Development in Pharma R&D

Charles Baum, MD, PhD
Senior Vice President, Pfizer

R&D Productivity

SPECTRUM A Service

Discovery and Innovation: Technologies, Strate

Barbara M. Bolten, M.S., M.B.A., Senior Program Manage

Rethinking Pharmaceutical R&D: Will New Strategies Yield a Pipeline

Barbara M. Bolten, M.S., M.B.A.

Decision Resources

"Pharmaceutical companies must rapidly reform R&D to meet pressing challenges facing the industry. However, restructuring and shrinking R&D units is not enough to increase R&D productivity: companies must identify the right targets and efficiently implement new technology to discover novel, innovative drugs."

Morgan Stanley

February 5, 2010

Industry View
Attractive

Pharmaceuticals

Research shrinkage. Even faster than we envisaged

Quick Comment – Impact on our views: Recent presentations at FY09 results by GSK and AZN support our recent industry thesis anticipating a much-accelerated shrinkage of significant parts of the small molecule research infrastructure, we believe. Given GSK and AZN comments, we expect Sanofi Aventis to outline a similar strategy at their results next week. We reiterate our thesis that small molecule

Morgan Stanley

January 20, 2010

Industry View
Attractive

Pharmaceuticals

Exit Research and Create Value

Still significant value in Pharma – we see material upside to ROIC, earnings and multiples as Pharma withdraws from most internal small molecule research and reallocates capital to in-licensing and other non-pharma assets. Worsening generic pressure

ANALYSIS

Lessons from 60 years of pharmaceutical innovation

nvestment in pharmaceutical research and development
proved by the US Food and Drug Administration (FDA)
s conundrum, this article investigates the record of
ysing data on the companies that introduced the
pproved by the FDA since 1950. This analysis shows that
eutical companies in this period has essentially been
e attempts to increase it. This suggests that, contrary to
output is not depressed, but may simply reflect the
L The implications of these findings and options to
aceutical industry are discussed.

REUTERS

Special Report: Big Pharma's stalled R&D machine

Wed, Jun 16 2010

By Ben Hirschler and Kate Kelland

LONDON (Reuters) - At just 28, Duncan Casey has already been from the university science bench to the world of Big Pharma research and back again. Now working in an Imperial College lab tucked behind London's famous Science Museum, he has no illusions about the prospects for researchers in the pharmaceutical industry.

"The unit I used to work in -- GlaxoSmithKline's place in Harlow -- has been closed down now," says Casey, dressed in signature protective goggles and white coat as he works on synthetic chemistry. "It used to be a job for life. Now it's a job until the next restructuring."

Across the western world, Big Pharma is cutting back on the number of scientists it employs in its labs and the money it spends on research and development. The hunt for new drugs continues, but the men and women in white coats -- traditionally viewed as the lifeblood of the industry -- are not as untouchable as they once were.

