Re-thinking Translational Research: The Contribution of Basic and Clinical Research to Biomedical Innovation and Drug Discovery

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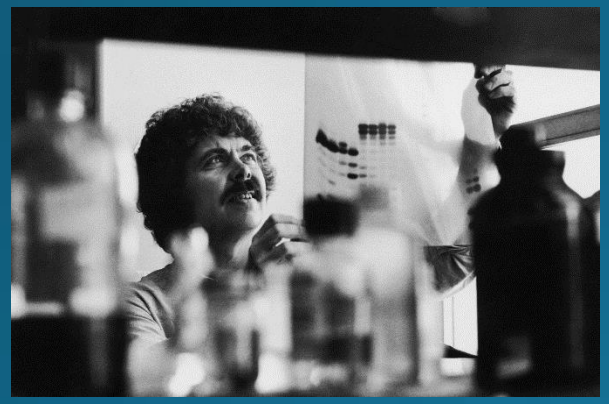
Robert E. Campbell Pharmaceutical Seminar Series
Rutgers Business School, Newark NJ
September 28, 2016

Broad research agenda: How does scientific research contribute to medical innovation?



Focus: What fields of science/scientific strategies are associated with successful drug discovery?

Today's talk

- A paradox in medical innovation, and current policy approaches to deal with it
- Critique of the policy
  - A little bit of history
- A framework for thinking bio-medical innovation
- Study of inventing teams at two leading research hospitals to test the framework

The revolution revisited: Clinical and genetics research paradigms and the productivity paradox in drug discovery

Research paradigms and useful inventions in medicine: Patents and licensing by teams of clinical and basic scientists in Academic Medical Centers (with Ayfer Ali)

Special Issue of Research Policy, Hospitals in Innovation, 2016

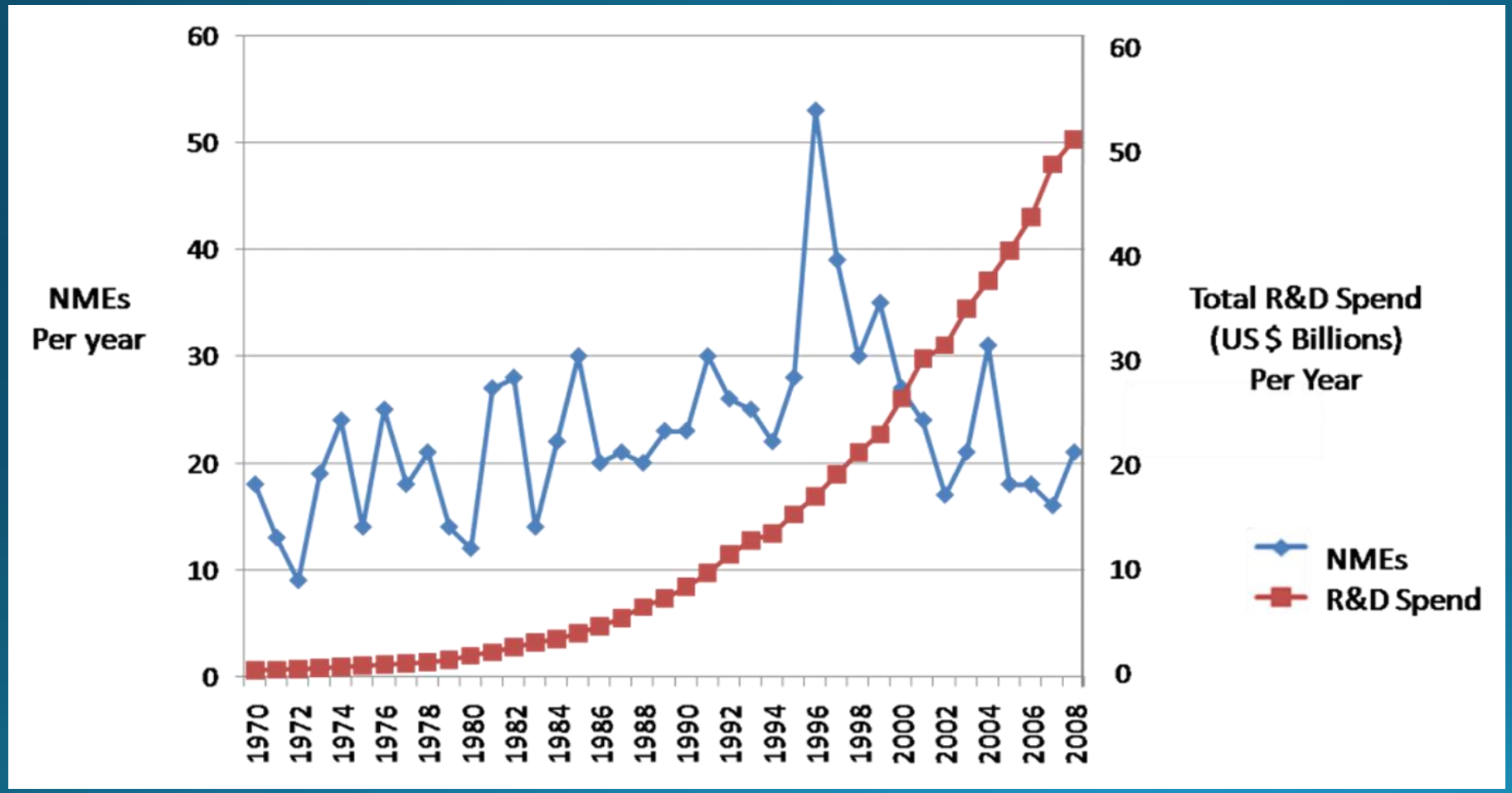
A paradox

There has been an explosion of scientific knowledge and analytical power in the life sciences. . .

. . .firms and public sector institutions have "correctly" adapted their policies to exploit these opportunities. . .

. . .yet the pace of medical discovery is *falling*

A paradox: Rising R&D, declining innovation rates



More compounds entering testing, but approved drugs falling, and fewer innovative drugs (GAO, 2006, BCG, 2010, Scannell, 2012)

A paradox: Rising R&D, declining innovation rates

"While biomedical research has experienced a golden age of progress over the past 25 years. . .the many remarkable advances in basic biomedical research over the past quarter-century have not yet led to significant increase in the flow of new medicines to the American public" (President's Council on Science and Technology, 2012, p. vi)

Diagnosing the problem: A broken chain

Perception that advances in scientific knowledge is not being effectively translated to the clinic

> "Something is broken in the long, complex chain of innovation that turns new findings in science into new products that benefit patients" (*Giovanni Migliaccio, EATRIS director)*

Diagnosing the problem: Failure to translate

Translational research

bench

bedside

Diagnosing the problem: Failure to translate

Translational scientists. . .[take] basic discoveries about **the causes of a disease** and transform this knowledge into a new treatment ”
NIH

bench

bedside

Diagnosing the problem: Failure to translate

NIH National Center for Advancing Translational Sciences

- Formed in 2011
- Budget ~$660 MM p.a.

bench

bedside

Inter-disciplinary teams are at the core of the translational model

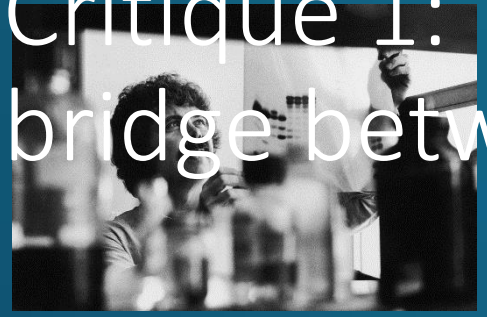
Inter-disciplinary teams are at the core of the translational model

