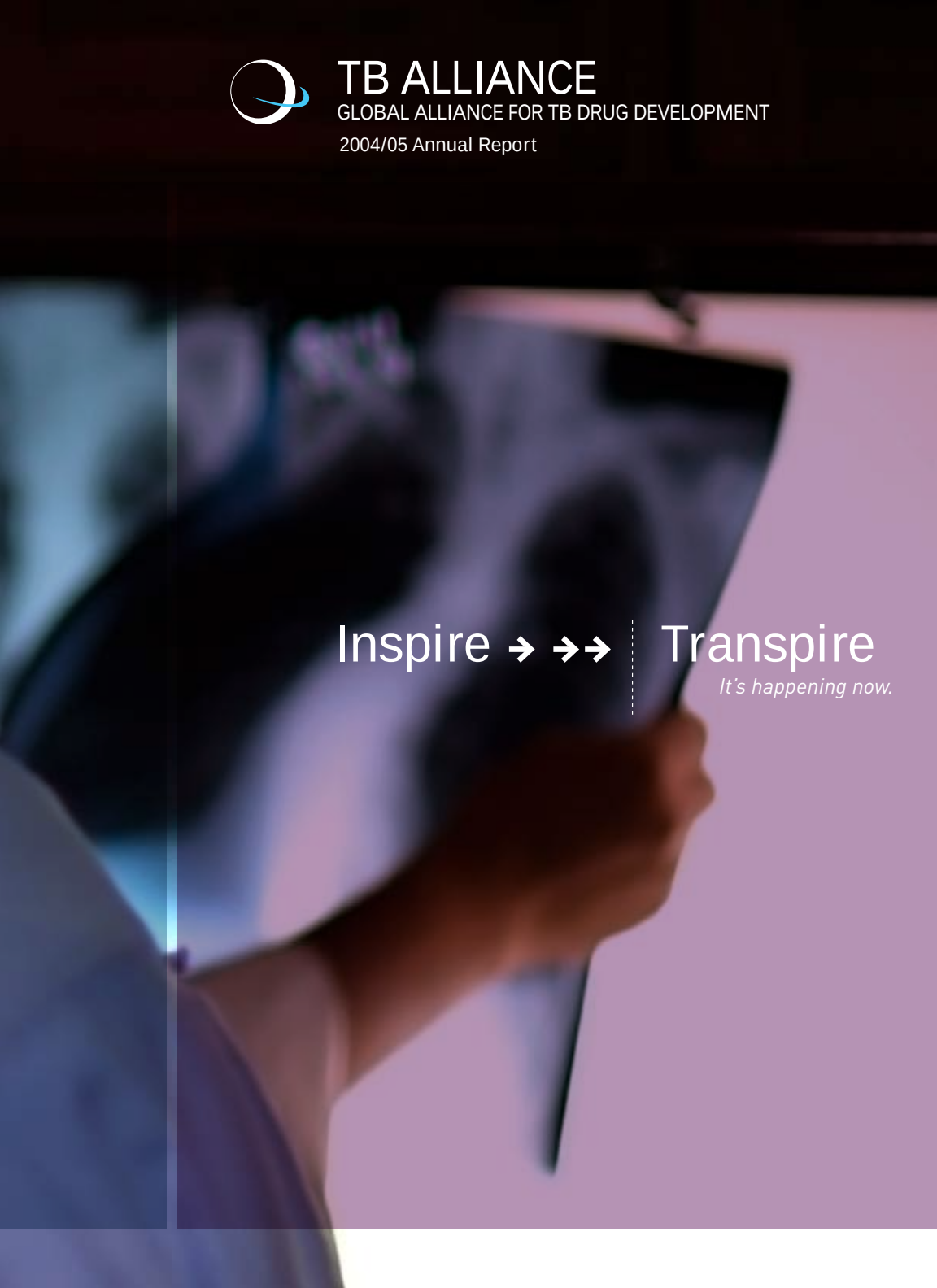
TB ALLIANCE

GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

2004/05 Annual Report



TB kills someone
every fifteen seconds.

It still takes at least
six months to treat.

*The TB Alliance is
changing that.*

Inspiring breakthroughs.
Inspiring action.
Inspiring change.

Tuberculosis, an ancient and relentless pandemic, continues to ravage continents, societies and families. Over two billion people carry the bacterium that causes the disease. Millions die every year.

Yet today the world still depends on outdated drugs delivered in a complex multi-drug regimen for six or more months. Patients must be monitored, often daily, by healthcare workers. TB is a leading killer of people with HIV/AIDS, but current therapy cannot be combined easily with most HIV therapies. And drug resistance is worsening.

The TB Alliance has the technology and the strategy to radically improve treatment. A robust pipeline with eight discovery projects and two drugs in clinical testing promises to deliver a significantly shorter, and better, cure.

In the next five years, we expect to cut treatment time almost in half. In the longer term, we will go further by designing completely novel TB drug regimens that combine better and faster-acting drugs. Our goal is to make the cure simple, short and lasting.

Today's treatment takes too long and requires too many pills.

→ →→ A faster cure with fewer pills will save lives.

Most TB patients today must complete 130 doses—up to eight pills a day over six months. Multi-drug resistant TB (MDR-TB) is worse, taking up to two years to treat and involving severe side-effects.

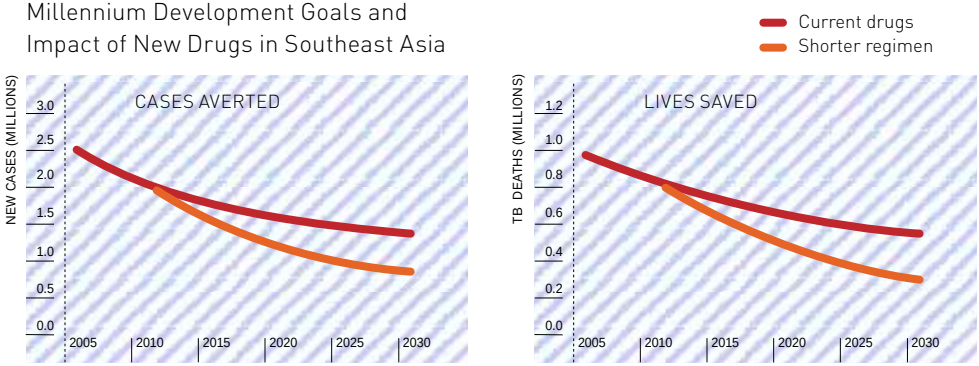
Current treatment strains healthcare workers and drains public health expenditures. TB also forces the world's families to forgo $12 billion each year in lost income, as it targets people in their most productive years. 300,000 children in India alone drop out of school every year to care for relatives stricken with TB.

A simpler, shorter regimen will allow patients to complete their treatment more easily and get back to work faster. It will also free up healthcare resources to reach more patients and save more lives.

The treatment objective: a regimen of only ten short doses, total.

130 → 10 Doses → Innovative science is the key.

Millennium Development Goals and Impact of New Drugs in Southeast Asia



Modeling the impact of a 2-month therapy. In Southeast Asia alone, a new regimen introduced in 2012 would save 8 million lives by 2030. J. Salomon *et al,* "Prospects for advancing tuberculosis control efforts through novel therapies" (publication forthcoming).

The TB Alliance has the strategy:

New combinations.
Shorter regimen.
Fewer pills.

A better cure.

The most comprehensive TB drug pipeline in history—built with enduring partnerships, the brightest minds and cutting-edge technology.

The TB Alliance is spearheading the development of new treatment regimens based on combinations of new and better drugs. A TB drug pipeline was virtually nonexistent a few years ago. Today, multiple drug candidates are in clinical trials and there are thousands of compounds being screened, synthesized or optimized in discovery and preclinical studies.

In the last year, the TB Alliance's portfolio doubled with the initiation of multiple discovery projects at GlaxoSmithKline's Tres Cantos facility and the launch of coordinated clinical trials centered on Bayer's existing antibiotic, moxifloxacin. We also advanced the first drug in our pipeline, PA-824, into Phase I clinical trials.

A shorter and simpler drug regimen is in sight. In the short term, it can help us reach the Millennium Development Goal for TB. In the longer term, it will pave the way for the elimination of TB as a public health menace.

