Balancing Hypothesis Driven and Empirical Drug Discovery

All we are saying is Give PDD a Chance

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Today’s Talk

• Background and Definitions
  – PDD/TDD
  – Pharma is a Risky Business
  – What happened to the Genomics Revolution?

• A PDD Case Study: Angiogenesis
  – Molecular Target and Chemical Diversity
  – Potent Actives: novel MOA, SOC, active in vivo
  – Target/Pathway Deconvolution

• PDD Thoughts and Observations
  – Multi-dimensional Trade-offs: Science/Business
  – Technical, Translational models, Competitive environment, SOC differentiation, project timelines, risk management….
Macro/Micro Views of Biology/Pharma

- Disease Models
- Mechanism Models
- Patients
- Cellular Surrogates
- Molecular Mechanisms
- Target Validation

- Classic Gene-specific
- Hypothesis & Mechanism
  - Targeted Drug Discovery “TDD”

- Physiology Based
- Empirical & Functional
  - Phenotypic Drug Discovery “PDD”
TDD and PDD: Integration/Differentiation

- **TDD:**
  - Molecular target hypothesis

- **PDD:**
  - Target agnostic/empirical
  - Functional, morphological translational readouts
  - Signal Transduction “Mechanism Informed PDD”

- **PDD should not be**
  - defined by # or types of compounds
  - confused with use of phenotypic assays for other purposes
Four Decades of Pharma Productivity

Data from FDA and PHRma
Courtesy of Ellen Berg and Bernard Munos
Drug Discovery is Risky Business

- 4-12 b$/drug (1997-2011)
- Increase p(TS) of Ph 2/3 provide greatest “bang for the buck”
- “there is no low-risk strategy in pharmaceutical R&D. There is good and bad risk that must be mitigated.”

- 835 drug developers (biotech, specialty & large pharma) 2003-2011
- 7300 development paths, all indications


- The productivity crisis in pharmaceutical R&D Fabio Pammolli (2011), Nature Reviews Drug Discovery 10, 428-438
- The Truly Staggering Cost Of Inventing New Drugs, Matthew Herper (Feb 2012) Forbes: Pharma & Healthcare

Clinical Failure, a Key Leverage Point

Failure Analysis: 359 Ph3 & 95 NDA/BLA
Clinical development success rates for investigational drugs

One solution...better target selection and validation

Validated Pairs ≥ 1 project finished clinical trials and pre-registration

74% are singletons, only one on market

22% ≥ 5 successful projects (multiple on market)

Many failures in “validated” Mechanism-Indication Pairs

The “Me Too” or “Fast Follower” strategy also has risk

Target Validation and Pharma Innovation


Target Validation is difficult
- Target Novelty decreases in clinical phase
- >50% Phase III targets are active in 3 or more major Pharma
- ~27% of Phase III targets are “unique”
- ~10 first in class drugs launched/year, fairly constant/perhaps improving
What happened to the Genomics Revolution?


Additionally, 65% of published TV studies show “inconsistencies” warranting project discontinuation - Prinz 2011, Nature Reviews Drug Discovery 10, 712

HGS: first human exon data


“Dark Matter” in Target Space

Plenty of Intellectual "Dark Matter" in Target Space
Drug Targets & Human Proteome
- Known Drugs (3%)
- Tool Compounds (6%)
- “Unliganded” Proteome (91%)
  - 53% some biological annotation
  - 38% no known function
  - 31% known drug target families (GPCR, NHR, kinase, channel, transporter, transcription factor, enzymes, or epigenetic proteins)

Sole reliance on TDD, in the long term, may be problematic and impede development of innovative medicines for unmet and underserved medical needs


http://www.nature.com/nrd/posters/druggablegenome/nrd_druggablegenome.pdf
Drug Discovery is a high risk business

Productivity and innovation is flat

“Me Too” drug strategies, although lucrative in the past, may not be sustainable in the future

The impact of the “genomic revolution” to drug discovery may have been mitigated by issues related to Target Validation

Drug Efficacy (possibly TV) is the primary reason for clinical failures
How are new medicines discovered?

