ONE GOAL:

A NEW TB DRUG

GLOBAL ALLIANCE FOR
TB DRUG DEVELOPMENT

2002–2003 ANNUAL REPORT

ONE OF HUMANITY'S OLDEST DISEASES IS MAKING A DEADLY COMEBACK

A GLOBAL EMERGENCY…

In 1993, the WHO declared tuberculosis (TB) a global health emergency. Ten years later, the problem is even worse, claiming more than 5,000 lives every day. TB's resurgence has largely been driven by the HIV/AIDS epidemic and kills one in three people co-infected with HIV/AIDS. With two-thirds of TB patients failing to receive adequate treatment, we now not only have the highest levels of TB infection in history but that number is growing.

…IS OVERWHELMING OUT-OF-DATE DRUGS…

TB treatment relies on drugs that are up to 50 years old and takes six to nine months to complete. Many patients fail to complete treatment, so they are not cured. They continue to spread the disease and can develop drug-resistant strains, which require two years of aggressive chemotherapy to treat, without guarantee of a successful cure.

…AND SHOWS NO SIGN OF LETTING UP.

If current trends continue over the next 20 years, there will be 1 billion new TB infections and 36 million people will die—one every 9 seconds. An affordable, faster-acting TB drug could effectively treat thousands more patients by reducing the time of therapy, combating drug-resistant strains and improving treatment of latent TB.

IT’S TIME FOR A FASTER CURE

JOINING FORCES TO CATALYZE SCIENCE AND INDUSTRY

The challenges of tuberculosis have tested the best scientific minds since the TB bacillus was first identified in 1882. Today, with one-third of the world infected, there has never been a greater need to apply recent breakthroughs in science and modern drug discovery methods to this reemerging threat. Speeding progress after forty years of delay in TB drug development means every scientific path must be explored and every lead uncovered. The Global Alliance for TB Drug Development (TB Alliance) is forging unique partnerships and introducing streamlined processes to catalyze this global effort. To build our portfolio, we engage expertise and resources in every discipline worldwide from academia, industry and public laboratories.

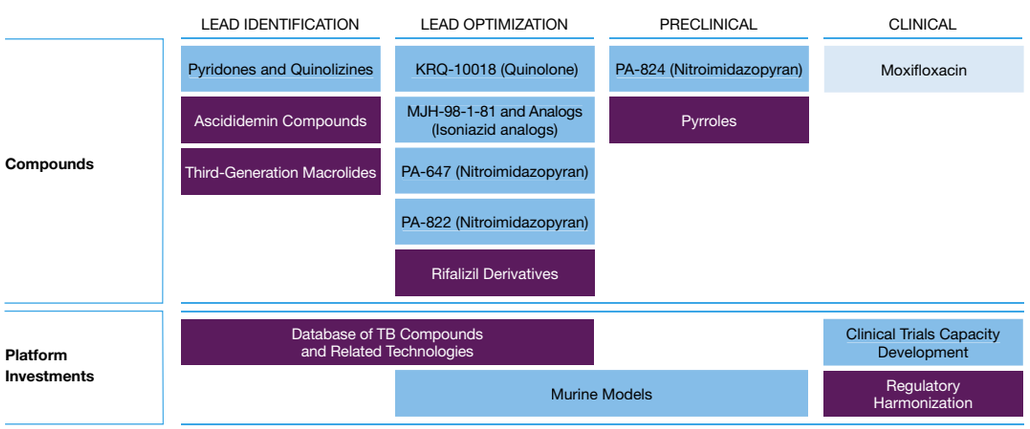
Rick O'Brien

CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC)

CHAIR, TB ALLIANCE SCIENTIFIC ADVISORY COMMITTEE

"To speed drug development for a faster cure, the world must collectively overcome the formidable scientific challenges of TB. This will take an unprecedented degree of collaboration and resource-sharing to transcend technical and national borders. The Scientific Advisory Committee evaluates every scientific lead, seeking opportunities that leverage global expertise and synergies to advance the field."

TB ALLIANCE PORTFOLIO



Paul Herrling

NOVARTIS

"Novartis elected to contribute discovery science to the fight against TB through a pioneering new institute in Singapore. Once we have novel compounds, Novartis will team with the TB Alliance to manage further development of TB therapies. Our standard is the same as the TB Alliance's: The result of our research will be available without royalties in endemic countries."

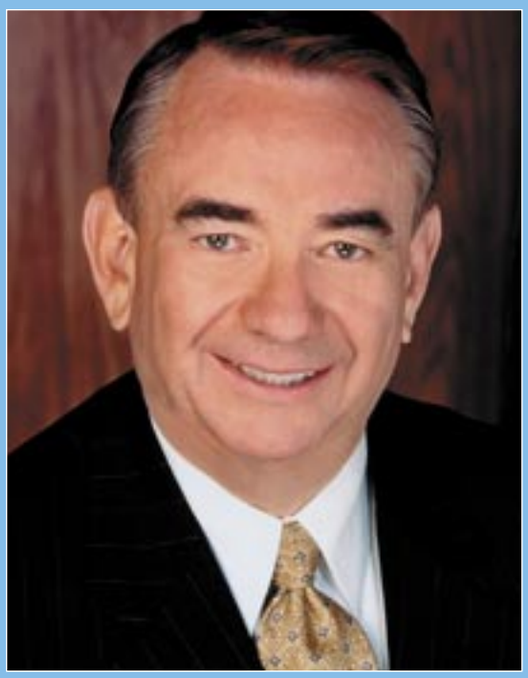
Ken Duncan

GLAXOSMITHKLINE / TB ALLIANCE

"By lending my time to the TB Alliance, GlaxoSmithKline is contributing my experience and knowledge of TB drug discovery to expedite R&D. I'm also helping the TB Alliance enlist greater participation from high-burden countries, such as the five scientists from India and South Africa whose attendance at the 2003 Gordon Research Conference on TB Drug Development was sponsored by the TB Alliance."