COMPOUNDS, ANALOGS AND DERIVATIVES

ACTIVE PROGRAM

PROGRAM IN DISCUSSION

→ DISCOVERY

- **Nitroimidazole Analogs** (University of Auckland, Novartis Institute for Tropical Diseases, National Institute of Allergy & Infectious Diseases)
- **Carboxylates** (Wellesley College)
- **Quinolones** (KRICT/Yonsei University)
- **Macrolides** (University of Illinois at Chicago)
- **InhA Inhibitors** (GlaxoSmithKline)
- **Isocitrate Lyase Inhibitors (ICL)** (GlaxoSmithKline)
- **Focused Screening** (GlaxoSmithKline)
- **Pleuromutilins** (GlaxoSmithKline)
- **Screening and Target Identification** (AstraZeneca)

→ PRECLINICAL

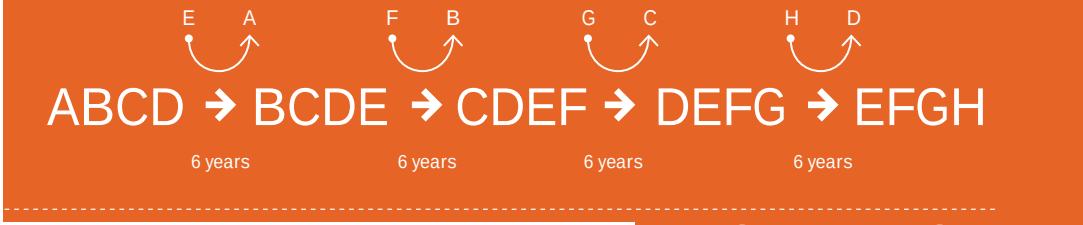
- **Nitroimidazo-oxazole Backup Compound** (Otsuka Pharmaceutical)

→ CLINICAL TESTING

- **Nitroimidazole PA-824** (Chiron)
- **Moxifloxacin** (Bayer)
- **Nitroimidazo-oxazole OPC-67683** (Otsuka Pharmaceutical)

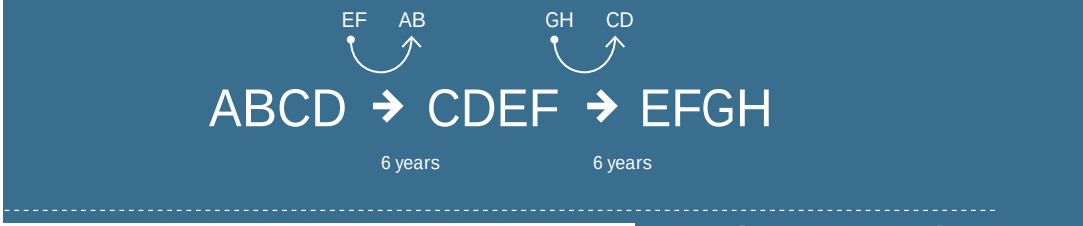
From Substitution to Revolution

Dilemma: Conventional TB Clinical Development Paradigm



ABCD → EFGH
24 YEARS

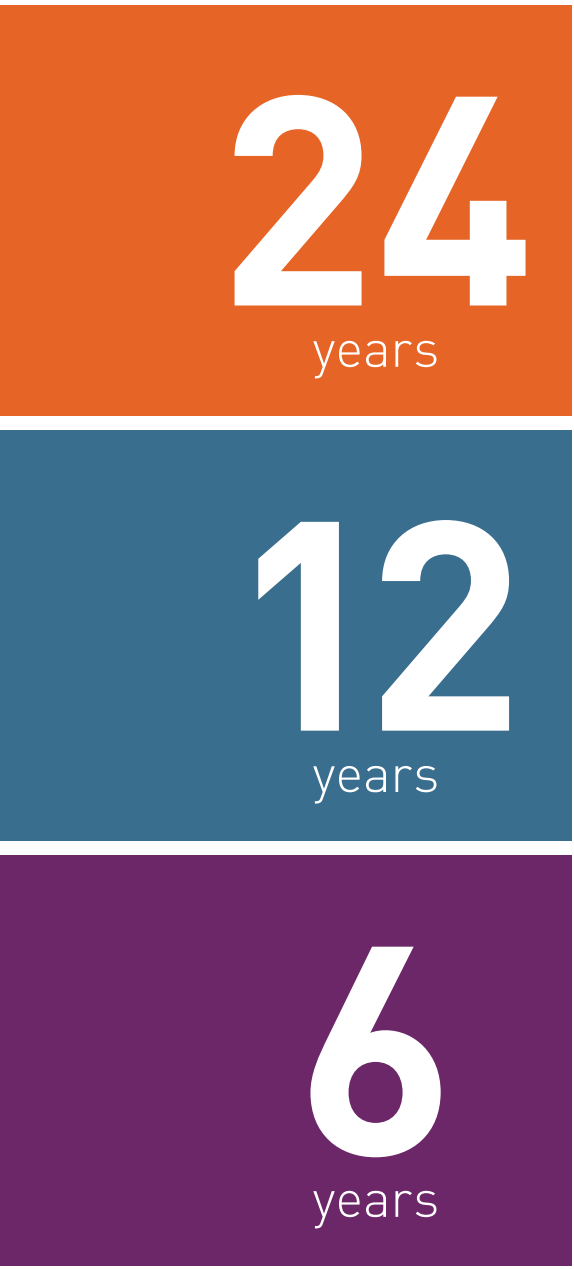
Alternative TB Clinical Development Paradigm



ABCD → EFGH
12 YEARS

Alternative TB Clinical Development Paradigm

ABCD → EFGH
6 YEARS



We are not just developing drugs. We're changing the way they are developed.

To radically improve TB therapy, the drugs used today must be replaced with new and better drugs in novel combinations. TB's complex biology demands no less. That is why our strategy rests on a robust pipeline.

The conventional approach to drug development would substitute each drug in the current regimen one-by-one—only after each new drug has been approved. This process takes at least six years per drug—meaning a combination of four novel drugs might take 24 years to develop. The world cannot afford to wait.

Our approach examines compounds with complementary modes of action in the preclinical phase of development, which allows us to generate a blueprint for testing combinations early on in the clinical phase. This means we could potentially deliver an entirely new regimen in as few as six years.

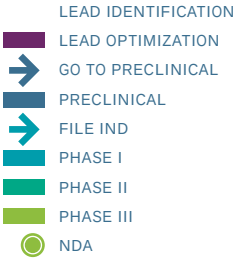
With this in mind, the pipeline must grow and advance at a rapid clip.

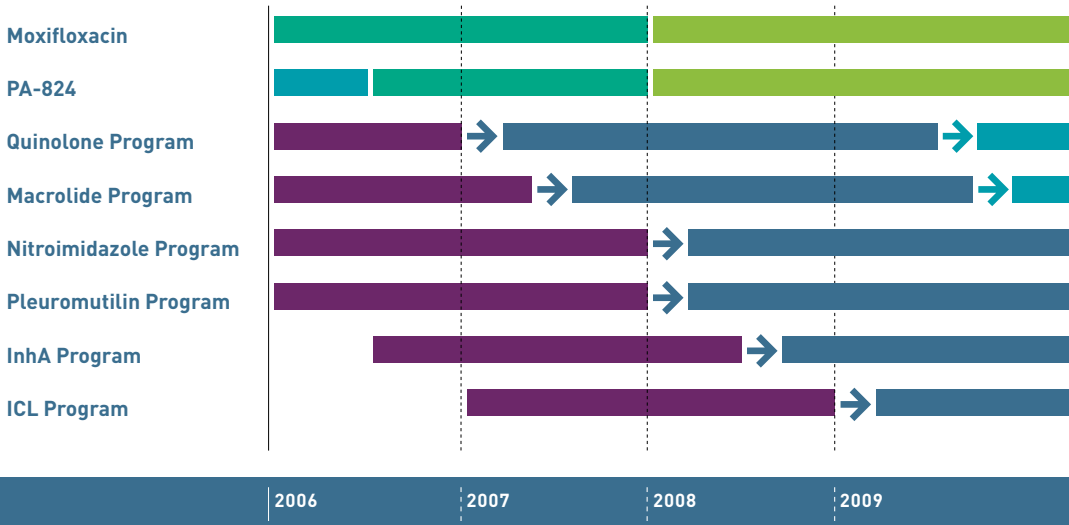
Objective:

Best Combination

Activity:

Sustain and Enhance a Portfolio of Promising TB Drug Candidates



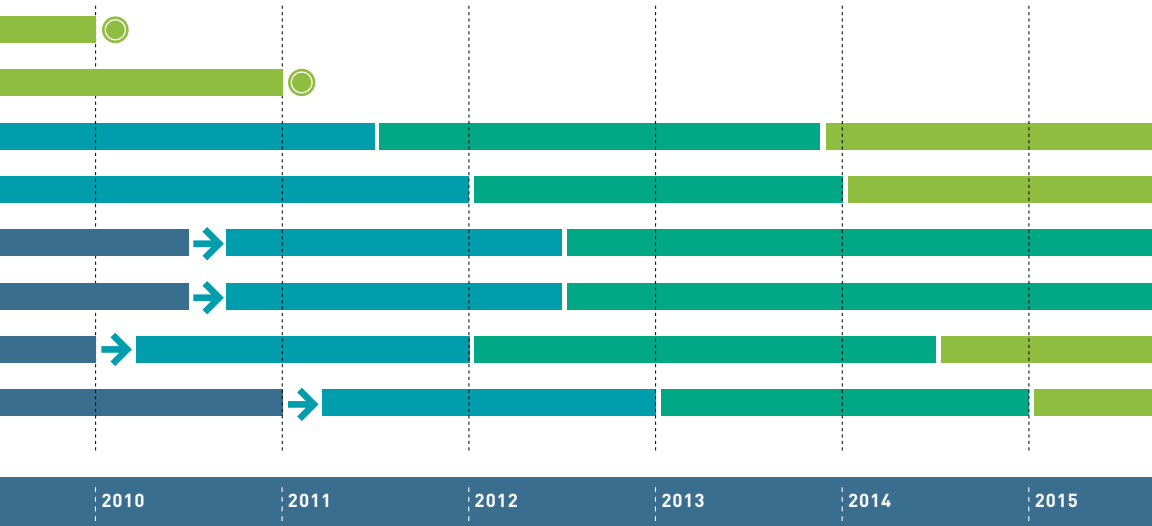


The TB Alliance manages and directs a comprehensive R&D program. Our scientists scout the world's laboratories for TB compounds, conducting exhaustive reviews before selecting programs for our portfolio.

Our approach varies based on the technology and the partner. Whether we work with researchers in academia, industry or at public institutes, we design a partnership that can move drugs forward as efficiently as possible. We either co-invest and co-develop a project, fund and manage it directly, or in-license technology and advance the compound ourselves.

Our discovery projects are based on novel pathways that quickly disarm the TB bacterium, *Mycobacterium tuberculosis (M.tb)*. The result is a diverse portfolio in which every drug candidate will help shorten, simplify and improve TB therapy.

Each project progresses through critical go/no-go milestones towards the goal of registering an improved, faster-acting regimen by 2010 and a regimen containing completely novel drugs by 2015.



USING MOXIFLOXACIN FOR TB

- Novel mechanism of action for TB
- Possibility of shortening therapy by 2-3 months
- Safe to use with HIV therapy
- Excellent oral bioavailablility & long T1/2
- Demonstrated safety record: 42 million exposures

MOXIFLOXACIN

Phase II Clinical Trials

Moxifloxacin, with an excellent profile in the most promising TB drug class available today, is now being tested in a combination regimen that could shorten treatment by 2–3 months.

Nearly 2,500 TB patients are now being enrolled around the world in this historic clinical program, coordinated through a partnership between the TB Alliance and Bayer Healthcare AG, the patent holder of moxifloxacin, a widely-used approved antibiotic. The program will assess its efficacy and safety as a front-line tool for TB care. Bayer and the TB Alliance have committed to delivering the drug on an affordable basis to patients in the developing world.

We have brought together the world's leading clinical trial experts to conduct a number of separate, but coordinated trials: the TB Clinical Trials Consortium of the U.S. Centers for Disease Control and

↘ Clinical Investigators

Trial Manager	Name of Trial	Study Arms	Approximate No. Patients	Locations	Funder
CDC–TBTC	Study 27	Standard Substitute Ethambutol Standard Intermittent Intermittent Substitute Ethambutol	350	USA/Canada Uganda South Africa	CDC
	Study 28	Standard Substitute Isoniazid	400	USA/Canada Uganda South Africa Brazil/Spain	CDC
Johns Hopkins University		Standard Substitute Ethambutol	200	Brazil	FDA
University College London/ British Medical Research Council		Standard Substitute Ethambutol Substitute Isoniazid	1500	Tanzania South Africa Zambia	EDCTP

Prevention (CDC), The Johns Hopkins University (JHU), and the University College London (UCL) working with the British Medical Research Council (BMRC).

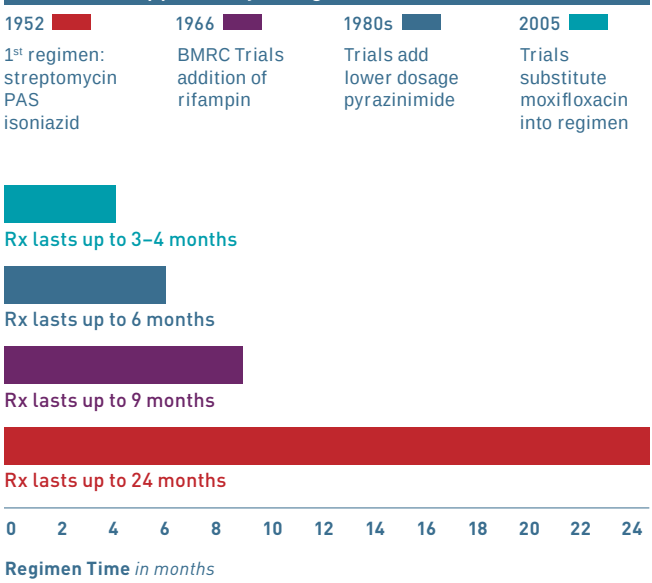
The studies will determine whether the substitution of moxifloxacin for one of the current standard TB drugs (isoniazid or ethambutol) eliminates TB infection faster than today's treatment protocol. In preclinical studies commissioned by the TB Alliance in 2002-03, investigators at The Johns Hopkins University found that substituting moxifloxacin for isoniazid in a mouse model system decreased the amount of time needed to eradicate TB infection by two months.

Moxifloxacin, a fluoroquinolone registered in 104 countries for the treatment of acute respiratory infections, has a novel mechanism of action that is not targeted by TB drugs now in use. Moxifloxacin kills *M.tb* by inhibiting an essential enzyme called DNA gyrase, which is important for both replicating and persistent states of bacterial growth. Moxifloxacin is also safe to use alongside antiretrovirals (ARVs) because it is not metabolized by the cytochrome P-450 enzyme system. With more than 42 million patient uses worldwide, moxifloxacin already has a demonstrated safety record, which could speed the process of registering the drug for a new indication.

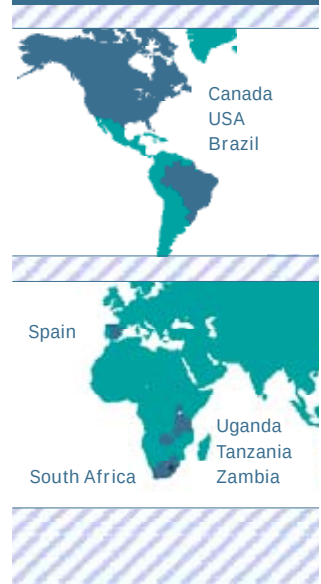
The program coordinates four Phase II clinical trials in eight countries. Bayer is donating moxifloxacin for each trial site and will sponsor regulatory filings. The TB Alliance is managing the overall clinical trial program, ensuring the coordination of information and results towards the goal of registration. The TB Alliance's financial support leverages substantial funding from the CDC, the U.S. Food and Drug Administration (FDA) Orphan Products Development Center and the European and Developing Countries Clinical Trials Partnership (EDCTP).

The Phase II studies are expected to be completed by 2007 and Phase III studies could get underway in the interim.

Historic Opportunity to Fight TB Better



Clinical Trial Locations



PA-824'S POTENTIAL FOR SHORTENING TB THERAPY:

- Novel mechanism of action
- Potent activity against slow-growing and actively growing *M.tb*
- Efficacy in initial and continuation phases of therapy
- Combines most effective features of INH and RIF, two cornerstone drugs

PA-824
Phase I Clinical Trials

After passing preclinical milestones in near record time, PA-824, the first compound in the TB Alliance portfolio, entered Phase I trials. It is the first TB drug developed by a non-profit organization to reach clinical trials.

A member of the novel nitroimidazole class, PA-824 has the potential to reach each of the TB Alliance's goals: to dramatically shorten treatment time, treat multi-drug resistant patients and those coinfected with TB-HIV, and improve the treatment of latent TB.

Preclinical studies directed by the TB Alliance verified PA-824's potential as an anti-tuberculosis agent. *In vitro* studies demonstrated its potent activity against both actively and slowly-growing *M.tb*. *In vivo* studies showed that the drug kills *M.tb* effectively in both the initial, intensive phase as well as in the later continuation phase of TB therapy. With both bactericidal and sterilizing activity, PA-824 combines, in a single compound, the most effective attributes of isoniazid and rifampin, the two cornerstones of TB drug therapy today.