Pfizer

February 2010; doi:10.1038/nrd3078

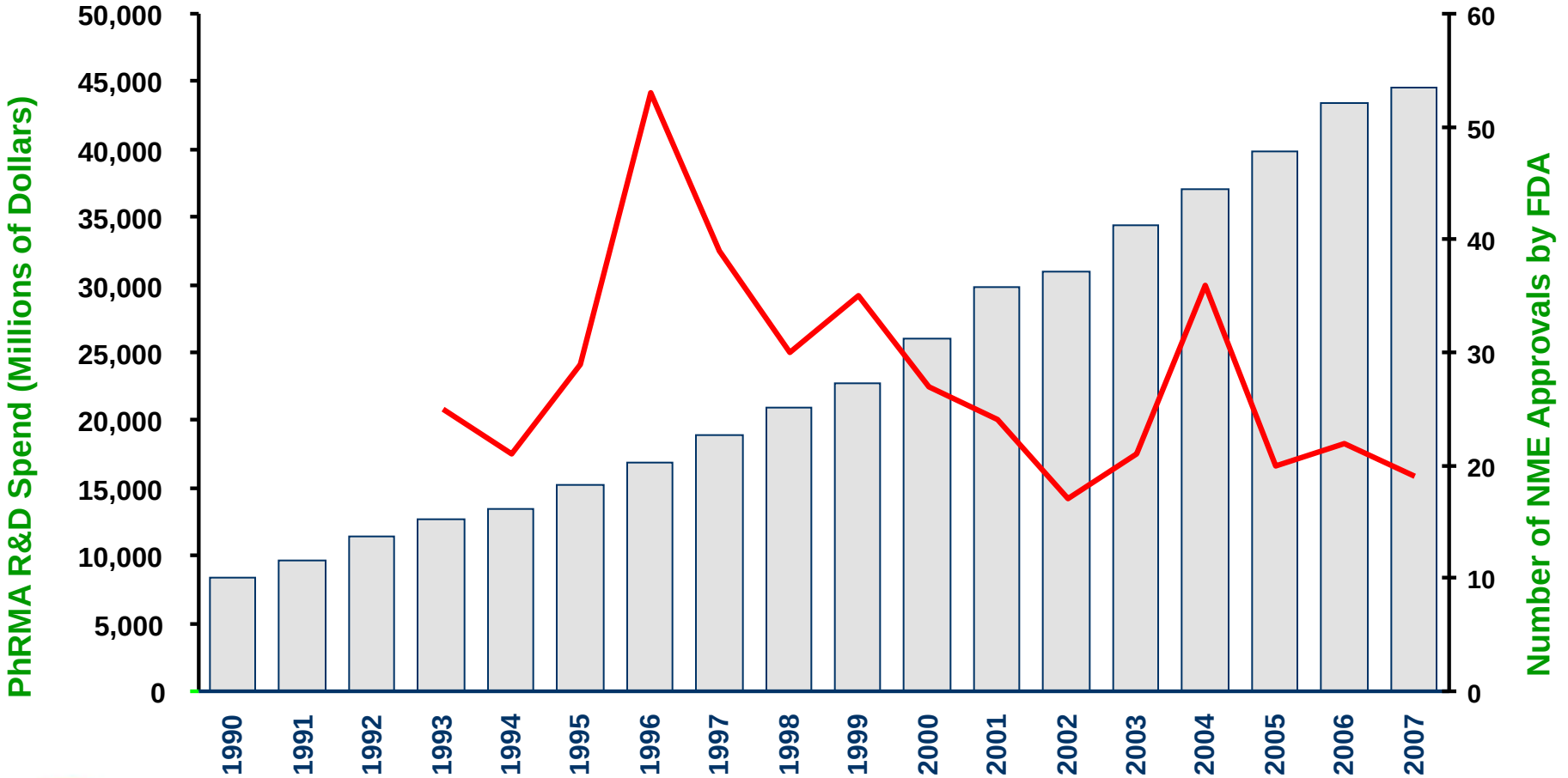
ANALYSIS

How to improve R&D productivity: the pharmaceutical industry's grand challenge

Steven M. Paul, Daniel S. Mytelka, Christopher T. Dunwiddie, Charles C. Persinger, Bernard H. Munos, Stacy R. Lindborg and Aaron L. Schacht

Abstract | The pharmaceutical industry is under growing pressure from a range of environmental issues, including major losses of revenue owing to patent expirations,

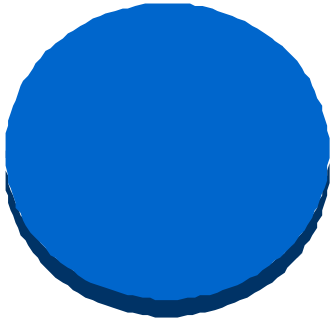
R&D Output Across The Industry Is Flat, Despite Increasing Investment Over The Last 20 Years



Source: Pharmaceutical Research and Manufacturers of America, PhRMA Annual Membership Survey, 2008; CDER

Cost To Launch Is Driven By Attrition

Cost Of One Program To Market



>$100 Million

Portfolio Cost Of One Program, Including Attrited Projects

>$1 Billion

Single Program **Attrited Programs**

Pfizer

Evolution of the R&D Organization

2003-2007

- 21 sites in 10 countries
- 14 layers from CEO to bench scientists
- 56 committees
- Complex, numerous “activity” & CAN output goals
- Numerous Research projects
  - *Multiple portfolio review processes*
  - *38 Disease Areas*
- Large Research groups up to 1000 scientists responsible only to First-in-Human
- 4 levels of review, approval for decisions
- No formal external science advisory body
- >90% science conducted in house

2010

- 4 major R&D sites
- 8 or fewer layers from CEO to bench scientists
- 11 committees
- New value-based goals that rewards positive POC
- Focus on Research projects with strong human disease correlation
  - *In-depth portfolio review prioritization*
  - *29 Disease Areas*
- Smaller Research Groups driving to POC
- Fully empowered Chief Scientific Officers
- Six Scientific Advisory Panels
- 30% of science conducted externally

Utilizing Independent Research Units Conveys Significant Benefits

- **Clarity of objectives**
- **Colleagues identify and connect with their projects**
- **Small size allows robust interactions and timely decisions**
- **Entrepreneurial spirit**
- **Concentration of expertise to share best practices and problem solve**
- **Strategy to optimize all aspects of the unit's operations**
  - Focus on identifying new opportunities and emerging Science and Technology
  - Deep understanding of the options at each stage of development
- **Specific funding earmarked for the unit's needs**

Focus **Alignment** **Nimbleness**

Pfizer

Scientific Advisory Board: Richard Lerner (Chair), Paul Greengard, David Goeddel, Gunter Bloebel, Greg Winter, Fred Appelbaum

Smaller Research Units Headed By An Accountable CSO

- Pain
- CV & Metabolic
- Inflammation
- Oncology
- Neuroscience
- Antivirals
- Antibacterials
- Allergy & Respiratory
- Genitourinary

