

**12<sup>th</sup> SAC Seminar-Combating Global Infections  
21-24 September 2009  
Irkutsk Russian Federation**

**Continuing Global Threat- MDR-XDR Tuberculosis  
Co-Chairs: Gail Cassell (USA), Tatiana Gremyakova  
(RF)**

## **Sobering Facts About Tuberculosis:**

**1/3 world's population infected with TB; 1 in 10 will become sick with active TB in their lifetime**

**On average, nearly 4 in 10 TB cases not being correctly detected and treated**

**TB is responsible for a death every 20 seconds**

**12 million people worldwide are co-infected with HIV & TB (1/3 of people living with HIV/AIDS)**

**“MDR-TB is too expensive to treat in poor countries; it detracts attention and resources from treating drug-susceptible disease.”**

***WHO, 1997***

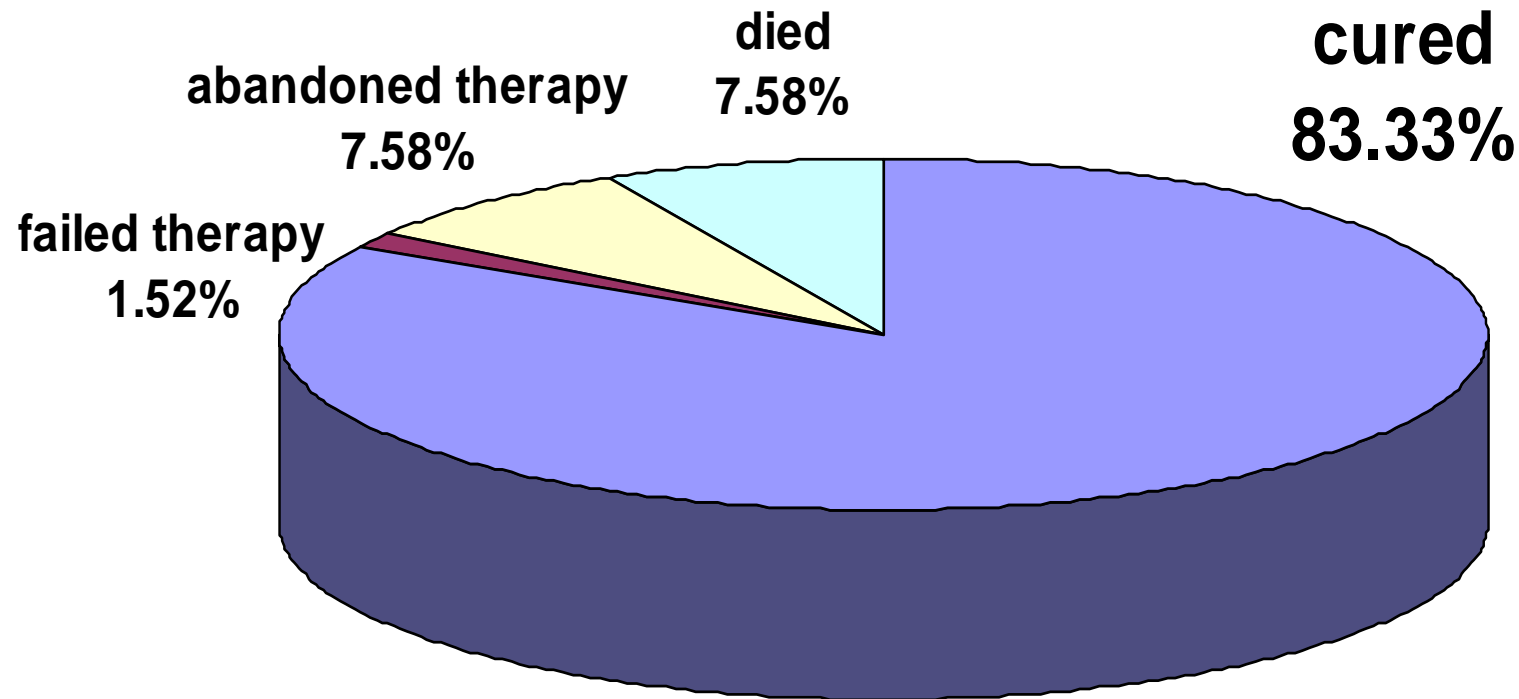
# Background

- ◆ **PIH (Socios en Salud) working in slum in N. Lima**
- ◆ **1992: US-PIH worker returns to Boston and dies of MDR-TB**
  - TB resistant to at least INH and RIF
- ◆ **Investigation of treatment failures reveals 16% prevalence of MDR-TB in Peru**
- ◆ **1996: Treatment begun in cooperation with the NTP using drug testing from Mass. State Laboratory**



# Outcomes in 66 MDR-TB patients in Lima, Peru receiving at least four months of therapy

*All patients initiated therapy between August 1996 and February 1999.*



Mitnick et al, *NEJM* 2003

# MDR-TB Challenge

- The required prolonged and more expensive treatment results in poor patient compliance and development of resistance; thus the need for intensive directly observed treatments



# Worldwide Emergence of XDR TB



## Morbidity and Mortality Weekly Report

Weekly

March 24, 2006 / Vol. 55 / No. 11

### **World TB Day — March 24, 2006**

World TB Day is March 24. This annual event commemorates the date in 1882 when Robert Koch announced his discovery of *Mycobacterium tuberculosis*, the bacterium that causes tuberculosis (TB). Worldwide, TB remains one of the leading causes of death from infectious disease. An estimated 2 billion persons (i.e.,

### **Emergence of *Mycobacterium tuberculosis* with Extensive Resistance to Second-Line Drugs — Worldwide, 2000–2004**

During the 1990s, multidrug-resistant (MDR) tuberculosis (TB), defined as resistance to at least isoniazid and rifampin, emerged as a threat to TB control, both in the United States



# Countries with Confirmed XDR-TB Cases, May 1, 2007



Source: WHO



# **Perceptions versus Realities**

**IOM (Institute of Medicine) Addressing the Threat of Drug-Resistant Tuberculosis: A Realistic Assessment of the Challenge, Workshop Summary. Washington, DC:**

**November 5, 2008**

# **Magnitude of Problem Underestimated**

**Certain to exceed 500,000 new cases estimated to occur each year**

**Only half of 22 countries with highest TB burden participate in WHO MDR-TB survey**

**Surveys most often represent data at least four to five years old**

**Many countries data derived by modeling not surveillance**

**Few countries have capacity for testing susceptibility to second line drugs**

**Less than half of African Region population represented in surveillance data**

# **Number Patients Receiving Treatment Small and Ineffective**

**Only ten percent of new MDR-TB cases are treated each year**

**Less than two percent receiving verifiable, quality assured, second-line anti-TB drugs**

**Even in the small proportion of patients that are being treated, many are not receiving drugs that actually address their drug resistance profile, and therefore their treatment is ineffective**

# **Human-to-Human Spread More common than Previously Appreciated**

**Until recently assumed drug resistant strains too weak to achieve human-to-human transmission**

**Therefore, infection control was not a public health priority**

**Unlike pattern in 1970s and 1980s, wherein most MDR-TB appeared to result from lack of patient compliance or sequential treatment regimens, today transmission of MDR and XDR-TB strains appears to dominate**

## **Need for Urgency:**

**Currently there are no consistent policies to deal with patients whose TB is untreatable.**

**What we do know is that proof that disease in these patients is untreatable may take months during which time they may spread their resistant organisms to family members and others in the community, including health care workers.**

# Treatment of Totally Drug Resistant TB (TDR)

**Even under the best of circumstances (Tomsk and Peru) 30 to 40% of cases of XDRTB are untreatable with existing drugs, ie represent TDR!!**

**Treatment of drug sensitive TB requires a cocktail of 3 or more antibiotics. *“Successful treatment of XDR and TDR TB requires 3-4 **new** classes of antibiotics simultaneously thus representing a HUGE technical and financial challenge.”***





# Lilly's MDR-TB Challenge

**In 1998 Lilly only approved supplier of two of five  
Remaining 2<sup>nd</sup> line drugs: Capreomycin and Seromycin  
for treating MDRTB. Lilly could not easily meet  
increased demand (complex synthesis & limited  
manufacturing capacity).**

# Lilly's Response to the Global Crisis of Drug Resistant TB

**Short Term Solution: Make Existing Drugs Matter**

**2. Long Term Solution: Develop New TB Drugs**

# Lilly's Commitment in TB



In 2003, Eli Lilly and Company launched The Lilly MDR-TB Partnership.

