The global TB pandemic has plagued humankind for millennia; its death toll and economic cost to countries, communities, and patients are incalculable. Despite increased global efforts to improve TB control measures, there are more than 9 million new TB cases each year—and still, the epidemic continues to worsen.

**Where’s the urgency? Where is the investment in global health?**

Today, there is more TB in the world than ever before, and resistance to the available drugs is growing. **Better, faster-acting, affordable treatments are urgently needed** to stem the tide of TB, including drug-resistant TB. Without increased efforts to support new weapons against tuberculosis, the world cannot defeat this disease.

With nearly 2 million people dying each year from TB, we need to ask:
WHAT IS THE WORLD’S THRESHOLD FOR A PANDEMIC OF DEADLY TB?
THE TB ALLIANCE IS CROSSING THRESHOLDS IN DEVELOPING THE BETTER, FASTER-ACTING, AND AFFORDABLE TB CURES NEEDED TO STOP THE PANDEMIC.

Armed with the world’s largest TB drug pipeline and an innovative approach to speed clinical trials, the TB Alliance has revolutionized TB research and development. Today, working with our partners, we stand at the threshold of revolutionizing TB treatment itself.
Globally, each year more women die from TB than all maternal conditions combined.

1/2 of MDR-TB cases occur in China and India.

More than 9 million new cases of TB emerge each year, resulting in nearly 2 million deaths.

TB IS THE #1 INFECTIOUS KILLER WORLDWIDE of people with HIV/AIDS.
VOICES OF TB

DR. SWEETNESS OUENDU
Clinical Investigator, TMC207

New, faster, and safer treatments are needed to scale up MDR-TB treatment and reduce its spread

Dr. Sweetness Ouendu is a clinical investigator on the TMC207 clinical trial, and based at Brooklyn Chest Hospital in Cape Town, South Africa. Her hospital is overrun with people suffering from MDR-TB and XDR-TB. Even with dedicated wards, the number of patients seeking treatment simply outstrips the hospital’s capacity to care for them—many are left on waiting lists, while others are treated on an outpatient basis, returning home after taking their complicated daily course of treatment to overcrowded dwellings where they can easily infect others. Saddened, Dr. Ouendu explains that MDR-TB perpetuates the poverty cycle, with patients infecting others in their family who can ill afford the costly treatment and the time out of work. Current MDR-TB treatment can take up to two years, and nearly half of people with the disease die. Dr. Ouendu says that research to develop promising novel TB drugs, like TMC207, are desperately needed to help countries like South Africa control the epidemic.

Clinic to Community: Empowering through Engagement

Within a community, says Taharqa Elnour, members should understand and participate in the TB research taking place. Working with TASK Applied Science in South Africa around the REMox TB clinical trial, Taharqa built towards that goal by catalyzing the development of a Community Advisory Board (CAB). “The CAB serves as a communication channel between the researchers and the community and works toward increasing awareness around TB,” he explains. The CAB has spread information about TB through World TB Day events and other workshops, resulting in a more educated and empowered community. Taharqa, and Community Engagement Officers at other REMox TB sites, help TB researchers and local communities both get the most out of their shared experiences.
Partners in the Fight
Dr. Dali Yin is a chemist working at the Institute of Materia Medica, in Beijing, China, where he is helping to develop a next-generation TB compound from the riminophenazine class. There is growing interest in this class of compounds, and its potential to yield components of tomorrow’s TB and MDR-TB treatments.

Riminophenazines have intrinsic activity against Mycobacterium tuberculosis, which causes TB, but the team is working to develop improved analogs with fewer side effects.

Dr. Yin recalls a friend contracting active TB more than 20 years ago. He visited his friend during his 3 months of confinement in a hospital and saw the severe impact of the disease firsthand. The hospital at which his friend was treated is the Beijing Thoracic Tumor and Tuberculosis Research Institute (BTTTRI), another partner in this development program.

Pediatric TB: Passing TB from Parent to Child
Children are a barometer of a community’s TB problems, says Dr. Anneke Hesseling, based at Stellenbosch University in Cape Town, South Africa. Researchers should not only study the disease in children, she said, but the disease in the context of children’s families and communities. That’s because the source of TB infection in children starts at home—with adults who pass on the disease.

