The Host Cancer Interface:
Obesity and Diabetes Promote Cancer Development and may Reduce Treatment Efficacy

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University of Colorado
Anschutz Medical Campus
Conflict of Interest

None
Objectives

1. Discuss host metabolism (obesity and diabetes) as risk and prognostic factors for human cancer.

2. Targeting metabolic dysregulation through our treatment of obesity and diabetes, to prevent and treat cancer
Cancer

- Multistep process, often taking years
- Variable subtypes, even for the same organ of origin
- Unrestrained growth
- Inability to undergo cell induced death
- Adaptable through clonal progression
- Ability to invade normal tissues-into the neighborhood
- Ability to spread via vessels-to other organs and sites
- Can send and receive local and distant signals to other cells
- Can evade natural immunity
What does Cancer Look Like?

normal

Lung Cancer
Age a Potent Risk Factor for Cancer

![Graph showing the incidence of cancer increases with age, peaking around adolescence and then rising again later in life.](image-url)
Many Risk Factors Can be Modified
.....is it true?

“Sugar and Fat that’s Where it’s At”

CD Young and SM Anderson, Br Ca Res 2008
Diabetes, Obesity and Cancer

- Disorders of carbohydrate and lipid metabolism are well recognized risk factors for cardiovascular disease.

- Much less recognized by health professionals and patients, metabolic dysregulation is also a major risk factor for cancer.

- The incidence of TII diabetes and obesity has risen significantly in the US, even in pediatric patients.
  - There are 14 M TII Diabetics, 5 M undiagnosed TII diabetics and 41 M prediabetic adults in the US.
  - Two thirds of the US adult population is overweight. Half are obese.
Cancer Pathogenesis

Endogenous Growth Promotion
- Cytokines, inflammatory factors
- Hyperinsulinemia, IGF
- Hyperglycemia
- Altered Metabolism
- Microbiome
- Hormones

Obesity
Type II Diabetes
Hyperlipidemia

Altered Immunity
- Wound healing-induction of growth factors, altered environment
- Decreased Immune Surveillance, immunodeficiency

Genetics/Transcriptomics/Epigenetics
- Inherited/somatic alterations, polymorphisms
- Acquired genetic instability, mutation
- Epigenetic changes

Exogenous Agents
- Viral carcinogenesis (HPV, EBV)
- Chemicals
- Radiation
- Hormone like agents
- Dietary factors
Metabolic Reprogramming in Cancer

- Cancer cells reorganize metabolic pathways to augment anabolic reactions...although the mechanisms that foster this shift are complex

- Intermediates of the glycolytic pathway provide building blocks of anabolic pathways that enable growth and proliferation
  - Amino acids
  - Nucleic acids
  - Lipids
Mechanisms of Cancer Specific Metabolic Reprogramming

Oncogenesis

Transformation

Metabolic reprogramming

Cancer Cell 13: 2008
Prevalence of Self-Reported Obesity Among U.S. Adults by State and Territory, BRFSS, 2017

*Sample size <50 or the relative standard error (dividing the standard error by the prevalence) ≥ 30%.
### BMI and Cancer Risk: Women