- A public-private affiliation of 18 organizations dedicated to eradicating multidrug-resistant tuberculosis in our lifetime.
- Promotes community support and patient advocacy, improves treatment and training programs, raises awareness, strengthens surveillance of drug resistance, increases access to medicines and transfers technology to pharmaceutical partners in high-burden regions.
- The Partnership is active on five continents with a special focus on the four countries hit hardest—China, India, Russia, and South Africa.

***Through many partners, and many actions, we are  
providing the Transfer of Hope***

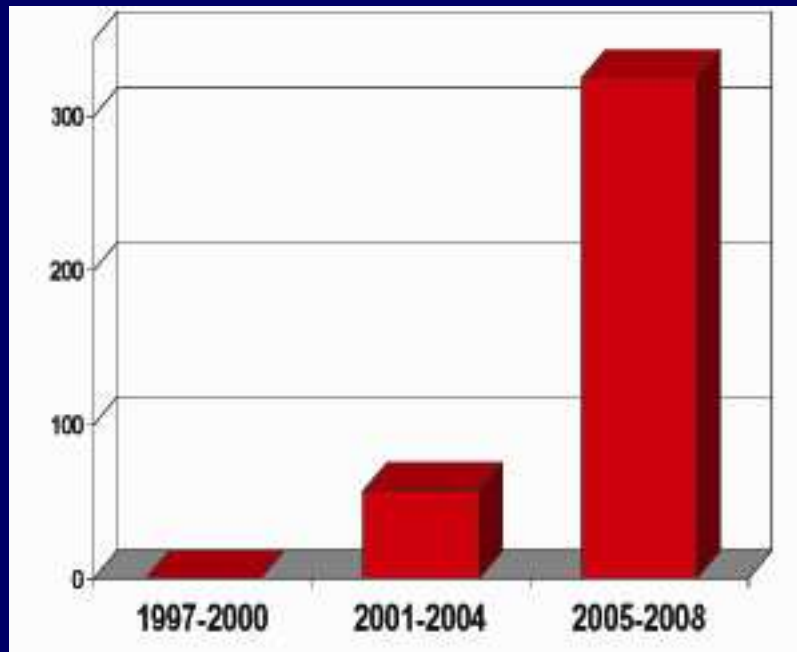


## Transferring of Technology

- Shares Lilly's specific and general manufacturing knowledge
- Creates self-sustaining centers of manufacturing excellence capable of providing additional products and employment
- Supports reliable generic producers to ensure expanded multi-source availability of the two drugs
- Offers manufacturing firms in MDR-TB “**hot spots**” the technology to produce **capreomycin** and **cycloserine**
- Gives training in GMPs and Good Business Practices
- Provides **10 full-time Lilly staff on-site over 4 years** for technical assistance/training
- Facilities in **China** and **India** receive technology to produce capreomycin and cycloserine API's respectively, and **South Africa** and **Russia** produce both products



# Impact of Lilly Funded Training Initiatives in Russia



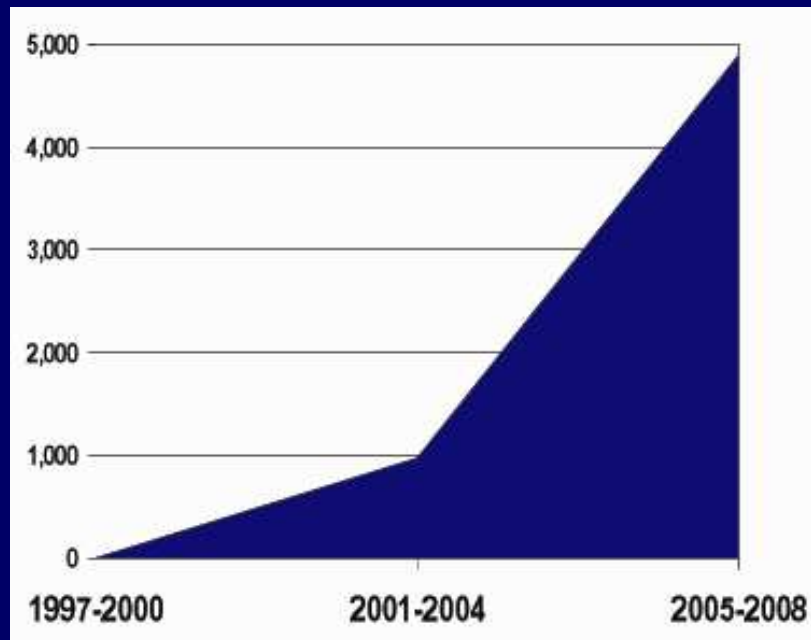
**Total TB Physicians and  
Program Managers Trained  
by Lilly funded trainings**





# Impact of Lilly Funded Initiatives

**Total MDR-TB Patients in  
Russia Receiving DOTS Plus  
Treatment**

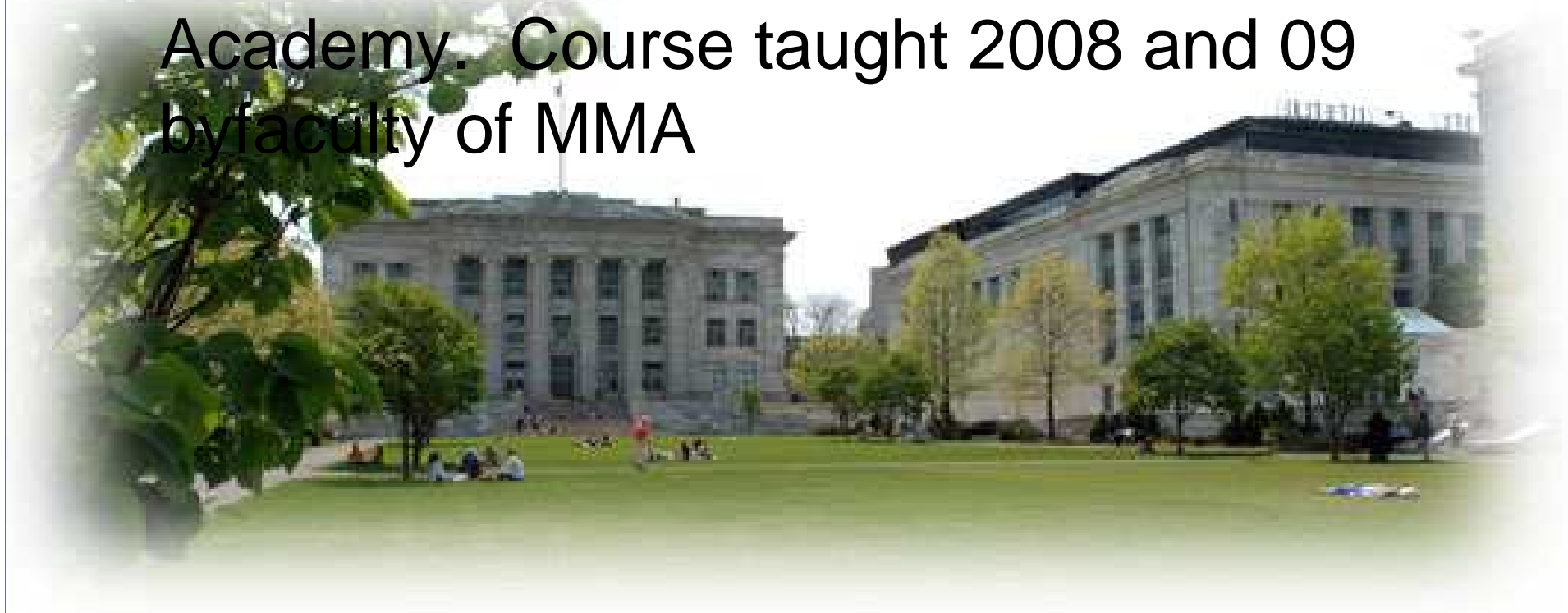


**By 2008 nearly 5000  
patients could be enrolled  
in treatment.**



# Harvard's Program in Clinical Effectiveness

- Focus on clinical research and evidence-based medicine
- Export of expertise to Moscow Medical Academy. Course taught 2008 and 09 by faculty of MMA



