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

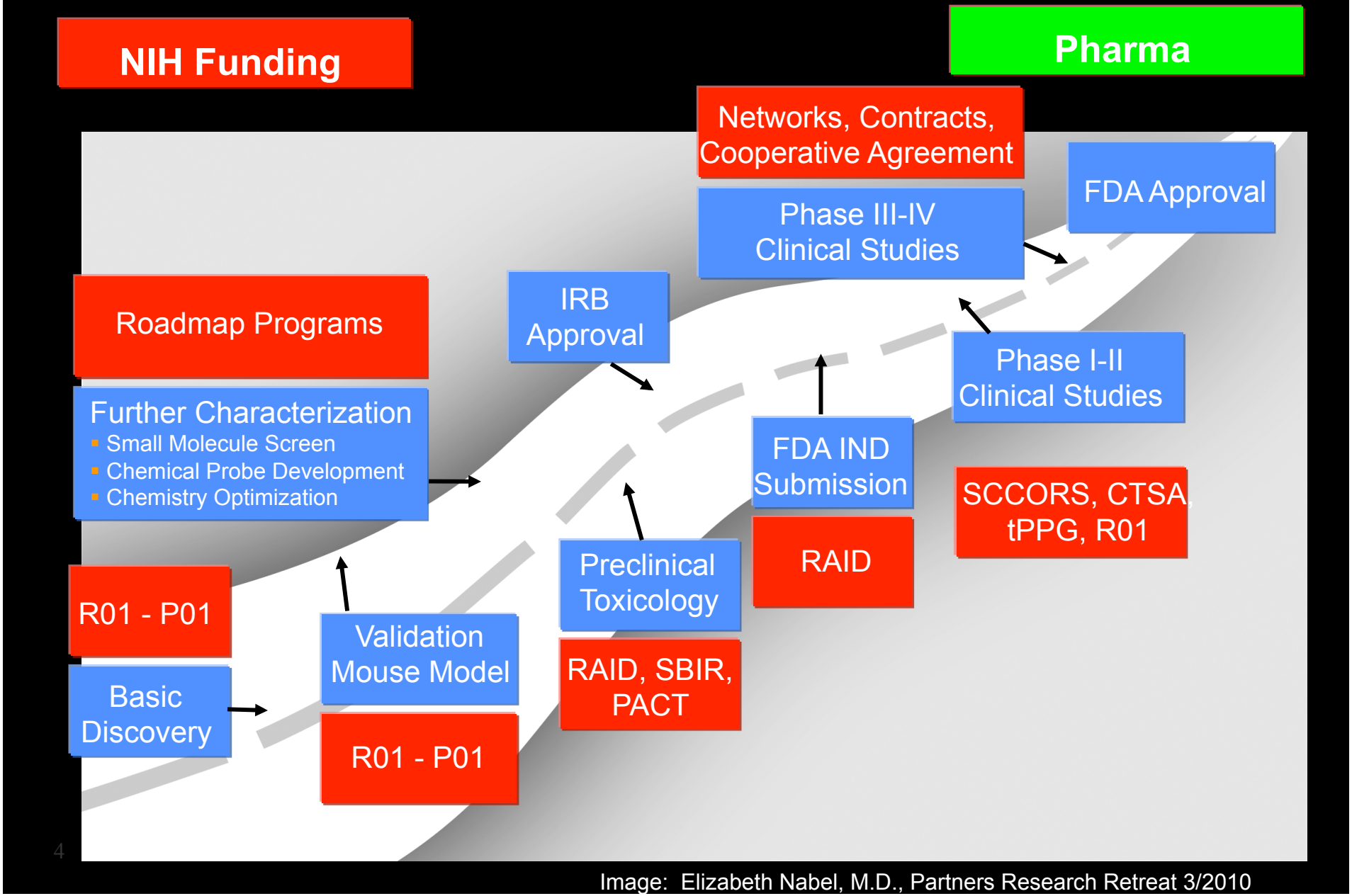
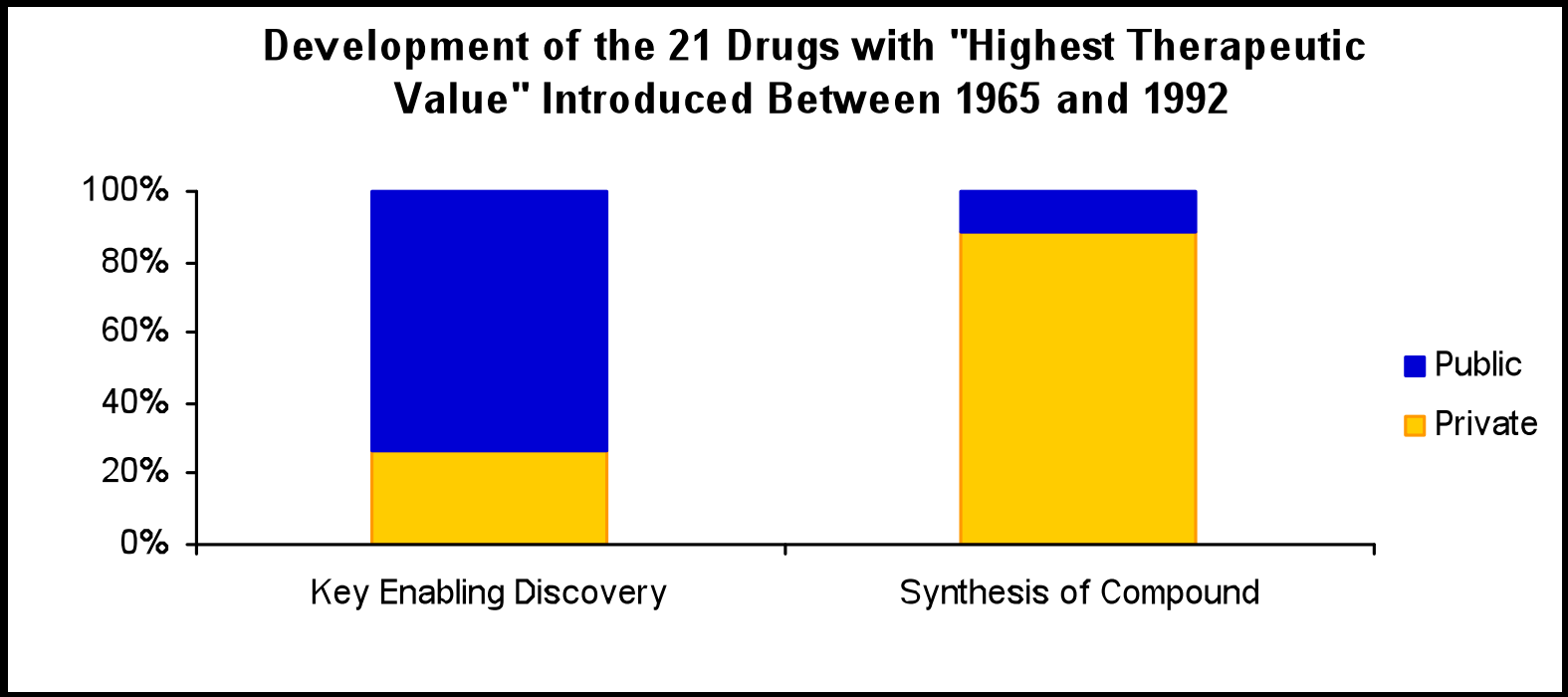


