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
euticel 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
aceut cal 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.

February 2010; doi:10.1038/nrd3078

ANALYSIS

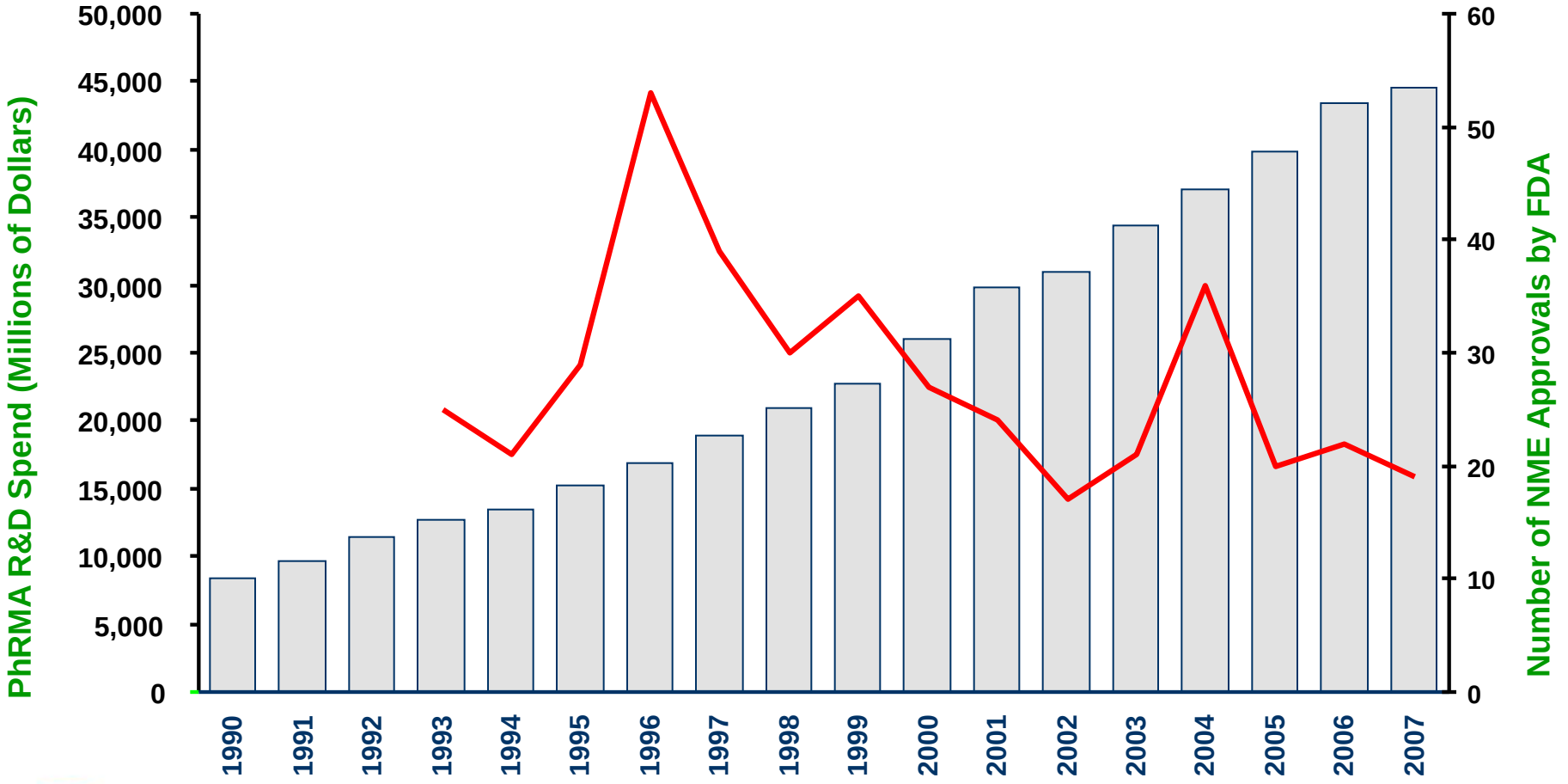
How to improve R&D productivity: the pharmaceutical industry's grand challenge

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,

Pfizer

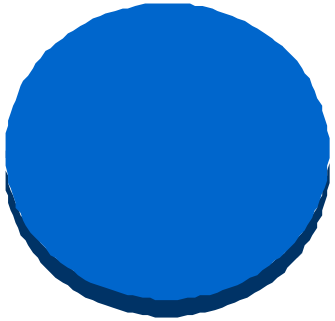
R&D Output Across The Industry Is Flat, Despite Increasing Investment Over The Last 20 Years



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

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…

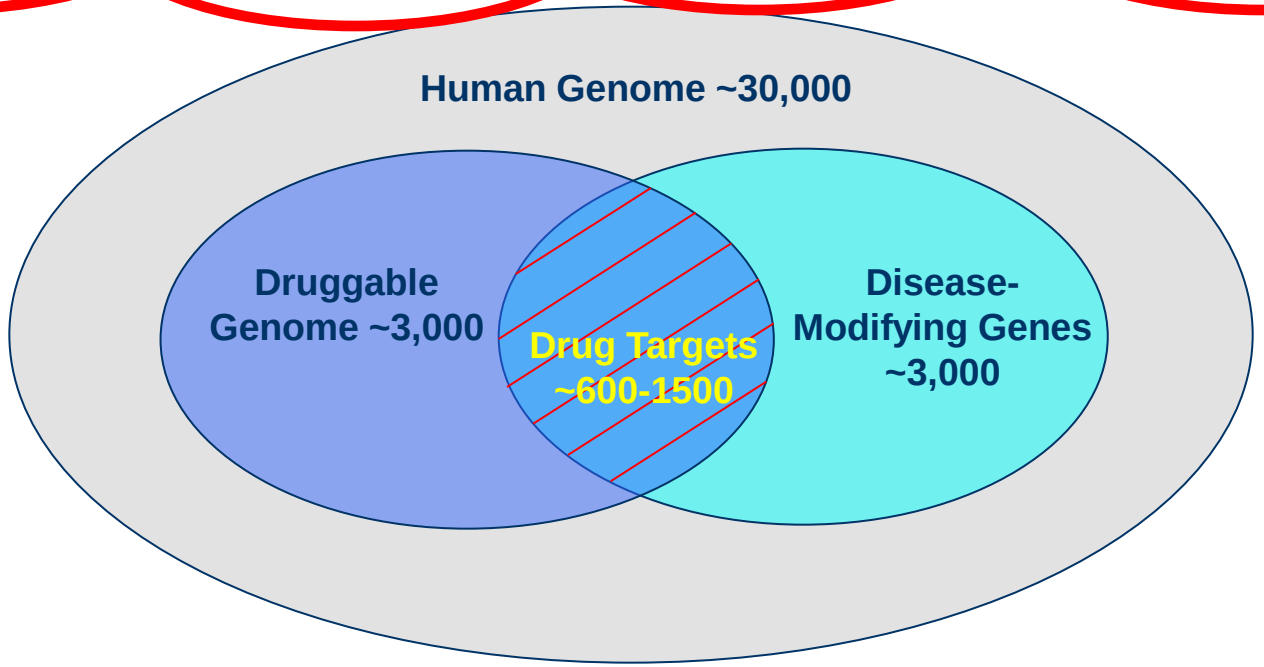
Pick A Target → Pick A Molecule → Clinical Test

Druggable Protein Classes

Validation in Animal Models

Small Molecule Chemistry

Phase I, Phase II Trials

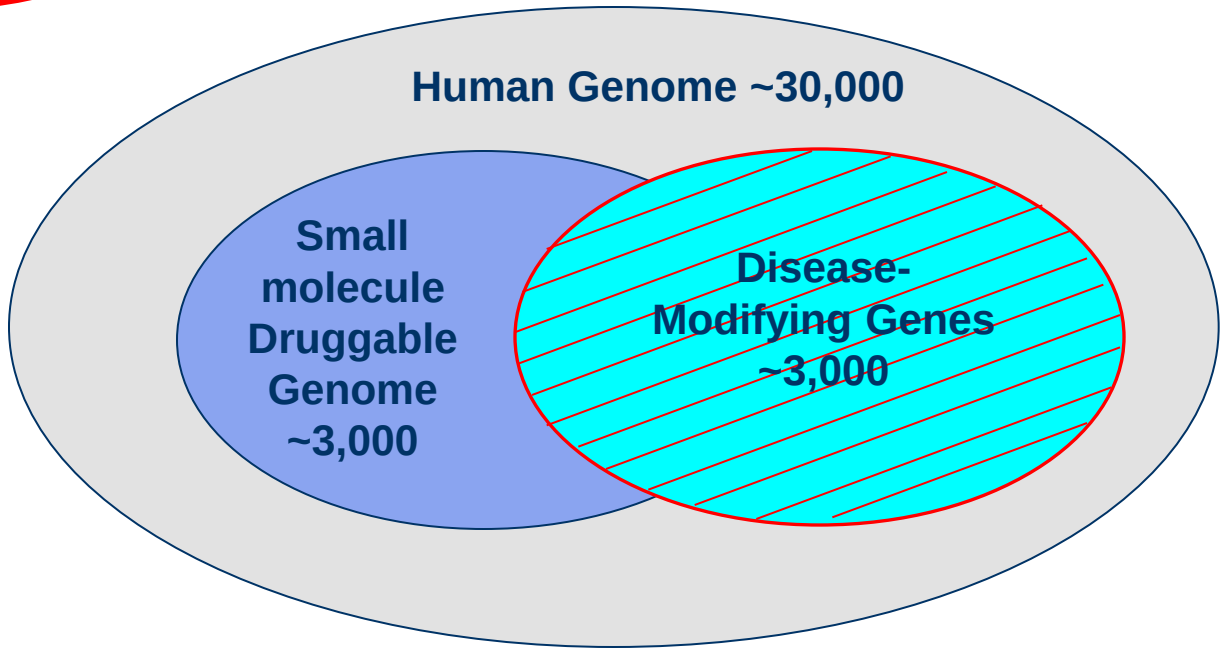


Source: Hopkins, A.L. and C.R. Groom, The druggable genome. Nat Rev Drug Discov, 2002. 1(9): p. 727-30.

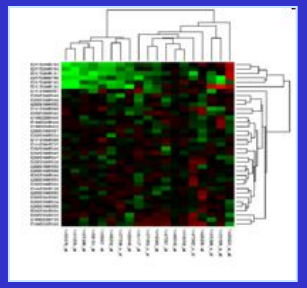
The Emerging Paradigm: In Depth Knowledge Of Targets And Pathways

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

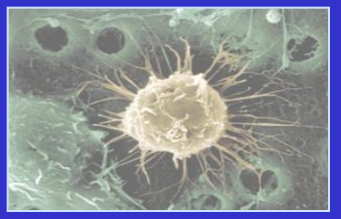
Human Biology Target Validation | ***Pathway Expansion*** | ***Expanding Target Tractability*** | ***Definitively Testing Mechanism***



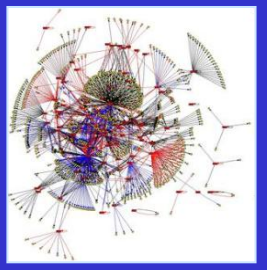
Human Genetics & Cell Biology Are Revolutionizing Target Selection



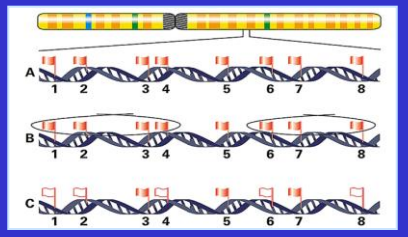
– *Molecular Profiling*



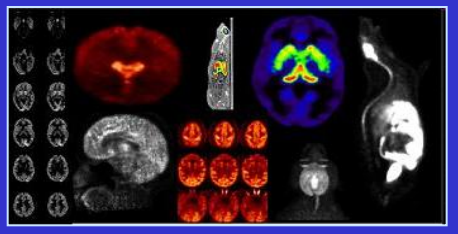
– *Stem Cells*



– *Systems Biology*



– *Human Genetics*



– *Bioimaging*

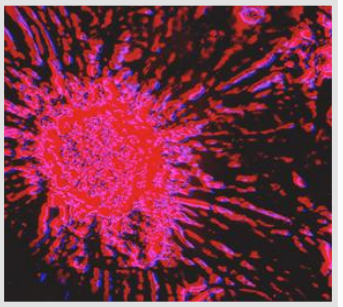
Innovative Therapies In Key Areas Of Unmet Medical Need

Neuroscience/Pain

Inflammation/ Immunology

Infectious Diseases

Oncology

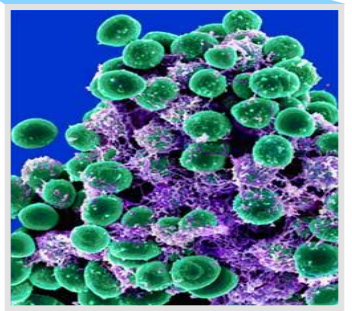


CV/Metabolic

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

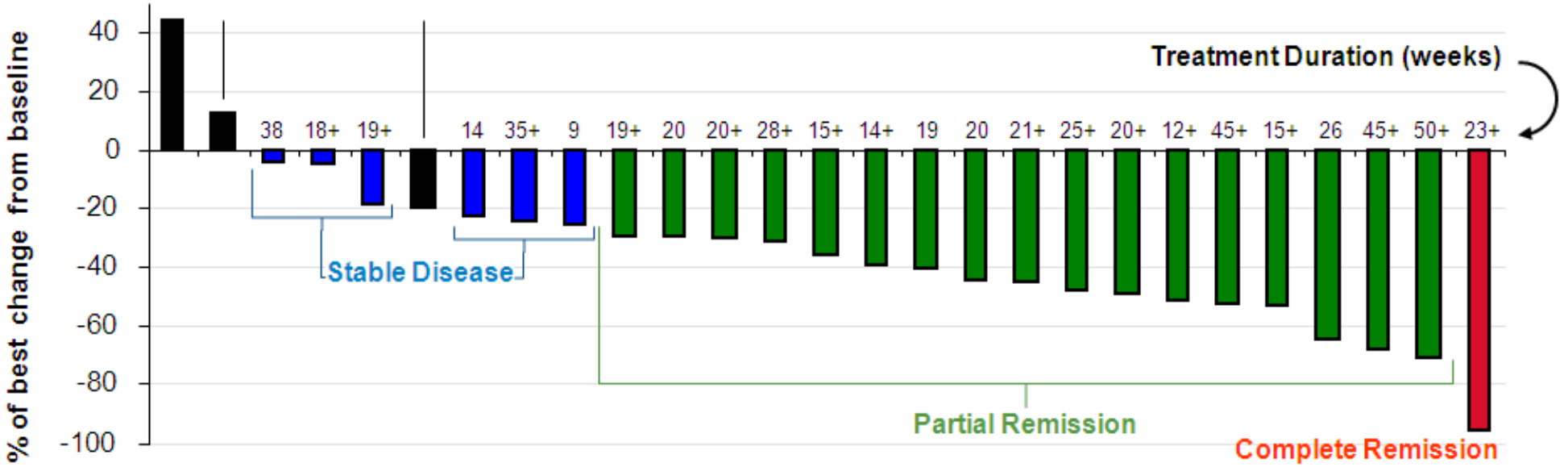
Accelerated clinical activities

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

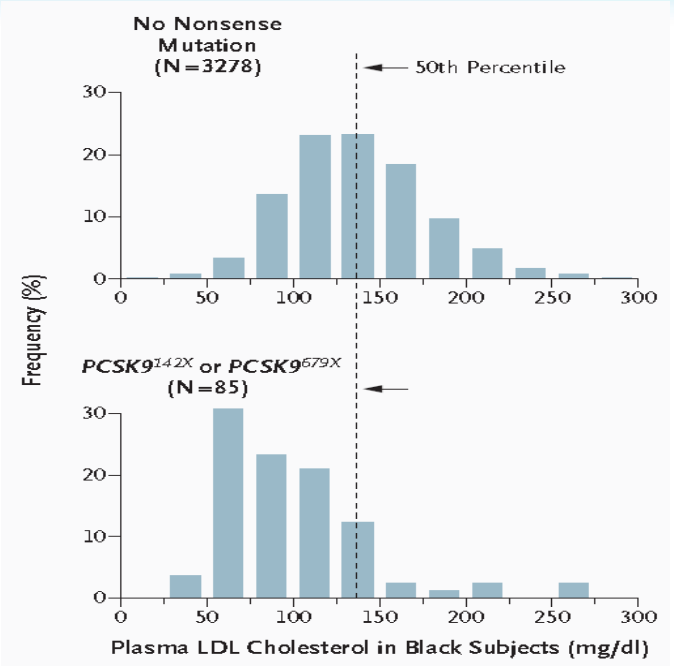
Tumor size change in NSCLC patients treated with C-Met/ALK inhibitor

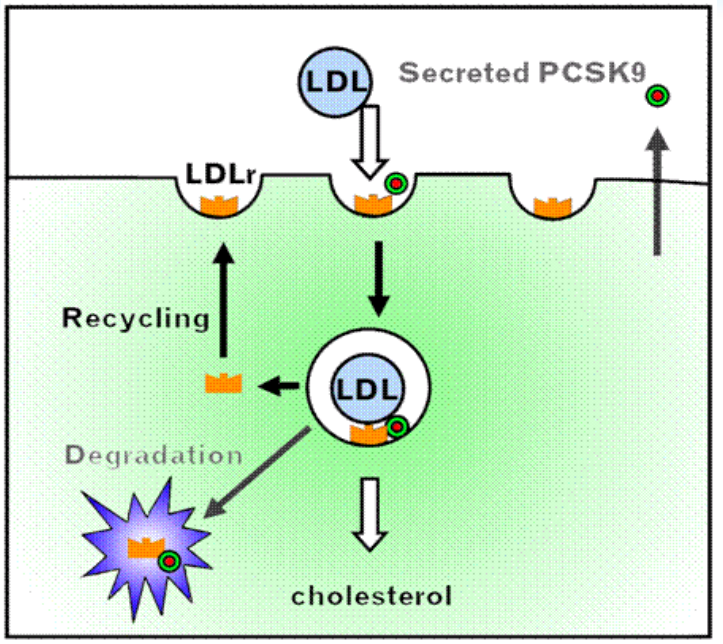


Note: Patients in trial composed of 2nd to 4th line. 1st line response to Standard of Care: ~50%, 2nd line: ~10%, 3rd line: 3-5%

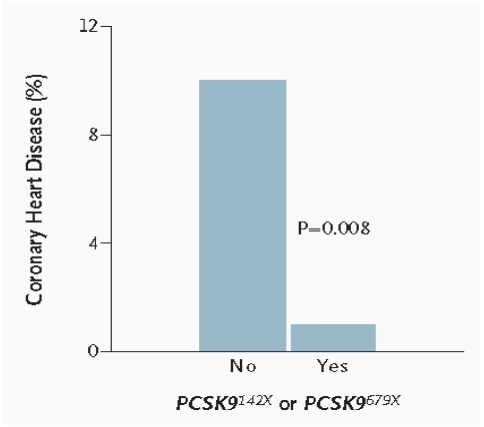
Loss Of Function of PCSK9 Result In Reduced LDL-C And CHD Events

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 and

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

Eli Lilly and Company, Merck & Co., Inc., and Pfizer Inc. announced that they have formed the Asian Cancer Research Group, Inc., a not-for-profit company formed to accelerate research and improve treatments for lung and gastric cancers. The ACRG's formation represents a collaboration between three large pharmaceutical companies to focus on lung cancer, the most commonly-diagnosed cancers in Asia and to accelerate drug discovery for lung and gastric cancers.

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) --

Company (NYSE: LLY | PowerRating), Merck (NYSE: MRK | PowerRating) declared on Tuesday that they have entered Cancer Research Group Inc (ACRG).

r-profit company formed to accelerate research and s affected with the most commonly-diagnosed cancers in and gastric cancers.

extensive pharmacogenomic cancer database over the next d of data from approximately 2,000 tissue samples from will be made publicly available to researchers and, over rom a longitudinal analysis of patients.

data to the research public through an open-source rch site. In addition the three ACRG partners will each

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.

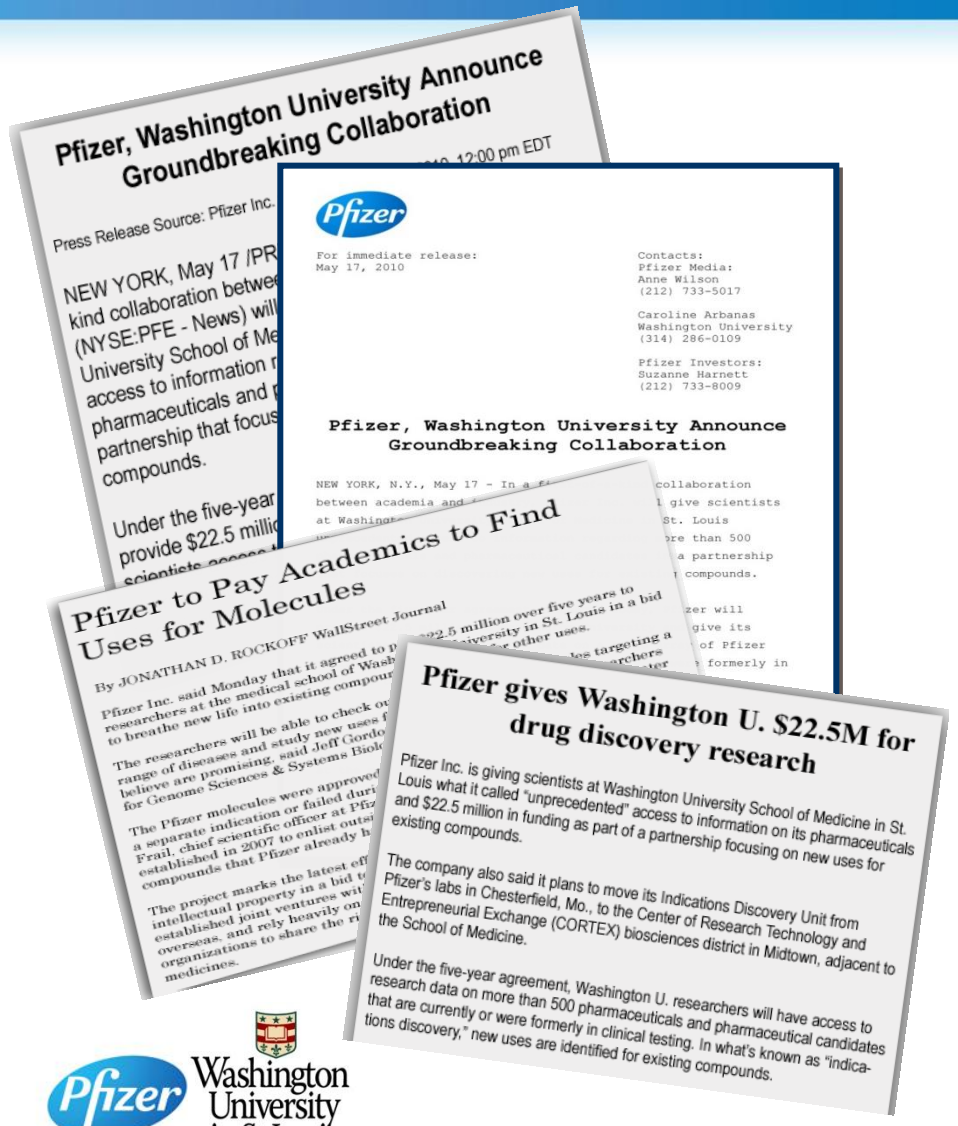
"The goal of the Asian Cancer Research Group is to improve the knowledge of cancers prevalent in Asia and to accelerate drug discovery efforts by freely sharing the resulting data with the scientific community," the companies said.

