Drug Repurposing and Reformulation: Opportunities, Risks, and Challenges

Boston University Office of the Vice President and Associate Provost for Research

BOSTON UNIVERSITY

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

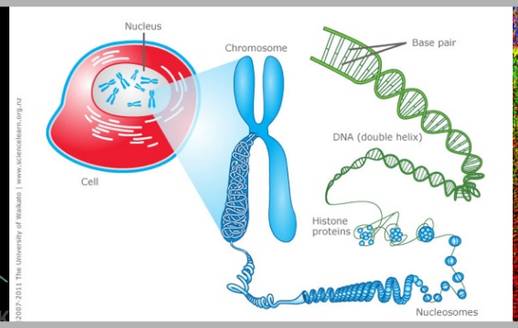
"openSESAME: matching drugs and diseases *in silico* using gene expression data"

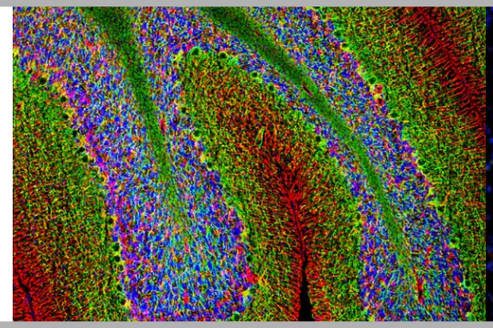
Marc Lenburg, PhD

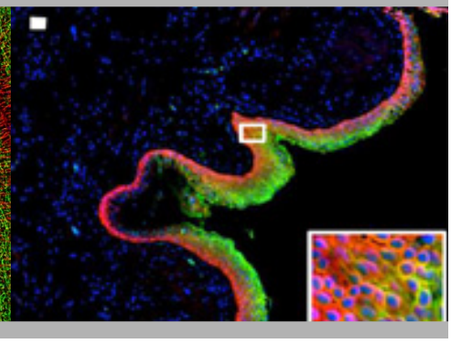
Professor, Medicine, School of Medicine

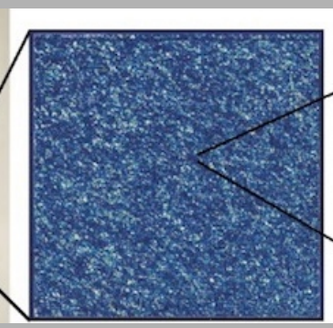
openSESAME: matching drugs and diseases *in silico* using gene expression data