Image: Elizabeth Nabel, M.D., Partners Research Retreat 3/2010

Representative Drugs with Strong Academic Roots to "Key Enabling Discovery"

Academic Home	Academic investigator/s	Target	Therapy	Indication	Trade
UT	Mike Brown, Joel Goldstein	Cholesterol	Statins	high cholesterol	**Mevacor, Crestor, Zocor, Lipitor, et al**
Many	David Ho, Martin Hirsch, many others	HIV replication	HAART	HIV/AIDS	**Combivir, Kaletra, Trizivir, Truvada, etc**
UCLA	George Sachs	Na/H proton pump	PPI's	GERD, PUD	**Prilosec, Nexium, et al**
MGH	Brian Seed	TNF	anti-TNF	RA, Crohn's etc	**Enbrel**

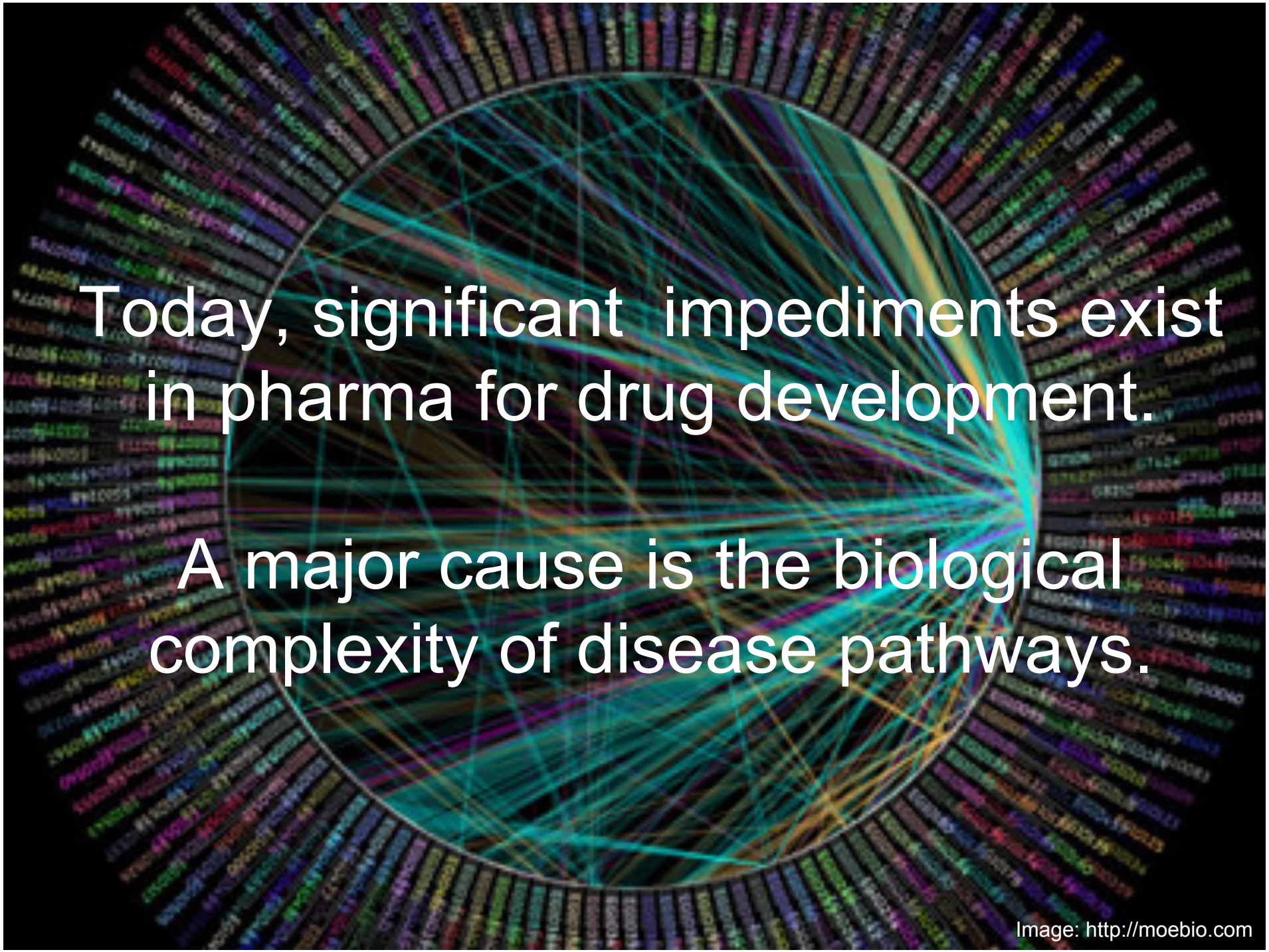
Economists Found That Most Important Products Are Discovered by Industry – Often Building on NIH-Funded Enabling Discoveries



