Drug Repurposing and Reformulation: Opportunities, Risks, and Challenges
Opening Remarks:
Avrum Spira Professor of Medicine | Director, BU-BMC Cancer Center
I. Discovery

- “openSESAME: matching drugs and diseases in silico using gene expression data”
  Marc Lenburg, PhD, Professor, Medicine, School of Medicine

- “Building the Lung CMap: a tissue-specific paradigm for drug repurposing”
  Elizabeth Moses, PhD Candidate, Pathology/Immunology

- “High-Throughput Transcriptional Screening of Chemicals and Drugs”
  Stefano Monti, PhD, Associate Professor, Medicine, School of Medicine

- “A computational method to reposition drug candidates via inversely correlated cellular functions”
  David Sherr, PhD, Professor, Environmental Health, School of Public Health

- "Using shRNA screens for finding new drug combinations"
  Michael Sherman, PhD, Professor, Biochemistry, School of Medicine
“openSESAME: matching drugs and diseases \textit{in silico} using gene expression data”

Marc Lenburg, PhD

\textit{Professor, Medicine, School of Medicine}
openSESAME: matching drugs and diseases *in silico* using gene expression data

mlenburg@bu.edu
"Building the Lung CMap: a tissue-specific paradigm for drug repurposing”

Elizabeth Moses

PhD Candidate, Pathology/Immunology
And compare this disease profile to a database of gene expression following drug exposure. We can improve this method of drug repurposing by building a database of normal (baseline) cell gene expression. For this patient with lung disease, we can identify lung therapeutics more effectively by looking at gene expression of normal lung cells. In addition, we can extrapolate this methodology to other tissues, and other diseases.
“High-Throughput Transcriptional Screening of Chemicals and Drugs”

Stefano Monti, PhD

Associate Professor, Medicine, School of Medicine
a Chemical Carcinogenicity “Crystal Ball”

Our Toolbox

**Assays/Models**
- Luminex-1000 (L1000)/Cmap
- Highly Multiplexed RNA-seq
- Malignant Cell Lines
- Minimally immortalized Cells
- ‘Genetically tailored’ Cells (CRISPR)

**Design**
- Long-Term Phenotypes
  - Genotoxicity
  - Carcinogenicity
- Short-Term Exposure

**Results**
- ~80% predictive AUC
- Captures dose-dependency
- Points to Modes of Action
- Biomarkers

**Understand Why**

High-Throughput Transcriptional Screening of Chemicals and Drugs

Chemical

Carcinogen
Toxic Endocrine Disruptor Obesogen Pathway X inhibitor

Non-carcinogen

Pathways affected
Driving genetic alterations

Advanced Machine Learning Network-Based Analysis Tools

Drug Efficacy Prediction Model

Boston University Office of the Vice President and Associate Provost for Research
“A computational method to reposition drug candidates via inversely correlated cellular functions”

David Sherr, PhD

Professor, Environmental Health, School of Public Health
1. Recall rates for FDA cancer drugs were 20/20 and 10/11 for breast and prostate cancer respectively.
2. Recall rates for drugs in trials were 131/154 and 82/106 for breast and prostate cancer respectively.
3. Better recall rates than previous methods (Lamb/cMAP alone)
"Using shRNA screens for finding new drug combinations"

Michael Sherman, PhD

Professor, Biochemistry, School of Medicine
Event, Date

Missing slide - Sherman
II. Pre-Clinical/Chemistry

- "Chemical Synthesis of Natural Product Variants to Probe Diverse Biological Pathways"
  
  John Porco Jr., PhD, Professor, Chemistry, College of Arts & Sciences

- "Repurposing Through Small Molecule Evolution"
  
  Aaron Beeler, PhD, Assistant Professor, Chemistry, College of Arts & Sciences

- “Design and synthesis of fungal-selective Hsp90 inhibitors"
  
  Lauren Brown, PhD, Research Assistant Professor, Chemistry, College of Arts & Sciences

- “Drugging the undruggable: Creating new opportunities for treating brain disorders”
  
  Tyrone Porter, PhD, Associate Professor, Mechanical Engineering, College of Arts & Sciences

- "Theranostics and In Vitro Models of Metastasis"
  
  Joyce Wong, PhD, Professor, Biomedical Engineering, College of Arts & Sciences

- “Inhibitors of transcription factor LSF oncogene in hepatocellular carcinoma"
  