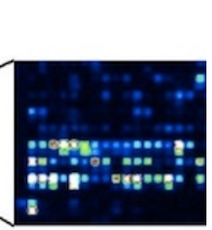
mlenburg@bu.edu

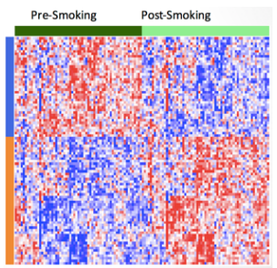


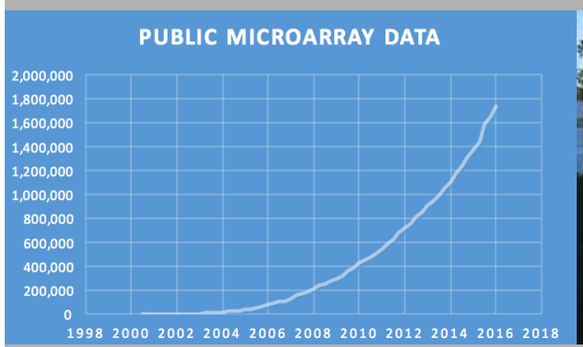


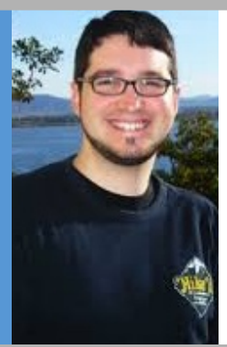


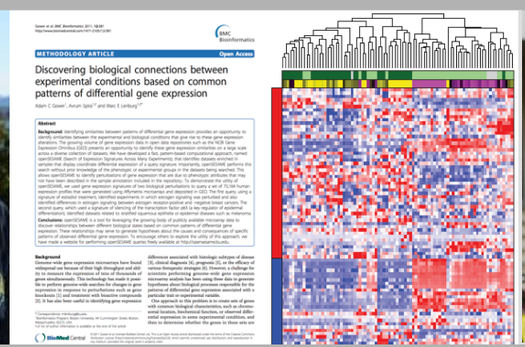


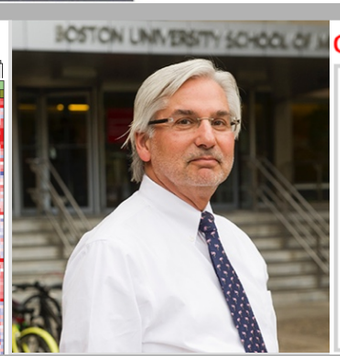


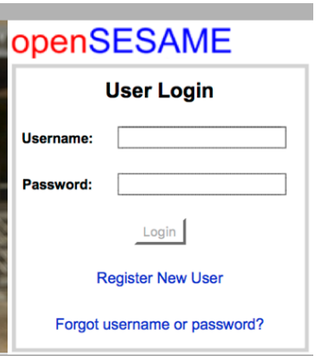


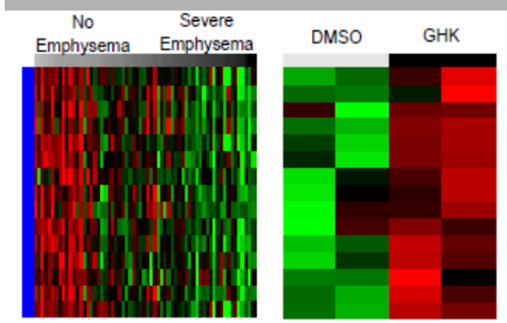


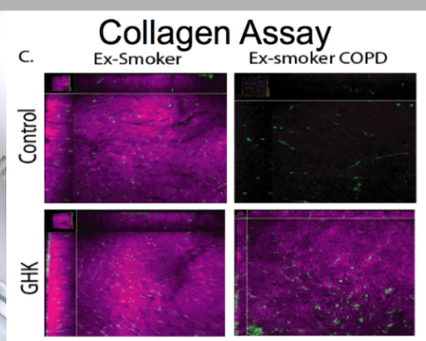


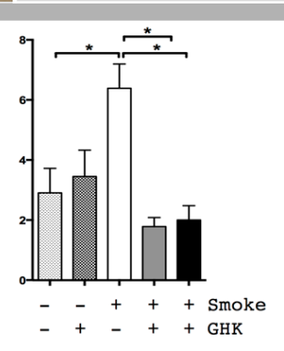












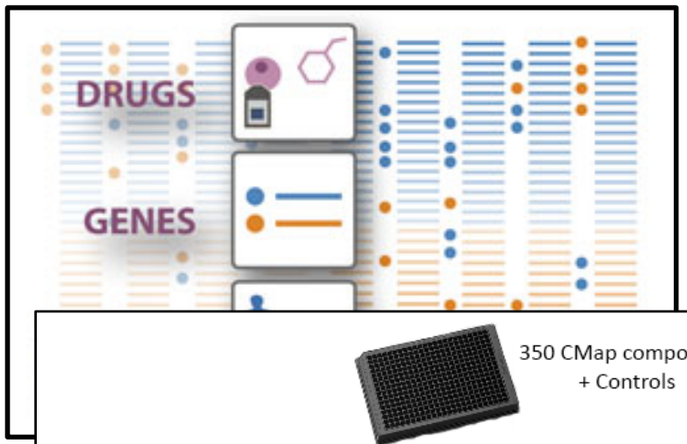
"Building the Lung CMap: a tissue-specific paradigm for drug repurposing"

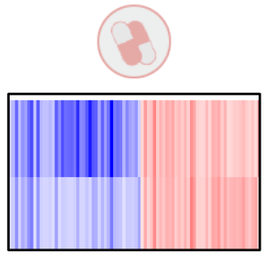
Elizabeth Moses

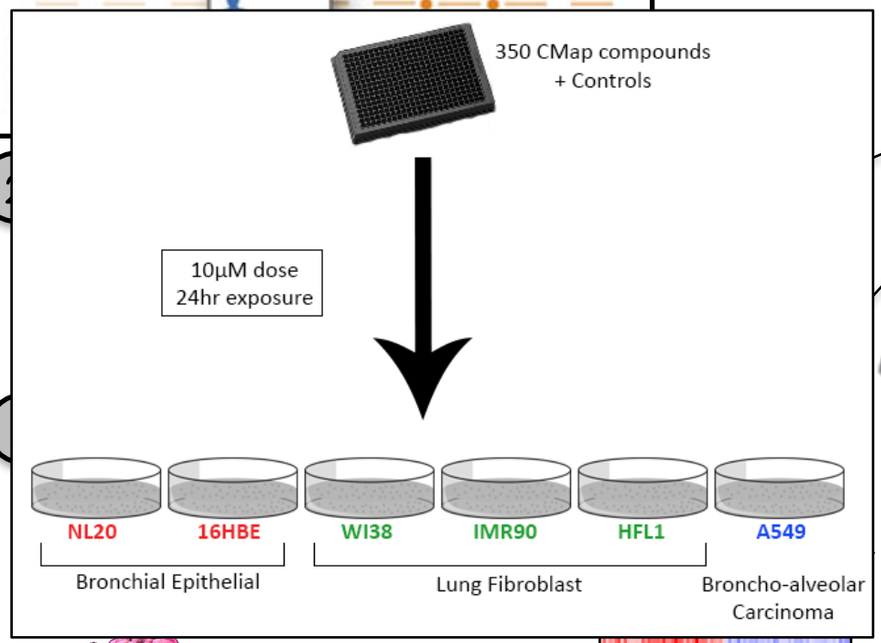
PhD Candidate, Pathology/Immunology

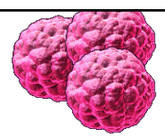
Research on Tap: Drug Repurposing and Reformulation

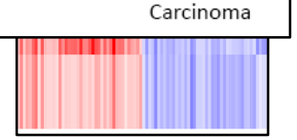
The Broad Institute







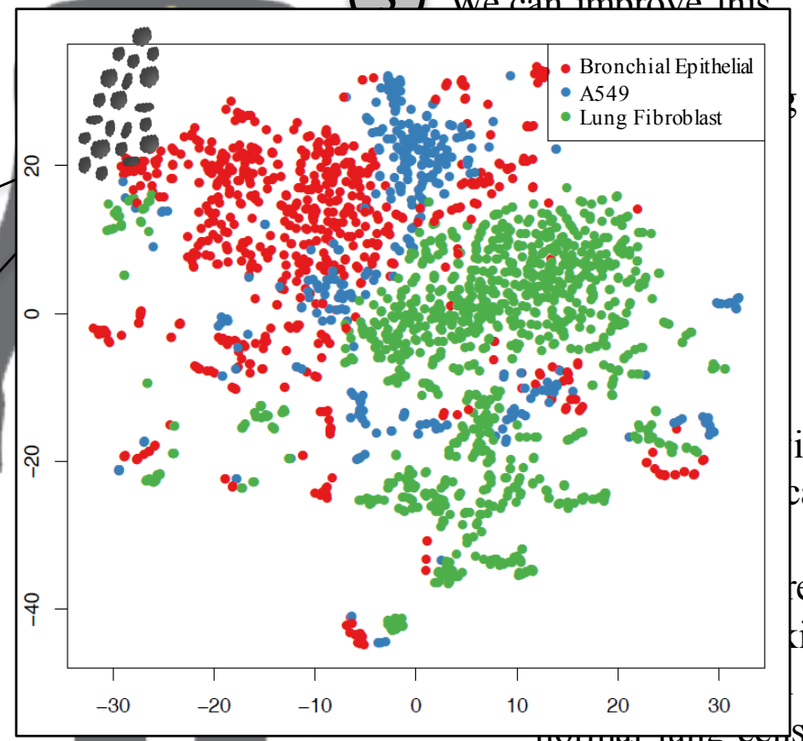




3

And identify a drug with the potential to treat this disease.

5 We can improve this



ith
can
re
king
of

7 In addition, we can extrapolate this methodology to other tissues, and other diseases.

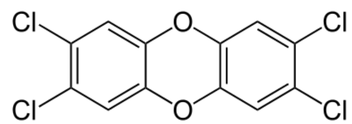
"High-Throughput Transcriptional Screening of Chemicals and Drugs"

Stefano Monti, PhD

Associate Professor, Medicine, School of Medicine

a Chemical Carcinogenicity "Crystal Ball"