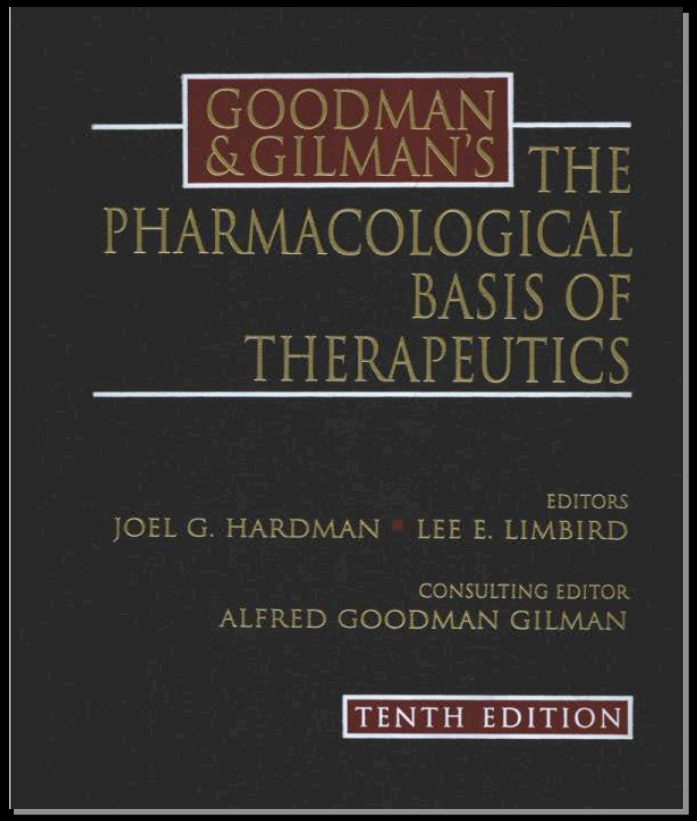
The average lag between the "key enabling discovery" and the introduction of the drug was 24 years.

Today, still 10-12 years from discovery to market

Cockburn I, Henderson R. Public-Private Interaction and the Productivity of Pharmaceutical Research. NBER working paper 6018; Apr. 1997.


Today, significant impediments exist in pharma for drug development.
A major cause is the biological complexity of disease pathways.
Image: http://moebio.com

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

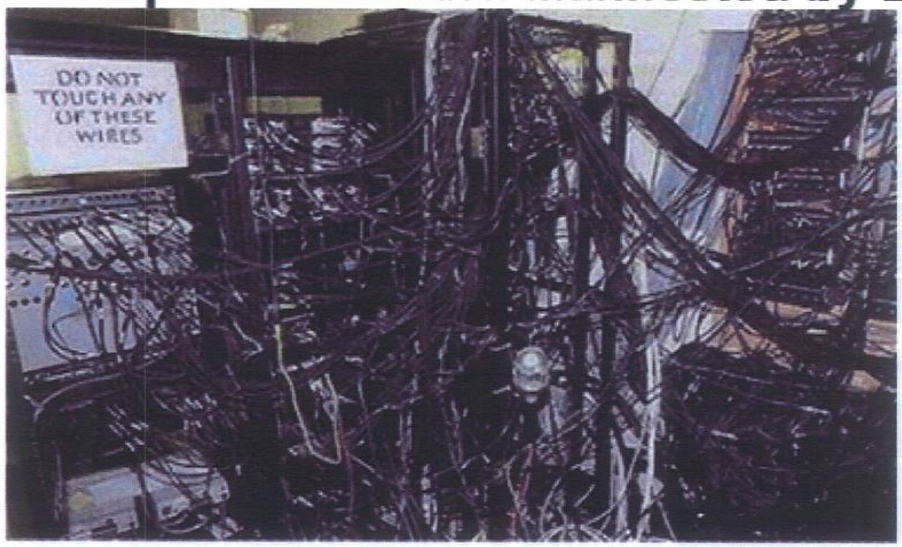

Image: Library of Congress

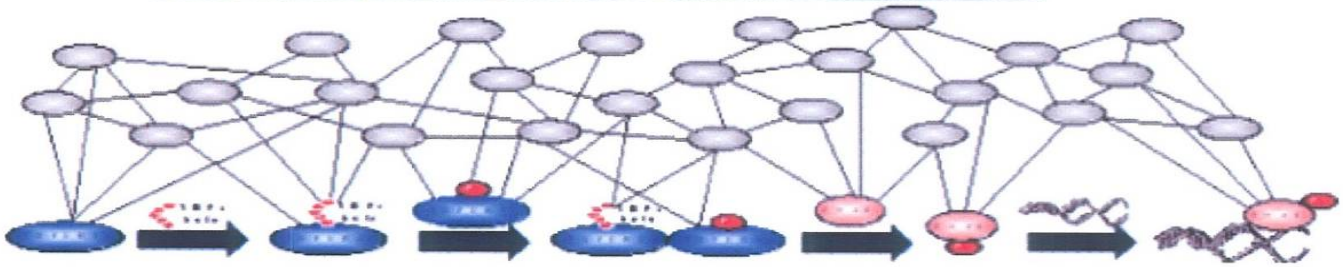
- Medicinal chemists focusing on small molecules that affected these targets
- Redundancy and repetition among companies which led to drugs that were effective some of the time with tolerable side effects

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.