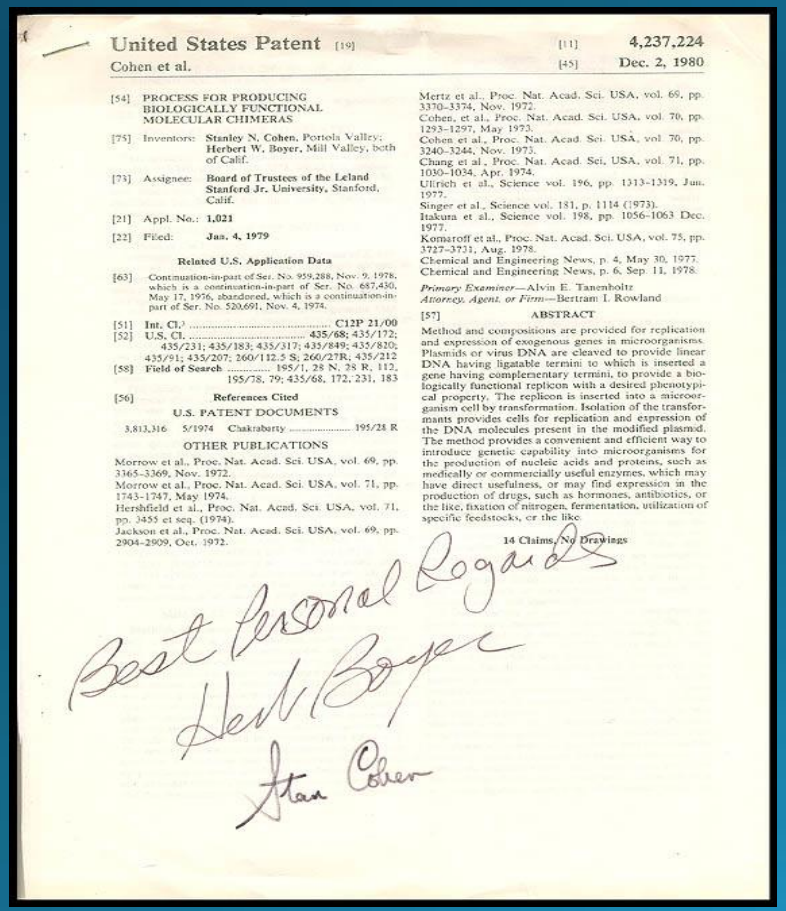
"the power of the molecular approach to health and disease is. . .poised to catalyze a revolution in medicine . . . The foundation of success in biomedical research has always been. . .the creative insights of individual investigators. But increasingly those investigators are working in teams, accelerated by interdisciplinary approaches and empowered by open access to tools, databases, and technologies" *Francis X. Collins, Science 2010*

Critique of the new translational paradigm: Is it new?

1. The biotech industry was supposed to bridge the science-technology gap
2. Collaborative networks already define the bio-medical R&D landscape
3. A linear model of innovation that does not reflect history of medicine
4. Based on a recombinant logic: scientists are not bits of knowledge that can easily combined on teams

Critique 1: The biotech industry was framed as bridge between academic science and industry





United States Patent [19]
Cohen et al.

[11] 4,237,224
[45] Dec. 2, 1980

[54] PROCESS FOR PRODUCING BIOLOGICALLY FUNCTIONAL MOLECULAR CHIMERAS

[75] Inventors: Stanley N. Cohen, Portola Valley; Herbert W. Boyer, Mill Valley, both of Calif.

[73] Assignee: Board of Trustees of the Leland Stanford Jr. University, Stanford, Calif.

[21] Appl. No.: 1,021

[22] Filed: Jan. 4, 1979

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 959,288, Nov. 9, 1978, which is a continuation-in-part of Ser. No. 687,430, May 17, 1976, abandoned, which is a continuation-in-part of Ser. No. 520,691, Nov. 4, 1974.

[51] Int. Cl.[3] C12P 21/00
[52] U.S. Cl. ..... 435/68; 435/172; 435/231; 435/183; 435/317; 435/849; 435/820; 435/91; 435/207; 260/112.5 S; 260/27R; 435/212
[58] Field of Search ..... 195/1, 28 N, 28 R, 112, 195/78, 79; 435/68, 172, 231, 183

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Primary Examiner—Alvin E. Tanenholtz
Attorney, Agent, or Firm—Bertram I. Rowland