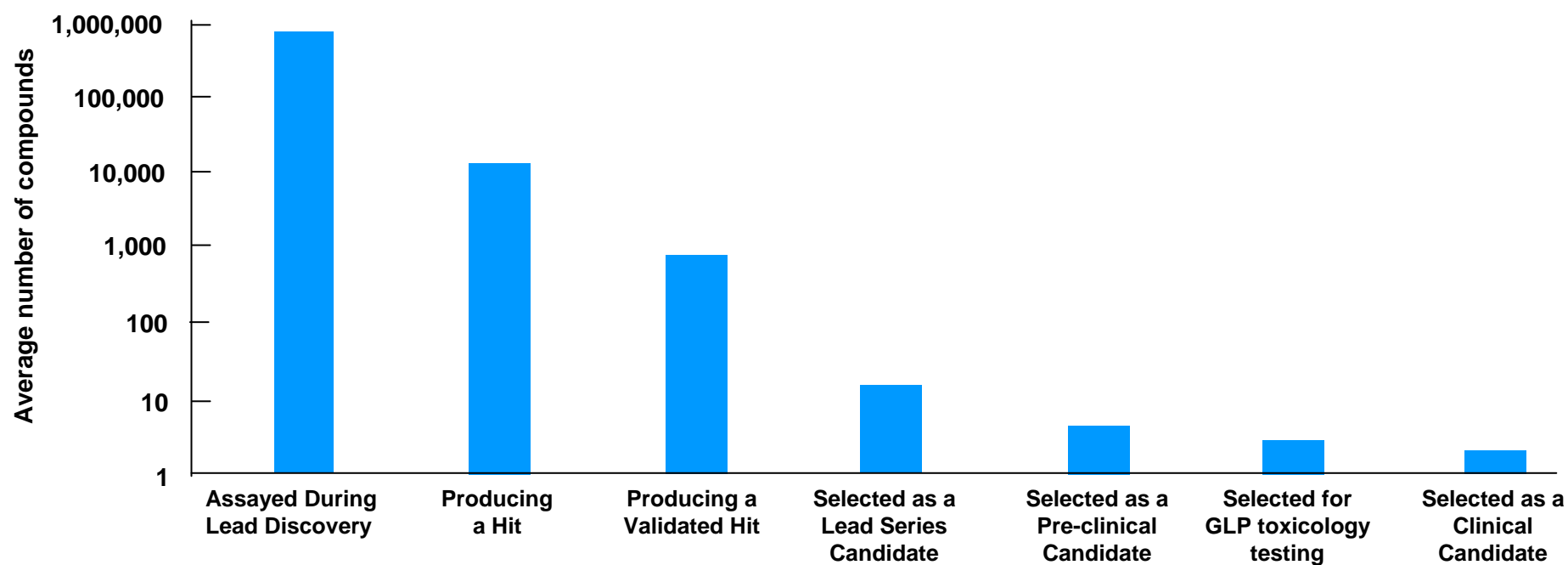
# Treatment of Totally Drug Resistant TB

**TB treatment requires cocktail of 3 or more antibiotics.  
*Thus successful treatment of XDR requires 3-4 new  
classes of antibiotics!!!***

# The Realities of Drug Discovery

# Average Number of Compounds Completing Each Phase of Discovery

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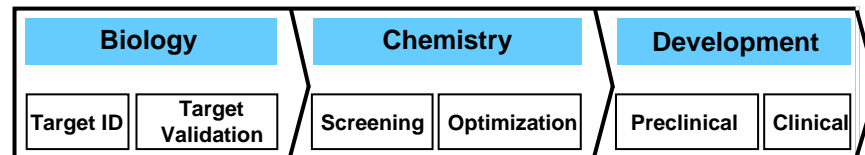
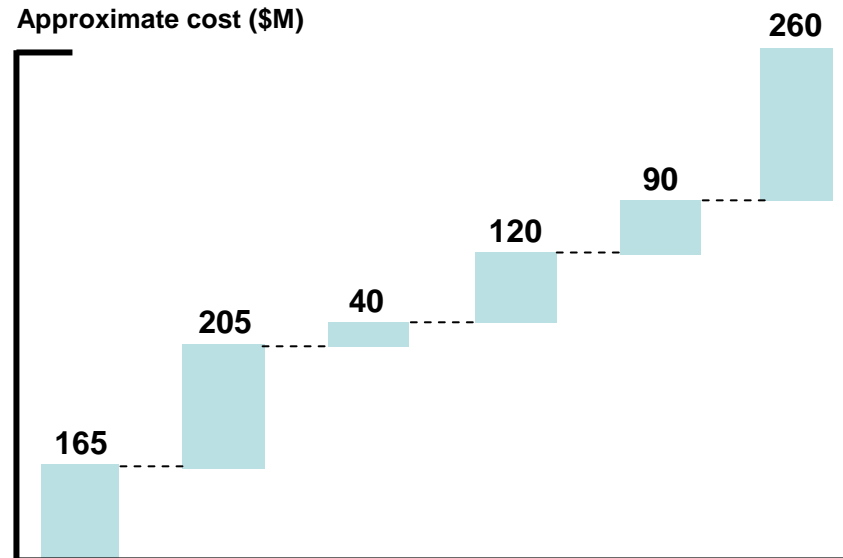
*Source: Parexel's Pharmaceutical R&D Statistical Sourcebook, 2001.*

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# Drug R&D is Expensive and Time Consuming

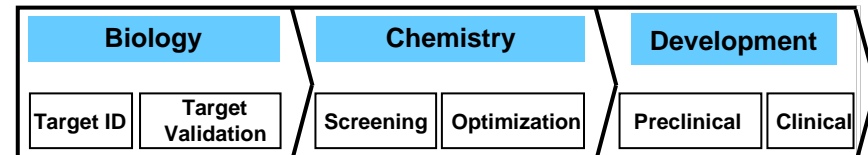
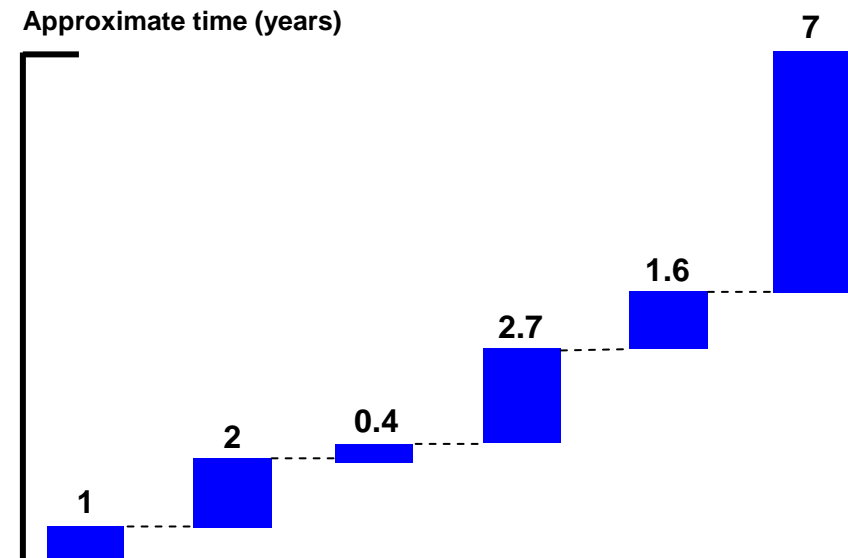
Cost: \$880 million total

Approximate cost (\$M)