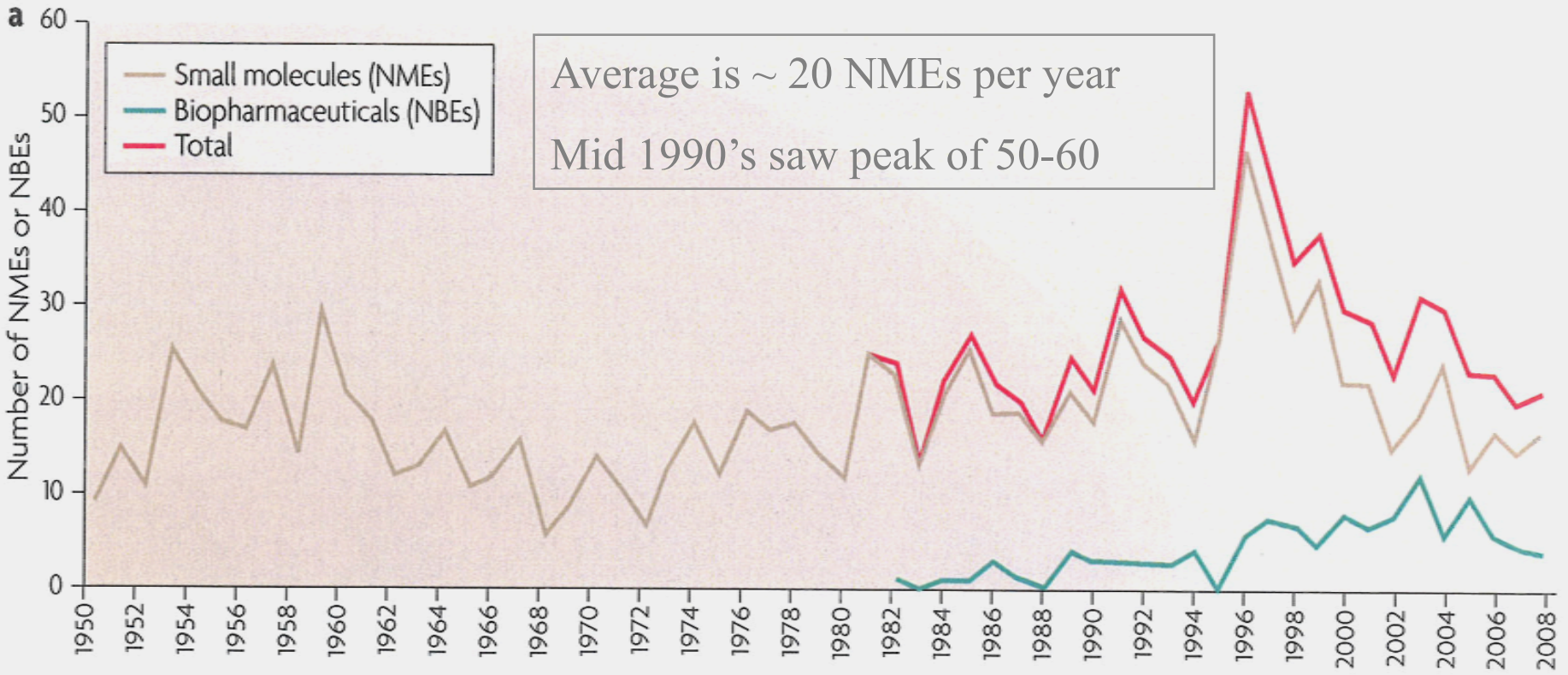
Reality of Complex Behaviors Manifested by Living Systems





