The Role of the Insulin and IGF-1 Receptors in Cancer: Implications for Therapy

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Mt Sinai School of Medicine
and
Lee Helman MD
NCI
Breast tumors express high levels of IGF-I receptors
Wild-type tumor suppressors

- BRCA1
- WT1
- p53
- ?others

The IGF-IR promoter: a downstream target for tumor suppressor action

Loss-of-function mutations abrogate the repressive action of tumor suppressors

Mutant tumor suppressors

IGF-IR promoter

mRNA

Sp1

TBP

Loss-of-function mutations
<table>
<thead>
<tr>
<th>Tumor Suppressor Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Transcription factors</td>
</tr>
<tr>
<td>• Phosphorylation</td>
</tr>
<tr>
<td>• Structural</td>
</tr>
<tr>
<td>• Signalling</td>
</tr>
<tr>
<td>• DNA repair</td>
</tr>
</tbody>
</table>

• Lane and Hupp April 2003

• Non-histone chromatin protein High Mobility Group A1 (HMGA1). HMGA1 reduces p53 and activates SP1, thereby increasing IGF-1R transcription. (Belfiore 2010 Eur J Cancer)
control vehicle  10ml/kg p.o.
20mg/kg p.o.
30mg/kg p.o.
50mg/kg p.o.
50mg/kg p.o. (no added inhibitor)

Days post therapy

Tumor volume mm$^3$ +/- SEM
# Anti-IGF1 receptor antibody efficacy in animal studies

<table>
<thead>
<tr>
<th>Antibody Name</th>
<th>Species</th>
<th>Tumour cell type</th>
<th>Model</th>
<th>Comment</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>αIR3</td>
<td>Mouse</td>
<td>Breast cancer</td>
<td>Athymic mice</td>
<td>Decreased tumour size</td>
<td>136</td>
</tr>
<tr>
<td>αIR3</td>
<td>Mouse</td>
<td>Rhabdomyosarcoma</td>
<td>Athymic mice</td>
<td>Decreased tumour size</td>
<td>137</td>
</tr>
<tr>
<td>αIR3</td>
<td>Mouse</td>
<td>Ewing sarcoma</td>
<td>Athymic mice</td>
<td>Decreased tumour size</td>
<td>138</td>
</tr>
<tr>
<td>αIR3</td>
<td>Mouse</td>
<td>Non-small-cell lung cancer</td>
<td>Athymic mice</td>
<td>Decreased tumour size</td>
<td>139</td>
</tr>
<tr>
<td>SCFV/FC</td>
<td>Mouse/human chimera</td>
<td>Breast cancer</td>
<td>Athymic mice</td>
<td>Decreased tumour size</td>
<td>164</td>
</tr>
<tr>
<td>SCF/FC</td>
<td>Mouse/human chimera</td>
<td>Breast cancer</td>
<td>Athymic mice</td>
<td>IGF1 receptor downregulation</td>
<td>165</td>
</tr>
<tr>
<td>SCF/FC</td>
<td>Mouse/human chimera</td>
<td>Breast cancer</td>
<td>Athymic mice</td>
<td>Decreased tumour size, enhanced effect combined with tamoxifen</td>
<td>143</td>
</tr>
<tr>
<td>EM/164</td>
<td>Mouse</td>
<td>Pancreatic</td>
<td>Athymic mice</td>
<td>Decreased tumour growth</td>
<td>166</td>
</tr>
<tr>
<td>A-12</td>
<td>Fully humanized</td>
<td>Breast cancer</td>
<td>Athymic mice</td>
<td>Decreased tumour size, apoptosis</td>
<td>167</td>
</tr>
<tr>
<td>Bispecific</td>
<td>Humanized anti-IGF1 and EGF receptor</td>
<td>Pancreatic/colon</td>
<td>Athymic mice</td>
<td>Induced receptor down regulation, inhibited tumour growth</td>
<td>141</td>
</tr>
<tr>
<td>A-12</td>
<td>Fully humanized</td>
<td>Prostate cancer</td>
<td>Athymic mice</td>
<td>Decreased tumour size, apoptosis</td>
<td>168</td>
</tr>
<tr>
<td>19D12</td>
<td>Fully humanized</td>
<td>Ovarian cancer</td>
<td>Athymic mice</td>
<td>Decreased tumour size</td>
<td>169</td>
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<tr>
<td>H7C10</td>
<td>Humanized</td>
<td>Non-small-cell lung cancer</td>
<td>Athymic mice</td>
<td>Decreased tumour size, prolonged lifespan</td>
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<tr>
<td>CP751-871</td>
<td>Fully humanized</td>
<td>Breast cancer</td>
<td>Athymic mice</td>
<td>IGF1 receptor downregulation, decreased tumour size</td>
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<tr>
<td>KM1468</td>
<td>Mouse (Anti-IGF2)</td>
<td>Colon cancer</td>
<td>Athymic mice</td>
<td>Blocked colon cancer metastases</td>
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<tr>
<td>SCFV/FC</td>
<td>Mouse/human chimera</td>
<td>Breast cancer</td>
<td>Athymic mice</td>
<td>Downregulated IGF1 and insulin receptors</td>
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<tr>
<td>A-12</td>
<td>Fully humanized</td>
<td>Prostate cancer</td>
<td>Athymic mice</td>
<td>Augmented doxaxel-induced inhibition of tumour growth</td>
<td>144</td>
</tr>
<tr>
<td>A-12</td>
<td>Fully humanized</td>
<td>Non-small-cell lung cancer</td>
<td>Athymic mice</td>
<td>Enhanced radiation-induced tumour cell apoptosis</td>
<td>142</td>
</tr>
<tr>
<td>A-12</td>
<td>Fully humanized</td>
<td>Multiple myeloma</td>
<td>SCID mice</td>
<td>Decreased tumour growth and vascularization</td>
<td>163</td>
</tr>
</tbody>
</table>