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**

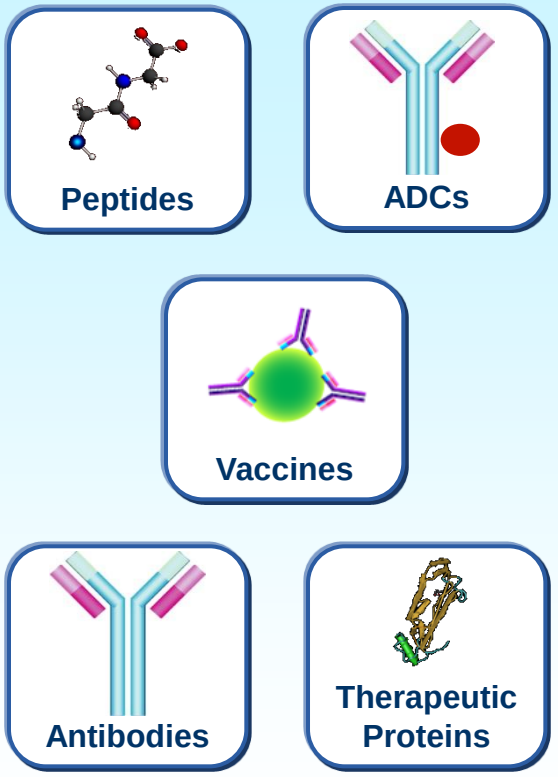
Medical School Partnerships: Pfizer, Broad & Massachusetts General Hospital

- 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

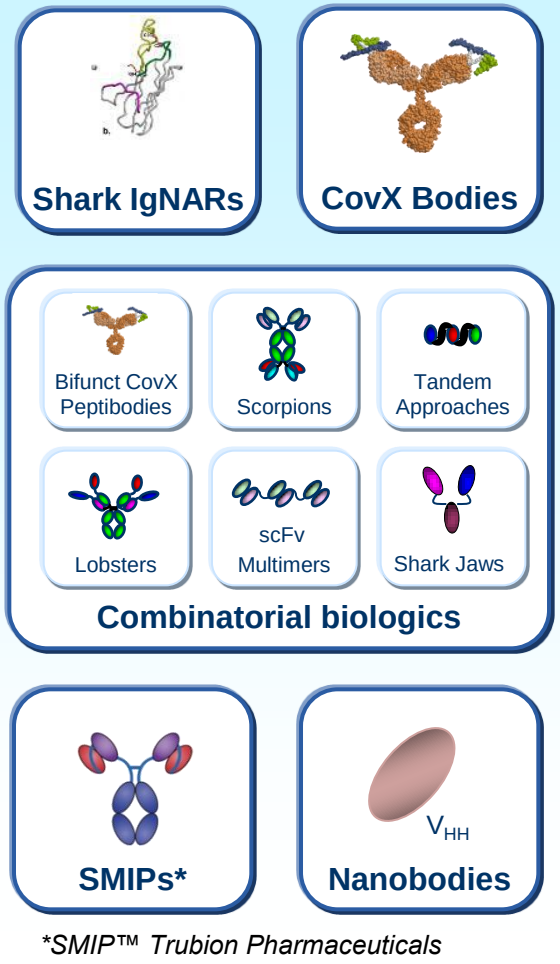
New Drug Design Platforms Are Emerging

Proven technologies to deliver high impact medicines



The Right Molecule for Every Patient

Emerging drug design technologies



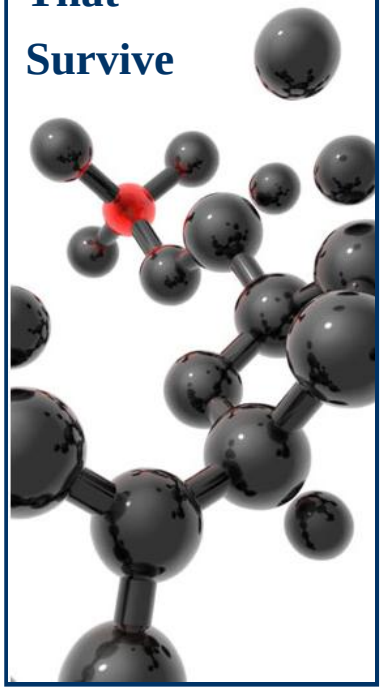
**SMIP™ Trubion Pharmaceuticals*

Four Imperatives For Success

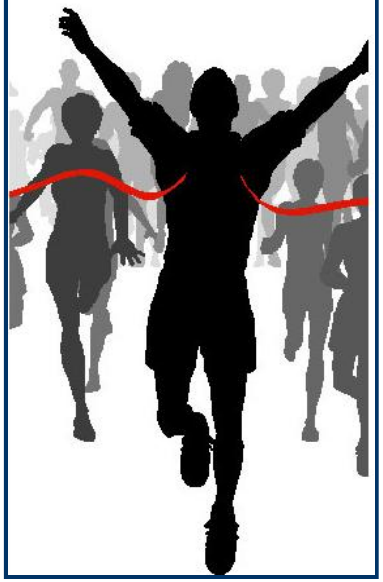
Be Right About Targets

Select the Right Patients

Design Molecules That Survive



Move Faster, Better Patient Outcomes



Scientific Discovery and Application are Driven by Technology and Tools

- Technology and tools drive science and accelerate the pace of significant discoveries.

- Technology/tools needed to advance a discipline can be:
  - Physical
  - Methodological
  - Educational

- The generation of transformational technology/tools requires innovation, scientific rigor, specific expertise, and culture change.

- There are many examples of technology or science infrastructure tools transforming intradisciplinary science.

Impact of Sequencing Technology on Human Genomics

MILESTONES TIMELINE

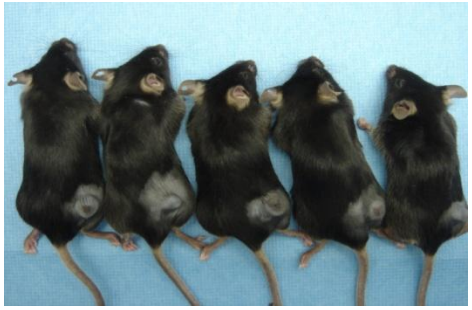
1952	Electophoresis (Milestone 1)
1967	Discovery of DNA ligase (Milestone 2)
1969	FISH (Milestone 3)
1970	Discovery of restriction enzymes (Milestone 4)
	Discovery of reverse transcriptase (Milestone 5)
1972	Cloning (Milestone 2)
1975	Southern blot (Milestone 6)
1977	DNA sequencing (Milestone 7)
1980	RFLP concept (Milestone 8)
1982	P-element-mediated manipulation of the fly genome (Milestone 9)
	Whole genome shotgun (Milestone 10)
1983	RFLP realization (Milestone 8)
1985	PCR (Milestone 11)
	DNA fingerprinting (Milestone 12)
1987	YACs (Milestone 13)
	Site-directed mutagenesis of the mouse genome (Milestone 9)
1988	ChIP (Milestone 14)
1990	BLAST — the key to comparative genomics (Milestone 15)
1992	BACs (Milestone 13)
1995	Microarray technology (Milestone 16)
1998	RNAi (Milestone 17)
	Sequencing by synthesis (Milestone 18)
	Full-length cDNA technologies (Milestone 5)
2002	Launch of UCSC Genome Browser (Milestone 19)
2003	DNA assembly programs (Milestone 20)
2004	ENSEMBL — an example of a gene annotation tool (Milestone 21)
2005	HapMap (Milestone 22)
	Sequencing by ligation/polony sequencing (Milestone 18)
2006	Genome-wide maps of DNA methylation (Milestone 23)

Sequencing of the Human Genome

www.nature.com

Impact of Mouse Modeling Technology on Cancer Biology

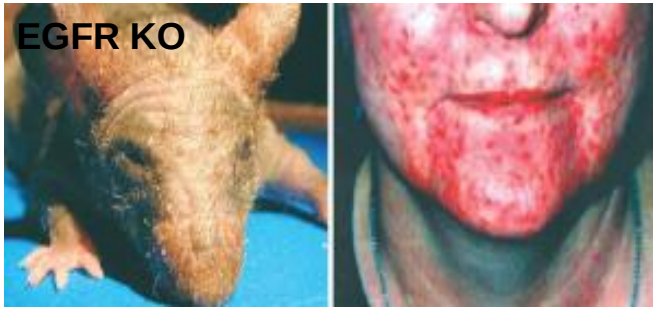
Inbred strains: 1920's



Nude: 1980s

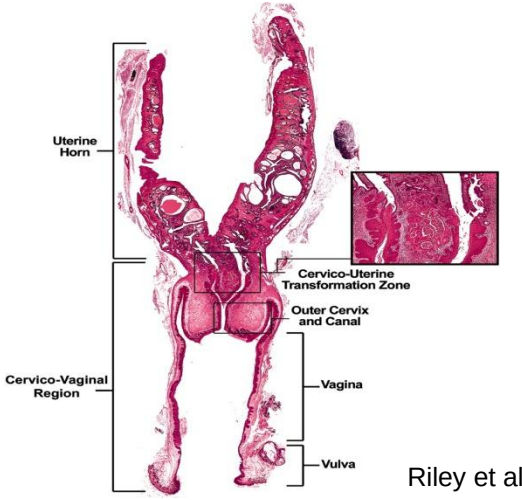
SCID: 1980s

Transgenics
Knock outs: 1990s



Roberts et al Ca Cell, 2004

Clones: 2000s



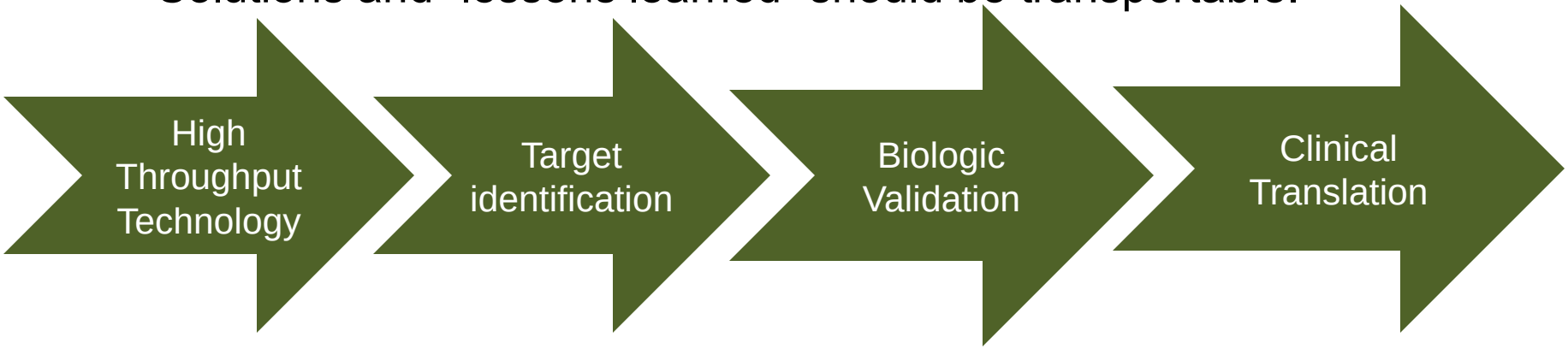
Riley et al Ca Res, 2003

Technology and Tool Development for Translational Science

- Many diverse technologies and tools held by different stakeholders.
  - In silos and scattered
- Until now, translational science technology and tool development has not been prioritized.
- Multidisciplinary research requires a broad array of technology/tools.
- Development often requires scientific collaboration of diverse disciplines.
  - Team approaches to resource development
- Translational research and discovery application requires active participation by the public.
  - Translational science not a public value

Unique CTSA Focus can Provide “Lessons Learned”

- Research the translational research process.
- Identify and solve barriers in innovative ways.
- Transform the environment and outdated translational technology.
- Accelerate translational science technology and tool application.
- Foster team science and eliminate silos.
- Engage the community as partners.
- Solutions and “lessons learned” should be transportable.

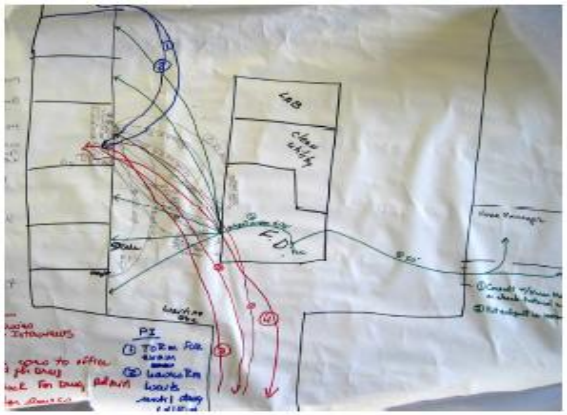


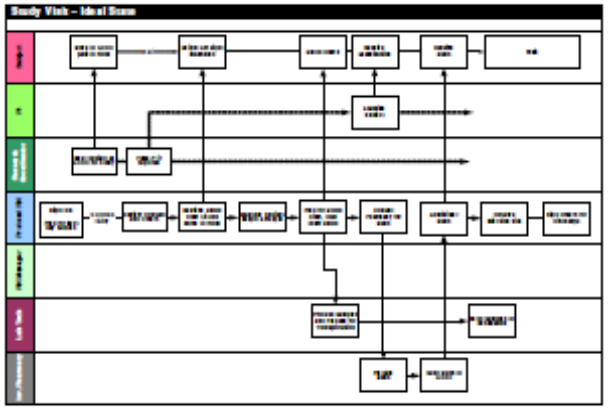
Enhancing the Role of NIH: **Identify and Solve Barriers in Innovative Ways**

CTSA

Transformation of existing CRCs using LEAN.

- Business oriented
- Services based on user need





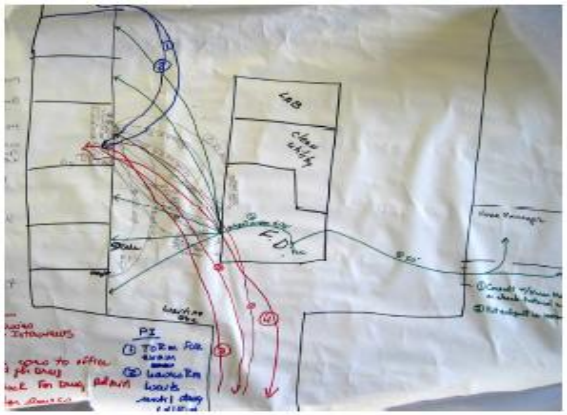
- Decreased nursing overtime costs by 40% while maintaining same number of patient visits.
- Streamlined processes, eliminating resource based administrative staff and cutting overhead.
- Reduced the time of scientific review and study start-up by 50%.
- Initiated 2 new services (high volume specimen collection in volunteers and clinical laboratory) in spite of an overall 40% reduction in the CRC budget.

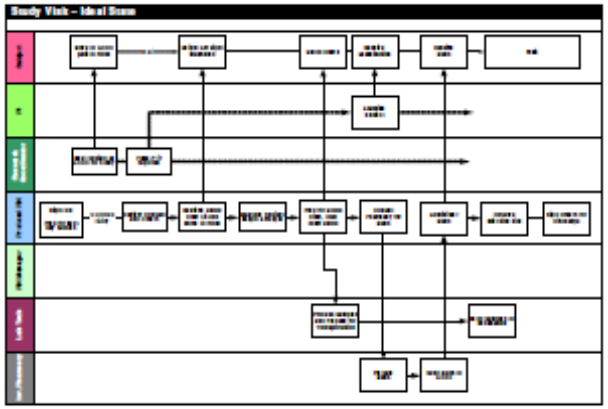
Enhancing the Role of NIH: **Identify and Solve Barriers in Innovative Ways**

CTSA

Transformation of existing CRCs using LEAN

- Business oriented
- Services based on user need





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NIH

NIH RAID Program

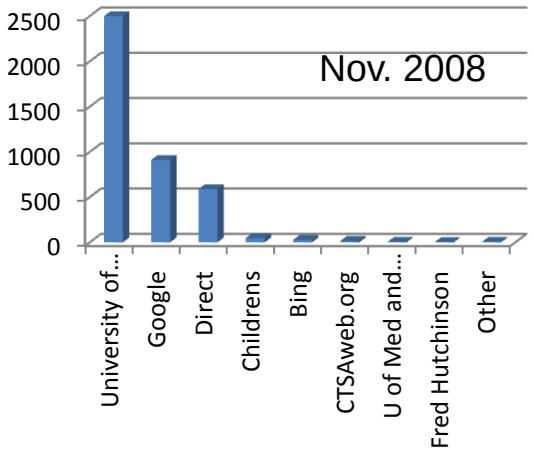
- Important and innovative program for translational science
- Slow application process
- Limited users based on eligibility restrictions
- Slow manufacturing
- Unclear capacity
- Complex outsourcing
- Lack of awareness of the resource

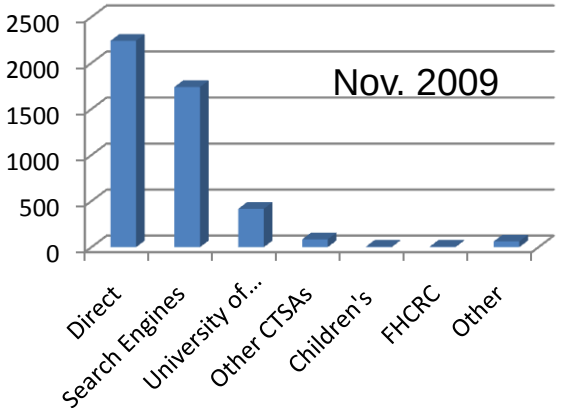
http://dpcpsi.nih.gov/eo/documents/NIH_Rapid_Access_to_Interventional_Development_Pilot_Program_Needs_Assessment_Evaluation_07-2010_NIMH.pdf

Enhancing the Role of NIH: **Accelerate translational science technology and tool application**

CTSA

- 135 accessible shared resources from a 5 state region
- Linked with educational material re: resource
- Live technology consulting via PhD level scientist





85% go onto to other web pages

Enhancing the Role of NIH: **Accelerate translational science technology and tool application**

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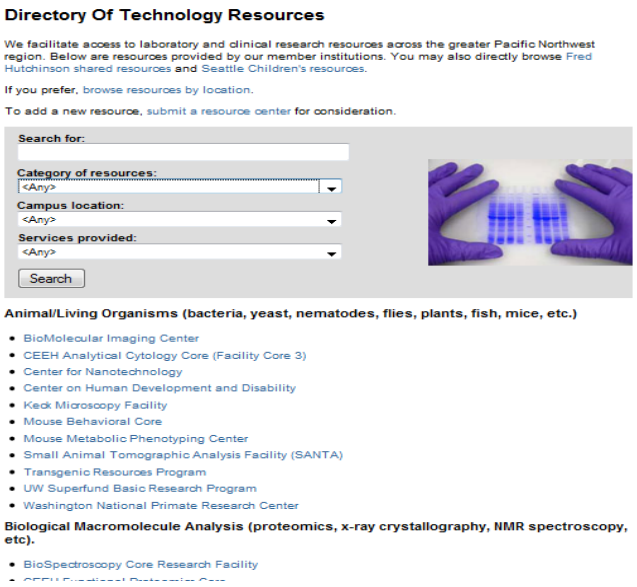

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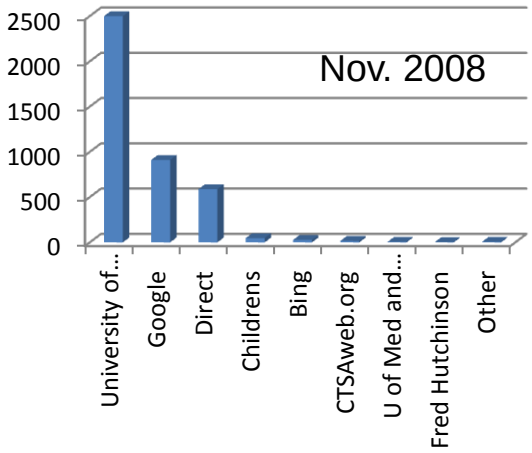

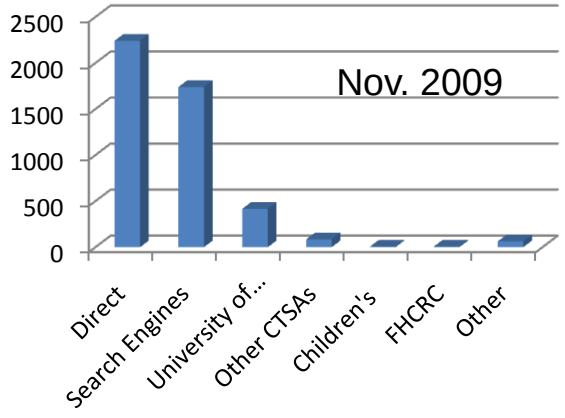

85% go onto to other web pages

NIH

HPV transgenic made in 1992
- 150 publications
- >80% biology based
- Few translational

NIH Repositories and Consortia

http://emice.nci.nih.gov/
http://cancermodels.nci.nih.gov
http://mouse.ncifcrf.gov/ …

Mouse models of human cancer consortium (MMHCC)
Comparative mouse genomics centers consortium (CMGCC)…

Enhancing the Role of NIH: **Engage the community as partners**

CTSA

2010 Summer Workshop for High School Science Students and Teachers

- *"I never realized how critical research is for medicine"*
- *"I would not think that a… researcher would be so caring, nice, and friendly"*
- *"I have always thought that research was for those who were extremely intelligent and tended to lack social skills"*

CTSA Partnership: WWAMI States Practice Based Research Network

- Research capacity in the community
- Teach principles and allow them to evaluate pressing problems
- Data warehousing-LC Data Quest
- Use of contraception in women taking teratogenic drugs
- 328 women identified across 7 rural pratcice sites: majority had no documentation of contraception, 12% evidence of informed consent-intervention
- Changed practice in these communities
- Strong interest for CTSA research partnerships

Enhancing the Role of NIH: **Engage the community as partners**

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NIH

- Numerous programs
- Little unification
- Common mission?
- Many superficial
- Need for a cohesive plan to galvanize the community to support translational research in many ways
- Need for leadership

Successful programs on a smaller scale:
Army of women:
www.dslrf.org/army/
Project LEAD, NBCC

Bridging the Gap: NIH and the CTSAs

- The CTSA program has developed many best practices and has many "lessons learned"-NIH should use it as a resource.

- Many existing resources within NIH could contribute greatly to translational science.
  - Catalogued appropriately?
  - Left in silos?
  - Operating efficiently?

- Evaluate data collected in the CTSA program to assess potential new resources for development.

- Encourage intramural integration around translational science (both within and outside NIH).

- National leadership in community integration and participation in translational science.