- Vaccines
- Regenerative Medicine
- Indications Discovery

Enabled By

- Medicinal Chemistry
- Clinical
- Biotherapeutics
- Comparative Medicine
- *PDM
- Centers of Emphasis
- Research Portfolio

–*Pharmacokinetics,
–Pharmacodynamics & Metabolism

New Operating Model

Nine Diverse Businesses Supported by an Integrated Research & Development Organization

Biopharmaceutical Businesses

- Primary Care
- Specialty Care
- Oncology
- Established Products
- Emerging Markets

Diversified Businesses

- Animal Health
- Capsugel
- Consumer Healthcare
- Nutrition

Worldwide Research & Development Including: PharmaTherapeutics, BioTherapeutics, Vaccines and Biotech units

Business Units Including: Development, Medical, Sales & Marketing

Manufacturing

Enabling Functions

Customer Focused

Traditional Drug Discovery Paradigm…

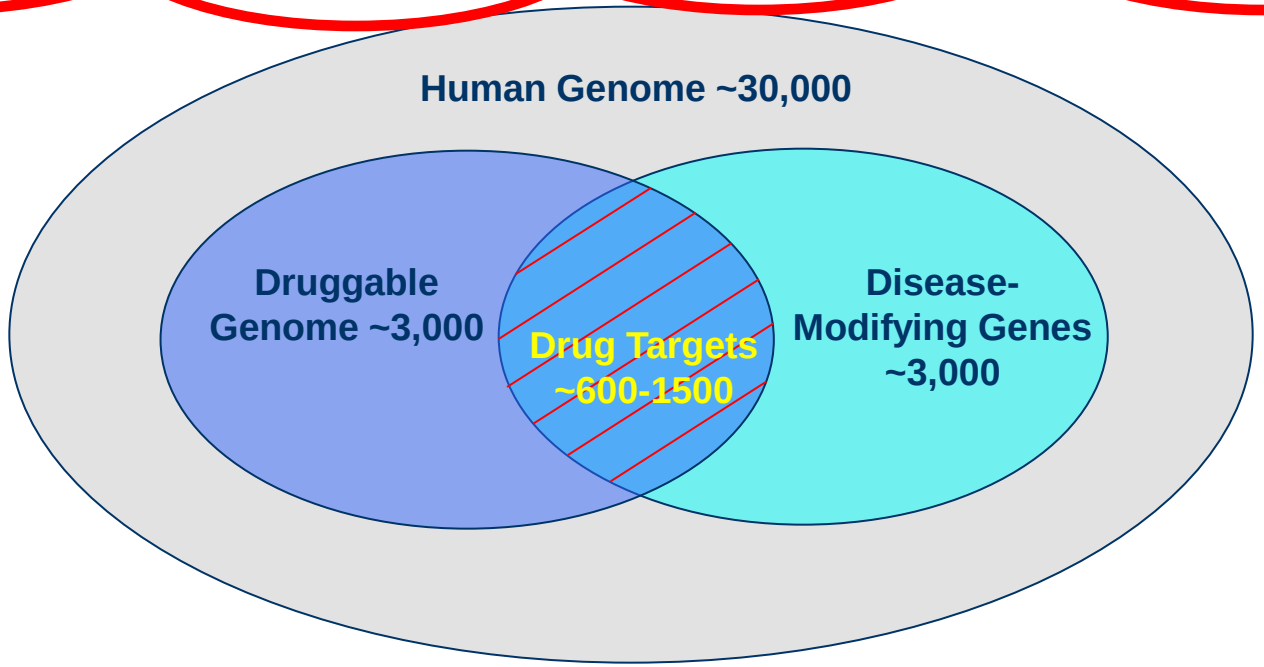
Pick A Target → Pick A Molecule → Clinical Test