Time: 14.7 years total

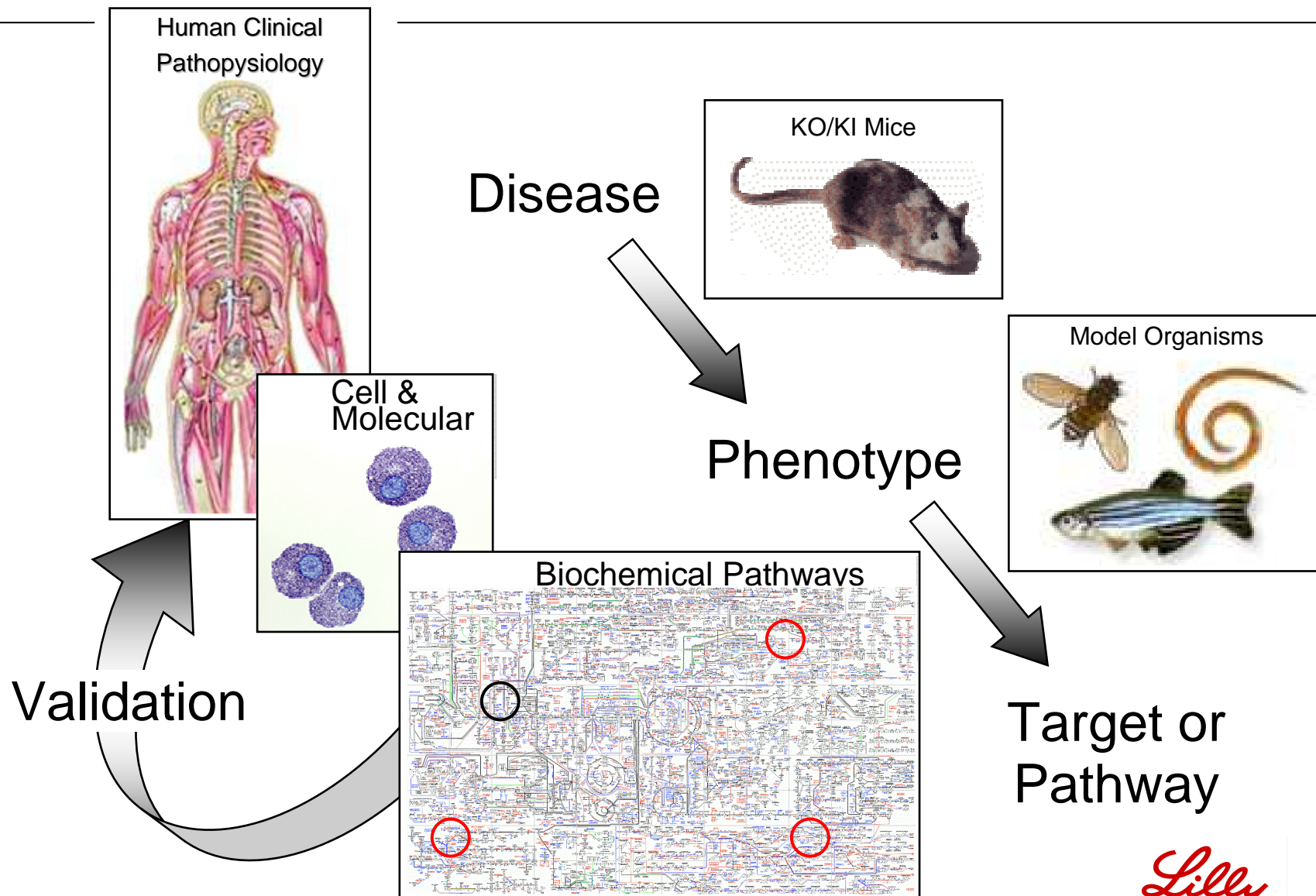
Approximate time (years)



Source: BCG, *A Revolution in R&D*



# Deriving the Phenomenology

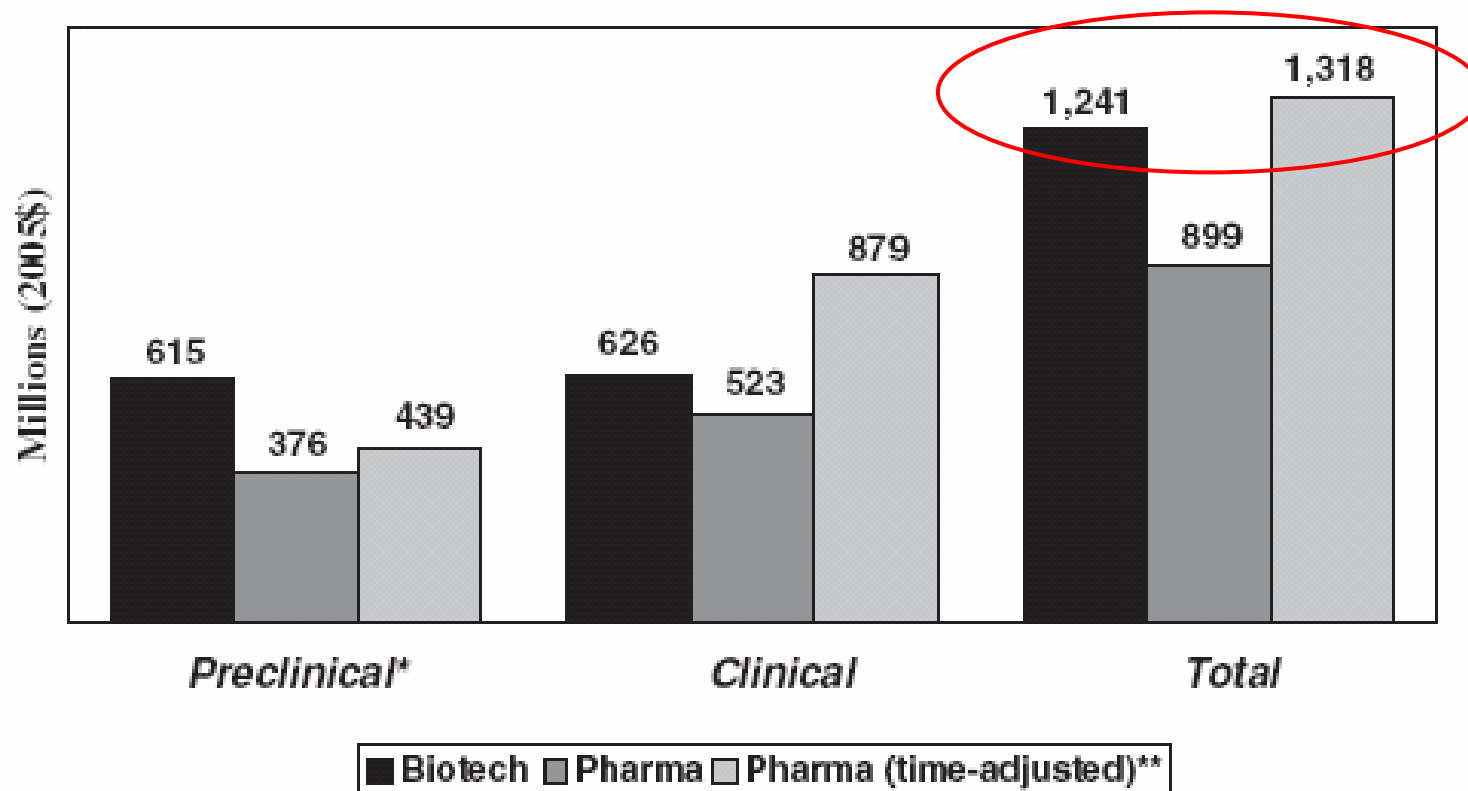


*Lilly*

Answers That Matter.