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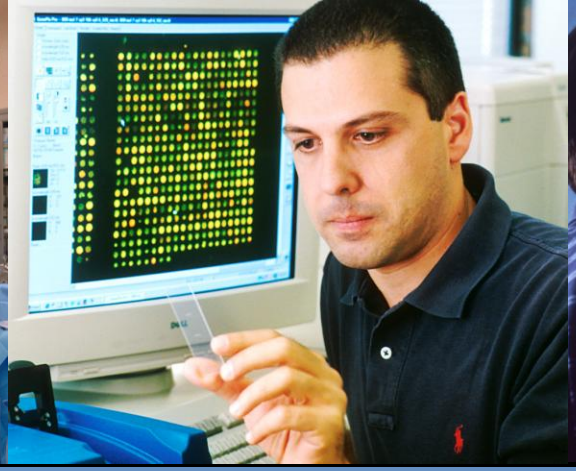



NCI's Experimental Therapeutics Program (NExT)

James H. Doroshow, M.D.
Director
Division of Cancer Treatment and Diagnosis, NCI

NIH Scientific Management Review Board

Bethesda, MD

September 14, 2010

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

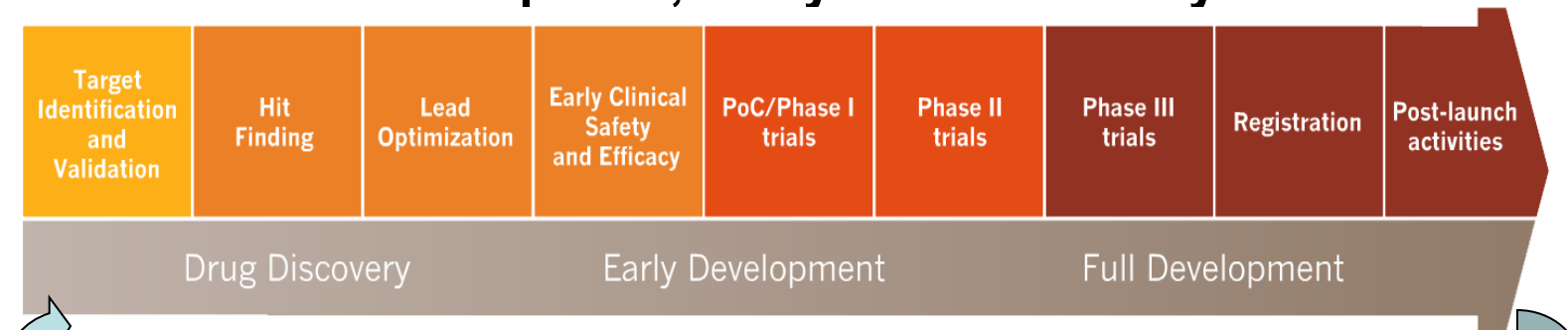
National Cancer Institute

Where Did We Need to Go?

Rapid translation of discoveries into public health benefits

NCI Experimental Therapeutics Program: Unified Discovery & Development

A single pipeline for all therapeutic development resources: One Pipeline, Many Points of Entry



Targets ***INCLUDES*** **Therapeutics**

- Investigational drugs and biologics
- Investigational imaging agents
- Academic & Biotech & Pharma projects
- Includes Phase 0, I and II Programs

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Therapeutics Discovery & Development Support Provided by NCI (NExT)

- Medicinal chemistry, HTS, lead optimization
- Synthesis of oligonucleotides
- Chemical synthesis of small molecules and peptides
- Scale-up production of small molecules and biologicals
- Development of analytical methods
- Isolation and purification of naturally occurring substances
- Exploratory toxicology studies and pharmacokinetic evaluation
- PK/efficacy/ADME studies (bioanalytical method development)
- Development of suitable formulations
- Range-finding initial toxicology and IND-directed toxicology
- Product development planning and advice in IND preparation
- Later-stage preclinical development of monoclonal antibodies, recombinant proteins, and gene therapy agents
- Manufacture of drug supplies, including biological agents
- Analytical methods development for bulk material
- Formulation studies
- Production of clinical dosage forms
- Stability testing of clinical dosage forms
- Regulatory support & Early phase clinical trials

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NCI Chemical Biology Consortium (CBC)

- ***Mission:*** **Dramatically increase flow of early stage drug candidates into NCI therapeutics pipeline**
- ***Vision:*** **Develop integrated network of chemists, biologists, and molecular oncologists, with synthetic chemistry support**
  - ✓ **Active management by NCI and external advisory boards**
  - ✓ **Unify discovery with NCI pre-clinical and clinical development**
  - ✓ **Linked to other NCI initiatives; CCR chemistry integral partner**
- **Focus on unmet needs in cancer therapeutics: "undruggable" targets, under-represented malignancies, high risk projects, longer time horizon**
- **Enable a clear, robust pipeline all the way from target discovery through PD-driven proof-of-mechanism clinical trials for academic, small biotech, and pharma investigators; involve CBC members in shared project development**

NExT FRONT END: Leveraged Molecular Libraries Investment

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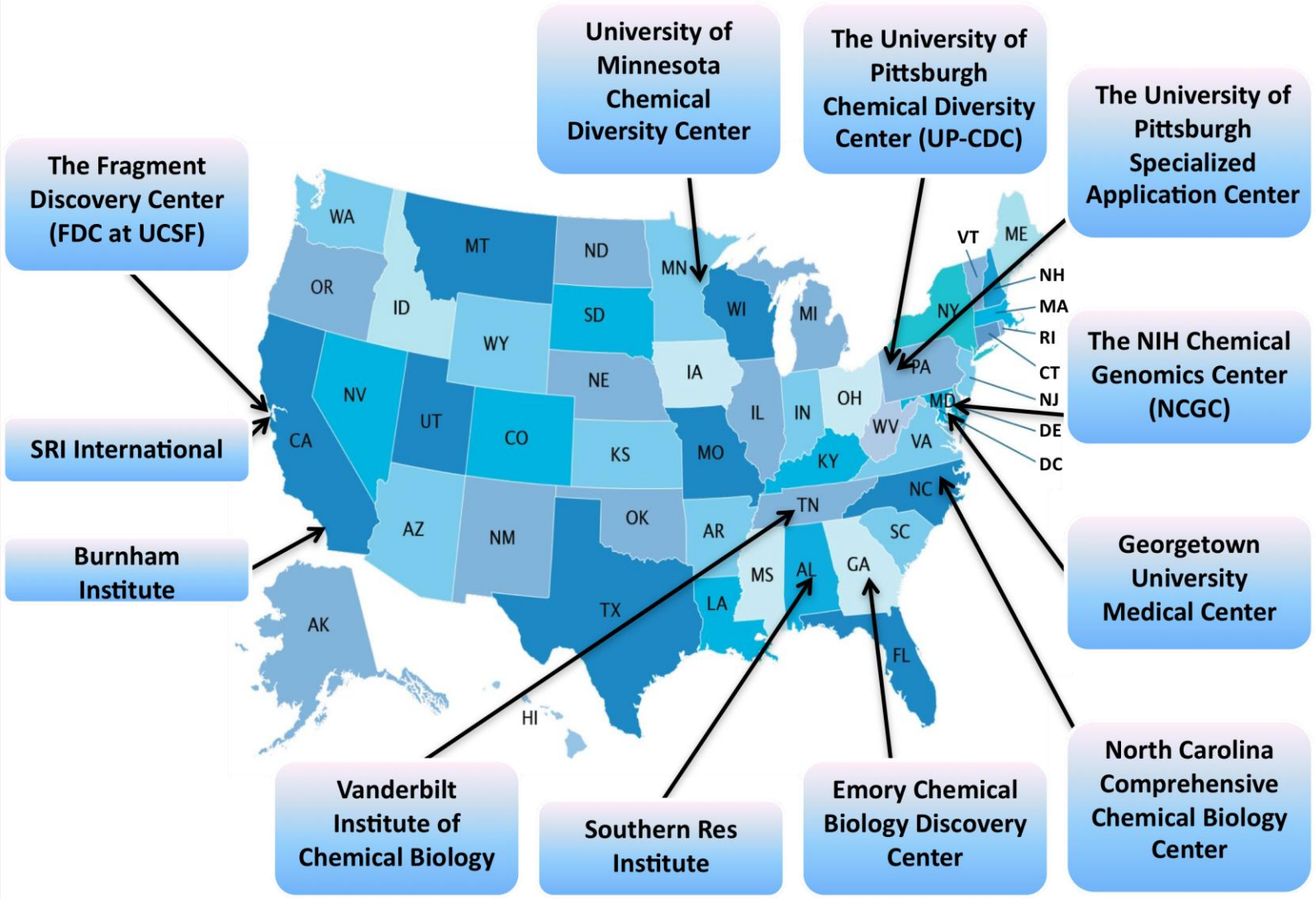
NCI Chemical Biology Consortium (CBC)



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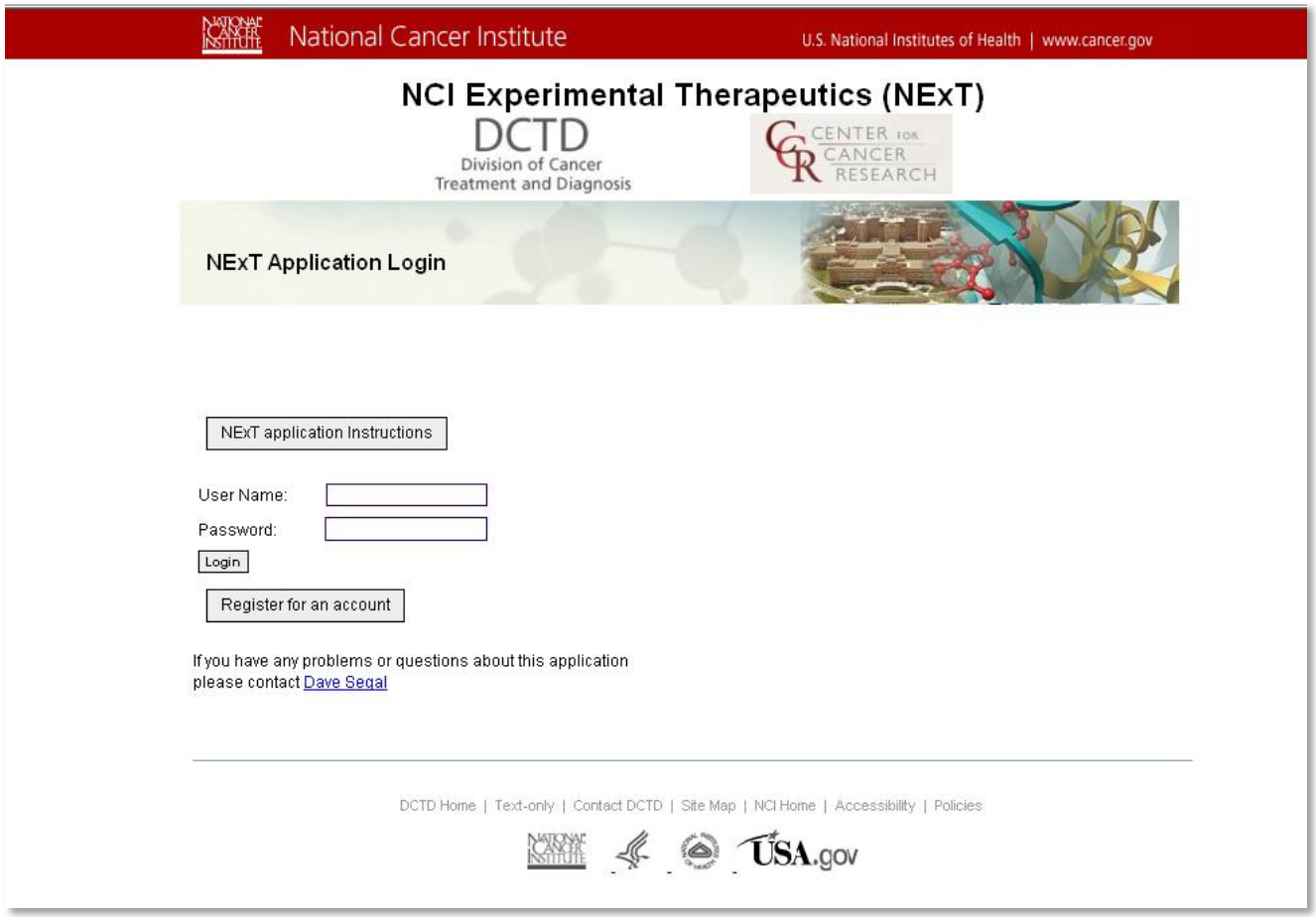
NExT Application Process

Extramural scientists may propose targets, screens, or molecules for entry into the NExT pipeline; receipt dates every 4 months

https://dctd.cancer.gov/nextapp or
https://dctd.cancer.gov/nextregistration



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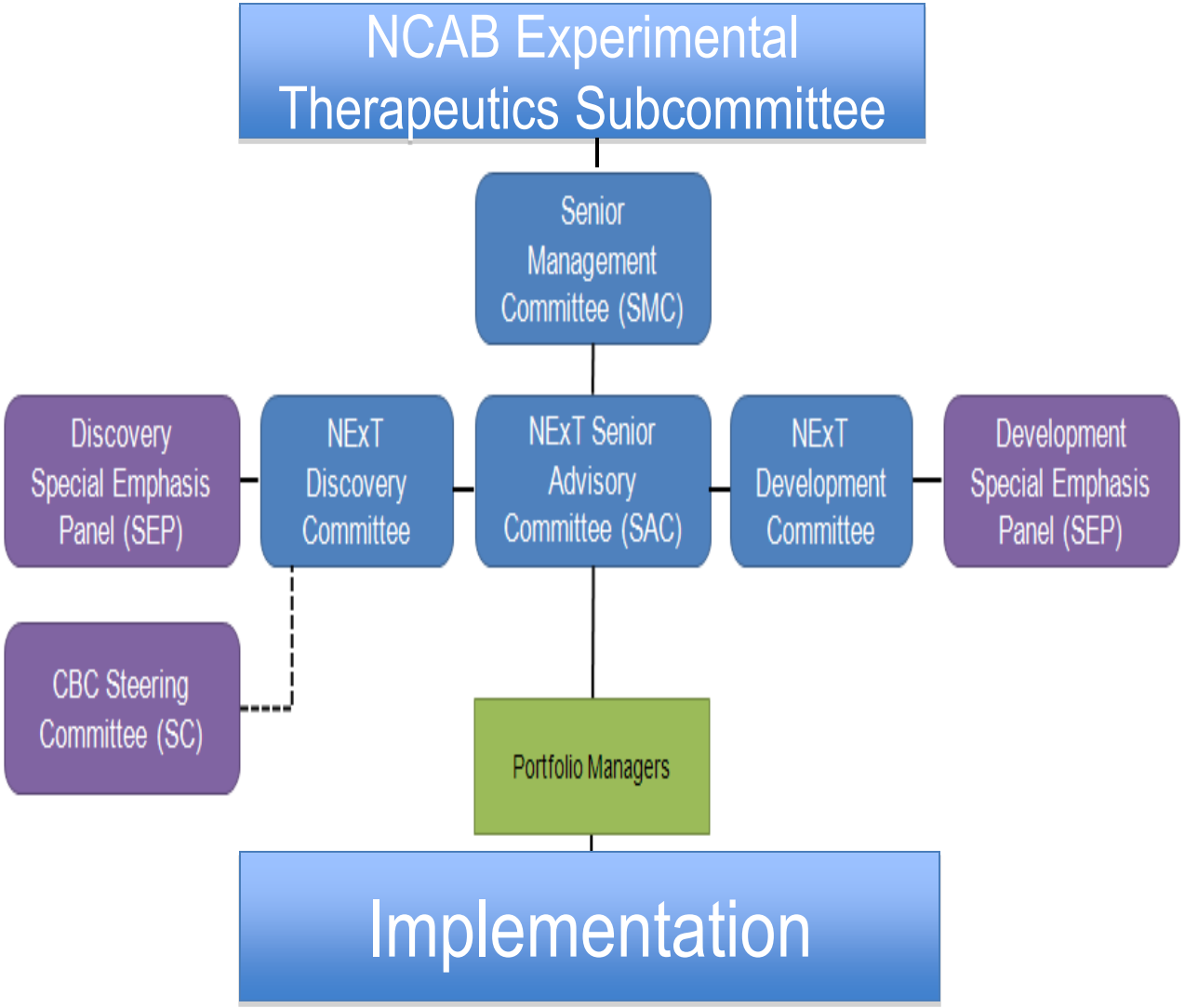
How Are Projects/Compounds Selected?



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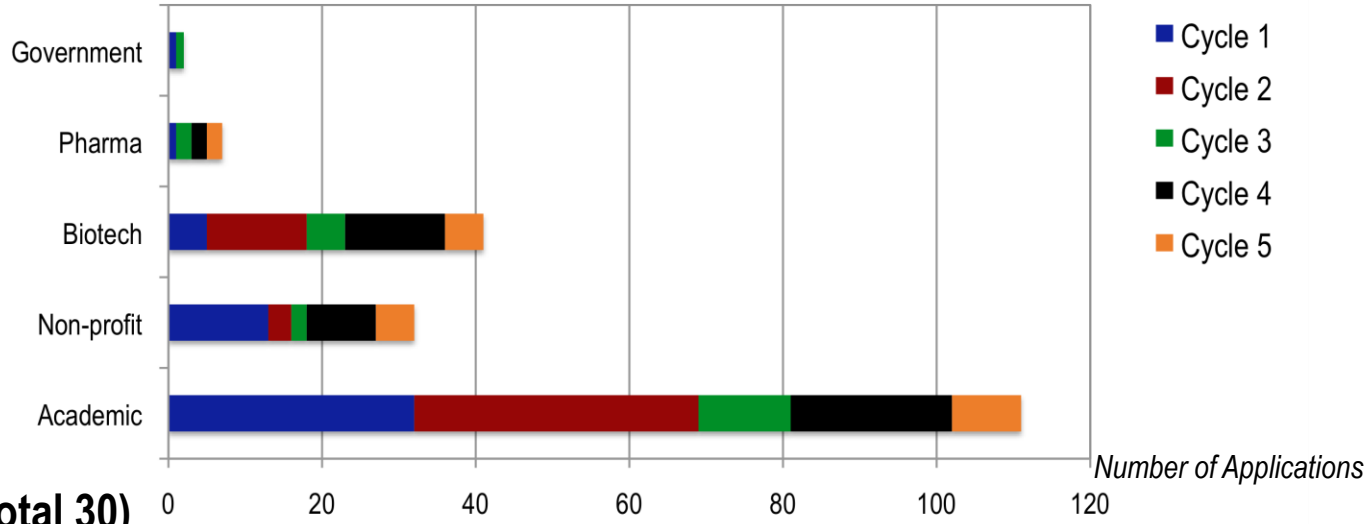
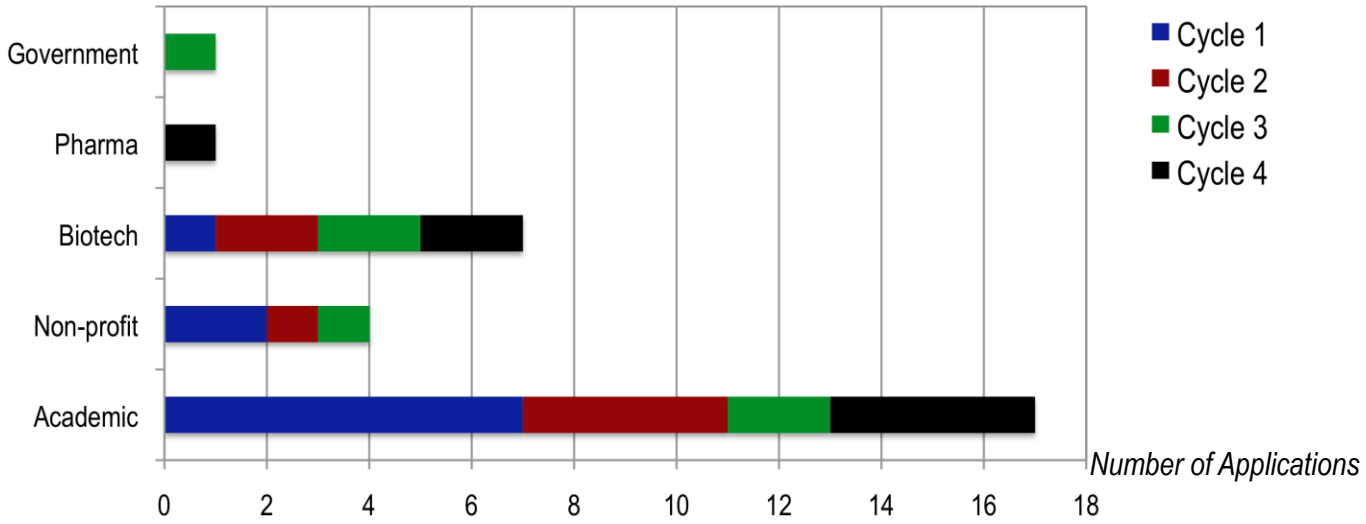
Number of Applications from Academic, Non-Profit, Biotech, Pharma or Government

All Applications (Total 193)



Top Tier (Total 30)



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NExT Projects

- **Discovery: Developing a Lactate Dehydrogenase A (LDHA) Inhibitor for Solid Tumors: Chi Dang, JHU**

- **Development: Biologics for Immunotherapy Trials**

- **Early Phase Clinical: Phase I Trial of the DMT inhibitor FdCyd + Tetrahydrouridine**

National Cancer Institute

LDHA: Therapeutic Target in Cancer

- The proto-oncogene c-myc can drive glutamine as well as glucose metabolism. In cancer, c-myc deregulation can result in the added uptake of glucose and its conversion to lactate, thereby contributing to the “Warburg Effect”.
- ChIP sequencing confirmed that Lactate Dehydrogenase A (LDHA), an enzyme that converts lactate to pyruvate, is a direct downstream target of Myc.
- Knockdown of LDHA decreased colony formation and reduced the growth of tumors in breast and lung cancer xenografts.
- Japanese families that completely lack LDHA are otherwise normal except for exertional myopathy.
- FX11 is a selective, small molecule, active site LDHA inhibitor identified from a malarial LDH screen that provides proof-of-concept for targeting cancer metabolism in human lymphoma and pancreatic cancer models.