Druggable Protein Classes

Validation in Animal Models

Small Molecule Chemistry

Phase I, Phase II Trials

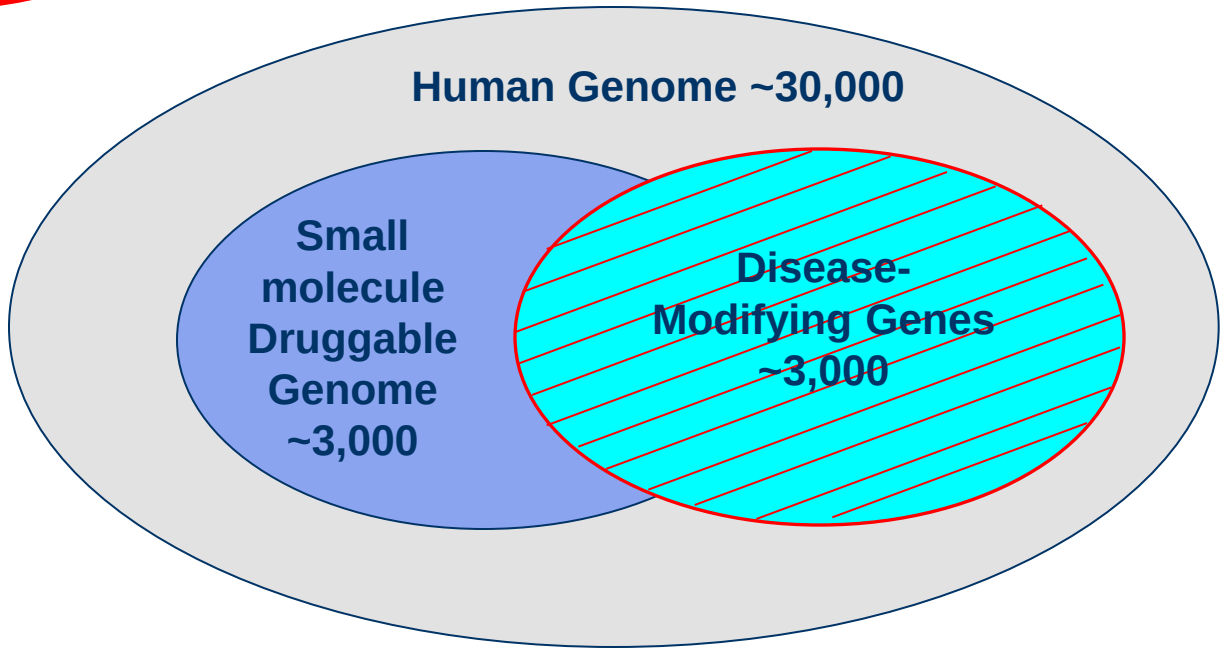


Source: Hopkins, A.L. and C.R. Groom, The druggable genome. Nat Rev Drug Discov, 2002. 1(9): p. 727-30.

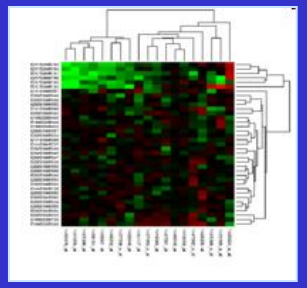
The Emerging Paradigm: In Depth Knowledge Of Targets And Pathways

The Best Target → **The Best *Small or Large* Molecule** → **Clinical Learning Loop**

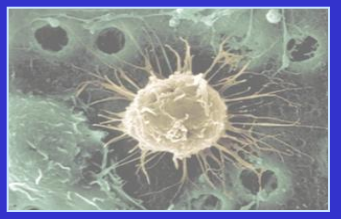
Human Biology Target Validation | ***Pathway Expansion*** | ***Expanding Target Tractability*** | ***Definitively Testing Mechanism***



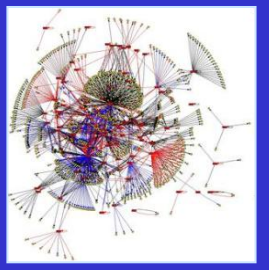
Human Genetics & Cell Biology Are Revolutionizing Target Selection



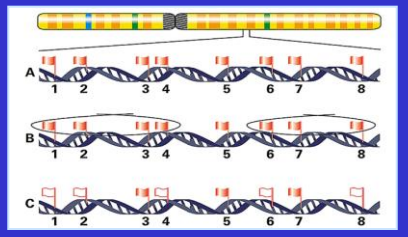
– *Molecular Profiling*



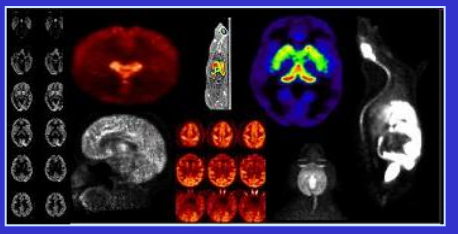
– *Stem Cells*



– *Systems Biology*



– *Human Genetics*



– *Bioimaging*

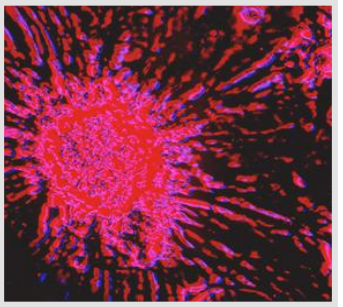
Innovative Therapies In Key Areas Of Unmet Medical Need

Neuroscience/Pain

Inflammation/ Immunology

Infectious Diseases

Oncology

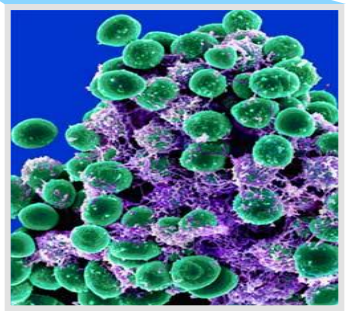


CV/Metabolic

Focus is on High Priority Disease Areas Using Various Modalities

Vaccines

Small Molecules



Biologics

11

Patient Segmentation Has Potential To Improve Clinical Outcomes

Research

- Patient segment understanding seeds new research
- Disease understanding drives more informed target selection

Development

- Higher probability of success
- Fast termination of projects that are going to fail
- Cheaper and potentially faster to patients