# The Capitalized Cost per New Molecule Approved is Now Estimated to Exceed \$1.2B

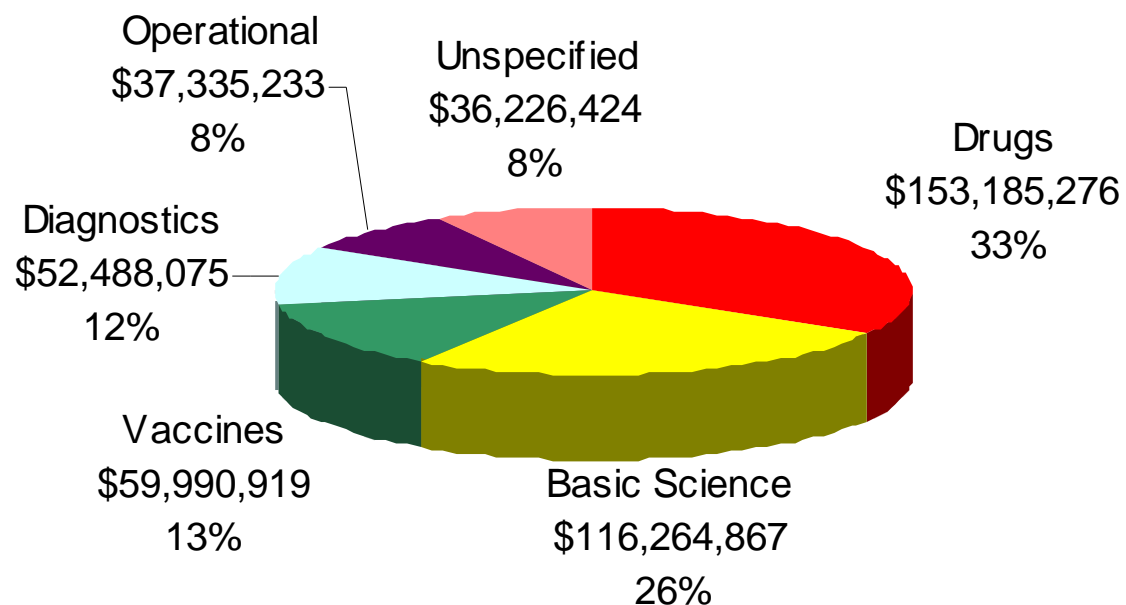
## THE COST OF BIOPHARMACEUTICAL R&D



\* All R&D costs (basic research and preclinical development) prior to initiation of clinical testing

\*\* Based on a 5-year shift and prior growth rates for the preclinical and clinical periods

# Global TB R&D Investment by Category (2007) \$455,490,794



# Total Global TB Drug Development Pipeline 10.15.08: Clinical

## PreClinical:

DC-159a (quinolone)

SQ 641

SQ 73

SQ 609

Nitroimidazole

## Clinical:

Phase I: **SQ-109** & **LL-3858**

Phase II: TMC207; OPC-67683; **PA-824**

Phase III: Gatifloxacin and Moxifloxacin

# Total Global TB Drug Development Pipeline

## 10.15.08: Discovery Projects

**High throughput screening or rational design  
(includes NIH/SRI screens now in Lilly Initiative)      12**

**Hit to lead      3**

**Lead optimization      7**



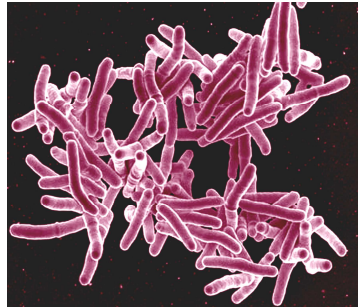
# **Public-Private Partnerships Make the Impossible Possible!**

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## The Lilly TB Drug Discovery Initiative



- Announced June 12, 2007  
Following ICOS Acquisition
- A not-for-profit, public-private partnership focused on accelerating early-stage drug discovery in TB through a systematic exploration of private molecular libraries.
- Lilly granted access to its library of 500,000 compounds and is contributing the latest drug discovery technology.
- Members of the Initiative include the U.S. National Institutes of Health (NIAID), the Infectious Disease Research Institute (IDRI) in Seattle and Lilly.
- More collaborators are needed -- governments, universities, research institutes, drug and biotech companies.

***Funding: \$9 Million in kind +\$6 Million cash over 5 years***

# Lilly's Commitment to TB



*Initiated in 2007*

## **Lilly Not-For-Profit Partnership for TB Early Phase Drug Discovery**

Facilitate the discovery and development of clinical candidates for TB by bringing together leading academic investigators and drug discovery capabilities and expertise.

*Initiated in 2003*

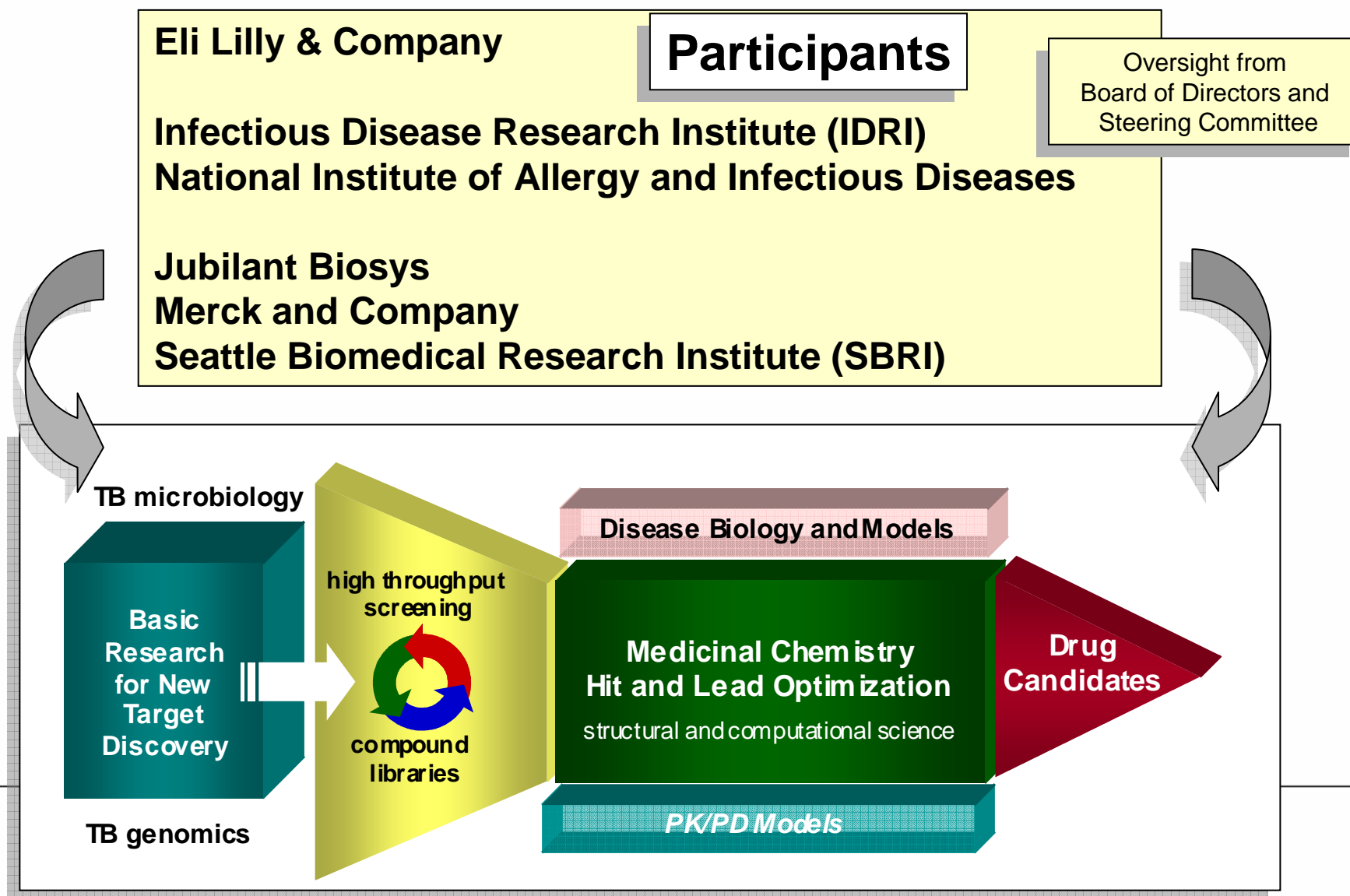
## **Lilly MDR-TB Partnership**

Focuses on expanded access for treatment of MDR-TB by technology transfer, concessionary pricing and working with the WHO. Improve training to maximize the effectiveness of existing drugs.



***Synergy with the Global Alliance for TB Drug Development***

# Partnership Brings Together Key Scientific Leadership and Capabilities



# Lilly's Contribution to the Partnership

## ➤ **\$15MM to establish the Partnership**

- \$9MM USD in kind including fully equipped high throughput screening and medicinal chemistry laboratories, research tools, databases, and scientific and technical expertise.
- \$6MM USD in cash over 5 years to seed research activities.