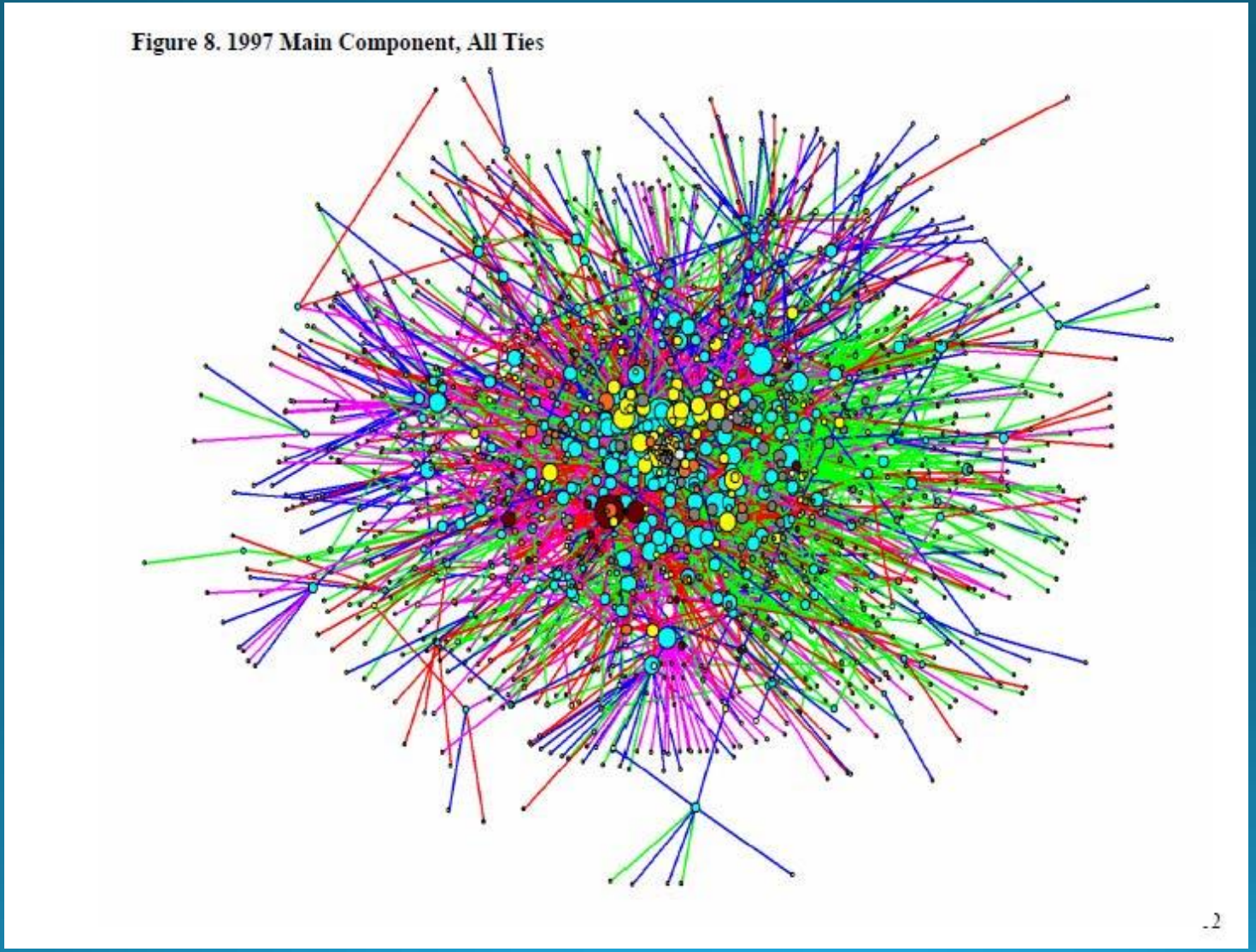
[57] ABSTRACT

Method and compositions are provided for replication and expression of exogenous genes in microorganisms. Plasmids or virus DNA are cleaved to provide linear DNA having ligatable termini to which is inserted a gene having complementary termini, to provide a biologically functional replicon with a desired phenotypical property. The replicon is inserted into a microorganism cell by transformation. Isolation of the transformants provides cells for replication and expression of the DNA molecules present in the modified plasmid. The method provides a convenient and efficient way to introduce genetic capability into microorganisms for the production of nucleic acids and proteins, such as medically or commercially useful enzymes, which may have direct usefulness, or may find expression in the production of drugs, such as hormones, antibiotics, or the like, fixation of nitrogen, fermentation, utilization of specific feedstocks, or the like.

14 Claims, No Drawings

Best personal Regards
Herb Boyer
Stan Cohen

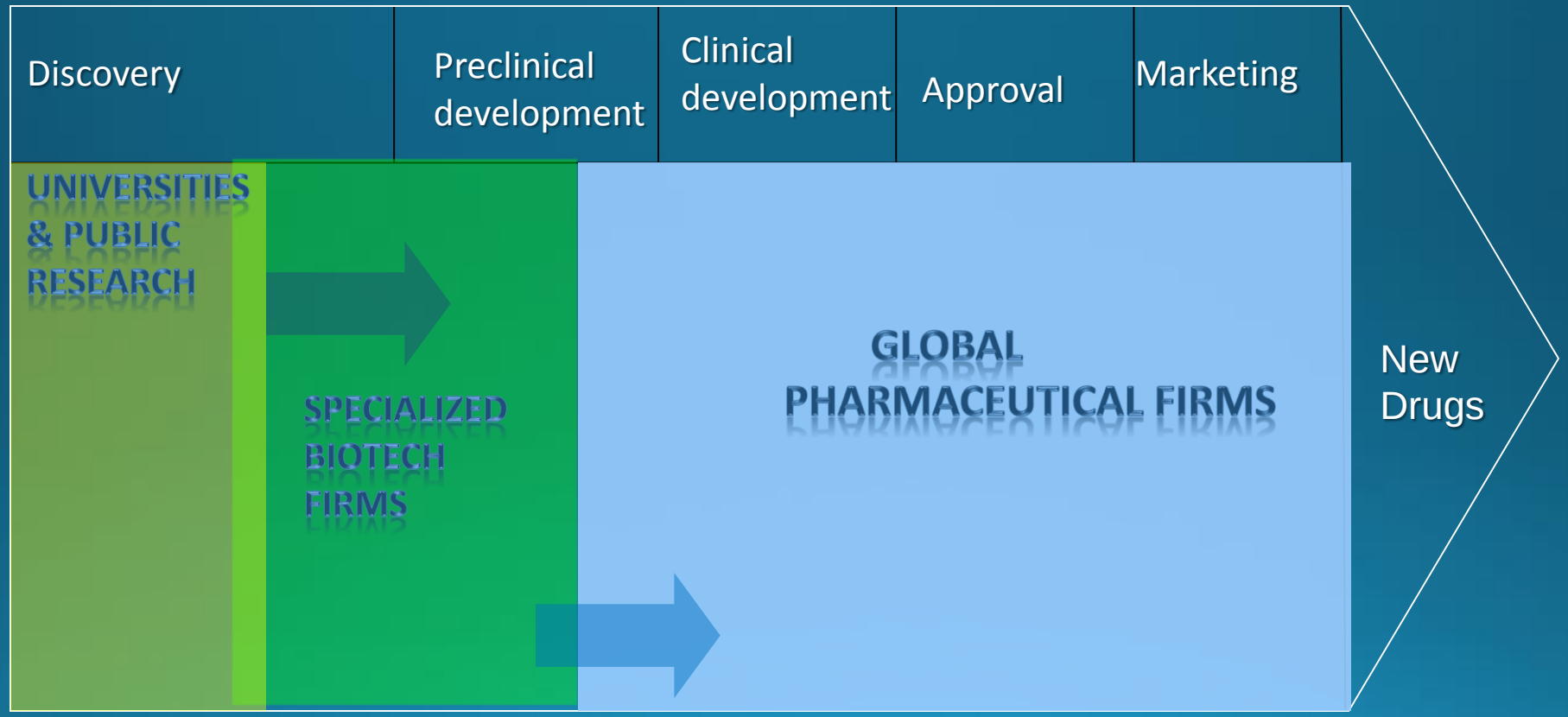
Critique 2: Collaborative networks already define the R&D landscape



