancer cells.

SmgGDS is expressed more in lung, prostate, and breast tumors compared to normal tissues.

Decreasing SmgGDS diminishes the malignant features of lung, prostate, and breast cancer cells.

Establish collaborative studies to identify small molecular weight compounds that suppress SmgGDS functions or expression in cancer cells.
Goal: Identify and validate new therapeutic targets

Existing assets:

- Access to patient samples through Froedtert Hospital and Children’s Hospital
- Established research programs in basic cancer biology and cancer medicine

Opportunities for growth:

- Expansion into new areas of investigation
Goal: Develop new approaches to sensitize cancer cells to chemotherapy and radiotherapy

Existing assets:
• Access to equipment needed for radiation of cells and animals
• Strong biophysics, radiation oncology, and radiobiology programs

Opportunities for growth:
• Expansion into new areas of investigation
• Collaborative interactions with chemists to develop/optimize chemotherapeutic agents and radiosensitizers
Goal: Design and optimize small molecular weight agents that inhibit malignancy

Existing assets:
- Resources for crystallography and NMR spectroscopy

Opportunities for growth:
- In silico screening of targets that have a solved crystal structure
- High throughput analysis of compounds for targets that do not have a solved crystal structure
- Collaborative interactions with chemists to develop/optimize lead compounds
Goal: Develop animal models to examine mechanisms of cancer development and to test anticancer agents

Existing assets:

• Equipment to image luminescence and fluorescence in live animals
• Established research programs in mouse, rat, and zebrafish animal models
• Rat Genome Database

Opportunities for growth:

• Develop more sophisticated transgenic animal models for different types of cancer, and use more species.
Goal: Establish a Bioenergetics Core Facility to define metabolic abnormalities in cancer cells

Existing assets:

- State-of-the-art equipment to analyze mitochondrial function and measure metabolism
- National Biomedical Electron Paramagnetic Resonance (EPR) Center
- Free Radical Research Center

Opportunities for growth:

- Expansion into new areas of investigation
Gary Stoner, PhD, Leader, Professor of Medicine, Hematology and Oncology
• Internationally recognized expert in the chemoprevention of esophageal and colon cancer using natural antioxidants.

Ron Hines, PhD, Co-Leader, Professor of Pediatrics and Pharmacology/Toxicology
• Internationally recognized expert in molecular mechanisms of carcinogenesis, developmental pharmacology, and environmental health
Better understand the molecular basis of neoplastic transformation and develop effective intervention strategies to prevent these diseases
Program Goals
Molecular Carcinogenesis & Chemoprevention

• To identify individuals at increased risk for cancer from exposure to environmental toxicants and carcinogens

• To further our understanding of key molecular events involved in the stepwise development of cancer at multiple organ sites.

• To develop effective cancer chemoprevention strategies using appropriate preclinical models and human trials in high-risk populations
• Chemoprevention of a variety of cancer types, including leukemia, head and neck, esophageal, colon, pancreas, kidney, lung, skin, bladder, and prostate

• Identification and characterization of genetic risk factors for cancer

• Identification and characterization of pathways involved in the metabolic activation and detoxification of environmental carcinogens and the role of genetic variation and life stage in modifying risk
Use of Black Raspberry Powder to prevent cancer
Effects of 5% and 10% Black Raspberry Diets on Tumor Development

<table>
<thead>
<tr>
<th>Species</th>
<th>Organ</th>
<th>Carcinogen</th>
<th>% Tumor Inhibition</th>
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<tbody>
<tr>
<td>Rat</td>
<td>esophagus</td>
<td>NMBA</td>
<td>50 – 75%</td>
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<tr>
<td>Rat</td>
<td>colon</td>
<td>AOM</td>
<td>50 – 80%</td>
</tr>
<tr>
<td>Mouse</td>
<td>small intestine</td>
<td></td>
<td>50%</td>
</tr>
<tr>
<td>Hamster</td>
<td>oral cavity</td>
<td>DMBA</td>
<td>50%</td>
</tr>
</tbody>
</table>

- Ongoing clinical trials of black raspberry powder as a chemopreventive agent for oral, esophageal, and colon cancer in high risk patients
Resource Needs/Areas of Collaboration
Molecular Carcinogenesis & Chemoprevention

• Expertise (areas for collaboration)
  • Pharmacokinetics and preclinical toxicology
  • Chemical synthesis and natural product isolation/characterization
  • Human chemoprevention clinical trials

• Capital resources
  • Instrumentation for pharmacokinetic analysis and natural product isolation
Xiaohua Peng, PhD
Assistant Professor of Chemistry, University of Wisconsin Milwaukee
Research focus: Understanding the chemical reactivity and function of DNA
• The chemistry of DNA damage with exogenous and endogenous carcinogens
• DNA-DNA and DNA-protein cross-linking by antitumor drugs and bifunctional carcinogens
• The use of modified nucleosides, nucleotides, and oligonucleotides as potential therapeutic agents
• Study of drug/nucleic acids interactions
• DNA/RNA recognition and DNA nanotechnology
Potential Partners
Molecular Carcinogenesis & Chemoprevention

Michael Laoisa, PhD
Assistant Professor, University of Wisconsin Milwaukee School of Public Health
Research focus: Translating how early life exposures adversely affect immune system development and function later in life
- Identifying developmental/early life environmental factors which influence cancer risks and autoimmune pathogenesis.
- Identifying pre- and early post-natal chemopreventative agents which may reduce risk for developing diseases such as leukemia, atopy, and autoimmune disease.
- Determine the impact of early life exposures to chemical mixtures on long term immunological health outcomes
Cancer Imaging Scientific Focus

- Perform cancer-related basic, translational, and clinical research in imaging sciences and technology.