- 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

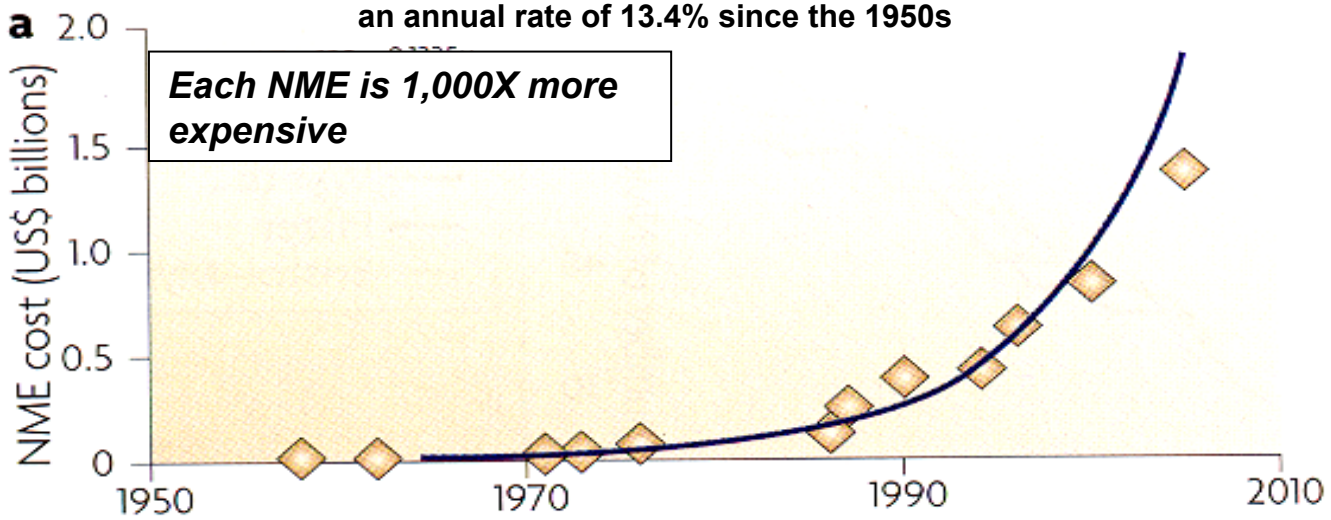


B. Munos Nature Reviews, Drug Discovery Dec 2009

Early human phases are increasingly expensive

Cost per NME

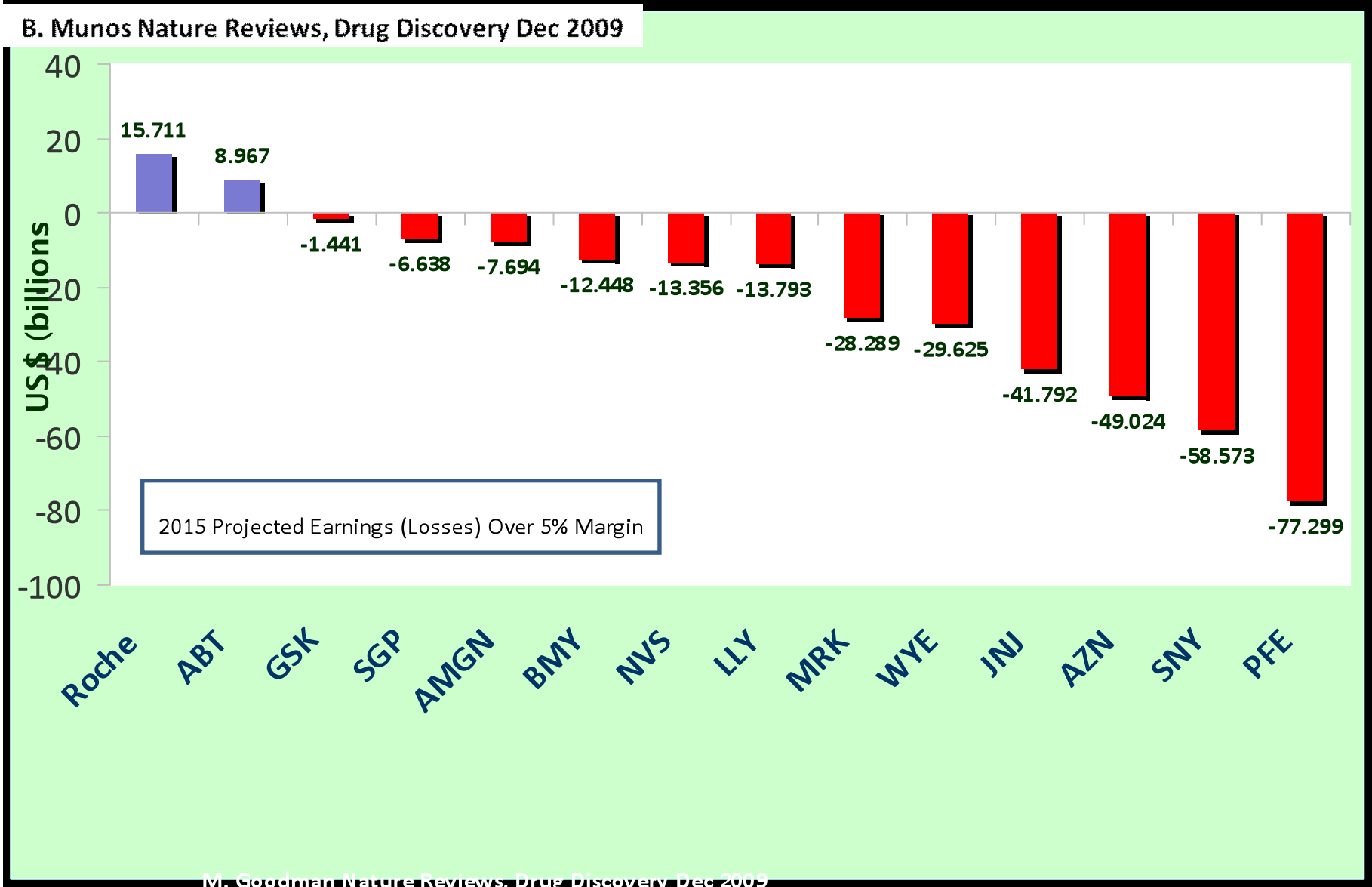
The cost of new molecular entities has been growing exponentially at an annual rate of 13.4% since the 1950s