CLINICAL DEVELOPMENT PROGRAM

The TB Alliance has created a clinical development plan for PA-824 to demonstrate its safety and efficacy as a first-line treatment for TB. The Phase I clinical study now underway is being conducted by the Nebraska-based MDS Pharma Services to evaluate the safety, tolerability and pharmacokinetics of single doses of PA-824. The TB Alliance has already identified a commercially available and effective formulation for oral dosing of PA-824.

After completing a standard series of Phase I studies, expected by mid-2006, the goal will shift to determining: (1) how PA-824 is best administered in the context of the other first–line TB drugs; and, (2) whether substitution of PA-824 into the standard regimen can simplify TB treatment.

ANALOG PROGRAM

We are also pursuing an analog program on several tracks to maximize the potential of this novel class. The TB Alliance is investigating 13 specific compounds in a related family of nitroimidazoles by working with researchers at the Novartis Institute of Tropical Diseases in Singapore and the National Institute of Allergy and Infectious Diseases (NIAID). Working with researchers at the University of Auckland (ACSRC) in New Zealand, the TB Alliance is identifying another set of discovery compounds. This program has already synthesized eleven analogs and aims to identify a new chemical structure to advance to lead optimization.

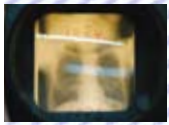
"That marriage of thinking differently really is what created PA-824. Without the involvement of the TB Alliance, I'm certain that this promising TB drug would not be where it is today."

Dr. Bill Baker
Vice President,
Research at Corus Pharma

"Tapping NIAID support to advance a biotech compound with a smart, aggressive plan is the very definition of the public-private R&D model. The TB Alliance led a team effort and the result was that PA-824 went into human testing in near record time."

Dr. Doris Rouse
Project Manager for PA-824
RTI International

PA-824 Timeline



Nature article published on the promising anti-TB activity of PA-824 based on work by Dr. Bill Baker and Dr. Ken Stover at Pathogenesis — 2000

Pathogenesis acquired by Chiron; TB Alliance launched — 2000

Chiron & TB Alliance start discussions — 2001

TB Alliance in-licenses PA-824 and analogs from Chiron—Chiron commits to make the TB technology available royalty-free in endemic countries — 2002

Initiated IND-enabling preclinical studies — 2003

Formulation studies and synthesis optimization begins; IND filed — 2004

Phase I starts — 2005

Discovery Projects

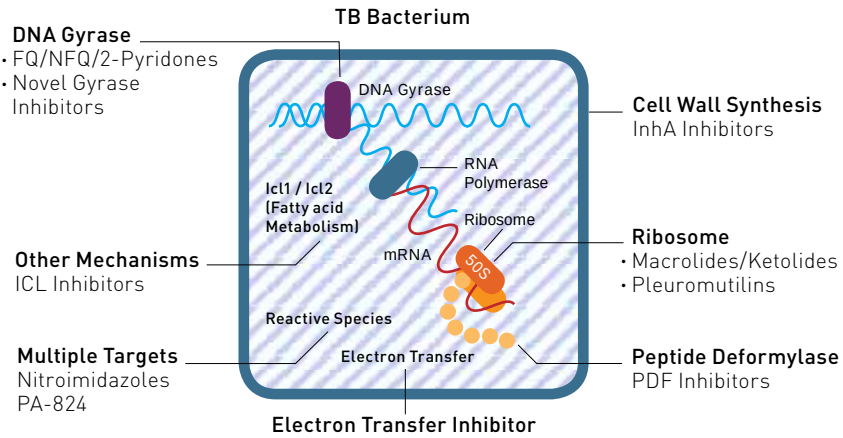
Investing in a diversified discovery portfolio is essential to finding a better cure and to ultimately eliminating TB.

The TB Alliance selects projects for their diversity of chemical classes and ability to target different pathways. The map of the TB genome provides greater precision in honing the selection of drug candidates and in advancing hits to leads, and leads to drug candidates.

As the accompanying diagram shows, each discovery project in the TB Alliance portfolio uses a different metabolic pathway to disarm the bacterium. Some drugs could have the same target but use different mechanisms, providing the diversity necessary for a balanced portfolio. These projects have a good chance of shortening therapy because these pathways are believed to be important to the bacterium's survival in the persistent stage, when it is most difficult to target.

The richer the discovery programs, the more opportunities we have to find multiple breakthrough drug candidates. These are the foundations for new combinations.

Genomic Tools Help Advance Drug Discovery



GSK PROJECTS

1.

In March 2005, the TB Alliance and GlaxoSmithKline launched a broad discovery portfolio consisting of four projects designed to yield new compounds that attack different targets of *M.tb.* With their novel mechanisms of action, drug candidates arising from these projects could shorten treatment time and treat patients resistant to conventional therapies. The program will only advance compounds that can be administered effectively and simultaneously with ARVs used to treat HIV/AIDS patients.

Dr. Tadataka (Tachi) Yamada, Chairman of Research and Development at GSK joins Dr. Maria C. Freire, President & CEO of the TB Alliance to launch the joint discovery program. Dr. Yamada called it the "type of partnership that is needed to speed the development of new therapies for the leading infectious diseases in developing nations."

PLEUROMUTILINS

The most advanced of the four projects is at the lead optimization stage, exploring a novel class of antibiotics, the pleuromutilins, for a TB indication. Pleuromutilins inhibit bacterial protein synthesis. Compounds in the class have already been shown *in vitro* to inhibit the growth of *M.tb.* Derived from natural products and possessing a unique mechanism of action, the pleuromutilins do not have cross-resistance with other antibiotics and produce resistance very slowly.

The program objective is to identify a pleuromutilin derivative active against *M.tb,* including MDR strains, which allows for the reduction of the duration of treatment. Some 600 pleuromutilin derivatives in the GSK collection have been tested *in vitro* against various strains of *M.tb* and leads have already emerged with anti-tuberculosis activity.

2.

ICL

An important target, Isocitrate Lyase (ICL) is essential for the survival of *M.tb* in its persistent state. In its persistent state, *M.tb* requires prolonged treatment with multiple drugs, which in turn prompts the development of drug resistance. Drugs that inhibit ICL will be effective against persistent infection and, thus, reduce the need for prolonged therapy and help prevent drug resistance.

This program will identify an ICL inhibitor active against the persisting *M.tb* bacilli. The resulting drug should be able to be given orally, have a low incidence of adverse effects and be effective against existing resistant strains. Some 900,000 compounds have been screened for their ability to inhibit ICL and another 400,000 compounds will be screened shortly.

3.

InhA

Another project in the identification stage is based on InhA, an enoyl-ACP reductase enzyme involved in the synthesis of fatty acids in *M.tb*. Strong evidence suggests that InhA is the primary target of isoniazid, which is one of the two more potent drugs in the existing standard therapy for TB. Compounds that inhibit InhA by a different mechanism may be effective against strains of the bacilli resistant to isoniazid. Given as part of an intensive therapy regimen in the early phase of the infection, such a drug could help reduce the transmission of TB and contribute to shortening therapy in an appropriate combination.

This program will identify a lead compound that inhibits InhA and kills MDR strains. Once this is achieved, the compound will be optimized and further developed to identify a candidate for clinical development.

4.

FOCUSED SCREENING

This project screens GSK's extensive antimicrobial library for novel compounds that have the ability to kill *M.tb*. The testing will select compounds that are active against specific molecular targets, including inhibitors of DNA gyrase, peptide deformylase (PDF) and analogs of quinolone electron transport inhibitors.

The DNA gyrase inhibitor program uses the same target as fluoroquinolones and has identified a number of compounds that are active against whole-cell *M.tb*.

PDF is an enzyme essential for bacterial growth but not required by human cells, making it a selective and promising target for the development of new antibacterial agents.

Electron transport, a process essential for maintaining the cellular membrane, is a good target for TB drugs because it governs even dormant bacteria.

Macrolides Structure

MACROLIDES

Optimizing an excellent antibiotic for TB

WHO	WHAT
Institute for Tuberculosis Research, University of Illinois-Chicago	Optimization of 3rd generation macrolides for TB

One of the most widely prescribed antibiotic classes, macrolides are safe, well tolerated and affordable—making them a desirable front-line drug for TB care. By inhibiting bacterial ribosomes, the macrolides have proven efficacy against the TB bacterium.

Macrolides accumulate in lung tissues and concentrate in macrophages, the locus of active TB disease in humans.