- The research efforts undertaken will include any imaging modalities that can contribute to cancer-related discovery in either (or both) pre-clinical or clinical research.
The Cancer Imaging program will:

• bring together imaging scientists from multiple institutions to collaborate on innovative developments in imaging technology and its applications

• support ongoing studies and help develop new projects in cancer imaging led by investigators conducting basic, clinical, applied, and translational research

• provide access to advanced imaging resources and equipment that facilitate cancer research.
Research conducted by this multi-disciplinary and multi-institutional group of investigators will result in the development of a cancer imaging research program nationally renowned for its innovative contributions to imaging technology, which result in new diagnostic and therapeutic approaches for cancer.
Cancer Imaging Program Goals

• Strengthen existing cancer imaging research efforts.
• Convert current imaging researchers into cancer imaging researchers.
• Develop key strengths in several imaging modalities (eg MRI, PET, SPECT/CT biophotonics, ultrasound, add your favorite technology here).
• Enable more cancer researchers to incorporate imaging into their research.
• Provide state-of-the art imaging for clinical trials.
The program promotes advanced research in multiple areas of cancer imaging:

- **Technology development:**
  - MRI technology (software, hardware, high-field (7T))
  - tracer development (ie Molecular Imaging)
  - new image acquisition or image processing strategies

- **New Imaging applications** (pediatric, non-neuro cancers)

- **Preclinical / multi-modality imaging**
### Imaging Technology

<table>
<thead>
<tr>
<th>Name</th>
<th>Research Interests</th>
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<tbody>
<tr>
<td>James Hyde</td>
<td>fcMRI, high-field MRI</td>
</tr>
<tr>
<td>Kathleen Schmainda</td>
<td>perfusion, diffusion</td>
</tr>
<tr>
<td>Jim Joers</td>
<td>pediatric, MRS, preclinical</td>
</tr>
<tr>
<td>Shi-Jiang Li</td>
<td>fcMRI</td>
</tr>
<tr>
<td>Tugan Muftaler</td>
<td>DTI, MRI coils</td>
</tr>
<tr>
<td>Eric Paulson</td>
<td>MRI acquisition / post-proc</td>
</tr>
<tr>
<td>Robert Prost</td>
<td>MRS / MRE</td>
</tr>
<tr>
<td>Andrew Nenka</td>
<td>high-field MRI</td>
</tr>
<tr>
<td>Sarah Patch</td>
<td>thermo-acoustic tomogr.</td>
</tr>
<tr>
<td>Taly Gilat-Schmidt</td>
<td>CT reconstruction</td>
</tr>
</tbody>
</table>

*We hope to include your name and research interest*
Cancer Imaging Research Interests

Imaging Applications

James Hyde  fcMRI in Cancer
Kathleen Schmainda  brain, breast, liver
Alan Bloom  fcMRI in breast cancer
Eric Paulson  pancreatic, liver, prostate
Sarah White  IR – liver cancer
Sean Tutton  IR – liver cancer
Bill Rilling  IR – liver cancer.
Sarah Patch  breast cancer
Kim Pechman  preclinical brain/br cancer
Scott Rand  brain cancer
Mary Beth Gonyo  breast cancer

We hope to include your name and research interest
# Pre-Clinical Multimodality

<table>
<thead>
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<td>James Hyde</td>
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<td>brain, breast, liver</td>
</tr>
<tr>
<td>Kim Pechman</td>
<td>preclinical brain/br cancer</td>
</tr>
<tr>
<td>Jim Joers</td>
<td>MRI technology</td>
</tr>
<tr>
<td>Bryon Johnson</td>
<td>biophotonics</td>
</tr>
<tr>
<td>Mike Dwinell</td>
<td>biophotonics</td>
</tr>
<tr>
<td>Balaraman Kalyanaraman</td>
<td>MRI, tracer development</td>
</tr>
</tbody>
</table>

We hope to include your name and research interest
The program promotes advanced research in multiple areas of cancer imaging:

- **Technology development:**
  - MRI technology (software, hardware, high-field (7T))
  - tracer development (ie Molecular Imaging)
  - new image acquisition or image processing strategies

- **New Imaging applications** (pediatric, non-neuro cancers)

- **Preclinical / multi-modality imaging**

- **Additional areas of focus, arising from interactions with researchers from other institutions and disciplines**
1992: MCW Biophysics: Pioneers in fMRI

James S. Hyde, PhD
The James S. Hyde Professor of Biophysics Director of the National Biomedical EPR Center

James Hyde

Peter Bandettini  Eric Wong  Bob Cox
1995: MCW Biophysics: Pioneers in fcMRI (functional *connectivity* MRI)

*Functional connectivity in the motor cortex of resting human brain using echo-planar MRI.*

*Biswal B, Yetkin FZ, Haughton VM, Hyde JS.*

Biophysics Research Institute, Medical College of Wisconsin, Milwaukee 53226-0509, USA.

**Abstract**

An MRI time course of 512 echo-planar images (EPI) in resting human brain obtained every 250 ms reveals fluctuations in signal intensity in each pixel that have a physiologic origin. Regions of the sensorimotor cortex that were activated secondary to hand movement were identified using functional MRI methodology (FMRI). Time courses of low frequency (< 0.1 Hz) fluctuations in resting brain were observed to have a high degree of temporal correlation (P < 10(-3)) within these regions and also with time courses in several other regions that can be associated with motor function. It is concluded that correlation of low frequency fluctuations, which may arise from fluctuations in blood oxygenation or flow, is a manifestation of functional connectivity of the brain.

