

DRAFT Q&A -- FOR INTERNAL PURPOSES ONLY
THE LILLY TB DRUG DISCOVERY INITIATIVE

1. What is The Lilly TB Drug Discovery Initiative?

The Lilly TB Drug Discovery Initiative is a not-for-profit public-private partnership with a mission to accelerate early-stage drug discovery by bringing together specialists from around the world for the systematic exploration of vast, private molecular libraries in search of new tuberculosis (TB) treatments. Its most important goal is filling the pipeline with new clinical candidates for future drug development. The Initiative brings together a team of the best minds in drug development and infectious diseases. It mobilizes the knowledge and resources of Eli Lilly and Company, the Infectious Disease Research Institute (IDRI), the U.S. National Institutes of Health (NIH), as well as their networks and communities.

2. Why was The Lilly TB Drug Discovery Initiative started?

TB is spreading globally and evolving rapidly into something more deadly than before, including strains resistant to all existing antibiotics. To fight the new strains we urgently need drugs with more muscle.

The pharmaceutical industry estimates that a million compounds need to be screened to get 10 candidates into clinical trial, and from these 10, chances are you won't find even one new medicine. With the odds of failure so high in drug development, we need to quickly evaluate many more compounds to find new TB drug candidates. The Lilly TB Drug Discovery Initiative was created with a mission to accelerate early-stage drug discovery by bringing together specialists from around the world for the systematic exploration of vast, private chemical libraries.

3. Which organizations are involved in the Initiative?

The Initiative brings together a team of the best minds in drug development and infectious diseases. It mobilizes the knowledge and resources of Lilly, IDRI, and NIH and as well as their networks and communities.

The Initiative is collaborating with the Microbial Chemistry Research Foundation (MCRF) of Tokyo and Summit plc of Oxfordshire, UK for two compounds that have shown significant potential in early testing.

Other companies of international stature and expertise have joined the fight, including Jubilant Biosys, a biotech in India with enormous chemistry expertise, and the American pharmaceutical company Merck, which has generously opened for screening its library of compounds that have shown anti-bacterial activity, as well as a library of purified natural products. Seattle Biomedical Research Institute is working with the Initiative on assay development. YourEncore is offering its "InnovationCommunity" technology for TB teams to securely and confidentially conduct their meetings, forums and collaborations.

The University of Washington's Department of Global Health is leading a monthly lecture series on Global Health and an annual Symposium on TB Drug Discovery.

4. What other organizations would you like to see involved in this effort?

Everyone is welcome to join. Everyone is needed – governments, universities, research institutes, drug and biotech companies, philanthropic organizations, people with all sorts of skills. Everyone has something to give. The Initiative is founded on the belief that people from different corners of the pharmaceutical and healthcare world will put aside differences and come together when confronted with a global threat.

5. How do collaborators who donate compounds or research tools benefit from this Initiative?

Organizations co-developing compounds with the Initiative or contributing research tools will receive added value in new information on their products as well as assist the Initiative's research process. This information may have potential use in developing the compounds for other indications. Those who donate compounds that may eventually prove useful against TB for the developing world will retain their intellectual property rights and may market in developed nations. Everybody wins.

Researchers working on promising compounds may apply to use NIH-sponsored core resources established to serve the entire TB research community. These include generation and testing of mutant strains, genome sequences of multiple strains of TB [including recent extensively drug-resistant TB (XDR-TB) strains from South Africa], microarrays, structural genomics, rational drug design via x-ray crystallography, bioinformatics, in vivo and in vitro screening for efficacy, in vitro and in vivo PK/PD models, drug resynthesis and formulation and safety testing.

6. What kind of success has the Initiative had?

We knew this effort was urgently needed, and our belief was confirmed by the immediate, positive response from researchers. Within 24 hours of announcing the initiative, we had people from India, China, South Africa, Japan and other countries knocking on the door to offer compounds for screening. Agreements were reached with the Microbial Chemistry Research Foundation (MCRF) of Tokyo and Summit plc of Oxfordshire, UK, for two compounds that have shown significant potential in initial testing. We had been worried about not having enough to work on, but now we're faced with the need to prioritize which compounds to work on first. It's a great problem to have and shows how badly this effort was needed.

Over the past year (2007-2008), the Initiative has organized operations, built labs and identified compounds (including early clinical candidates) for the first round of work. Within the next few months, we will begin high throughput screening of new, validated targets against well-characterized chemical libraries.