*EGF, epidermal growth factor; IGF, insulin-like growth factor; SCID, severe combined immunodeficiency.*

IGF1 receptor tyrosine kinase inhibitor efficacy in animal studies

<table>
<thead>
<tr>
<th>Compound</th>
<th>Tumour Type</th>
<th>Model</th>
<th>Comment</th>
<th>Refs</th>
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<tbody>
<tr>
<td>NVP-AEW541-A</td>
<td>Fibrosarcoma</td>
<td>Athymic mice</td>
<td>Inhibited tumour growth</td>
<td>173</td>
</tr>
<tr>
<td>BMS-536,924</td>
<td>Salivary Gland</td>
<td>Athymic mice</td>
<td>Inhibited tumour growth</td>
<td>174</td>
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<tr>
<td>BMS-554,417</td>
<td>Salivary gland</td>
<td>Athymic mice</td>
<td>Inhibited tumour growth</td>
<td>175</td>
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<tr>
<td>Cyclolignan</td>
<td>Uveal melanoma</td>
<td>Athymic mice</td>
<td>Inhibited tumour growth</td>
<td>151</td>
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<tr>
<td>TAE226</td>
<td>Glioma</td>
<td>Athymic mice</td>
<td>Inhibited tumour growth, increased survival</td>
<td>176</td>
</tr>
<tr>
<td>NVP-AEW541</td>
<td>Neuroblastoma</td>
<td>SCID mice</td>
<td>Inhibited tumour invasiveness</td>
<td>177</td>
</tr>
<tr>
<td>Cyclolignan</td>
<td>Myeloma cells</td>
<td>Syngeneic mice</td>
<td>Inhibited tumour growth, increased survival</td>
<td>152</td>
</tr>
<tr>
<td>NVPADW742</td>
<td>Myeloma cells</td>
<td>SCID mice</td>
<td>Inhibited tumour growth, metastases and increased survival</td>
<td>178</td>
</tr>
<tr>
<td>NVPAEW541</td>
<td>Ewing sarcoma</td>
<td>Athymic mice</td>
<td>Inhibited tumour growth and angiogenesis</td>
<td>179</td>
</tr>
<tr>
<td>PQ401</td>
<td>Breast cancer</td>
<td>Syngeneic mice</td>
<td>Inhibited tumour growth</td>
<td>180</td>
</tr>
<tr>
<td>NVP-AEW541</td>
<td>Ewing sarcoma</td>
<td>Athymic mice</td>
<td>Combined with vitronectin inhibited tumour growth</td>
<td>147</td>
</tr>
</tbody>
</table>