**Figure 1.** Journal on fcMRI started by MCW faculty.
Correlation coefficients between the amygdala seed and all other voxels were transformed to normally distributed Fisher Z values for statistical comparisons. One-sample t-tests were performed and results are shown for the group of (A) control subjects, (B) breast cancer patients prior to treatment as well as (C) patients following 4 cycles of chemotherapy. All group maps are thresholded at p<0.05.
Scientific Story (Advanced MRI in Brain Tumors)

**Perfusion-MRI (“rCBV”)**
- Angiogenesis

- NIH funding since 2000
- 5 Scientific Awards
- 3 U.S. Patents
- RTOG 0625/ACRIN 6677

**Diffusion-MRI (“fDM”)**
- Tumor Invasion / Cell Density / Death

- NIH funding since 2007
- 2 Young Investigator Awards
- 1 Poster Award
- 1 U.S. Patent
TRANSLATIONAL RESEARCH: preclinical Brain Tumors

- **Perfusion MRI:**

- **Diffusion MRI:**
  - fDM: functional diffusion maps
  - DTI: diffusion tensor imaging
CXCL12 treatment inhibits metastasis in a preclinical mouse model

Drury et al., PNAS, 2011 (Mike Dwinell Laboratory)
Existing Assets

- MRI Facilities / Equipment
- Strong MRI research programs – MCW / MU / UWM
- Small Animal Imaging Core: MRI, SPECT/CT, biophotonics

GE “Short Bore” 3T MRI

Specialty Imaging

Magnetencephalography (MEG)

The brain regulates the function of many organs and is at the center of our speech, movement, memory and thoughts. Brain diseases such as epilepsy or a tumor can greatly affect the way the brain functions and the quality of a person’s life. These diseases can also be life-threatening.

For certain people with epilepsy or a brain tumor, surgery may be a treatment option. For epilepsy, surgery is done to remove the area(s) of brain tissue causing seizures. For people with a brain tumor, the goal of surgery is to remove as much of the tumor as possible.

1st in Wisconsin
Existing Assets: Small Animal Imaging Core

- 9.4T Bruker Animal MRI
- MicroSPECT / MicroCT
- Lumina IVIS from Caliper LifeSciences (formerly Xenogen)
  - Bioluminescence
  - Single bandwidth fluorescence
- Biophotonics
- Maestro Multi-Spectral Imaging System from CRI
  - Multi-spectral fluorescence
Opportunities for Collaboration

- Expansion into new areas of investigation – both in terms of research focus and imaging modality
- Incorporation of imaging into other basic and clinical cancer initiatives
- Opportunities to develop larger multi-modality imaging programs focused on a particular cancer

Join the cancer imaging break-out session!
Program Leadership

Program Leader:

William R. Drobyski, MD, Professor of Medicine, Pediatrics and Microbiology

- Member of the Adult Bone Marrow Transplant Program in the Division of Hematology/Oncology, Department of Medicine
- Laboratory Research program in the MACC Fund Building focused on the area of transplantation immunology
The focus of the Transplantation Biology and Immunotherapy Program is to develop new approaches designed to augment the immune response against cancer and to reduce complications that are associated with bone marrow transplantation so that more patients may benefit from this life-saving therapy.
Program Vision

- Develop new approaches to enhance the ability of the immune system to eliminate cancer cells (e.g. cancer vaccines, gene therapy). Principles gained from these studies can be applied to many more cancers, not just cancers of the blood.
- Reduce complications from bone marrow transplantation so that patients have improved survival and an overall better quality of life.
- By reducing complications, expand the number of patients that can benefit from this therapy (i.e. older patients, patients who do not have good family donors, patients from diverse racial and ethnic groups).
- Use bone marrow transplantation as a platform to treat other diseases that are not due to cancer (e.g. sickle cell anemia, autoimmune diseases).
• To further our understanding of the processes which interfere with the restoration of normal immunity post transplantation and contribute to the deleterious pro inflammatory environment that arises as a consequence of graft versus host disease.

• To discover novel mechanisms by which cancer cells evade the immune system and develop strategies to overcome these inhibitory pathways.

• To translate preclinical findings into the clinical setting in order to decrease morbidity and mortality attendant to bone marrow transplantation and improve overall survival and patient quality of life.
Program Research Interests

- Hematological Malignancies (e.g. multiple myeloma, leukemia, lymphoma—preclinical and clinical)
- Immunological reconstitution (Adaptive and Innate arms)
- Graft versus host disease biology (pre-clinical and clinical studies)
- Immunotherapy-strategies to enhance the immune response against cancer
- Use of alternative donors (i.e. non-HLA-matched family donors) for transplantation
- Clinical outcomes-based research (Dr. Horowitz)
Current Membership

Adult BMT Program
William Drobyski, MD
Mary Horowitz, MD
Doug Rizzo, MD
Parameswaran Hari, MD
Jeanne Palmer, MD
Marcelo Pasquini, MD
Wael Saber, MD
Mary Eapen, MD
Michael Bishop, MD
Carolyn Taylor, PhD

Pediatric BMT Program
David Margolis, MD
James Casper, MD
Julie Talano, MD
Monica Thakar, MD

Basic Research
William Drobyski, MD
Bryon Johnson, PhD
Jack Routes, MD
S Malarkannan, PhD
Xiao Chen, MD PhD
Jill Gershan, PhD
Laurent Malherbe, PhD
Robert Truitt, PhD
Amy Hudson, PhD

Non-BMT Clinical
Richard Komorowski, MD (Pathology)
Horation Olteanu, MD (Pathology)
Eric Cohen, MD (Nephrology)
Marcy Neuberg, MD (Dermatology)