RALLYING GOVERNMENTS AND POLICYMAKERS

The Global Plan to Stop TB, a roadmap to fight tuberculosis, was outlined at the turn of the millennium when the world's nations committed to reversing the onslaught of one of humanity's oldest diseases. The Plan places equal emphasis on the priorities of TB control and on investing now in research and development for better tools, such as drugs. The Plan's Working Group on TB Drug Development, led by the TB Alliance, acts as a forum to coordinate worldwide TB research and development activities for novel therapeutics. The result of these efforts—a new, faster-acting, affordable TB drug—will save millions of lives, improve global prosperity and reduce healthcare expenses by up to 65 percent. Reducing TB treatment to two months or less will help everyone fight the epidemic more successfully and help the war on HIV/AIDS.



Tommy Thompson

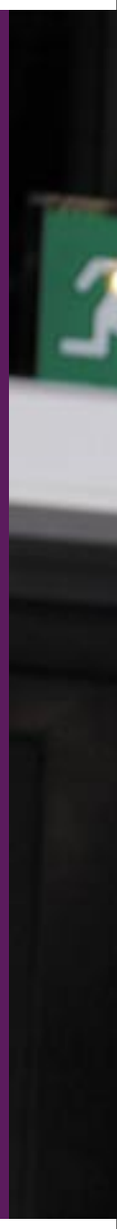
US SECRETARY OF HEALTH AND HUMAN SERVICES AND
CHAIR, GLOBAL FUND TO FIGHT AIDS, TB AND MALARIA

"Investing in biomedical research and enhancing international partnerships like the Global Fund and the TB Alliance are indispensable to solving the critical health challenge presented by tuberculosis. The U.S. Government, through the Department of Health and Human Services, supports the TB Alliance's development of faster-acting tuberculosis medicines. With our active support, the TB Alliance is building a seamless pipeline of TB drug candidates to achieve this goal."

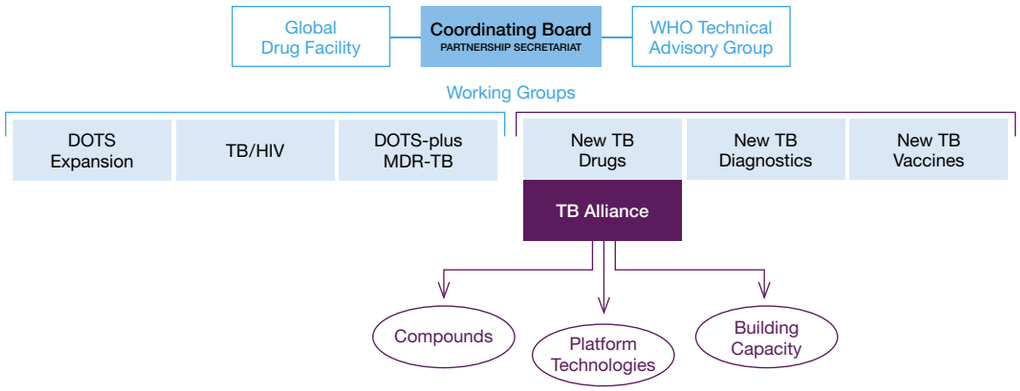
Agnes van Ardenne

NETHERLANDS MINISTER FOR
DEVELOPMENT COOPERATION

"The Dutch government takes its commitment to the Millennium Development Goals very seriously. Our support of the TB Alliance signals the importance of investing in TB drug development today. This task is so urgent, and the public benefit so obvious, that it requires broad and shared public investments."



THE STOP TB PARTNERSHIP



The TB Alliance leads the Stop TB Working Group on TB Drug Development, a forum to coordinate TB research and development activities worldwide. The Working Group is an integral part of the Stop TB Partnership whose secretariat is hosted by the World Health Organization.

"Now that we have the Global Plan, the world must invest in better treatment today and tomorrow. If we fail to back such a simple roadmap, future generations will remember us, not for stemming the tide, but for choosing to permit an airborne contagion to team up with HIV and sweep the globe."

Dr. LEE Jong-Wook

DIRECTOR-GENERAL,
WORLD HEALTH ORGANIZATION

MOBILIZING HEALTH AND ADVOCACY COMMUNITIES

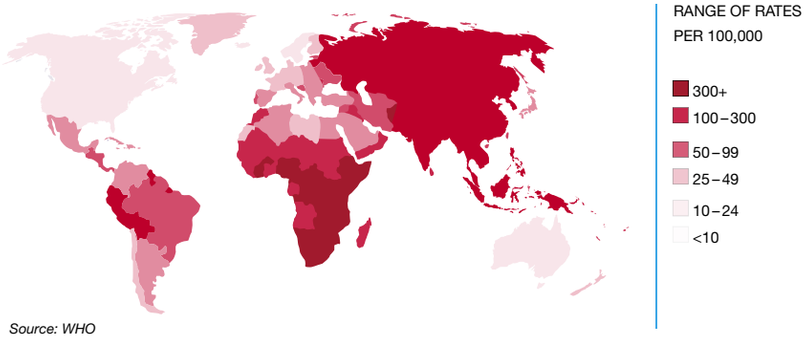
Efforts to expand TB control today are slowed by the current, lengthy treatment. Faster-acting drugs are crucial, especially in the context of TB's triple threat: rapid spread, growing drug-resistance, and a deadly symbiosis with HIV/AIDS. Despite the highest levels of infection in history, TB does not get the attention it deserves because its victims are often poor and voiceless. The TB Alliance Stakeholders lend support to patients and health workers by mobilizing support for new TB drugs. Patients, doctors and health advocates are calling for action now to banish a disease that claims 2 million lives every year.