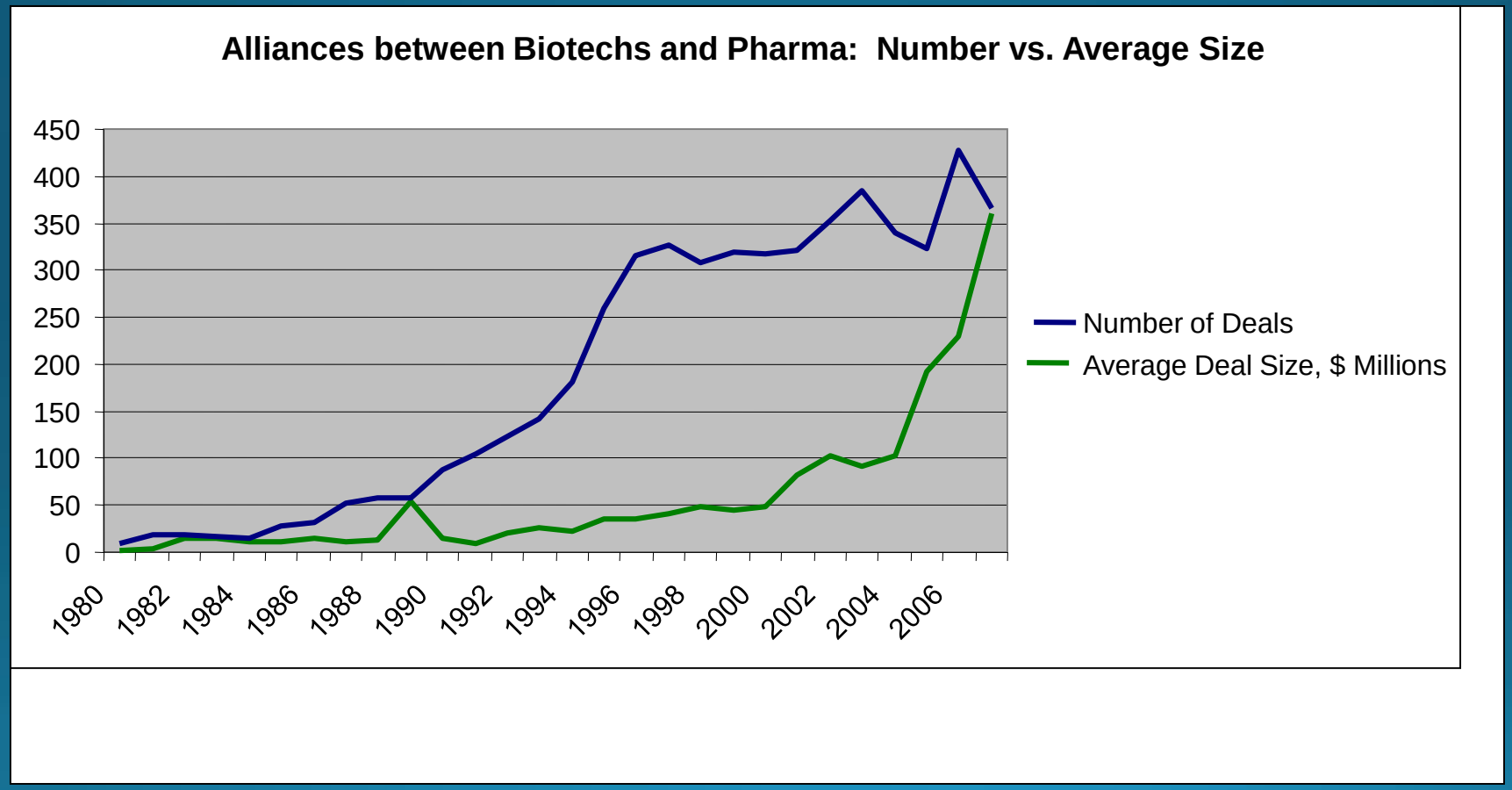
Source: Powell et al, 2005

The pharmaceutical industry value chain
Old Organizational Paradigm

The pharmaceutical industry value chain
New Organizational Paradigm



Collaboration defines the pharma value chain



Source: Recombinant Capital

Critique 3: A linear model of innovation

Basic science

Historically, most medical innovations originated at the bedside before travelling to the laboratory

Bedside

Complexity in biological systems

[T]here remains a real problem about the relevance of many model systems, and the inability of many to understand that in biology, unlike physics, we don't have great general laws or large forces operating that allow us to work from the bottom up in terms of clinical prediction

Rees, Jonathan. 2002. "Two Cultures?" J Am Acad Dermatol, 46:313-6.

Different predictive logics in science

The great physicist-turned biologist Leo Szilard said that once he changed fields (no pun intended) he couldn't enjoy a long bath as he could when he could dream abstract physics in the bath.

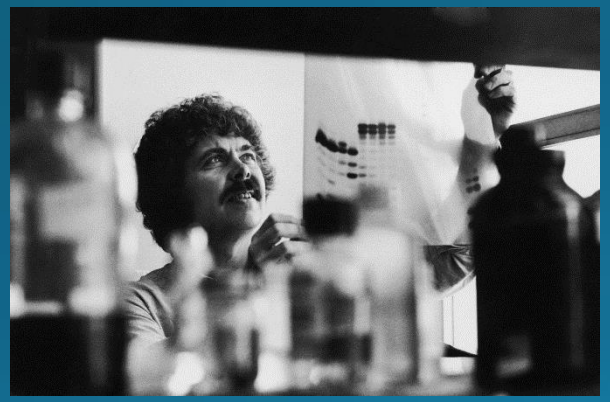
As a biologist he was always having to get out to check on some annoying little fact. It is the problem of predicting across several levels of biologic explanation, and the absence of the all encompassing general laws in biology, that accounts for the fact that most clinically relevant discoveries come from the clinic rather than the laboratory and not, contrary to what many believe, vice versa.

Rees, Jonathan. 2002. "Two Cultures?"

Serendipity and bench-to-bedside learning in medicine

- The treatment for pernicious anemia was discovered from the mechanistic insight that feeding patients liver cured them – the underlying vitamin deficiency (b12), identified decades later as the cure, was one of many complex causes
- A new sedative used on hospitalized mental patients reduced hallucinations – this observation paved the way for the discovery of an effective new treatment for schizophrenia.
- Similarly, a major drug for depression was serendipitously discovered when it caused schizophrenics to become agitated, pointing towards its potential use for depression.
- The discovery of both drugs subsequently facilitated new theories of brain activity associated with schizophrenia and depression and the advent of modern psychiatry

Critique 4: Based on a recombinant logic of teams



Innovation in medicine: Individual creativity

"When Withering discovered and used digitalis in 1785, he needed little help from those in other branches of science because he himself was a botanist, clinician, mineralogist, and chemist. The interfaces in his discovery were between his own brain cells that stored information in botany, chemistry, and medicine, and these neural connections quickly enabled him to identify the foxglove as the only ingredient of a Shropsire potpourri that was likely to have potent biological activity" -Comroe, quoted in Vos, 1991

Where you start the innovation process matters: "Go *first* to the hospital" Claude Bernard

In physiology, analysis, which teaches us the properties of isolated elementary parts, can never give us more than a most incomplete knowledge . . . Physiologists and physicians must therefore always consider organisms as a whole. . .To study disease, "Go first to the hospital"
Claude Bernard, cited in Schnaffner (1985) and Weiner and Souter (2003)

"Organisms, tissues and cells are composed of molecular components. However, as they interact with eachother they form a system that. . .is more than the sum of its parts. Components are to systems as words are to poems and pigments are to paintings. The decomposition of poems and paintings into words and pigments is not reversible" *Pharmacologist/Nobel Laureate James Black*

Working with patients (clinical research) and working with genetic and molecular data are distinct and sometimes conflicting research strategies in drug discovery

The explosion of genomics and molecular biology (1980s-2000s) positioned basic science at the center of medical research – a major shift.

I argue that translation is a flawed diagnosis and policy – and provide a different framework for thinking about declining rates of medical innovation

The logic of basic science:

Predictive, reduces complexity to essential properties

Seeks to understand universal cause-effect relationships

“Offline”: studies models objects in de-contextualized experimental settings; experiments are abstractions of the real world

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Predictive, reduces complexity to essential properties

Seeks to understand universal cause-effect relationships

"Offline": studies models objects in de-contextualized experimental settings; experiments are abstractions of the real world

The logic of technological innovation:

Observation of phenomena in their full complexity as they exist in nature

Seek to understand mechanistic, functional relationships

"Online": Feedback-based learning using real world objects in real-world contexts

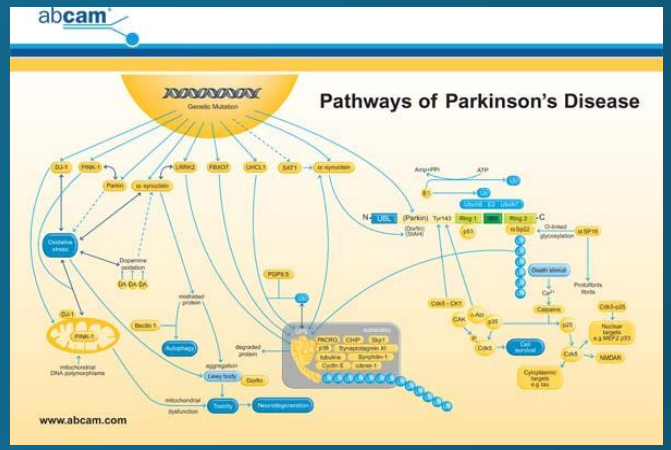
Genomics
Molecular
science
(1980s-2000s)

Hospital-based
Clinical Research
(1940s-1970s)

Clinical discovery paradigm: Phenotypic screening

Clinical observation (e.g. reaction to a drug)