26 Members, 8 Departments/Divisions
What do we hope to accomplish?

- Develop new approaches to enhance the ability of the immune system to eliminate cancer cells (e.g. cancer vaccines, gene therapy). Principles gained from these studies can be applied to many more cancers, not just cancers of the blood.
- Reduce complications from bone marrow transplantation so that patients have improved survival and an overall better quality of life.
- By reducing complications, expand the number of patients that can benefit from this therapy (i.e. older patients, patients who do not have good family donors, patients from diverse racial and ethnic groups).
- Use bone marrow transplantation as a platform to treat other diseases that are not due to cancer (e.g. sickle cell anemia, autoimmune diseases).
Examples:
- Vaccine based-treatment post transplantation for the treatment of neuroblastoma/multiple myeloma
- Suicide gene-modified T cells for the therapy of recurrent hematological disease post allogeneic stem cell transplantation
- Blockade of inflammatory cytokine pathways for the treatment of corticosteroid refractory graft versus host disease.
- Treatment of Sickle Cell Anemia with Haploidentical Stem Cell Transplantation
- Use of Natural Killer Cells as Adoptive Immune Therapy in Hematological Malignancies
- Immunotherapy for relapsed lymphoproliferative disorders and viral diseases
Available Resources within TBI Program:

- Small Animal Expertise
- Immunology (Adaptive and Innate Immunity)
- Cell Processing/Graft Engineering Laboratory (Dr. C. Taylor)
- Immune Monitoring Core
- Flow Cytometry Core
- Clinical Trials Design/Biostatistical Support
- Clinical Outcomes Analysis
Elimination of Leukemia in a Transplant Patient by the Immune System
Resource Needs/Areas of Collaboration

- Immunologists (Adaptive and Innate Immunity)
- Pharmacologists (Drug metabolism, pharmacogenomics)
- Microbiologists (Immune responses to pathogens, effect of the microbiome on immunity)
- Research Focus on disorders of the skin, gastrointestinal tract, liver (major target organs of graft versus host disease)
- Dentists (oral manifestations of GVHD)
**Program Scientific Focus**

**Transplantation Biology and Immunotherapy:** To develop new approaches to augment immune response against cancer & reduce complications associated with BMT so that more patients may benefit from this life-saving therapy.

- CIBMTR: Assess new therapies and provide a platform for determining the biologic, clinical and socio-demographic factors that affect BMT outcomes.

**Prevention, Control and Population Sciences:** To facilitate outstanding research to implement optimal preventive, screening, and therapeutic interventions for cancer, and reduce disparities in outcomes.

- CIBMTR: Use BMT as a paradigm for delivery of high tech medical care in the US to understand socio-demographic and structural barriers to access and successful outcomes.
Center for International Blood and Marrow Transplant Research

Sharing knowledge.....

.......Sharing hope
The CIBMTR Grew Out of Two Important Collaborative Efforts in BMT

- International Bone Marrow Transplant Registry (IBMTR): outcomes registry collecting data on BMT recipients since 1972; headquartered at MCW

- National Marrow Donor Program (NMDP): donor registry for unrelated donor BMT established 1987; also maintains large outcomes registry and biorepository of donor-recipient samples; headquartered in Minneapolis
July 2004 Affiliation Agreement between MCW and the NMDP to support clinical research in BMT & related fields
180 staff including, 6 PhD statisticians, 14 MS statisticians, 11 MD-MS faculty; Active program of statistical methodology research specifically focused on transplant outcomes in addition to supporting clinical studies
Some Key Features of CIBMTR Data

• Participation Mandatory for US Centers since 2007
  – Voluntary for non-US Centers *but* all participating centers must report all consecutive transplants

• Two levels of data detail:
  ▪ Basic (transplant essential data)
  ▪ Comprehensive (research data) – selected by weighted randomization

• Longitudinal: 100 days, 6 months, 1, 2, 3 years, then every other year
  ▪ Data provided by transplant centers (no direct communication with patients) - electronic data entry
  ▪ Centers audited on four-year cycle
CIBMTR Scientific Activities

Observational Research

- Clinical outcomes
- Immunobiology
- Health Services

Prospective Clinical Trial Support

- BMT CTN
- RCI BMT

Statistical Methodology
CIBMTR
>350,000 Cases Registered, 1984-2011
>650 Publications

- **Autologous**
- **Allogeneic**

**QOL, Long-term Follow-up**
**Multicenter Clinical Trials**
**Immunobiology**
**Technology Assessment**
**Prognostic factors**
**Descriptive**

*Biorepository - Specimens for >22,000 donor-recipient pairs.*

(Source Zw11_10) Mnh11_5.ppt
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<td>Unique Unrelated Recipients</td>
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<td>Unique Umbilical Cord Grafts</td>
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<td>Unique Related Recipients</td>
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<tr>
<td>Related Donor/Recipient Pairs</td>
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</tr>
</tbody>
</table>
Sample Types

- Whole blood
- Plasma and serum
- Blood spotted on filter paper
- Peripheral blood mononuclear cells (PBMC) viable and non-viable
- B-Lymphoblastoid cell lines (B-LCL) viable and non-viable
- Granulocytes
- DNA
CIBMTR Scientific Activities

- Observational Research
  - Clinical outcomes
  - Immunobiology
  - Health Services
- Prospective Clinical Trial Support
  - BMT CTN
  - RCI BMT

