The Complexity of Drug Discovery – New Models for the Future

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Academy and Industry in Era of Reform

- Health care payment reform will likely result in decreasing clinical revenue in AMCs, putting pressure on the Academy

- Decreased revenue from declining productivity in drug discovery pressures the pharmaceutical industry

- Exigencies create hurdles, but possibly opportunities
Convergence of Opportunities

• Drug discovery is complex

• The current pharma business model is not sustainable

• Is there a new business model building upon industry/academy collaboration?
The Road from Discovery to Clinical Product

**Roadmap Programs**
- Further Characterization
  - Small Molecule Screen
  - Chemical Probe Development
  - Chemistry Optimization

**NIH Funding**
- R01 - P01
- Basic Discovery
- Validation Mouse Model
- R01 - P01

**Pharma**
- FDA Approval
- Networks, Contracts, Cooperative Agreement
- Phase III-IV Clinical Studies
- Phase I-II Clinical Studies
- SCCORS, CTSA, tPPG, R01
- FDA IND Submission
- RAID
- Preclinical Toxicology
- RAID, SBIR, PACT
- IRB Approval

**Validation Model**
- R01 - P01

Image: Elizabeth Nabel, M.D., Partners Research Retreat 3/2010
## Representative Drugs with Strong Academic Roots to “Key Enabling Discovery”

<table>
<thead>
<tr>
<th>Academic Home</th>
<th>Academic investigator/s</th>
<th>Target</th>
<th>Therapy</th>
<th>Indication</th>
<th>Trade</th>
</tr>
</thead>
<tbody>
<tr>
<td>UT</td>
<td>Mike Brown, Joel Goldstein</td>
<td>Cholesterol</td>
<td>Statins</td>
<td>high cholesterol</td>
<td>Mevacor, Crestor, Zocor, Lipitor, et al</td>
</tr>
<tr>
<td>Many</td>
<td>David Ho, Martin Hirsch, many others</td>
<td>HIV replication</td>
<td>HAART</td>
<td>HIV/AIDS</td>
<td>Combivir, Kaletra, Trizivir, Truvada, et al</td>
</tr>
<tr>
<td>UCLA</td>
<td>George Sachs</td>
<td>Na/H proton pump</td>
<td>PPI’s</td>
<td>GERD, PUD</td>
<td>Prilosec, Nexium, et al</td>
</tr>
<tr>
<td>MGH</td>
<td>Brian Seed</td>
<td>TNF</td>
<td>anti-TNF</td>
<td>RA, Crohn’s etc</td>
<td>Enbrel</td>
</tr>
</tbody>
</table>
Economists found that most important products are discovered by industry – often building on NIH-funded enabling discoveries.

The average lag between the “key enabling discovery” and the introduction of the drug was 24 years.

Today, still 10-12 years from discovery to market.

Today, significant impediments exist in pharma for drug development. A major cause is the biological complexity of disease pathways.
Biological Complexity of Disease Pathways

- Targets of pathophysiological relevance
  - 1980’s: 100’s (receptors, enzymes, antimicrobial proteins)
  - 2000’s: tens of thousands (multiple pathways)
    - Some druggable; but prioritization difficult
    - Non-druggable targets, even if validated, require untested biological therapies (monoclonal antibodies, peptides, vaccines, RNAi, gene therapy, etc)
Historically, Pharma = Chemical Companies

- Medicinal chemists focusing on small molecules that affected these targets
- Redundancy and repetition among companies which led to drugs that were effective some of the time with tolerable side effects
Now

• Biological understanding, including human genetics, has yielded tens of thousands of targets to modify disease.

• The network based view is replacing the familiar gene->pathway->disease linear causality model since this traditional representation generally fails to account for the exceptional complexity of human biology and the intricate web of interactions associated with a particular disease phenotype.

• Many diseases, including type 2 diabetes, coronary artery disease, type 1 diabetes, and glioblastoma typically result from small defects in many genes, rather than catastrophic defects in a few genes.
The truth is we have little idea on the underlying causes of common human diseases.