- Phenotypic Drug Discovery
  - Overall rate higher, ~10% Pharma LG used PDD
  - Under estimated intrinsic pTS of PDD
  - Disproportionate NME contribution

- PDD Small Molecule
  - 62% First in class
  - 27% Follower

- TDD Small Molecule
  - 38% First in class
  - 74% Follower
A PDD Case Study: Neovascularization MTS

Model Selection:
- What is “validation”?
- Incomplete knowledge
- Rule of 3
- Chain of Translatability
- In vitro / in vivo correlations

Traktuev et al 2009 Circ Res 104, 1410

Z’ >0.4
MSR = 2.2
Hit expansion: 11% hit @ >60% confirm
Structure-based, chemo-informatics methods can model phenotypic endpoints

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<table>
<thead>
<tr>
<th>Hit Expansion Method</th>
<th>Hit Expansion Actives (%)</th>
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<tr>
<td>2-D Scaffold Hopping</td>
<td>20</td>
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<tr>
<td>ROCS</td>
<td>17</td>
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<td>Similarity Searching</td>
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<td>SVM</td>
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Hundreds of new clusters identified
Phenotypic Actives are Biologically Diverse

Chemical Diversity Selection

What’s the goal?
- Repurposing
- New function/known drug class
- Novel MOA

Annotated libraries
- Tool compounds/drugs
  - “expected” pharmacology?
- MOA collections
  - Informs on known targets and cellular mechanisms
- Used for flow scheme design!

Consider the compounds
- Promiscuity
- Activity profile redundancy
- in silico properties

Confirmed IC50 < 3.5 uM
No overt cytotoxicity
No G2M activity
## Comparison of PDD Actives With Standards of Care

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<th>Compound A</th>
<th>Compound B</th>
<th>Compound C</th>
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<tr>
<td>Tube Area Inhib (IC50)</td>
<td>0.021 uM</td>
<td>0.041 uM</td>
<td>0.144 uM</td>
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<td>NA (Nuc. Area) Cytotoxicity (IC50)</td>
<td>&gt; 10 uM</td>
<td>&gt; 10 uM</td>
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<tr>
<td>G2M Cell Cycle (EC50)</td>
<td>&gt; 10 uM</td>
<td>&gt; 10 uM</td>
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**Kinome**

**Sutent**
- Tube Area Inhib (IC50) | 0.0096 uM | 0.00421 uM | 5.4 uM |
- NA (Nuc. Area) Cytotoxicity (IC50) | > 10 uM | 5.46 uM | > 10 uM |
- G2M Cell Cycle (EC50) | > 10 uM | > 10 uM | >10 uM |

**Nexavar**

**Dasatinib**

**Kinome**
Phenotypic Active Inhibits Vascularization in a U87MG Xenograft Model After Oral Dosing

- Establishes in vitro/in vivo correlation
- Highlights potential of in vitro ECFC ADSC cord model
- PDD “front loads” in vivo resources
- Used for early confirmation/determination of in vitro-in vivo correlations

**CD31** (endothelial cords)  
**Hoechst** (nuclei)  
**SMA** (pericytes)
Novel Angiogenesis Targets Identified

Prompted investigation of “functional” deconvolution approaches
Metabolon Technology

- Metabolite analysis by mass spectroscopy
- Performed in Angio cellular system

Global Biochemical Pathway Changes

- Disease Biomarkers
- Mechanistic Toxicology
- Drug MOA
- Cellular Characteristics

Biochemical Interpretation

- Pathway analysis
- Literature

Heat Maps by Pathway
**Metabolon Highlights**

- 385 Analytes detected
- Metabolite changes related to angio inhibition
- PDD lead differentiated from standard of care
- Verification of unique MOA for PDD lead
BioSeek Technology: BioMAP® Systems

- BioMAP Systems integrate biological complexity
- Complex Cell-Based In Vitro Models of “Human Disease”
BioMap and Mechanism of Action

Lilly-5 (HDAC inhibitor) Versus Vorinostat

- Vorinostat – HDAC inhibitor

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<tr>
<td>mTor Inhib Bioseek</td>
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<td>HMG CoA reductase</td>
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<td>PI3K BioSeek</td>
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<td>Combretastatin</td>
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<tr>
<td>Nocodazole</td>
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<tr>
<td>Sutent</td>
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<td>oligomycin</td>
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Lilly-20 (combretastatin) Versus Colchicine