Chemical



Carcinogen
Toxic
Endocrine Disruptor
Obesogen
Pathway X inhibitor

Non-carcinogen

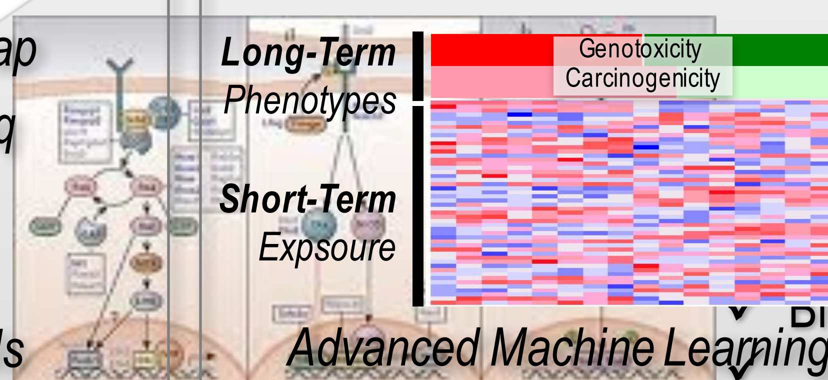
Our Toolbox

Assays/Models

Luminex-1000 (L1000)/Cmap
Highly Multiplexed RNA-seq

Malignant Cell Lines
Minimally immortalized Cells
'Genetically tailored' Cells (CRISPR)

Design



Advanced Machine Learning
Network-Based Analysis Tools

Results

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

athways affected
iving genetic alterations
Biomarkers
...

Understand Why

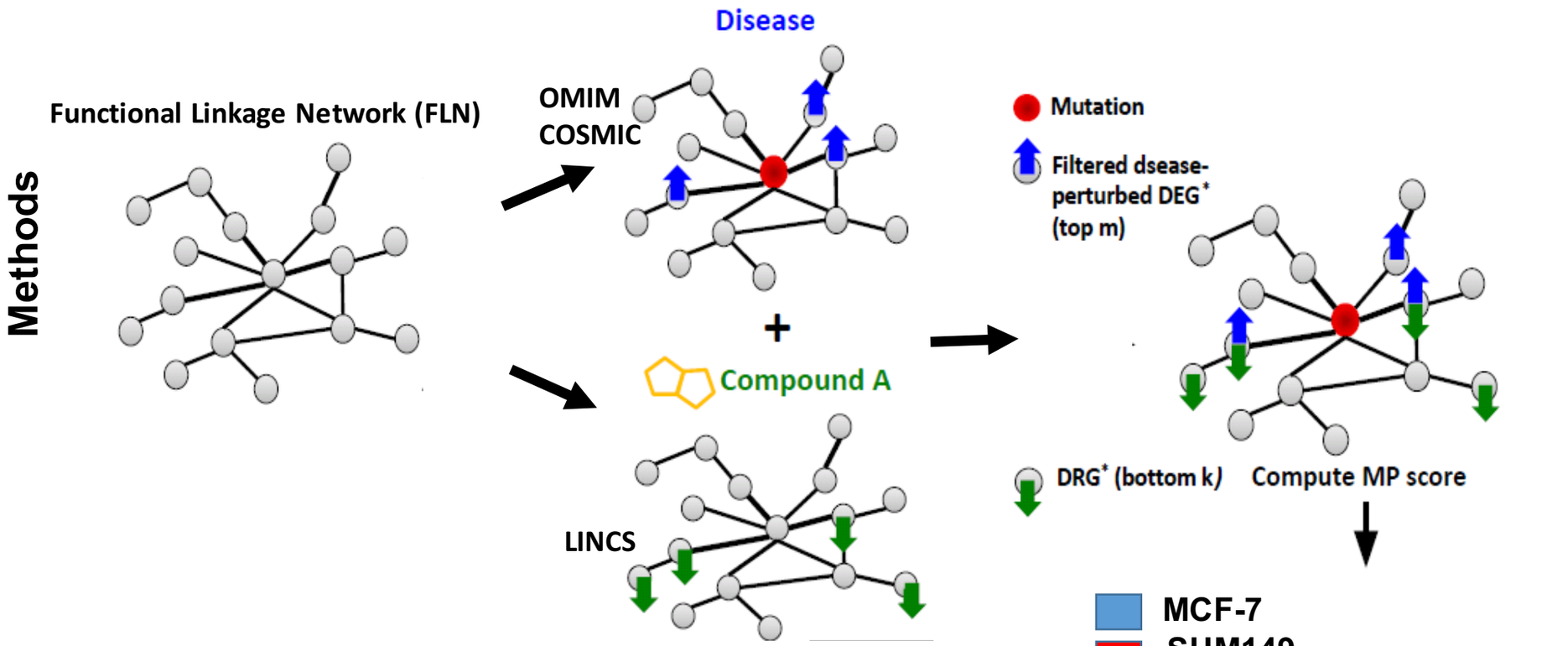
BOSTON UNIVERSITY

"A computational method to reposition drug candidates via inversely correlated cellular functions"

David Sherr, PhD

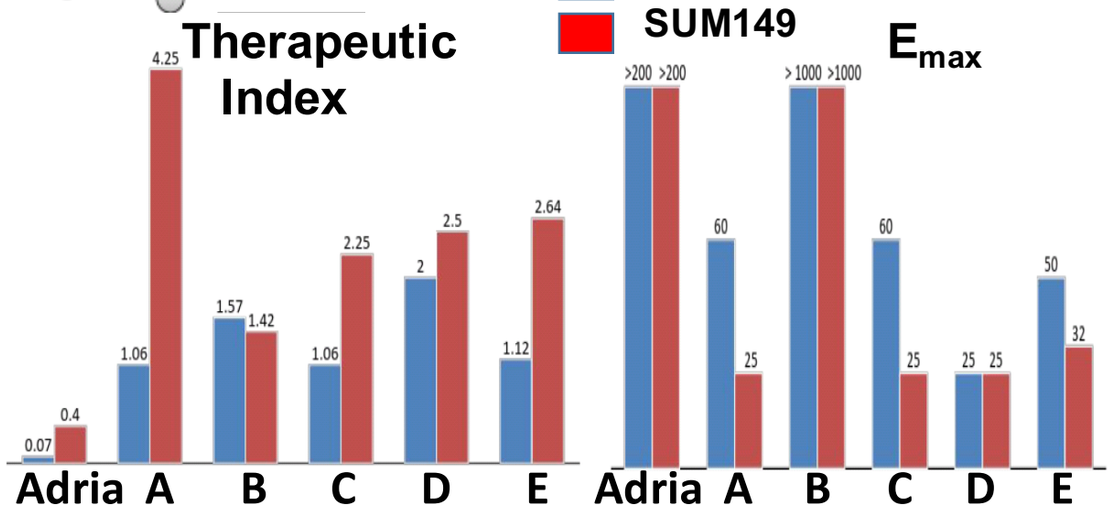
Professor, Environmental Health, School of Public Health

The Method of Functional Modules



Outcomes

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 were131/154 and 82/106 for breas 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