Regulatory, Payers, and Market

- Greater assurance for payers on outcome for spend
- More confidence in risk/benefit ratio
- System benefits of healthier population

Patients

- Get drugs that work better, with less risk
- Won't waste valuable time on drugs that won't work
- Improved compliance resulting from greater efficacy

Pfizer

Targeting Lung Cancer Treatments In Patient Subsets To Improve Outcomes

Crizotinib: A potent and selective oral inhibitor of MET and ALK

... initially being developed for MET mechanism

Academic discovery of new patient segment redefined lung cancer

10-15%[1] of non small cell lung cancer (NSCLC) patients with fusion oncogene ELM4-ALK[2] are unresponsive to conventional EGFR inhibitor[1] treatment

New Phase I trial targeting advanced NSCLC patients harboring ALK rearrangement

Highly effective therapy

Overall response rate = 65%

Disease control rate = 84% at a median of ~24 weeks

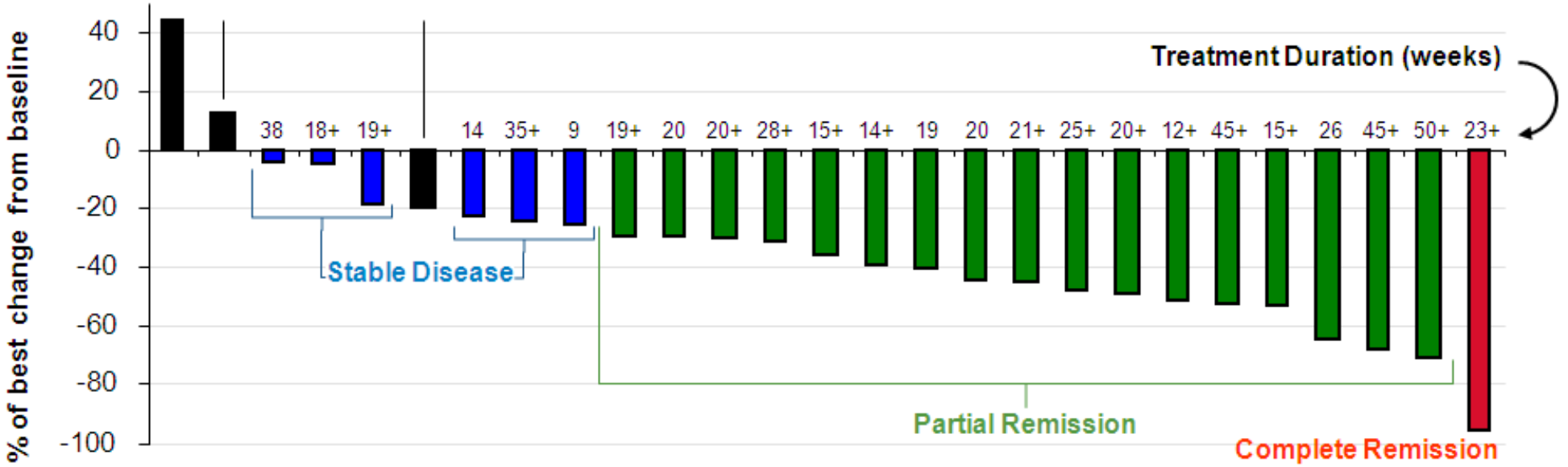
Accelerated clinical activities

Initiated Phase 3 trial based on Phase 1 results, bypassing Phase 2 and accelerating development timeline

1. Shaw AT et al., J Clin Oncol. 2009; 27:4247-4253
2. Manabu Soda et al., Nature 2007; 448, 561-566

Clinical Outcome For NSCLC Patients After Crizotinib Treatment

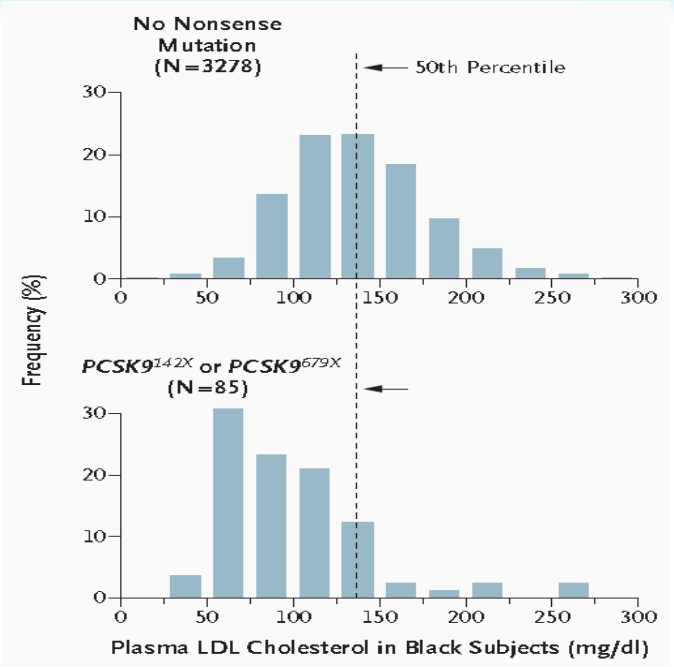
Tumor size change in NSCLC patients treated with C-Met/ALK inhibitor