<table>
<thead>
<tr>
<th>Cancer site and type</th>
<th>Number of studies</th>
<th>RR (95% CI)</th>
<th>P</th>
<th>I²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrium</td>
<td>19</td>
<td>1.59 (1.50–1.68)</td>
<td>&lt;0.0001</td>
<td>77%</td>
</tr>
<tr>
<td>Gallbladder</td>
<td>2</td>
<td>1.59 (1.02–2.47)</td>
<td>0.04</td>
<td>67%</td>
</tr>
<tr>
<td>Oesophageal adenocarcinoma</td>
<td>3</td>
<td>1.51 (1.31–1.74)</td>
<td>&lt;0.0001</td>
<td>0%</td>
</tr>
<tr>
<td>Renal</td>
<td>12</td>
<td>1.34 (1.25–1.43)</td>
<td>&lt;0.0001</td>
<td>45%</td>
</tr>
<tr>
<td>Leukaemia</td>
<td>7</td>
<td>1.17 (1.04–1.32)</td>
<td>0.01</td>
<td>80%</td>
</tr>
<tr>
<td>Thyroid</td>
<td>3</td>
<td>1.14 (1.06–1.23)</td>
<td>0.001</td>
<td>5%</td>
</tr>
<tr>
<td>Postmenopausal breast</td>
<td>31</td>
<td>1.12 (1.08–1.16)</td>
<td>&lt;0.0001</td>
<td>64%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>11</td>
<td>1.12 (1.02–1.22)</td>
<td>0.01</td>
<td>43%</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>6</td>
<td>1.11 (1.07–1.15)</td>
<td>&lt;0.0001</td>
<td>0%</td>
</tr>
<tr>
<td>Colon</td>
<td>19</td>
<td>1.09 (1.05–1.13)</td>
<td>&lt;0.0001</td>
<td>39%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>7</td>
<td>1.07 (1.00–1.14)</td>
<td>0.05</td>
<td>47%</td>
</tr>
<tr>
<td>Liver</td>
<td>1</td>
<td>1.07 (0.55–2.08)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastric</td>
<td>5</td>
<td>1.04 (0.90–1.20)</td>
<td>0.56</td>
<td>4%</td>
</tr>
<tr>
<td>Ovarian</td>
<td>13</td>
<td>1.03 (0.99–1.08)</td>
<td>0.30</td>
<td>55%</td>
</tr>
<tr>
<td>Rectum</td>
<td>14</td>
<td>1.02 (1.00–1.05)</td>
<td>0.26</td>
<td>0%</td>
</tr>
<tr>
<td>Malignant melanoma</td>
<td>5</td>
<td>0.96 (0.92–1.01)</td>
<td>0.05</td>
<td>0%</td>
</tr>
<tr>
<td>Premenopausal breast</td>
<td>20</td>
<td>0.92 (0.88–0.97)</td>
<td>0.001</td>
<td>39%</td>
</tr>
<tr>
<td>Lung</td>
<td>6</td>
<td>0.80 (0.66–0.97)</td>
<td>0.03</td>
<td>84%</td>
</tr>
<tr>
<td>Oesophageal squamous</td>
<td>2</td>
<td>0.57 (0.47–0.69)</td>
<td>&lt;0.0001</td>
<td>60%</td>
</tr>
</tbody>
</table>

*Renehan et al. Lancet 2008;371:569–78*
Obesity: an Independent Risk Factor for Breast Cancer

- The magnitude of risk for obese patients is at least 2 fold.....

- In post-menopausal obese women, estrogen levels are increased 50-100 %

- Obesity is associated with suppressed fatty acid oxidation, making cells more dependent on glucose and promoting aerobic glycolytic capacity...*The Warburg Effect*

- Increases with BMI (3% per 1 kg/m²) post menopausal ER+, PR+ CA

- More profound in patients with a strong family history (5-10 fold)
Breast Cancer and Obesity