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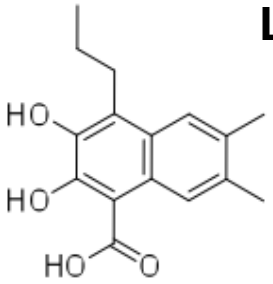
FX11 Treatment Leads to Regression of Tumors in Lymphoma and Pancreatic Xenograft Models

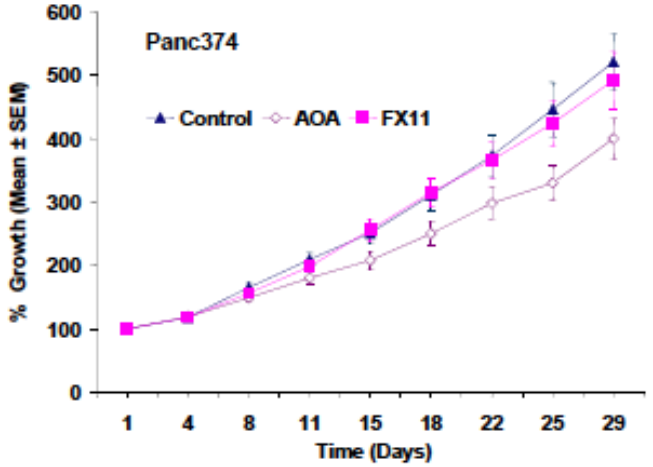
Lymphoma

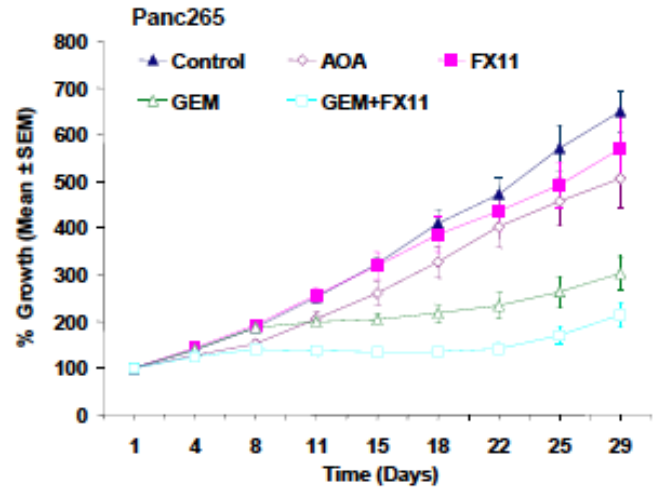


Control
42μg FX11
150μg E
100μg FK866
42μg FX11 + 100μg FK866

FX11

Pancreas





National Cancer Institute

LDHA : Next Steps

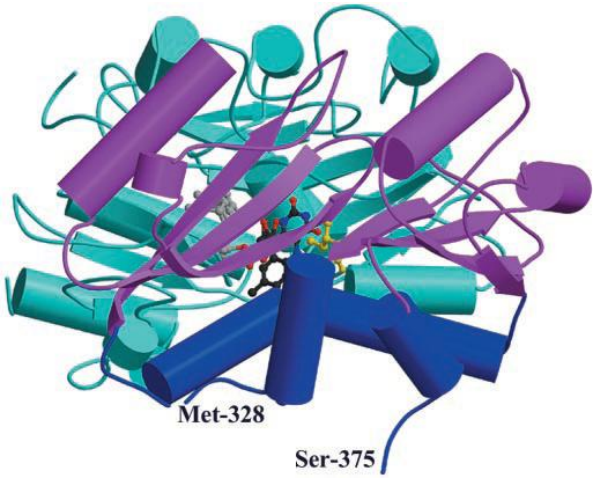
Screen development and high-throughput screening → **Hit to Lead** → **Lead Optimization** → **Candidate Seeking**

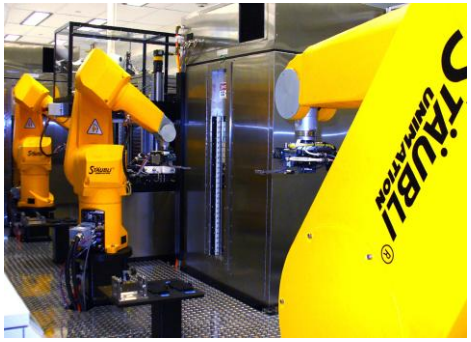
Primary uHTS ⇄ **NCGC: hit validation/med chemistry**

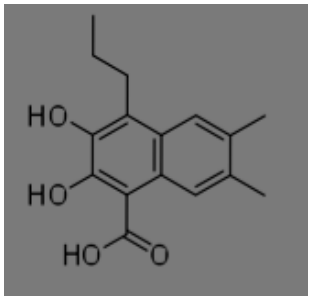
NIH Chemical Genomics Center

Secondary biochemical and cell-based screens *Dang Lab*

Co-crystallization with HTS "hits"







FX11 Lead Compound
Ki 4 uM

- ✓**HTS screen to identify new scaffolds**
- ✓**Co-crystallization with FX11**
- ✓**Optimize SAR for lead compound FX11, increase potency and improve solubility**

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Prioritized Needs of the Immunotherapy Community

Agents with High Potential for Use in Cancer Therapy and Infrastructure

AGENT	FUNCTION	AVAILABILITY
IL-15	T-cell growth factor	**NCI-in production; NCI IND approved**
Anti-PD-1	T-cell checkpoint inhibitor	Commercial
IL-12	Vaccine adjuvant	**NCI—in hand**
Anti-CD-40	APC stimulator	Commercial
IL-7	T-cell growth factor	**NCI-in production**

GMP 80L fermentation of rhIL-15: Production and pooling in Frederick of several products from multiple fermentations needed for one 1gram lot of rhIL-15

Cancer Immunotherapy Network:

- **established to stimulate multisite phase I and II clinical immunotherapy trials across a range of malignancies**
- **bring novel immunotherapy agents, combinations, and approaches to the clinic**
- **up to 25 institutions**
- **standardized immunomonitoring and biomarker studies**
- **funded end of 2010**
- **NCI Frederick will produce reagents that lack a commercial sponsor**

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Phase I Trial of 5-Fluoro-2'-Deoxycytidine (FdCyd) with Tetrahydrouridine (THU) in Advanced Malignancies

- FdCyd: an inhibitor of DNA methyltransferase
- In pre-clinical models, FdCyd administered along with THU (inhibits cytidine/deoxycytidine deaminase) activates a series of hypermethylated genes (GSTπ; p16)
- FdCyd is administered as an IV infusion over 3 hours along with THU daily for 5 consecutive days of treatment per week for 2 consecutive weeks, followed by 2 weeks of no treatment, for 28-day cycles
- NCI-RAID program produced both drugs for clinical trial at USC, UC Davis, COH, and NIH CC

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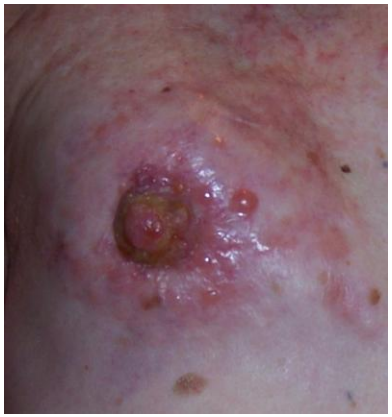
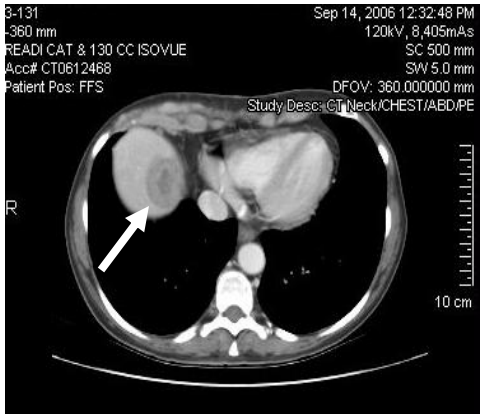
Phase I Activity of FdCyd + THU

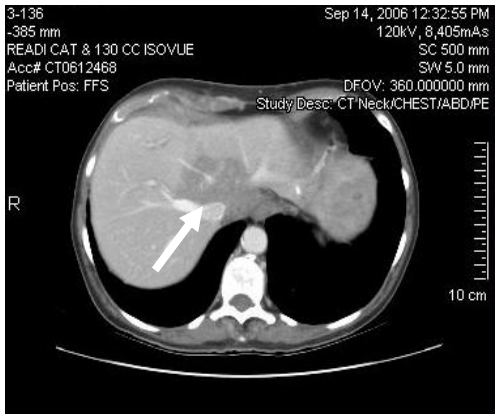
61 yo F with metastatic breast cancer, high dose chemo followed by autotransplant, multiple hormonal and chemo regimens.

Pre-study



September 2006





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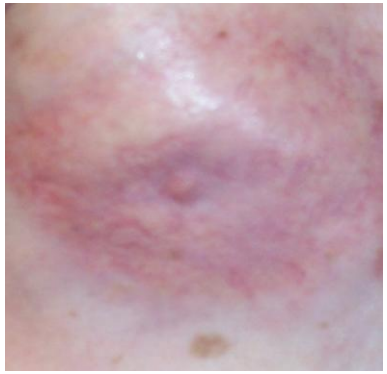

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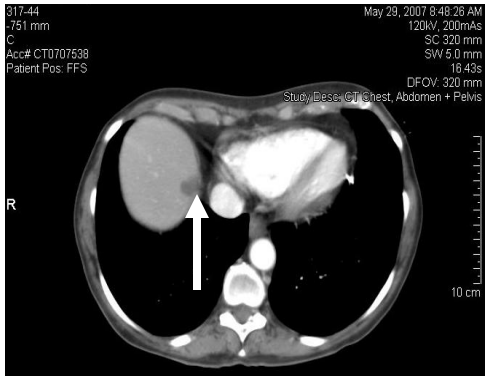

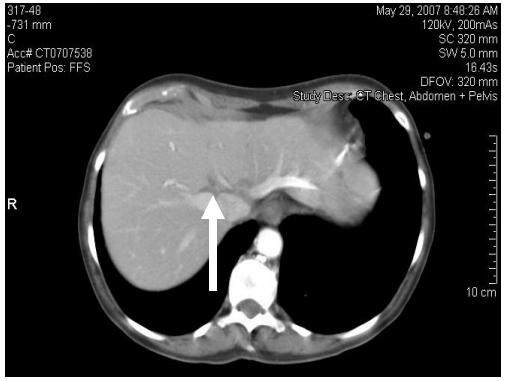

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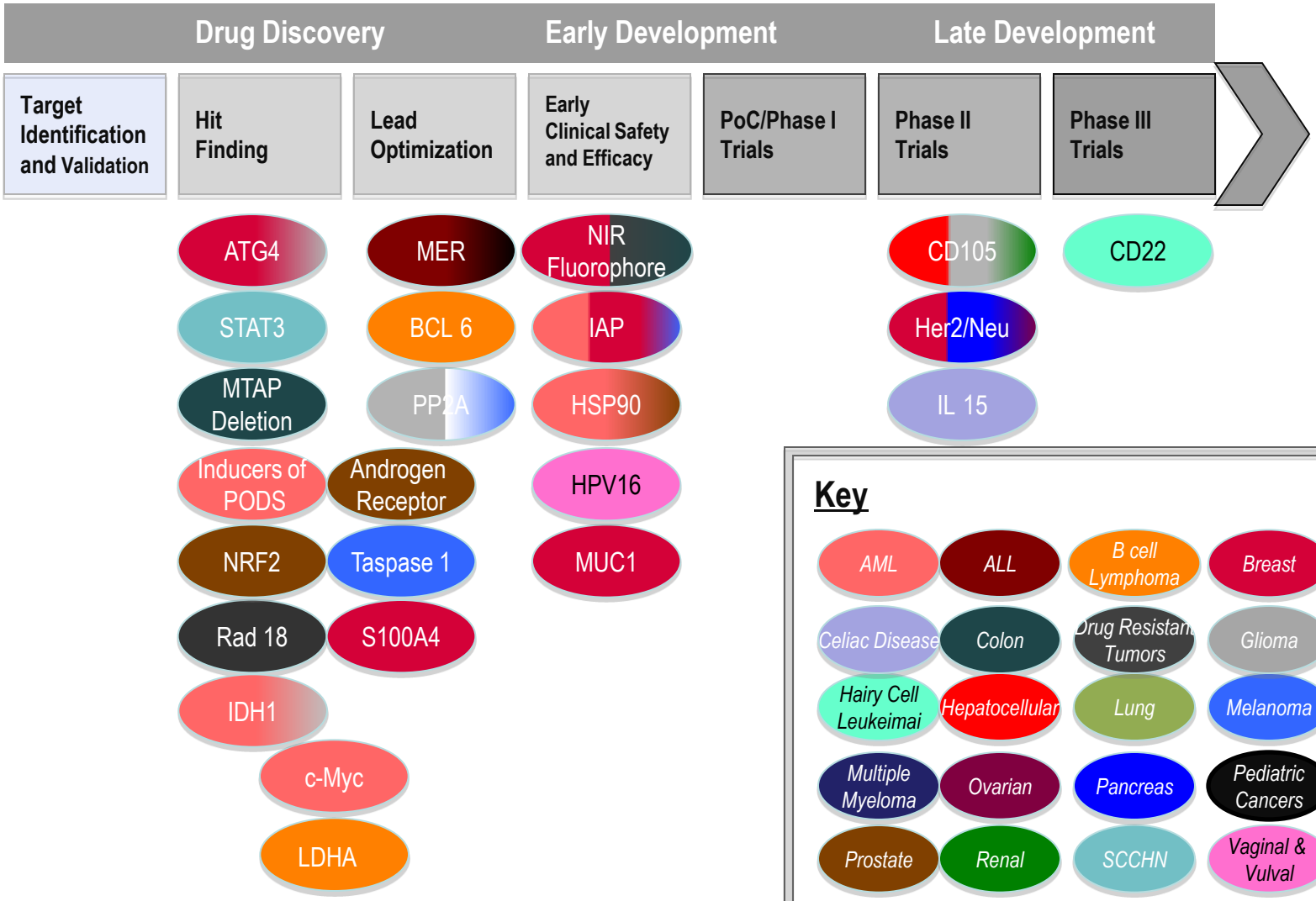
NCI Experimental Therapeutics Pipeline



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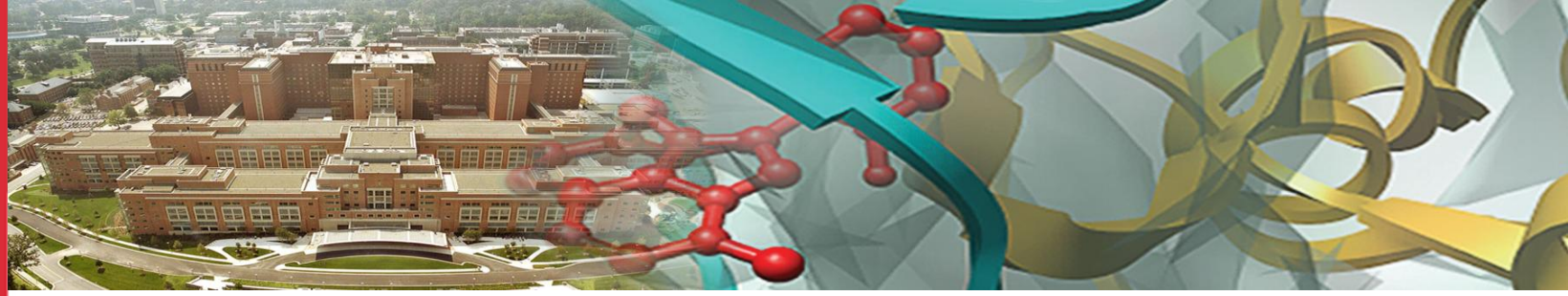
Goals of the NCI's Therapeutics Platform

- **Develop treatments for unmet medical needs (e.g, rare cancers and pediatric tumors)**
- **Provide resources for natural product development and the development of high risk targets**
- **Move discoveries from TCGA into drug discovery**
- **Support development of biological agents**
- **Success measured by:**
  - **IND filings (first in human studies)**
  - **Licensing of novel therapeutics**
  - **Improved cancer therapeutics success rate**
  - **Approved NDA's developed from academic and small biotech research**

National Cancer Institute



https://dctd.cancer.gov/nextregistration

NExT/CBC Implementation Team

Jeff Abrams	Sanjay Malhotra
Heba Barazi	Barbara Mroczkowski
Michelle Bennett	Ralph Parchment
Jerry Collins	David Segal
James Crowell	Shizuko Sei
Jason Cristofaro	Tom Stackhouse
Mike Difilippantonio	Joe Tomaszewski
Gina Hayman	Robert Wiltrout
Lee Helman	Jamie Zweibel

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Intellectual Property: CBC Participants Agreement

The Consortium Agreement addresses:

- Data generated by the CBC is a defined deliverable that will be accessible to all other CBC participants via a proprietary database; management of shared IP.
- Materials generated by the CBC will also be defined deliverables and be available to the government for use and future development.
- Projects will be managed by NCI project team managers who will ensure that data delivered to the NCI is appropriately distributed among CBC members.

Cultivating Partnerships: Setting Goals and Defining Success

Session III

Aims

- **Explore the defining features of a successful partnership**
- **Emphasis on establishing metrics and defining goals**
- **Focus on lessons learned from existing partnerships between the public and private sectors**
  - **Priority-setting,**
  - **Decision-making, and**
  - **Intellectual property agreements**

NIH and Public-Private Partnerships (PPPs)

- A range of differing scales
- Three examples
- Challenges
- Considerations
- Outcomes and deliverables

The Scale of NIH Involvement in PPPs

- **Scale:** Can be measured in number of ways including participants and partners, complexity of projects, and magnitude of resources invested (e.g., dollars, time, expertise, personnel, data etc.)
  - *"Small" scale PPPs:*
    - Single IC with a single partner on a single project
  - *"Mid-size" PPPs:*
    - One or more ICs with a single focus area and one core project with spin-offs
  - *"Large" complex PPPs:*
    - Multiple ICs with multiple partners (20+) and multiple projects

NIH PPPs: Example #1

Osteoarthritis Initiative (OAI)

Goal: Further development of OA drugs

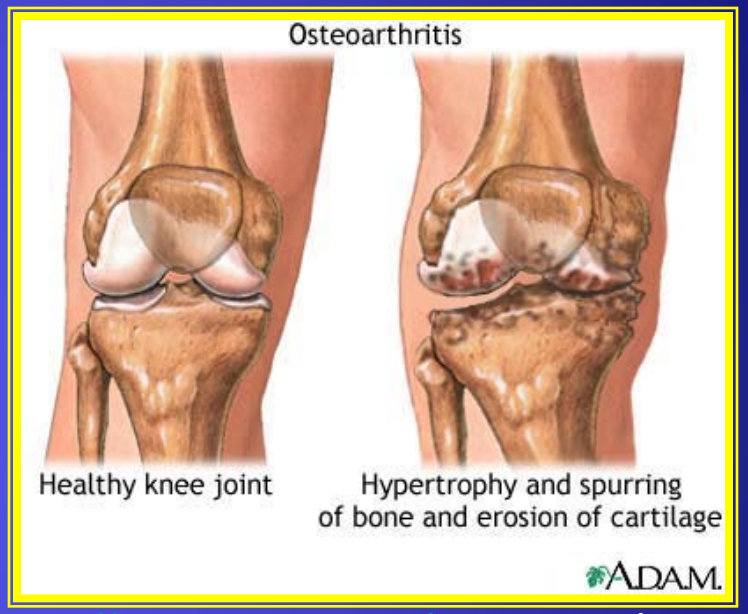
Overarching Aims: Establish resource for testing much-needed biochemical and imaging markers of disease progression

Partners: NIH, FDA, biopharmaceutical industry

Major deliverables:
Public repository of:

- Patient data
- Radiological information
- Biological specimens

Budget: $50 million



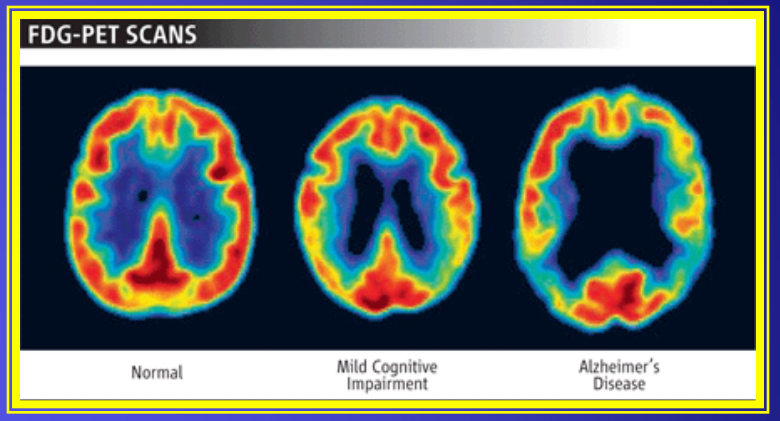
http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001460/

NIH PPPs: Example #2

Alzheimer's Disease Neuroimaging Initiative (ADNI)

Goal: Identify biomarkers of mild cognitive impairment and Alzheimer's Disease in elderly subjects

Overarching Aims: Combine serial magnetic resonance imaging, positron emission tomography, other biological markers (in blood, urine, and cerebrospinal fluid), and clinical and neuropsychological assessment



Miller, Science, 16 October 2009

Partners: NIH, FDA, biopharmaceutical industry, non-profitand advocacy groups

Major deliverables: Establishment of a public resource for testing biochemical and imaging markers of disease progression

Budget: >$60 million

ADNI Private Sector Supporters:

19 companies and 2 non-profits

FOUNDATION FOR THE National Institutes of Health

Abbott A Promise for Life

AstraZeneca UNITED KINGDOM

Bayer HealthCare

Bristol-Myers Squibb

Eisai

élan

GE

Genentech IN BUSINESS FOR LIFE

gsk GlaxoSmithKline

INNOGENETICS

Johnson & Johnson

Lilly

MERCK

NOVARTIS

Pfizer

Roche

Schering-Plough

SYNARC Start here, finish first.

Wyeth

alzheimer's association

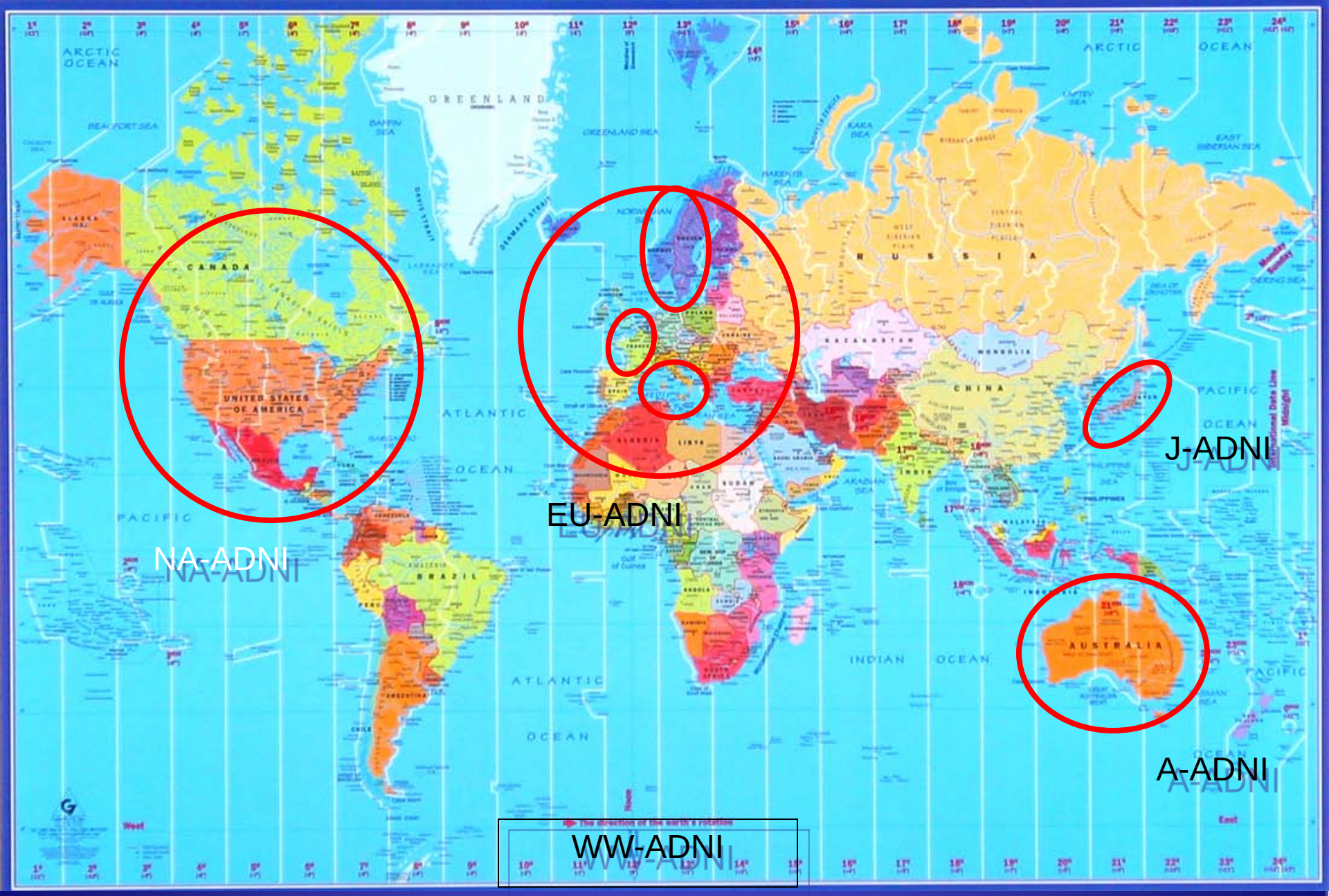
INSTITUTE FOR THE STUDY OF AGING

PIB/PET Supplement : *Alzheimer's Association and GE Healthcare*

Cerebrospinal Fluid Extension: *Alzheimer's Association, AstraZeneca, Cure Alzheimer's Fund, Merck, Pfizer and an anonymous foundation*

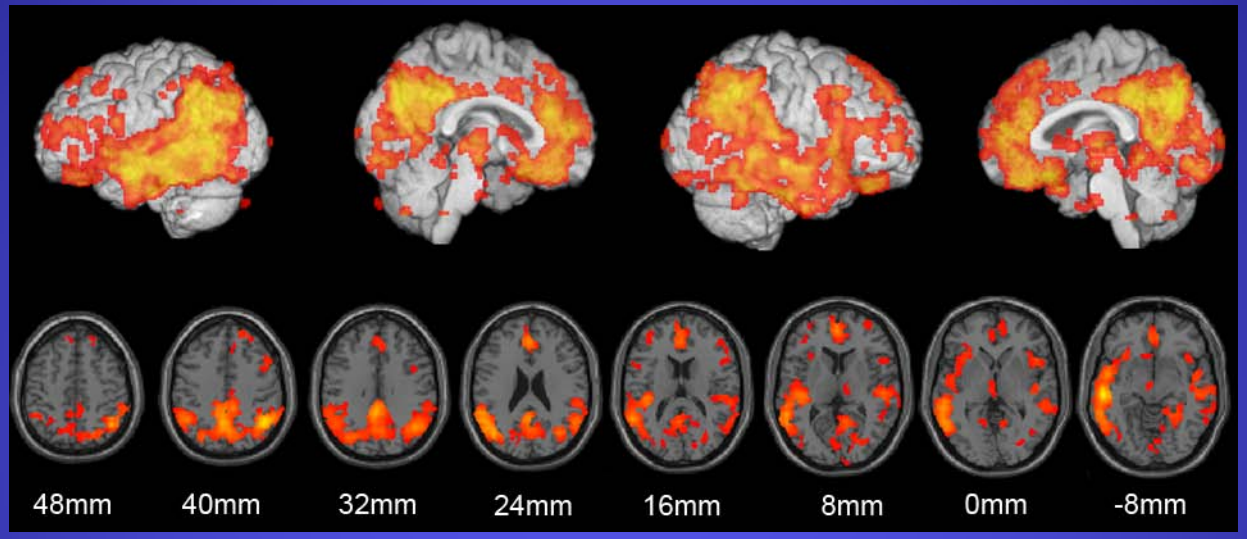
Genome-Wide Genotyping :*Gene Network Sciences, Merck, Pfizer and an anonymous foundation*

Genome-Wide Genotyping Genetic Analysis: *NIBIB, Merck, Pfizer and an anonymous foundation*


NA-ADNI
EU-ADNI
J-ADNI
A-ADNI
WW-ADNI

Empirically pre-defined statistical ROI for the assessment of 12-Month CMRgl declines in AD patients

Defined using data from 27 training-set patients using bootstrap with replacement



Number of AD patients per group needed in a 12-month multi-center RCT to detect a 25% treatment effect with power=80%, p=0.05 & no need to correct for multiple comparisons

FDG PET	ADAS-COG11	MMSE
61	612	493

Characterized in 29 test-set patients (excluding HiRez & HRRT scanners)

Reiman et al
Banner Alzheimer Institute

NIH PPPs: Example #3

Genetic Association Information Network (GAIN)

Science Daily (Nov. 30, 2007)

Goal: identify specific points of DNA variation associated with occurrence of particular common diseases (studies focused on ADHD, bipolar disorder, diabetic nephropathy, major depressive disorder, psoriasis and schizophrenia).