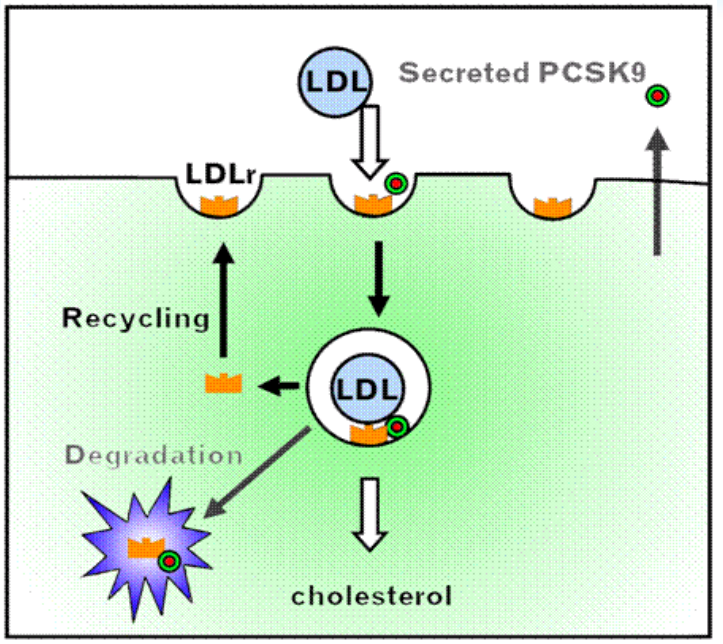


Note: Patients in trial composed of 2nd to 4th line. 1st line response to Standard of Care: ~50%, 2nd line: ~10%, 3rd line: 3-5%

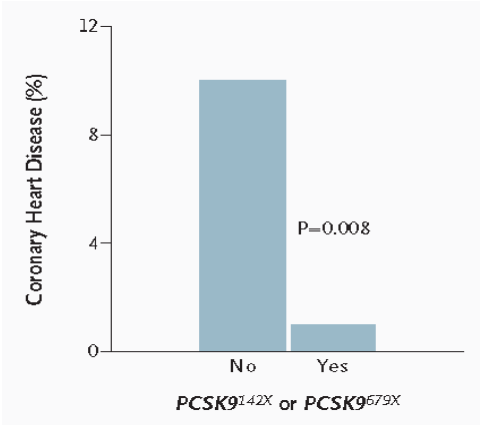
Loss Of Function of PCSK9 Result In Reduced LDL-C And CHD Events

28%
in LDLc





88% in CHD events in 15 yrs



No Ab:
- PCSK9 ↑
- LDLr ↓
- LDL ↑

With Ab:
- PCSK9 ↓
- LDLr ↑
- LDL ↓

Characterization Of RN316

- **Anti-PSCK9 antibody (RN316; PF-04950615)**
  - Humanized monoclonal antibody
  - Binds to LDLR binding domain of PCSK9
  - Specific to human (5pM), mouse, rat and cynomolgus PCSK9
  - Completely blocks PCSK9 function in binding and cell base assays

- **Efficacy and safety in animals**
  - Reduces cholesterol in rodents
  - Selectively reduces LDL-c by 80% in NHP, without significant effects on HDL-c
  - LDL lowering effect is additive with a statin in hypercholesterolemia NHP
  - No drug related toxicity observed in rodents and NHP

Significant Limitations For Meaningful Patient Segmentation

- **Our disease understanding lags our desire to match mechanisms and targets with patient and disease subsets, *a priori***
- **Lack of translational cell / animal models and tools needed to predict human segments and select therapeutic targets**
- **Few biomarkers clinically validated to support patient segmentation, predisposition to disease and therapeutic response**

Biomarker Challenges For Rapid Efficacy And Safety Testing Of Innovative Drugs

Challenges	Examples
Develop and qualify biomarkers for early disease modification	Cerebral spinal fluid Aß for Alzheimer's
Synchronize biomarker and drug development, including approval of biomarker as diagnostic at launch	KRAS not identified as biomarker for EGFR inhibitors until post-marketing
Partner with payers for clinical translation of biomarkers, conduct of clinical trials and reimbursement of diagnostics	PBMs conducting clinical trials on diagnostic-drug pairs for private payer industry in US
Engage patient groups for support in biomarker development and biomarker-driven clinical trials	Alzheimer's Association quality control program to standardize cerebrospinal fluid biomarker measurement
Develop better models to assess biomarker-driven drug development costs and market fragmentation by biomarkers/diagnostics	MIT stratified medicine model

Understanding Disease Biology Is Not A Competitive Activity

Lilly, Merck, Pfizer Join Forces For Lung, Gastric Cancers In Asia

Eli Lilly, Merck (Merck Sharp & Dohme (MSD)) and Pfizer have formed an independent, not-for-profit company Asian Cancer Research Group (ACRG) to accelerate research

RESEARCH & DEVELOPMENT NEWS

Lilly, Merck, And Pfizer Announce the Formation of the Asian Cancer Research Group, Inc.