Statistical Methodology
Characteristics of BMT that are relevant to HSR

- Highly specialized – good paradigm for high-tech care
- Limited to few centers/hospitals – issues of access; assessing a large fraction of the population is feasible
- Expensive/Resource-intense – financial issues for both provider and patient
- Lack of RCTs/many competing technologies – technology dissemination/decision analysis
- Practice variation – mandatory center-specific analysis
- High morbidity/mortality – patient utilities/decision making
• HSR conducted using available observational data
  ▪ Constrained by data availability
• Examples of completed projects
  ▪ Race and gender and access to HCT
  ▪ Race and socio-economic status and outcomes of unrelated donor HCT
  ▪ Rural-urban disparities in outcomes
  ▪ Race and outcomes of autologous HCT for myeloma
  ▪ Center effects in HCT
  ▪ Physician practice and supportive care variation
Main areas of interest:

- Barriers to access: income, referral patterns, etc.
- Workforce and infrastructure issues; international comparisons
- Economic analyses
- Practice variation and quality of care
- Long-term quality of life and health behaviors

Requires supplementing standard CIBMTR data with data available in public databases, or collected directly from centers, patients, families

Would benefit from input from experts in health economics, social sciences, access to other databases

- 20 Core Centers/>75 affiliate centers
- Data and Coordinating Center: CIBMTR with subcontracts to NMDP & EMMES

Goal of the Program:

- Provide the infrastructure needed to allow promising HCT therapies to be developed/evaluated in high quality multicenter studies
Early and ongoing collaboration with cooperative groups to synergize and avoid duplication (intensified since 2005)

Other trials to be opened in 2011 or later:
- 0903 Allo-HCT in HIV+ Patients
- 1101 Haplo vs. Double Cord UCB with RIC
- 1102: Hypomethylating Therapy vs. RIC BMT for MDS

Collectively Administer DCC

- Governance and leadership
- Established 16 Core Centers
- Manual of Policies/procedures
- Electronic data capture system
- Per patient reimbursement model
- Websites for members & public

2000 State of Science Symposium #1 sets scientific agenda for 2001-2007 ⇒ 7 focus areas for HCT trials
1. Expanding donor/graft source
2. Reduce regimen related toxicity
3. GVHD prevention/therapy
4. Decrease relapse
5. Decrease infections
6. Improve late effects/QOL
7. Rare diseases (added by Steering Committee and 2005 RFA)

2007 State of Science Symposium #2 sets scientific agenda for 2008-2012+ ⇒ 12 Working Committees
11 high priority trials – 6 in development; 1 anticipated for release in 2011
- Chemo + Dasatinib vs. Allo HCT for Ph+ ALL – 0805/SWOG lead

Note: See July 2011 Progress Report for list of all high-priority trials
Ancillary Studies

- Biomarkers for Transplant Complications and Response to Therapy
- Pharmacokinetics of High-Dose Therapies
- Evaluation of minimal residual disease
- Cost-effectiveness of Transplant Drugs/Strategies
- Symptom Burden of Various Therapies
Summary – Opportunities for Research Partnerships

• Large database capturing almost all BMTs in the US and many BMTs in other countries
  ▪ Opportunity to study delivery, accessibility and outcomes of high tech care
• Biospecimens for patients in observational database and on prospective trials
• Opportunities for ancillary studies in prospective trials
Resource Needs/Areas of Collaboration

- Immunologists (Adaptive and Innate Immunity)
- Pharmacologists (Drug metabolism, pharmacogenomics)
- Geneticists (Candidate gene, gene-wide association studies)
- Health economists (Cost-effectiveness)
- Social scientists
  - Health care infrastructure
  - Health disparities
  - Patient-reported outcomes/quality of life
Program Scientific Focus
Prevention, Control, & Population Science

Laboratory Research Settings → T1 → Clinical Trial Setting (Efficacy) → T2 → Patient Care & Community Settings (Effectiveness) (Outcomes Assessment)

IOM Clinical Research Roundtable,
JAMA 2008;299:211-213
To facilitate the conduct of outstanding research to implement optimal preventive, screening, and therapeutic interventions for cancer, as well as to reduce disparities in outcomes.
• Study adoption of cancer-related discoveries into clinical practice, as well as barriers to or disparities in that adoption
• Test new approaches to cancer implementation science, i.e., the fielding and/or evaluating of interventions in real world settings
• Identify novel methods to improve cancer outcomes by influencing human behavior, organizational inertia and/or public policies
Mission: To conduct cutting-edge research on the provision of effective and efficient patient care services and on related health outcomes.
Scientific Story: Survey and Claims Data

- **Patient’s Predisposing Characteristics** (e.g., age, race, ethnicity, education)
- **Patient’s Need** (e.g., extent of disease, presence and severity of health conditions)
- **Patient’s Enabling Resources** (SES, medical insurance)
- **Systematic use of Quality Processes**
- **Overall Mortality**
- **Breast Cancer Mortality**
- **Hospital and Surgeon Volume of Cases**
Improving the Care and Outcomes of Women Undergoing Breast Surgery

- Opt-out recruitment procedures resulted in 70% initial participation; wave 2-4 participation was >90% of eligibles
- Telephone surveys at median of 30, 36, 48, 60 months after surgery
- Information available includes sociodemographic, treatment, adherence to HT, QOL, ADL; Medicare claims, tumor registry

*Am J Epidem* 2010;172:637-44
• Nattinger AB, Pezzin LE, Sparapani RA, Neuner JM, King TK, Laud PW. Heightened attention to medical privacy: Challenges for unbiased sample recruitment, and one solution. *Am J Epidemiol* 2010;172:637-44.