Post-menopausal Caucasian
Pre-menopausal Latino and AA
BMI and CANCER RISK: MEN

<table>
<thead>
<tr>
<th>Cancer site and type</th>
<th>Number of studies</th>
<th>RR (95% CI)</th>
<th>P</th>
<th>I²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oesophageal adenocarcinoma</td>
<td>5</td>
<td>1.52 (1.33–1.74)</td>
<td>&lt;0.0001</td>
<td>24%</td>
</tr>
<tr>
<td>Thyroid</td>
<td>4</td>
<td>1.33 (1.04–1.70)</td>
<td>0.02</td>
<td>77%</td>
</tr>
<tr>
<td>Colon</td>
<td>22</td>
<td>1.24 (1.20–1.28)</td>
<td>&lt;0.0001</td>
<td>21%</td>
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<tr>
<td>Renal</td>
<td>11</td>
<td>1.24 (1.15–1.34)</td>
<td>&lt;0.0001</td>
<td>37%</td>
</tr>
<tr>
<td>Liver</td>
<td>4</td>
<td>1.24 (0.95–1.62)</td>
<td>0.12</td>
<td>83%</td>
</tr>
<tr>
<td>Malignant melanoma</td>
<td>6</td>
<td>1.17 (1.05–1.30)</td>
<td>0.004</td>
<td>44%</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>7</td>
<td>1.11 (1.05–1.18)</td>
<td>&lt;0.0001</td>
<td>7%</td>
</tr>
<tr>
<td>Rectum</td>
<td>18</td>
<td>1.09 (1.06–1.12)</td>
<td>&lt;0.0001</td>
<td>3%</td>
</tr>
<tr>
<td>Gallbladder</td>
<td>4</td>
<td>1.09 (0.99–1.21)</td>
<td>0.12</td>
<td>0%</td>
</tr>
<tr>
<td>Leukaemia</td>
<td>7</td>
<td>1.08 (1.02–1.14)</td>
<td>0.009</td>
<td>0%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>12</td>
<td>1.07 (0.93–1.23)</td>
<td>0.33</td>
<td>70%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>6</td>
<td>1.06 (1.03–1.09)</td>
<td>&lt;0.0001</td>
<td>0%</td>
</tr>
<tr>
<td>Prostate</td>
<td>27</td>
<td>1.03 (1.00–1.07)</td>
<td>0.11</td>
<td>73%</td>
</tr>
<tr>
<td>Gastric</td>
<td>8</td>
<td>0.97 (0.88–1.06)</td>
<td>0.49</td>
<td>35%</td>
</tr>
<tr>
<td>Lung</td>
<td>11</td>
<td>0.76 (0.70–0.83)</td>
<td>&lt;0.0001</td>
<td>63%</td>
</tr>
<tr>
<td>Oesophageal squamous</td>
<td>3</td>
<td>0.71 (0.60–0.85)</td>
<td>&lt;0.0001</td>
<td>49%</td>
</tr>
</tbody>
</table>

Renehan et al. Lancet 2008;371:569–78
Diabetes and Cancer

“It would appear that either diabetics tend to develop cancer or that cancer patients tend to develop symptoms recognised as diabetic”

- Wilson and Maher Am J Cancer 1932
Insulin and Glucose Dysregulation with Type 2 Diabetes

A. Insulin rises over years, then declines with prolonged resistance

B. Glucose fluctuates over years

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Glucose Levels High with Significant Fluctuation, typically measured by A1c
Nutritional Stress and Cancer

ROS Exceed Physiological Need, Mitochondrial Respiration

Warburg Effect

Oncogene Activation

Growth Factors

Inflammation

Promotion of Cell Signaling
Proliferation
DNA mutation

Amino Acid Dependent mTOR Activation

Metabolite Sensitive Protein Modifications

CANCER

Review: Wellen and Thompson, Mol Cell 40, 2010
# Diabetes and Cancer Incidence

<table>
<thead>
<tr>
<th>Cancer</th>
<th>RR (95% CI)</th>
<th>Study References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver (El-Serag et al. 2006)</td>
<td>2.50 (1.8–3.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.51 (1.9–3.2)</td>
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<tr>
<td>Pancreas (Huxley et al. 2005)</td>
<td>1.94 (1.53–2.46)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.73 (1.59–1.88)</td>
<td></td>
</tr>
<tr>
<td>Kidney* (Lindblad et al. 1999, Washio et al. 2007)</td>
<td>1.50 (1.30–1.70)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.22 (1.04–4.70)</td>
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</tr>
<tr>
<td>Endometrium (Friberg et al. 2007)</td>
<td>2.22 (1.30–2.74)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.62 (1.21–2.16)</td>
<td></td>
</tr>
<tr>
<td>Colon–rectum (Larsson et al. 2005)</td>
<td>1.36 (1.23–1.50)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.29 (1.16–1.43)</td>
<td></td>
</tr>
<tr>
<td>Bladder (Larsson et al. 2006)</td>
<td>1.37 (1.04–1.80)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.43 (1.18–1.74)</td>
<td></td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma (Mitri et al. 2008)</td>
<td>1.41 (1.07–1.88)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.12 (0.95–1.31)</td>
<td></td>
</tr>
<tr>
<td>Breast (Larsson et al. 2007)</td>
<td>1.18 (1.05–1.32)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.20 (1.11–1.30)</td>
<td></td>
</tr>
<tr>
<td>Prostate (Kasper &amp; Giovannucci 2006)</td>
<td>0.89 (0.72–1.11)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.81 (0.71–0.92)</td>
<td></td>
</tr>
</tbody>
</table>