Every 5 minutes, a child dies from TB. New TB drugs are instrumental in helping children receive appropriate and safe TB cures, and also to treat adults to stop the spread of the infection.

Using Fame to Further a Cause
TB is considered a disease of poverty, but it can infect anyone. Gerry Elsdon, a former model and celebrity TV show host, should know—she contracted the disease at the height of her career, just as she was trying to get pregnant and start a family.

At first, Gerry could not find out what was wrong. Finally, a physician identified that she had a TB infection in her womb, rendering her infertile. As she sought treatment, the magnitude of the epidemic began to sink in. Instead of hiding her disease, Gerry decided to go public, appearing in magazines and in interviews and talking about TB. This work has continued long after her cure. Gerry now spends much of her time advocating for TB sufferers, and has used her platform to raise awareness of the disease.
CHENNAI, INDIA / India accounts for more than 20% of all estimated MDR-TB cases worldwide.
The first novel TB drug regimen trial successfully validates the theory of regimen development—and reveals promising data on a novel combination.

The TB Alliance’s first novel drug regimen trial was a pioneering study that validated a new clinical development paradigm’s ability to speed development of improved novel treatment regimens. The NC001, or New Combination 1, trial was the first study to simultaneously test multiple novel TB drug candidates in a new development paradigm. In meeting its milestones, it shows the potential of a novel regimen to shorten, simplify, and transform treatment worldwide.

As the TB pandemic continues to spread and resistance to existing treatment grows, novel TB regimens are needed now more than ever. Novel regimens contain drugs for which there is little or no pre-existing resistance, therefore enabling the potential of these regimens to treat both drug-sensitive TB and MDR-TB in a single combination therapy. The novel three-drug regimen tested in NC001 could revolutionize TB treatment, particularly for drug-resistant disease, by reducing the duration of treatment from 2 years to 4 months—and costing a fraction of today’s therapies. This could shorten and simplify TB therapy around the world, facilitate the global scale-up of MDR-TB treatment, and provide ARV-compatible TB treatment for those coinfected with HIV/AIDS.

Novel regimen development represents a major focus of the TB Alliance’s R&D efforts and is positioned to emerge as the gold standard for all TB drug clinical development.

Today, more than a decade after the TB Alliance was established, there is a robust pipeline of promising TB drug candidates and an opportunity to test them in combination early in the development process to identify the most promising regimens for further development. But it takes more than promising science to speed new TB regimens to those in need; improvements in infrastructure, resources, and collaboration are necessary as well. It is on these fronts that the cross-sector initiative, the Critical Path to TB Drug Regimens (CPTR), has made much progress. Founded by the Bill & Melinda Gates Foundation, the TB Alliance, and the Critical Path Institute, CPTR is working to facilitate regimen development by bringing sponsors together to identify the most promising combinations and by identifying the regulatory pathways and other tools that accelerate the development process.

CPTR is also galvanizing the regulatory landscape. The US FDA issued draft guidance around combination drug development in December 2011. FDA’s Dr. Janet Woodcock also co-authored an opinion piece in the New England Journal of Medicine proposing “co-development” as a useful paradigm to find new tools for life-threatening diseases. Dr. Woodcock specifically recognized the TB Alliance as an organization that was well positioned to continue to evolve and advance this paradigm for TB.

“Drug developers must embrace a new paradigm that emphasizes sharing of information and collaboration in testing combinations...The TB Alliance and similar groups may be in a position to facilitate these kinds of studies.”

JANET WOODCOCK, M.D.
Director, Center for Drug Evaluation and Research, FDA
Active TB must be treated with combinations of drugs for maximum efficacy and to prevent resistance. Previously, promising new compounds were tested by substituting or adding treatments into the current therapy, one drug at a time. However, this approach meant that developing a novel 4-drug regimen could take more than a quarter of a century. Today, for the first time in decades, there is a robust pipeline, and an opportunity to test TB drugs together early in the development cycle to speed the development of novel cures. Using a regimen-based development approach could reduce the time to develop a novel TB regimen by 75 percent.

