2019 Scientific Retreat
Friday, April 26, 2019
Discovery World Pavilion

Together, Taking on Cancer’s Toughest Challenges
mcw.edu/departments/cancer-center
@MCWCancerCenter
Together, Taking on Cancer’s Toughest Challenges
mcw.edu/departments/cancer-center
@MCWCancerCenter
CB PROGRAM CO-LEADERS

Balaraman Kalyanaraman, PhD
Harry & Angeline E. Quadaracci Professor in Parkinson’s Research Professor and Chair of Biophysics
- Expertise in EPR spectroscopy and reactive oxygen species
- Developing mitochondria-targeted antioxidant chemotherapeutic drugs
- Research focus on metabolism and bioenergetics
- NIH funded since 1985

Carol Williams, PhD
Kathleen M. Duffey Fogarty Eminent Scholar in Breast Cancer Research Professor in Pharmacology & Toxicology
- Expertise in small GTPases in cancer initiation and progression
- Developing splice-switching oligonucleotide drugs to SmgGDS
- Research focus on cell signaling
- NIH funded since 1991

mcw.edu/departments/cancer-center  @MCWCancerCenter
CB PROGRAM

Focusses on the interrelated themes of oncogenic signaling cascades and mitochondria and redox biology

Discovers cancer-specific signaling events and bioenergetic abnormalities that can be exploited for cancer prevention and treatment

Capitalizes on the historic strength in bioenergetics research at MCW and strong collaborative groups studying oncogenic signaling

2019 Scientific Retreat
2019 UPDATE

Inter-programmatic and inter-institutional collaborations addressing CB themes

Kalyanaraman (MCW) and You (MCW)
*Nature Communications*, 2019

Williams (MCW) and Goessling (Harvard)
*Nature Genetics*, 2019

Bonini (MCW) and Rosen (U. Chicago)
*Nature*, 2019

2019 Scientific Retreat

mcw.edu/departments/cancer-center   @MCWCancerCenter
You laboratory is exploring novel therapies to inhibit lung cancer initiation and progression.

Kalyanaraman laboratory is developing mitochondria-targeted drugs to disrupt cancer cell bioenergetics.

Collaboration focusses on enhancing the efficacy of the anti-glycolytic drug lonidamine in lung cancer.
You laboratory is exploring novel therapies to inhibit lung cancer initiation and progression.

Kalyanaraman laboratory is developing mitochondria-targeted drugs to disrupt cancer cell bioenergetics.

Collaboration focusses on enhancing the efficacy of the anti-glycolytic drug lonidamine in lung cancer.

Generated Mito-lonidamine (Mito-Lon) by conjugating the triphenylphosphonium cation (TPP+) to lonidamine (Lon).

Mito-Lon has enhanced:
- lipophilicity
- cellular uptake
- accumulation in mitochondria

B. Kalyanaraman (MCW) and M. You (MCW) Collaboration
Targeting lonidamine to mitochondria mitigates lung tumorigenesis and brain metastasis
*Nature Communications*, 2019
In lung cancer cells, Mito-Lon
- inhibits mitochondrial bioenergetics
- stimulates ROS generation
- inactivates AKT/mTOR signaling
- induces autophagic cell death
In lung cancer cells, Mito-Lon
• inhibits mitochondrial bioenergetics
• stimulates ROS generation
• inactivates AKT/mTOR signaling
• induces autophagic cell death

Tested *in vivo* activity of Mito-Lon on tumorigenesis and metastasis of H2030-BrM3 lung cancer cells (drug delivered by oral gavage, five days per week).
Mito-Lon accumulates 100-1000 fold in the mitochondria of lung cancer cells, inhibiting complex I in the electron transport chain.

Mito-Lon disrupts lung cancer bioenergetics, promoting signaling cascades that lead to autophagy.
Identifies autophagy resulting from inhibition of mitochondrial complexes as a key pathway used by mitochondria-targeted compounds to inhibit tumorigenesis and metastasis of lung cancer cells.

Demonstrates that FDA-approved drugs with moderate mitochondrial activity can be made more efficacious by targeting them to the mitochondria using TPP+ conjugation.

Defines a new mitochondrial and autophagy-related therapeutic approach for lung cancer.
Goessling laboratory conducted whole genome sequencing of members of two families with high prevalence of cancer.