Adoption of Newer Hormone Agents


Poverty is a carcinogen

- Samuel Broder, NCI Director, 1990
Emerging Program Research Interests

• Implementation Science
  – Association between neighborhood disadvantage factors and colon cancer screening  *PI* Kirsten Beyer, PhD, MPH

  – Improving racial and socioeconomic disparities in breast cancer mortality and adverse events  *PI* Joan Neuner MD, MPH
Methodologic Expertise

– Analysis of complex databases
  • Cancer registries, Administrative databases (e.g., Medicare)

– Survey research

– Community-based participatory research

– Knowledge synthesis
  • Decision and cost-effectiveness analysis, Meta-analysis

– Comparative effectiveness research
Areas of Potential Collaboration

• Health psychology
• Sociology
• Communication
• Decision Sciences
• Biostatistics
• Economics
• Operations Research/Human Factors
• Public Policy
Program Goals
Experimental Therapeutics

- To be a major source of innovative cancer clinical trials and advance the treatment of cancer
- To increase early phase clinical trials
- To foster translational cancer research
- To provide efficient, compliant clinical cancer research
- To increase NCI/NIH funding
- To provide state of the art patient-centered cancer care through interdisciplinary clinical programs
- To educate patients, trainees and community physicians
Scope of Clinical Operation

Bar chart showing new patients from 2008 to 2011.

- 2008: 3500
- 2009: 3000
- 2010: 2500
- 2011: 2000

Pie chart showing percentages:
- 84%: Solid
- 15%: Heme
- 1%: Other
Faculty Disease Committees

- Breast Cancer
- Genitourinary Cancers
- Endocrine Cancers
- Colorectal Cancers
- Liver, Pancreas and Bile Duct Cancers
- Blood and Lymph Node Cancers
- Bone Marrow Transplant
- Brain and Spine Tumors
- Bone and Connective Tissue Cancers
- Head and Neck Cancers
- Skin Cancers
- Lung Cancers
- Gynecologic Cancers

**Faculty Disease Leaders**

- Co-leaders selected from relative disciplines
  - e.g. surgery, med onc and rad onc
- Identified by the respective department and division leaders in conjunction with Cancer Center Leadership
Clinical Trials Office

Regulatory and Administrative Offices

- FMLH Office
- Clinical Research & Innovative Care Compliance
- Institutional Review Board
- MCW Grants and Contracts

Surgical Oncology

Hematology Oncology

GU

Radiation Oncology

Other

GYN

IR

Neuro

To...

Clinical Trials Office

IRB

OCRICC

MCW Grants and Contracts
Centralized Leadership

CTO

Centralized Resources

Clinical Trials Office

Disease Based Approach

CTO Medical Director
James Thomas MD, PhD (interim)

CTO Research Manager

Associate Director of Administration
Andrea Brown

CTO Business Manager

Regulatory Group Leader

Regulatory Coordinators

CTO Disease Team Leader

Budget / Contract / HR Coordinators

Research Nurses and Coordinators

Administrative Assistant

Data Coordinators

Faculty Disease Committee Leaders

Faculty Disease Committees

Cancer Center Informatics

IRB

DSMB

OCRICC

Research Informatics
Clinical Trial Management Software

Comprehensive Subject Management

- Patient Tracking
- Clinic Visit Tracking
- Internal Auditing and Quality Assurance
- Data Safety Monitoring Committee
- Accrual Reporting
- Patient Account Tracking
- Sponsor Billing
Cancer Registries/Biospecimens

- **Cancer Registries**
  - Recruiting patients
  - Tracking treatment plans
  - Determining study feasibility
  - Retrospective chart reviews
  - Oncore URM to provide a uniform, scalable, flexible solution

- **Biospecimen management**
  - Tissue banking
  - Correlative specimens
  - Integration with clinical trial management system and electronic medical record
Cancer Translational Research Unit

**Cancer Phase I Unit**

- Formation of a specialized cancer treatment area for the delivery of early phase, investigational agents
- A facility that will allow investigators to conduct Phase I and Phase II clinical translational research in a methodologically sound, expedient and cost-effective manner.
- A discrete approximately 8-station unit encompassing both infusion beds and chairs that would be utilized primarily for patients receiving protocol-directed therapy.
- Dedicated Senior Nursing staff experienced in administering investigational agents, who will be involved in the development and evaluation of research protocols.
- A facility that can accommodate the collection, processing, storage and shipping of research related samples such as plasma for pharmacokinetics.
Program Scientific Focus
Experimental Therapeutics

- **Personalized Medicine**
  - Providing cutting edge regimens tailored to the individual patient
  - Neoadjuvant Pancreatic Cancer Trial
    - Biopsy taken prior to surgery for phenotypic and genotypic analysis
      - IHC
      - mRNA
      - Sequencing
    - Preoperative chemotherapy determined by tumor profiling
Program Strengths
Experimental Therapeutics

• Large adult cancer population
• Institutional Commitment
  – State of the art cancer treatment facility
• Successful recruitment of key translational research faculty
• Active Participation in Cooperative Groups
  – RTOG
  – BMT CTN
  – ACOSOG
  – ECOG
  – NSABP
  – ACRIN
  – Wisconsin Oncology Network
Experimental Therapeutics
Collaborations

- Development of correlative assays to improve the therapeutic delivery of anti-cancer agents
- Translate discoveries from CTSI laboratories into the clinic through novel clinical trials
• **Future Directions**
  - Increase accrual to clinical trials
  - Increase the number of clinical trial opportunities for our patients
  - Increase investment in investigator-initiated cancer trials
    - Therapeutic Cancer Trials Grant Program
  - Increase the number of Therapeutic Phase I Clinical Trials
    - Cancer Translational Research Unit
  - Leverage the unique resources of the Medical College of Wisconsin and the CTSI to improve the treatment of cancer patients
Pediatric Oncology

- Experimental Therapeutics
- Cancer Cell Biology
- Molecular Carcinogenesis & Chemoprevention
- Prevention, Control & Population Sciences
- Transplantation Biology & Immunotherapy
- Cancer Imaging