SCID, severe combined immunodeficiency.
Clinical Studies in Ewing’s and other Sarcomas

Lee Helman

NCI
Refractory 25yo with EWS and Retinal Metastasis

Baseline

Week 6
9/9/08 MRI: Right orbital mass

1.6 X 1.4 X 1.6 CM

10/14/08 MRI
13 YO female with refractory Ewing’s Sarcoma
Rx with R1507 27mg/kg q3wkx 2

Now 14, 1 year on Rx, CR
Overall Results Summary

• 115 eligible patients with refractory ES treated
• Overall objective response rate 16.5%
  – 11 durable (2CR), 8 short-lived
• Toxicity
  – Thrombocytopenia-7%, anemia-7%, pain-7%
  • Hyperglycemia-3%
Science-Driven Rationale for combined mTOR and IGFR1 Targeted Therapy

Feedback activation of AKT following mTOR inhibition by rapalogs

Tumor sample of a patient on treatment with everolimus

Pre-therapy vs. on-therapy staining

Tabernero J et al., J Clin Oncol 2008; 26(10):1603
Science-Driven Rationale for combined mTOR and IGFR1 Targeted Therapy

Feedback activation of AKT following mTOR inhibition by rapalogs

Tumor sample of a patient on treatment with everolimus

Co-treatment with IGFR1 inhibitor prevents feedback activation of AKT by mTOR inhibition in preclinical models

Di Cosimo S et al., J Clin Oncol 2007; 25 (18S): 3511
Representative IHC from Serial Tumor Biopsies

Tumor biopsies from a 77 year old female with ER+/high proliferation breast cancer with partial metabolic response on FDG-PET and SD by RECIST.
Incomplete responses to IGF-1R Antibodies.

- Compensation of inhibited IGF-1R function using an antibody, may result in increased IR activation.
- IR-A maybe important in certain cancers.
- EGFR, PDGFR may cause resistance.
Aberrant IR-A expression in cancer
Insulin Receptor Isoforms

High Levels of Expression in Fetal and Neoplastic Tissues


IR-A is overexpressed in human cancer

Belfiore & Frasca, 2007
Increased risk of cancer in obesity and Type 2 Diabetes

Derek LeRoith
Mt Sinai
Order:

1. Epidemiology
2. Animal model
3. Discuss mechanisms
Cancers Associated with Obesity

**In Women**
- Breast (postmenopausal)
- Endometrium
- Cervical
- Uterine
- Ovarian
- Colorectal
- Kidney
- Liver/Gall Bladder
- Pancreatic
- Esophageal
- Hematopoietic

**In Men**
- Prostate
- Stomach
- Colorectal
- Kidney
- Liver/Gall Bladder
- Pancreatic
- Esophageal
- Hematopoietic

Calle, et al., NEJM, 4/24/03.
Does Bariatric Surgery Affect Mortality?
University of Utah 2007

- Retrospective cohort study
  - 9,949 gastric bypass pts.
  - 9,628 severely obese driver’s license applicants (BMI ≥ 35 kg/m²)