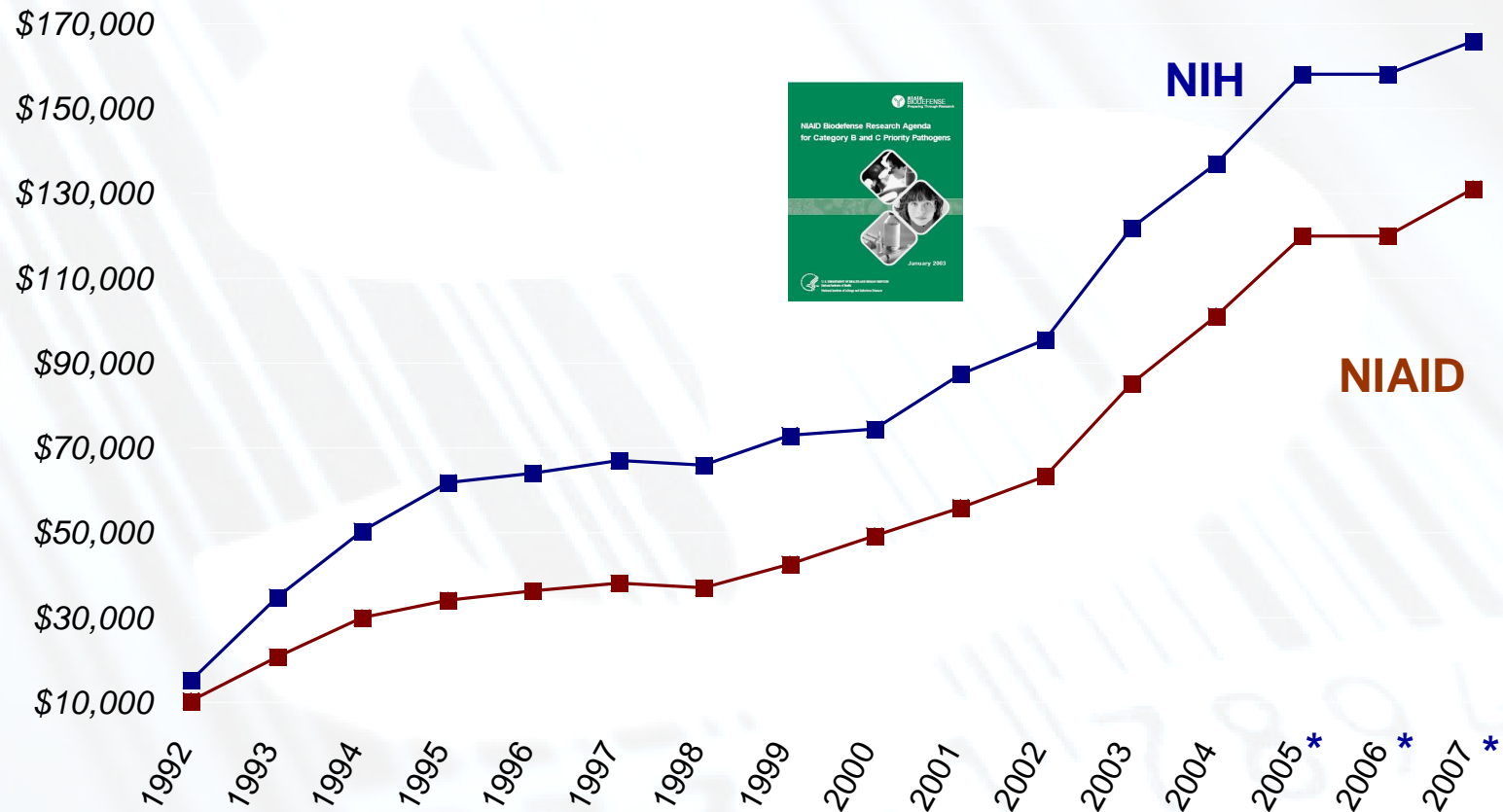
## ➤ **Access to ~500,000 Lilly compounds for screening against prioritized TB targets as well as the Lilly library of virtual compounds.**

## ➤ **Access to non-proprietary computational tools to aid in data analysis and modeling.**

## ➤ **Lilly Chemistry Steering Committee composed of six experienced drug discovery scientists representing the disciplines of medicinal chemistry, computational science and quantitative biology. This group will provide formal reviews and informal counsel to the Partnership.**

## ➤ **Discovery leadership participation on Partnership Steering Committee and Board of Directors.**

# History of NIH / NIAID Funding for Tuberculosis

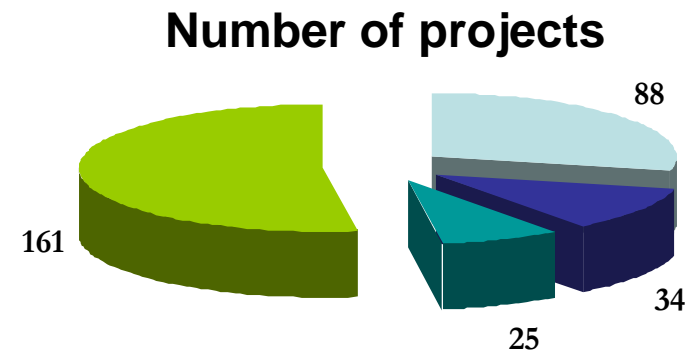
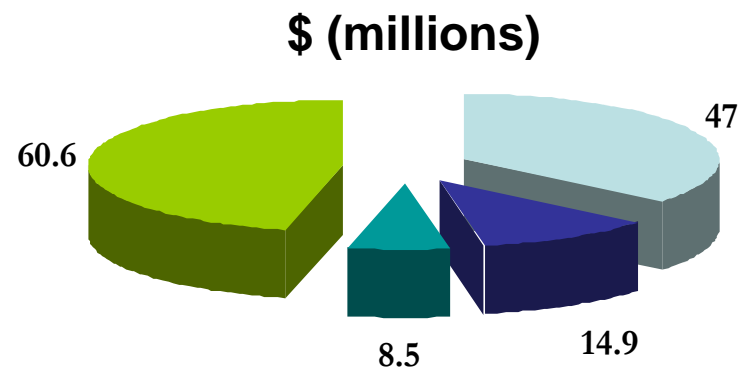