With funding from the TB Alliance, researchers at the University of Illinois-Chicago began investigating the potential of macrolides as a new TB drug class in June 2004 and have made significant progress. More than 160 derivatives have been synthesized and three series were identified as having potent *in vitro* anti-tuberculosis potency superior to the benchmark macrolide, clarithromycin. The 9-oxime series was further identified as a promising lead series, exhibiting potent anaerobic activity and shown to be safe in use with ARVs because they reduced P-450 enzyme inhibitions.

While continuing to optimize the *in vitro* activity of the three promising series, the project plans to quickly move 20 of the most promising compounds into *in vivo* tolerability and efficacy studies. A final clinical candidate will be selected in the 2nd quarter 2007.

"Macrolides have a long history of effectively treating respiratory infections. If we identify a compound that kills non-replicating bacteria, that could drastically cut treatment duration—the holy grail of TB drug research."

Scott Franzblau, Ph.D
Institute for Tuberculosis Research
University of Illinois-Chicago

Quinolones Structure

QUINOLONES

Identifying the next generation drug for TB

WHO	WHAT
Korean Research Institute of Chemical Technology; Yonsei University	Optimization of quinolones and identification of a new sub-class

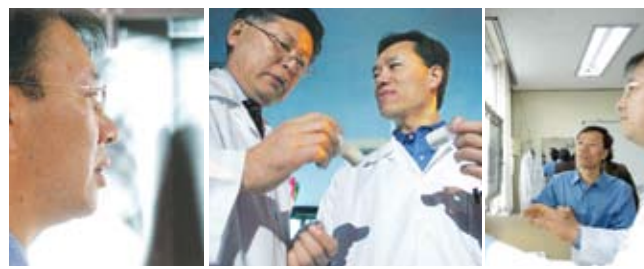
For over a decade, antibiotics in the quinolone class have been explored as a potential new breakthrough drug for TB. This class holds some of the greatest potential for shortening treatment duration, overcoming MDR-TB and improving therapy of TB-HIV co-infections.

Working with TB Alliance support and guidance, Korean researchers have identified a particularly promising sub-class after an intense compound synthesis ramp-up phase. The program, now under an accelerated time-frame, was given an additional boost in 2005 when the TB Alliance approached Abbott and was granted rights to develop a class of quinolones that falls under certain Abbott patents. This will allow the Alliance and its research partners the scientific freedom to fully explore and advance the discovery program and ensure that any resulting drug would be priced affordably in developing countries for a TB indication.

After synthesizing over 450 quinolones, researchers determined that a novel sub-class called the 2-pyridones has the most potent activity against *M.tb* in both its growing and persistent states. Researchers are now focusing on modifying a key position in the molecule that governs antimicrobial potency, pharmacokinetics and safety profiles.

The lead compounds are highly active against mycobacteria with potent efficacy in mice. They exhibit better activity than moxifloxacin and gatifloxacin, two lead quinolones in clinical development for TB.

The project, now in the lead optimization stage, aims to select a final candidate by the end of 2006.



Zhenkun Ma, Ph.D., Head of Research consults with Korean researchers

We are making it happen.

Dr. Maria C. Freire
President and CEO

Dr. Gijs Elzinga
Chairman of the Board

Dear Friends, Donors and Stakeholders,

As you have seen, this year's annual report did more than outline our achievements from the last year. We have introduced a groundbreaking new concept which is designed to deliver new, better medicines faster so we can start saving lives as quickly as possible. The epidemic demands no less and science has given us an opportunity to do this.

Over the last five years, the TB Alliance has built the largest portfolio of potential TB drugs in the world. We are particularly proud that this year, two drugs entered clinical trials. One of those, PA-824 was the first drug in the TB Alliance pipeline. The other, an approved antibiotic, moxifloxacin, provides the opportunity to deliver an improved therapy to patients by the end of this decade.

Few could have imagined this when the TB Alliance received its mandate to reinvigorate a virtually non-existent pipeline in 2000. The trials with moxifloxacin are historic and noteworthy because there is a realistic expectation that a moxifloxacin-containing regimen may be the first to dramatically shorten active TB treatment since the 1960s. If successful, this shorter regimen could be

Timeline of Milestones in the Development of New TB Tools

2000 →
Amsterdam Ministerial Conference on TB & Sustainable Development

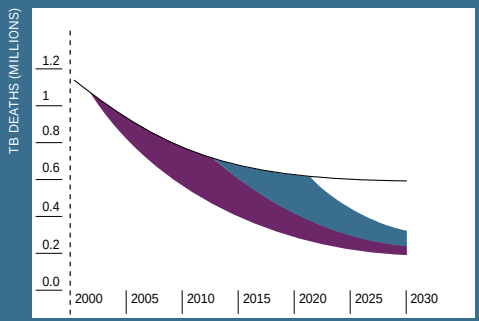
2000 →→
Stop TB Partnership created, TB Alliance launched

registered as early as 2010. Moreover, Bayer Healthcare AG has made an unprecedented commitment to provide the antibiotic at an affordable price for patients with TB in the developing world. Clinical experts will conduct the trials in eight countries, on four continents. This unique partnership also leaves an important legacy—enhancing clinical trial capacity for future TB drugs now moving through the pipeline.

Particularly satisfying this year has been shepherding the first drug of the TB Alliance pipeline, PA-824, from a "drug on a shelf" to a "drug in humans." Leveraging the in-kind support of NIAID and mobilizing 26 contractors around the globe, the TB Alliance designed a smart, aggressive preclinical program that allowed the drug to pass its preclinical milestones in slightly over two years. Chiron Corporation's commitment to provide PA-824 royalty-free in endemic countries paved the way for us to demonstrate how a non-profit organization can capably develop a drug to the same standards as industry but with a public health bottom-line.

At the same time, we continue to devote significant resources to discovery programs that will eventually bear fruit so we can design new regimens composed of entirely new drugs. Four such projects are underway at GlaxoSmithKline's Tres Cantos facility.

Lives saved from a new regimen



This graph shows why it is critical to adopt new therapies early on by modeling the impact of delay. This shows the projected impact of new therapies in WHO's Southeast Asia region. The purple area represents the additional deaths that would have been averted if a two-month therapy had been available as early as 2002, compared to availability in 2012. The blue area shows the additional deaths that can be averted if the new regimen becomes available in 2012 rather than waiting to introduce it in 2022.

Source: J. Salomon *et al*, "Prospects for advancing tuberculosis control efforts through novel therapies" (publication forthcoming).

2006 →

Introduction of the first improved and new TB diagnostics

2010 →

Introduction of first new TB drugs

2010 → →

Introduction of Point of Care TB diagnostic

→ 2012 → →

Introduction of diagnostic for latent TB for use in developing country settings

As page 17 illustrates, our discovery portfolio is diverse and designed to deliver the first regimen composed exclusively of novel drugs to radically change TB therapy as it is known today.

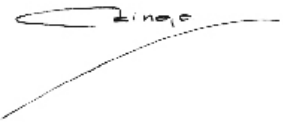
By taking advantage of the growing pipeline, we have a plan to advance new combinations of drugs, rather than evaluate single compounds sequentially (see pages 8–9). This new plan will decrease the time and resources needed to develop a new regimen. This contrasts with the conventional approach, which would likely take two to three decades to capitalize on the available compounds in development. The result will be a better cure that will shorten and simplify treatment of active TB to the greatest extent possible.

As we reach each of these scientific milestones, we are engaging the broad constituencies who are the key to the successful implementation of new therapies: governments, international health organizations, health care providers, patients and their advocates. Their input is key to our comprehensive "AAA" strategy so that together we can ensure these new therapies reach the patients who need them most (see pages 26–27). Today, policy-makers are exploring new financing and procurement mechanisms designed to help these new therapies reach patients quickly and effectively. With the guidance and support of this larger community, we are doing more than finding temporary fixes—we are developing a holistic treatment solution tailored to today's global health reality.

Together, we are moving closer to the world's goal of eliminating TB by 2050—a vision being realized through the combined efforts of groups within the Stop TB Partnership, which is outlined as a timeline below.

A remarkable transformation in the TB drug pipeline has occurred in a few short years. With the continued commitment of institutions across the globe, sustained cutting-edge research and expanding grassroots support, we are poised to deliver a steady pipeline of new antimicrobials that will help eradicate TB in the 21st century.

