TRANSLATING SCIENCE TO BETTER HEALTH: 
THE POWER OF DIVERSITY AND MULTICULTURAL ENGAGEMENT

CONCURRENT SCIENTIFIC SESSION 12
Challenges and Treatment Approaches to Combat Triple Negative Breast Cancer in the 21st Century

KARAM F. A. SOLIMAN
Florida A&M University
BREAST CANCER: A COMPLEX HETEROGENEOUS DISEASE

Clinical and Pathological Classification
- Tumor size (T1 – T4)
- Lymph node status (+ - ?)
- Histological grade (1 – 3)

Early Molecular Characterization
- Estrogen receptor (ER) and progesterone receptor (PR) (+ / -)
- erbB2/HER2 (EGFR2) status (+ / -)

CHARACTERIZATION OF BREAST CANCER BY GENE EXPRESSION SIGNATURES: ER+

Luminal A
Therapies
- Antiestrogen
- Aromatase inhibitors

60 – 70% of all BC
Good prognosis for survival.

Luminal B

CHARACTERIZATION OF BREAST CANCER BY GENE EXPRESSION SIGNATURES: HER2 and ER+

HER2 (+ ER)
Therapies
- HER2 receptor and other EGFR inhibitors
- Cytotoxic therapy
- No targeted therapies

15 – 20% of all BC
Overexpressing

Basal (Triple Negative (PR / ER / HER2))
15 – 30% of all BC
HER2-OVEREXPRESSING / TRIPLE NEGATIVE BREAST CANCER

- Herceptin (in combination) treatment is successful for HER2+ tumors but has adverse side-effects
- TN breast cancer – cytotoxic drug therapy is highly toxic
- Prognosis for both tumor types is moderate to poor
- New mechanism-based drugs are needed

ARYL HYDROCARBON (Ah) RECEPTOR: A LIGAND-INDUCED NUCLEAR TRANSCRIPTION FACTOR

- a member of the bHLH family of transcription factors
- Ah receptor knockout mice: lymphoid depletion, bile duct fibrosis, liver size decreased
- endogenous ligand for the receptor has not been identified
- binds different structural classes of xenobiotics as well as natural products

Ah RECEPTOR-MEDIATED ENDOCRINE EFFECTS: CROSSTALK BETWEEN SIGNAL TRANSDUCTION PATHWAYS

- Target organ-specific modulation of endocrine responses
- Steroid hormones
- Thyroid hormones
- Pituitary hormones
- Growth factors
- Neurotransmitters

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Estrogenic Responses Inhibited by AhR-ER Crosstalk

- Mammary tumor formation and growth (rodent & human)
- Uterine and endometrial responses (rodents)
- Breast cancer cell responses

\[ \text{TCDD (\(\Delta\))} \]

INHIBITION OF ER NEGATIVE BREAST CANCER

- TCDD also inhibits HER2 and triple negative breast cancer
- Exhibits antimetastatic activity


DEVELOPMENT OF NON-TOXIC AhR-BASED ANTIESTROGENS

- Alternate-substituted Alkyl PCDFs (synthetic)
- Diindolylmethane (DIM)

\[ \text{Indole-3-carbinol (I3C)} \]

\[ \text{CH}_2\text{OH} \]
**I3C-DIM: PHYTOCHEMICAL ANTICANCER AGENTS**

- High levels in "anticarcinogenic" vegetables ( cruciferous vegetables )
- I3C/DIM exhibit anticarcinogenic activities; most studies are related to change carcinogen metabolism into inactive, non-toxic metabolites
- Minimal data on AhR-based antitumorigenic activity

**ANTITUMORIGENIC ACTIVITY OF DIM: RAT MAMMARY TUMOR MODEL (0.5 - 5.0 mg/kg/2d)*

*No effect on organ weight/histopathology, or induction of CYP1A1/A2 (Carcinogenesis 19:1631)