C. Williams (MCW) and W. Goessling (Harvard) Collaboration
Mutations in RabL3 alter K-Ras prenylation and are associated with hereditary pancreatic cancer
*Nature Genetics*, 2019

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreas (P)</td>
<td>11 patients</td>
</tr>
<tr>
<td>Breast (B)</td>
<td>6 patients</td>
</tr>
<tr>
<td>Melanoma (M)</td>
<td>4 patients</td>
</tr>
<tr>
<td>Colon (C)</td>
<td>2 patients</td>
</tr>
<tr>
<td>Brain (N)</td>
<td>2 patients</td>
</tr>
<tr>
<td>Liver (L)</td>
<td>1 patient</td>
</tr>
<tr>
<td>Stomach (S)</td>
<td>1 patient</td>
</tr>
<tr>
<td>Gynecologic (G)</td>
<td>1 patient</td>
</tr>
<tr>
<td>Unknown (U)</td>
<td>1 patient</td>
</tr>
</tbody>
</table>
Goessling laboratory conducted whole genome sequencing of members of two families with high prevalence of cancer.

Identified a truncation of the small GTPase RabL3 in family members with cancer.

Contacted the Williams laboratory when mass spectrometry showed binding of truncated RabL3 to SmgGDS.

C. Williams (MCW) and W. Goessling (Harvard) Collaboration
Mutations in RabL3 alter K-Ras prenylation and are associated with hereditary pancreatic cancer
Nature Genetics, 2019

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreas (P)</td>
<td>11 patients</td>
</tr>
<tr>
<td>Breast (B)</td>
<td>6 patients</td>
</tr>
<tr>
<td>Melanoma (M)</td>
<td>4 patients</td>
</tr>
<tr>
<td>Colon (C)</td>
<td>2 patients</td>
</tr>
<tr>
<td>Brain (N)</td>
<td>2 patients</td>
</tr>
<tr>
<td>Liver (L)</td>
<td>1 patient</td>
</tr>
<tr>
<td>Stomach (S)</td>
<td>1 patient</td>
</tr>
<tr>
<td>Gynecologic (G)</td>
<td>1 patient</td>
</tr>
<tr>
<td>Unknown (U)</td>
<td>1 patient</td>
</tr>
</tbody>
</table>
SmgGDS is a chaperone protein that binds small GTPases in the Ras and Rho families.

Interactions with SmgGDS promote the prenylation and membrane trafficking of small GTPases, which is required for their oncogenic activity.
SmgGDS is a chaperone protein that binds small GTPases in the Ras and Rho families. 

Interactions with SmgGDS promote the prenylation and membrane trafficking of small GTPases, which is required for their oncogenic activity.
Identifies RabL3 truncation as a new gain-of-function mutation in pancreatic cancer. Truncated RabL3 may be a new biomarker for pancreatic cancer.

Defines a previously unsuspected mechanism for K-Ras activation in pancreatic cancer: enhanced K-Ras prenylation due to augmented interaction with SmgGDS.

Characterizes RabL3 and SmgGDS as new therapeutic targets for altering K-Ras activity in pancreatic cancer and other K-Ras-driven cancers.
BACH1 is a transcription factor that is overexpressed in triple-negative breast cancer (TNBC) and is associated with poor prognosis.

Discovered that BACH1 decreases glucose utilization in the TCA cycle, and negatively regulates the electron transport chain (ETC).
BACH1 promotes expression of pyruvate dehydrogenase kinase (PDK).

PDK phosphorylates and inactivates pyruvate dehydrogenase (PDH), which regulates glycolysis.

BACH1 also inhibits transcription of genes in the electron transport chain (ETC).
RNAi-mediated depletion of BACH1 makes breast cancer cells more dependent on mitochondrial respiration.
RNAi-mediated depletion of BACH1 makes breast cancer cells more dependent on mitochondrial respiration.

Hypothesis: BACH1-depleted cells will be more sensitive to drugs that inhibit the ETC, such as metformin.
Tested effects of metformin and depletion of BACH1 on tumorigenesis of MDA-MB-436 breast cancer cells.

Observed reduced tumorigenesis by combining metformin with
- RNAi-mediated depletion of BACH1
- the drug hemin, which degrades BACH1
First demonstration that BACH1 is a key regulator of mitochondrial metabolism.

Repurposing the FDA-approved drugs metformin and hemin for combination therapy may provide a new strategy for treatment of TNBC.

Enhancing the dependency of cancer cells on mitochondrial respiration may improve sensitivity to drugs that target the ETC, such as metformin.
2019 UPDATE

Scientific Theme 1
Oncogenic Signaling Cascades

Scientific Theme 2
Mitochondria and Redox Biology

mcw.edu/departments/cancer-center  @MCWCancerCenter
CB PROGRAM SPEAKERS

Carmen Bergom, MD, PhD
Utilizing Genetic Models of Cardio-Oncology: Getting to the Heart of the Matter

Michael Dwinell, PhD
Activating Anti-Pancreatic Cancer Immunity

Ben Gantner, PhD
Reprogramming Neutrophils to Control Tissue Injury

Peter LaViolette, PhD
Prostate Cancer Radio-Pathomics