Clinical

Basic

Translational
CTSI-Cancer Center Workshop

Future Directions & Opportunities for Cancer-related Research Collaborations:

MCW Cancer Center Pediatric Oncology-Developing
Marcio Malogolowkin, MD
Section Chief, Pediatric HOT

Michael Kelly, MD, PhD
Director, Pediatric Cancer Program

David Margolis, MD
Director, Pediatric Hematopoietic Stem Cell Transplantation
Children Are Not Little Adults

Unique Cancers
Dynamic developmental physiology
• Impacts drug metabolism
• Unique susceptibilities to environmental exposures

Neurocognitive and Psychosocial development
• Spectrum of understanding and coping
• Different and unique exposures

Longer life expectancy of survivors
Goals

Increase interaction of physician and laboratory scientists to further our understanding of disease and to provide unique therapy options for children and young adults with cancer

- Increase preclinical and translational capabilities for pediatric cancers
- Increase early phase clinical trials
- Increase NIH/NCI funding
- Support training programs for pediatric cancer investigators
Program Research Interests

Investigators

**Oncology**
Michael Kelly, MD, PhD
Meghen Browning, MD
Bruce Camitta, MD
Sachin Jogal, MD
Richard Tower, MD

**HSCT**
David Margolis, MD
James Casper, MD
Julie Talano, MD
Monica Thakar, MD

**Psychology**
Kristin Bingen, PhD
Mary Jo Kupst, PhD

**Pathology**
Paula North
Jason Jarzembowski
Gabriela Gheorghe
Annette Segura

**Dermatology**
Beth Drolet
Dawn Siegel
Valerie Lyons

**Genetics**
David Dimmock

**Surgery**
David Lal
Sean Lew

**HOT**
Bryon Johnson +
Gill Gershan
Carolyn Taylor
Andrew Chan*
Fritz Sieber
Sid Rao+

**Cell biology**
Ramani Ramchandran+

**Immunology**
Jack Routes *

**Areas of focus**

- Tumor Immunology
- Cellular therapies
- Signal transduction mechanisms in cancer cells
- Mediators of tumorigenesis and metastasis
- Leukemia stem cells
- Mitigation of therapy related toxicities

* Current NCI
+ Current NIH
Large pediatric cancer population
MACC Fund
CTO
CIBMTR, CTSI

Key CRI cores for basic and translational research:

- Tissue and Serum Bank
- Pharmacokinetic/genomics core
- Genomics, GWA
- Zebrafish facility (Zebrafish drug screening core)
- Histology and Imaging
- Flow Cytometry
- Transgenic Facility
## Average Number of New Patients per Year (2008-2010)

<table>
<thead>
<tr>
<th></th>
<th>Per Year</th>
<th></th>
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<th></th>
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</thead>
<tbody>
<tr>
<td><strong>Total New Patients</strong></td>
<td></td>
<td>232</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Transplants</strong></td>
<td></td>
<td>42</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Solid Tumor CNS</strong></td>
<td></td>
<td>34</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Solid Tumor Non-CNS</strong></td>
<td></td>
<td>66</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Liquid</strong></td>
<td></td>
<td>44</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Benign / Other</strong></td>
<td></td>
<td>46</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Interventional Trial Accruals: Pediatric Cancer

<table>
<thead>
<tr>
<th></th>
<th>Industry</th>
<th>Investigator Initiated</th>
<th>Cooperative</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008</td>
<td>1</td>
<td>7</td>
<td>58</td>
<td>66</td>
</tr>
<tr>
<td>2009</td>
<td>9</td>
<td>5</td>
<td>88</td>
<td>102</td>
</tr>
<tr>
<td>2010</td>
<td>7</td>
<td>11</td>
<td>55</td>
<td>73</td>
</tr>
<tr>
<td>Average</td>
<td>5</td>
<td>8</td>
<td>67</td>
<td>80*</td>
</tr>
</tbody>
</table>

*Currently a Member of the COG Phase 1 Consortium

*95% of pediatric cancer centers*
Clinical Research Staff

People

Services

Provide support from study design to publication for:
- Phase I – III interventional trials
- Prospective observational studies
- Retrospective reviews

Coordination Services
- Pre-study feasibility analyses
- Grants & contracts applications
- Budget negotiations
- Human Research Review Board Submissions
- FDA Investigational New Drug applications
- Logistics and project coordination

Current State

Current Studies
- Consortium trials (Phase I/II-III)
- Pharma-sponsored drug trials (Phase I-III)
- Expanded / Compassionate Use
- Investigator initiated studies
- Translational studies
Pediatric Tissue and Serum Bank

Bio-Bank

Capture, store, analyze and distribute tissue, bone marrow, and blood products

<table>
<thead>
<tr>
<th>Technical Services</th>
<th>Logistical Services</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Biospecimen accessioning and storage</td>
<td>• Pre-identification of relevant cases</td>
</tr>
<tr>
<td>• High-resolution digital microscope slide scanning</td>
<td>• Obtain informed consent</td>
</tr>
<tr>
<td>and image post-processing and analysis</td>
<td>• Timely sample procurement</td>
</tr>
<tr>
<td>• DNA Extraction from tissue and blood samples</td>
<td>• Linkage to relevant clinical data</td>
</tr>
<tr>
<td>• Tissue Micro Array</td>
<td>• Recurring acquisition of specimens from same patient</td>
</tr>
<tr>
<td>• Laser Scanning Cytometry</td>
<td>• Disbursement of correct materials and data to investigators</td>
</tr>
</tbody>
</table>
Laboratory Research

1. Cancer Immunotherapy
2. Signal transduction mechanisms in cancer cells
3. Mediators of tumorigenesis and metastasis
4. Leukemia stem cells
5. Mitigation of therapy related toxicities
Education