Winstone Zulu

TB/HIV PATIENT AND ADVOCATE, ZAMBIA

"I lost all of my brothers—four of them—to the deadly TB-HIV twin-epidemic. I can't keep quiet, and now it's time for TB patients to mobilize, like the HIV community. We know TB won't take care of itself. The only way we are going to get better drugs is through efforts like the TB Alliance. We can no longer sit on the sidelines, or millions more lives will be lost."

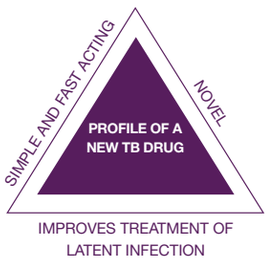
WORLD MAP OF INFECTION TB INCIDENCE RATES, 2001



Source: WHO

Tuberculosis kills one person every 15 seconds and infects one-third of the world.

THE FOCUS OF OUR EFFORTS—A NEW FASTER DRUG



A new TB drug will:

- Shorten the total duration of effective treatment,
- Improve the treatment of MDR-TB, which cannot be treated with isoniazid and rifampicin; and
- Provide a more effective treatment of latent TB infection, which is essential for eliminating TB.

Joanne Carter

LEGISLATIVE DIRECTOR, RESULTS, U.S.

"TB has remained a silent, global emergency for too long. A growing circle of advocates is changing that perception in capitals around the world. The U.S. Congress understands that support for TB programs abroad is not just the right thing to do, but also key to TB elimination at home. Now we need to convince policymakers that investments in new drugs have concrete dividends. A faster cure will be the cornerstone of tomorrow's TB control. Getting us there requires investment today."

Dr. Charles Yu

PRACTICING PULMONOLOGIST AND
PRESIDENT OF THE PHILIPPINES
COALITION AGAINST TB (PHILCAT),

MEMBER OF TB ALLIANCE STAKEHOLDERS

"I refuse to watch another patient die because the drug regimen is simply too long and complicated to follow. This is why I am a Stakeholder of the TB Alliance – I have the means to advocate on a global level for investments in a faster cure. Imagine what a two-month therapy would do for the Philippines, where 75 people die every day and 36 percent of our total population is infected with TB."

WE PUT SCIENCE TO WORK

Forging unique R&D partnerships with industry, governments and academia to build a portfolio of promising drug candidates.

Status of PA-824: Meeting Key Milestones

"With each milestone PA-824 passes, we feel like trailblazers."

Dr. Doris Rouse, Project Manager for PA-824, Research Triangle Institute

PA-824, the first compound acquired by the TB Alliance, has moved briskly through the R&D pipeline. Since the TB Alliance signed an exclusive license agreement with Chiron Corporation in June 2002, PA-824 has reached several important milestones in preclinical development, which address key issues of compound synthesis, toxicology and preclinical efficacy.

Early research during the discovery stage showed that PA-824 and its analogs demonstrated activity against both drug-sensitive and multi-drug resistant strains of TB, signaling possible improvements in TB treatment.

In the preclinical stage, results so far have been promising in all areas. Studies have demonstrated the feasibility of PA-824 synthesis at the larger scale required for animal and clinical trials. In extensive testing, PA-824 exhibited neither damage to genes nor toxic effects on normal metabolic or hormonal systems.

With support provided by the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institue of Health (NIH), Doris Rouse, Ph.D., director of Global Health at the Research Triangle Institute, is the project manager of the Development Team, which includes Drs. Barbara Laughon, Christopher Lipinski, Clifton Barry, Christine Sizemore and Ken Stover of the Scientific Advisory Committee.

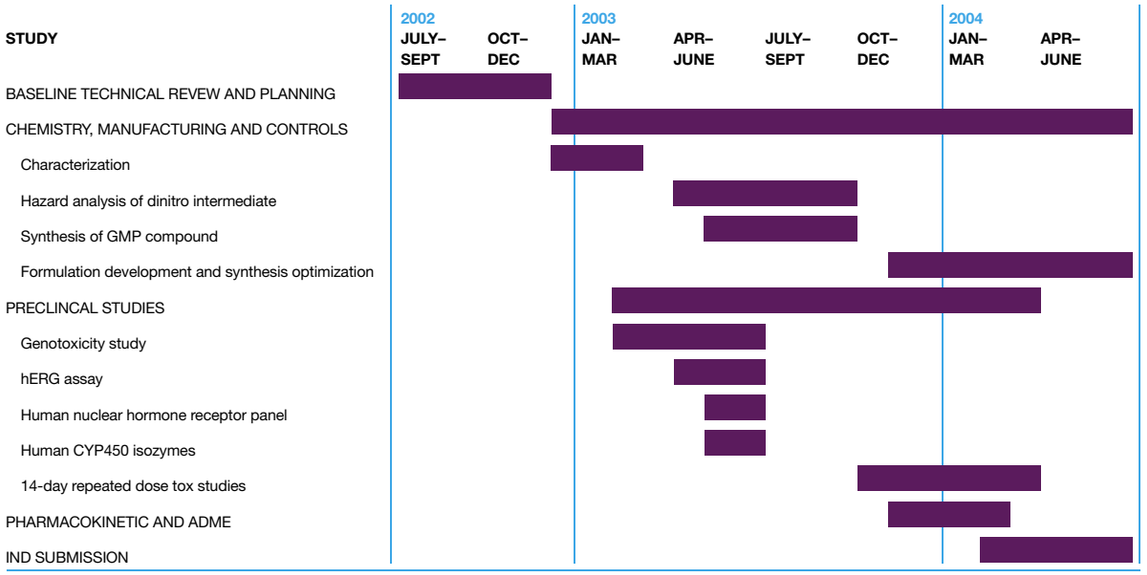
Dr. Rouse said, "We are excited about the progress of PA-824. At each go/no-go decision we've passed, we feel like trailblazers. Now we want to move it as quickly as possible through the next phase of animal studies."

