Personalized Cardiovascular Medicine and Drug Development

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Outline

• Overview of Pharmacology and Drug Development
• Disease Networks and Identification of Drug Targets
• Quantitative (Patho)phenotypes in Clinical Trials
• Network Dynamics and Implications for Clinical Trial Design
• Approaches to Clinical Trial Design in the Era of Personalized Therapies
Overview of Pharmacology and Drug Development
Brief History: Key Paradigms

• *Empirical Physiological Effects*: Phenotypic Screening

• *Toxicity Assessment*: Animal (and Human) Experimentation

• *Reductionist Drug Target Identification*—Ehrlich’s ‘Magic Bullet’ Concept

• *Chemotherapy & Receptor Constructs*


• *Protein Structure and Rational Drug Design*
FDA Approved Drugs: 2000-2012

Approved Drugs

Year

2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
Reasons for Declining Productivity

• Regulatory environment
• Increasing need to explore novel targets
• Easy targets have been exhausted.
• Increasing attrition rate for developing drugs

• The intrinsically flawed reductionist approach to drug development, i.e., the need to identify a single drug target with a single “magic bullet”…a timely example follows.
Homocysteine Theory of Atherothrombosis

• First proposed by McCully (Am.J.Path. 1969; 56:111)

• Evidence from over 30 studies suggests that even mild-to-moderate elevations of plasma homocysteine confer a significant, independent risk for atherothrombosis.

• Hyperhomocysteinemia found in 20-40% of patients with vascular disease, but in only 2% of unaffected individuals
Homocysteine Metabolism

1: Methionine Synthase
2: MTHF Reductase
3: Betaine-homocysteine Methyltransferase
4: Cystathionine-beta-Synthase
Vitamin Rx, Homocysteine, & CV Risk

NORVIT Trial

3749 pts. s/p AMI

- Folic acid/B₁₂ and B₆
- B₆
- Folic acid/B₁₂

Placebo

Folic Acid (mg) 0.8 0.8 0 0
B₁₂ (mg) 0.4 0.4 0 0
Pyridoxine (mg) 40 0 40 0

No. at Risk
Folic acid/B₁₂ and B₆ 937 795 745 517
Folic acid/B₁₂ 935 812 764 518
B₆ 934 805 766 511
Placebo 943 823 771 523

Years of Follow-up

HOPE-2 Trial

5522 pts. w/ CVD or diabetes

- 2.5 mg Folic Acid
- 1.0 mg B₁₂
- 50 mg pyridoxine

Log-Rank P=0.406

No. at Risk
Placebo 2758 2633 2481 2327 2180 948
Folate 2764 2633 2479 2330 2179 965

Years
Folate, B$_{12}$, and Homocysteine

Methionine

Folate, B$_{12}$

Homocysteine

B$_6$

Cystathionine
Biomedicine in Network Context
Biomedicine in Network Context

Folate Metabolism

HCY Metabolism
Biomedicine in Network Context

Intermediary Metabolism

Folate Metabolism

HCY Metabolism
Folate, B₁₂, and Homocysteine

DNA Synthesis → Cell Proliferation

Increased Angiographic Restenosis post-PCI (Lange et al., NEJM, 2004)

N⁵,1⁰-CH₂-THF
N⁵-CH₃-THF

dTMP → DHF → THF → Methionine → SAM

Betaine → DMG

Homocysteine ← SAH

Modify Gene Expression ← CpG DNA Methylation
Impair NO Synthesis/EC Function ← ADMA Synthesis

Acceptor
Methyl-Acceptor
Disease Networks
and
Identification of Drug Targets
Enhancing Productivity in Drug Discovery

Can we move from reductionism to systems-based approaches in drug discovery? The universe within which a drug acts considered as a complex networked biological system....
Essential vs. Disease Genes in Network Medicine

*Disease genes are largely nonessential and do not encode hubs.*

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--Barabasi, et al., Nat Revs Genet 2011;12:56-68
Network Modularity and Disease

*Disease modules are topologically and functionally distinct network modules.*

Disease Module Derivation

- Identify disease phenotype of interest (example--*pulmonary arterial hypertension*).
- Ascertain disease network components.
- Construct disease network (*i.e.*, determine the structural or functional linkages among module components).
- Identify disease module(s) within network.
PAH Network Derivation

Disease components derived from curated literature, or gene, protein, or metabolite profiles.
PAH Network Derivation

PAH Network Components
(131 Nodes, 26 Functional Pathways)

Consolidated Interactome
(11,643 Nodes, 100,791 Edges)

Consolidated interactome of all known physical interactions: PPIs and Protein Complexes (CORUM), Regulatory Protein-DNA Interaction (TRANSFAC), Metabolic Enzyme-coupled Interactions (MCIs), Kinase Network
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PAH Network Derivation

PAH Network
(115 Nodes, 255 Edges, Largest Connected Component = 82 Nodes)
Interactome-derived PAH Network

--Parikh et al., Circulation 2012;125:1520-1532
MicroRNAs as Network Filters

- Select miRNAs are induced by stresses and disease states.
- Unbiased ascertainment of miRNA targets
- Induced miRNAs target common pathways.
- Induced miRNAs suppress common mRNA targets.