7. What happens if one of these compounds is a success; what are the next steps?

Candidates that emerge from this process ready for clinical trial could be further developed by the Initiative, the TB Alliance, the private sector, the donor or some combination of these organizations, as is being done now for other compounds.

8. Does the Initiative take the compound through the FDA approval process?

Not at the present time. The new drug approval process is resource-intensive and we are exploring additional collaborators interested in clinical development.

9. Does this Initiative administer the clinical trials? Or does the compound go back to the private sector for the company to develop further for market?

It will depend upon the circumstances and resources available at the time.

10. What do you anticipate to be the challenges for the Initiative?

Our immediate challenge is the need to prioritize which compounds to work on first. Our long-term challenge faces everyone in drug discovery. The companies and organizations working on TB have been fairly successful in getting some drugs into clinical trials, but we have too few promising compounds in the early stages of development.

The current clinical trials are like fighter planes that have taken off toward an unknown fate, leaving behind an empty runway. As many as 50% of clinical candidates can still fail. We need to line up many more compounds for evaluation in order to enhance the chances of success.

What's more, we don't need just one new drug. Treating TB, like treating HIV, requires a cocktail or combination of drugs. We need at least four new drugs because the ones we have now are 50 years old, complex to administer and result in many incomplete and ineffective treatments. A growing number of TB strains are resistant to all available drugs for treating TB.

11. How is this Initiative different from other organizations like the Novartis Institute for Tropical Diseases and the Global TB Alliance?

The Initiative is focused on early-stage TB drug discovery with emphases on the application of synthetic and medicinal chemistry and the screening of large numbers of well-characterized compounds. Its most important goal is to fill the pipeline with new clinical candidates for future drug development.

This public-private organization has unique access to proprietary libraries of compounds. The Initiative operates as a sort of Mission Control, coordinating dedicated researchers and investigators globally in a methodic, geographic search for molecules, compounds and targets ready to be explored. They come from government, academia, not-for-profit organizations and the pharmaceutical industry to create a truly "industrial strength" team. This kind of rigorous search will put us on the radar of even more companies and universities with compounds, targets or libraries that we might not know about yet.

12. Why would this model succeed over others involved in TB drug discovery?

The Initiative functions as a catalyst drawing together microbiologists, molecular biologists, synthetic chemists, medicinal chemists, pharmacologists, toxicologists, and process chemists to expedite the testing and optimizing of compounds for development. They come from government, academia, not-for-profit organizations and the pharmaceutical industry to create a truly "industrial strength" team.

This kind of cooperation produces fresh ideas and new molecular approaches. It produces new targets and assays. It offers fresh perspectives from the best minds which have access to the latest, most innovative technologies.

13. What kind of financial commitment has the Initiative received? What about non-financial?

Lilly has opened access to its greatest assets, a library of 500,000 compounds. The company is lending its immense drug discovery expertise and organizational savvy. It is contributing the latest, most innovative technologies used in drug discovery to be applied to the search for new drugs to fight TB. And, Lilly has given \$15 million to support the historic undertaking.

IDRI provides substantial expertise in microbiology, molecular biology and chemistry, as well as manages the Initiative's own laboratory. It serves as the principal coordinator for all partnership efforts.

NIH's NIAID has a wide variety of existing resources that can be leveraged to develop a portfolio of prioritized and validated molecular targets and chemical hits. In fiscal year 2007, NIAID invested more than \$47 million in almost 90 projects focused on TB drug development.

The Microbial Chemistry Research Foundation of Tokyo and Summit plc of Oxfordshire, UK signed agreements for two compounds that have shown significant potential in early testing.

Merck has provided its library of 560 pure natural product compounds and an additional ~300 antibacterial compounds for screening, none of which have been screened against TB. One of the most valuable contributions to early phase drug discovery for infectious agents, particularly TB, is access to an optimized and well characterized library of natural products.

14. Will you be asking for further funding?

The Initiative is funded by a \$15 million grant from Lilly. It will seek grants and contracts for additional funding with the ultimate goal of becoming self-sustaining. Any profits from research would be returned to the Initiative.

15. Will the Initiative need to expand its facilities and employees?

All the promising research projects uncovered by the Initiative will require additional resources to properly explore.