Ongoing development tasks include additional animal studies to assess the safety and efficacy of PA-824. Further, the TB Alliance is working to optimize the synthesis of PA-824 to reduce production costs. If extensive animal toxicology studies in the next year are similarly successful, the TB Alliance will be able to enter Phase I clinical trials.

To ensure further development of this most promising class of drug candidate, the TB Alliance is also pursuing research into analogs of PA-824.

PA-824 DEVELOPMENT PLAN*

PROJECT SCHEDULE



*This chart, featuring selected studies, is a condensed version of the PA-824 development plan.

WHO

Research Triangle Institute (RTI)

ABC Laboratories

BioReliance

Cambridge Major Laboratories, Inc.

EMS DOTTIKON

The John Hopkins University

MDS Pharma

National Institute Of Allergy and Infectious Diseases (NIAID)

National Institute of Pharmaceutical Education and Research (NIPER)*

Novartis Institute of Tropical Diseases*

*Collaboration in discussion.

LOCATION

Canada

India

Singapore

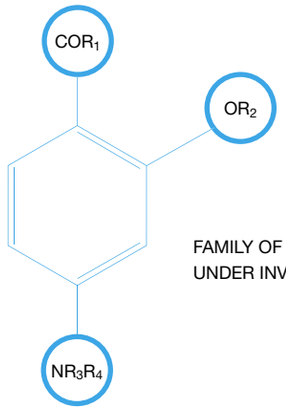
Switzerland

USA

WHAT

PA-824's rapid progress in preclinical development

Engine of Discovery — Chemical Diversity



FAMILY OF ISONIAZID ANALOGS UNDER INVESTIGATION

WHO

Wellesley College

Veterans Administration Medical Center (Syracuse)

LOCATION

Wellesley, MA, USA

Syracuse, NY, USA

WHAT

Synthetic organic chemistry to improve existing drugs

"After forty years of delays in drug development, we can't afford to leave any stone unturned," explains Dr. Michael Hearn, who heads a Wellesley College laboratory that is engaged in painstaking, crucial work. Along with fellow chemists Michaeline Chen and Eleanor Webster, Dr. Hearn synthesizes new molecules to improve on the best of existing treatment. By expanding the range of chemical diversity as widely and quickly as possible, Dr. Hearn hopes to stay ahead of the increasing problem of drug-resistance.

Six months into the two-year research project with the TB Alliance, Dr. Hearn has synthesized over 300 distinct molecules at Wellesley College. Emphasizing diversity, the goal is to find a path to a new drug using a wealth of existing and novel chemistry. One lead compound from this research is MJH-98-1-81, an analog of isoniazid (INH), the cornerstone of current therapy. The new compound has excellent activity *in vitro* against *M. tuberculosis*, a high selectivity index, outstanding bioavailability and potent activity in the mouse model. Other early tests show that it does not cause any gene damage.

Dr. Hearn's new molecules also aim to lessen a problem known as xenobiotic transformation, a process whereby the human system protects itself by ridding the body of anything foreign, including medicine. This affects current anti-TB drugs, and Dr. Hearn hopes to overcome this hurdle by deepening our understanding of how INH is processed. To understand how INH, once activated, interacts with the mycobacterium, Dr. Hearn uses X-ray crystallography and TB's genetic code to identify the exact "lock-and-key" fit between drug and a target in the bacterium, which can then guide rational drug design of novel chemical entities.

Even in a laboratory endowed with sophisticated organic chemistry equipment, Dr. Hearn is mindful of the practical challenges of delivering a new drug. To ensure affordability, he must anticipate the logistics of manufacturing, so that costs can be minimized.

Once compounds are generated, Dr. Hearn partners with biological laboratories that conduct the *in vitro* and *in vivo* studies that narrow the field of candidates and point him in the right direction. The laboratory of Dr. Michael Cynamon at the Veterans Administration Medical Center in Syracuse, New York, is one of the partners. In addition, Dr. Hearn receives support from the Tuberculosis Antimicrobial Acquisition and Coordinating Facility (TAACF) established by the NIAID.

Support from the TB Alliance has greatly accelerated Dr. Hearn's progress. "With the tools we now have available, I know we can discover a faster cure."

"We must exhaust all approaches at our disposal on the TB bacterium."

Dr. Michael Hearn, Wellesley College

CLOCKWISE FROM TOP: MICHAELINE CHEN, DR. MICHAEL HEARN, ELEANOR WEBSTER

Novel Quinolones

FROM LEFT TO RIGHT: DR. SANG-HO LEE, MS. SUN-JOO KIM, DR. LONG XUAN ZHAO, MR. HYUNG-MOOK OHOI

"Korea shares the burden of TB, to which no one is immune, and we hope our contribution will be an asset to the global effort."

Dr. Tae-Ho Park, KRICT

In Taejon, South Korea, Dr. Tae-Ho Park's team at the Korea Research Institute of Chemical Technology (KRICT) has accelerated the work on quinolones via a two-year agreement signed with the TB Alliance in April 2003.

KRICT, a government-funded research institute, was selected by the TB Alliance because of its excellent track record in quinolone synthesis and for its success in developing the early lead quinolone compound, KRQ-10018, which has demonstrated activity and specificity for tuberculosis.

Quinolones, a family of compounds already on the market for other indications and having great potential for the treatment of TB, may play a vital role in reducing the duration of treatment and in the treatment of drug resistant TB. Optimization of quinolones is considered a key avenue for developing new TB drugs.