**TRADITIONAL TB DRUG DEVELOPMENT**

- New Drug 1
- New Drug 2
- New Drug 3
- New Drug 4

*6 YEARS* 12 YEARS 18 YEARS 24 YEARS

**INNOVATIVE CO-DEVELOPMENT PARADIGM**

- New Drug 1
- New Drug 2
- New Drug 3
- New Drug 4

Fully Novel Regimen

6 YEARS

*Years are approximations, and regimens may not always consist of 4 drugs

**THE PROMISE OF NOVEL TB DRUG REGIMENS**

Novel TB drug regimens could have a transformational effect on the TB treatment landscape, reducing the burden of TB cures for patients and providers alike, and restoring health and hope around the world. These new TB drug regimens show:

- Potential to treat TB and MDR-TB with a single combination treatment
- Potential to dramatically reduce the cost of MDR-TB treatment, facilitating global scale-up of treatment
- Potential to shorten and simplify treatment for both TB and MDR-TB
- Validation of a clinical paradigm that speeds new drugs to people who need them
NC001 validates a new clinical paradigm, and shows the promise of a novel TB drug regimen.

NC001 was a Phase II Early Bactericidal Activity (EBA) trial launched in November 2010 and funded by the Bill & Melinda Gates Foundation, UK’s Department for International Development, and the United States Agency for International Development. The six-arm, first-of-its-kind study tested the novel TB drug candidate PA-824, the antibiotic moxifloxacin, which is not yet approved for treatment of TB, and pyrazinamide, one of the four drugs in today’s standard first-line TB therapy. The three-drug regimen (PaMZ) performed extremely well as compared to the standard of care, showing the potential for a single regimen to treat both drug-sensitive TB and MDR-TB in four months. Furthermore, PaMZ has potential for use by TB/HIV coinfected patients, with no anticipated drug-drug interactions with antiretrovirals.

A TRIAL OF A NOVEL THREE-DRUG COMBINATION MEETS ITS MILESTONES

PaMZ

<table>
<thead>
<tr>
<th>PA-824</th>
<th>Moxifloxacin</th>
<th>Pyrazinamide</th>
</tr>
</thead>
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<tr>
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</table>

6 YEARS

MAJOR FINDINGS OF THE NC001 STUDY

SUITABILITY OF PaMZ AS A REGIMEN. NC001 tested the efficacy of a novel regimen (PaMZ) and found that it compared favorably to the standard of care in drug-sensitive TB (isoniazid, rifampin, pyrazinamide, and ethambutol). We are now preparing for an 8-week study, which will begin in early 2012 and will test the PaMZ regimen in both drug-sensitive and drug-resistant patients, setting the stage for pivotal registration trials.

“BUILDING BLOCKS” OF FUTURE REGIMENS. NC001 also tested promising two-drug combinations that can serve as the building blocks, or components of future regimens. Importantly, TMC207 and PA-824, each combined with pyrazinamide, were found to be much more efficacious than either drug alone.

NEW ENDPOINTS THAT ALLOW SCALABILITY. The study lent further support to the suitability of time to positivity (TPP) in addition to the more widely accepted Colony Forming Unit (CFU) as an appropriate endpoint in short-term studies. The ability to use TPP as an endpoint would eliminate the need for specialized, cost-intensive mycobacteriology laboratory capabilities, which severely restrict the sites available for the conduct of EBA trials.

THE MOUSE MODEL IS PREDICTIVE. The NC001 trial has provided the first positive, truly prospective testing of mouse model predictions in TB patients. Importantly, it confirmed the murine findings of the utility of the PaMZ regimen; the synergy from the combination of TMC07 and pyrazinamide; the additivity of PA-824 and pyrazinamide; and also the lack of additivity of TMC207 and PA-824.
**THE PROMISE OF OUR PIPELINE**

The TB Alliance advanced on all fronts throughout 2011 in the pursuit of its mission to develop faster-acting, affordable drugs to fight TB. In addition to the NC001 trial, there were many notable successes this past year.

Along with its partners, the TB Alliance continued to enroll participants in its Phase III clinical trial, REMox TB, to test the ability of two moxifloxacin-containing regimens to reduce treatment time of drug-sensitive TB from 6 months to 4 months. In 2011, additional sites were opened in India, China, and Africa. In particular, additional sites that are part of the NIH’s AIDS Clinical Trial Group (ACTG) will participate in REMox TB with the goal of completing enrollment by the end of 2011. At many sites, there are active community engagement initiatives that empower community members with the knowledge to meaningfully participate in TB clinical trials.