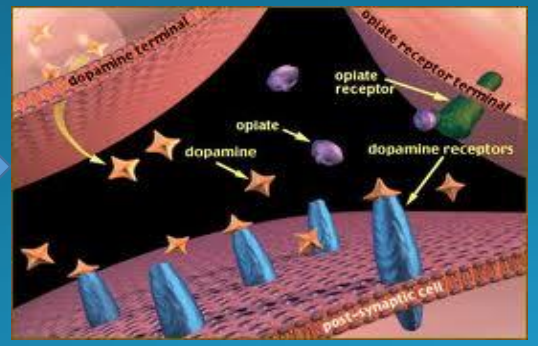
Test treatment experimentally



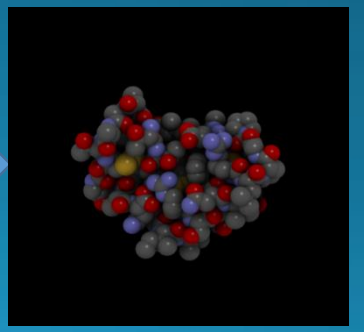
Theorize disease mechanisms

Genomics discovery paradigm: Genotypic screening

DNA mutation associated with pathology



Targets in cells



Design a drug to bind to target

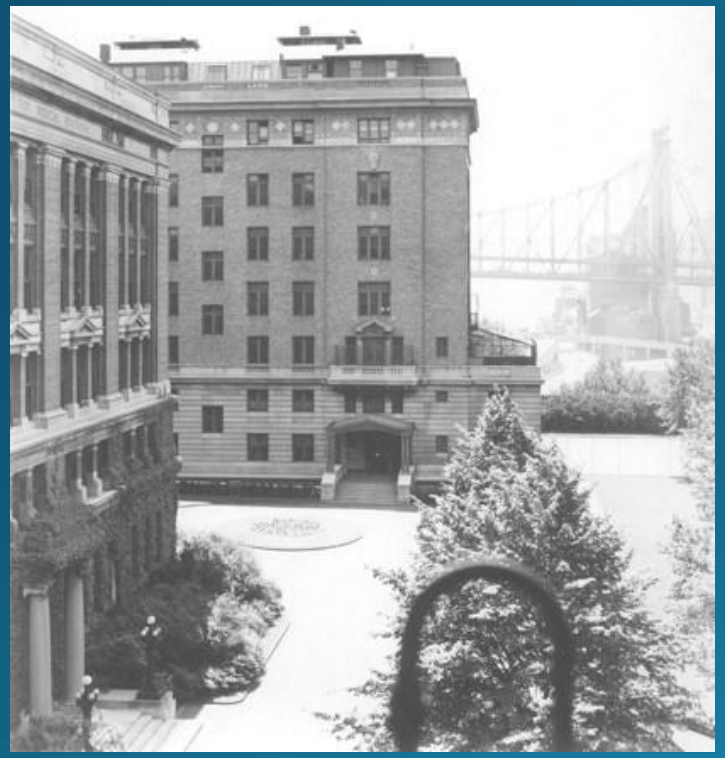
Clinical and basic research as distinct practices in drug discovery research

Clinical research	Basic research
Medical training (MD)	Science training (PhD)
Search for functional relationships in complex phenomena in natural states	Search for causal relationships in complex phenomena in essential states
In vivo data: whole organisms; afflicted patients	In vitro data: molecular, intra-cellular and sub-systems
Feedback based	Predictive
Small n cases, observational	Big data, analytics
Intuition/serendipity	Logic/predictive
Individuals	Teams

Patient-oriented clinical research

- “Research performed by a scientist and a human subject working together, both being warm and alive” (Schechter, 1998)
- Rejects the idea of *disease causality* as a useful starting point for drug discovery
  - Causal understanding is not useful in finding treatments.
- A dominant paradigm in bio-medicine in post-War USA, spurred by the federalization of research (NIH)

Rockefeller Institute (1901) and Rockefeller Hospital (1910)



- First institution to combine laboratory and clinical research to find treatments for major infectious diseases of the day.
- Goal was transfer lab discoveries to the clinic – but most discoveries were the other way around (Ahrens, 1992)
- Major breakthroughs in basic science stimulated by clinical research, e.g. the discovery of DNA

Organizing POR: The NIH Clinical Center (1955) and GCRC network

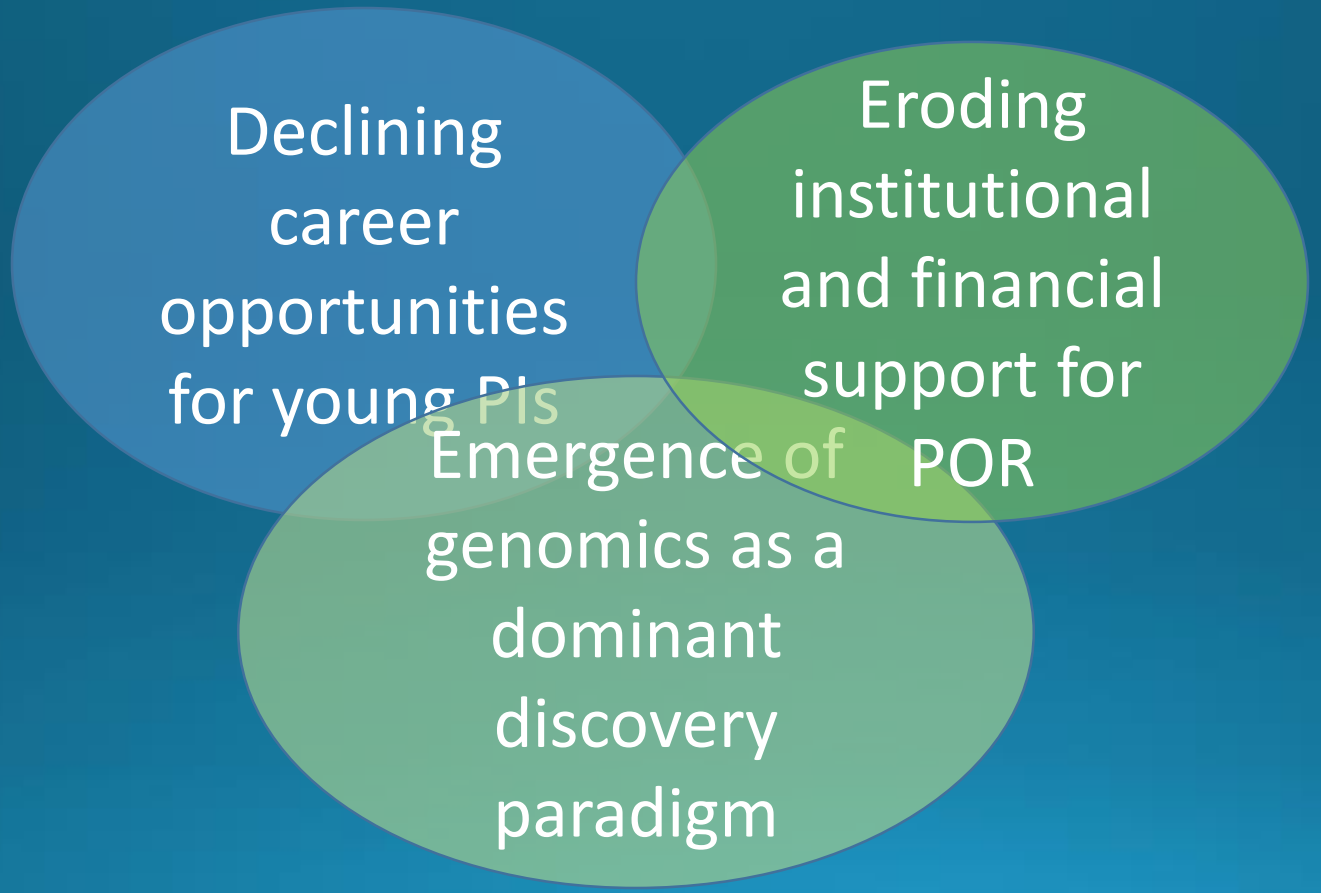
- Modeled on the Rockefeller Institute – 10x larger: 500 beds
- A model for a network of clinical sites in AMCs
- “Mini-hospitals”
- Built upon prevailing mode of healthcare: long term hospitalization and close doctor-patient interactions