With TB Alliance support, a total team of six chemists at KRICT will synthesize several hundred compounds. The compounds will then be tested *in vivo* and *in vitro* for specific activity against TB by KRICT's partner, a biology laboratory at Yonsei University. Selected candidates will be tested in *in vivo*, short-term and extended animal efficacy studies.

KRQ-10018, the lead compound in the family, will be further evaluated for efficacy and safety. In addition, the project aims to yield up to three other lead candidates in the TB Alliance portfolio for further development.

With rising incidences of multi-drug resistant TB, Korea is no stranger to the challenges of this global epidemic. The team at KRICT recognizes a dual-incentive behind the TB Alliance project, the first R&D partnership in Asia and the first in a country with a high TB burden.

"Korea shares the burden of TB, to which no one is immune, and we hope our contribution will be an asset to the global effort," explained Dr. Park.

WHO

Korea Research Institute of Chemical Technology (KRICT)

Yonsei University

LOCATION

Taejon and Seoul, South Korea

WHAT

Synthesis, optimization and testing of novel quinolones, pyridones and quinolizines

OUTSOURCING IN PRACTICE

The TB Alliance R&D strategy is to advance the TB drug development process as quickly and efficiently as possible. To do that effectively, it has embraced outsourcing, a practice increasingly becoming an industry norm. Outsourcing will help the TB Alliance develop many compounds simultaneously, smoothly and cost-effectively. The discipline it requires also ensures that a thorough scientific review occurs at every key go/no-go decision point.

While outsourcing adds complexity, it also offers the benefits of additional flexibility and capacity. Deriving those benefits requires focused management, careful oversight and clear scientific decision-making.

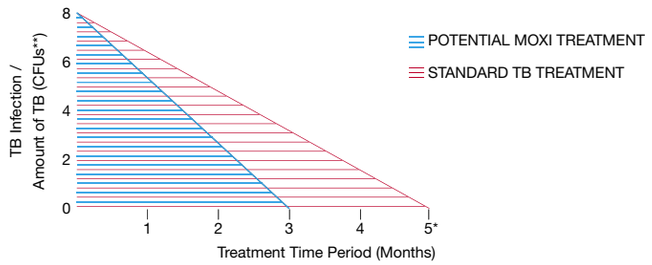
To direct the outsourcing process, the TB Alliance assigns a management team for every compound in the portfolio. Initially, the team prepares a development plan and detailed specifications for the studies and tasks required. The team then evaluates and recommends contractors for outsourcing and monitors the performance on each study.

"The outsourcing process for PA-824 has developed a flexible, efficient approach that can also be used to rapidly evaluate other lead compounds in the TB Alliance portfolio," says Dr. Doris Rouse, director of Global Health at the Research Triangle Institute.

Innovative outsourcing worldwide

The Power of Moxifloxacin: Shortened Therapy on the Horizon

POTENTIAL MOXI-CONTAINING DRUG TREATMENT VS. STANDARD TB DRUG TREATMENT



** The duration of treatment in the control group of a murine TB model is 5 months using current drugs.*
*** CFUs: colony-forming units*

WHO

The Johns Hopkins University

LOCATION

Baltimore, MD, USA

WHAT

In vivo model in which moxifloxacin replaces or enhances current drugs

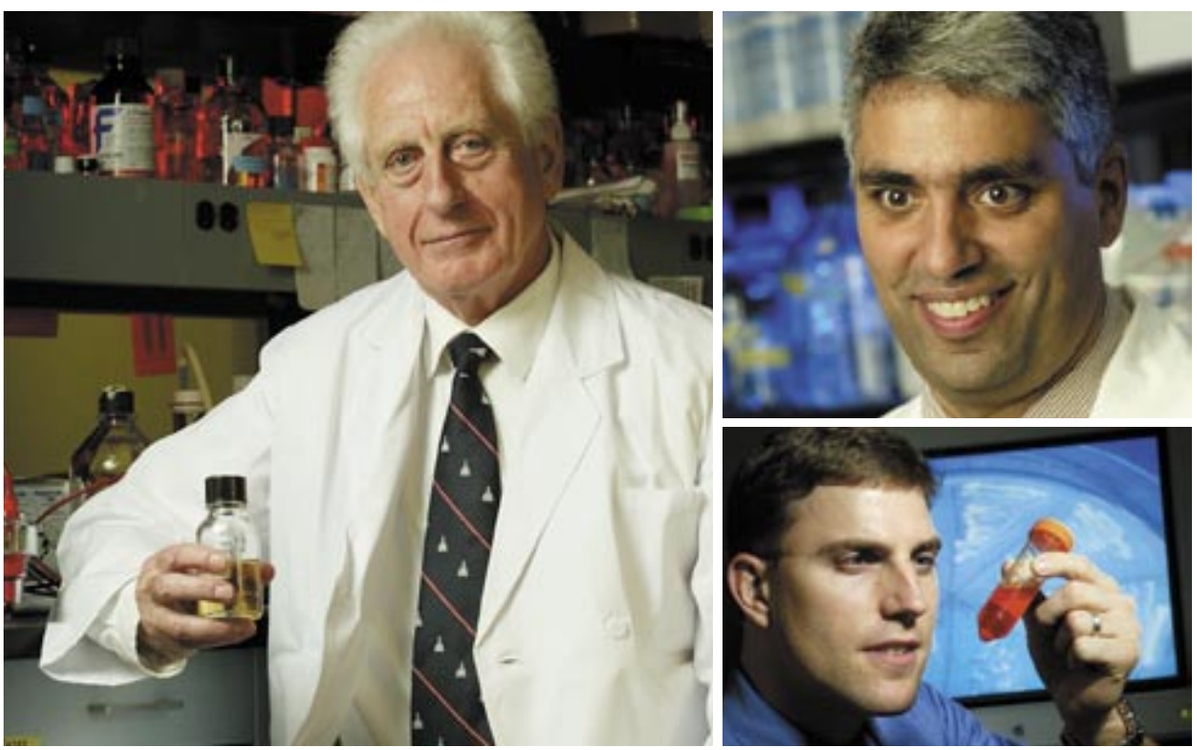
Moxifloxacin, a quinolone that has received virtually worldwide regulatory approval, has shown high levels of activity against *M. tuberculosis* in *in vitro* models. Developed by Bayer AG, the drug is currently approved for use in the U.S. for treatment of skin and upper respiratory tract infections and pneumonia. Research funded by the TB Alliance has affirmed moxifloxacin's early promise for shorter therapy through *in vivo* experiments utilizing a murine (mouse) model developed by Dr. Jacques Grosset. Support from the TB Alliance also helps ensure that the murine model, a platform technology, will continue to be available for other TB drug development studies.