# Does Bariatric Surgery Affect Mortality?

University of Utah 2007

<table>
<thead>
<tr>
<th></th>
<th>Surgery Group (#/10,000 person-yr)</th>
<th>Control Group (#/10,000 person-yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All causes of death</td>
<td>37.2</td>
<td>61.1</td>
</tr>
<tr>
<td>CV disease</td>
<td>8.5</td>
<td>19.3</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.3</td>
<td>3.5</td>
</tr>
<tr>
<td>Cancer</td>
<td>5.4</td>
<td>15</td>
</tr>
<tr>
<td>Other disease</td>
<td>11.4</td>
<td>17</td>
</tr>
<tr>
<td>Non-disease causes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accident</td>
<td>3.7</td>
<td>2.7</td>
</tr>
<tr>
<td>Poisoning</td>
<td>1.9</td>
<td>0.6</td>
</tr>
<tr>
<td>Suicide</td>
<td>2.7</td>
<td>1.2</td>
</tr>
</tbody>
</table>

Direct correlation exists between circulating insulin and/or C-peptide with cancer development in obesity.
How Can Obesity And Diabetes Affect Breast Cancer Development?

- Nutrients
- IGF-I
- Leptin
- Adiponectin
- Cytokines
- Chemokines
- Diabetes?

- Obesity
- Diabetes
- Cancer

- Hyperinsulinemia
- Hyperglycemia
- Hyperlipidemia
Cancer and Diabetes,

Both diseases have very much the same age distribution. (2) They stand almost alone as being on the increase, while other causes of death show declining rates. (3) The aetiology of both diseases is obscure. (4) Both being diseases of old age ...

... (5) If there were a common factor in the causation of the dual increase a correlation between these diseases might be discovered.
Diabetes and Cancer Mortality in Men (CPS II)

Relative Risk of Death (95% Confidence Interval)

- Kidney
- Prostate
- All Other Cancers
- Stomach
- All Cancers
- Esophageal
- Colon
- NHL
- Multiple Myeloma
- Bladder
- Gallbladder
- Pancreas
- Liver

Coughlin et al. Am J Epidemiology 2004: 159;1160-1167
Diabetes and Cancer Mortality in Women (CPS II)

Multiple Myeloma  0.87
NHL  0.93
Ovarian  1.02
Kidney  1.12
All Other Cancers  1.14
All Cancers  1.15
Gallbladder  1.19
Colon  1.24
Stomach  1.25
Breast  1.27
Uterus  1.33
Pancreas  1.44

Relative Risk of Death (95% Confidence Interval)
A mouse model of Type 2 diabetes
Etiology of Type 2 Diabetes
Impaired Insulin Secretion and Insulin Resistance

Genes and environment

Impaired insulin secretion + Insulin resistance

Impaired glucose tolerance

Type 2 diabetes
Summary

Type 2 Diabetes

Muscle Insulin Resistance

IGF-I/insulin receptor hybrids in muscle

Increased lipolysis in visceral fat

Insulin resistance in adipocytes

Increased fatty acids

Increased fatty acids in visceral fat

Increased glucose output

Impaired glucose tolerance

Increased gluconeogenesis in liver

Insulin resistance in liver

Insulin resistance in liver

β cell compensation

β cell decompensation

Loss of 1st phase insulin secretion

Type 2 Diabetes

Fernandez et al Genes and Development

NON-OBESE
<table>
<thead>
<tr>
<th>Metabolic Abnormalities in MKR Mice</th>
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</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Males</strong></td>
</tr>
<tr>
<td>Fed state hyperglycemia</td>
</tr>
<tr>
<td>Glucose intolerance</td>
</tr>
<tr>
<td>Hyperinsulinemia</td>
</tr>
<tr>
<td>Insulin resistance</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
</tr>
<tr>
<td>Obesity</td>
</tr>
</tbody>
</table>
Insulin resistance

Blood and tissue:
\[ \downarrow \text{IGFBP-1} \]

\[ \uparrow \text{IGF-1/2 serum and/or tissue bioavailability} \]

\[ \uparrow \text{Insulin} \]