Dr. Maria C. Freire
President and Chief Executive Officer



Dr. Gijs Elzinga
Chairman of the Board

2013–2015
Introduction of new generation TB vaccines

2015
Introduction of first entirely novel drug regimen for TB

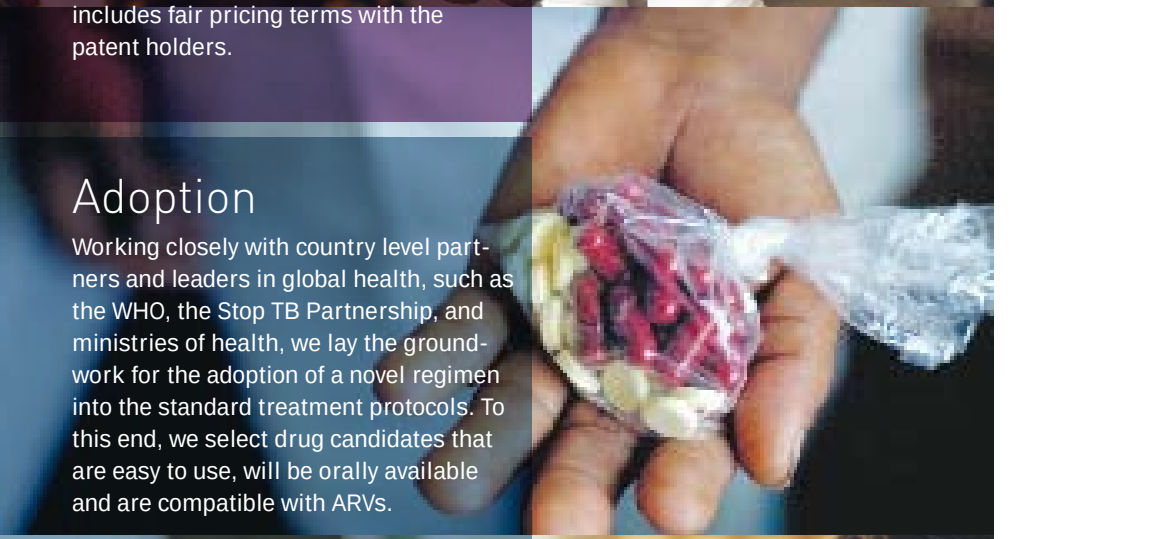
2018
Introduction of a new drug therapy for latent TB

2018
Introduction of new vaccine to prevent reactivation disease

2050
Elimination of TB as a public health threat

Affordability

Every project undertaken by the TB Alliance is committed to making resulting drugs affordable to patients in developing countries. In addition to selecting drug candidates with low costs of goods, every contract includes fair pricing terms with the patent holders.



Adoption

Working closely with country level partners and leaders in global health, such as the WHO, the Stop TB Partnership, and ministries of health, we lay the groundwork for the adoption of a novel regimen into the standard treatment protocols. To this end, we select drug candidates that are easy to use, will be orally available and are compatible with ARVs.

Access

We are committed to leveraging current and prospective funding and procurement mechanisms to ensure that TB patients receive new therapies. We are working with organizations such as the Global Fund for AIDS, Tuberculosis and Malaria, the Global TB Drug Facility, and with national TB programs, patient networks and other community-based organizations.

These companies support the TB Alliance so it can fulfill its "AAA" mission:

Abbott

Bayer

Chiron

GlaxoSmithKline

Novartis

At the TB Alliance, drug development does not stop at registration. The magnitude of this disease and our public health mandate requires us to ensure a better cure actually reaches patients.

Our mission includes an explicit commitment to Affordability, Adoption and Access—our "AAA" strategy. All our partners, including the companies listed on the left, support our commitment to ensure new medicines are priced affordably in developing countries. Drugs must also be easy to take, adopted into the standard of care and used by practitioners everywhere. Innovative distribution and financing mechanisms will ensure these medicines are delivered to healthcare providers and leverage the procurement channels in developing countries.

It is not enough to make a drug.
We must deliver the solution.

Financials

Independent Auditors' Report

Board of Directors of The Global Alliance for TB Drug Development, Inc.

We have audited the accompanying statement of financial position of The Global Alliance for TB Drug Development, Inc. ("TB Alliance") as of December 31, 2004, and the related statements of activities, functional expenses and cash flows for the year then ended. These financial statements are the responsibility of TB Alliance's management. Our responsibility is to express an opinion on these financial statements based on our audit.

We conducted our audit in accordance with auditing standards generally accepted in the United States of America. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. An audit includes consideration of internal control over financial reporting as a basis for designing audit procedures that are appropriate in the circumstances, but not for the purpose of expressing an opinion on the effectiveness of the TB Alliance's internal control over financial reporting. Accordingly, we express no such opinion. An audit also includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements, assessing the accounting principles used and significant estimates made by management, as well as evaluating the overall financial statement presentation. We believe that our audit provides a reasonable basis for our opinion.

In our opinion, the financial statements referred to above present fairly, in all material respects, the financial position of The Global Alliance for TB Drug Development, Inc. as of December 31, 2004, and the changes in its net assets and its cash flows for the year then ended, in conformity with accounting principles generally accepted in the United States of America.

Information for the year ended December 31, 2003 is presented for comparative purposes only and was extracted from the financial statements of The Global Alliance for TB Drug Development, Inc. for that year, on which we expressed an unqualified opinion, dated April 7, 2004.

BDO Seidman, LLP

April 28, 2005

Statement of Financial Position

(with comparative totals for 2003)

YEAR ENDED DECEMBER 31,	**2004**	2003
Assets		
Cash and cash equivalents (Note 2)	**$ 12,091,368**	$ 21,004,225
Cash – restricted (Notes 2 and 5)	**136,225**	125,087
Investments at fair value (Note 3)	**7,775,000**	—
Other assets	**245,969**	228,404
Property and equipment, net (Notes 2 and 5)	**320,534**	136,989
	$ 20,569,096	$ 21,494,705
Liabilities and net assets		
Liabilities:		
Accounts payable and other liabilities	**$ 482,530**	$ 632,607
Accrued payroll and payroll related liabilities	**94,976**	91,959
Capital lease obligation (Note 7)	**39,659**	65,089
Deferred revenue (Note 6)	**2,490,632**	—
Deferred rent	**109,156**	—
Total liabilities	**3,216,953**	789,655
Commitments (Note 8)		
Net assets:		
Unrestricted net assets (Note 2)	**17,352,143**	20,705,050
	$ 20,569,096	$ 21,494,705

See accompanying notes to financial statements.

Statement of Activities

(with comparative totals for 2003)

YEAR ENDED DECEMBER 31,	UNRESTRICTED	TEMPORARILY RESTRICTED	TOTAL **2004**	TOTAL 2003
Public support and other revenue:				
Contributions	$ 3,770,709	$ 20,000	**$ 3,790,709**	$ 4,741,143
Grants	69,741	—	**69,741**	—
Contributed services (Note 4)	674,829	—	**674,829**	487,628
Interest and dividend income	235,721	—	**235,721**	231,082
Miscellaneous income	571	—	**571**	3,182
Net assets released from restrictions	20,000	(20,000)	**—**	—
Total public support and other revenue	4,771,571	—	**4,771,571**	5,463,035
Expenses:				
Program services:				
Research and development	5,722,936	—	**5,722,936**	3,319,207
Business development	350,916	—	**350,916**	276,038
Public affairs and policy	1,189,295	—	**1,189,295**	888,055
Total program services	7,263,147	—	**7,263,147**	4,483,300
Supporting services:				
Management and general	905,344	—	**905,344**	1,055,814
Fundraising	124,070	—	**124,070**	119,136
Total supporting services	1,029,414	—	**1,029,414**	1,174,950
Total expenses	8,292,561	—	**8,292,561**	5,658,250
Change in net assets before foreign translation gain	(3,520,990)	—	**(3,520,990)**	(195,215)
Foreign translation gain (Note 2)	168,083	—	**168,083**	236,831
Change in net assets	(3,352,907)	—	**(3,352,907)**	41,616
Net assets, beginning of year	20,705,050	—	**20,705,050**	20,663,434
Net assets, end of year	$ 17,352,143	$ —	**$ 17,352,143**	$ 20,705,050

See accompanying notes to financial statements.