Missing slide - Sherman

II. Pre-Clinical/Chemistry

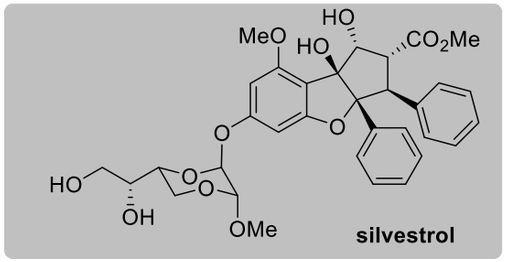
- **"Chemical Synthesis of Natural Product Variants to Probe Diverse Biological Pathways"**
  John Porco Jr., PhD, Professor, Chemistry, College of Arts & Sciences
- **"Repurposing Through Small Molecule Evolution"**
  Aaron Beeler, PhD, Assistant Professor, Chemistry, College of Arts & Sciences
- **"Design 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

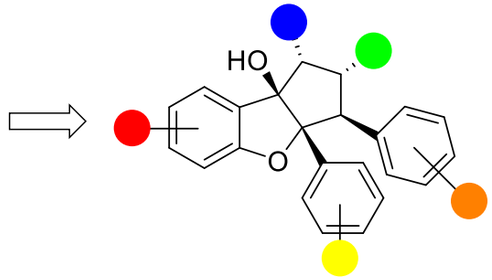
"Chemical Synthesis of Natural Product Variants to Probe Diverse Biological Pathways"

John Porco Jr., PhD

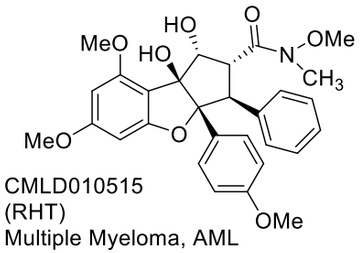
Professor, Chemistry, College of Arts & Sciences
porco@bu.edu

BOSTON UNIVERSITY

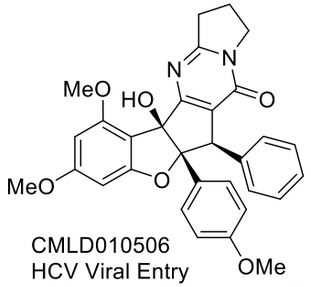




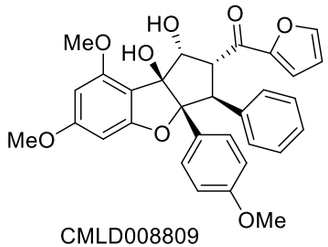
rocaglate analogs



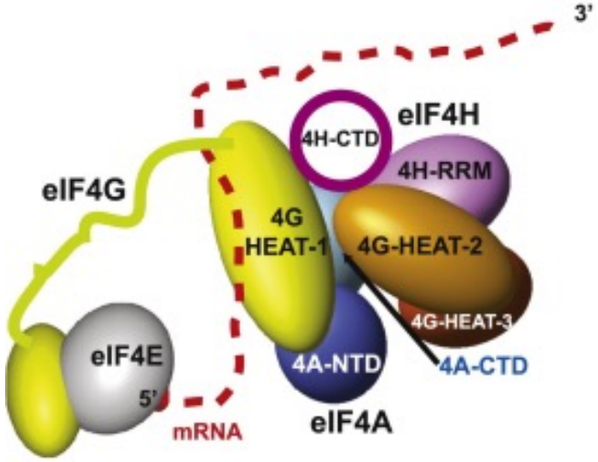
CMLD010515
(RHT)
Multiple Myeloma, AML
with Jerry Pelletier, Luke Whitesell



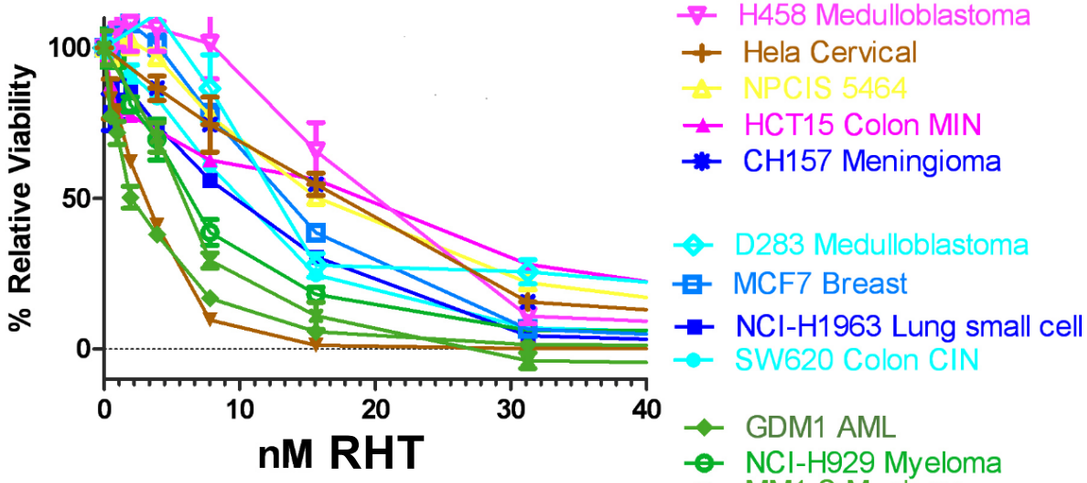
CMLD010506
HCV Viral Entry
Inhibitor with Tony Wang (SRI).



CMLD008809
Tuberculosis
with Igor Kramnik



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

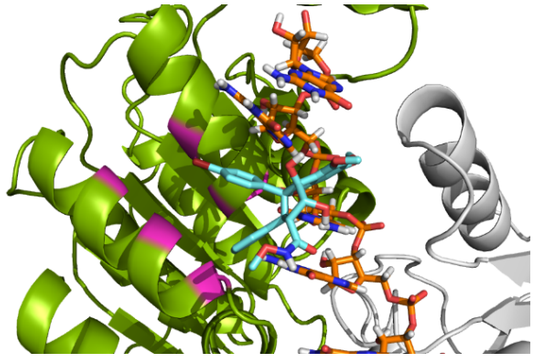


H458 Medulloblastoma
Hela Cervical
NPCIS 5464
HCT15 Colon MIN
CH157 Meningioma

D283 Medulloblastoma
MCF7 Breast
NCI-H1963 Lung small cell
SW620 Colon CIN

GDM1 AML
NCI-H929 Myeloma
MM1.S Myeloma
M091 ETV6-NTRK3

Science **2013**, *341*, 1238303



Homology model for eIF4A
(with Sandor Vajda and Dmitri Beglov)

BOSTON UNIVERSITY

"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"