Overarching Aims: Conduct Genome-Wide Association Studies

Partners: NIH, FDA, biopharmaceutical industry, non-profit and advocacy groups

Major deliverables: Data disseminated through the database of Genotype and Phenotype (dbGaP) of the National Library of Medicine

Budget: $32 million

PPP Outcomes and Deliverables

- **Foster Research**
  - Generate general new knowledge and new insights
  - Offer the potential for commercialization as one means of translating discovery into public health improvements
- **Enhance Clinical Trials**
  - Increase access to clinical trials
  - Facilitate recruitment and retention
- **Expand the pre-competitive space**
  - Create general public resources such as data sets, samples, reagents, platforms
- **Develop Medical Products and Technologies**
  - Collaborative and complementary work to translate discovery to marketable drugs, devices, diagnostics, and/or tools

Challenges

- Achieving an understanding and appreciation of the similarities and differences between and among partners—for example, with respect to processes, capabilities, resources, and constraints
- Developing common goals
- Reaching agreement on the tasks and requirements inherent in the collective effort to achieve the goals of the partnership
- Making and sustaining a shared commitment to open, regular communication

Considerations for PPPs with NIH

- **Source of funding**
- **Expenses supported**
- **Exchange of non-monetary resources**
- **Products of the partnership (e.g., *data, samples, reagents, databases, etc.,*)**
- **Intellectual property rights**
- **NIH review and management**
- **Privacy and integrity**

Questions for Discussion

1. **What attributes are key to the formation and sustention of a successful partnership?**
2. **In reference to existing partnerships:**
   - **How was success for each partner defined?**
   - **How were the expectations and responsibilities of each partner negotiated?**
   - **How were appropriate benchmarks for each partner determined?**
3. **In reference to NIH, what are appropriate metrics for success?**
4. **How should decisions be made in selecting and prioritizing projects? What factors need to be taken into consideration?**
5. **What have been the successes of public-private partnerships? What hurdles have been encountered in realizing the potential of these partnerships?**

Partnerships in Drug Discovery & Development

NIH Scientific Management Review Board

September 15, 2010

Stephen L. Eck, MD, PhD
Vice President
Translational Medicine & Pharmacogenomics
Eli Lilly & Company

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Long History of Productive Academic & Government Collaborations with the Pharmaceutical Industry

- Industry-Academia relationships flourished between WWI & WWII.

- Increasing independent research capability by industry required academic expertise
  - Basic research began to replace “botanicals” a source of new medicines
  - Lilly and U of Toronto (1922) collaboration to produce insulin
  - Lilly & Indianapolis City Hospital (1926) open Research Clinic to study pellagra and other disorders
  - Lilly & U of Rochester (1931) collaboration to Rx pernicious anemia

- Nat’l Res. Council Survey (1940)
  - 50 companies supporting 370 projects at 70 universities

D. Blumenthal, NEJM, 2003, 349:2452-8

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Historical Perspective

(continued)

Later decline in collaborations post WWII

- Greater independence of industry
- Increasing federal support of academic research through mid ~1970's

Fully integrated pharmaceutical firms owned & controlled most of the drug development process.

- Attempted to mimic AT&T's Bell laboratories, IBM's Watson Research Center and Xerox's Palo Alto Research Center which produced Nobel Prize winning research.

Bayh-Dole Act 1980

- Foster translation of scientific discovery to commercial products.
- Collaboration seen by Congress as a means to advance product development
- Allowed universities to patent & license IP derived from federally funded research
- $MM flowed to universities with shift from chemistry & engineering to life sciences
- Late 1990's: 90% of firms, 25-50% of faculty
- Most universities had equity in their sponsoring companies

D. Blumenthal, NEJM, 1996, 335:1734-9; K. Lim, Research Policy 2004, 33,287-321

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Widely Acknowledged Conflicts in Industry-University Collaborations

- "Industry-sponsored clinical research: a double edged sword", (J .Montaner Lancet 2001)

- "Collaborating with Industry-Choices for the Academic Medical Center,"
(H. Moses et al NEJM 2002)

- "Regulating Academic-Industrial Research Relationships",
(T. Stossel, NEJM 2005)

- "Uneasy Alliance: Clinical Investigation and the Pharmaceutical Industry",
(T. Bodenheimer, NEJM 2000)

"In simple terms industry has a primary responsibility to generate profits for shareholders while academics are preoccupied with issues pertaining to scientific inquiry and career advancement."

(J. Montaner Lancet 2001)

- There needs to be a clear separation between research and marketing activities.

- The financial arrangements need to be transparent and well justified.

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Distinct Cultures and Resources

Academia

- Resource limited
- Institutional support limited
- Diverse talent pool
- Project is premier
- Any interesting outcome is valued
- Continuous focus of activity (decades)
- Several missions

Industry

- Limited Intellectual & legal freedom to operate.
- Strong Institutional support
- Narrowly talent pool
- Portfolio is premier
- Only specific outcomes valued
- Areas of interest changes with business climate
- Single mission

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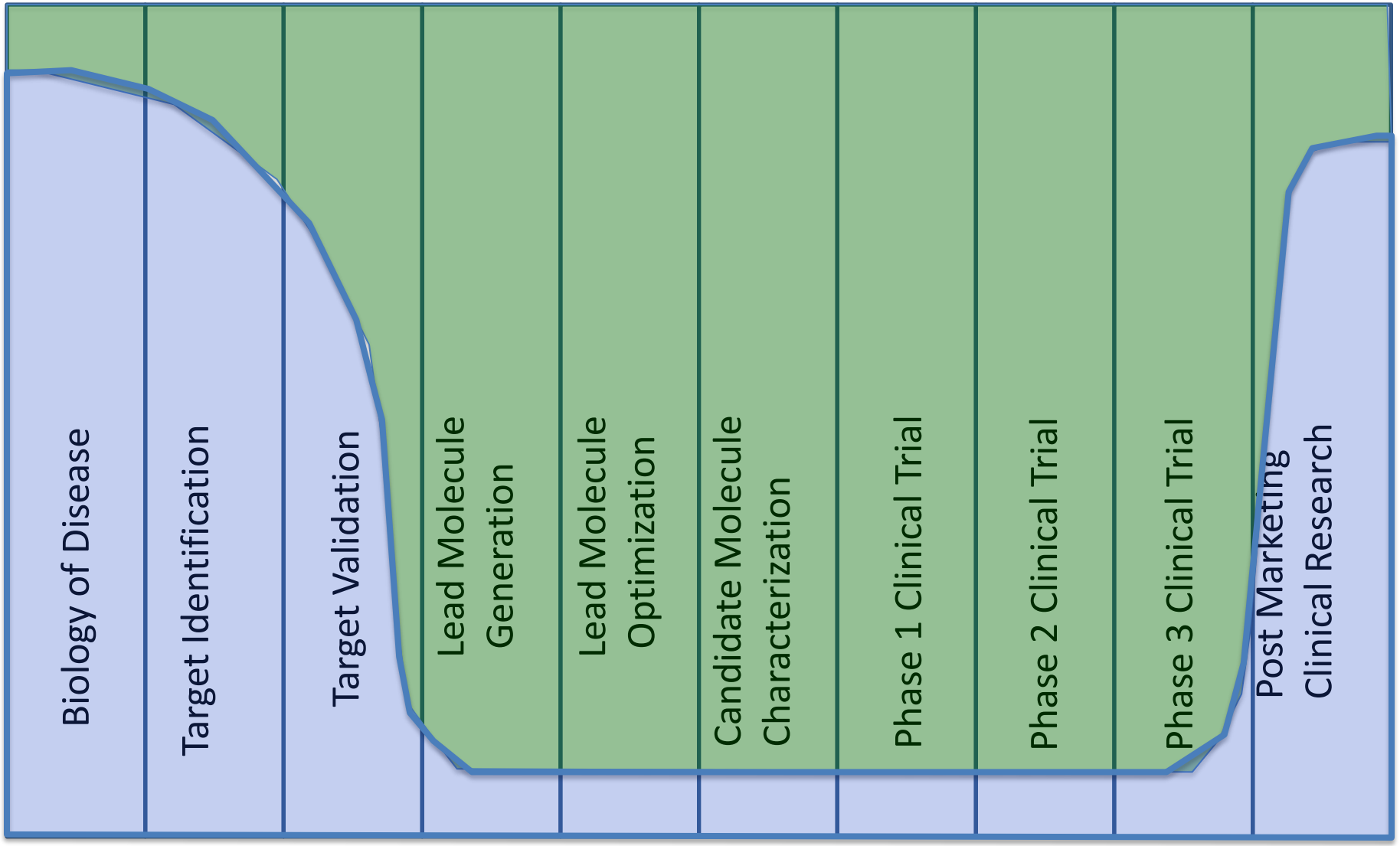
Balance of Drug Discovery and Development



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Collaboration must address concerns & likely benefits

areas for concerns

Integrity of the university's teaching and research mission

Willingness to disseminate new discoveries

Exchange of scientific reagents, tools and technologies

Patient protection

Conflict of interests at several levels

Ownership

expected benefits

Expedites the public's access to new and important medicines

Returns public value from government investment in research

Fosters business development

Increases support for educational institutions

Enhances the performance of both institutions

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Where does the industry need help in advancing innovative medicines?

1. **Target identification and validation**
2. **Understanding patient heterogeneity**
3. **Biomarker development**
4. **Identifying unique subsets of patients responsive to a new drug with a novel mechanism of action**
5. **Providing tools to help physicians manage complex information and derive therapeutic decisions**

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1. Target Identification and Validation

Older drugs were based on chance pharmacology

- The observation of clinical activity of a compound leads to clinical development. The mechanism of action is later uncovered.

- Physiologic observations
  - Alkylating agents
  - Natural Products (ACE inhibitors, Digitoxin)
  - Aspirin

Newer drugs are derived from basic academic research

The genetics of rare diseases with extreme phenotypes gives insight into biochemical pathway that lead to new drug targets.

- CETP (cholesterol metabolism)
- PCSK9 (cholesterol metabolism)
- CTLA4 (autoimmunity)*
- NAV1.7 (pain) †
- SOST (bone mineralization)
- Retinoblastoma (cancer)
- Amyloid Precursor Protein/Aβ peptide (Alzheimer's Disease)
- Myostatin (muscle growth)

*P Lindsey, BMS, † D. McHale, Pfizer

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2. Understanding Patient Heterogeneity

- *"The suppression of participant heterogeneity in rigorous clinical trials helps to explain why the published clinical literature is overwhelmingly explanatory rather than pragmatic; that is, focused on what works rather than on informing real-world decisions among alternative clinical interventions"*
- **Davidoff, F. Heterogeneity is not always noise: lessons from improvement.** JAMA. 2009 Dec 16;302(23):2580-6.

We need to use patients' clinical and molecular information to make better treatment decisions

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About half of all patients fail to respond to medicines they are prescribed

Therapeutic Area	Efficacy Rate (%)
Alzheimer's	30
Analgesics (Cox-2)	80
Asthma	60
Cardiac Arrhythmias	60
Depression (SSRI)	62
Diabetes	57
HCV	47

Therapeutic Area	Efficacy Rate (%)
Incontinence	40
Migraine (acute)	52
Migraine (prophylaxis)	50
Oncology	25
Osteoporosis	48
Rheumatoid arthritis	50
Schizophrenia	60

Source: Spear B., et al. Trends in Molecular Medicine 7(5):201-204, 2001

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Using markers to target patients results in smaller possible market, but peak sales are increased

Example: Peak sales increase for marker with 25% frequency

Measure	Base	With marker (3 scenarios)		
Market size (patients)	200k	50k	50k	50k
Response rate	25%	50%	75%	90%
Peak share	20%	80%	80%	95%
Patients prescribed	40k	40k	40k	47.5k
Responders	10k	20k	30k	42.75k
Non-responders	30k	20k	10k	4.75k
Total cycles*	120k	160k	200k	266k
Price per cycle	$1k	$1k	$1k	$1k
Peak sales	$120m	$160m	$200m	$266m
*6 per Responder, 2 per Non-responder		+33%	+66%	+122%

Extent of benefits depends on frequency of and response rate with marker.

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3. Biomarker Development

- **Biomarkers serve a variety of needs**
  - Target engagement –does the drug inhibit the target in humans?
  - Pharmacodynamic effect- does the drug modulate the pathway of interest?
  - Efficacy- can the short term biochemical effects be related to overall clinical benefit?
- **Most biomarker have very little "proprietary value".**
  - The value of the biomarker goes up when widely used, understood and accepted.

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The Biomarkers Consortium:

Projects Supported by Lilly (through 2009)

Project Name/ Committee	Description	Total Project Value & Duration	Eli Lilly Investment
Adiponectin Project (Metabolic Disorders SC)	Determine whether adiponectin has utility as a predictive biomarker of glycemic control	$0 (in-kind data sharing project) (18 months) Completed April 2009	1 of 4 companies to provide data and in-kind legal/scientific support
Sarcopenia Consensus Summit (Metabolic Disorders SC)	Generate a consensus definition of sarcopenia to provide guidelines for diagnosis/better regulatory decisions	$463,000 over 24 months 2010-2011	$100,000 (1-time payment; project to conclude in 2011)
Alzheimer's Disease Targeted CSF Proteomics Project (Neuroscience SC)	Qualify a multiplexed panel of known AD CSF-based biomarkers; examine Beta-Site APP Cleaving Enzyme levels in CSF; and qualify a mass spectroscopy panel	$586,100 over 12 months 2Q 2010-1Q 2011	$100,000 (1-time payment; project to launch in 2Q 2010)
PET Radioligand Project (Neuroscience SC)	Develop improved, more sensitive radioligands with higher binding to the peripheral benzodiazepine receptor	$560,500 over 24 months 2009-2010	$93,417 (payable over 2 years in 2009 and 2010)
Placebo Data Analysis in AD and MCI Cognitive Impairment Clinical Trials (Neuroscience SC)	Combine placebo data from large industry trials and analyze them to provide better measures of cognition and disease progression	$556,620 over 36 months 2010-2012	$95,000 (1-time payment)
I-SPY TRIAL 2 (Cancer SC)	A personalized medicine trial that promises to accelerate the pace of identifying effective novel agents for breast cancer; patients will be classified according to biomarker profiles and randomized to control therapy	$26,000,000 over 60 months 2010-2014	$200,000 (to date)
TOTAL (Consortium Programs)			**$588,417**

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FOUNDATION FOR THE National Institutes of Health

FNIH Partnerships with Lilly

Project	Description	Federal Investment	Private Investment	Total Investment	Lilly Contribution
Neuroscience Fellowship Program (2004-06)	Allows a young physician researcher apply clinical experience and cellular/molecular research techniques to the field of neurophysiology. *NIH partner: NIMH*	$0	$200,000	$200,000	$200,000
Overcoming Barriers to Early Phase Clinical Trials (2002-2008)	Investigate barriers that prevent patients, especially minority and elderly populations, from participating in early-phase clinical trials of innovative cancer therapies. *NIH partner: NCI*	$2,450,000	$2,550,000	$5,000,000	$600,000
Fogarty International Center 40th Anniversary (2008)	Scientific meetings on global health, other events. *NIH partner: Fogarty*	Not quantified	$200,000	$200,000	$50,000
Promise of Public Private Partnerships: Forging New Alliances in Global Health (2008)	Meeting to explore implementation science and training needs and forge new collaborations to improve global health. *NIH Partner: Fogarty*	$0	$21,000	$21,000	$5,000
The Science of Eliminating Health Disparities Summit (2008)	Summit to establish research agenda. *NIH partner: NCMHD*	Not quantified	$1,375,000	$1,375,000	$25,000
Psychiatric Genome-Wide Association Consortium (2007-2009)	Analyze GWAS data for ADHD, autism, bipolar disorder, major depression disorder, and schizophrenia, to move the entire field of mental health genetic research forward. *NIH partner: NIMH*	$0	$125,000	$125,000	$125,000
Alzheimer's Disease Neuroimaging Initiative (2003-10)	Collects clinical and biomarker data as a public resource to identify promising biomarkers of disease progression for use in AD clinical trials. *NIH partner: NIA*	$40,000,000	$20,000,000	$60,000,000	$2,500,000
Mutational Analysis of the Melanoma Genome (2010-11)	Sequence whole genome of 5 tumor samples and 5 normal samples, analysis, gene sequencing, deep sequencing of mutated genes. *NIH partner: NHGRI*	Not quantified	$250,000	$250,000	$225,000
Best Pharmaceuticals for Children Fund (2001-present)	Clinical trials of drugs approved for adults that are used to treat children. Supports studies of baclofen and hydroxyurea. *NIH partner: NICHD*	Not quantified	$5,000,000	$5,000,000	$500,000
Measures for Clinical Trials of the Treatment of Cognitive Impairment (2006-present)	Identify a widely accepted model for assessing efficacy of cognition enhancing drugs for schizophrenia and translate and adapt an assessment battery for use in international trials of new drug treatments. *NIH partner: NIMH*	Not quantified	$2,233,000	$2,233,000	$203,197
ADNI Cerebral Spinal Fluid (CSF) Extension (2007-present)	Extends collection of cerebral spinal fluid (CSF) in ADNI subjects for a second year. *NIH partner: NIA*	$0	$913,954	$913,954	$100,000
Drug Induced Liver Injury Network *pledged* (2010-2015)	Increase understanding of DILI and effective screening, diagnostic, and treatment options. *NIH partner: NIDDK*	$16,250,000	$1,000,000	$17,250,000	$500,000
Observational Medical Outcomes Partnership (2007-present)	Improve the monitoring of drugs for safety by researching methods that are feasible and useful to analyze existing healthcare databases to identify and evaluate safety and benefit issues of drugs already on the market. *Federal partner: FDA*	$0	$20,000,000	$20,000,000	$1,500,000
Biomarkers Consortium Membership (2007-present)	Core infrastructure to facilitate development of biomarkers projects. *Federal partners: NIH, FDA, CMS* (projects listed on next page)	Not quantified			$350,000
TOTAL, general programs					**$6,883,197**

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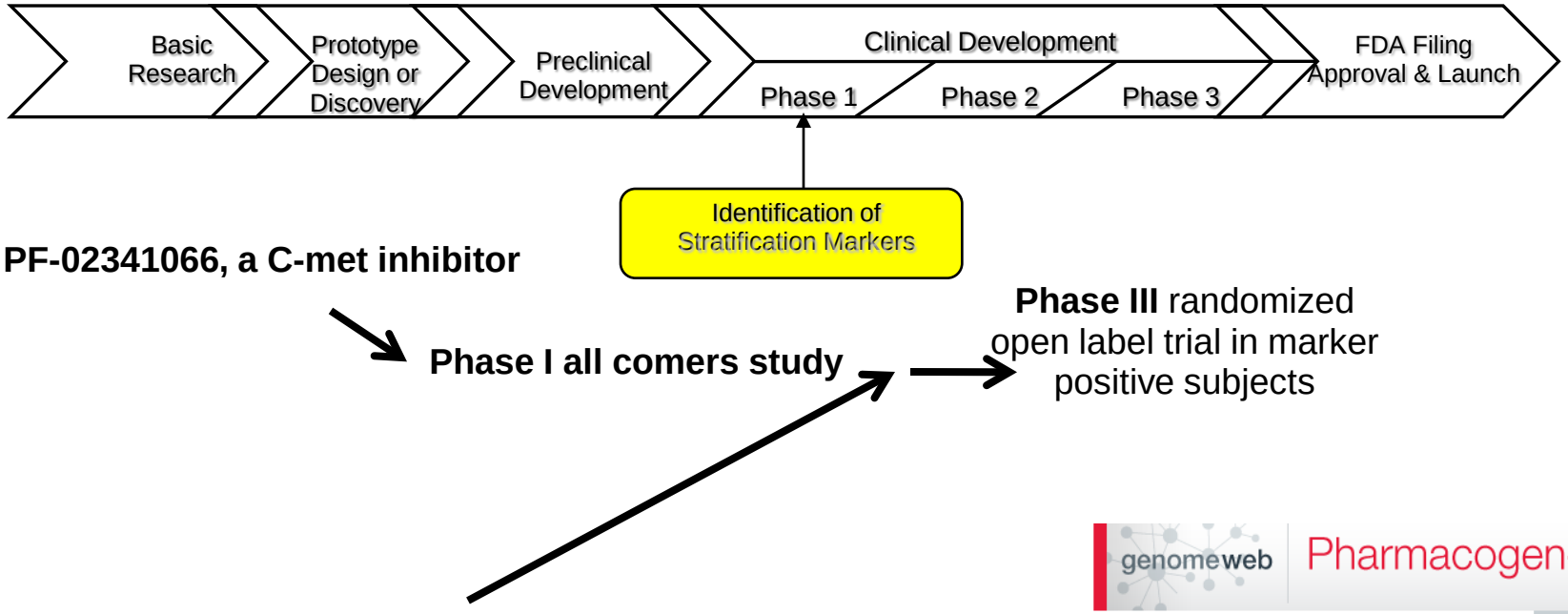
4. Identifying unique subsets of patients responsive to a new drug with a novel mechanism of action



Manabu et al, "Identification of the transforming *EML4–ALK* fusion gene in non-small-cell lung cancer", *Nature* 448, 561-566 (August 2007)

"Our data demonstrate that a subset of NSCLC patients may express a transforming fusion kinase that is a promising candidate for a therapeutic target as well as for a diagnostic molecular marker in NSCLC."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Pfizer, Abbott Ink Deal to Develop Companion Dx for PGx-based NSCLC Drug

September 02, 2009

Type size: Email Printer-friendly version RSS Feed

Pfizer has previously touted PF-02341066 as "the first agent in clinical development that selectively targets a unique genetic feature of cancer cells." The drug is currently in Phase III trials, while Abbott is in the process of designing validating trials for a companion test with the capability to detect ALK gene rearrangements.