By mimicking human disease, Dr. Grosset's world-renowned mouse model helps test drug candidates prior to undertaking clinical trials in patients. Developed at the Hôpital St. Pieté-Salpêtrière in Paris, the model was recently transferred to the Center for Tuberculosis Research at The Johns Hopkins University in Baltimore, where Dr. Grosset works with Dr. William Bishai, a TB researcher and practicing physician.

The Hopkins team substituted moxifloxacin in various combinations to replace or enhance elements of existing treatment. Dr. Grosset explains that "the next step is to confirm the *in vivo* results in clinical trials."

In a collaboration with Bayer AG facilitated by the TB Alliance, the CDC TB Trials Consortium (TBTC) has undertaken a large Phase II clinical trial to determine the acceptability and short-term efficacy of a moxifloxacin-containing regimen for the initial treatment of patients with newly diagnosed tuberculosis. Patients are already being enrolled at TBTC sites throughout North America and Uganda.

CLOCKWISE FROM LEFT: DR. JACQUES GROSSET, DR. WILLIAM BISHAI, DR. ERIC NUERMBERGER



As leading TB scientists and former TB patients, Drs. Grosset and Bishai know first-hand the potential impact of shorter TB therapy, a driving force behind their work.

Upgrading Clinical Capacity

"Most patients do not understand what a clinical trial is, yet they are desperate for a treatment that takes only weeks, not months. Our project doubles as a way to educate patients to demand better drugs."

Dr. Amina Jindani, IUATLD

Dr. Amina Jindani maintains a fierce conviction in the role of clinical trials for developing better TB therapeutics. For her, "It is the gold standard for devising any kind of treatment. It's the final proof. If you don't know what happens in practice, it won't do you much good."

Dr. Jindani should know. In 1967, she coordinated the landmark study by the British Medical Research Council that reduced TB treatment from two years to six months. Dr. Jindani's experience establishes her as one of the leading authorities on TB.

Based at the International Union Against Tuberculosis and Lung Disease (IUATLD), Dr. Jindani is evaluating the efficacy of TB therapy using World Health Organization—recommended fixed dose combinations (FDCs), where four drugs are combined in a single pill. Support from the TB Alliance is enabling the standardization of a network of 15 global sites, with a total of 1,500 patients, in Africa, Asia and South America.

By training staff and upgrading laboratories, Dr. Jindani's project can also provide the TB community with a set of potential clinical trial sites and the highest standard of practical and ethical guidelines for clinical trials with new molecules.

While the first step for these clinical trials is approval by local and international ethics committees, many hurdles still exist and involve cultural, religious and political realities.

Dr. Jindani is unequivocal. "If we don't get the patients on our side, we don't have a trial. That's going to be even more important when we're testing new molecules. This is not about experimenting with people. We really want them to get better. We are caregivers."

WHO

International Union Against Tuberculosis and Lung Disease (IUATLD)

LOCATION

Africa

Asia

South America

WHAT

Building capacity for TB clinical trials

WORKSHOP TO ADDRESS LATENCY

Since the TB bacillus was first identified, scientists have wrestled with its unusual ability to persist in an apparent non-replicating latent state. Of the world's 1.9 billion cases of TB, 99.5% exhibit no outward symptoms, but the patients still carry the bacterium that causes TB. Complicating matters is the apparent response of the human immune system to the bacterium and its interaction with HIV/AIDS: people co-infected with latent TB and HIV/AIDS are 30–50 times more likely to convert latent TB into the active, transmissible form of tuberculosis.

This dire public health situation raises some vexing questions: What causes the bacillus to go "active"? How critical is the immune system response? What is the bacillus doing in a persistent state? How can we begin to answer these questions, and what do they mean for the design of better drugs?

Early research suggests that non-replicating bacteria behave similarly in active and latent cases. The hope is that drugs developed to fight persistent bacteria will ultimately prove effective in treating latent disease and thereby reduce the length of treatment of both active and latent TB.

Providing drugs that suffice when taken for a relatively short period of time will ensure that more patients comply with the full course of therapy and thereby receive proper treatment. This will limit the opportunity for the bacterium to evolve into strains resistant to current antibiotics.

Shorter therapy would also allow many more cases of latent infection to be treated before they become active cases, boosting efforts now underway to treat those co-infected with HIV and lower the transmission of active TB.

The TB Alliance convened a workshop in January 2003 to address these questions and begin to identify key latency targets. At this meeting a group of leading TB scientists discussed initial strategies to tackle latency and chart a course for new drug development.

This workshop was co-chaired by Dr. Clifton Barry of the NIAID and Dr. Peter Small of the Bill and Melinda Gates Foundation.

How can the latest science on latency inform TB drug development?