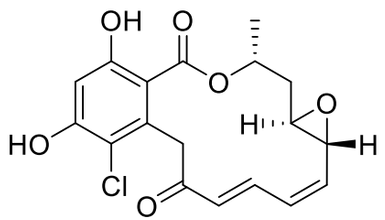
Lauren Brown, PhD

Research Assistant Professor, Chemistry, College of Arts & Sciences

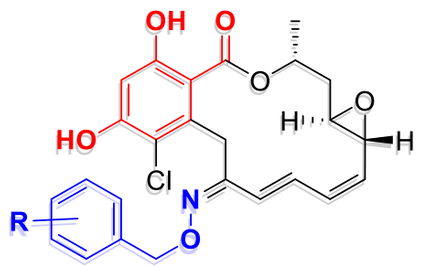
“Repurposing” anticancer drugs to target antifungal drug resistance

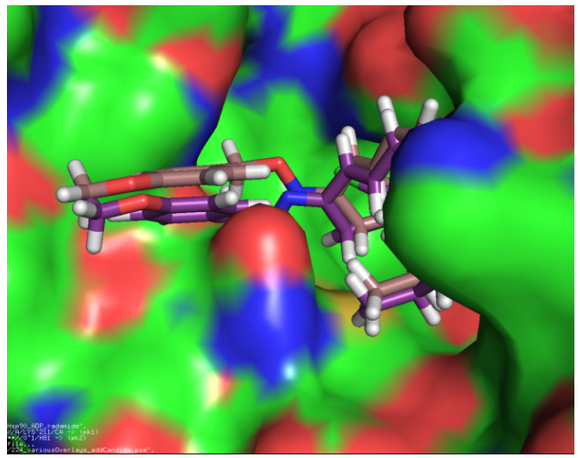
Leah Cowen (University of Toronto) *Luke Whitesell (The Whitehead Institute)*

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

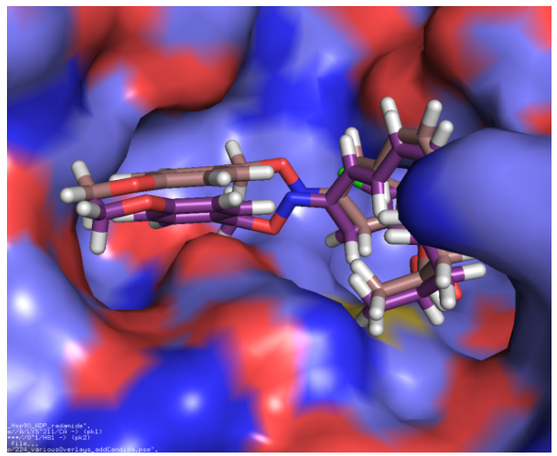


radicicol

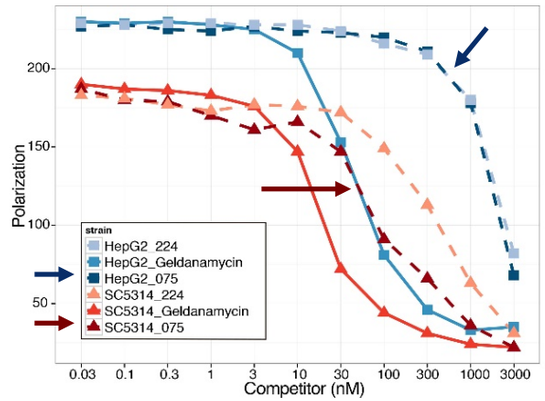


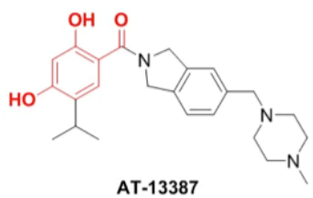


Human Hsp90

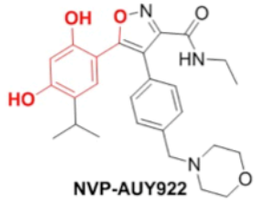


***C. Albicans* Hsp90**

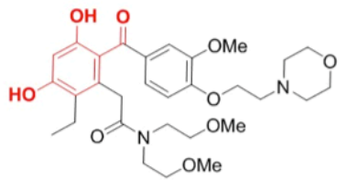




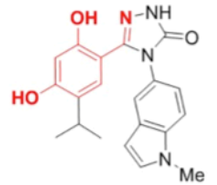
AT-13387
Astex Therapeutics
Hsp90 IC_{50} = 0.7 nM



NVP-AUY922
Novartis
Hsp90 IC_{50} = 13-21 nM



KW-2478
Kyowa Hakko Kirin
Hsp90 IC_{50} = 3.8 nM



STA-9090 (Ganetespib)
Synta Pharmaceuticals
Hsp90 IC_{50} = 4 nM

BOSTON UNIVERSITY

"Drugging the undruggable: Creating new opportunities for treating brain disorders"