Full-text access for premium subscribers only. Existing premium subscribers login here.
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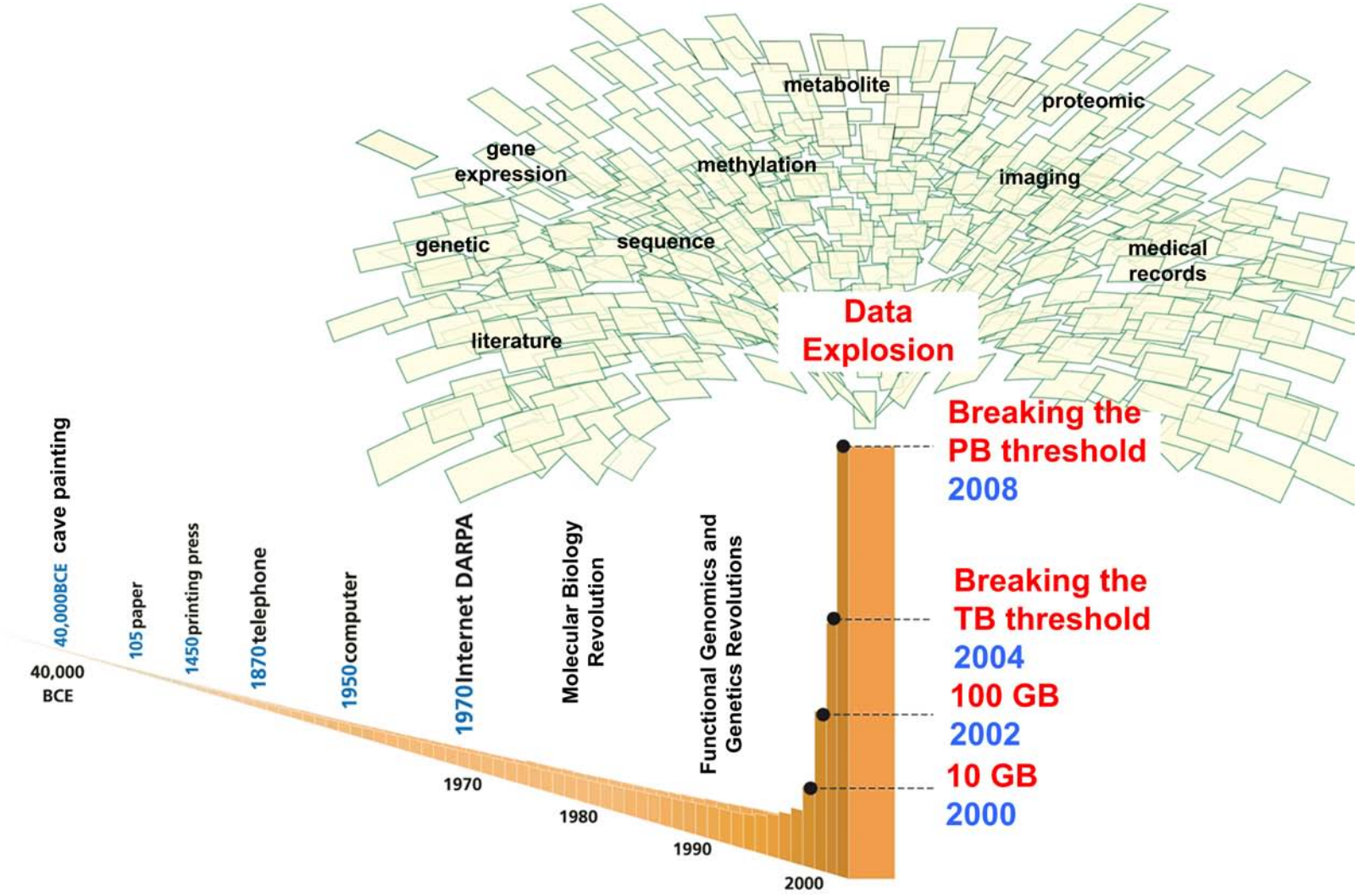
Information Overload



Stephen Friend 2009

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5. Tools to help physicians manage complex information and derive therapeutic decisions.

- **Significant limitations of current guidelines**
  - Guidelines not patient-specific enough to be useful and rarely allow for individualization of care.
  - Most guidelines have a one-size-fits-all mentality and do not build flexibility or contextualization into the recommendations. (Shaneyfelt & Centor JAMA, 2009)
- **There are limits on our capacity for processing information**.

  The magic number is 7 ± 2. (Miller, Psych. Review,1956;63(2):81-97)

- **Clinicians may already be discarding important information simply due to cognitive limits**.
- **Many new medicines will require the co-launch of a decision-making tool**

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Tests to Select Therapies

- Safety

  ⇒ CYP2D6 genotypes' effect on metabolic rate for drugs

  ⇒ HLA allele B*1502 as a marker for carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis

  ⇒ HLA B5701 genotype for risk of hypersensitivity in patients taking abacavir and flucloxacillin

  ⇒ KRAS mutation for inefficacy of cetuximab, panitumumab

- Effectiveness

  ⇒ HER2 positive breast cancer patient selection for trastuzumab

  ⇒Oncotype Dx screen for ER+, node negative patients considering treatment options

- Dosing

  ⇒ VKORC1 and CYP2C9 genotype to predict warfarin dose.

c.f. Gene Pennello, DIA Statistics Forum, April 2010

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Coumadin Label Information

1/22/2010

Table 5: Range of Expected Therapeutic Warfarin Doses Based on CYP2C9 and VKORC1 Genotypes†

VKORC1	CYP2C9					
	*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3
GG	5-7 mg	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg
AG	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg
AA	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg

Ranges are derived from multiple published clinical studies. Other clinical factors (e.g., age, race, body weight, sex, concomitant medications, and comorbidities) are generally accounted for along with genotype in the ranges expressed in the Table. VKORC1 –1639 G → A (rs9923231) variant is used in this table. Other co-inherited VKORC1 variants may also be important determinants of warfarin dose. Patients with CYP2C9 *1/*3, *2/*2, *2/*3 and *3/*3 may require more prolonged time (>2 to 4 weeks) to achieve maximum INR effect for a given dosage regimen.

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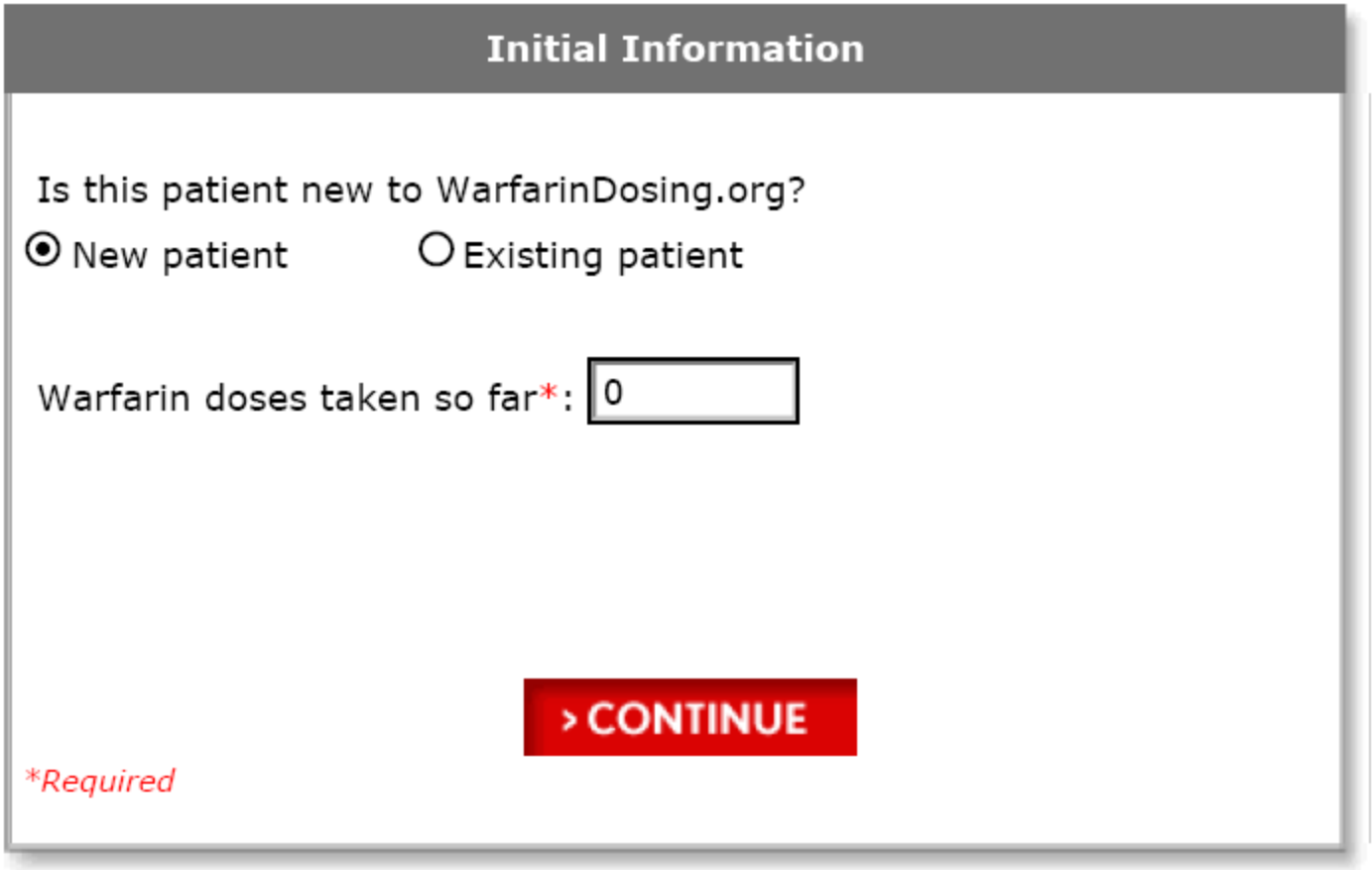
Warfarin Dosing



http://www.warfarindosing.org/Source/DoseResults.aspx

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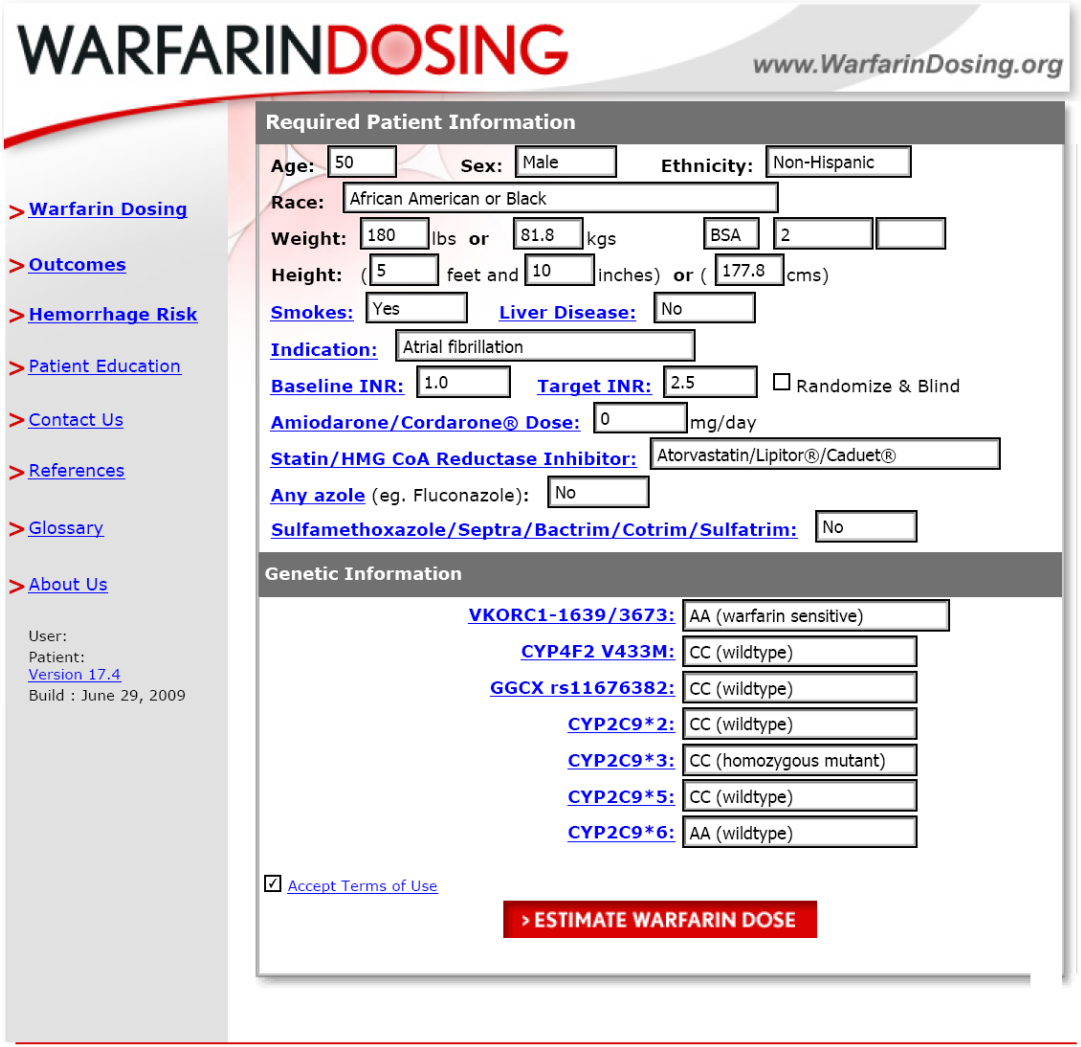
Warfarin Dosing



http://www.warfarindosing.org/Source/DoseResults.aspx

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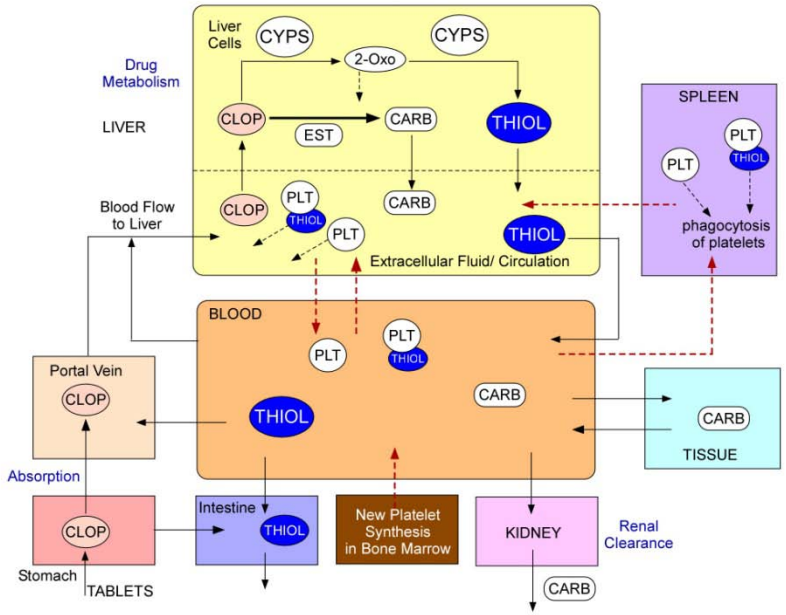
Clopidogrel Mechanistic Model

PK ⇒ PD ⇒ Clinical Outcomes



Data used for this model includes:

- ***in vitro* liver microsomal data**
- ***in vitro* competitive inhibition data**
- **Published data about Ki**
- **Healthy volunteer PK data**
- **Diseased patient PK data**
- **Healthy volunteer PD data**
- **Healthy volunteer PD data with other drugs**
- **Diseased patient PD data**
- **Published data on platelets**
- **ACS patients' genotype, PD and clinical outcomes**

- 31 ordinary differential equations for PK
- 30 ordinary differential equations for PD
- 25 input variables
- 11 baseline patient characteristics
- 6 genetic parameters (including 2C19, 2C9, & ABCB1)
- 8 concomitant medications
- PK/PD to clinical outcomes still being constructed

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Summary of Areas of Collaboration

- **Pre-clinical Research**
  - Target Identification and Validation
  - Understanding which patient subgroups would benefit from targeted therapies with specific mechanisms of action.

- **Clinical Research**
  - Biomarker Research
    - Pharmacogenomics
    - Disease specific markers of benefit
  - Comparative Effectiveness Research
    - Who needs what medicine and why?
  - Pharmacoeconomic Research
    - What is valued? What benefit at what cost?
  - Advance Regulatory Science
    - What constitutes the appropriate data?
  - Implementing Personalized Medicine in a Regulated Environment
    - Designing robust decision-making tools for Physicians and Healthcare providers

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Key Aspects of Successful Collaborations

- Clear expectations of the objectives, timelines, resources and overall mission
- Frequent interactions
- Interdependence of knowledge and resources.
- Consistent with both the corporate goals and the academic mission.
- Absolute transparency in all aspects of collaboration

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Answers That Matter.

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GMP Facilities at the NIH Clinical Center




John I. Gallin, M.D.

Director, NIH Clinical Center

September 14, 2010

Clinical GMP Facilities

Pharmaceutical Development Service

Positron Emission Tomography

Cell Processing Service

Pharmaceutical Development Section

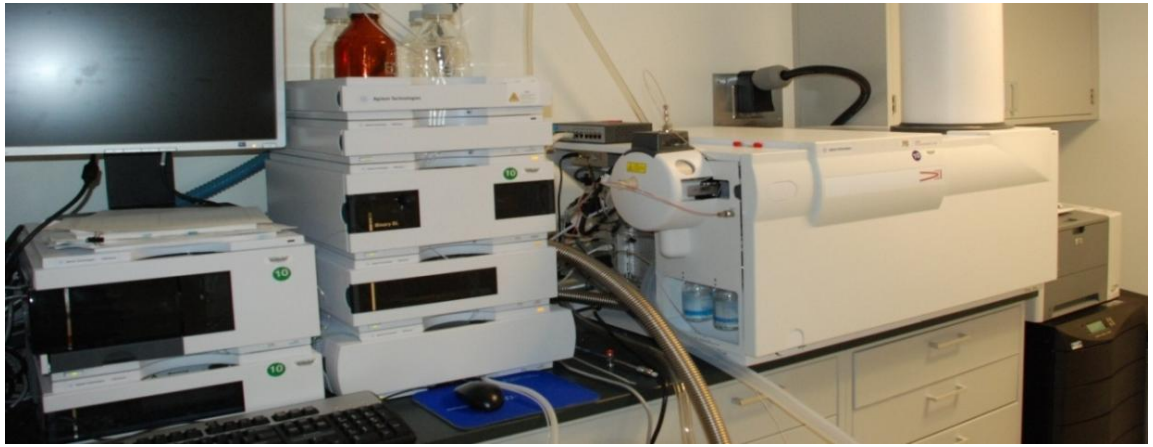
Pharmacy Department

George Grimes, RPh, BS Pharm, Chief

In existence sine 1956 - - - - New Facility 2010

Pharmaceutical Development Section

- Product Development
- Analytical and Quality Control
- Pharmacokinetics



Pharmaceutical Development Section Functions

- Responsible for ~1100 investigational drugs currently studied at the CC
- Formulates tablets, capsules, sterile parenterals, and topical products, including placebos
- Ensures that raw materials used and finished products are suitable for human use
- Maintains accountability records for sponsor and FDA review
- Assists in filing INDs

Manufacturing Capability
(8 hour day)

- 75,000 capsules
- 150,000 tablets
- 220 liters
- 5,000 syringes
- 8,000 vials (includes vaccines and biologics)

Capacity could be tripled by operating 3 shifts.

Department of Positron Emission Tomography

Peter Herschovitch, M.D., Chief

PET Resources

- **Three medical cyclotrons**
  - CS-30 (4-particle; 1985)
  - Two GE PETtrace cyclotrons

- **Radiochemistry**
  - 10 hot cells for synthesis of radiopharmaceuticals
  - Lab for radiopharmaceutical QC and dispensing

- **Scanners**
  - Three GE Advance whole body scanners (PET/CT scanner in procurement)
  - High Resolution Research Tomograph

Cyclotron Radionuclides

Standard PET nuclides

Radionuclide	Half-Life (min)
O-15	2
N-13	10
C-11	20.4
F-18	110

Other PET and non-PET nuclides (CS-30 cyclotron)

Radionuclide	Half-Life (hrs)
At-211	7.2
Br-76	16.2
Cu-60	0.40
Cu-64	12.7
Bi-205	367.4
I-124	100.2
Pb-203	51.9
Re-186	90.6
Sr-85	1556.1
Tc-94m	0.88
Y-86	14.7
Zr-89	78.4

PET Radiopharmaceuticals

[^{18}F]FDG	glucose metabolism (brain, body)
[^{15}O]water	blood flow (brain, body)
[^{18}F]FDOPA	presynaptic dopaminergic function (brain); NETs
[^{18}F]FDopamine	peripheral sympathetic function, NETs (body)
[^{13}N]ammonia	myocardial perfusion
[^{11}C]raclopride	dopamine D2 receptors (brain)
[^{11}C]palmitic acid	fatty acid metabolism
[^{11}C]arachidonic acid	second messenger via PI turnover (brain)
[^{18}F]FP-TZTP	muscarinic acetylcholine M2 receptors (brain)
[^{18}F]FCWAY	serotonin 5HT1A receptors (brain)
[^{11}C]carbon monoxide	blood volume (brain, body)
[^{11}C]flumazenil	benzodiazepine receptors (brain)
[^{11}C]docosahexaenoic acid	incorporation of DHA (brain)
[^{11}C]DASB	serotonin transporters (brain)
[^{11}C]DTBZ (2006)	VMAT2 (brain, body)
[^{11}C]leucine (2006)	protein synthesis rate (brain, body)
[^{94m}Tc]Sestamibi (2007)	MDR probe in cancer
[^{11}C]NNC (2007)	dopamine D1 receptors (brain)
[^{18}F]fallypride (2007)	dopamine D2 receptors (brain)
[^{11}C]acetate (2008)	prostate cancer (membrane lipid)
[^{11}C]carfentanil (2010)	opiate receptors (IND in preparation)

N = 21

PET GMP Facility

Purpose: Manufactures GMP radiopharmaceuticals

- **PET scans for patients under IRB-approved protocols**
- **21 PET radiopharmaceuticals currently available**
- **New GMP facility will replace 1985 facility**

New PET GMP Facility

- **Location:** 6,280 sq ft on the B3 level of CRC
- **Will include:**
  - Up to 19 hot cells to handle large (Ci) amounts of radioactivity
  - Clean room
  - Analytical laboratory for quality control
- **Capabilities:**
  - Meets FDA GMP regulations
  - Doubles current capacity
  - Extramural shipment of GMP F-18 radiopharmaceuticals (2-hour half-life)

Cell Processing Section
Department of Transfusion Medicine

David Stroncek, M.D., Chief

Mission:

Provides cellular and gene therapies

Cell Processing Section

Resources:

- Product Development Laboratory
- GMP Laboratory
- Regulatory affairs

Standard of Care Activities:

- Supports hematopoietic stem cell transplant programs

IND protocols for Phase I/II Clinical Trials Activities:

- Gene Therapy
- Dendritic Cells for Cancer Therapy
- Cytotoxic Cells for Cancer/Lymphoma Therapy
- Donor Leukocyte Infusions

NIH Bone Marrow Stromal Cell (BMSC) Transplant Center

Cell Processing Manufacturing Capability

- **12 hour days, 5 days a week**
  - **25 intense procedures could be performed each week; or**
  - **8 to 12 products could be produced per week**
- **24 hour days, 5 days a week**
  - **The capacity could be doubled to 16 to 24 products per week**
- **24 hour days, 7 days a week**
  - **The theoretical capacity is 23 to 35 products per week**

In Conclusion…

The Clinical Center's three GMP facilities support the NIH intramural programs but could be expanded to assist outside investigators.