ENLISTING GLOBAL EXPERTISE

The development of a new TB medicine is a global endeavor. To fulfill its mission, the TB Alliance builds on existing networks and mobilizes industry, public and academic researchers worldwide.

Americas

UNITED STATES
SCIENCE AND INDUSTRY NETWORKS

The TB Alliance leverages scientific expertise, facilities and research capacity in academic, industrial and public research laboratories throughout the United States. In-kind support, as provided by NIAID, and contractual outsourcing arrangements are helping the TB Alliance develop its portfolio. Through early R&D partnerships, as well as board members and scientific advisors from industry, the TB Alliance is assessing innovative strategies to further tap pharmaceutical and biotechnology companies.

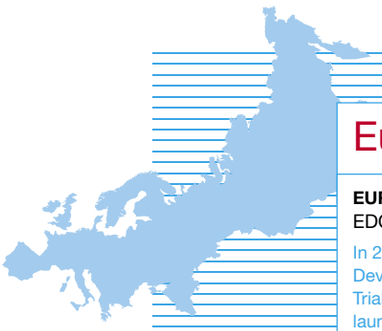
BRAZIL & PERU
PRECLINICAL AND CLINICAL EXPERTS

A strong R&D commitment and extensive TB research network, coupled with an increasing prevalence of TB, make Brazil and Peru natural partners for the TB Alliance. After visiting laboratories, clinical trial sites and manufacturing facilities, the TB Alliance is in partnership discussions with several Brazilian and Peruvian organizations.

Africa

SOUTH AFRICA
MEDICAL RESEARCH COUNCIL

Hosting the office in South Africa, the Medical Research Council (MRC) is a key partner of the TB Alliance, providing expertise to the SAC and actively participating as a Stakeholder. The MRC helped establish the South African Clinical Trials Consortium to upgrade clinical capacity, a critical foundation for anticipated TB clinical trials.



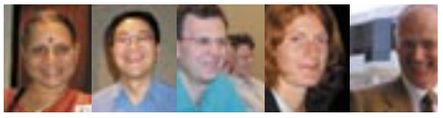
Europe

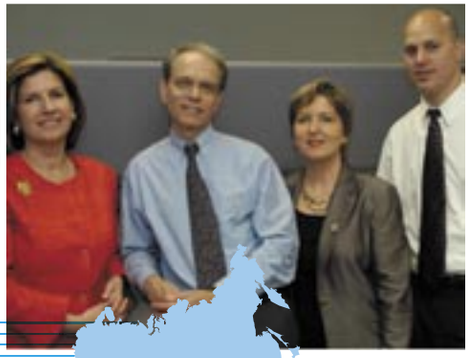
EUROPEAN UNION
EDCTP

In 2003, the European and Developing Countries Clinical Trials Partnership (EDCTP) was launched to support Phase II and III trials in, with and for developing countries, with a focus on AIDS, TB and malaria. This expansion of laboratory and human capacity will be critical to upcoming TB drug clinical trials.

EUROPE
NEW DEVELOPMENTS WITH INDUSTRY

- The TB Alliance catalyzed a groundbreaking meeting between Bayer AG and CDC on a clinical trial of moxifloxacin for first-line TB treatment.
- Basel-based Novartis launched its Institute for Tropical Diseases in Singapore, pledging to collaborate with the TB Alliance in the development of novel TB compounds.
- GlaxoSmithKline seconded Dr. Ken Duncan, an expert in TB drug discovery, to the TB Alliance.





Asia

JAPAN
SCIENCE AND INDUSTRY NETWORKS

Japan recognizes TB as both a domestic and a global health issue and spearheaded the G-8 commitment on infectious diseases. The TB Alliance works closely with the Research Institute of Tuberculosis (RIT) of the Japan Anti-TB Association (JATA), a Stakeholder, and the Kyoto Pharmaceutical University. The TB Alliance is also in discussions with Japanese companies to establish R&D partnerships.

KOREA
KRICT AND YONSEI UNIVERSITY

Bolstering the TB Alliance's portfolio of drug candidates, KRICT and Yonsei University in Taejon are optimizing novel quinolones and exploring new quinolizines and pyridones to treat TB.

INDIA
SCIENCE, INDUSTRY AND CLINICAL NETWORKS

India's chemical, pharmaceutical and clinical research experts are critical to the development of new drugs. The TB Alliance is building strong alliances there and is currently negotiating partnerships for the development of promising compounds.

"Every project we undertake engages the best minds, laboratories and facilities in the pursuit of an affordable, faster cure."

Maria C. Freire, Ph.D.
CHIEF EXECUTIVE OFFICER

Seán P. Lance
CHAIRMAN OF THE BOARD

Dear Friends and Stakeholders

This year, the world celebrated the completion of the sequencing of the human genome, one of the greatest scientific achievements of our time. Yet, this year, we also saw the rise of the highest levels of tuberculosis ever, now infecting one-third of the world's population and killing one person every 15 seconds.

This juxtaposition between today's stark global health situation and remarkable scientific progress highlights the critical role of the TB Alliance as we bridge these two realities in our quest to develop novel, faster anti-TB drugs. Every project we undertake engages the best minds, laboratories and facilities in the pursuit of an affordable, faster cure. We know that the TB Alliance occupies a unique place in the world because our mission and our strategy combine technical objectives with social goals.

Therefore, we are pleased to report that this year the TB Alliance has made great strides in the search for a novel, faster TB drug. This report highlights some of the accomplishments and progress realized over the past year and provides an overview of our fast-paced and exciting activities.

Our investments of human capital and financial resources are designed to maximize efficiencies and speed results. Driven by a commitment to health equity, we operate under the same drug development guidelines as the best models of the private sector. Our criteria center on whether a compound can make a marked, profound improvement in the treatment of TB to all patients in need. Our ultimate accountability in this enterprise rests with the one-third of the world infected with TB.