Statement of Cash Flows

(with comparative totals for 2003)

YEAR ENDED DECEMBER 31,	**2004**	2003
Cash flows from operating activities:		
Change in net assets	**$ (3,352,907)**	$ 41,616
Adjustments to reconcile change in net assets to net cash used in operating activities:		
Depreciation and amortization	**82,575**	59,294
Loss on disposition of fixed assets	**2,248**	—
Increase in assets:		
Restricted cash	**(11,138)**	—
Security deposits and other receivables	**(17,565)**	(62,970)
Increase (decrease) in liabilities:		
Accounts payable and other liabilities	**(150,077)**	421,653
Accrued payroll and related liabilities	**3,017**	61,991
Deferred revenue	**2,490,632**	(1,800,000)
Deferred rent	**109,156**	—
Net cash used in operating activities	**(844,059)**	(1,278,416)
Cash flows from investing activities:		
Purchase of investments	**(10,800,000)**	—
Proceeds from sale of investments	**3,025,000**	—
Additions to property and equipment	**(268,368)**	(61,325)
Net cash used in investing activities	**(8,043,368)**	(61,325)
Cash flows from financing activities:		
Repayments of capital lease obligation	**(25,430)**	(23,492)
Net decrease in cash and cash equivalents	**(8,912,857)**	(1,363,233)
Cash and cash equivalents, beginning of year	**21,004,225**	22,367,458
Cash and cash equivalents, end of year	**$ 12,091,368**	$ 21,004,225
Supplemental disclosure of cash flow information:		
Cash paid for interest	**$ 4,265**	$ 6,203

See accompanying notes to financial statements.

Notes to Financial Statements

1. Organization

The Global Alliance for TB Drug Development, Inc. ("TB Alliance") is a nonprofit organization incorporated on July 24, 2000 under the General Corporation Law of Delaware and authorized to conduct business in New York under the Not-for-Profit Corporation Law of New York. It operates as a not-for-profit, with offices in Brussels, Cape Town and New York.

The TB Alliance was formed to accelerate the development of effective new medicines to treat tuberculosis and ensure their affordability and availability in high-endemic countries.

Advocating for a worldwide mobilization against the TB epidemic through innovative research into new therapeutics, the TB Alliance develops innovative partnerships and involves scientists and researchers globally. It builds a portfolio of promising drug candidates and outsources research and development projects to public and private labs to develop affordable new drugs that will shorten the treatment of tuberculosis, be effective against multi-drug resistant strains and improve treatment of latent infection.

2. Summary of Significant Accounting Policies

(a) Basis of Presentation

The financial statements have been prepared on the accrual basis.

(b) Financial Statement Presentation

The classification of a not-for-profit organization's net assets and its support, revenue and expenses is based on the existence or absence of donor-imposed restrictions. It requires that the amounts for each of three classes of net assets, permanently restricted, temporarily restricted, and unrestricted, be displayed in a statement of financial position and that the amounts of change in each of those classes of net assets be displayed in a statement of activities.

Income from investment gains and losses, including unrealized gains and losses, dividends, interest and other investments should be reported as increases (or decreases) in unrestricted net assets unless the use of the income received is limited by donor-imposed restrictions.

These classes are defined as follows:

(i) Permanently Restricted — Net assets resulting from contributions and other inflows of assets whose use by TB Alliance is limited by donor-imposed stipulations that neither expire by passage of time nor can be fulfilled or otherwise removed by actions of TB Alliance.

(ii) Temporarily Restricted — Net assets resulting from contributions and other inflows of assets whose use by TB Alliance is limited by donor-imposed stipulations that either expire by passage of time or can be fulfilled and removed by actions of TB Alliance pursuant to those stipulations. When such stipulations end or are fulfilled, such temporarily restricted net assets are reclassified to unrestricted net assets and reported in the statement of activities.

(iii) Unrestricted — The part of net assets that is neither permanently nor temporarily restricted by donor-imposed stipulations.

(c) Cash and Cash Equivalents

TB Alliance considers short-term investments with original maturities of three months or less to be cash equivalents.

(d) Restricted Cash

Restricted cash consists of cash held by banks providing collateral for TB Alliance's leased equipment.

(e) Investments

Investments are valued at fair value in the statement of financial position. Unrealized gains and losses are included in the statement of activities.

(f) Depreciation and Amortization

The cost of property and equipment is depreciated over the estimated useful lives of the assets using the straight-line method. Leasehold improvements are amortized over the lesser of the life of the lease or asset. The estimated useful lives of the assets are as follows:

Computer equipment	3 – 5 years
Furniture and equipment	3 – 5 years
Leasehold improvements	5 – 10 years

(g) Income Taxes

TB Alliance is exempt from Federal and state income taxes under Section 501(c)(3) of the Internal Revenue Code (the "Code") and therefore has made no provision for income taxes in the accompanying financial statements. The Internal Revenue Service (the "IRS") has made a determination that TB Alliance can be treated as a publicly supported organization described in Code Sections 509(a)(1) and 170(b)(1)(a)(vi) during an advance ruling period beginning on July 24, 2000 and ending December 31, 2004. After the advance ruling period expired, TB Alliance filed for a final determination of its public charity status and is awaiting a ruling by the IRS. There was no unrelated business income for 2004.

(h) Contributions and Promises to Give

Contributions and promises to give are recorded as revenue when either unsolicited cash is received or when donors make a promise to give. Contributions and promises to give are classified as either unrestricted, temporarily restricted, or permanently restricted support.

(i) Contributed Goods and Services

Contributed goods and services are recognized as revenue and expenses if such goods and services meet the criteria for recognition as stated in Statement of Financial Accounting Standards ("SFAS") No. 116, "Accounting for Contributions Received or Contributions Made."

(j) Program Services

(i) Research and Development — TB Alliance creates and manages a portfolio of new anti-TB drug candidates by identifying, evaluating and acquiring promising molecules from scientific laboratories worldwide and outsourcing their development to appropriate public and private partners. Further, TB Alliance invests in infrastructure research projects that accelerate anti-TB drug development and analyzes existing scientific gaps to address these as part of the overall development strategy.

(ii) Business Development — TB Alliance negotiates, implements and manages agreements with public and private organizations worldwide and does so by adhering to sound business practices while ensuring the public good. Specifically, TB Alliance negotiates terms that support the development and access of new affordable anti-TB drugs equitably to those areas most in need while encouraging the private sector to help develop new medicines for TB indications.

(iii) Public Affairs and Policy — TB Alliance manages critical alliances with public and private organizations to raise awareness about tuberculosis ("TB") and advocate for public and private involvement in research for new anti-TB medicines. It develops landmark studies to support policy developments seeking to accelerate anti-TB drug research and mobilizes networks of researchers and investigators worldwide to focus on the development of these medicines.

(k) Use of Estimates

In preparing financial statements in conformity with generally accepted accounting principles, management is required to make estimates and assumptions that affect the reported amounts of assets and liabilities and the disclosures of contingent assets and liabilities at the date of the financial statements and revenues and expenses during the reported period. Actual results could differ from those estimates.

(l) Comparative Financial Information

The financial statements include certain prior year summarized comparative information. With respect to the statement of activities, the prior year information is presented in total, not by net asset class. With respect to the statement of functional expenses, the prior year expenses are presented by expense classification in total rather than functional category. Such information does not include sufficient detail to constitute a presentation in conformity with accounting principles generally accepted in the United States of America. Accordingly,

such information should be read in conjunction with the TB Alliance's financial statements for the year ended December 31, 2003, from which the summarized information was derived.

(m) Concentration of Credit Risk

Financial instruments which potentially subject TB Alliance to concentration of credit risk consist primarily of temporary cash investments. At various times during the year, TB Alliance had cash deposits at financial institutions which exceeded the FDIC insurance limit.

(n) Foreign Currency Translation

All elements of the financial statements reflecting TB Alliance's operations in Brussels are translated into U.S. dollars using applicable exchange rates. For assets and liabilities, this is the rate in effect at the statement of financial position date, with the exception of property and equipment which is measured at the historical rate. For revenue and expense items, translation is performed monthly using the average rate for the month. The exchange rate as of December 31, 2004 was 1.3644 EUR/USD.

Foreign currency is translated in accordance with the provisions of SFAS No. 52, "Foreign Currency Translation". Under the provisions of SFAS No. 52, the local currency used in TB Alliance's foreign operations is considered to be the functional currency of these operations. Translation of the financial statements of these operations resulted in a translation gain as follows:

DECEMBER 31, 2004	
Cumulative translation gain adjustment, beginning of period	$ 295,837
Translation adjustment	165,835
Cumulative translation gain adjustment, end of period	$ 461,672

The cumulative translation gain is included in unrestricted net assets.

(o) Reclassifications

Certain prior year balances have been reclassified to conform with the current year's presentation.

3. Investments at Fair Value

TB Alliance's cost and fair value of investments are summarized as follows:

DECEMBER 31, 2004	FAIR VALUE	COST
Marketable debt securities	$ 7,775,000	$ 7,775,000

In addition to the above investments, the portfolio included $6,048,279 of cash and cash equivalents at December 31, 2004.