Results from REMox TB, which requires 1-year follow-up post-treatment to ensure patients don’t relapse, are scheduled to be available by 2014.

Meanwhile, the TB Alliance’s preclinical and discovery portfolios continued to advance. The preclinical novel drug combination study, initiated four years ago in collaboration with Johns Hopkins University and the University of Illinois at Chicago, has identified multiple novel drug regimens that could potentially shorten therapy to 2 months or less based on mouse models. These promising regimens, containing both novel and existing drugs, are being evaluated systematically for their suitability for further development to treat both drug-sensitive and drug-resistant TB.

Two late-stage discovery programs, the nitroimidazoles and riminophenazines, have completed lead optimization and are entering final candidate selection. If the lead compounds meet drug candidate criteria, they will be advanced into development and add valuable new

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**DISCOVERY**

<table>
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<tr>
<th>TARGET- OR CELL-BASED SCREENING</th>
<th>LEAD IDENTIFICATION</th>
<th>LEAD OPTIMIZATION</th>
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<td>Mycobacterial Gyrasc Inhibitors GSK</td>
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<td>Diaryquinolines Tibotec/U. of Auckland</td>
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<td></td>
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**PRECLINICAL DEVELOPMENT**

- **Nitroimidazoles**
  - U. of Auckland/U. Ill Chicago

- **Preclinical TB Regimen Development**
  - JHU/U. Ill Chicago
agents to the TB compound pool from which future regimens will be identified. Projects within “mini-portfolios” in collaboration with GlaxoSmithKline, AstraZeneca, and Novartis continue to make progress and, importantly, leverage the resources of all partners involved. Several novel compound classes have demonstrated efficacy in in vivo mouse models and are positioned to enter into preclinical development in the coming year or two.

In addition, the TB Alliance, through active portfolio management, has terminated projects that no longer fit strategically within the larger global pipeline or failed to meet milestones. The following projects were discontinued during the past year: Protease inhibitors, Phenotypic Screening, Malate Synthase Inhibitors, InhA Inhibitors, and Menaquinone Biosynthesis Inhibitors.

**NEW PROMISE FROM A FAMILIAR CLASS**

Clofazamine is a drug from the riminophenazine class that was developed in the 1950s for use against leprosy, but which has also shown activity against *M. tb*. Unfortunately, riminophenazines cause a particularly problematic side effect—skin discoloration—that exacerbates the stigma associated with TB. But researchers are finding new promise in this old compound as a component of shorter, faster-acting novel regimens.

Since 2007, the TB Alliance has been working with the Institute of Materia Medica (IMM), the Chinese Academy of Medical Sciences, and the Beijing Thoracic Tumor and Tuberculosis Research Institute (BTTRI) to discover improved next-generation riminophenazines. IMM, in collaboration with the TB Alliance, has designed and synthesized close to 1,000 riminophenazine analogs, and identified a short list of anti-TB compounds that are potent, safe, and stable, and that demonstrate efficacy in murine models of acute infection. Our partners, supported by Chinese government grants, have worked with the Shanghai Institute of Materia Medica and the National Institute for the Control of Pharmaceutical and Biological Products, bringing in further resources to enable the conduct of pharmacokinetic and safety studies. Further excitement around this chemical class is based on its potency and synergy as identified through the preclinical drug combination studies. A lead candidate for preclinical development is expected in 2012. With continued success, a pivotal building block for future novel TB regimens could be on the horizon.

**OUR R&D PARTNERS**

- AstraZeneca (AZ)
- Bayer Healthcare AG (Bayer)
- Beijing Tuberculosis and Thoracic Tumor Research Institute (BTTRI)
- GlaxoSmithKline (GSK)
- Institute of Materia Medica (IMM)
- Institute of Microbiology, Chinese Academy of Sciences (IMCAS)
- Johns Hopkins University (JHU)
- Johnson & Johnson/Tibotec (Tibotec)
- New York Medical College (NYMC)
- Novartis Institute for Tropical Disease (NITD)
- Novartis Pharmaceutical (Novartis)
- University of Auckland (U. of Auckland)
- University of Illinois at Chicago (U. Ill Chicago)
- University of Pennsylvania School of Medicine (U. Penn)
- Yonsei University (Yonsei)
NEW PARTNERS IN THE FIGHT AGAINST TB

- The economic impact of TB on India reaches $24 billion per year.
- More than 400 people die from TB every day in China.
The TB Alliance is extending our reach across the globe through platforms and collaborations that enable us to cross new thresholds.