Exploration in the clinical model

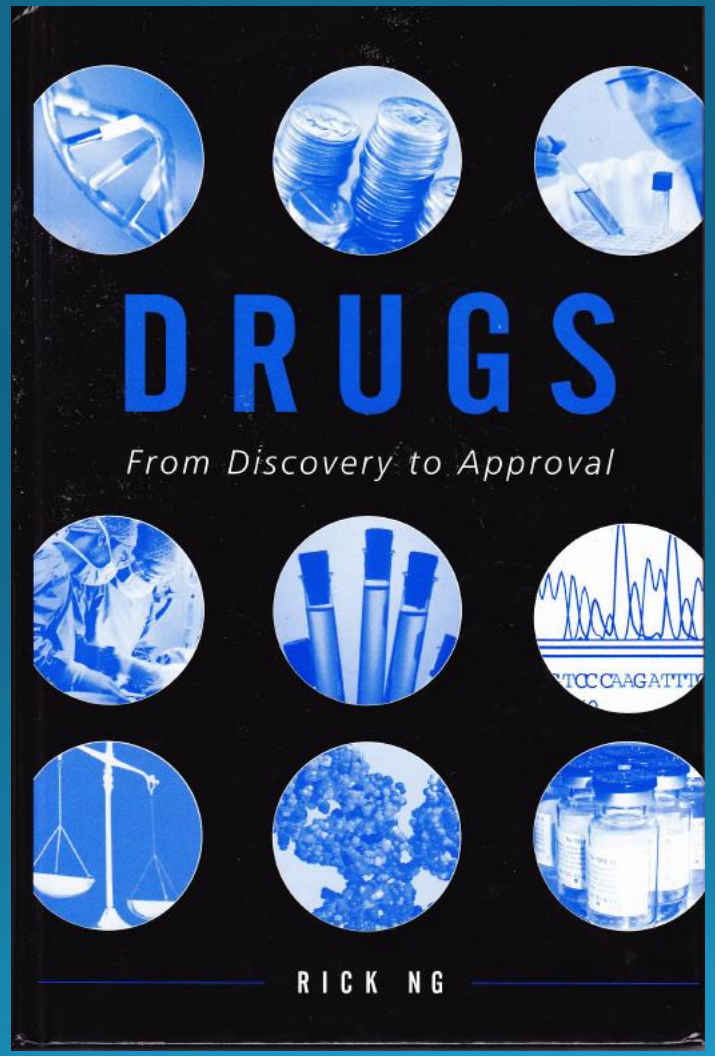
"When a drug with a new pharmacological action becomes available it is liable to be tried clinically in disorders which were not foreseen during its laboratory development. The umbilical connexion with the laboratory has been cut and we must rely on the vision of the clinician and be grateful for this." As a result of explorations in clinical settings, seven new indications emerged within a few years for the beta blocker pronethalol, fuelling the emergence of a new field of cardiovascular research in the mid 1960s. (James Black)

Two (three) factors accounting for the decline in POR

High med school debt
Publication pressures
Time pressures
Redtape/IRBs



Managed care
More outpatient care
AMCs budget pressures


DRUGS
From Discovery to Approval
RICK NG

1.5 TRENDS IN DRUG DISCOVERY AND DEVELOPMENT

The approach to drug discovery and development can generally be classified into the following areas:

- Irrational Approach
- Rational Approach

Irrational Approach: This approach is the historical method of discovering and developing drugs. It involves empirical observations of the pharmacological effects from screening of many chemical compounds, mainly those from natural products. The active component that gives rise to the observed effects is isolated. The chemical formula is determined, and modifications are made to improve its properties. This approach has yielded most drugs available today.

Rational Approach: This approach requires three-dimensional knowledge of the target structure involved in the disease. Drugs are designed to interact with this target structure to create a beneficial response. This is an emerging field in drug discovery.

If the effort [to **sequence the Human Genome**] is successful, health care will shift from a paradigm of detect and treat, typically with toxic drugs that sometimes do no

"Death is a series of preventable diseases"
William Haseltine, Founder, Human Genome Sciences, 1999

cancer and heart disease, some experts say, the science of the genome, or genomics, may make it possible for a child born today to live to 150 -- or, some say, much longer.
(NYT, 1999)

Genomics and drug discovery: Few results

- Genomics has been a disappointment as a drug discovery platform
  - Only a few drugs have come out of the paradigm
- Target-based model of disease causation acknowledged to be a vast oversimplification
  - Complexity of the genotype-phenotype problem persists

Mid 1990s: Genetically engineered mice lacked leptin expression and became obese

Amgen licensed rights to leptin to develop obesity drug

Two decades later: Leptin one of many complex triggers in obesity, still no drug

Recent study at Brigham Hospital: 101 **genetic markers** that have been statistically linked to **heart disease** were shown to have **no value** in forecasting disease among 19,000 subjects followed for 12 years; a more valid predictor was the old-fashioned method of **a family history**.

We theorize that despite the rise of molecular science in medical research. . .

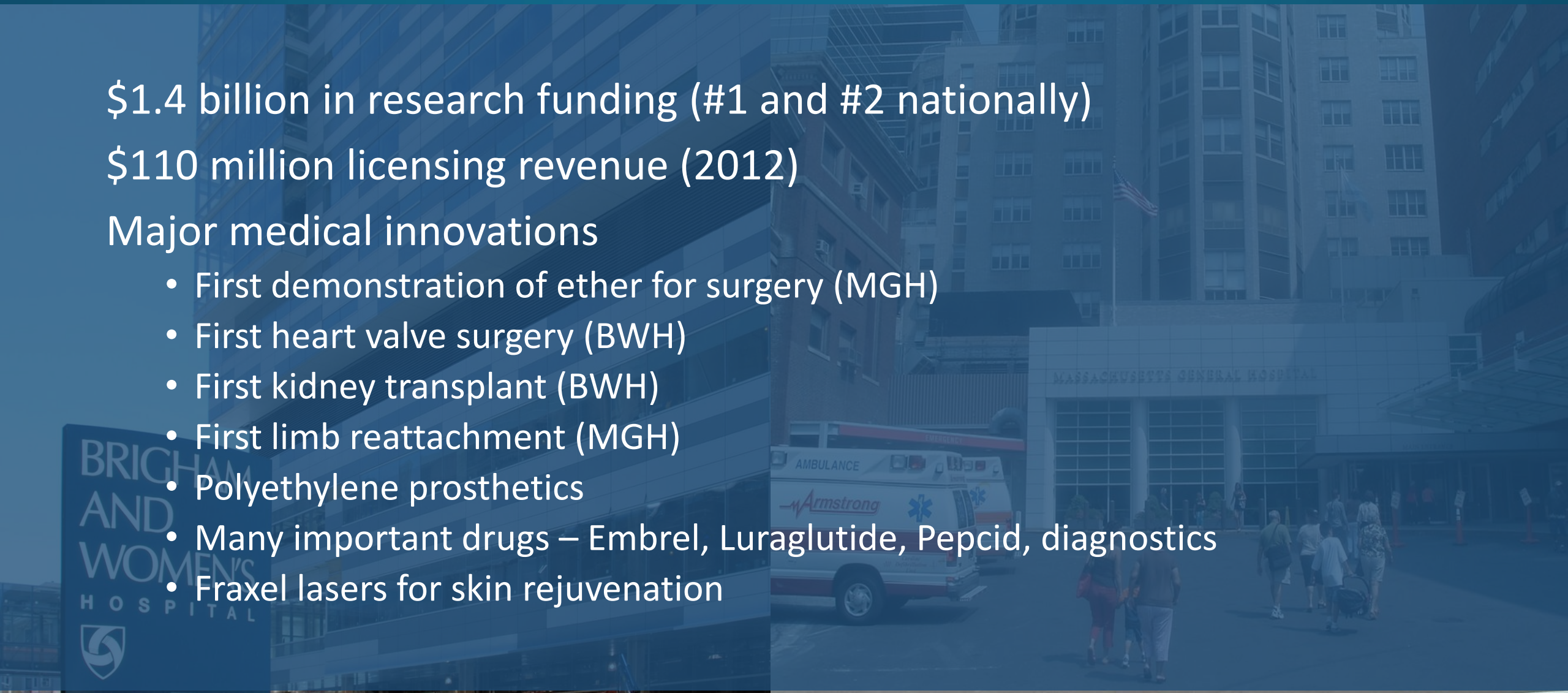
Physician-researchers remain advantaged in innovation as compared to basic scientists