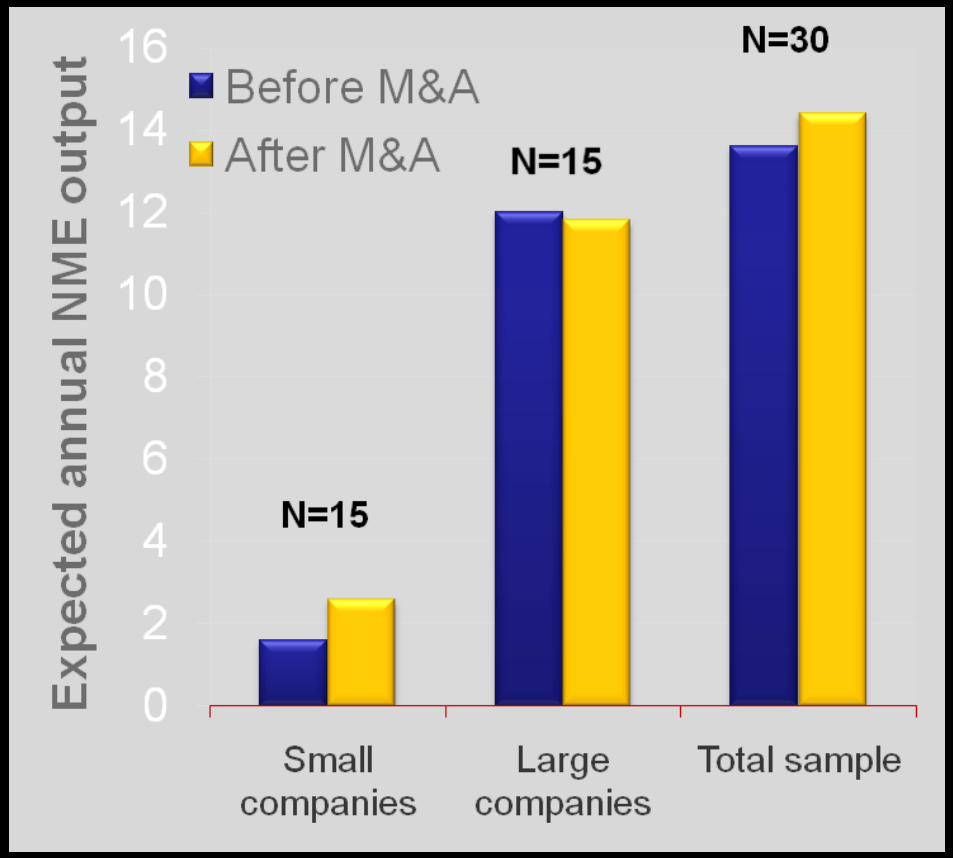
Each NME is 1,000X more expensive

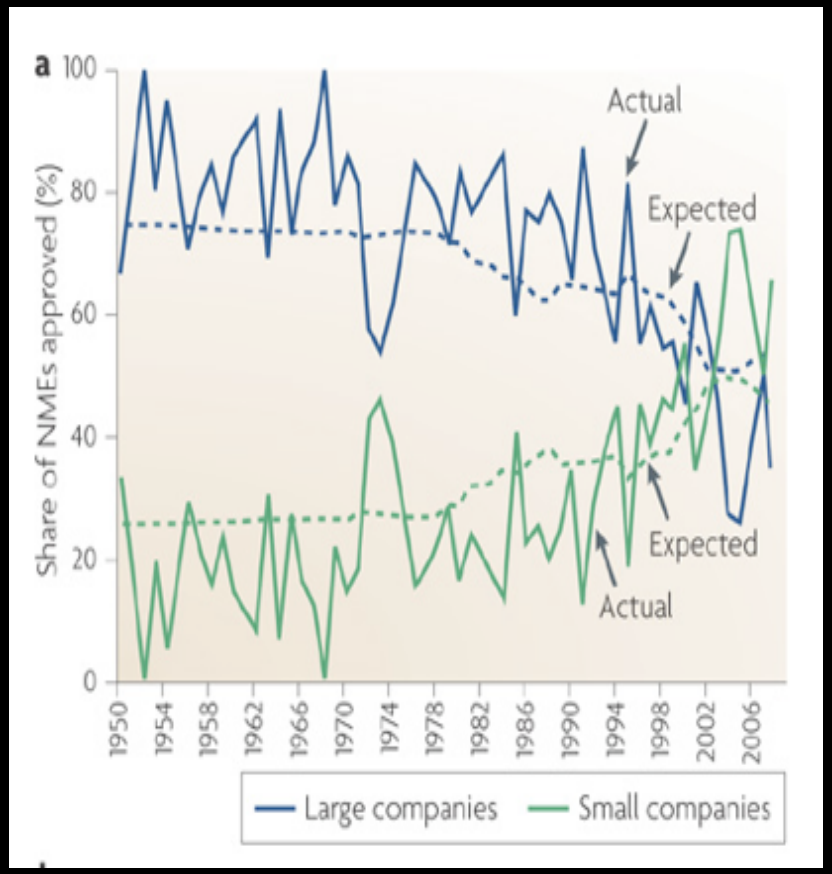
Drug Discovery Today; 11, 17/18 (2006);Business & Med Report Windhover Info. 21, 10 (2003); Bain Drug Economics Model (2003);Nat rev drug discovery 3: 711-715; CMR international, Industry success rates 2003. B. Munos Nature Reviews, Drug Discovery Dec 2009

The big Pharma model looks increasingly broken



Mergers likely won't improve NME output





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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