**DIM AND SUBSTITUTED DIMs ACTIVATE MULTIPLE PATHWAYS**

- Antiandrogen (DIM/X=DIM) Androgen CX DIM
- Multiple Genes (+)
- Decreased MMP
- Stress Activation
- ER antagonist (DIM)
- ER agonist (DIM/Fish)
- Inhibit pancreatic cancer cell growth (Oncogene)
A NEGATIVE CONTROL TURNED POSITIVE

INHIBITION OF TUMOR GROWTH BY C-DIMs
DMBA-INDUCED MAMMARY TUMORS

C-DIMs: A NEW CLASS OF ANTICANCER DRUGS
ACTIVATE GROWTH INHIBITION & APOPTOSIS
C-DIMs ACTIVATE PPARγ

Screening receptors that bind lipophilic compounds

R = RAR, RXR AhR, PPARα or PPARγ
P = Arnt or RXR

GROWTH INHIBITORY PATHWAYS OF PPARγ IN CANCER CELLS

Ligand

• PPARγ-dependent induction of p21 and caveolin-1
• PPARγ-independent induction of ER stress

Endocrinology 145, 5774, 2004
J. Biol. Chem. 280, 16508, 2005
Carcinogenesis 27, 717, 2006
Carcinogenesis 24, 1139, 2009
Endocrinology 145, 5774, 2004
Cancer Res. 66, 412, 2006
J. Biol. Chem. 280, 16508, 2005
Mol. Cancer Ther. 5, 1362, 2006
Mol. Pharm. 68, 1782, 2005
Clin Cancer Res 15, 5431, 2009

C-DIMs WHICH INHIBIT TUMOR/CELL GROWTH BUT EXHIBIT LOW ACTIVATION OF PPARγ

• DIM-C-pPhOCH3 (X=OCH3) and DIM-C-Ph (X=OH) inhibit growth of multiple cancer cell lines
• Both compounds also block DMBA-induced mammary tumor growth in vivo

Minimal activation of PPARγ, RAR, RXR, AhR

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OTHER NRs AS POTENTIAL TARGETS FOR C-DIMs

- RXR HETERODIMERS
  - receptors with known ligands (endogenous or synthetic)

- DIMERIC ORPHAN RECEPTORS
  - orphan receptors with no known ligands (except RXR)

NGFI-B: AN ORPHAN RECEPTOR FAMILY OF STRUCTURALLY RELATED PROTEINS*

<table>
<thead>
<tr>
<th>A/B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nur77 (TR3)</td>
<td>27%</td>
<td>92%</td>
<td>67%</td>
<td></td>
</tr>
<tr>
<td>Nurr1</td>
<td>21%</td>
<td>91%</td>
<td>64%</td>
<td></td>
</tr>
</tbody>
</table>

* Initially identified after treatment of PC12 cells with NGF

TR3/Nur77: MULTIPLE TISSUE-SPECIFIC FUNCTIONS

- TR3 protective against vascular disease
- Anti-arthritis in mouse models
- Modulates glucose metabolism and adipocyte differentiation
- Suppression of acute myeloid leukemia (+NR4A3)
- Proapoptotic in cancer
FUNCTIONS OF TR3/NR4A1 IN CANCER CELLS

- Overexpression
  - Breast Cancer Cells
  - Inhibition of migration but not growth (cell-dependent)

- RNAi (knockdown)
  - Lung, Liver, Thyroid, Leukemia, Pancreatic, Colon
  - Apoptosis, inhibition of growth and migration

TUMOR SUPPRESSOR?

IDENTIFICATION OF C-DIMs AS NR4A1 AND NR4A2 INACTIVATORS

- Luc. Activity Fold (NBREx3)

TR3 / NR4A1 AS A PRO-ONCOGENIC FACTOR: A TARGET FOR DRUG-MEDIATED INACTIVATION

- ssiNR4A1 or C-DIM
- Anti-apoptotic genes (survivin, bcl2, etc)
- Cell growth, Proliferation, Invasion

TR3-dependent

Inhibition of mTOR
Inhibition of survival / cell growth

* Similar results for NR4A2
TR3 / NR4A1 AND Nurr1 / NR4A2 DECREASE SKBR3 CELL GROWTH AND MIGRATION