- working with living patients provides unique opportunities for useful insights

Successful innovation is not a simple arithmetic of combining basic and clinical researchers on teams – dominant research paradigms matter for innovation outcomes

Research context: Two leading Academic Medical Centers

Research context: Two leading Academic Medical Centers



$1.4 billion in research funding (#1 and #2 nationally)

$110 million licensing revenue (2012)

Major medical innovations

- First demonstration of ether for surgery (MGH)
- First heart valve surgery (BWH)
- First kidney transplant (BWH)
- First limb reattachment (MGH)
- Polyethylene prosthetics
- Many important drugs – Embrel, Luraglutide, Pepcid, diagnostics
- Fraxel lasers for skin rejuvenation

Clinical and basic research as distinct search paradigms within Academic Med Centers

Clinical research	Basic research
Medical training	Research training
le organisms; afflicted patients	In v intra-cellular and sub-ems
S relationships in phenomena omplexity (natural states)	Searc ships in phenomena with
ck based (serendipity)	ctive
Small n cases, observational	Big data, analytics

Dr. David Borsook
MD-PhD

Dr. Charles Serhan, PhD

Clinical and basic research as distinct search paradigms

Clinical research	Basic research
Medical training	Research training
Research focuses on studying pain and developing new pain-relieving drugs by using observational studies based on neuroimaging technologies in humans and animals. Discovered a new drug in the clinic.	Research identifies novel mediators, signaling pathways, and cellular targets involved in inflammation, and use structural elucidation of novel molecules and pathways to develop new pain-relieving drugs. Discovered a drug through predictive science.

Data and key measures

495 patented inventions and licenses, 1977-2007

- screened by Technology Transfer Office
- approved by USPTO
- excludes sponsored research
- 42% of inventions were licensed to private sector

We identify the training of inventors on patenting teams to measure *research paradigms*

- MDs – clinical researchers
- Phds – basic researchers
- Md-Phd – cross trained

Four types of inventing teams

Single Domain Teams: All MD or All PhDs

Cross domain teams: Any combination of MD and PhD

Team Leaders

Hazard Models

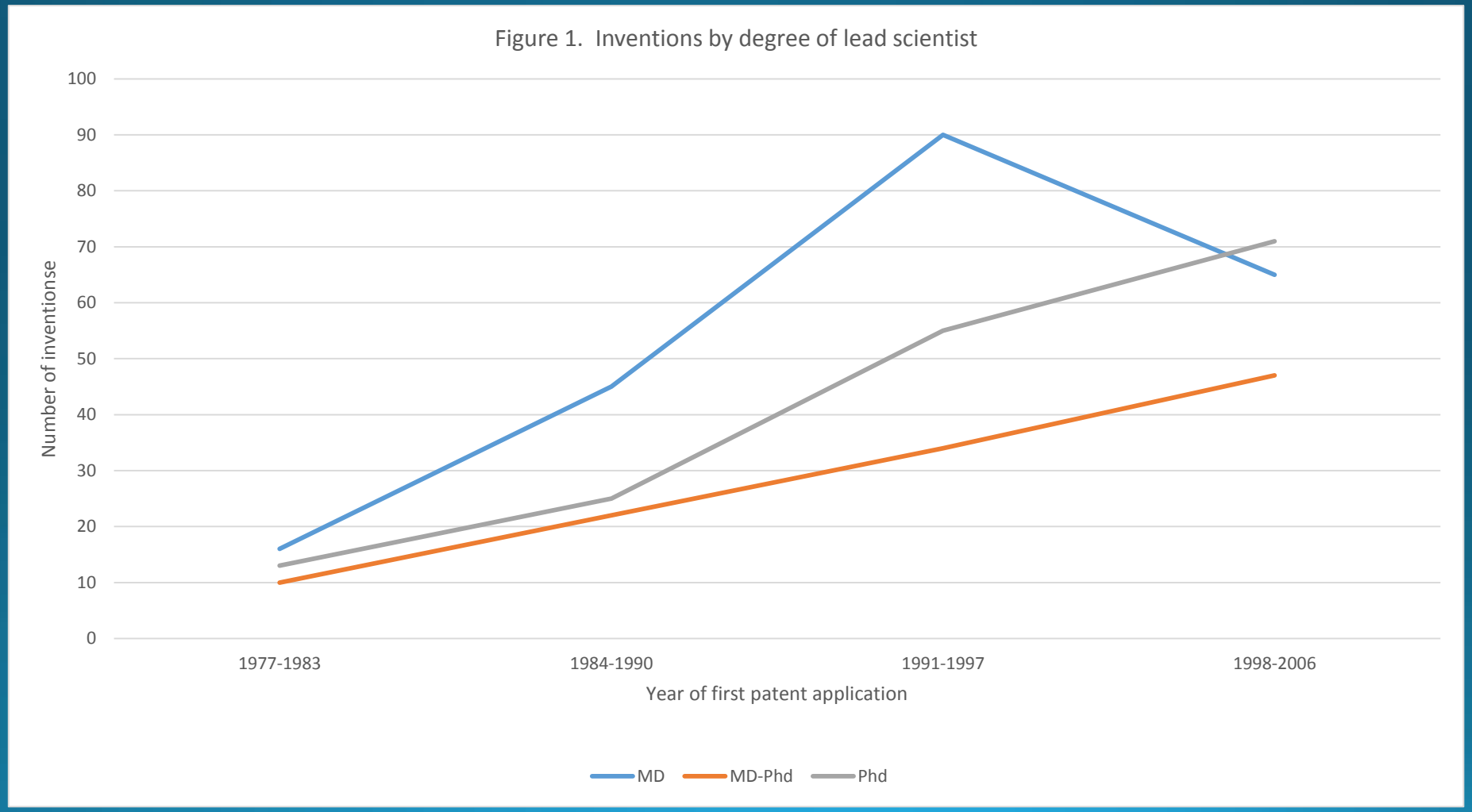
Dependent Variable - Time to license ~ Risk of ever being licensed

Explanatory variables:

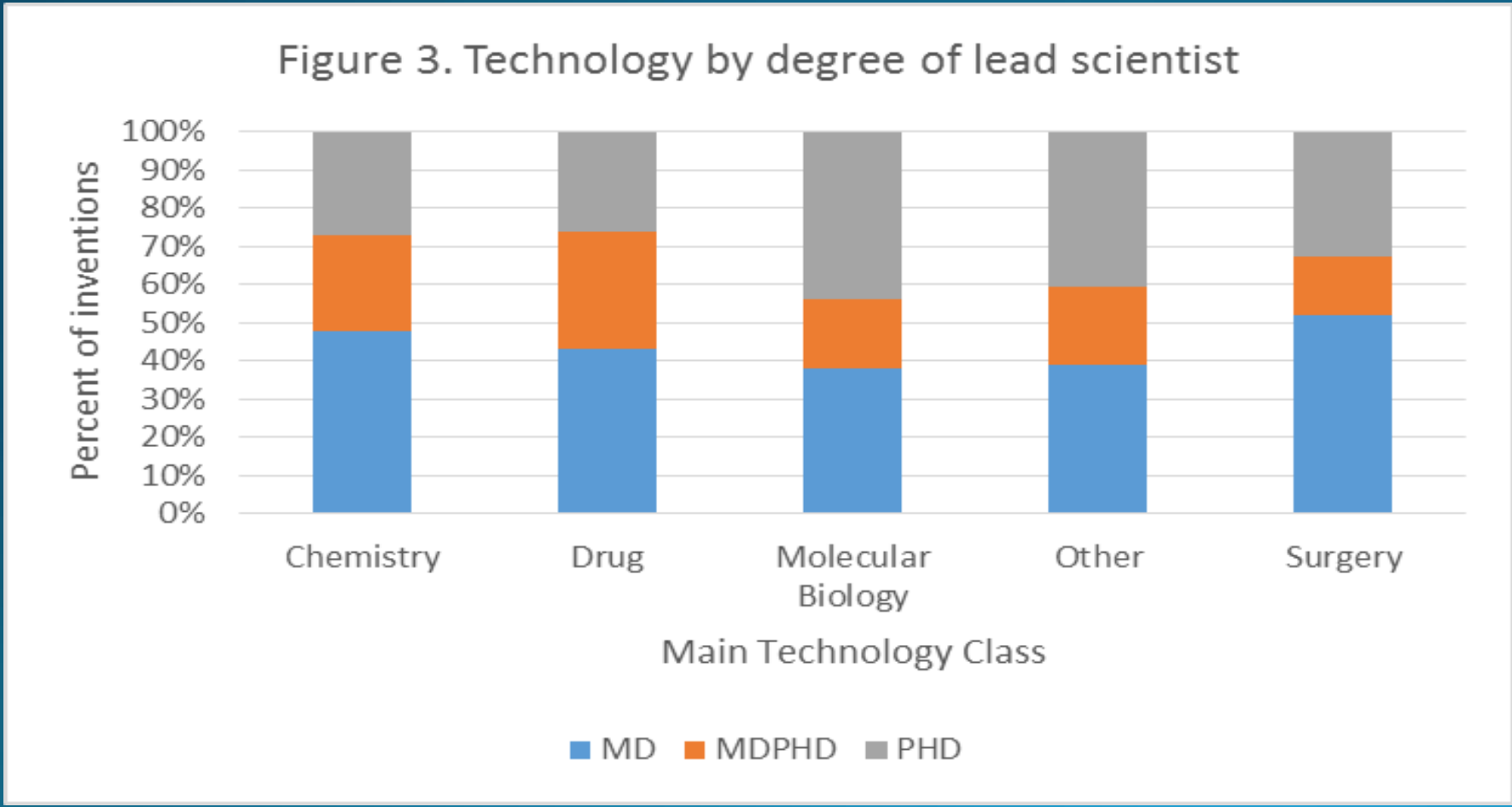
Team composition – all MDs, all Phds, Mixed MD/PhD Teams
Team leaders – MD, PhD, MD-Phd

Controls
Prior patents of inventors
Fixed Technology effects – seven technology groups
Scientific specializations of inventors
Scientific Stars
Bibliometric variables (*prior art, number of inventors, forward citations. . .)*

Steady rise in inventions by PhDs, reflects rise of basic science in medical research



MDs and PhDs patent across a wide range of technology classes – results not driven by field effects



- Half of molec. biology patents by clinicians
- One third of surgery inventions by Phds

	Controls	MD vs All Other Teams	Basic Research vs. All Other Teams	Cross Domain Teams	Team Leader Effects
Single Domain Clinical		0.52***			
		(0.193)			
Single Domain Research			-0.54**		
			(0.230)		
Cross Domain Integrated				-0.06	-0.42
				(0.206)	(0.325)
Cross Domain Distributed				-0.10	-0.15
				(0.244)	(0.249)
Lead MD					0.48**
					(0.207)
Lead MD-PhD					0.75**
					(0.350)
Clinician Star Scientist	0.91*	0.71	0.62	0.88*	0.72
	(0.484)	(0.497)	(0.501)	(0.492)	(0.504)
PhD Star Scientist on Team	-0.62	-0.50	-0.35	-0.58	-0.52
	(0.455)	(0.461)	(0.475)	(0.462)	(0.471)
Lead Inventor Experience	0.05***	0.05***	0.05***	0.05***	0.05***
	(0.015)	(0.0151)	(0.0153)	(0.0154)	(0.0158)

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	(0.455)	(0.461)	(0.475)	(0.462)	(0.471)
Lead Inventor Experience	0.05***	0.05***	0.05***	0.05***	0.05***
	(0.015)	(0.0151)	(0.0153)	(0.0154)	(0.0158)

	Controls	MD vs All Other Teams	Basic Research vs. All Other Teams	Cross Domain Teams	Team Leader Effects
Single Domain Clinical		0.52***			
		(0.193)			
Single Domain Research			-0.54**		
			(0.230)		
Cross Domain Integrated				-0.06	-0.42
				(0.206)	(0.325)
Cross Domain Distributed				-0.10	-0.15
				(0.244)	(0.249)
Lead MD					0.48**
					(0.207)
Lead MD-PhD					0.75**
					(0.350)
Clinician Star Scientist	0.91*	0.71	0.62	0.88*	0.72
	(0.484)	(0.497)	(0.501)	(0.492)	(0.504)
PhD Star Scientist on Team	-0.62	-0.50	-0.35	-0.58	-0.52
	(0.455)	(0.461)	(0.475)	(0.462)	(0.471)
Lead Inventor Experience	0.05***	0.05***	0.05***	0.05***	0.05***
	(0.015)	(0.0151)	(0.0153)	(0.0154)	(0.0158)

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	(0.015)	(0.0151)	(0.0153)	(0.0154)	(0.0158)

Discussion of results

- Controlling for fields and specializations, our results show
  - patented inventions by MD are more likely to be licensed than inventions by PhDs
  - teams that are led by MDs are more likely to be licensed than teams led by Phds
- Results support the proposition that the clinical research paradigm remains an important driver of medical innovation, even in an era of rising basic science and analytical techniques
- Teams that combine MDs and Phds are not more likely to be licensed
  - Results question translational policies that promote integration of knowledge through large teams

Has basic science been a setback for medical progress?

- More medical researchers are going into basic science, but basic science may be poorly adapted to medical innovation
  - Does not accommodate the enormous complexity of human disease
  - Was over-hyped as a discovery platform
  - Might explain why discovery has been flagging in recent decades
  - Despite the poor record, more resources continue to be spent on basic science and "hyped" fields
- We argue that research on patient populations is a more optimal starting point for the discovery process
- Most valuable resource likely to be clinical data – creating, accessing and sharing it will be key for private sector discovery efforts

Thank you!

"Improving Success In Collaborative R&D"

By Selecting An Optional Alliance Structure And Partner Type

Wednesday, October 26th

11:30AM –1:00PM

Room 1123

1 Washington Park,

OFF CAMPUS? Join us via

Live-Webcast

Jeongho Choi, Ph.D.

Farok Contractor, Ph.D.