\* includes overhead, not reported in prior years for disease-specific funding



# .....FY07

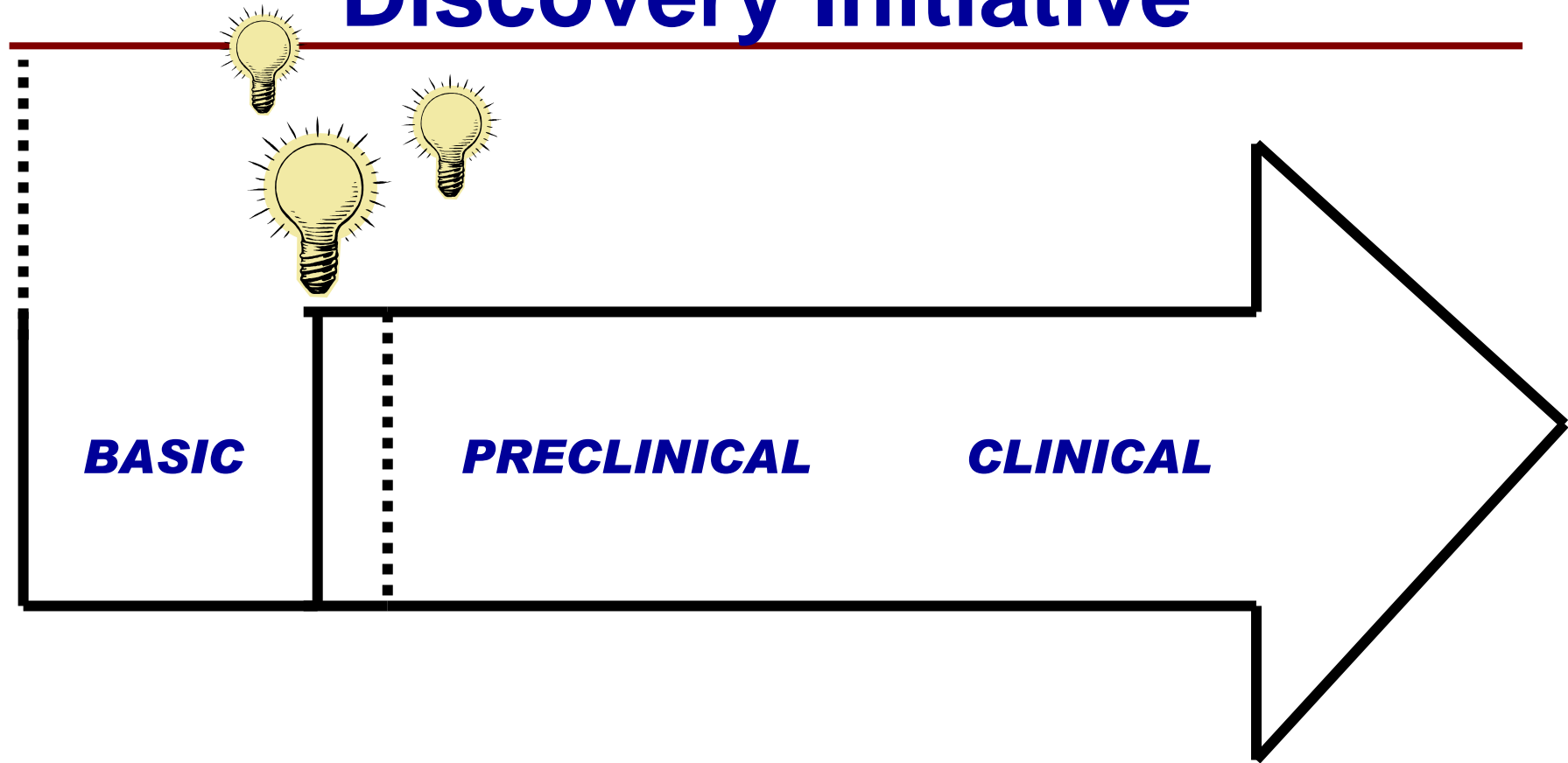
Total TB \$ - 131.1 million



Drugs Vaccines Diagnostics Basic



# NIAID Role in Lilly TB Drug Discovery Initiative



# NIAID will...

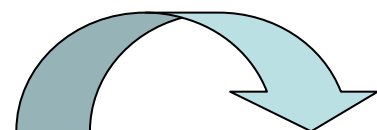
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- Assist in networking the Lilly Initiative with its large portfolio of TB research grants and contracts
- Provide access to its comprehensive IND-enabling services available to research efforts like the Lilly Initiative
- Provide expertise, guidance and research resources to help translate discoveries into safe and effective drug candidates
- Share the latest state-of-the-art science from its public databases in drug screening, structural genomics and microbial genetics





# NIH Resource Access for TB Drug Discovery



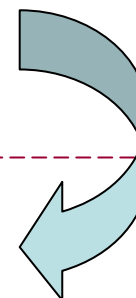
"Lilly Partnership"



Senior Scientist for  
Tuberculosis Drug  
Development  
Partnerships

NIAID/DMID

## DMID's Therapeutics Development Resources



Screening (HTS)

*In vivo* assays &  
counter-screens

PK/PD (Dose  
Selection)

Formulations

Lead Optimization  
Chemistry

Clinical Trials

Animal Efficacy

Metabolism  
Toxicology  
Studies

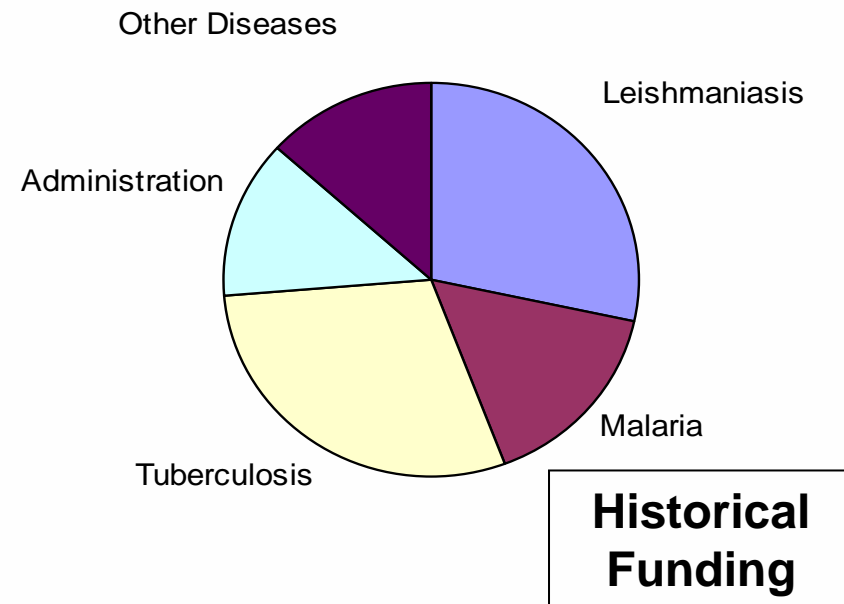
Clinical  
Microbiology

GMP

# IDRI's Role in Lilly TB Drug Discovery Initiative

- TB expertise (30 FTEs)

**\$17 Million**



- Administrative infrastructure
-

# Contributors

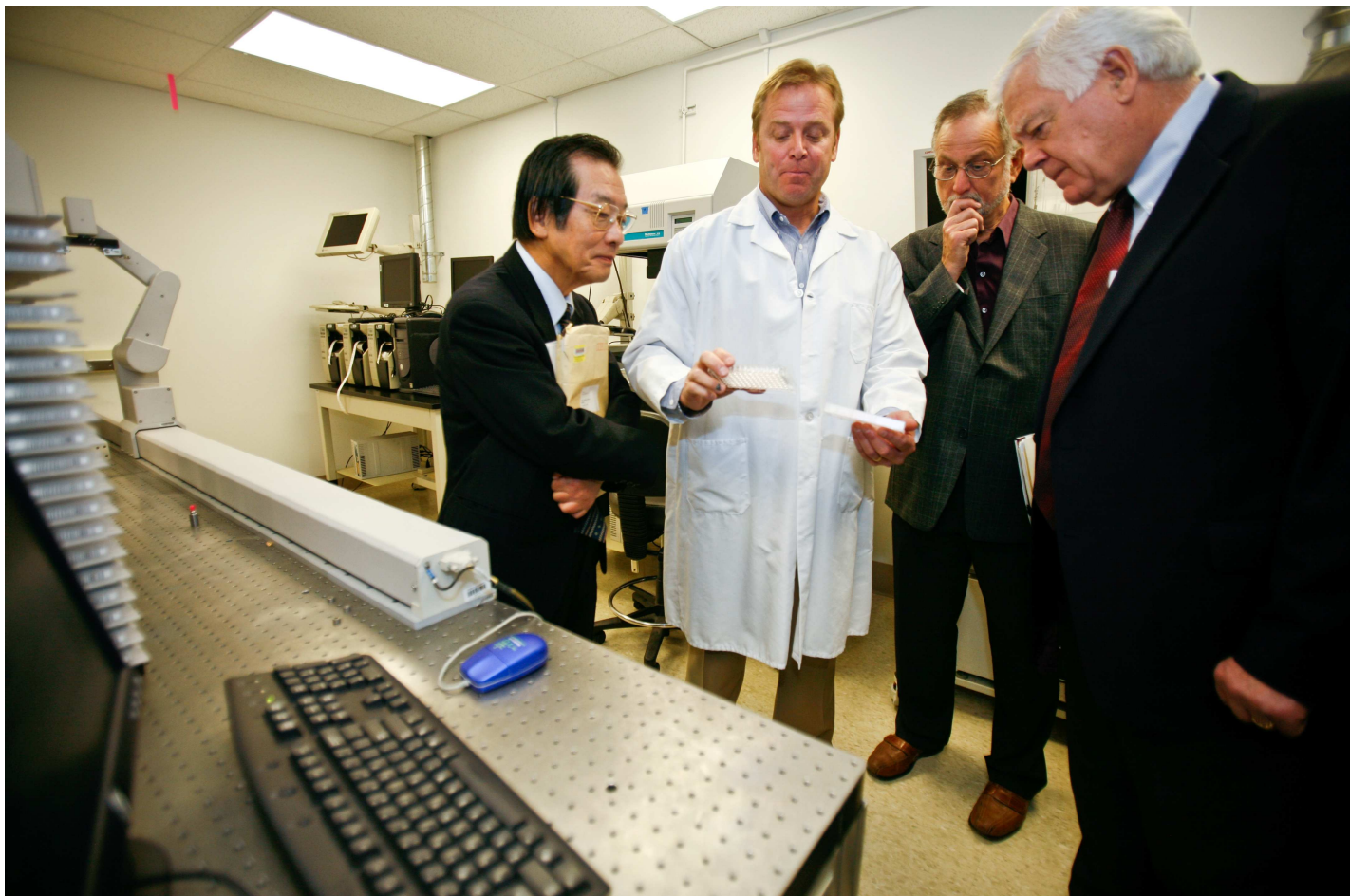
## **Merck**

- **560 pure, natural products**
- **~300 antibacterial compounds never tested for anti-TB activity**
- **Natural product extracts**