SKBR3 cell migration

siScr siTR3 siNR4A2

Cell migration (% of control)

0 20 40 60 80 100 120

siScr siTR3 siNR4A2

Cell survival (% of control)

0 20 40 60 80 100

TR3 / NR4A1 INACTIVATION BY C-DIM INDUCES APOPTOSIS

MCF-7 (p53-wt)

7.50 DIM-C-pPhCOOMe 15 (µM)

MDA-MB-231 (p53-mt)

7.50 DIM-C-pPhCOOMe 15 (µM)

TR3 / NR4A1 INACTIVATION BY C-DIM INDUCES ER STRESS

MCF-7 (p53-wt)

7.50 DIM-C-pPhCOOMe 15 (µM)

MDA-MB-231 (p53-mt)

7.50 DIM-C-pPhCOOMe 15 (µM)
TR3 KNOCKDOWN INHIBITS mTOR (p53-WT)

MCF-7 (p53-wt) MDA-MB-231 (p53-mt)

SESN2 β-actin S6RP p-S6RP p-p70S6K AMPK α p-AMPK α p70S6K β-actin S6RP p-S6RP p-p70S6K AMPK α

TR3 / NR4A1 AND Nurr1 / NR4A2 IN BREAST CANCER

- Both NR4A1 and NR4A2 are pro-oncogenic in some breast cancer cells (RNAi).
- C-DIM-mediated inactivation of NR4A receptor inhibits growth, survival and migration, and this represents a new class of mechanism-based anticancer agents.
- ACKNOWLEDGEMENTS: Syng-Ook Lee, Un-Ho Jin and Mandip Singh

MANDIP S. SACHDEVA
Florida A&M University
TUMOR HOMING NANOCARRIERS FOR IMAGING AND TREATMENT OF LUNG CANCER

Dr. Mandip Sachdeva
Florida A&M University
College of Pharmacy And Pharmaceutical Sciences

BACKGROUND

- Lung cancer is the leading cause of cancer-related death worldwide.
- The lung is a common site of primary malignancy and for metastasis from other primary locations.
- 70-80% of newly diagnosed cases are defined as Non-small cell lung cancer (NSCLC).

CLINICAL UTILITY OF CURRENT CHEMOTHERAPEUTICS IS LIMITED by poor clinical outcome and associated adverse effects.

Targeted nanoparticles: The targeting of systemically-administered delivery systems has been limited by the lack of ligands specific to lung cancer cells, thus need of molecular targets to target the tumors.

PEGylated nanoparticles: Modification with polyethylene glycol on the surface of the nanoparticle allows for a reduction in opsonization, which reduces removal by the reticuloendothelial system (RES).

Currently Explored Nanoparticles For Cancer Therapeutics:
dendrimers, liposomes, polymeric nanoparticles, peptides, protein nanoparticles, ceramic nanoparticles, viral nanoparticles, metallic nanoparticles, and carbon nanotubes.

Presented at the 13th RCMI International Symposium on Health Disparities | December 9-13, 2012 | San Juan, Puerto Rico

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Angiogenesis

The Angiogenic Switch Is Necessary for Tumor Blood Vessel Targeting/Retention Effect [EPR]

Proposed Model For Tumor Blood Vessel Targeted CREKA Peptide Coated nanocarrier system.

A) Tumor infiltrated with blood vessels; i) administration of PCNCs-D; B) Expanded view of PCNCs-D targeting/accumulation at tumor blood vessels, ii) clotted plasma proteins on tumor blood vessels iii) NCs binding to tumor blood vessel, the encapsulated drug is released slowly at tumor blood vessels and drug enters into the tumor by enhanced permeation and retention (EPR) effect. C) Expanded view of delivery of YNCs unable to attach to plasma clot in tumor blood vessel.