Tyrone Porter, PhD

Associate Professor, Mechanical Engineering, College of Arts & Sciences

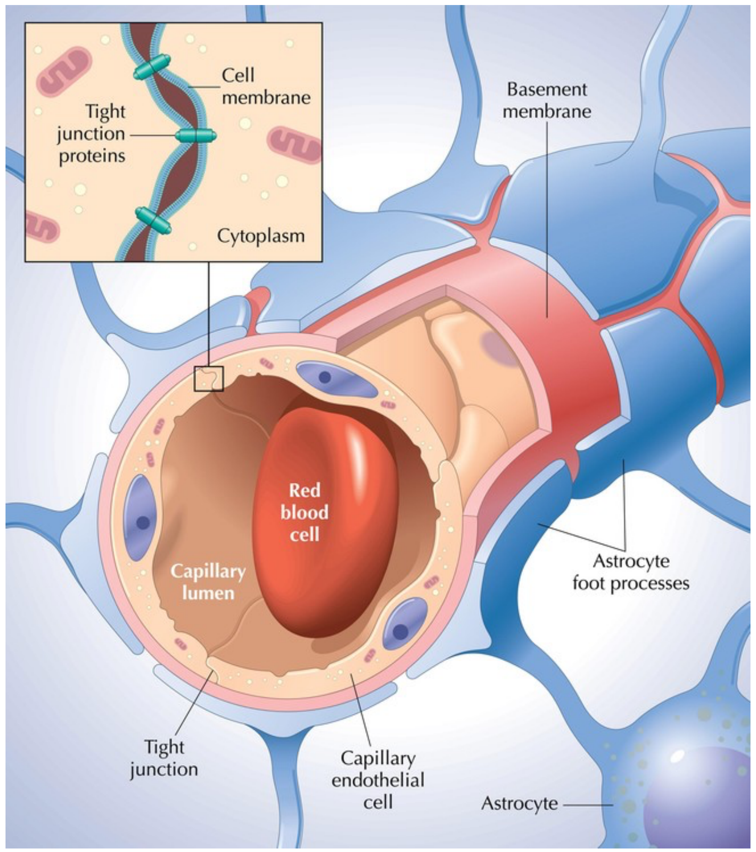
Receptor-mediated transcytosis

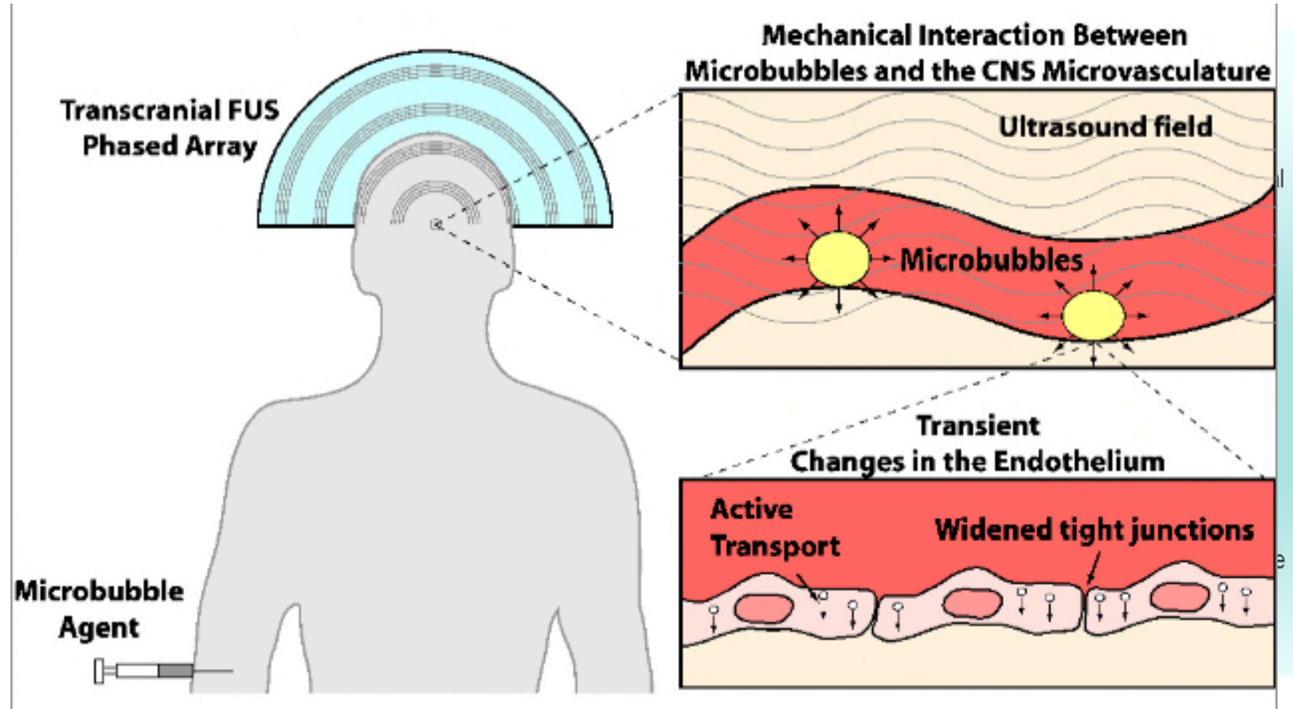
Ultrasound-mediated BBB disruption

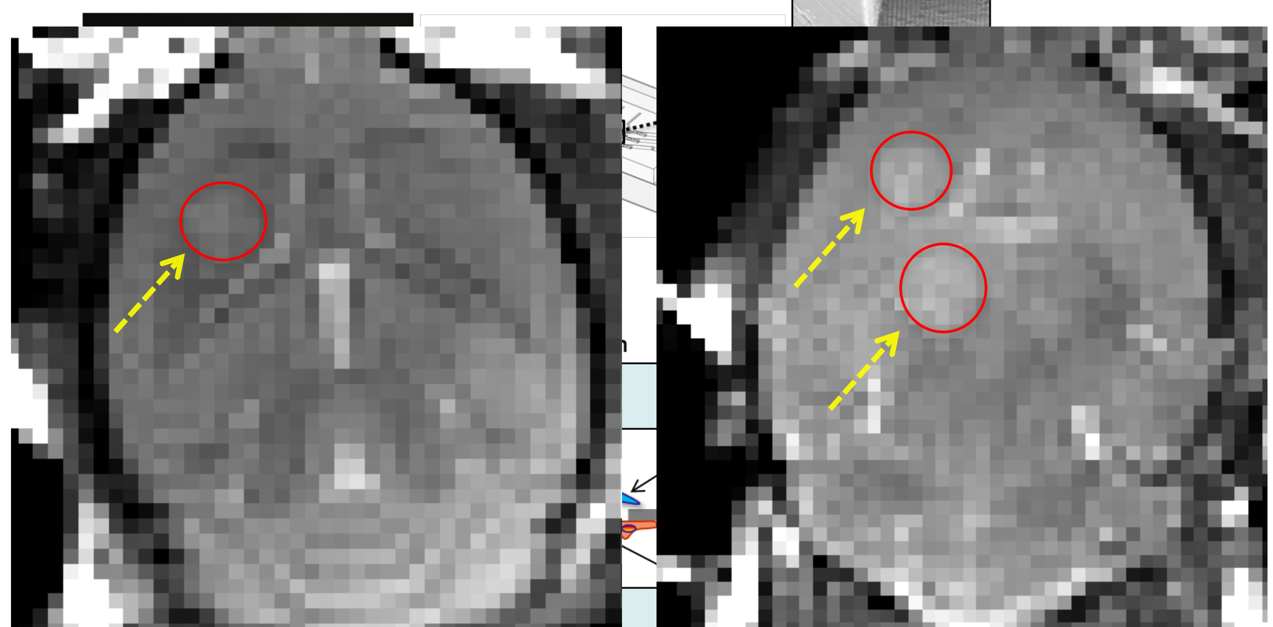
Static BBB model

The brain is the most protected organ in the body. Less than 5% of pharmaceuticals circumvent the BBB and systemically gain access to the brain due to the activity of the blood-brain barrier.

We are pursuing biochemical/biomolecular and mechanical approaches to circumvent the BBB and administered systemically and enable delivery of various therapeutic agents to the brain.