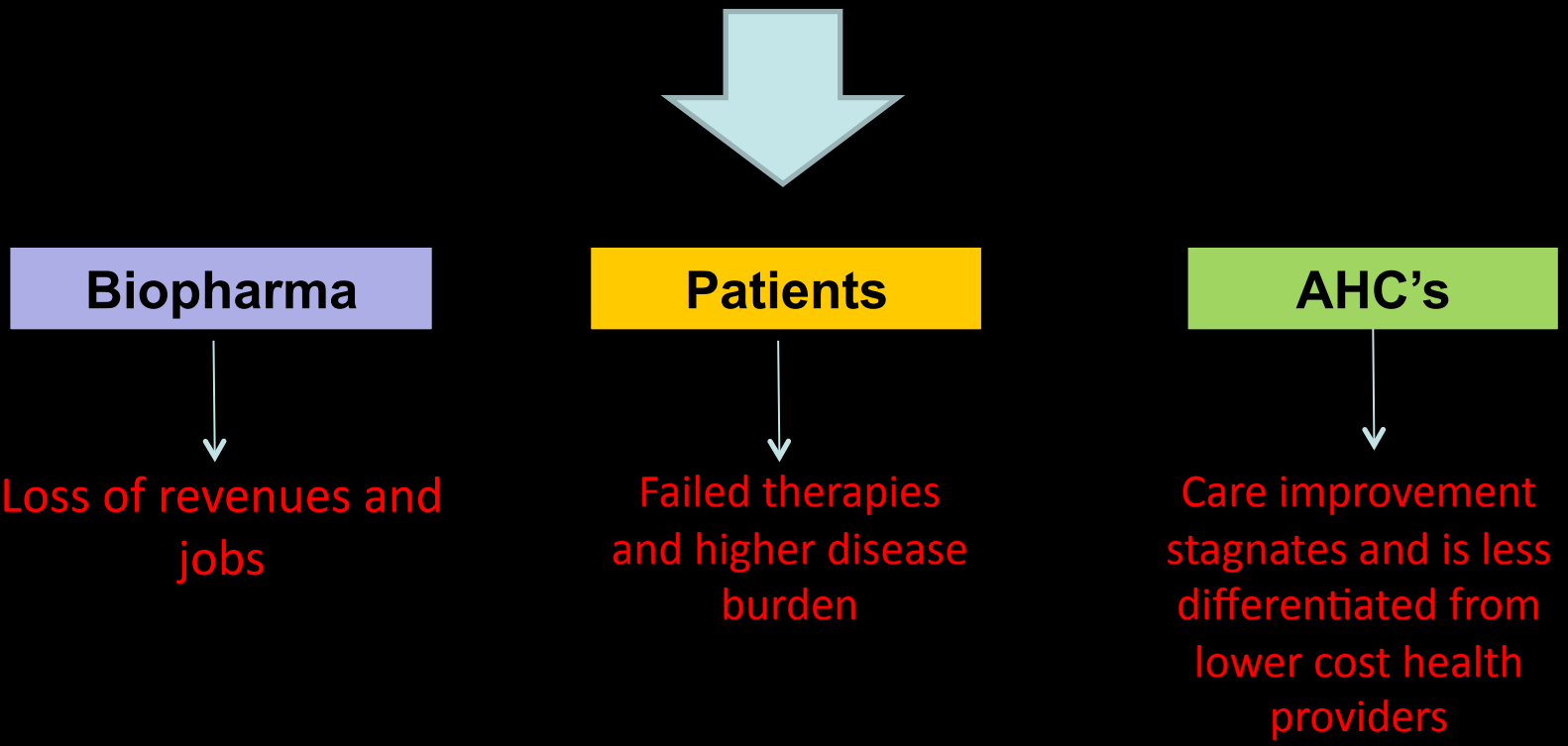
- Multiple factors contribute:
  - Medicinal chemistry not strongly supported in academia
  - Financial costs of development beyond academy's budgets
  - Expertise in key regulatory, CMC, and toxicology disciplines lacking
  - Timelines of academia not focused on patent expirations and speed
  - Promotions & 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



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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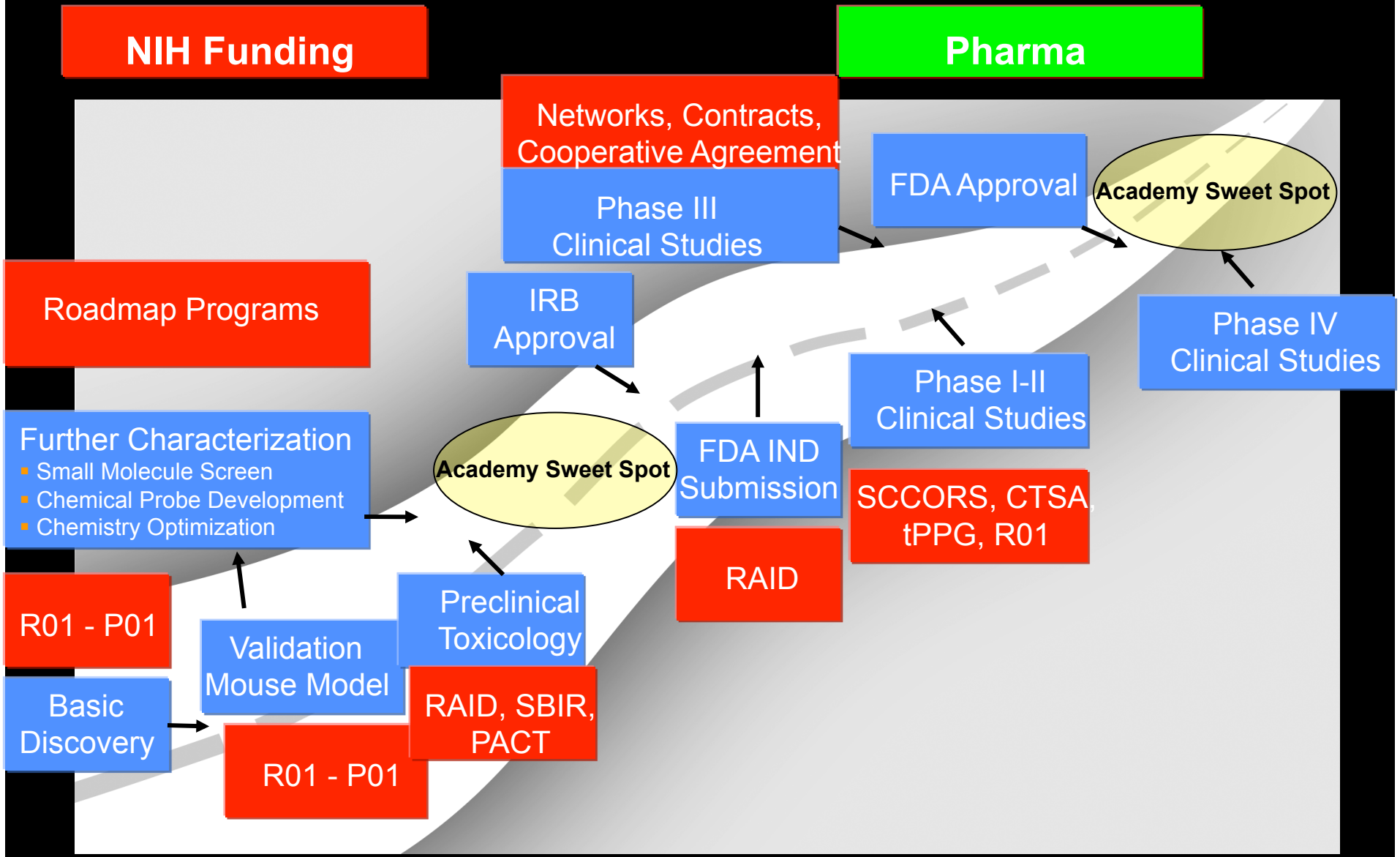