New mechanisms help ensure that the TB Alliance and other stakeholders can mount a long-term, sustainable fight for new tools and deliver the improved TB regimens the world so desperately needs, even in the face of financial, scientific, and other challenges.

**Coordinating Capabilities through CPTR**
The TB Alliance continues to play a lead role in charting the course of the Critical Path to TB Drug Regimens, a cross-sector initiative that aims to speed the introduction of shorter, safer, more effective new TB drug regimens. By expediting testing of promising TB drug candidates in combination and by identifying new regulatory pathways and other tools to accelerate the development process, CPTR aims to facilitate the delivery of dramatically improved treatment to TB patients worldwide.

Since its launch in March 2010, CPTR has grown in size and scope. Now that NC001 has proven the underlying premise of regimen development, CPTR plays an increasingly important role in bringing TB drug sponsors together to identify promising future regimens. Several sponsors have now signed on to share information that will facilitate identification of promising drug combinations and testing.

In 2010, TB was responsible for
MORE THAN 5 TIMES
as many deaths as all natural disasters combined

MORE PEOPLE IN SOUTH AFRICA DIE FROM TB EACH YEAR THAN GRADUATE COLLEGE

1/3
of the more than 42 million people living with HIV worldwide are infected with TB

In Afghanistan, a woman is
more likely to die of TB than as a result of violence

**The GHRC is expected to play a major role in TB drug development in China and abroad.** **2. SOUTH KOREA** / TB Alliance research conducted in partnership with collaborators around the world has produced the largest portfolio of new TB drug candidates in history.

**Critical Path to TB Drug Regimens**
The Critical Path to TB Drug Regimens is a cross-sector initiative that aims to speed the development and introduction of shorter, safer, more effective new TB drug therapies.

**CPTR-PARTICIPATING ORGANIZATIONS:**
- TB Alliance
- Bill & Melinda Gates Foundation
- Critical Path Institute
- Anacor
- AstraZeneca
- Bayer
- European & Developing Countries Clinical Trials Partnership
- GlaxoSmithKline
- Johnson & Johnson
- Novartis
- Otsuka
- Pfizer
- Sanofi-Aventis
- Sequella
- Treatment Action Group
- Vertex

**WATCH THE CPTR LAUNCH—ADDRESSED BY FDA COMMISSIONER DR. MARGARET HAMBURG**
[WWW.TBALLEIANCE.ORG/NEWSCENTER]
Advocacy surrounding the harmonization of diagnosis and treatment of TB and HIV/AIDS continued throughout 2011. But there are also opportunities to harmonize management of the co-epidemic further upstream—beginning with the clinical development of new tools. This year, the TB Alliance has partnered with the United States National Institute of Allergy and Infectious Diseases (NIAID) to use available clinical trial sites from NIAID’s AIDS Clinical Trial Group (ACTG) for use in TB drug development trials. The addition of these new sites to the REMox TB clinical trial network will help expand capacity as the REMox TB Phase III global clinical trial advances toward completion of enrollment.

**Funding, and a Future, for Regimen Development**

This past year, the donor community has offered TB Alliance its vote of confidence. The organization received a landmark donation from the Bill & Melinda Gates Foundation for a 5-year renewal grant totaling $165 million to support regimen development. In addition, the TB Alliance also gained a new donor, the United States Food and Drug Administration (FDA), which is a contributor and a partner in a consortium dedicated to discovering and developing biomarkers, which can, if successful, drastically accelerate the pace of TB drug development. In addition, the FDA is supporting programs to help further establish and improve the accuracy of preclinical models for predicting sterilizing activity and resistance suppression for novel drug combinations.

These commitments enable the TB Alliance to perform the work necessary to unleash the promise in our pipeline, but they are also an acknowledgement of the essential nature of our mission, an affirmation of our performance, and recognition of our scientific accomplishments and capabilities.