16. How is the Initiative governed?

The Initiative is governed by a Board of Advisors which includes distinguished leaders from Harvard University, The Global Alliance for TB Drug Development, The Bill and Melinda Gates Foundation, The Burroughs Wellcome Fund, and research is reviewed by a multinational panel of scientific advisors.

17. What is the role of the Board of Advisors? How often will they meet? Will they be issuing a Progress Report?

The primary duties of the Board of Advisors are to ensure continuity of the Initiative and to review and approve progress on an annual basis. The Board will meet as necessary, but no less frequently than annually and will report progress to the IDRI Board on an ongoing basis. The Board's responsibilities include, but are not limited to: reviewing and reporting the overall performance of the program; the direction of the program for the next year, including the budget; potential business developments and other opportunities; overseeing transfer of technologies including access by the Initiative to external compounds and partnering with external companies for clinical; and assisting in identifying and recruiting new collaboration partners.

18. Why are you focusing on early stage drug discovery?

The companies and organizations working on TB have been fairly successful in getting some drugs into clinical trials, but we have too few promising compounds in the early stages of development.

The pharmaceutical industry estimates that a million compounds need to be screened to get 10 candidates into clinical trial, and from these 10, chances are you won't find even one new medicine. With the odds of failure so high in drug development, we need to quickly evaluate many more compounds to find new TB drug candidates.

The current clinical trials are like fighter planes that have taken off toward an unknown fate, leaving behind an empty runway. As many as 50% of clinical candidates can still fail. We need to line up many more compounds for evaluation in order to enhance the chances of success.

19. Why did Lilly get involved? What's in it for them?

Lilly has a longstanding history of fighting TB. Years ago, as one of the world's leading pharmaceutical innovators, Lilly was on the front lines developing medicines to combat TB. Two of the second-line drugs used to treat MDR-TB, capreomycin (Capastat[®]) and cycloserine (Seromycin[®]), are Lilly medicines.

The \$15 million Lilly has given so far to support this historic undertaking is part of Lilly's \$135 million commitment to control MDR-TB through The Lilly MDR-TB Partnership, which mobilizes 18 partners on five continents to confront MDR-TB, a disease so daunting that no single organization can fight it alone. These partners are some of the world's most skilled and knowledgeable experts on the disease, and have the experience needed to attack it from a 360-degree perspective.

20. Why should people in the U.S. care about TB – a disease that is mostly prevalent in third-world countries?

People think of TB as a disease of the past, but without the right treatment, TB will be a disease of the future right here at home.

In the United States, a study published in August 2008, showed 18 cases of drug-resistant TB between 1993 and 2006 in California alone, and 77 cases that were one

step away from XDR-TB. It also showed the proportion of patients with pre-XDR increased between 1993 and 2005 from seven percent to 32 percent.

As many as half a million or more TB cases identified each year are resistant to multiple drugs. XDR-TB has now been found in more than 49 countries, including the U.S., England, Japan, Italy and Norway. Some strains are resistant to all existing antibiotics used for treating TB. Every country is vulnerable. More and more cases are being found.

Meanwhile, throughout the world, 1.5 million people (one every 15 seconds) die each year from TB. If we fail to find promising compounds to treat people today, we won't have the drugs to fight the more severe strains tomorrow. Every person in every country is at risk.

21. Will Lilly or the Initiative sell the drug if it is approved to treat TB? Who will receive any profits from the sale of those drugs?

Lilly will not sell the drugs or derive any profits from this Initiative. Those companies that donate compounds that may eventually prove useful against TB retain their intellectual property rights and their ability to sell the TB drug in wealthier, developed nations.

Candidates that emerge from this process ready for clinical evaluation could be further developed by the Initiative, the TB Alliance, the private sector, the NIH or some combination of these organizations, as is being done now for other compounds.

22. Would competitive data on the compound be accessible to researchers at Lilly?

Only to those employees directly involved in the Initiative and only on a need-to-know basis.

23. What's the status of the former ICOS?

Lilly was focused on what was next for ICOS employees and finding good outcomes. Several ICOS employees are now a part of The Lilly TB Drug Discovery Initiative and are here today. The recent announcement of the expansion of the contract manufacturing unit of ICOS, following the acquisition by CMC, promises to have a positive impact on the Seattle life sciences industry.

24. Is Afya still a collaborator of the Initiative?

Upon reflection, the founders of Afya realized that their mission was very similar to IDRI's, and they decided to merge organizations. They are now a part of The Lilly TB Drug Discovery Initiative.