  Ulla Hansen, PhD, Professor, Biology, College of Arts & Sciences
"Chemical Synthesis of Natural Product Variants to Probe Diverse Biological Pathways"

John Porco Jr., PhD

Professor, Chemistry, College of Arts & Sciences
porco@bu.edu
Our collaboration with the Pelletier laboratory (McGill) has identified (rocaglates) as novel inhibitors of translation initiation that act as chemical inducers of dimerization (CID) forcing an engagement between eIF4A and RNA. PLoS ONE. 2009, 4, e5223

Homology model for eIF4A
(with Sandor Vajda and Dmitri Beglov)
"Repurposing Through Small Molecule Evolution"

Aaron Beeler, PhD

Assistant Professor, Chemistry, College of Arts & Sciences
Missing Slide - Beeler
“Design and synthesis of fungal-selective Hsp90 inhibitors"

Lauren Brown, PhD

Research Assistant Professor, Chemistry, College of Arts & Sciences
“Repurposing” anticancer drugs to target antifungal drug resistance

Leah Cowen (University of Toronto)                            Luke Whitesell (The Whitehead Institute)

Heat Shock Protein 90
• Stabilizes multiple oncogenic proteins, enables malignancy
• Promotes drug resistance in invasive fungal infections

Heat Shock Protein 90

Human Hsp90

C. Albicans Hsp90

Boston University Office of the Vice President and Associate Provost for Research
“Drugging the undruggable: Creating new opportunities for treating brain disorders”

Tyrone Porter, PhD

Associate Professor, Mechanical Engineering, College of Arts & Sciences
The brain is the most protected organ in the body. Less than 5% of pharmaceuticals administered systemically gain access to the brain due to the activity of the blood-brain barrier (BBB). We are pursuing biochemical/biomolecular and mechanical approaches to circumvent the BBB and enable delivery of various therapeutic agents to the brain.

Receptor-mediated transcytosis
Static BBB model
Dynamic BBB model
Ultrasound-mediated BBB disruption
"Theranostics and In Vitro Models of Metastasis"

Joyce Wong, PhD

Professor, Biomedical Engineering, College of Arts & Sciences
In vitro models of cancer to test theranostic agents
“Inhibitors of transcription factor LSF oncogene in hepatocellular carcinoma”

Ulla Hansen, PhD (Presenter) & Scott Schaus, PhD

Depts. Biology & Chemistry, College of Arts & Sciences
Unmet Medical Need:
HCC – Second leading cause of cancer deaths worldwide
Numerous failed clinical trials, using Protein Kinase inhibitors

Solution? – Additional Target
Transcription factor LSF – Drives HCC Oncogenesis

Novel, 1st-in-class specific LSF inhibitors:
DMSO FQI1 FQI2

Tumor growth inhibition, regression
No detectable toxicity

Effective Combinatorial Therapies for Hepatocellular Carcinoma?

Boston University Office of the Vice President and Associate Provost for Research
III. Legal/IP

• “Repositioned Medicines: Overview of Patent and Regulatory Interactions”
  Warren Kaplan, PhD, JD, MPH, Clinical Assistant Professor, Global Health, School of Public Health

• “Market failures in pharmaceuticals”
  Kevin Outterson, LL.M., JD, Professor, Law, School of Law
“Repositioned Medicines: Overview of Patent and Regulatory Interactions”

Warren Kaplan, PhD, JD, MPH

Clinical Assistant Professor, Global Health, School of Public Health
Original Development → Repositioned Development → Approved Repositioned Product

- **Original API patent:** 20 years
- **New Use/Indication patent:** 20 years
- **Market Approval of Repositioned Product**
- **NCE Exclusivity:** 5 years
- **ANDA/505(b)(2) Patent Challenge**
- **Generic Competition/Modified Product**
- **30 month 'stay'**

Adapted from Drug Discovery Today 8 (3-4):131
“Market failures in pharmaceuticals”

Kevin Outterson, LL.M., JD

Professor, Law, School of Law
CW: Off-patent or unpatentable drugs have no commercial value

But consider:

- Combinations (Vytorin, BiDil, Avycaz)
- Exclusivities (BLAs, ODA, GAIN, NCE, NCI, Ped, ??)
- Vouchers