**REMox TB: A GLOBAL PHASE III TRIAL**

Additional sites have been launched to enable the REMox TB trial to complete enrollment by the end of 2011.

**NEW ACTG SITES AND COUNTRIES**

- Guatemala
- Lusaka
- Cape Town
- Stellenbosch
- Kericho
- Eldoret
- Nairobi
- Moshi
- M'Be
- Tembisa
- BRtS
- Johannesburg
- Durban
- Soweto
- India
- China
- Thailand
- Malaysia
CROSSING THE ULTIMATE THRESHOLD:
THE PATIENT’S DOOR

- A person dies from TB every 20 seconds.
- There are nearly 500,000 new MDR-TB patients each year.

CAPE TOWN, SOUTH AFRICA / WHO estimates that one million children suffer from TB each year.
The TB Alliance will not be satisfied until new treatments cross the ultimate threshold—and reach patients in need. That’s why we are planning today for product launch, to ensure the rapid uptake of new and improved TB treatment regimens tomorrow.

New TB drug regimens will only have their intended major public health impact when they reach the millions of patients in need. Our commitment to access is defined by our “AAA Mandate”—that is, that new and improved TB regimens will be available to, adopted by, and affordable for those who need them. It is through this work that we link clinical research to the realities experienced by patients, providers, and programs, thereby ensuring that our efforts, above all else, benefit people around the world suffering from TB.

As the date for the introduction of new TB drugs approaches, the TB Alliance continues to build on its foundational work in mapping the pathway from pipeline to patients. Over the past year, the TB Alliance has defined key dynamics of the global TB market, informed the field, brokered important collaborations, and advocated for mechanisms to support the introduction of new, improved TB treatment.

Collaborations as Cornerstone

As a Product Development Partnership, the TB Alliance operates based on a model of collaboration. This concept extends to the area of access, where meaningful global partnerships are needed to ensure that new TB treatments are available to, adopted by, and affordable for those who need them.

As the organization looks forward, expanding our partnerships is a critical step in preparing for the launch of TB drugs, starting with a moxifloxacin-based regimen. Over the past year, there have been many efforts to coordinate and leverage the full expertise of additional PDPs, which have relevant experience and also share similar challenges. In so doing, the groups are realizing efficiencies that can help advance global health.

The TB Alliance continues to lead the PDP Access Steering Committee, a group formed in 2008 to enhance the capabilities of PDPs in the area.

THE PRIVATE SECTOR—TOO MANY PATIENTS TO IGNORE

TB is widely considered a public health concern and its treatment a public sector responsibility, but the reality of public and private sector involvement was highlighted by TB Alliance and IMS Health research published in the PLoS ONE journal. This study found that in some countries, the volume of TB drugs sold in the private sector equals or exceeds the volume distributed in the public sector. Additionally, TB drug dosages sold in the private sector varied widely. The resulting irregular TB treatment practices could be driving treatment failures and contributing to the emergence of MDR-TB.

This research fundamentally shifts the global understanding of the TB market, showing the need for the private sector to become a partner in the provision of rational, appropriate TB treatment. It is the first detailed study of the private TB drug market across multiple high-burden countries. Sixty percent of the world’s TB burden is present in the 10 study countries.

Since publication, TB Alliance staff has been speaking with government officials and other key constituents about the importance of scaling up public-private mix programs for TB care and investing in quality improvements of private sector TB care.
NEW, MORE AFFORDABLE MDR-TB drug regimens will help enable scale up of treatment

The average TB patient loses nearly 1/3 of yearly household earnings. We manage a grant from the Netherlands Directorate-General for International Cooperation on behalf of the group, which has funded eight discussion papers on critical topics including pharmacovigilance, manufacturing and supply, economics and financing, and country decision-making, and also a summit on access with an eye toward improving the efficiency and cost-effectiveness of PDPs. The TB Alliance also participates in the PDP Regulatory Group, which identifies the information needed to make informed decisions that reduce delays in product introduction and the added costs often associated with the regulatory process.