5 hrs after FUS/BBBD

24 hrs after FUS/BBBD

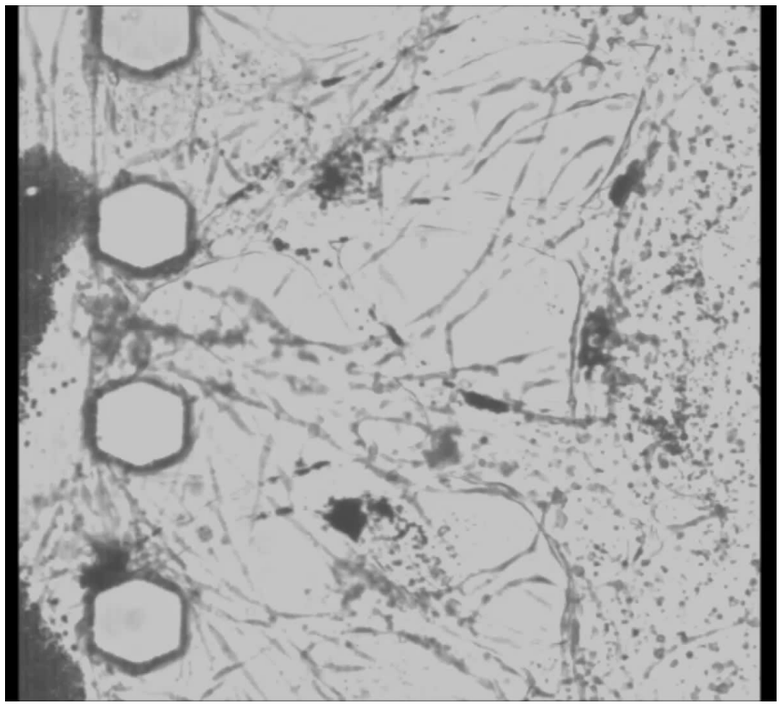
Dynamic BBB model

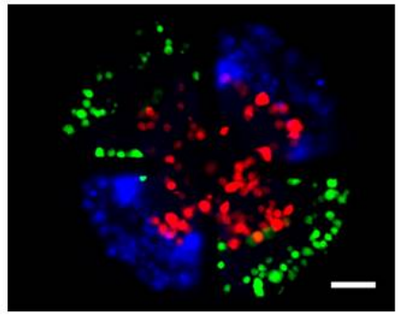
"Theranostics and In Vitro Models of Metastasis"

Joyce Wong, PhD

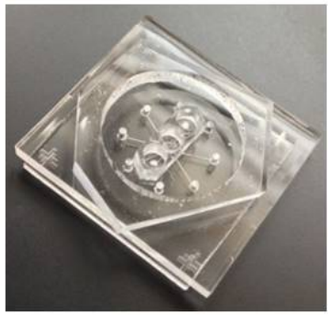
Professor, Biomedical Engineering, College of Arts & Sciences

In vitro models of cancer to test theranostic agents

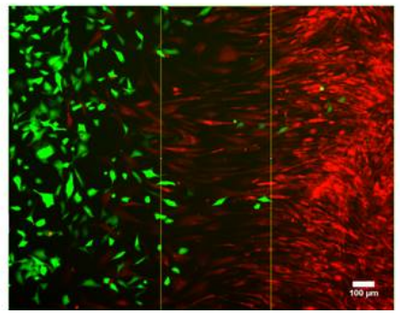




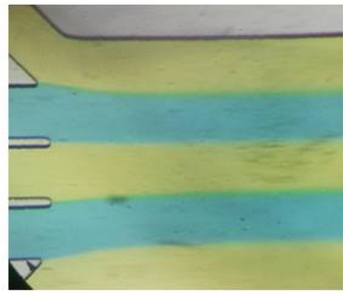
Biomimetic

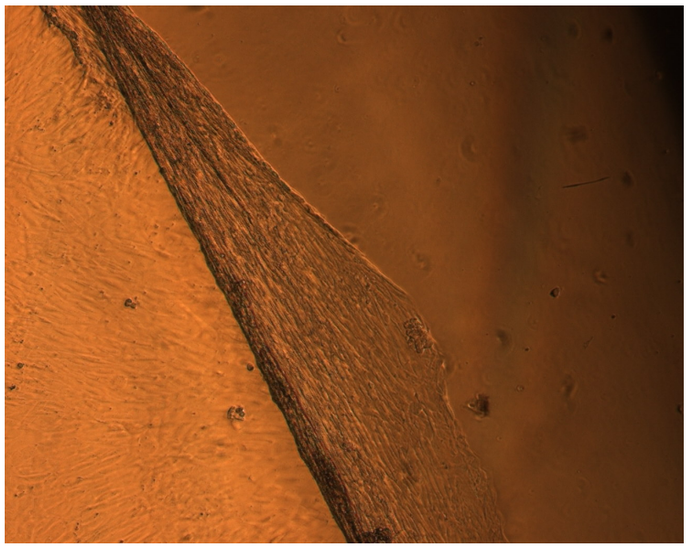


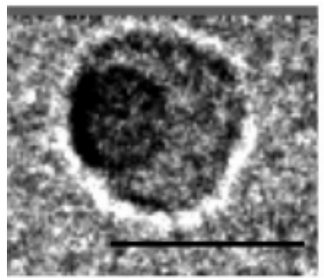
Microfabrication + Engineering

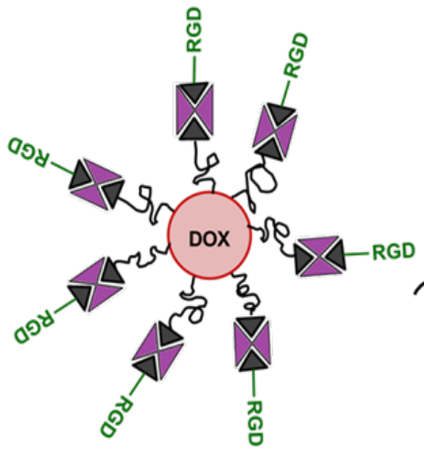


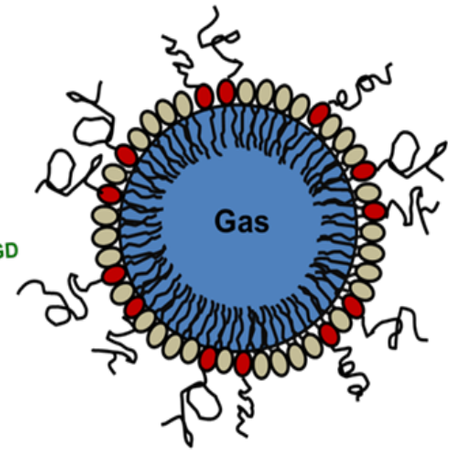
Cancer











"Inhibitors of transcription factor LSF oncogene in hepatocellular carcinoma"