NIH-RAID

Common Fund Translational Resources

Thomas Miller

September 14, 2010

NIH-RAID Facts

- Approved projects gain access to:
  - Therapy development expertise
  - Government contract resources
- No funds are awarded to the applicant organization
- Eligible organizations
  - Not-for-profit
  - Businesses eligible for SBIR

Available Services

- Small molecules, peptides, oligonucleotides, natural products, gene vectors, antibodies, recombinant proteins
- Product development planning
- Non-GMP and GMP Manufacture
- Formulation
- pK/ADME
- IND-directed toxicology
- Clinical supply

NIH-RAID Structure

- NIH-RAID office
  - NINDS
- Scientific staff
  - NCI
- Project Team
  - 13 ICs
  - Two subcommittees
- Contract resources
  - NCI
  - NHLBI
  - TRND
- Strategic oversight
  - NIAMS and NINDS Directors
  - OD/DPCPSI/OSC

NIH-RAID Project Team

- NCI – Jim Cradock
- NHLBI – Traci Mondoro
- NIA – Chhanda Dutta
- NIAAA – Nanwei Cao
- NIAID – Beth Spinelli
- NIAMS – Gail Lester
- NICHD – June Lee
- NIDA – Jane Acri
- NIDCD – Gordon Hughes
- NIDCR – Dwayne Lunsford
- NIDDK – Myrlene Staten
- NIMH – Jamie Driscoll
- NINDS – Linda McGavern

NIH-RAID Process

- Electronic submission
  - X01 Resource Access Award
- Responsiveness
- CSR review
- Meeting to formulate development plan
  - Brainstorm
  - Inherent flexibility
- Funding recommendation
  - Project Team subcommittee

NIH-RAID Successes

- 23 approved projects
- Six INDs
- Five clinical trials
- Three development partnerships

Approved Projects

Diseases

- Alzheimer's
- Beta-thallasemia
- Congenital hyperinsulinism
- Cytomegalovirus
- Depression
- Drug Abuse
- Epilepsy
- Friedreich’s Ataxia
- Hepatic Fibrosis
- Hypogonadotropic hypogonadism
- IBD/Crohn's
- Neuro-oncology
- Nieman-Pick
- Osteoarthritis
- Parkinson's
- Pleural Loculation
- Radioisotope contamination
- Schizophrenia
- Sickle cell
- Spinal Cord Injury

ICs

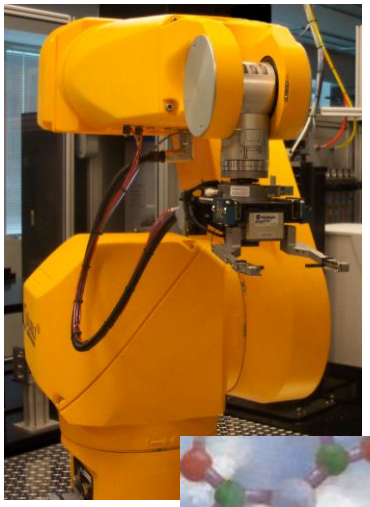
- NCI
- NHLBI
- NIA
- NIAAA
- NIAID
- NIAMS
- NICHD
- NIDA
- NIDDK
- NIMH
- NINDS

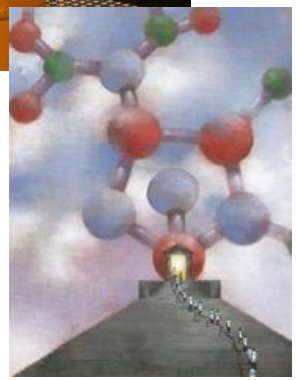
Application Receipts

- 2005 – 9 submissions
- 2006 – 22 submissions
- 2007 – 13 submissions
- 2008 – 29 submissions
- 2009 – 33 submissions
- 2010 – 56 submissions (including LOIs)

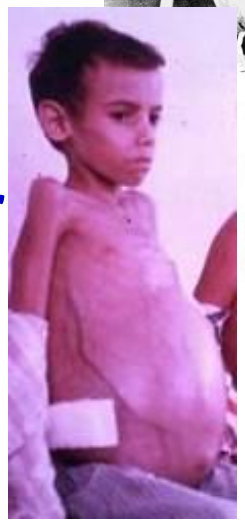
Outlook

Potential to start 14 projects with “Excellent” or better priority scores in FY2011





Bridging the Gap: Defining and Understanding the Necessary NIH Capabilities and Infrastructure

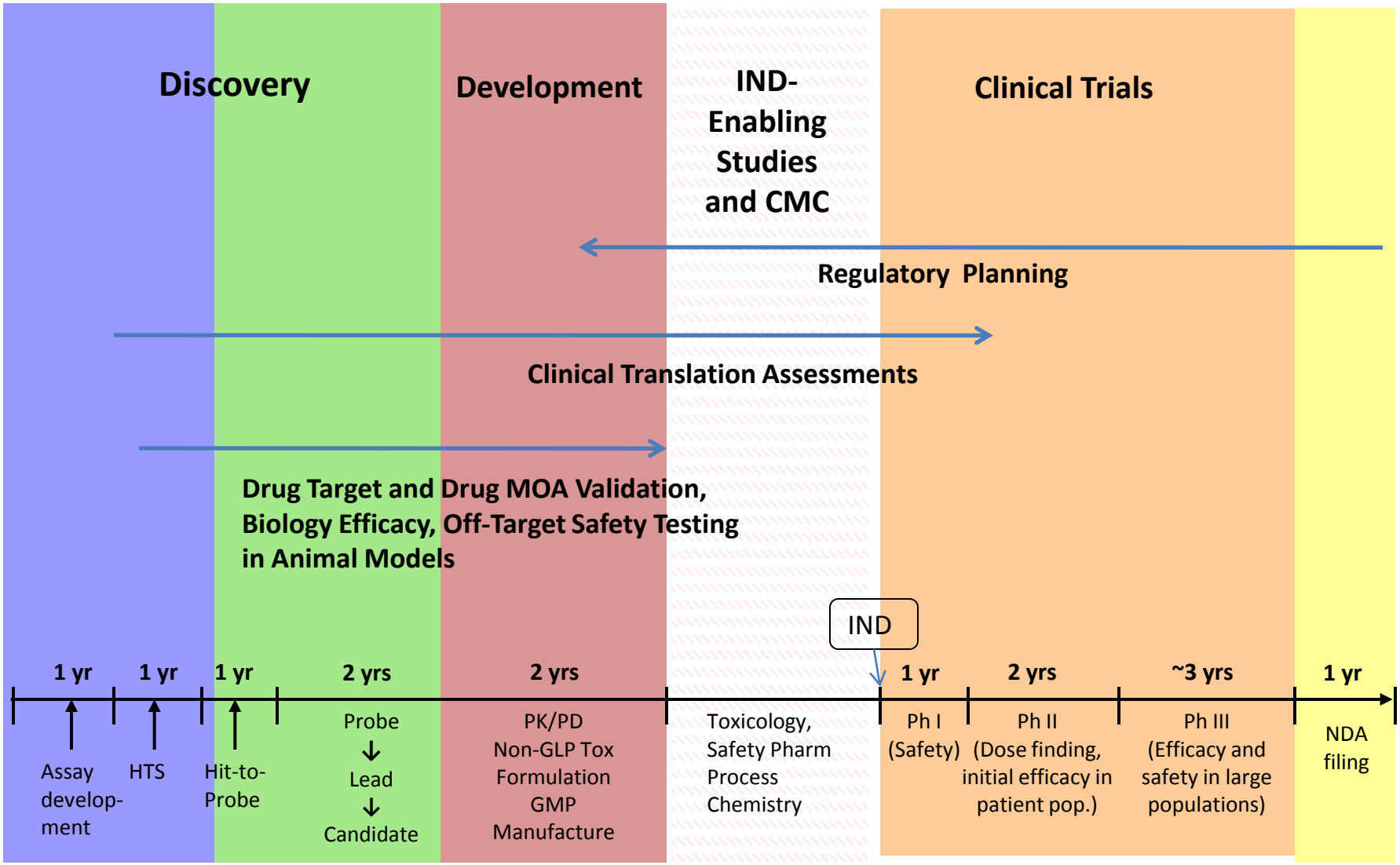


NIH Chemical Genomics Center and Therapeutics for Rare and Neglected Diseases

Susan E. Old, Ph.D.
Special Advisor
Acting Deputy Director
NIH Center for Translational Therapeutics
National Institutes of Health

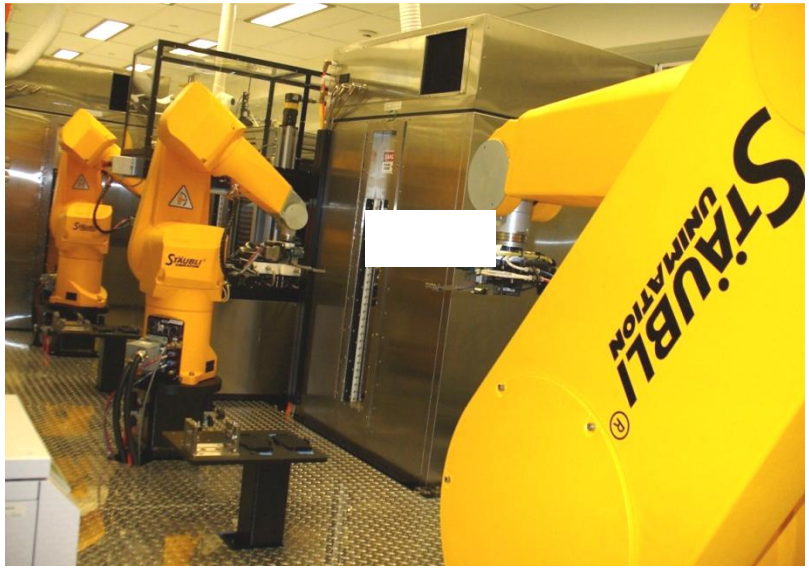
Science and Management Review Board
September 14, 2010

Therapeutic Development Pipeline



NIH Chemical Genomics Center

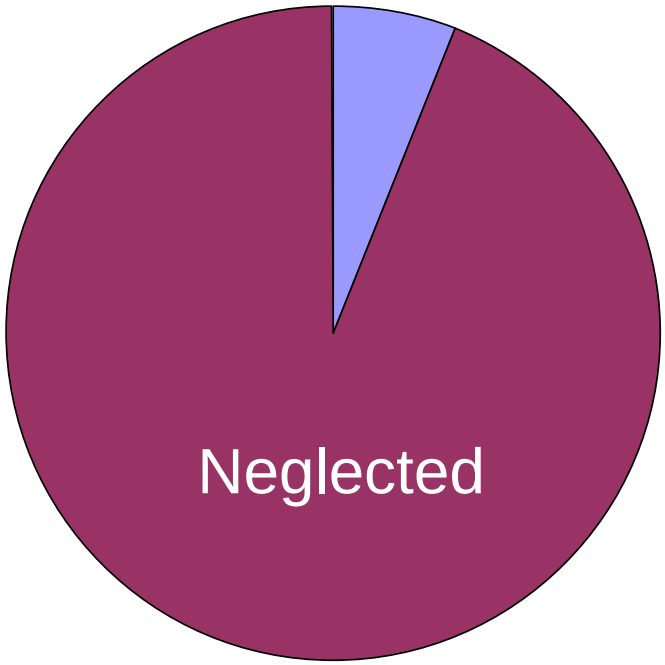
- Founded as part of Roadmap – *Molecular Libraries Program*
- 75 scientists
- > 100 collaborations with investigators worldwide
  - 75% NIH extramural
  - 15% Foundations, Research Consortia, Pharma/Biotech
  - 10% NIH intramural
- Focus on novel targets, rare/neglected diseases
- Produces
  - chemical probes/leads
  - new paradigms for assay development, screening, informatics, chemistry



Only a small % of genome-encoded targets and diseases are being addressed for drug development

Current drug targets:

Well understood proteins

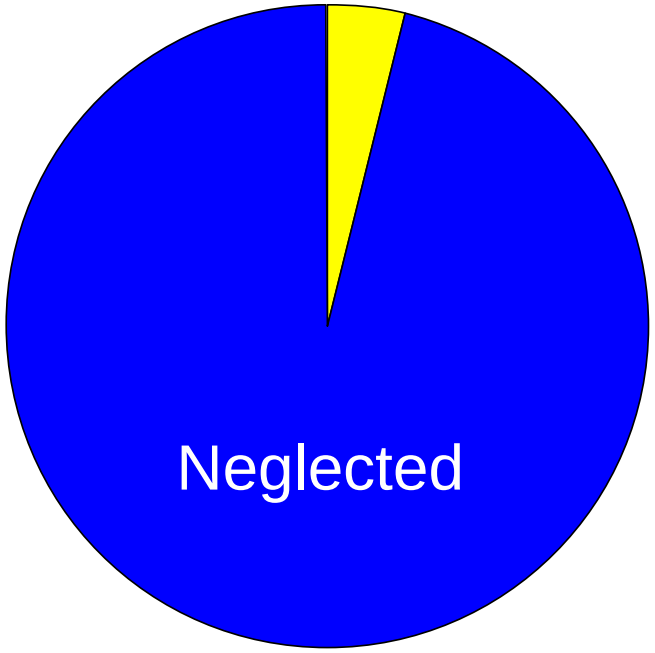


Human Genome

20,000 genes

Current targeted diseases:

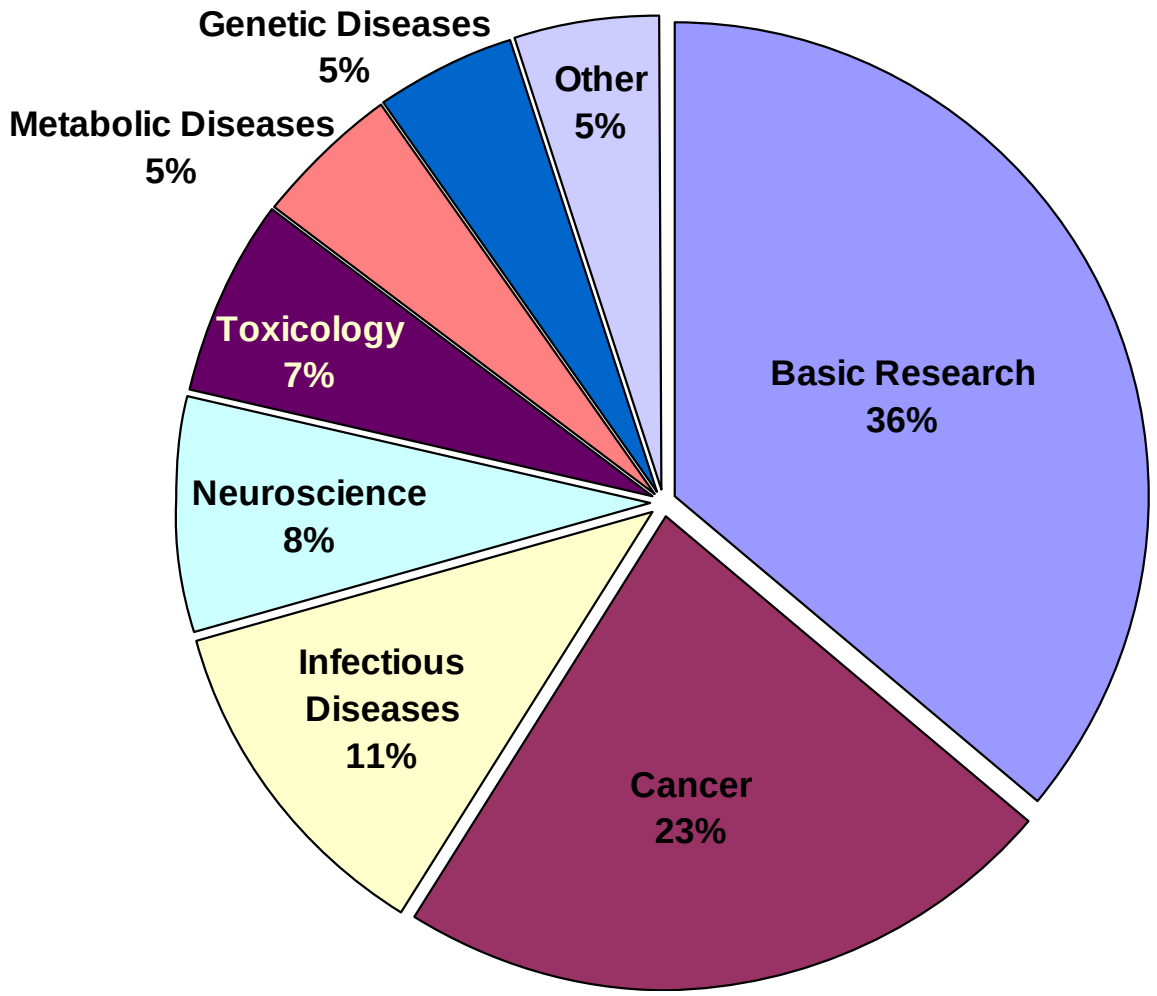
Prevalent diseases that affect developed world



Human Diseases

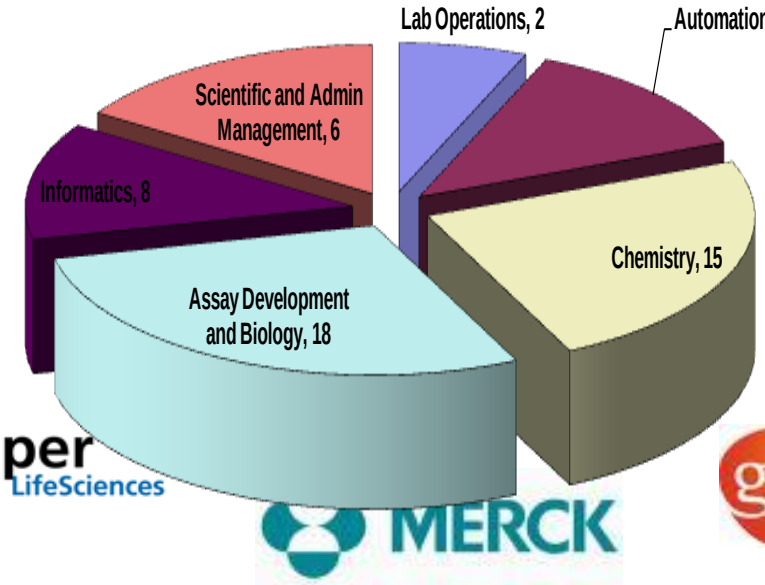
7000 diseases

Disease areas of NCGC assays



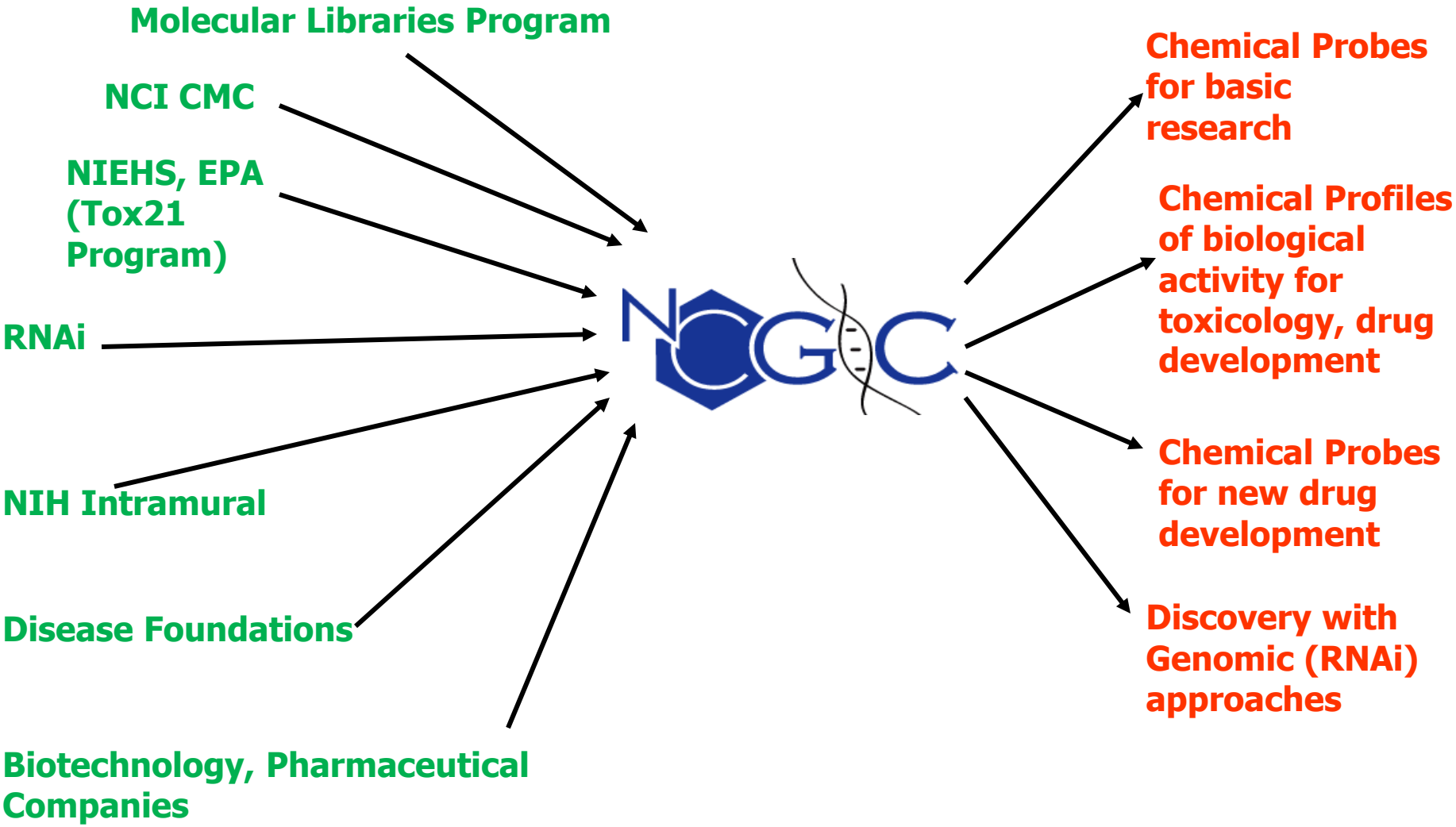
NIH Chemical Genomics Center

NCGC Staff



Amphora
Lilly
LARGE SCALE BIOLOGY
CELERA
an Applera Corporation Business
Pfizer
HGS
NORTHROP GRUMMAN
DEFINING THE FUTURE
AMGEN
ArQule
Caliper LifeSciences
MERCK
Johnson & Johnson
gsk GlaxoSmithKline
Pharmacopeia
BD
BD Biosciences
Lexicon pharmaceuticals
NCGC
NIH Chemical Genomics Center

The NCGC: Facilitating Drug Discovery



The long pathway to drug development

Basic and Clinical Research

NCGC, Molecular Libraries Initiative

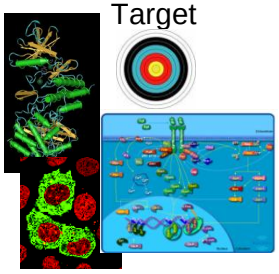
"Valley of Death"