Building on the 2010 Open Forum conference, we continue to collaborate, both formally and informally, with National TB Programs, WHO, and regulators. Over the past year, the TB Alliance has participated in reviews of National TB Programs in Indonesia and Nigeria. These visits provided opportunities to improve TB treatment today, and to gain an in-depth view of these TB programs and the challenges they face—information that can be fed back into the R&D process and the market access strategy to ensure that the most useful and promising TB treatments are developed and made available for tomorrow.

Getting the Word out: Past and Future Regimen Change
As part of our continuing commitment to inform the treatment landscape, this year the TB Alliance published two research studies in the International Journal of Tuberculosis and Lung Disease. The papers are based on a study by the TB Alliance and Management Sciences for Health in which country stakeholders in 21 TB high-burden countries were interviewed. The papers offer a wake-up call to the TB community on the need for planning and preparation to speed regimen change.

Preparing for Launch
Today, the TB Alliance is taking steps toward product introduction. This includes gathering patient perceptions of the moxifloxacin-based regimen and also patient expenditure data to understand the full cost of first-line treatment, not only to the health system but also to patients. Additionally, the TB Alliance has formed an Access Advisory Committee, which will help guide TB Alliance strategy while also championing the introduction of new regimens.

INFORMING THE TB TREATMENT LANDSCAPE

- 35% of all TB drug dosages sold in the private sector fall outside national and international treatment recommendations. There were 111 different first-line TB drug dosages and combinations detected in the private sector, compared with the 14 deemed necessary. The dissemination of non-standard treatment can contribute to escalating rates of MDR-TB.

- Several of the highest-burden countries had particularly large private markets. In India, Indonesia, Pakistan, and the Philippines, enough TB drugs are sold in the private sector to treat all, or nearly all, incident TB patients with a full TB drug regimen. This is without even considering the 60 to 80 percent of cases covered by the public sector.

- The private sector is distributing drugs to treat fewer than 10% of MDR-TB patients, indicating that the gap in access to MDR-TB treatment in the private sector mirrors that of the public sector in many countries.
DEAR DONORS, STAKEHOLDERS, PARTNERS AND PATIENTS,

As we look back on the significant accomplishments over this past year, it is clear that the TB Alliance—and the field of TB drug development—has crossed a threshold. Since 2000, the TB Alliance and our partners have been working to build history’s largest TB drug portfolio. But in 2011, with the successful completion of the landmark NC001, or New Combination 1, trial, we have entered a new era. NC001 validated an innovative clinical paradigm that builds on our previous advances by testing promising combinations of TB drugs together. In so doing, the approach can dramatically speed the development of novel TB drug regimens, fast tracking scientific breakthroughs that would have previously taken decades to achieve.

Novel TB drug regimens show promise to be shorter, simpler, and safer TB cures, and can transform the epidemic by treating TB and MDR-TB in a single combination pill. Today, regimen development represents the focus of the TB Alliance’s efforts and is an emerging gold standard for the field at large.
Nearly 2 million people die each year from TB. Although the new tools to turn the TB tide are on the brink of becoming a reality, the challenging funding environment demands that we mount more long-term sustainable approaches to support the development of new TB cures. Over the past year, the TB Alliance has forged several new partnerships that help us achieve that goal, and open new doors that multiply our impact around the world.

These collaborations include a new Product Development Partnership in China—the country’s first—and a collaboration with the National Institute of Allergy and Infectious Diseases’ AIDS Clinical Trial Group to provide clinical trial site capacity to help us complete the Phase III REMox TB trial. Additionally, the Critical Path to TB Drug Regimens initiative continues to gain momentum as several companies with clinical-stage TB drugs have agreed to share information about their drug candidates with one another, with the goal of assembling and developing the best possible TB regimens, regardless of sponsor.

Indeed, we have reached a new era in the search for TB cures, but the final threshold is still before us—getting new treatments into the hands of those who need them. To this end, we are working all over the world, connecting with National Treatment Program managers, the WHO, governments, regulators, and other key players to secure the necessary partnerships critical to ensuring that improved new TB treatments are adopted, available, and affordable to those who need them.

In the face of heightened global economic fears and an unrelenting TB pandemic, the TB Alliance remains focused and committed to our mission. We are grateful for the support and vision of our donors and partners, but still more is needed. We invite all those committed to global health, international development, and a healthy and TB-free world to join us in our quest to vanquish one of humanity’s most resilient pandemics—once and for all.