## **Jubilant Biosystems**

- **8 Full time chemists (synthetic and medicinal)**
-

# Lilly TB Drug Discovery Launch 10.7.08



# Lilly TB Drug Discovery Initiative - Chemistry facilities

Six chemical fume hoods

Bruker 300 MHz NMR

Agilent 1100 HPLC/MSD

Parr hydrogenator

Microwave synthesizer

Virtis lyophilizer

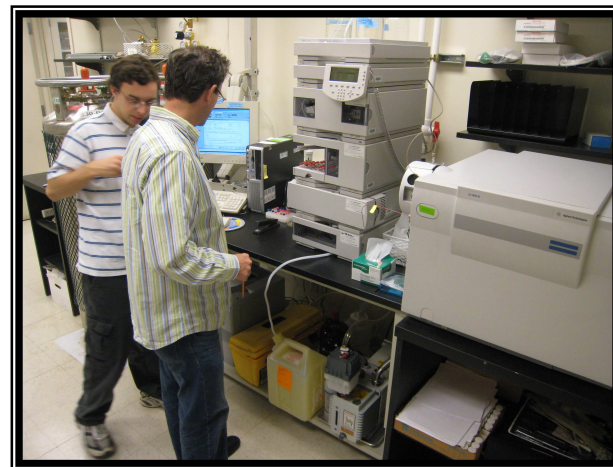
Biotage flash chromatography system

ISCO Automated flash chromatography workstation

Agilent 1100 HPLC (rev. phase and chiral HPLC)

Two Gilson 215 automated HPLC purification systems

All required glassware and lab items—up to 12 L scale





# Lilly TB Drug Discovery Initiative - Biology facilities

## Microbiology

- In vitro BL3 facility
- Culture
- Genetic manipulation
- Liquid handling system
- In vivo BL3



## • Screening

- HTS facility
- Robotics



# Lilly TB Drug Discovery – Laboratory Team



# Acquisition of First Compound

**Microbial Chemistry Research Foundation, Japan**

**CPZEN-45 *donated***

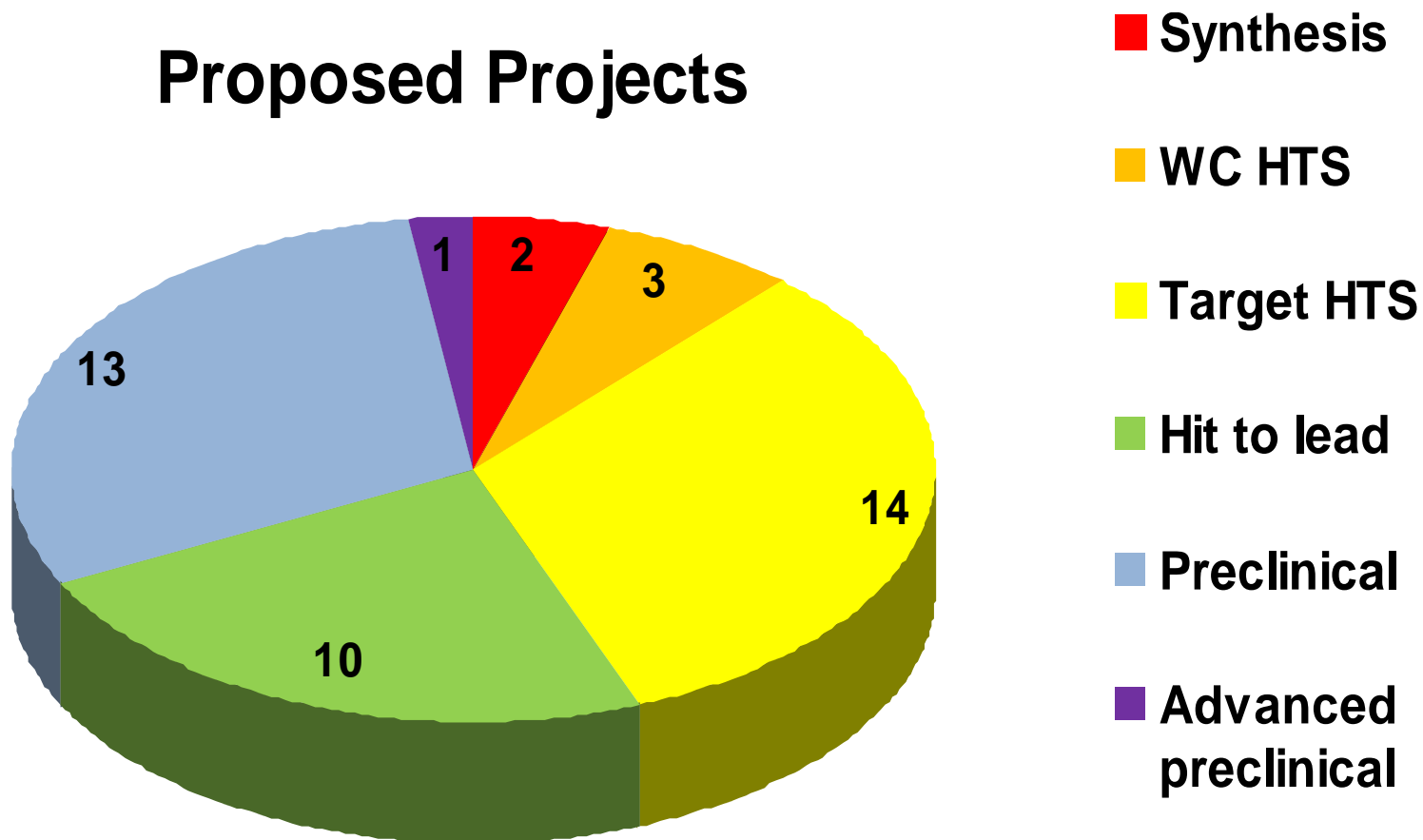
- **Early stage clinical candidate (natural product, complex synthesis)**
- ***In vitro* and *in vivo* activity, including drug resistant strains**
- **Novel mode of action**
- **Specificity for mycobacteria**
- **Acute tox/adme mice**
- **Oral bioavailability?**





## The Lilly TB Drug Discovery Initiative

### Proposed Projects



# Deliverables

- Year 01-02 identify in-licensing opportunities and establish inventory of existing NIH targets, assays for screening, validated hits from previous NIH screens and prioritize those for further development
  - Years 01-02 run 3-5 screens
  - Years 03-05 focus on portfolio prioritized in years 01-02
  - September 29, 2009 addition of Academia Sinica of Taiwan will bring capacity to unlimited number of biochemical screens and follow-up plus unlimited number of drug resistant genomes sequenced.
-

# Conclusions:

- **Need is great and extremely urgent!! Lilly Initiative well positioned to have an impact.**
  - **Lot of momentum and good progress**
  - **Need more global collaborators wishing to provide compounds, chemistry expertise, in silico screening, new targets.**
  - **The not-for-profit Lilly TB Drug Discovery Initiative was founded on the belief that in the face the global crisis of Drug Resistant TB, scientists from around the world working in government, academia, and industry would put aside their differences to develop new TB drugs. All indications are thus far this is the case. Please contact us if you would like to be involved.**
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# Opportunities to Encourage Collaboration in Spring 2010\*

- Institute of Medicine of the US Academy of Sciences and Russian Academy of Medical Sciences will co-host a meeting to establish barriers in making existing drugs matter.
- National Institute of Allergy and Infectious Diseases of the National Institutes of Health will host a TB research meeting focused on development of new drugs and diagnostics.

\*Under the auspices of Russia/US MOU signed at the Presidential Summit, July 6, 2009.

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# Contact Information

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# Questions