Better Drugs and Vaccines (III)

Possible Solutions;
Academic-Industry-Government Partnerships

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**Translating Science Into Innovation in Healthcare**  
*Columbia—Weill Cornell*

William W. Chin, M.D.

**Disclosures**

<table>
<thead>
<tr>
<th>Name of company</th>
<th>Type of relationship</th>
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<tr>
<td>Eli Lilly &amp; Company</td>
<td>Former employee; no current equity/comp</td>
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<tr>
<td>Catabasis</td>
<td>Member, Clinical AB</td>
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<td>Rhythm</td>
<td>Member, Scientific AB</td>
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<td>Johnson &amp; Johnson</td>
<td>Consultant—CV and Metab</td>
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<td>Takeda</td>
<td>Member, Global AB</td>
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High Hurdles

Productivity Decline in Pharma

- Costs rising faster than launches; cost/time
- Significant patent expirations
- Innovation has been incremental; defined by payors
- Pricing pressures based on generic and other considerations; SOC; CER; HTA
- Regulatory expectations are increasing; higher bars for efficacy and safety
- Personalized medicine
High Hurdles

Growing Challenges in Academia

- Declining Federal and local funding
- Lack of sufficient growth of endowments
- Increasing domestic and global competition
- Higher compliance and other reporting needs
- Erosion of political and public confidence
But A Common Problem

The promise of genomics. Not yet fulfilled.

Complexity of disease:
- Target/pathway biology is complex.
- Disease definition is imprecise.
- A disease often has multiple causes.
- Drugs work with multiple mechanisms.
- Patients with the same disease are different.

Patients and clinical samples define relevance.

Translation science and medicine: key roles.
Translational Medicine: High Hopes

- To understand better the mechanisms of human disease;
- To catalyze the discovery and development of potential medicines, devices and diagnostics.
Major source of innovation/ideas = academia. Measured by publications, IP, etc. Funding: Pharma—65%; NIH—25%; and biotech—10%. Academia is source of significant IP; but few startups. “Valley of Death;” Limited angel/VC monies.

Solutions
Create an environment that fosters innovation.

• Steven Johnson: “Reef, city and Web.”
  □ Ecosystem of academia, industry, government, NGO
  □ NCATS, other initiatives with FDA, DARPA, etc.
  □ HMS CTSC experience: Harvard Catalyst.
  □ HMS Program in Therapeutics:
    • Systems Pharmacology.
  □ Private-public partnerships.
• Need for “honest broker” or third party convener.
Solutions [Academic Perspective]

--Proactive technology offices.
--Academic and other venture-funded programs.
--Collaboration with companies and others: longer lasting collaborative relationships via--
  (1) sponsored research (individual PI and institutional);
  (2) fellowship support;
  (3) collaborative pilot grants;
  (4) shared risk-reward research;
  (5) shared laboratories;
  (6) coordinated efforts of academia, pharma, government (NIH & FDA, etc.), foundations and CROs to bridge “valley of death;”…
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(5) shared laboratories; joint
(6) coordinated efforts of academia, pharma, government (NIH & FDA, etc.), foundations and CROs to bridge “valley of death”+… joint
Translational Science and Medicine

Common Ecosystem; Common Goals
National Center for Advancing Translational Science (NCATS)

Mission: To catalyze the generation of innovative methods and technologies that will enhance the development, testing and implementation of diagnostics and therapeutics across a wide range of human diseases and conditions.