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

Depts. Biology & Chemistry, College of Arts & Sciences

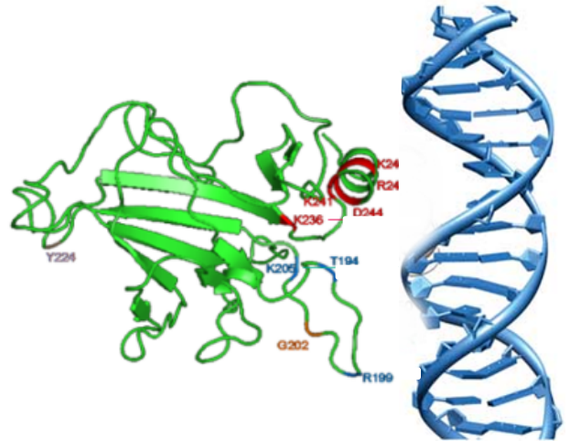
Unmet Medical Need:

HCC – Second leading cause of cancer deaths worldwide

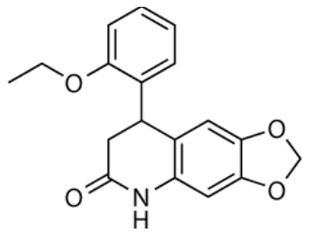
Numerous failed clinical trials, using **Protein Kinase** inhibitors

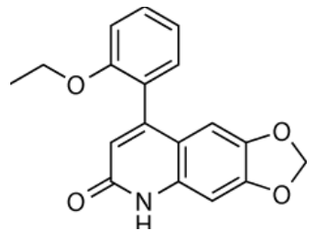
Solution? – Additional Target

Transcription factor LSF – Drives HCC Oncogenesis

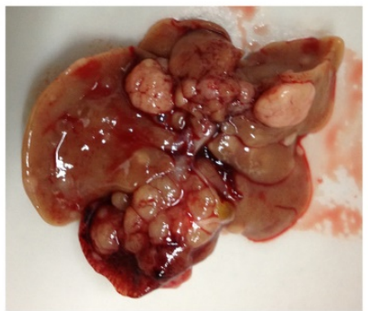


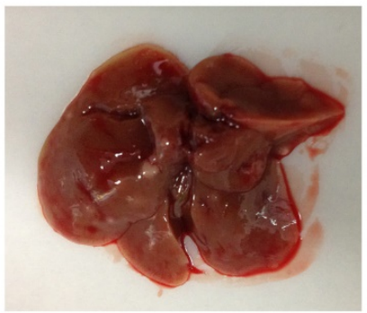
Novel, 1st-in-class specific LSF inhibitors:





DMSO FQI1 FQI2





Tumor growth inhibition, regression

No detectable toxicity

Effective Combinatorial Therapies for Hepatocellular Carcinoma?

III. Legal/IP

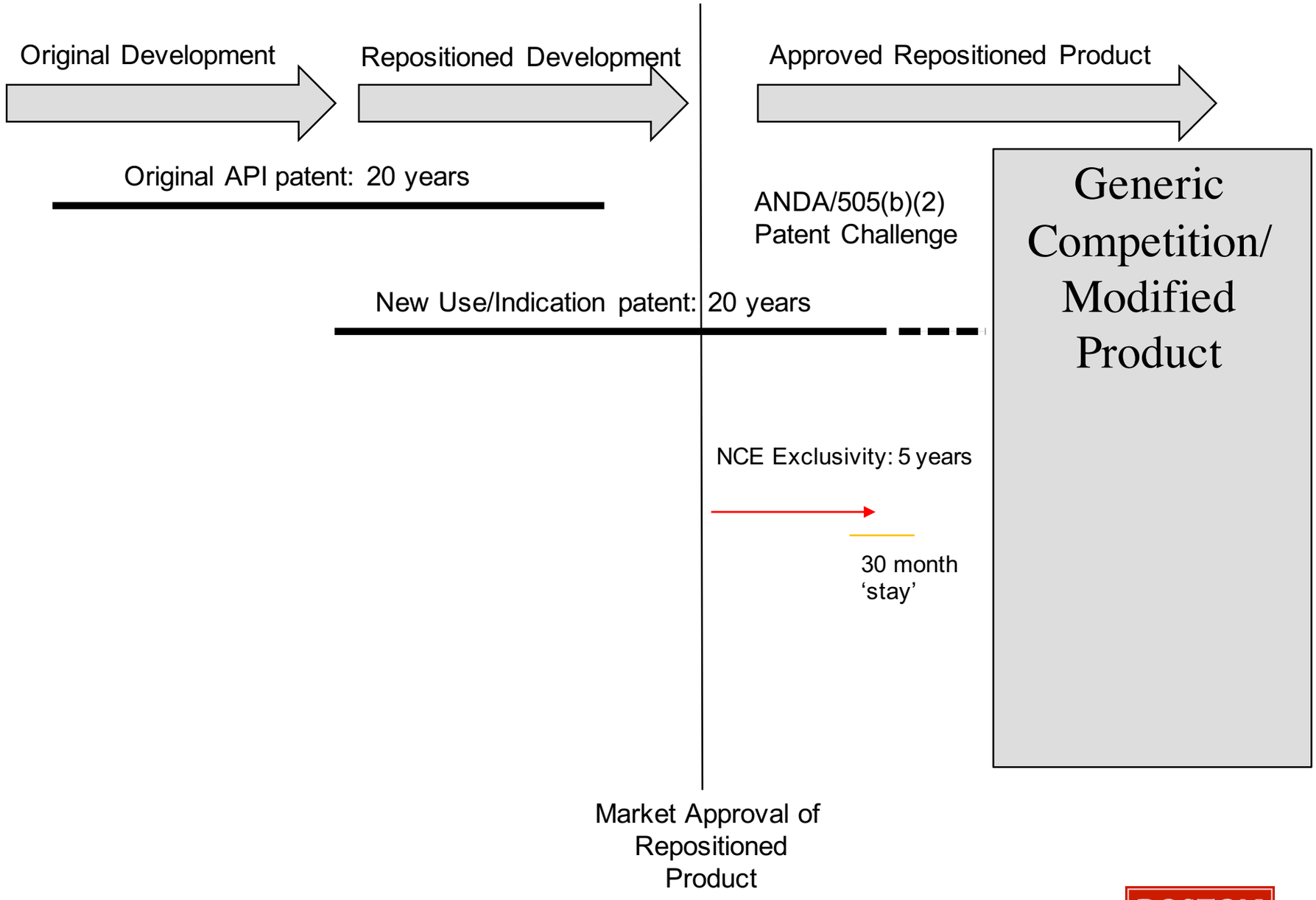
- **"Repositioned Medicines: Overview of Patent and Regulatory Interactions"**
  Warren Kaplan, PhD, JD, MPH, Clinical Assistant Professor, Global Health, School of Public Health

- **"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



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**