Pharmas, Biotechs NIH Clinical Center, Academic Clinical Centers

FDA

IND

Indefinite	3 yrs	4 yrs	1 yr	2 yrs	~3 yrs	1 yr
Identify Target	Identify chemical starting point for drug	Make many chemical modifications to give drug beneficial effect without side effects	Ph I	Ph II	Ph III	Review	Patient Use



NIH Therapeutics for Rare and Neglected Diseases (TRND) Program

Creating a Drug Development Pipeline at NIH

- Congressionally-mandated effort to speed development of new drugs for rare and neglected diseases
- Administration and governance at NIH
  - Governance/oversight by Office of Rare Diseases Research
  - Administered by NHGRI
- Operations: collaboration between intramural and extramural labs with appropriate expertise
- Projects will:
  - Enter TRND at a variety of stages of development
  - Be taken to phase needed for external organization to adopt for clinical development

NIH Therapeutics for Rare and Neglected Diseases (TRND) Program

Distinguishing features

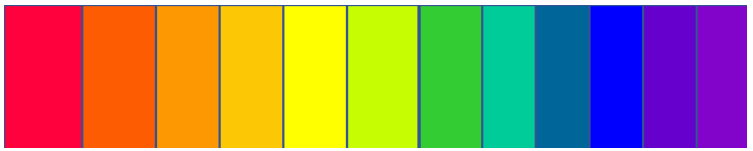
- Collaboration / Partnerships (not service center)
  - Government, Academics, Non-Profit, For-Profit collaborations
- Building the laboratory and expertise infrastructure at NIH
- Disease agnostic, take advantage of cross-cutting mechanisms
- *Science* of preclinical drug development
- Technology/paradigm development (20% of effort, toward improving success rates)
- Large-scale systematic repurposing

Project-specific activities

- Medicinal chemistry, efficacy, pharmacology, absorption, distribution, metabolism, and excretion (ADME), toxicology, pharmacokinetics/pharmacodynamics (PK/PD)
- Chemical Manufacturing and Controls (CMC), Compound scale-up, formulation
- First in Human or Proof of Concept clinical trials as needed for project

NIH Therapeutics for Rare and Neglected Diseases (TRND) Program

- FY09: infrastructure (May 2009)
- FY10: infrastructure and pilot projects (June 2009)
  - Budget $24M
  - Focus: governance, hiring, research community outreach, pilot projects
- **FY11:** infrastructure and project solicitation
  - **President's budget recommends $50M**
  - **Solicitation of projects in Sept 2010 to begin in April 2011; 3-5 projects**
- FY12: fully operational
  - Laboratories completed Early 2012
  - Work on several new projects per year
  - Average project should take ~3 years
  - Projects will be monitored closely for progress



TRND Pilot Projects

Chosen to establish processes in advance of solicitation, with diversity of project stage, type of disease and collaborators

Disease	Type	Pathology	Collaborators	Compound type	Stage
Schistosomiasis, Hookworm	Neglected	Infectious parasite	Extramural	NME	Early (lead optimization)
Niemann Pick C	Rare	CNS, liver/spleen	Disease Fnd, Extramural, Intramural	Repurposed approved drug	Mid-stage
HIBM	Rare	Muscle	Biotech, Intramural	Intermediate replacement	Pre-IND
Sickle Cell Disease	Rare	Blood	Nonprofit, Intramural, Extramural	NME	Mid-stage
Chronic Lymphocytic Leukemia	Rare	Cancer	Disease Fnd, Extramural	Repurposed approved drug	Pre-IND

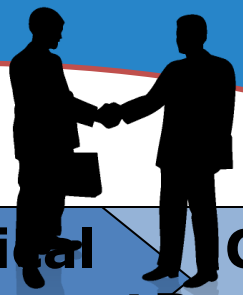
NIH Therapeutics for Rare and Neglected Diseases (TRND) Program

Pilot Program Discoveries

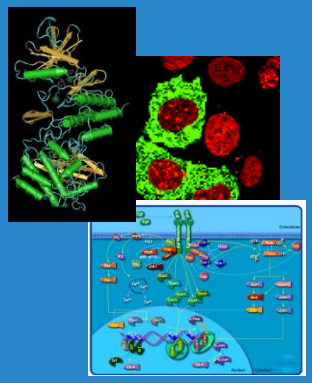
- **Funding Collaborators**
- **Collaboration Agreements**
- **Intellectual Property**
- **Project Management**
- **Expert Advice: inside and outside**
- **Excitement and Anticipation**

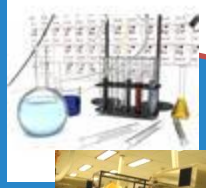
Filling the Gaps Between Discovery and Product

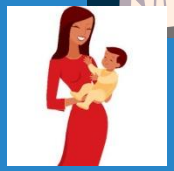
Partnerships and Collaborations



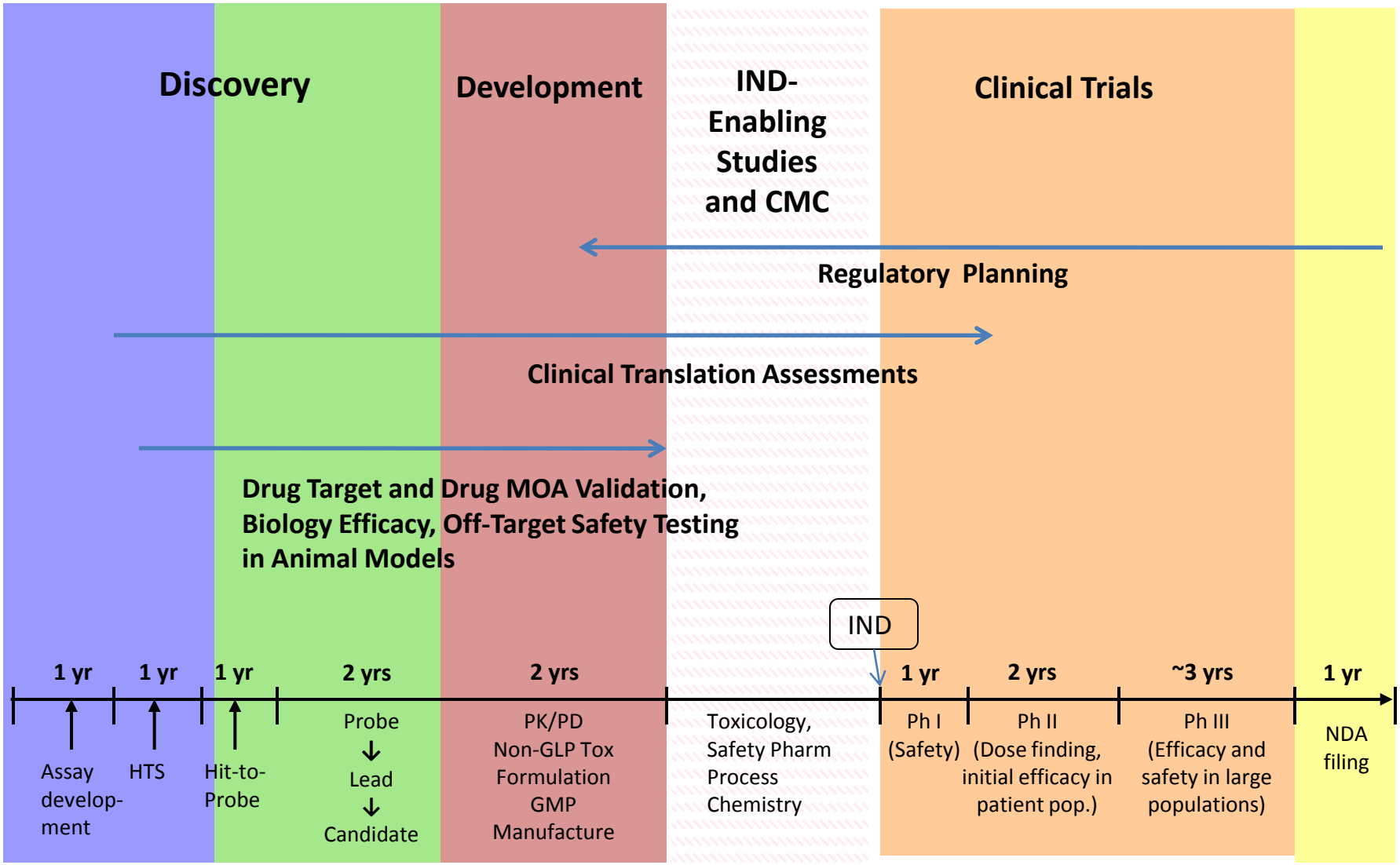
Discovery → Target ID & Validation → Preclinical Development → Clinical Development → Licensed Product







Therapeutic Development Pipeline



NIH Scientific Management Review Board

Substance Use, Abuse, and Addiction Working Group

Report and Recommendations

September 15, 2010

William Roper, MD, MPH
Dean of the School of Medicine and Vice Chancellor for Medical Affairs, University of North Carolina; CEO Of the UNC Health Care System

SUAA

Working Group Charge

"… to recommend whether organizational change within NIH could further optimize research into substance use, abuse, and addiction and maximize human health and/or patient well being."

Working Group Membership

Non-Federal

William Roper, MD, MPH
(Chair)

Deborah Powell, MD

Eugene Washington, MD, MSC

Huda Zoghbi, MD

Norman Augustine
(ad hoc)

Federal

Josephine Briggs, MD

Richard Hodes, MD

Griffin Rodgers, MD, MACP

Lawrence Tabak, DDS, PhD

Francis Collins, MD, PhD
(ex officio)

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Process & Consultations

- **Since April 2009, the working group has held 12 teleconferences and 3 in-person meetings and has heard from:**
  - **Current and former NIAAA & NIDA Directors**
  - **Prevention and treatment specialists**
  - **Patient advocates**
  - **Policy specialists**
  - **Scientists with diverse areas of expertise**
  - **Leaders of academia**
  - **Industry representatives**
  - **Judicial system representatives**
  - **NIAAA and NIDA Advisory Councils**

Summary of Findings: Opportunities in Science and Public Health

- **Emerging scientific research indicates:**
  - **Similar reward pathways underlie compulsive behavior**
  - **Many substances that pose the potential for abuse may have similar effects on the brain**
  - **Common genetic sites associated with risk for disorders related to abuse**
  - **Addiction is a developmental disease, often beginning in adolescence with common early risk factors across substances**
- **Many substance abusers suffer from multiple drug dependencies and/or co-morbid conditions**

Research/Public Health Needs Not Currently Addressed – NIAAA Perspectives

- A compendium of the pharmacokinetic and pharmacodynamic interactions between alcohol and the therapeutics used to treat general medical and psychiatric conditions (e.g., hypertension, diabetes, epilepsy, depression, etc.)
- Research on the generation of novel metabolites resulting from the in situ interaction of alcohol with opiates, stimulants, hallucinogens, or inhalants (e.g., the production of coco-ethylene) and their pharmacokinetic and pharmacodynamic properties and toxicity
- Mechanisms by which alcohol increases risk for certain cancers
- Encouraging the hesitant patient to seek treatment

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Research/Public Health Needs Not Currently Addressed – NIDA Perspectives

- **Lack of pharmaceutical industry interest in developing medications to treat addiction/alcoholism**
- **Insufficient involvement of the medical community in preventing and treating drug addiction and alcoholism**
- **Although treatments for substance abuse are available, they are not being widely used by those who need them**
- **There is a bottleneck in translating treatments for substance abuse from bench to bedside to the community**

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Summary of Findings: Stakeholder Perspectives

- Arguments in favor of structural reorganization
  - Scientific synergies
  - Underserved patient populations
  - Impediments to collaboration and integration
- Arguments in favor of non-structural reorganization
  - Potential loss of research
  - Establishment of a research dogma
  - Examples of current, successful collaborations
  - Licit vs. illicit substances

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Deliberative Process: Framework

(DOCE Process for Considering Change)

- **STEP 1:**

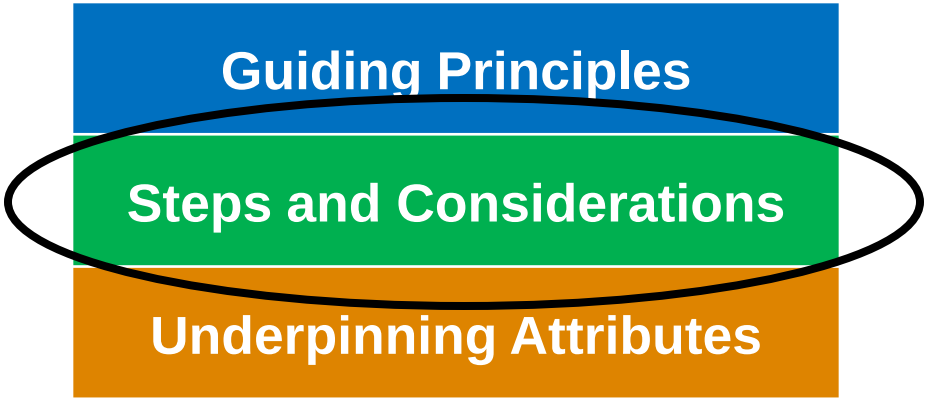
  Assess the need for change

- **STEP 2:**

  Evaluate options for change

- **STEP 3:**

  Implement and navigate the change



SUAA

Deliberative Process: Framework

(DOCE Process for Considering Change)

- **Criteria for Assessing the Need for Change:**
  - **Immediate Crisis**
  - **Unaddressed Scientific Opportunities**
  - **Changes in Scientific Landscape**
  - **Evolving or Emergent Public Health Needs**
  - **Need for Improvements in Quality and/or Efficiency of Research**

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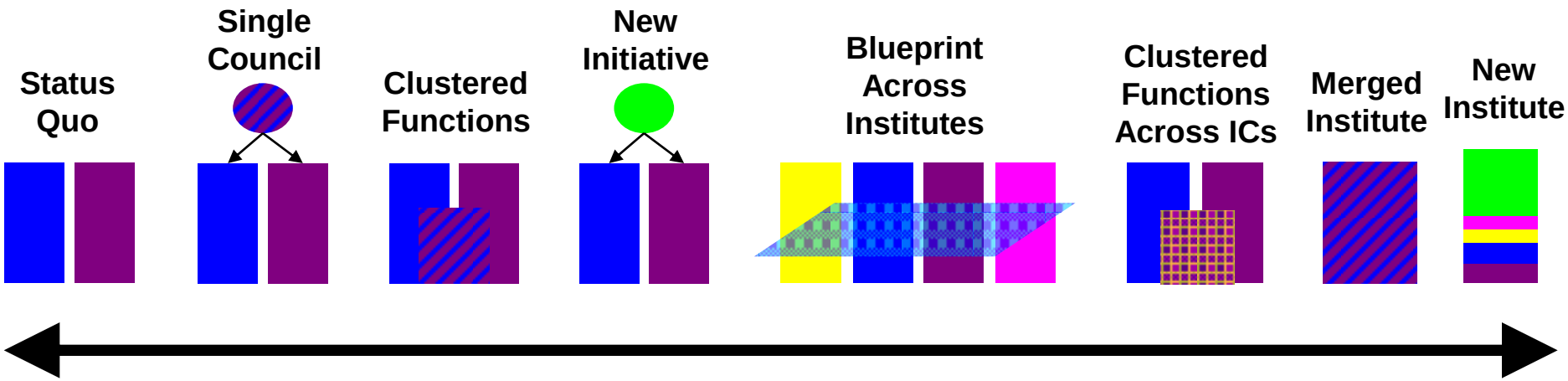
Deliberative Process: Spectrum of Potential Options



CONCLUSIONS & RECOMMENDATIONS

SUAA

Working Group Conclusions

- **<u>Status quo is not ideal</u> for fulfilling NIH mission and optimizing research into substance use, abuse and addiction**

- **<u>Reorganization is needed</u> for NIH to optimize science and best serve public health**

Identified Needs for Change

- **Unaddressed scientific opportunities, including:**
  - Preventing adolescent use, abuse, and addiction
  - Promote an understanding of both alcohol and drug abuse as diseases
  - Understanding drug-drug interactions
- **Changes in the scientific landscape, including:**
  - Advances in systems-level understanding that warrant a joint approach for many aspects of SUAA research
- **Emergent public health needs, including:**
  - Populations suffering from co-morbid conditions associated with substance use, abuse, and addiction
  - Rises in other forms of addiction (e.g. gambling, food, sex, etc.)
- **Needs for improvement in the quality and/or efficiency of research:**
  - Development of an integrated discipline of addiction research
  - Cross-training tracks need to be developed across fields

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Key Features of Reorganization

- **Integration of addiction research portfolios across NIH**
  - **Scope of reorganization focused on addiction-related research**
  - **Broader than drug and alcohol research**
  - **Include other substances (e.g., tobacco) and behaviors (e.g., gambling)**
  - **Mission statement should promote**
    - **Unified vision for addiction research**
    - **Interdisciplinary approach**
    - **Flexibility for new areas of study**
    - **Multidisciplinary approach to training**

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Key Features of Reorganization *(cont.)*

- **Commitment by all participants to success of reorganization**
  - **Strong leadership from NIH Director & IC Directors**
  - **Participation and contribution from NIH staff, community of affected researchers, and other stakeholders**
- **Functional integration**
  - **Shared goals**
  - **Enhanced communication and collaboration**
  - **Engagement and participation from all relevant parties**
  - **Identification, creation, and sustention of synergies**
  - **Cultural shifts**
  - **Cannot be a change “in name only”**

Two Recommended Approaches

- **Reorganization Option 1:**
  - **Create a New Addiction Institute**

- **Reorganization Option 2:**
  - **Form a Trans-NIH Initiative on Addiction**

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Option 1: A New Addiction Institute

- **Integrate all relevant addiction portfolios from NIAAA, NIDA, and other ICs. Include, for example:**
  - **Drug addiction research from NIDA**
  - **Alcohol addiction research from NIAAA**
  - **Tobacco addiction research from NCI**
  - **Gambling addiction research from NIDA and NIMH**
- **Transfer non-addiction research portfolios at NIAAA and NIDA to other ICs, as appropriate. For example:**
  - **Research on alcohol liver disease reassigned to NIDDK**
  - **Research on Fetal Alcohol Spectrum Disorders reassigned to NICHD**

Option 1: A New Addiction Institute *(cont)*

- **Funding**
  - **Addiction research funding relocated from existing ICs to the new institute**
  - **Funding for non-addiction and end-organ research programs relocated, as appropriate**
  - **No net change in level of funding for addiction research**
- **Recruit new director**
- **Reassign current staff**
- **Develop a new strategic plan to advance addiction-related research**

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Option 1: A New Addiction Institute *(cont)*

- **Establish a transition committee**
  - **Implement reorganization**
  - **Outline process for development of new mission statement**
  - **Perform NIH-wide portfolio analysis to identify relevant programs for inclusion**
  - **Develop organizational structure**
  - **Establish timelines**

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Option 2: A New Trans-NIH Initiative on Addiction

- **Modeled after the NIH Blueprint for Neuroscience Research or the Basic Behavioral and Social Science Opportunity Network (OppNet)**
- **Participation by NIAAA, NIDA, and all other ICs with relevant addiction portfolios. Include, for example:**
  - **NIDA (drug addiction)**
  - **NIAAA (alcohol addiction)**
  - **NCI (tobacco addiction)**
  - **NIMH (compulsive behaviors, gambling addiction)**
  - **NICHD (adolescent use)**

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Option 2: A New Trans-NIH Initiative on Addiction *(cont)*

- **Stable, dedicated funding**
  - **May require a majority of each IC's addiction funds**
  - **Contributions from Office of the Director**
  - **Larger investment than, for example, Neuroscience Blueprint**
- **Dedicated staff support provided by NIAAA and NIDA**
- **Evaluation to monitor initiative progress and success**

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Option 2: A New Trans-NIH Initiative on Addiction *(cont)*

- **Organization**
  - **Steering committee to lead the initiative:**
    - **Include IC directors from respective Institutes**
    - **Co-chaired by 4-5 IC Directors, including NIDA and NIAAA**
  - **Working groups or coordinating committees carry out main work of initiative. For example:**
    - **Strategic planning activities**
    - **Identification of scientific and public health priority areas**
    - **Development of an evaluation plan**

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Arguments in Favor of a New Institute

- Changes in the scientific landscape, research opportunities, public health needs, and the potential for more efficient interdisciplinary research provide the rationale for change
  - These goals cannot be met through a trans-NIH initiative on addiction
- Divergence in scientific communities doing alcohol and drug research can only be remedied by establishing a new institute
- Provides a highly visible home for addiction research at NIH
- Enables effective promotion of research on polysubstance abuse, greater understanding of adolescent use, and development of a cohesive public health message that alcohol and illicit drugs can have similar effects on the brain and body

SUAA

Arguments in Favor of a New Trans-NIH Initiative

- Changes in scientific landscape, research opportunities, public health needs, and the potential for more efficient research provide the rationale for change
  - These goals could be met through the trans-NIH initiative
- Functional strategies have worked in the past, in other scientific areas, with varying degrees of success
- Establishing a new Institute could create research gaps in understanding alcohol's ubiquitous effects on the body and unique factors contributing to its abuse
- Establishing a new institute constitutes a significant undertaking that will demand considerable effort and cause considerable disruption in the research community
- Trans-NIH initiative would maintain an inherently interdisciplinary component

DISCUSSION

NIH Scientific Management Review Board

Translational Medicine and Therapeutics Working Group

September 14, 2010

Arthur Rubenstein, M.B.B.Ch.
Executive Vice President of the University of Pennsylvania for Health System and Dean of the University of Pennsylvania School of Medicine

TMAT Working Group Charge

- **Identify the attributes, activities, and functional capabilities of an effective translational medicine program for advancing therapeutics development; and**

- **Broadly assess, from a high-level view, the NIH landscape for extant programs, networks, and centers for inclusion in this network and recommend their optimal organization**

TMAT Working Group Roster

Non-Federal

- Arthur Rubenstein, MBBCh *(Chair)*
- William Brody, MD, PhD
- Gail Cassell, PhD
- William Roper MD, MPH
- Solomon Snyder, MD
- Huda Zoghbi, MD
- Norman Augustine *(ad hoc)*

Federal

- Josephine Briggs, MD
- Anthony Fauci, MD
- Stephen Katz, MD, PhD
- Griffin Rodgers, MD MACP
- Susan B. Shurin, MD
- Harold Varmus, MD
- Francis Collins, MD, PhD *(ex officio)*

TMAT Working Group Considerations

- **The Working Group will consider how the Agency could leverage and organize a wide range of existing NIH resources and effectively implement the Cures Acceleration Network**
- **In addressing its charge, the Working Group will consider:**
  - **Current NIH-supported infrastructure, initiatives, and resources with direct relevance to the therapeutics development pipeline**
  - **Methods to synergize, and avoid competition with, resources in the private sector**

TMAT Working Group Considerations *(cont)*

- **In addressing its charge, the Working Group will consider:**
  - **Prior recommendations for strengthening the clinical and translational research enterprise at NIH, including recommendations of the IOM, and relevant lessons learned from industry, academia, non-profit organizations, etc.; and**
  - **Metrics and methodologies that could be used for evaluating the impact of changes in the organization and management of the therapeutics development program**

TMAT Working Group Deliverables

- **The Working Group's report to the full board will include:**
  - **Description of attributes, activities, and associated functional capabilities of a translational medicine program optimized to enhance therapeutics development;**
  - **Recommendations for organizing the Agency's existing components to optimize a translational medicine and therapeutics program; and**
  - **Metrics for evaluating successes and any untoward consequences of organizational and/or management changes, in particular consequences for the progress of research in areas affected by the proposed changes.**

TMAT Consultation: Agenda Overview

- **Session I**
  - **New Paradigm Opportunities for Translational Medicine and Therapeutics Discovery: Establishing A Role for NIH**
- **Session II**
  - **Bridging the Gap: Defining and Understanding the Necessary NIH Capabilities and Infrastructure**
- **Session III**
  - **Cultivating Partnerships: Setting Goals and Defining Success**
- **Session IV**
  - **Engaging in a Dialogue with the Public**