Patients and families

Health Care Professionals
- Nurses
- Residents
- Fellows
- Psychologists

Community
Areas of Future Growth/Collaboration

1. Preclinical models of pediatric cancer
2. Outcomes research pediatric cancer and bone marrow transplantation
3. Cancer Immunotherapies
4. AYA Program
5. Cancer Imaging
6. Tumor and Host genetics to individualize therapy
7. Biomarkers
Women’s Reproductive Cancers

• Uterine Cancer – endometrium
• Ovarian Cancer
• Cervical Cancer
99.7% of cervical cancer patients have a persistent human papillomavirus infection (HPV)

- 6 million people become infected with HPV each year
- Over 7% of all cancers are caused by HPV
- A vaccination is available for prevention of HPV 16/18
  - vaccine not therapeutic
  - present vaccine only covers 70% viral types and screening still needed
  - 45% of females 13-17 in Milwaukee have received at least 1 dose - completion of all 3 doses much lower
  - poor and minority teens less likely to finish the vaccine series
Utilizing peer teen advocates to increase HPV vaccination rates in adolescents

- Increase intention to vaccinate among parents/guardians and adolescents
- Expand efforts to include other STDs and reduction of high risk sexual behavior

- Development of a practical curriculum based on information regarding HPV infection and vaccination created in conjunction with:
  - Boys and Girls Club of Greater Milwaukee
  - Milwaukee Health Department
  - MCW

Disseminate this information to the larger community served by the Boys and Girls Club through social media channels such as YouTube, Facebook and Twitter web pages

HWPP: Denise Uyar, MD; Staci Young, PhD; Angela Hagy, Jeanette Kowalik
Genetic polymorphisms in genes involved in the host cellular response to HPV enhances the progression of cervical carcinogenesis

**Candidate gene approach**

1. Keratinocyte response to viral infection
2. Merged data from analysis of tumors
3. Immune cell response to viral infection

Janet S. Rader, MD
Family-based Tests
Transmission Disequilibrium Test (TDT)

Case genotype - AC
Constructed control genotype - BD

1500 affected subjects
3400 family member
70 multiple affected families
1200 tumors (in situ, invasive)
HPV sequence data on 700 samples
HPV infection

NK cell

KIR

HLA Class I

Epithelial cell

JAK

STAT

HLA Class II

Dendritic cell

CD83

CD4 T cell
Women’s Reproductive Cancers
Ovarian Cancer

Risk factors:

↑ Age
Genetic – BRCA1, BRCA2

↓ Ovarian suppression - OCP
420 new cases per year

Over 1000 women living with recurrent ovarian cancer
Ovarian Cancer
The Cancer Genome Atlas (TCGA) Network


Janet S. Rader, MD
Personalized treatment for patients with recurrent ovarian cancer

575 ovarian cancer patient samples

Available chemotherapy

Colon cancer
Ovarian cancer
Melanoma

Medical College of Wisconsin
William Bradley
Oleg Moskin
Janet Rader

University of Wisconsin
Christina Kendziorski
Kevin Eng
Risk Profiles and Core Signaling Pathways

Subgroups pick treatments for recurrences
Time to next event
Cancer predisposition DNA-based signature
**Women’s Reproductive Cancers**

**Endometrial Cancer**

- **Risk factors**
  - Estrogen excess
  - Obesity
    - Incidence (risk ratio, per 5kg/m\(^2\) increase: 1.59)
    - Mortality (risk ratio, normal vs. obese, BMI>40) : 6.25
  - Polycystic ovarian syndrome
  - Family History - HNPCC
• Proteomic biomarkers for screening and response to therapy
• To further study the role of these protein in carcinogenesis of endometrial cancer
• Resource: collection of serum samples from patients before and after hysterectomy for their cancer

Denise Uyar, MD; Shama Mirza, PhD
• Membership 175,000
• Phase I: 1993-1997 Genetics of Obesity
  – 55,000 questionnaire – health, weight history and family structure
  – 620 families (3007 individuals) & 183 diabetics
    DNA/serum/plasma, anthropometrics, biochemical measurements
• Phase II: 1998-2003
  – 503 subjects from 39 families – extensive testing, sample collection
• Genotyping: ~3000-4000 adults genome wide SNP typing
• Resource for cancer questionnaire – for studying obesity and cancer (uterine, breast, colon, others)

Ahmed Kissebah, MD, PhD, Michael Olivier, PhD, Omar Ali, MD
Endometrial cancer

Hypermethylated loci can be prognosis/diagnosis and therapies.

Example

miR-129-2

CpG site

Normal
(n=8)

Recurrent
(n=34)

Non-recurrent
(n=83)

N/A

100%

90

70

60

40

30

20

10

0

Overall survival (years)

Survival probability

Low
(n=54)

High
(n=51)

P = 0.039

Methylation (%)

P = 1.62E-4

P = 2.45E-5

MSI (-) (n=70)

MSI (+) (n=47)

MLH1 (u) (n=76)

MLH1 (m) (n=41)

P = 0.066

Recurrent
(n=28)

Non-recurrent
(n=77)

0

20

40

60

80

100

Methylation (%)

Model

KO_Leptin

EndoCa X ??

KO_adiponectin

Yi-Wen Huang, PhD

Obesity, DNA methylation and endometrial cancer

Promotion adipokine: leptin
Inhibition adipokine: adiponectin

Example

Obesity, DNA methylation and endometrial cancer

Promotion adipokine: leptin
Inhibition adipokine: adiponectin

Model

KO_Leptin

EndoCa X ??

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Yi-Wen Huang, PhD