-- Chan et al., Cell Metab 2009;10:273-84
PAH Network Derivation

PAH Network Components
(131 Nodes, 26 Functional Pathways)

Consolidated Interactome
(11,643 Nodes 100,791 Edges)

PAH Network
(115 Nodes, 255 Edges,
Largest Connected Component = 82 Nodes)

PAH miRNAs
(155 Nodes)

PAH miRNAs
(29 Groups)

Hypergeometric Analysis and Ranking

Hypoxia
Inflammation
TGF-β

--Parikh et al., Circulation 2012;125:1520-1532
MicroRNA Network Analysis in PAH:

--Parikh et al., Circulation 2012;125:1520-1532
MicroRNA Network Analysis in PAH

--Parikh et al., Circulation 2012;125:1520-1532
miR-21 serves as a negative regulator of pathogenic pulmonary vascular responses in PAH.

--Parikh et al., Circulation 2012;125:1520-1532
PAH and miR-21 Disease Module: Potential Drug Targets

--Parikh et al., Circulation 2012;125:1520-1532
Disease Modules and Therapeutics

*Drug targets are typically characterized in isolation from the disease module.*

--Modified from Barabasi et al., Nat Revs Genet 2011;12:56-68
Target-based Screening

Facilitated by:

- Genomic datasets for target identification
- Structural tools, including protein X-ray crystallography, NMR spectroscopy, computational modeling
- Large real and virtual compound libraries
- High-throughput screening technologies
Disease Modules and Therapeutics

*Drug targets are better characterized with regard to their effects on phenotype.*

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Topological module

Functional module

Disease module

- Topologically close genes (or products)
- Functionally similar genes (or products)
- Disease genes (or products)
- Undirectional interactions
- Directional interactions

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--Modified from Barabasi et al., Nat Revs Genet 2011;12:56-68
Drug Discovery Strategies: Success Rates

<table>
<thead>
<tr>
<th>Screen</th>
<th>N=83</th>
<th>N=30</th>
</tr>
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<tbody>
<tr>
<td>Target-based</td>
<td></td>
<td></td>
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<tr>
<td>Phenotype</td>
<td></td>
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</tbody>
</table>

Percentage of NMEs

First-in-Class

N=17

N=28

The Promise of Personalized Medicine: Find the Target

Before Rx

--Wagle et al., J Clin Oncol 2011;29:3085-3096
The Promise of Personalized Medicine: Inhibit the Target

Before Rx  
BRAF mut  
Activated oncogenic pathway

Vemurafenib—15 wks

Inhibition of oncogenic pathway

Disease response

--Wagle et al., J Clin Oncol 2011;29:3085-3096
The Peril of Personalized Medicine with Conventional Strategy

Before Rx

Vemurafenib—15 wks

Vemurafenib—23 wks

BRAF<sup>mut</sup>

MEK<sub>1</sub><sup>C121S</sup>

--Wagle et al., J Clin Oncol 2011;29:3085-3096
Pathway Targeting: Combination Rx

Combination therapy: dabrafenib (BRAF inhibitor) & trametinib (MEK inhibitor)

--Flaherty et al., NEJM 2012;367:1694-1703
Disease Modules and Therapeutics

Disease modules should be targeted with rational polypharmacy for optimal effects on phenotype.

--Modified from Barabasi et al., Nat Revs Genet 2011;12:56-68
Drug Toxicities as Systems Response

Unrecognized drug targets lead to toxic phenotypes.

Topological module

Functional module

Disease module

Unrecognized Drug Targets

Toxic Phenotype

--Modified from Barabasi et al., Nat Revs Genet 2011;12:56-68
Drug Toxicities as Systems Response

Increased upstream species can yield toxic phenotypes.

---Modified from Barabasi et al., Nat Revs Genet 2011;12:56-68
Drug Side-effect Predictions: CETP Inhibitors

Structural similarity networks coupled with systems analysis of pathways can be used to predict adverse effects of drugs.