REUTERS EDITION: IN News & Money Sectors & Industries Analysis & Opinion

LATEST KEY DEVELOPMENTS

Eli Lilly and Company, Merck & Co., Inc. And Pfizer Establish Asian Cancer Research Group, Inc.

Tuesday, 23 Feb

Lilly, Merck and Pfizer establish Asian Cancer Research Group to accelerate drug discovery for lung and gastric cancers

Feb 23, 2010 (M2 EQUITYBITES via COMTEX) --

Major U.S. Drugmakers Form Asian Research Center

NEW YORK (AP) -- Three major U.S. drugmakers, Eli Lilly and Co., Merck & Co. and Pfizer Inc., said Tuesday they have formed a not-for-profit company in Asia to focus on cancer research and treatments.

The companies said they formed the Asian Cancer Research Group to focus on the most commonly diagnosed cancers in Asia, including lung and gastric cancers.

They did not say in a news release how much funding they were committing to the project.

Over the next two years, Lilly, Merck and Pfizer said they will create an extensive database that will be made available to researchers.

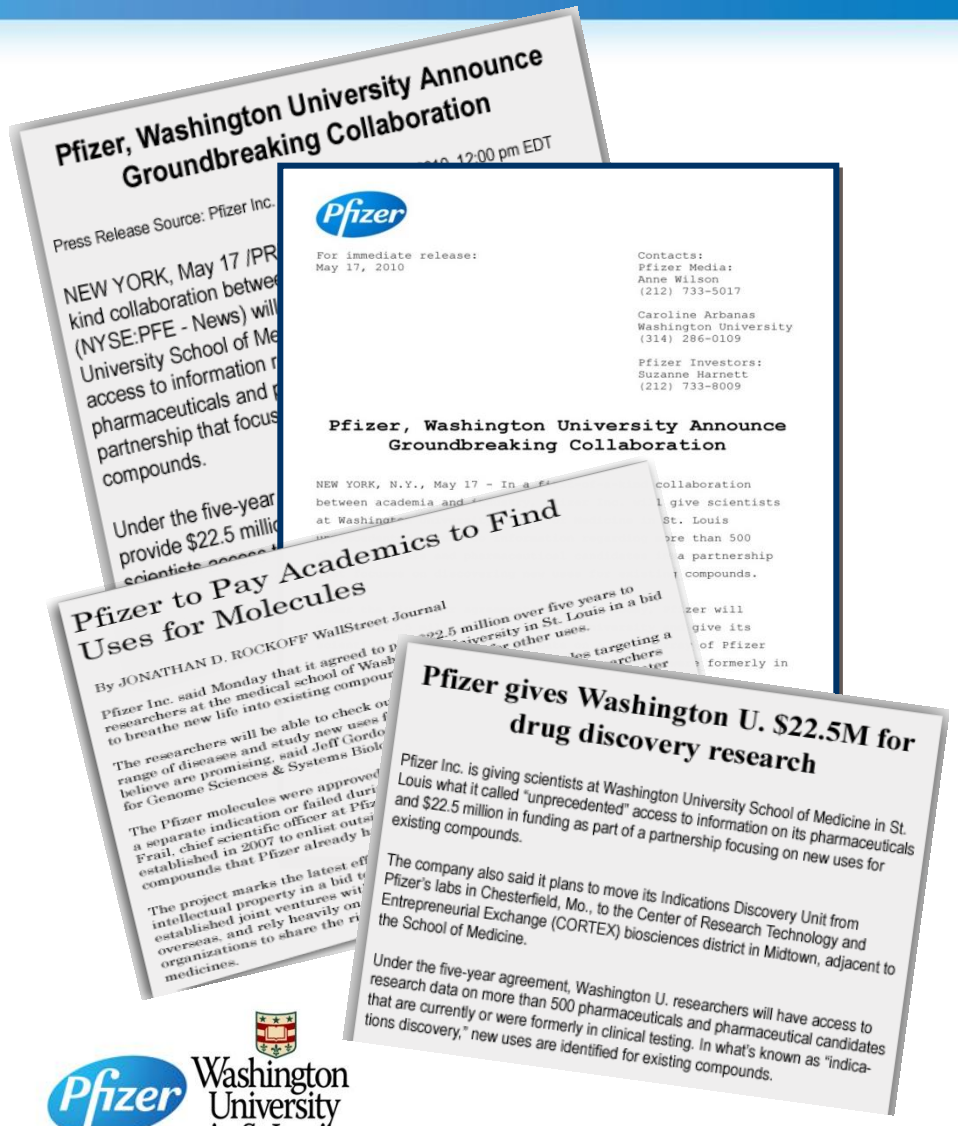
"The goal of the Asian Cancer Research Group is to improve the knowledge of cancers prevalent in Asia and to accelerate drug discovery efforts by freely sharing the resulting data with the scientific community," the companies said.