*Vigneri et al., Endocrine-Related Cancer 2009; 16 1103–1123
Hyperglycemia and Cancer Mortality

Figure 2. Hazard Ratios for All Cancer Deaths by Fasting Serum Glucose Levels in Korean Men by BMI, 1993-2002

Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. CI indicates confidence interval.

Jee et al. JAMA. 2005;293:194-202
Cancer Risk by Diabetes Treatment over Time

Unadjusted

Adjusted for Confounding Factors (age, sex, smoking status, prior cancer)

Currie et al. Diabetologia 2009; 52:1766-1777
### Table 3. Pooled Hazard Ratios of Long-term, All-Cause Mortality in Cancer Patients With and Without Preexisting Diabetes Mellitus in Selected Cancer Sites

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Studies (Estimates), No.</th>
<th>Total Patients, No.</th>
<th>Patients With Diabetes, No.</th>
<th>Pooled HR (95% CI)(^a)</th>
<th>I(^2), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrial</td>
<td>4 (4)</td>
<td>2900</td>
<td>429</td>
<td>1.76 (1.34-2.31)</td>
<td>44.3</td>
</tr>
<tr>
<td>Breast</td>
<td>4 (4)</td>
<td>13019</td>
<td>1107(^b)</td>
<td>1.61 (1.46-1.78)</td>
<td>0</td>
</tr>
<tr>
<td>Prostate</td>
<td>3 (3)</td>
<td>6264</td>
<td>555(^b)</td>
<td>1.51 (0.94-2.43)</td>
<td>47.1</td>
</tr>
<tr>
<td>Gastric</td>
<td>3 (3)</td>
<td>6200</td>
<td>687(^b)</td>
<td>1.36 (0.92-2.01)</td>
<td>83.6</td>
</tr>
<tr>
<td>Colorectal</td>
<td>6 (7)</td>
<td>54740</td>
<td>8028(^b)</td>
<td>1.32 (1.24-1.41)</td>
<td>52.4</td>
</tr>
<tr>
<td>Hepatocellular</td>
<td>3 (5)</td>
<td>3724</td>
<td>848(^b)</td>
<td>1.30 (0.99-1.70)</td>
<td>68.9</td>
</tr>
<tr>
<td>Lung</td>
<td>4 (5)</td>
<td>11109</td>
<td>989(^c)</td>
<td>1.15 (0.99-1.34)</td>
<td>47.7</td>
</tr>
<tr>
<td>Pancreas</td>
<td>4 (4)</td>
<td>1681</td>
<td>477(^b)</td>
<td>1.09 (0.70-1.69)</td>
<td>73.4</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio.
\(^{a}\)Estimates calculated using a random-effects model.
\(^{b}\)Number is extrapolated because 1 study did not report prevalence of diabetes.
\(^{c}\)Number is extrapolated because 2 studies did not report prevalence of diabetes.