Budget: AY12: $576M ($488M CTSAs); AY13: $639M

Selected Programs:
• Rescuing and Repurposing Drugs (58 agents from 8 large pharma)*
• Identifying and Validating Drug Targets (repository and assay platform)*
• Toxicology in the 21st Century (Tox21)*
• Tissue Chip for Drug Screening
• Phenotypic Drug Discovery (NCATS Pharmaceutical Collection with 3800 known drugs/agents; collaboration with Lilly)*

*precompetitive consortia
Translational Medicine: Other Hurdles

- Insufficient workforce in the field
- Culture of the academy and institutions
- Focus on the individual versus team
- Inadequate cross-disciplinary education
- Conflict of interest; intellectual property
- Constrained fiscal resources
- Selecting the right questions
- Putting the right people together
- Access to tools and technologies
Harvard Catalyst: Translational Medicine
Improve Health Through Disruptive Innovation

- Creatively educate and grow a workforce
- Develop tools and technologies that connect and enable investigators
- Determine the best approaches to create communities of diverse investigators to solve the right questions
- Share tools and learning across the consortium
Harvard Medical School
Therapeutics Initiative

Why? Better future medicines produced faster and less expensively for patients.

How? Capitalize on HMS talent--
◆ To understand better the mechanisms of human disease using translational science and medicine;
◆ To catalyze the discovery and development of molecular tools and potential medicines (therapeutics).
What? Guiding Principles:

◆ To establish a knowledge base and culture conducive to therapeutics at HMS;
◆ To develop novel approaches to the discovery of therapeutics using the strengths of HMS;
◆ To provide a set of “vehicles” to help create molecules for use in translational medicine and science;
◆ To complement similar activities at HMS, AHCs and other affiliated institutions.
HMS Therapeutics

Disease Pathogenesis/Mechanism
Heterogeneity of Disease

Idea
Basic Science

Regulatory Science

Chemical Biology

Patients

Pharmacology (Systems Pharmacology)

Three Science Pillars
A Matrix—

Y-Axis: Science—HMS 3 Pillars
X-Axis: Education
- Virtual Drug Discovery
- Therapeutics Network
- Therapeutics Commons
Building the Harvard Medical School Therapeutics Initiative

Chemical Biology

Systems Pharmacology (LSP)

Regulatory Science

Education
Drug Discovery
Therapeutics Network
Therapeutics Commons
Interfaces
The Harvard Medical School Initiative in Systems Pharmacology (ISP) aims to transform the process of drug discovery by taking our understanding of the interactions between drugs and biological systems to a new level.

http://isp.hms.harvard.edu
Reframe pharmacology as a core discipline of translational medicine

- Determine precise drug mechanisms.
- Couple systems biology and medicinal chemistry (chemical biology).
- Understand and predict patient-patient variability.
- Understand and predict combination therapy.
Develop intellectual foundation for improving drug discovery and mitigating emerging crisis

- Improve target validation.
- Improve assays and animal models.
- Develop systematic approaches to understanding adverse drug reactions.
- Failure analysis; why do potential drugs “fail.”
Key concepts in systems pharmacology

• Combine new and classical approaches.
• Horizontal-vertical Integration.
• Multi-scale informatics.
• Multi-scale modeling.
Achieving horizontal and vertical integration in systems pharmacology
Outcomes

• Personalized (precision) medicine.

• New and better biomarkers.

• More indications and better efficacy.

• Minimizing adverse events.

• Less expensive drugs.
Shifting Knowledge Curves

(after Pisano)

[Diagram showing the shift in knowledge over time from 'Now' to 'Tomorrow']
"I see by the current issue of 'Lab News,' Ridgeway, that you've been working for the last twenty years on the same problem I've been working on for the last twenty years."
Sustainable Innovation in Challenging Times

◆ Expansion of the knowledge market is required due to novelty and complexity of diseases.
◆ Collaborative consortia are necessary to improve flow of information and consequent innovation.

Being competitive.

✓ Understand need for growing innovation.
✓ Match work with current budget realities.
✓ Marketplace rewards are needed.
✓ Expand access to information.
✓ Improve utilization of knowledge markets.
✓ Influence changes in policies that limit innovation.
What is a precompetitive consortium?

A collaborative partnership that focuses on work that increases the overall knowledge or technology base in a field, shares risks and costs, reduces duplication of effort and resource expenditure in that work, and does not ordinarily provide a competitive advantage to a specific company. The output of the consortium may be restricted or public. Unlike the competitive space, such a consortium engages in areas that are shared challenges important for progress usually involving novel and/or highly complex problems, requires a longer time-frame for resolution, and generally cannot be performed by one company.
Many examples of precompetitive or open-source consortia in pharma/academia.