Formulation of NCs, NCs-D and PCNCs-D

- NCs-D prepared with triglycerides were stable and particle size was approximately 180-200 nm.
- Encapsulation efficiency of DIM-P was found to be more than 75%.
- Differential scanning calorimetric (DSC) results also showed that most of the drug was associated with NCs-D.
**CLOT BINDING ASSAY**

Significantly (p<0.001) 3 fold higher binding of PCNCs-D to the clotted plasma proteins was observed compared to the NCs-D and YNCs, a nonspecific peptide coated NPs.

- 152 µM CREKA peptide was found to be optimal for binding to the plasma clot.
- PCNCs-D formulation a binds to the plasma clots and illustrate the specificity of functionalized PCNCs-D formulations.

**In vitro Angiogenesis Assay**

Figures. Tube formation assay with HUVEC cells. After seeding on Matrigel, HUVEC cells were incubated on 20% FBS, Doc and 0% Doc on polymerized Matrigel at 37°C. After 24 hrs, the tube formation assay was performed and whitish-pink color capillary tube branch formation was quantified (n = 3).

**In-Vivo imaging using IVIS SpectrumCT**

Fig. In-Vivo Imaging; A) A549 and H460 lung cancer cell tumor bearing Mouse in In-Vivo imaging system and Spectrally Unmixed Image of Vasculature with B) NCs-Di and C) DiR.
In-Vivo Anticancer Activity

Therapeutic Activity of Treatment estimated by Differences in Lung Weight, Tumor Volume

A) A549 Orthotopic tumor model
B) H1650 Metastatic tumor model

Ultrasound In-vivo Tumor analysis

Lung Cancer Tissue Among Lung in Mouse

Control Mouse VevoCQ Analysis: Bolus Perfusion Kinetics
Ultrasound In-vivo Tumor analysis

After Treatment Mouse VevoCQ Analysis: Bolus Perfusion Kinetics

Ultrasound In-vivo Tumor analysis

VEGFR2 Expression Pre and Post Destruction in Control Mouse

Ultrasound In-vivo Tumor analysis

VEGFR2 Expression Pre and Post Destruction in Treated Mouse
Nanotheranostics as a link between detection, diagnosis, and treatment

- Mice with subcutaneous H460-luc2 tumors imaged with Nano-luc
- Mice with 4T1-luc2 Orthotopic Tumors imaged with Nano-luc

**Luciferin Nanoparticle Kinetics**

- Formula 1
- Formula 1

**Total Flux [p/s]**

- Nano-luc
- Nano-luc + CREKA
- Nano-luc-CREKA

**Imaging**

- Spectrum CT/DLIT/FLIT imaging of subcutaneous tumor model in mice followed by Nano-Dluc (Dual chromophores: DiR & Luciferin) for detection of tumor multimodality.
CONCLUSIONS

CREKA peptide can be used to target the tumor vasculature by linking it to nanoparticles with its payloads.

Luciferin alone or in combination with fluorophore can be incorporated in nanoparticles with extended residence time in tumors and can be used for tumor imaging.

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Thank You
Background (Hepatitis C)

- Hepatitis C is an infectious disease caused by the hepatitis C virus (HCV)
- Hepatitis C virus infection leads to chronic liver disease
- About 3-4 million people are infected per year, and more than 350,000 people die yearly
- Standard therapy for HCV: Interferon alpha (IFN-α) + Ribavirin
- Limitations: Only effective 50%, side effects
Why Interferon alpha (IFN-α) + Ribavirin are ineffective for some patients?

IFN-α

Hepatocytes

Cell membrane

Cytoplasm

Nucleus

Alternative antiviral strategies: siRNA

Anti-viral strategy: siRNA

5' 3' (HCV virus)

siRNA having complementary sequence of HCV

3' 5'

siRNA hybridize HCV genome

Cleavage and subsequent degradation of HCV

Small interfering RNA (siRNA) is double-stranded RNA molecule, 20-25 nucleotides in length that can silence specific gene expression

Experimental Strategy

siRNA

nanoparticles

siRNA nanosomes

To Cure HCV

Kundu AK et al., 2010 (J Pharm Pharmacol)
Kundu AK et al., 2012 (Eur J Pharm Biopharm)
Kundu AK et al., 2012 (Int J Pharm)
Chandra PK, Kundu AK et al., 2012 (Mol Therapy)
Major Challenges...