Mammary epithelium:
\[ \uparrow \uparrow \uparrow \text{IR} \]
\[ \uparrow \text{IGF-IR, IR/IGF-IR} \]

\[ \downarrow \text{Apoptosis} \]
\[ \uparrow \text{Proliferation} \]

\[ \uparrow \text{Tumor development} \]
Insulin Receptor Isoforms

High Levels of Expression in Fetal and Neoplastic Tissues

WT vs. MKR All Data

WT: IGF-1R v. IR P=0.0923; IGF-1R v. hybrid P=0.0116; IR v. hybrid P=0.0514; n=3 for all

MKR: IGF-1R v. IR P=0.0391; IGF-1R v. hybrid P=0.1096; IR v. hybrid P=0.048; n=3 for IGFIR, *n=2 for IR and hybrid
Mouse Models of Breast Cancer

**Transgenic Model**

- *PyVmT* x *MKR*
- *PyVmT/MKR*

**Orthograft Model**

- *WT* and *MKR* models
- *PyVmT+ Met-1 cells* injected into *WT* and *MKR* mice
Transgenic Model: Early Stages of Mammary Tumorigenesis

PyVmT, 6 wk

PyVmT/MKR, 6 wk
Xenograft Model

**Orthotopic Inoculation of Met-1 Cells**

Monitoring of primary tumor formation and development of pulmonary metastases

**Heterotopic Inoculation of Met-1 Cells**

Monitoring of pulmonary metastases in mice devoid of primary tumors
Tumor volume (cm³)

2 weeks of age

4 weeks
A

Tumor volume at the end of the experiment
N=8     p< 0.05

B

Serum insulin levels mmol/liter
N=8        p<0.05
PyVmT and IR / IGF-IR Share Signal Transduction Pathways

PyVmT

IR / IGF-IR

Shc

PLCγ

PI3K

PP2A.A+C

Src

IRS-1

PI3K

14-3-3

14-3-3

257

pS

250

pY

322

PLCγ

315

PI3K

pp32

pp32

pp32

pp32

14-3-3

14-3-3

257

pS

250

pY

322

PLCγ

315

PI3K

pp32

pp32

pp32

pp32
Crosstalk Between IR/IGF-I and PyVmT: It Takes Two to Tango...
Crosstalk Between IR/IGF-I and PyVmT: It Takes Two to Tango...
Crosstalk Between IR/IGF-I and PyVmT: It Takes Two to Tango...
Crosstalk Between IR/IGF-I and PyVmT: It Takes Two to Tango...
Crosstalk Between IR/IGF-I and PyVmT: It Takes Two to Tango...

Cell transformation, Proliferation, Migration, Invasion

Invasive Malignant Growth

Mitogenic and other biological effects

Oncogene (published) Novosyadlyy et al
Molecular Mechanisms Underlying Tumor-Promoting Activity of T2D

Insulin resistance ↔ ↑ Insulin

IR / IGF-IR

IRS

PI3K

Akt

↓ Apoptosis
↑ Proliferation
↑ Migration
↑ Invasion

↑ Tumor progression
Strategies to Abrogate Tumor-Promoting Activity of T2D

Insulin resistance

↑ Insulin

IR / IGF-IR

IRS

PI3K

Akt

↓ Apoptosis

↑ Proliferation

↑ Migration

↑ Invasion

↑ Tumor progression
Effect of IGF-IR/IR Pharmacological Blockade on Tumor-Promoting Activity of T2D

Blood Glucose

Glucose Tolerance Test

Plasma Insulin

Tumor Weight

Molecular Mechanisms Underlying Tumor-Promoting Activity of T2D

Insulin resistance

↑ Insulin

IR / IGF-IR

IRS

PI3K

Akt

↓ Apoptosis
↑ Proliferation
↑ Migration
↑ Invasion

↑ Tumor progression
Figure 5

A

Tumor volume (cm³)

weeks after cell inoculation

WT, V

WT, CL

MKR, V

MKR, CL

B

Tumor weight (g)

WT

MKR

*
Metastases

- Metastases were measured both by in-vivo imaging of c-myc (Mvt1)-induced tumors; cells were transfected with luciferase expression vector.
Figure 2
Figure 3

(A) Graph showing the number of pulmonary metastases in control and MKR groups. The number of metastases is significantly higher in the MKR group compared to the control group.