Innovative Medicines Initiative
Biomarkers Consortium; HGP
Predictive Safety Testing Consortium
Alzheimer’s Disease NeuroImaging (ADNI)
SNP/HapMap Consortia; 1000 Genomes Project
Health and Environmental Sciences Institute
Serious Adverse Events Consortium
Drug Safety Executive Council
Dundee Signaling Consortium
Animal Models Consortium; C-Path
Health Commons; Enlight; Structural Genomics
Transcelerate
Key challenges faced by academia in PPPs and precompetitive consortia

- **Education/Culture**: lack of expertise and experience; applied science as a pejorative.
- **Alignment of goals**: among academia, industry government, and non-governmental organizations; need to publish and freely communicate.
- **Reward and recognition**: not optimal to promote team efforts.
- **Intellectual property**: assiduous and poorly prioritized efforts to protect IP may serve to limit collaborative opportunities; tech transfer office—friend or foe?
- **Conflicts of interest concerns**: may limit some participation.
Overlap of pre-/procompetitive and competitive spaces
Eight models of precompetitive collaboration

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<th>Build enabling platforms</th>
<th>Conduct research</th>
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<td>Develop standards/tools</td>
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<td>Linux</td>
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<td>Wikipedia</td>
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<td>Synaptic Leap</td>
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<td>Open Health NLP</td>
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<td>Generate/aggregate data</td>
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<td>Alliance for Cell Sig</td>
<td>Diabetes Genetics Init</td>
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1. Open source initiatives

4. Public-private consortia for knowledge creation

5. Prizes

6. Innovation incubators

7. Industry complementors

8. Virtual pharma companies

- Prize4Life
- X Prize Genomics
- InnoCentive
- Netflix Prize
- P&G Connect/Develop
- Biogen biP
- Siemens Tech to Bus
- Merck-AZ
- Pfizer-GSK
- MMRF
- CHDI
Asian Cancer Research Group

In early 2010, Lilly, Merck and Pfizer in collaboration with Chinese entities created an independent, not-for-profit, research “company,” ACRG, to study several cancers in the Asian population: NSCLC, HCC and gastric cancer. Patients and their tumors (2000 in each tumor-type) will be subjected to extensive phenotypic, genotypic, proteomic and ultimately longitudinal analyses to provide information about novel cancer pathways, heterogeneity of the diseases, and response to therapy. The final output will be open.

Sung et al; Nature Genetics 44:765 (2012): “Genome-wide survey of recurrent HBV integration in hepatocellular carcinoma.” HBV integration patterns in liver cell genome in hepatocellular carcinoma (HCC); ID of novel targets for treatment of HCC—CCNE1, SENP5, ROCK1 beyond TERT, MLL4
The PD² Initiative

Rationale: To enhance collaboration with academia/biotechs and increase available compound diversity for Lilly PD² efforts
Potential areas of focus for precompetitive consortia in academia and pharma

• Biomarkers: efficacy and safety.
• Predictive animal and human disease models.
• Target identification and validation (genetics and translational science).
• Reagents, assays.
• Human PoP, PoC.
• Novel informatic approaches to “big data.”
“Opportunities for sharing…hold the hope for energizing therapeutic discovery.”

“Change will require bold initiatives from senior industry and academic leaders as well as policy makers to build the incentives that are now lacking.” [Culture]

“Greater collaboration upstream…(will) expand foundational knowledge…(which will facilitate) downstream research…through which new drugs and competitive advantage are created.”

“Companies should compete in areas that offer a viable ROI, and share where precompetitive collaboration helps all of us discover new therapies more efficiently and effectively.”

“A call to action to industry, academia and governmental agencies.”

Munos and Chin, 2009
Translational Science and Medicine

Common Ecosystem; Common Goals

Academia

NGOs

Industry

Gov’t

Patients