They said as many as 40 percent of patients with lung cancer in Asia demonstrate a mutation that is relatively rare in Western patients, suggesting a different research approach is needed for developing treatments.

Pfizer

Building Networks: Collaborations With The Best Science Across The Globe

Open Innovation:
Industry – Academy Partnerships



- **Unprecedented access via a confidential web portal to more than 500 Pfizer compounds**
- **Enables new discoveries with existing compounds**

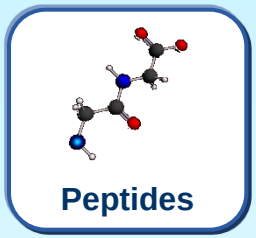
Medical School Partnerships: Pfizer, Broad & Massachusetts General Hospital

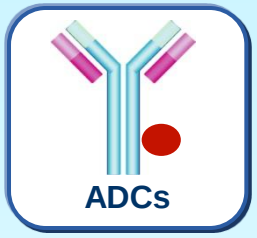
- Identifying human gene variants that protect diabetics from heart-attacks, and people from becoming diabetic
- Collaboration focus is on understanding this complicated disease, identifying novel therapeutic pathways and targets, and developing genetic risk models to guide clinical study patient selection
- Daily, no-holds barred scientific exchange exemplifies the collaboration

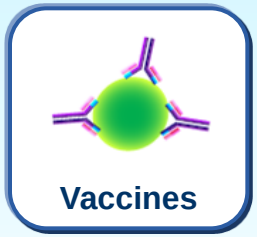
Pfizer MGH 1811 Pfizer BROAD INSTITUTE LUND UNIVERSITY

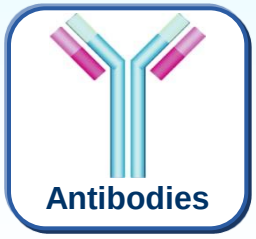
New Drug Design Platforms Are Emerging

Proven technologies to deliver high impact medicines


Peptides


ADCs


Vaccines

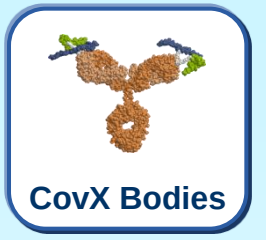

Antibodies

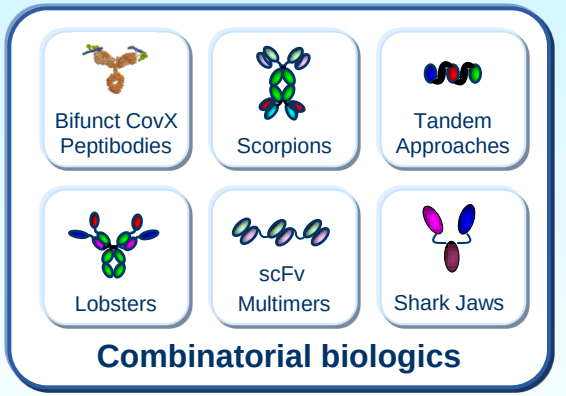

Therapeutic Proteins

The Right Molecule for Every Patient

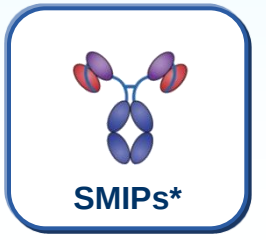
Emerging drug design technologies

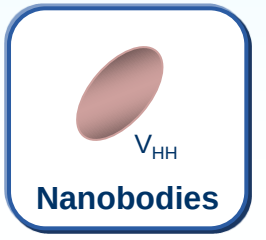

Shark IgNARs


CovX Bodies



Combinatorial biologics


SMIPs*



Nanobodies

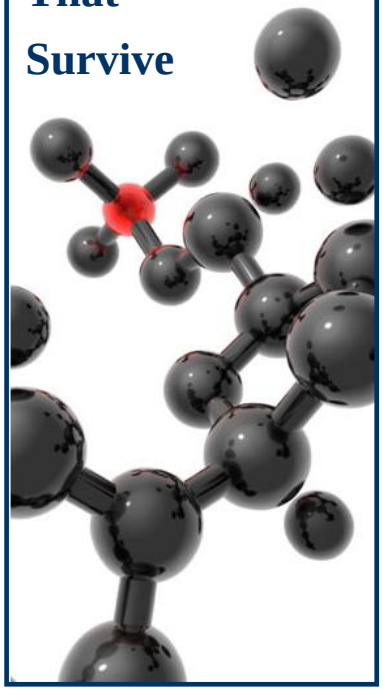
**SMIP™ Trubion Pharmaceuticals*

Four Imperatives For Success

Be Right About Targets

Select the Right Patients

Design Molecules That Survive



Move Faster, Better Patient Outcomes