- Colchicine – Microtubule Destabilizer
- Inhibits microtubule polymerization

Pilot: Correct classification of all “standards” from BioMap profile in blinded study
Active/Inactive Analogs: PDD Compounds

- BioMap Profiles reflect Angio related activity
FHA Molecules & Mitochondrial Dysfunction

Oligomycin (Lilly 40) Identified by BioSeek

TP @ 300 nM and Oligomycin

Rotenone – Inhibitor of mitochondrial complex I

Consistent with Metabolon data
PDD Actives: Unfavorable MOA
Metabolism-Angio Connection

- Mitochondrial Dysfunction
- Prolyl hydroxylase Activation
- Increased HIF degradation
- Downstream HIF events

Metabolite changes thought to affect HIF activity (*) Unique to ANGIO+:
- Ascorbate
- α-KG
- X-11866

Metabolism - Angio Connection

HIF (HIF-1α/ HIF-2α)

ANGIOGENESIS
1. Aminopeptidase Activity
   - Glycine
   - Glutamate
   - Glutamine
2. ECM Modulation
   - Trans 4-Hydroxyproline
   - Proline

GLUCOSE UPTAKE
1. Glucose
2. TCA Metabolism
   - Citrate
   - Succinate
   - Fumarate
   - Malate

GLYCOLYSIS
1. Glycolytic Activity
   - Fructose 6-P04
   - P-1,2-BPG
   - 1,8-BP
   - 3-PG
   - DHAP
   - Lactate

LIPID METABOLISM
1. Fatty Acid Synthesis
   - Omega-6FA
   - EFA
2. TCA Metabolism
   - Citrate
3. Pentose Phosphate Metabolism
   - Ribulose 5-P04
   - Xylose 5-P04
   - UDP-Glucose

Metabolite changes consistent with decreased HIF activity
Takeaways

- Tactical concerns mitigated
  - Specificity, SAR and optimization w/out molecular target
- Physiological relevant in vitro system
  - In vitro-in vivo biology correlated
- Ready identification of novel MOAs
- PDD is difficult
  - Resource front loading, time to enable flow schemes, prioritization of actives, earlier ADME and in vivo resources
- PDD is risky, no magic bullet
  - Ongoing learning, Dynamic flow schemes, “out of box” mindset to evaluate novel MOAs is very helpful
- PDD provides access to the unliganded proteome (91%)
- PDD may help break the “Me Too” Pharma mentality
Striking the Molecular-Empirical Balance

**Resources and Prioritization:**
- TDD seems easier
- TDD is “process friendly”
- PDD is not easy..."less clear"
- Operations in a cost/FTE limited environment
- Prioritize TDD vs/& PDD?

**Opportunity:**
- >90% proteome not drugged
- Biological relevance of orthogonal chemical diversity
- Leverage network biology & poly-pharmacology
- Genome wide technologies

**Innovation:**
- Fewer “Me Too”?
- Potential longer market exclusivity?
- Unmet Medical Needs?

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**Balance:**
- Risk, Timelines, Profits
- Innovation, Unmet medical need, Novel therapeutic mechanisms, are we mining the "tip of the iceberg"?
- Appropriate risk/benefit for current organizations?

**Pharma Productivity:**
- Empirical vs Hypothesis driven LG
- Clinical Failure Rates and TV
- Crowded Drug Target Space
  - First in Class...few winners
  - Differentiation from SOC
  - “Me Too” sustainable?
Final Thoughts:

‘We don’t know a millionth of one percent about anything.’
– Thomas Edison

‘Mr. Edison, please tell me what laboratory rules you want me to observe.’ ‘Hell! There ain’t no rules around here! We are tryin’ to accomplish somep’n!’

– Conversation between Thomas Edison and M. A. Rosanoff, a recent hire at the ‘Invention Factory’ West Orange, New Jersey in 1903.
Many, Many Thanks!

Eli-Lilly & Company

- Ellen Berg
- Eugene Butcher
- Bernard Munos
- David Swinney

### Lab
- Wendy Gough
- Sarah Oliver
- Renee Vaughn
- Brian Getman

### Angiogenesis
- Mark T. Uhlik
- Chris Moxham
- Dirk Tomandl
- Daniel J. Sall

### OIDD/PD² Science
- Shaoyou Chu
- Karen L. Cox
- Rachelle Galvin
- Francis S. Willard
- Alan Palkowitz

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