--Xie et al., PLoS Comp Biol 2009;5:e1000387
Systems-based Drug Discovery

Experimental Focus

**Disease**
- Characterize Disease Network

**Drug**
- Characterize Pharmacologic Action
- Identify Emergent Properties (‘off-target,’ unanticipated)

Network Analysis
- Perturb Network: Characterize Emergent Properties & Control Nodes

Initial Conditions

Iterative Refinement

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Quantitative (Patho)phenotypes in Clinical Trials
Why Does Phenotype Screening Continue to Surpass Target-based Screening?

• The chosen target is wrong.
• The chosen target is reasonable, but the networked architecture of the system within which it functions is redundant, clustered, and adaptive.
• The phenotype is imprecise.
• Combinations of the above
Why Does Phenotype Screening Continue to Surpass Target-based Screening?

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Toward Precision Medicine

National Research Council
of the National Academies
Recommendation for New Disease Taxonomy

“A new disease taxonomy should be developed that would:

– describe and define diseases based on their intrinsic biology in addition to traditional physical ‘signs and symptoms’;

– go beyond description and be directly linked to a deeper understanding of disease mechanisms, pathogenesis, and treatments; and

– be highly dynamic…continuously incorporating newly emerging…information.”
Approaches to ‘Exquisite’ Phenotyping: Clinical Phenotypes

• Database of Genotypes and Phenotypes (dbGaP)

• Phenome-wide Association Studies (PheWas) (cf. Denny et al., Bioinformatics 2010;2605-1210)

• Electronic Medical Records and Genomics (eMERGE)

Approaches to ‘Exquisite’ Phenotyping: Other

• Imaging Data Sets & Machine Learning
• Orthogonal Unbiased Information (UK BioBank & Keystroke Data)
• Diagnostic and Drug Data Bases (cf. Ponda et al., Circulation 2012;126:270-7)
Network Dynamics
and
Clinical Trial Design
### Systems-based Clinical Trial Design

#### A. Original CoumaGen Trial Design
- 200 patients were recruited and underwent randomization
  - 101 PGx
  - 99 STD
  - Initial dose = PGx algorithm x 2 (days 1 - 2)
  - CoumaGen PGx dose adj. protocol (days 3 - 7)
  - Intermountain protocol (days 8 - 90)
  - Measure INR and adjust dose based on specific protocol (days 2 - 90)
  - Compute results of PGx arm

#### B. CoumaGen Simulation 1
- 200,000 clinical avatars were generated and underwent randomization
  - 101,000 PGx
  - 99,000 STD
  - Initial dose = 10 mg (days 1 - 2)
  - CoumaGen PGx dose adj. protocol (days 3 - 7)
  - Intermountain protocol (days 8 - 90)
  - Predict INR and adjust dose based on specific protocol (days 2 - 90)
  - Randomly select 101 PGx and 99 STD avatars and compute trial outcomes. Repeat 1,000 times.
  - Compute results of PGx arm

#### C. CoumaGen Simulation 2
- 200,000 clinical avatars were generated and underwent randomization
  - 101,000 PGx
  - 99,000 STD
  - Initial dose = PGx algorithm x 2 (days 1 - 2)
  - CoumaGen PGx dose adj. protocol (days 3 - 7)
  - Intermountain protocol (days 8 - 90)
  - Wilson dose adj. protocol (days 3 - 90)
  - Predict INR and adjust dose based on specific protocol (days 2 - 90)
  - Randomly select 101 PGx and 99 STD avatars and compute trial outcomes. Repeat 1,000 times.
  - Compute results of PGx arm

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--Fusaro et al., Circulation 2013;127:517-526
Systems-based Clinical Trial Design

---Fusaro et al., Circulation 2013;127:517-526---
Systems-based Clinical Trial Design

--Fusaro et al., Circulation 2013;127:517-526
Approach to Clinical Trial Design in Systems Pharmacology Era
Clinical Trial Design

Basic Trial Design

Adaptive Trial Design

--Antman et al., WIREs Syst Biol Med 2012;10.1002
Developing New Biomarkers and Patient Reported Outcomes Measures (PROs)

- C-Path Institute (nonprofit): new biomarkers for drug-induced (renal) injury (data produced by a consortium); FDA and EMA accepted; undergoing clinical evaluation
- PROMIS (NIH PRO effort)
- C-Path Institute: PROs for specific diseases
Systems Pharmacology: Visualizing Therapeutic Actions

Summary

• There are major problems with current drug development paradigms.
• Systems biology and network science provide useful approaches to identifying drug targets and rational combinations of targets.
• Clinical phenotyping must become more precise and more discriminating for optimal identification of effective therapies.
• The clinical research enterprise and the drug approval process must be transformed *pari passu*. 
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