We need to more fully embrace the complexity to develop a better understanding.
New Molecular Entities (Drugs) 1950-2008

Average is ~ 20 NMEs per year
Mid 1990’s saw peak of 50-60

B. Munos Nature Reviews, Drug Discovery Dec 2009
Early human phases are increasingly expensive

The cost of new molecular entities has been growing exponentially at an annual rate of 13.4% since the 1950s.

Each NME is 1,000X more expensive

The big Pharma model looks increasingly broken

- Roche: 15.711
- ABT: 8.967
- GSK: -1.441
- SGP: -6.638
- AMGN: -7.694
- BMY: -12.448
- NVS: -13.356
- LLY: -13.793
- MRK: -28.289
- WYE: -29.625
- JNJ: -41.792
- AZN: -49.024
- SNY: -58.573
- PFE: -77.299

2015 Projected Earnings (Losses) Over 5% Margin
Mergers likely won’t improve NME output

B. Munos Nature Reviews, Drug Discovery Dec 2009
Consequences of these trends

- Biotech struggling to get venture capital funding
- Pharma cutting costs
  - Mergers are a major strategy for cost reduction
    - Pfizer-Wyeth
    - Merck-Schering-Plough
    - Roche-Genentech
  - Productivity of post-merger companies not higher
  - Much of Pharma is cutting R&D expenses as well
- Reduced R&D will not fill the therapeutic pipeline
- Pharma is looking for a new model of drug discovery
- Academia also looking for a new model for its future
The academy doesn’t make drugs

- Multiple factors contribute:
  - Medicinal chemistry not strongly supported in academia
  - Financial costs of development beyond academy’s budgets
  - Expertise in key regulatory, CMC, and toxicology disciplines lacking
  - Timelines of academia not focused on patent expirations and speed
  - Promotions & recognition incentives not aligned with drug discovery process
  - Financial rewards of drug development not central to academic mission

- Unlikely that academia can overcome many of these barriers

This means that the academy will remain a minor contributor to the development of NMEs, but could be a major partner in the overall process of drug discovery
Why should academy participate in drug discovery?

- If the current system fails to deliver new drugs

- Biopharma: Loss of revenues and jobs
- Patients: Failed therapies and higher disease burden
- AHC’s: Care improvement stagnates and is less differentiated from lower cost health providers
Drug productivity crisis presents opportunity

- Academia and industry, driven by new financial exigencies, can form a new kind of partnership
- Industry brings:
  - Molecules
  - Money
  - Methodologies for moving molecules into clinic
- Academia brings:
  - Basic science knowledge of disease pathways
  - Expertise in human biology and pathophysiology
  - Patients with the disorders that need treatment
  - New technologies for assessing disease and measuring response
  - Genomic/other technologies for improved stratification of patients
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- Academy Sweet Spot
- Phase IV Clinical Studies

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Image Adapted from: Elizabeth Nabel, M.D., Partners Research Retreat 3/2010
A new partnership

- Interdisciplinary teams working in collaboration with biotech and pharma scientists
- Project management responsibilities shared, with academia overseeing activities inside our walls
- Emphasis on “pre-competitive” activities involving patient stratification, biomarkers, novel imaging, etc
- Involvement of academic teams with expertise in study design, human systems modeling, informatics
- Opportunities for collaboration with other schools such as business and law
- New approaches to IP in these relationships
Industry Needs

• Target prioritization
  – Focus on understanding “pathways”, not individual proteins

• Minimize attrition
  – Not just succeed, but fail fast

• Scientific nimbleness
  – Increase the number of smaller, more focused units while maintaining a broad portfolio (advantage of scale of big pharma)

• Early, thoughtful access to the human organism as an experimental model
Academy Needs

• Project Management
  – Ability to work according to deadlines

• Streamlined regulatory process
  – Turnaround times for:
    • IRB review
    • Contracts

• Human organism as the experimental model
  – Hallmark of Academy today with early in man capacity
    and non-invasive imaging technology
Necessity of the Consortium to Use the Human Organism as Experimental Model

- Dominant paradigm of future medical research
- Need to unite science and patient
- Facilitated by technological advances
  - Stratification of phenotype and genotype
  - Sophisticated phenotyping
  - IT growing and enabling via EMR, PHR and other networks
  - Non-invasive imaging
  - The patient as a partner in discovery