4. Contributed Services

Included in TB Alliance's statement of activities is approximately $675,000 and $490,000 for the years ended December 31, 2004 and 2003, respectively, of in-kind contributions which were related to project management costs.

5. Property and Equipment, Net

Property and equipment, net, stated at cost, consists of the following:

DECEMBER 31, 2004	
Computer equipment	$ 198,888
Furniture and equipment	196,993
Leasehold improvements	130,855
Total property and equipment	526,736
Less: Accumulated depreciation and amortization	(206,202)
Property and equipment, net	$ 320,534

6. Deferred Revenue

In December of 2004, the Department of Development of the Netherlands Ministry of Foreign Affairs ("DDC") approved a seven-month research and development project grant to be used by June 30, 2005. The contract stipulates that any unused funds be returned to the DDC at the expiration of the grant term. As of December 31, 2004, TB Alliance received $2,751,869 and incurred $260,237 of expenses related to this grant. The remaining unspent funds of $2,490,632 are recorded as deferred revenue as of December 31, 2004.

7. Capital Lease Obligation

At December 31, 2004, capital lease obligation consisted of the following:

TB Alliance financed the cost of certain equipment with a lease obligation in various monthly installments of $2,475 until May 2006, including interest at 7.96%; secured by restricted cash accounts totaling $136,225	$	39,659
Less: Current maturities		27,529
	$	12,130

Future minimum lease payments due under these capital lease obligations at December 31, 2004 are as follows:

DECEMBER 31,		
2005	$	27,529
2006		12,130
	$	39,659

8. Commitments

TB Alliance has operating lease agreements for office space in New York, Brussels and Cape Town. TB Alliance moved its New York office in March 2004. The Brussels lease agreement expires in November 2009. The Cape Town lease expired in January 2004 and has not yet been renewed.

The following is a schedule of future minimum rental payments under the Brussels and New York operating leases as of December 31, 2004:

DECEMBER 31,		
2005	$	200,278
2006		236,279
2007		240,656
2008		245,121
2009		262,613
Thereafter		1,302,684
	$	2,487,631

TB Alliance has research and development agreements with several research institutions to fund various research and development contracts useful for treatment of TB. The agreements' expiration dates are undeterminable as of December 31, 2004.

The following is a schedule of future minimum research and development payments under the above agreements as of December 31, 2004:

DECEMBER 31,	
2005	$1,185,285
2006	653,026
2007	500,000
2008	500,000
2009	500,000
Thereafter	500,000 per year

9. Related Parties

A member of the Board of Directors of TB Alliance is an employee of the Rockefeller Foundation, a grantor of TB Alliance.

Another member of the Board of Directors of TB Alliance is affiliated with Chiron Corporation, a company from whom the TB Alliance has licensed rights to a family of compounds.

Acknowledgments

Stakeholders The following institutions formally pledged to accelerate the development of TB drugs. They advise, guide and support the efforts of the TB Alliance:

American Lung Association (ALA)

American Society for Tuberculosis Education and Research (ASTER)

American Thoracic Society (ATS)

Association of the British Pharmaceutical Industry (ABPI)

Bill and Melinda Gates Foundation

European Commission

Global Forum for Health Research

The Global Fund to Fight AIDS, Tuberculosis and Malaria

International Union Against Tuberculosis and Lung Disease (IUATLD)

JATA Research Institute of Tuberculosis

KNCV Tuberculosis Foundation

Lupin Laboratories

Médecins Sans Frontières/Doctors without Borders (MSF)

Medical Research Council of South Africa (MRC)

National Institute of Allergy and Infectious Diseases, National Institutes of Health (NIAID/NIH)

National Institute of Pharmaceutical Education and Research, India (NIPER)

New Jersey Medical School
National Tuberculosis Center

Novartis India, Ltd

Partners in Health (PIH)

Philippines Coalition Against Tuberculosis (PhilCAT)

RTI International

RESULTS

Rockefeller Foundation

Sequella

Stop TB Partnership

TB Alert

U.K. Department for International Development (DFID)

UNDP-World Bank-WHO Special Programme for Research and Training in Tropical Diseases (TDR)

U.S. Agency for International Development (USAID)

U.S. Centers for Disease Control and Prevention (CDC)

Wellcome Trust

World Bank

World Health Organization

Scientific Advisory Committee

The TB Alliance established a Scientific Advisory Committee to assist in evaluating proposals and projects under consideration for investment as part of its portfolio.

Clifton Barry, III, Ph.D.
National Institute of Allergy and Infectious Diseases, National Institutes of Health

Ken Duncan, Ph.D.
Imperial College, London

Bernard Fourie, Ph.D., *Secretary*
Medical Research Council of South Africa

Maria C. Freire, Ph.D.
Global Alliance for TB Drug Development

Jacques Grosset, M.D.
The Johns Hopkins University

Yoshiaki Kiso, Ph.D.
Kyoto Pharmaceutical University

Barbara Laughon, Ph.D., *Chair*
National Institute of Allergy and Infectious Diseases, National Institutes of Health

Christopher Lipinski, Ph.D.
Pfizer Inc., Retired

Denis Mitchison, M.D.
St. George's Hospital Medical School

Richard O'Brien, M.D.
Foundation for Innovative New Diagnostics

Ramesh Panchagnula, Ph.D.
School of Biomedical Sciences, University of Ulster

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Johnson & Johnson

Mel Spigelman, M.D.
Global Alliance for TB Drug Development

C. Kendall Stover, Ph.D.
Pfizer Inc.

Recognition of Support The TB Alliance gratefully acknowledges the generosity of the following institutions that provide key funding or in-kind support and expertise:

Bill and Melinda Gates Foundation
Rockefeller Foundation
Netherlands Ministry for Development Cooperation
GlaxoSmithKline
U.S. Agency for International Development
World Health Organization/Stop TB Partnership
U.S. National Institute of Allergy & Infectious Disease
U.S. Centers for Disease Control & Prevention
RTI International

Staff and Consultants

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President and Chief Executive Officer

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Director, Research and Development

Bradley Jensen
Director, Finance and Administration

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Heather Ignatius
Policy Officer

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Executive Assistant to President & CEO

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Head of Research

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Project Leader, Research

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Finance and Administration Specialist

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Portfolio Project Manager

Muntaha Sabah Lazim
Administrative Manager – Europe

Denielle Sachs
Senior Public Affairs Officer

Gerald J. Siuta, Ph.D.
Consultant, Business Development

Stephanie Seidel
Assistant, Public Affairs

Jennifer Walia
Assistant, Policy

Karen Wright
Senior Advisor

Board of Directors

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Chairman of the Board
Deputy Director-General,
Netherlands' National
Institute of Public Health
and the Environment

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Novartis International AG

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Eli Lilly and Company

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of Communicable Diseases,
The World Bank

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Chief Executive Officer,
ZymoGenetics

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(FIOCRUZ)

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Executive Director,
New Jersey Medical School
National Tuberculosis Center

Charles Yu, M.D., M.Sc.
President, TB Alliance
Stakeholders Association
Board Member, Philippines Coalition
Against Tuberculosis (PhilCAT)

In Memoriam

John R. La Montagne, Ph.D.
Deputy Director, National Institute of Allergy and Infectious Diseases (NIAID)
Secretary, TB Alliance Board of Directors
1943–2004

This year, the Board of Directors was saddened by the loss of one its members, Dr. John La Montagne. Dr. La Montagne was a dear friend and a tireless supporter of the TB Alliance and his gentle presence and fierce loyalty will be missed.

"Through his efforts to create and guide the Alliance, John inspired all of us and reaffirmed the moral imperative to overcome this ancient disease of poverty," said Dr. Maria C. Freire, President and CEO. "Our greatest tribute to him will be achieving our goal of a faster cure and knowing that his efforts will be felt wherever people suffer from TB."

The Global Alliance for TB Drug Development is a not-for-profit, tax-exempt organization recognized under section 501(c)(3) of the United States Revenue Code; and contributions are tax-deductible in the United States. Its Belgium branch office was also registered in the Annex of the Belgian State Gazette for non-profit organizations on February 28, 2002.

For inquiries, please contact the New York office: Global Alliance for TB Drug Development, 80 Broad Street, 31st Floor, New York, NY 10004

Principal photography: front cover, pages 4, 26 (bottom photograph), and back cover, John-Michael Maas; inside front cover, page 26 (top photograph), and inside back cover, WHO/STP Gary Hampton; page 2, WHO/STP Pierre Virot; pages 3 and 26 (middle photograph), WHO/STP Jad Davenport; pages 4–5, John-Michael Maas for Scojo Foundation; pages 6–7, Getty Images; pages 16–17, Juliana Thomas

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