1. Design and selection of novel siRNA

We have to design nearly 400~500 siRNAs (20-25 nucleotides).

Targets of siRNAs in 5' UTR of HCV

si74, si73, si206, si244, si261, si279, si298, si315, si321, si333, si351, si359, si369

Virus

siRNA design-strategy

siRNA (20-25 nucleotides)

HCV virus

We have to design nearly 400-500 siRNAs.
Targets of siRNAs in 5'UTR of HCV

Major Challenges...

Composition and electron micrographs of siRNA nanosome

Composition of siRNA-nanosome

DOTAP, Cholesterol, Protamine sulphate, Trehalose and siRNA

Electron micrograph of siRNA nanosomes and HCV

Kundu AK et al., 2010 (J Pharm Pharmacol)
siRNA's integrity during prolonged sonication of siRNA nanosomes

Non-sonicated siRNA nanosome

Sonicated siRNA nanosome

<table>
<thead>
<tr>
<th>Nanosome</th>
<th>Sonication time (min)</th>
<th>Particle size (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B1</td>
<td>0.0</td>
<td>211±19</td>
</tr>
<tr>
<td>B2</td>
<td>0.5</td>
<td>122±26</td>
</tr>
<tr>
<td>B4</td>
<td>2.0</td>
<td>108±28</td>
</tr>
<tr>
<td>B6</td>
<td>4.0</td>
<td>101±18</td>
</tr>
<tr>
<td>B8</td>
<td>6.0</td>
<td>129±41</td>
</tr>
<tr>
<td>B9</td>
<td>7.0</td>
<td>112±19</td>
</tr>
</tbody>
</table>

Major Challenges...

1. Cell internalization pH=7.5
2. Acidification of the endosome pH= 5.5-6
3. Organelle membrane lysis, siRNA release pH=7.5

Cytoplasm

Nucleus

Endosomal escape following endocytosis by siRNA nanosome

1. Cell internalization pH=7.5
2. Acidification of the endosome
3. Organelle membrane lysis, siRNA release

Green dot: Endosome only
Red dot: siRNA only
Orange: siRNA inside the endosome
Measurement of siRNA amount in powder siRNA nanosomes over time

<table>
<thead>
<tr>
<th>Liquid liposome</th>
<th>siRNA</th>
<th>Liquid nanosome</th>
<th>siRNA nanosome</th>
<th>Powder siRNA nanosome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.16 ± 0.03</td>
<td>0.95 ± 0.04</td>
<td></td>
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</tr>
</tbody>
</table>

HCV knock-down: Liquid vs. Powder siRNA nanosome in the long term study

Kundu AK et al., 2012 (Int J Pharm)

Major Challenges...

- Cytoplasm
- Endosome
- Viral genome
- Genome fragmented
- No virus
- Complete clearance of HCV
Sustained anti-HCV effects: *in vitro* Colony Assay

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Untreated</th>
<th>Si359</th>
<th>si321+si359</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd Day</td>
<td></td>
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<td></td>
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<tr>
<td>3rd Day</td>
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<td>4th Day</td>
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<td>5th Day</td>
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<tr>
<td>6th Day</td>
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<td></td>
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<tr>
<td>10th Day</td>
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</table>

In *vivo* inhibition of HCV replication in sub-cutaneous mouse model

Chandra PK, Kundu AK et al., 2012 (Mol Therapy)

In *vivo* inhibition of HCV replication in the liver (mouse model)

[Tumor (HCV replicon cells)]

[Tumor (HCV replicon cells)]

[Body weight (g)]

Intrasplenic injection of Huh 7.5 HCV replicon cells

siRNA nanosome via IV
Colony selection of HCV that escape siRNA inhibition

**In vivo inhibition of HCV replication in the liver (mouse model)**

Mice HCV GAPDH

Untreated siRNA nanosome treated

RPA to check HCV after siRNA treatment

**Major Challenges...**

- Cytoplasm
- Nucleus
- Endosome
- siRNA Nanosome
- Viral genome
- siRNA could not bind
- Virus

5. Prevention of escape mutant formation

**Sequence analysis of HCV clones in the in vivo liver delivery**

Untreated siRNA nanosome treated
Assessment of *in vivo* toxicity

![Graphs and images showing serum chemistry results for various enzymes.]

