



Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285
U.S.A.

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Backgrounder

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

The Concept.

There are many aspects of early phase drug discovery that have been identified as missing from current efforts aimed at finding new tuberculosis treatments. These include access to quality libraries of diverse chemical molecules, medicinal chemists to facilitate lead optimization, and the integration of this expertise with biological expertise.

To address these gaps, a not-for-profit partnership will be established in Seattle, Washington, by Eli Lilly and Company in collaboration with the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH) and the Foundation for the NIH. The partnership will provide access to medium and high throughput screening (HTS) of well characterized chemical libraries. It will also provide medicinal and synthetic chemistry to advance likely molecules to clinical candidates. Lilly, Merck and Company, Afya Worldwide Medicines and Jubilant Biosys have agreed to contribute chemistry expertise and compound libraries.

Integrating Scientific Disciplines.

The cornerstone of this partnership will be the tight integration of medicinal chemistry expertise within the pharmaceutical industry with academic expertise in both chemistry and TB microbiology. Diverse approaches will be used to access the academic skill set involved in TB drug discovery: pathogenesis, molecular biology, and genetics. Target identification, validation, and assay development, research and clinical expertise in TB will be provided by the Infectious Disease Research Institute of Seattle (IDRI), the Seattle Biomedical Research Institute (SBRI), and academic investigators funded by the NIAID who are interested in contributing to this partnership. Expansion of knowledge and interest in these areas, as well as others, will be facilitated through a dedicated program manager who will be supported through funding to the Foundation for the NIH. The NIAID's existing resources, which are key to the ability of investigators supported by the institute to advance clinical candidates, will be available to the Partnership.

Lilly Not-For-Profit Partnership for TB Early Phase Drug Discovery is an independent, not-for-profit organization governed by a Board of Directors and Steering Committee. To enhance the chances of sustainability, the partnership organization will actively compete for grants and contracts and the profits will return to the 501 (3) (c).

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The Global Alliance for TB Drug Development.

The Lilly Not-For-Profit Partnership for TB Early Phase Drug Discovery will work closely with the Global Alliance for TB Drug Development (TB Alliance) and other TB initiatives to insure there is no redundancy or competition. With the TB Alliance moving drugs through discovery and clinical trials, the Partnership for TB Early Phase Drug Discovery will focus on developing high quality clinical candidates. The TB Alliance will have representation on the governing committees of the partnership to insure coordination of efforts.

The Participants.

Eli Lilly and Company. Lilly will provide \$15 million to establish the Partnership. Included in the donation is \$9 million in-kind, including fully equipped high throughput screening and chemistry laboratories, research tools, databases, and scientific and technical expertise, plus \$6 million in cash over five years to seed the organization.

Lilly will also provide access to ~500,000 solubilized Lilly compounds for screening against well characterized TB targets, as well as the Lilly library of virtual (in silico) compounds. A Lilly Chemistry Steering Committee composed of six senior research advisors and research fellows representing medicinal chemistry, computational and quantitative biology will provide formal reviews and informal counsel.

Lilly will also partner with the University of Washington to create the monthly “Lilly Lecture Series in Global Health” (see details below).

Afya World Medicines (formerly ICOS chemists). With the acquisition of ICOS, Inc. based in Seattle, Lilly learned of the desire of a number of talented ICOS chemists to contribute their expertise to the development of drugs for neglected diseases. These individuals led by Drs. Edward A. Kesicki, and Joshua O. Odingo, who founded Afya World Medicines, a 501 (3) (c), will provide the core medicinal chemistry expertise of the partnership.

Infectious Disease Research Institute (IDRI). To gain critical mass in expertise and to create synergy, the Lilly not-for-profit TB partnership will be housed within IDRI, a unique “non-profit biotech” that combines discovery, manufacturing, and clinical testing for the development of vaccines, diagnostics, and therapeutics for diseases of developing countries.

IDRI, who will play a key leadership role in the partnership, already has a large TB adjuvant therapy effort involving more than 25 scientists funded from both public and private sources. IDRI has appropriate biocontainment laboratories which will enable whole cell TB screens. The new partnership will benefit from the IDRI infrastructure including strong business development, legal, administration, grant specialist, and product development expertise. IDRI played a key role in the development of the first new TB vaccine that is now in clinical trials.

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Jubilant Biosys. Jubilant Biosys of Bangalore, India has agreed to provide eight full-time chemists to the TB Early Phase Discovery partnership. These chemists will provide synthetic chemistry support and will work as an extension of the medicinal chemists working in Seattle.

Merck and Company. Merck will provide its library of 560 pure natural 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.

National Institutes of Health (NIH). A worldwide leader in biomedical research, the NIH, through NIAID, currently invests \$120 million in TB research, including \$42 million in 70 projects focused on TB drug development. The Partnership will leverage the NIH-funded TB drug discovery projects to develop a portfolio of prioritized and validated molecular targets and chemical hits. Funding will be provided to the Foundation for the NIH for a full-time, senior program manager who will convene, mobilize, synergize, and coordinate the efforts of the academic community who wish to participate in this Partnership. These efforts will include identification and evaluation of new targets and new lead compounds with the best potential for further development/optimization and identification of potential collaborators.

NIH-sponsored core resources that have been established to serve the TB research community as a whole will also be accessible to the Partnership for the following activities: generation and testing of mutant strains, genome sequences of multiple strains of TB (including recent 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, formulation, and manufacturing.

The TB Alliance and investigators funded by the Bill and Melinda Gate Foundation may also provide targets for screening, as well as requests for synthetic chemistry. Candidates for clinical trial could be further developed by the TB Alliance, the private sector, the NIH or some combination of these organizations, as is being done now for other compounds.

Seattle Biomedical Research Institute (SBRI). Founded in 1976, SBRI has nearly 200 employees and is the largest independent, non-profit organization in the U. S. focused solely on infectious disease research related to the developing world. David Sherman, one of the leading TB drug development investigators, will collaborate with the Lilly partnership in TB target identification and validation.

University of Washington Department of Global Health. To leverage the efforts of the newly established partnership and to maximize synergy with other scientists working in the area of Global Health and Drug Discovery, the Lilly Lecture Series in Global Health will be



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established in collaboration with the University of Washington – Department of Global Health. The goal of this series will be to bring together investigators working in global

health to reinforce existing collaborations or establish new ones. The lecture series will culminate in an annual international symposium to share research results and provide a better understanding of the challenges of drug discovery and the barriers to access in resource-poor countries. Lilly will also donate laboratory equipment to five new laboratories in the Department of Global Health to facilitate Seattle-based clinical research and enhance work with international partners.

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