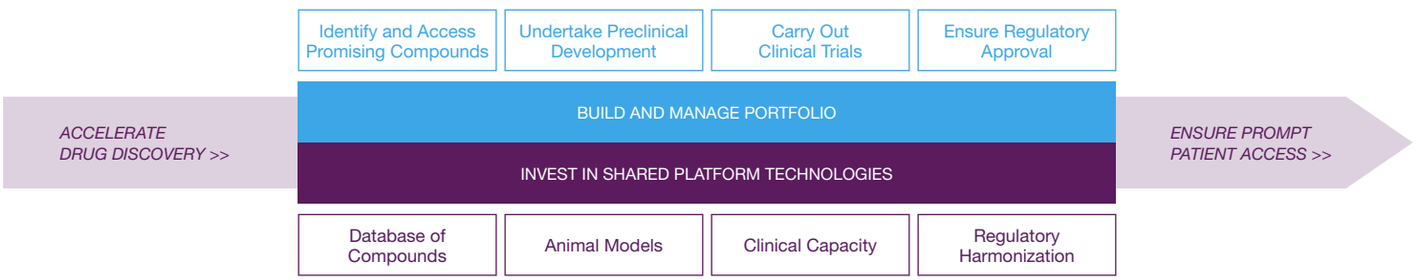
The TB Alliance assembles and manages a portfolio of promising compounds, carefully selected from a wide range of public, private and academic facilities. To ensure a successful, global, cooperative enterprise, we catalyze the involvement of researchers all over the world and invest in platform technologies that accelerate scientific progress. Through our leadership on the Stop TB Working Group on New Drugs, we ensure that others benefit from these platform technologies, share information and collaborate to achieve our goal.

Under the skillful direction of Dr. Mel Spigelman, our R&D team is swiftly identifying and accessing portfolio compounds, while capitalizing on private and public resources for development activities. Through our ongoing evaluations of clinical trial and drug development capacity around the world, we further position the TB Alliance for the rapid clinical validation of promising compounds.

We have built a growing portfolio with diverse compounds. The lead investment, PA-824, is recognized as one of the most promising novel compounds for TB treatment. With generous support from the U.S. National Institute of Allergy and Infectious Diseases (NIAID), this compound is progressing quickly through key preclinical development milestones. Similar strategic outsourcing will help to develop the analogs of PA-824, a project we are in the process of finalizing with partners.

On parallel tracks, our investments in innovative chemistry are helping to optimize quinolones at Korea Research Institute of Chemical Technology (KRICT) and to refine an isoniazid analog in the United States; both efforts are targeted to improve first-line drugs. Additionally, our most recent Request for Proposals has led to the identification of new lead compounds with the potential to further enhance our portfolio. We are also exploring the use of existing drugs such as moxifloxacin in first-line therapy which could help shorten therapy for TB in the near term. Finally, in funding projects for murine models and clinical trial capacity, we provide essential infrastructure support to the community of TB drug researchers worldwide.

OVERVIEW OF TB ALLIANCE APPROACH



The TB Alliance selects and manages a portfolio of drug candidates that are outsourced to industry, academia and public laboratories for development. We invest in process development and clinical infrastructure for TB drug development to facilitate discovery and development by the TB Alliance and third parties. Our innovative agreements with R&D partners accelerate research and development and ensure affordablity of the drugs developed.

In 2002-2003, three leading pharmaceutical companies pledged to enhance TB research. These investments help support the work of the TB Alliance in concrete ways. GlaxoSmithKline is contributing drug discovery expertise by seconding Dr. Ken Duncan, the architect of its Action TB program, to the TB Alliance. AstraZeneca and the TB Alliance co-hosted a conference on TB drug development at AstraZeneca's TB research facility in Bangalore, India. We especially welcome the commitment of Novartis to provide us with core R&D support, using the newly created Novartis Institue for Tropical Diseases, as well as its pledge of royalty-free pricing in endemic countries.

The TB Alliance capitalizes on the newest scientific advances to generate novel drug candidates. In recent years, a wealth of new scientific information on TB has been forthcoming, including a better understanding of the interaction between the mycobacterium and the human host as it relates to latent infection. To address the challenges of latency in the context of drug development, we hosted a scientific workshop to explore possible strategies and to identify top drug targets for TB latency. The results of this meeting, to be reported in a scientific publication, provided the basis for a submission to the Grand Challenges in Global Health initiative of the Bill and Melinda Gates Foundation.

As recognition of global health priorities increases, we have witnessed growing consensus around the goals of the TB Alliance from leaders in science, business and policy. Yet, translating this consensus into concrete results depends on everyone's support and involvement. As a public-private partnership, we engage a wide circle of participants in our endeavor. This year's accomplishments reflect the continued support of our donors, the counsel of our Scientific Advisory Committee and the global reach of our Stakeholder network. Our staff, expanding in scope and expertise, is comprised of dedicated individuals who ensure we meet our milestones and enlist strategic partners to achieve our mission.

The TB Alliance has conceived of creative ways to partner with pharmaceutical and biotechnology companies with drug development know-how and capacity. Likewise, we have established strong links with public research organizations and with advocacy groups worldwide. And our enterprise relies on a firm commitment from donor governments to the Global Plan to Stop TB to ensure effective TB control through the new drugs that promise dividends on a profound scale.

As we fully grasp an impending global health catastrophe—the twin TB-HIV epidemic combined with the rise of multi-drug resistant strains—we must redouble our efforts to bridge the gap between the promises of science and the need of millions worldwide.

This is no small task, yet the returns are equal to the energy and resources required to turn this vision into reality. Together we have a chance to turn a daring experiment into a legacy.

Maria C. Freire, Ph.D
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