**Serum Chemistry:** Mouse
- **ALT (Alanine transaminase):** 17-77 U/L
- **AST (Aspartate transaminase):** 54-298 U/L

Chandra PK, Kundu AK et al., 2012 (Mol Therapy)

**Conclusion**

We have developed and optimized siRNA nanosome formulations that can:
- Significantly deposit siRNA into the liver hepatocytes
- Effectively silence and clear IFN resistant HCV
- Be stably stored for long term use
- Show minimal or no *in vivo* toxicity

Then the question is ………

How can we use this technology to treat cancer including triple negative breast cancer?
Two recent publications of our collaborators at Tulane university


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LSU Health Sciences Center
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That's all
Thank you
JANET V. COWINS
Clark Atlanta University

OBJECTIVES

- Prostate Cancer
- Demographic
- Current treatments
- Cyclodextrins
- β-Cyclodextrin (Host)
- Phytosterols
- β-Sitosterol (Guest)
- β-Cyclodextrin:β-Sitosterol inclusion complexes
- Characterization techniques
- Future implications of a target specific drug delivery vehicle

Presented at the 13th RCMI International Symposium on Health Disparities | December 9-13, 2012 | San Juan, Puerto Rico
Background

- Cancer
  - Prostate Cancer
    - 240,000 (new cases)
    - 28,000 (estimated death)
    - African American men
- Current Treatments
  - Chemotherapy
  - Radiation
  - Cryotherapy

Introduction

- Cyclodextrins
  - α-Cyclodextrin
  - β-Cyclodextrin
  - γ-Cyclodextrin

Beta-Cyclodextrin

- Upadhyay S., Kumar S., Chemistry Central Journal, 2009, 3 (9).
Awad A.; Fink, C., American Society for Nutritional Sciences, 2000, 130, 2127–2130.

Figure 1: The effect of β-Cyclodextrin supplementation on the viability of PC3 and DU145 cells.

Figure 2: qRT-PCR showing differential modulation of the expression of the p-53 gene by β-sitosterol.

Figure 3: DSC endotherm of physical mixture.

Figure 4: DSC endotherm of inclusion complex.
HYPOTHESIS

- We hypothesize that the β-Cyclodextrin-Poly-(ethylene glycol)-Folic Acid (β-CD-PEG-FA):β-Sitosterol bio-conjugate will be an efficient tumor-specific complex for drug delivery.

METHODS

- Phase I
- Characterize functional groups using IR
- Investigate β-CD:β-Sitosterol inclusion complexes using 1H NMR
  - 1:0 (β-CD:β-Sitosterol)
  - 1:0.2 (β-CD:β-Sitosterol)
  - 1:0.4 (β-CD:β-Sitosterol)
  - 1:0.6 (β-CD:β-Sitosterol)
  - 1:0.8 (β-CD:β-Sitosterol)
  - 1:1.0 (β-CD:β-Sitosterol)

FT-IR SPECTRUM

Blue = β-Cyclodextrin
Red = β-Sitosterol
Green = β-CD:β-Sitosterol inclusion complex
As β-Sitosterol ratio is increased, H3, H5, and H6 of β-CD shifts upfield:
- Indicates that β-sitosterol interacts with β-CD.
- 1:1 inclusion complex demonstrates the highest chemical shift in H5.
- Indicates this ratio may be the better inclusion complex.
CURRENT/FUTURE WORK
- Tosyl β-CD
- PEGylated β-CD
- β-CD-PEG-FA

Phase 3
Possible testing on a prostate cancer cell line in the future

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- Mr. Artez Sims (Vanderbilt University)
- Mrs. Lillian Florey

Questions???
Questions & Answers

Thank you for participating!