*Barone et al. JAMA. 2008;300(23):2754-2764*
Lipid Dysregulation Promotes CA

• High cholesterol and lipid dysregulation are associated with a significant and independent risk of cancer, poor outcomes and treatment resistance

• Two patterns of breast CA risk with lipid dysregulation
  • Premenopausal, TNBC, minority women
  • Post menopausal, ER+, PR+, HER2- in Caucasians
Metformin (Glucophaghe-Aventis)

- The most commonly drug used worldwide to treat type II and pre-diabetic syndromes
- Oral, low cost agent
- Significant anti-cancer activity
- Extremely low toxicity

Galega officinalis
(Goat’s rue, French lilac)
Evidence of Metformin’s Anti-Cancer Activity

**EPIDEMIOLOGIC**
Metformin / cancer associations in DM

**MECHANISTIC**

**METABOLIC**
Associations of obesity and insulin with risk / prognosis

**THERAPEUTIC**
Emerging evidence of metformin activity in human cancer

**PRECLINICAL**
- *In vivo* evidence of anticancer activity
- *In vitro* evidence of anticancer activity

Not seen with other anti-diabetic agents!
Reduction of Incidence of CA with Metformin

Epithelial Derived Cancers

Breast
Prostate
Head and Neck
Colon
Pancreas

Ovary
Endometrium
Liver
Lung
Brain

Soft Tissue and Bone

Fibrosarcoma
Osteosarcoma

** 125 Clinical trials listed with metformin and CA on ClinicalTrials.gov

IB Sahra et al. Metformin in Cancer Therapy, Mol Cancer Ther 9:2010
Del Barco S et al. Metformin: Multi-faceted Protection Against Cancer Oncotarget 2: 2011
Metformin

- Inhibition of Mitochondrial Complex I
- Hepatic gluconeogenesis
- Glucose production by liver
- Glucose uptake and transport by periphery

Owen MR et al, Biochem, 2000
Metformin Has Complex Effects *In Vitro* and *In Vivo*

- Cell cycle arrest
- Cell growth
- Protein production (cap dependent translation)
- Carcinogen induced transformation
- Glycolysis
- Glucose transport
- Mitochondrial respiration, decrease ROS
- Clonogenicity
- Fatty acid synthetase (FAS)
- Stem cell growth
- Apoptosis
- Autophagy in **p53** competent cells

? Angiogenesis
Metformin Acts to Normalize Glucose Metabolism in Cancer

• Downregulation of Glucose Transport Proteins (Gluts 1, 10, 12, 14)

• Downregulation of glucose-6-phosphate transporter, triose phosphate isomerase and 18 other key genes in glucose metabolism

• Downregulation of lactose dehydrogenase (LDH), which is a key enzyme catalyzing conversion of pyruvate to lactate.

Metformin Broadly Inhibits Glycolysis

J Oncol Transl Res 4: 129. 2018
Metformin Targets Aberrant Lipid Metabolism in CA: FASN in TNBC

- FASN critical step in fatty acid synthesis.
- FASN one of most downregulated genes in TNBC Rx metformin
- Hypothesis: FASN downregulation facilitates metformin-induced apoptosis.
- Results: Metformin induction of cell death, proliferation and inhibition of stemness mediated by reduction of fatty acid synthase (FASN) via miRNA-193b

Wahdan-Alaswad RS, Cochrane DR, Spoelstra NS, Howe EN, Edgerton SM, Anderson SM, Thor AD and Richer JK. Metformin-Induced Killing of Triple Negative Breast Cancer Cells is Mediated by Reduction in Fatty Acid Synthase via miRNA-193b Hormones and Cancer. 5:374-89, 2014
Cholesterol Biosynthesis Targeted by Metformin in TNBC

Wahdan-Alaswad et al., Cancer Therapy and Oncology 2018
Metformin Downregulates EGFR and Lipid Raft Stabilization: Enhancing Sensitivity to Tyrosine Kinase Inhibitors

Wahdan-Alaswad RS, Edgerton SM, Salem HS, Thor AD. Metformin targets cholesterol biosynthesis pathway, GM1 lipid raft stabilization, EGFR signaling and proliferation in triple negative breast cancers. Can Therapy Oncol Int J 9:555765 2018
Intrinsic and Extrinsic Pathways of Apoptosis via the Death Receptor TRAIL