(B) Images comparing control and MKR groups. The MKR group shows a higher number of metastases compared to the control group, as indicated by the arrows pointing to the metastatic lesions.
To determine whether the increased metastases in MKR hyperinsulinemic mice was due to larger tumors, we removed tumors when still small (at different stages; earlier in MKR than WT controls. After recovery from survival surgery, mice were followed for another few weeks and then lung metastases quantified.

**Results:** The increased metastases in MKR mice occurred whether from small or larger tumors.

(Also IV injection of cells to bypass the primary tumor effect gave the same results).

**Conclusions:** Hyperinsulinemia maybe the direct cause for increased metastases.
Figure 4

A. Small tumor vol (mm$^3$)

B. Small tumor weight (g)

C. No. of pulmonary metastases/mouse
A few groups have shown that human breast cancer samples with greater expression of the IR as well as increased tyrosine phosphorylation (activation) are associated with a worse prognosis. Furthermore, these tumor samples have an increased expression of IR-A (the mitogenic sub-type of the IR).
How Can Obesity And Diabetes Affect Breast Cancer Development?

Nutrients
IGF-I
Leptin
Adiponectin
Cytokines
Chemokines
Diabetes?

Obesity

Diabetes

Cancer

Hyperinsulinemia
Hyperglycemia
Hyperlipidemia
Congenital IGF-I deficiency tends to confer protection against postnatal development of malignancies

Rachel Steuerman, Orit Shevah, Zvi Laron
Growth Hormone Receptor Deficiency Is Associated with a Major Reduction in Pro-Aging Signaling, Cancer, and Diabetes in Humans

Jaime Guevara-Aguirre,¹⁺ Priya Balasubramanian,²,³⁺ Marco Guevara-Aguirre,¹ Min Wei,³ Federica Madia,³ Chia-Wei Cheng,³ David Hwang,⁴ Alejandro Martin-Montalvo,⁵,⁶ Jannette Saavedra,¹ Sue Ingles,⁷ Rafael de Cabo,⁵ Pinchas Cohen,⁴ Valter D. Longo²,³,⁸⁺
A

- **Relatives**
  - Stroke: 12%
  - Liver cirrhosis: 5%
  - Others/unknown: 34%
  - Accidents: 2%
  - Diabetes: 5%
  - Cardiac disease: 21%
  - Convulsive disorders: 1%

- **GHRD**
  - Stroke: 3%
  - Liver cirrhosis: 3%
  - Others/unknown: 17%
  - Accidents: 20%
  - Alcohol related: 13%
  - Cardiac disease: 27%
  - Convulsive disorders: 17%

B

<table>
<thead>
<tr>
<th>Age</th>
<th>Relatives</th>
<th></th>
<th></th>
<th>GHRD</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Cancer</td>
<td>Total</td>
<td>Cancer</td>
<td></td>
</tr>
<tr>
<td></td>
<td>deaths</td>
<td>deaths (%)</td>
<td>deaths</td>
<td>deaths</td>
<td></td>
</tr>
<tr>
<td>10-30 yr</td>
<td>60</td>
<td>3 (5)</td>
<td>5</td>
<td>0</td>
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<tr>
<td>30-50 yr</td>
<td>208</td>
<td>46 (22.1)</td>
<td>12</td>
<td>0</td>
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<tr>
<td>50-70 yr</td>
<td>370</td>
<td>84 (22.7)</td>
<td>12</td>
<td>0</td>
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<tr>
<td>70-90 yr</td>
<td>446</td>
<td>89 (20)</td>
<td>1</td>
<td>0</td>
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</tbody>
</table>
Thanks to:

- Ruslan Novosyadlyy
- Terri Wood (UMDNJ)
- Yvonne Fierz-Maerk
- Archana Vijayakumar
- Rosalyn Ferguson
- Nyosha Alikhani

Shoshana Yakar, Hui Sun