Image Adapted from: Elizabeth Nabel, M.D., Partners Research Retreat 3/2010

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

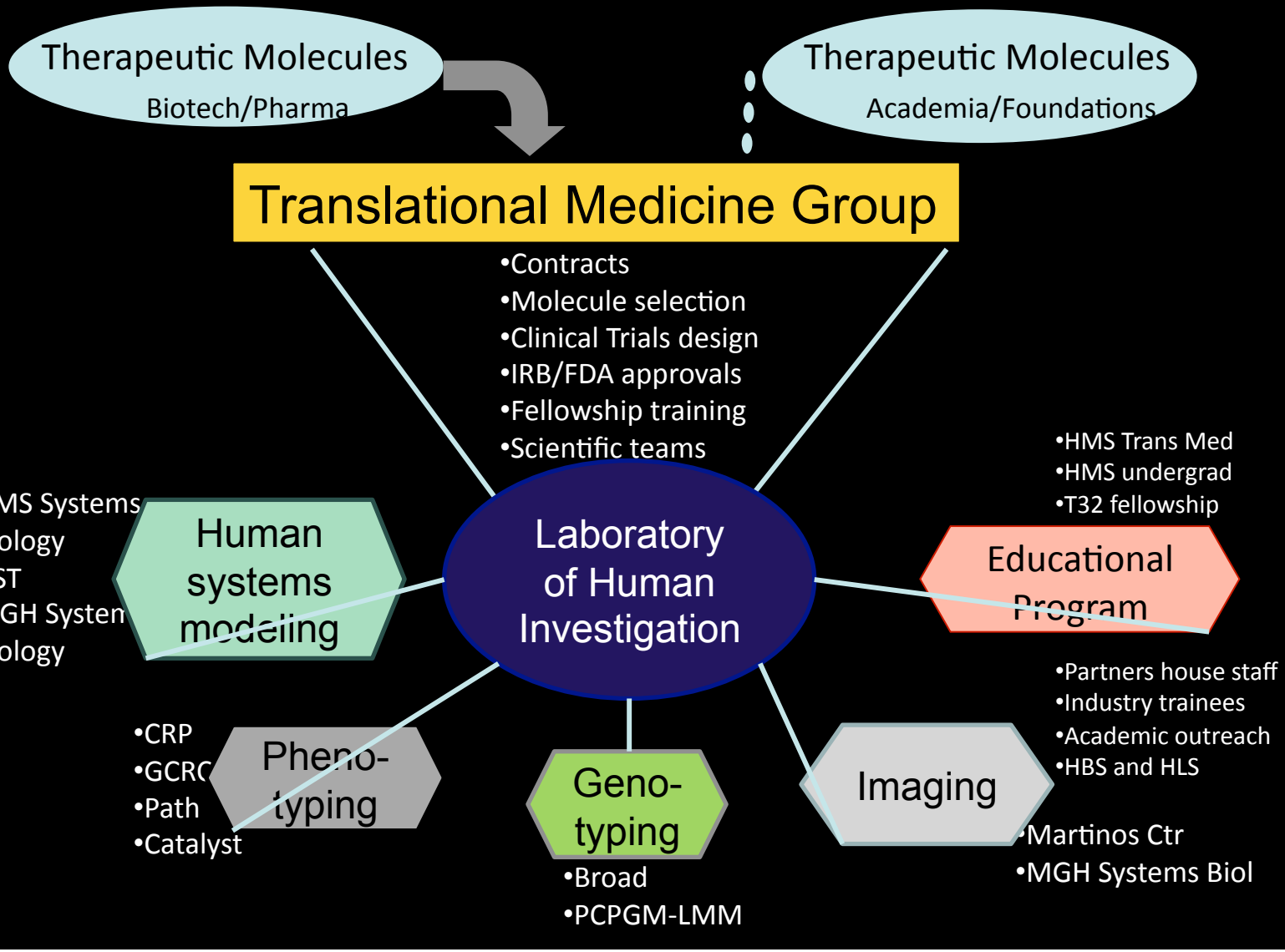
Industry Needs

- 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

The Laboratory of Human Investigation



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