Elrod et al., Cancer Biology & Therapy 7: 163
Metformin Induces Cell Death via Intrinsic and Extrinsic Pathways of Apoptosis

- Metformin selectively kills cancer stem cells/mammospheres

<table>
<thead>
<tr>
<th>Control</th>
<th>Metformin (1mM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDA-468</td>
<td>MDA-468</td>
</tr>
</tbody>
</table>

Mammospheres (MDA468)

- Control
- Met 1mM
- Met 2mM
Metformin Provides Improved Survival if Combined with Chemo

Dynamic Equilibrium between Stem and Non-Stem Cells *In Vitro*
Metformin Inhibits Cancer Motility and Metastasis

Moesin: Membrane Organizing Extension Spike Protein

- Cross links plasma membranes and actin-based cytoskeleton
- Interacts with CD43, ICAM3, NCF 1, NCF4, VCAM-1, EZR
- Downregulated at least 2 fold in TNBC with Metformin
Moesin and Breast Cancer Cell Motility


**Figure 4**

**A. MDA-MB-231**

![Images of cellular assays](Image)

A. and B. Wound Closure Associated Cell Motility Assay

Moesin Green
F-Actin Red
DAPI Blue

**B.**

<table>
<thead>
<tr>
<th></th>
<th>MDA-MB-231</th>
<th>MDA-MB-468</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Wound Closure</td>
<td><img src="Image" alt="Graphs" /></td>
<td><img src="Image" alt="Graphs" /></td>
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<tr>
<td>G17</td>
<td><img src="Image" alt="Data Points" /></td>
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</tr>
<tr>
<td>G17 + Met</td>
<td><img src="Image" alt="Data Points" /></td>
<td><img src="Image" alt="Data Points" /></td>
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<tr>
<td>G5</td>
<td><img src="Image" alt="Data Points" /></td>
<td><img src="Image" alt="Data Points" /></td>
</tr>
<tr>
<td>G5 + Met</td>
<td><img src="Image" alt="Data Points" /></td>
<td><img src="Image" alt="Data Points" /></td>
</tr>
<tr>
<td>P&lt;0.001</td>
<td><img src="Image" alt="P Values" /></td>
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<td>P&lt;0.001</td>
<td><img src="Image" alt="P Values" /></td>
<td><img src="Image" alt="P Values" /></td>
</tr>
</tbody>
</table>

**C. High Glucose Drives**

Co-localization of F-Actin and Moesin in filopodial extensions, Enhancing TNBC Motility

Metformin inhibits Moesin, Actin reassembly and motility
Summary: Metformin

- Metformin has shown potent anti-cancer activity in clinical, preclinical and epidemiologic studies.

- Its effects extend beyond patients with metabolic disease, obesity or diabetes. The potent anti-cancer action likely reflects critical defects in cellular biology of cancer cells, for example, the Warberg effect.

- Metformin can have very different and widespread anti-growth and death inducing effects on molecular subtypes, and subtypes of subtypes of cancer. In general, it appears most potent against cancers that are highly aggressive and more stem like (EMT).

- Metformin’s anti-stem activity may be particularly important for reducing dormancy, that promotes recurrence and treatment resistance.

- Its activity can be modified by the environmental milieu, in including extracellular glucose and ligands that bind to specific membrane receptors or transporters.

- Metformin is a well tolerated, inexpensive oral agent administered worldwide with decades of clinical use.

- ~100 clinical trials underway to test its efficacy against cancer.
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X-S Deng, MD

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Xiaohe Yang, MD*
Carol Sartorius, PhD
Steve Anderson, PhD
E Wellberg, Ph.D.

McLean Lab
A Checkley, Ph.D.
E Giles, Ph.D.
Paul McLean, PhD

C Perou
C Harrell, Ph.D.

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Additional References on Metformin from Thor et al