All the best,

Dr. Mel Spigelman
President and CEO, TB Alliance

Dr. Bruce Carter
Chairman of the Board, TB Alliance
FINANCIALS AND ACKNOWLEDGEMENTS

Statement of Financial Position

<table>
<thead>
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<td><strong>$57,660,049</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Liabilities and Net Assets:</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Liabilities:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Accounts payable and other liabilities</td>
<td>$10,678,121</td>
</tr>
<tr>
<td>Accrued payroll and payroll-related liabilities</td>
<td>1,015,892</td>
</tr>
<tr>
<td>Deferred revenue (Note 6)</td>
<td>14,600,176</td>
</tr>
<tr>
<td>Deferred rent</td>
<td>935,078</td>
</tr>
<tr>
<td>Total Liabilities</td>
<td><strong>$27,229,267</strong></td>
</tr>
</tbody>
</table>

| Commitments                  | $—      |

<table>
<thead>
<tr>
<th>Net assets:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Unrestricted net assets</td>
<td>$30,430,782</td>
</tr>
<tr>
<td></td>
<td><strong>$57,660,049</strong></td>
</tr>
</tbody>
</table>

Statement of Activities

<table>
<thead>
<tr>
<th>YEAR ENDED DECEMBER 31, 2010</th>
<th>PUBLIC SUPPORT AND OTHER REVENUE:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unrestricted</td>
</tr>
<tr>
<td></td>
<td>Contributions</td>
</tr>
<tr>
<td></td>
<td>Grants</td>
</tr>
<tr>
<td></td>
<td>Interest and dividend income</td>
</tr>
<tr>
<td></td>
<td>Net realized and unrealized gains on investments</td>
</tr>
<tr>
<td></td>
<td>Miscellaneous income</td>
</tr>
<tr>
<td></td>
<td>Total public support and other revenue</td>
</tr>
</tbody>
</table>

| Expenses:                     |         |

<table>
<thead>
<tr>
<th>Program services:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Research and development</td>
<td>$38,973,162</td>
</tr>
<tr>
<td>Business development</td>
<td>494,009</td>
</tr>
<tr>
<td>Public affairs and policy</td>
<td>2,660,120</td>
</tr>
<tr>
<td>Total program services</td>
<td><strong>$42,127,291</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Supporting services:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Management and general</td>
<td>$3,549,222</td>
</tr>
<tr>
<td>Fundraising</td>
<td>670,806</td>
</tr>
<tr>
<td>Total supporting services</td>
<td><strong>4,220,028</strong></td>
</tr>
</tbody>
</table>

| Total expenses               | 46,347,319 |

| Change in net assets before foreign translation gain | 245,113 |

| Foreign translation gain     | (377,985) |

| Change in net assets         | (132,872) |

| Net assets, beginning of year | $30,563,654 |

| Net assets, end of year      | **$30,430,782** |
Statement of Cash Flows

YEAR ENDED DECEMBER 31, 2010

CASH FLOWS FROM OPERATING ACTIVITIES:

<table>
<thead>
<tr>
<th>Description</th>
<th>Program Services</th>
<th>Supporting Services</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in net assets</td>
<td>$ (132,872)</td>
<td>$ 4,220,028</td>
</tr>
<tr>
<td>Adjustments to reconcile change in net assets to net cash provided by operating activities:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depreciation and amortization</td>
<td>430,256</td>
<td>—</td>
</tr>
<tr>
<td>Loss on disposal of fixed assets</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Realized gain on sales of investments at fair value, net</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Unrealized losses [gains] on investments at fair value</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>(Increase) decrease in assets:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assets limited to use</td>
<td>(2,819)</td>
<td>(2,020,439)</td>
</tr>
<tr>
<td>Accounts receivable</td>
<td>(2,020,439)</td>
<td>(2,819)</td>
</tr>
<tr>
<td>Pledges receivable</td>
<td>1,439,551</td>
<td>—</td>
</tr>
<tr>
<td>Other assets</td>
<td>42,916</td>
<td>—</td>
</tr>
<tr>
<td>Increase (decrease) in liabilities:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accounts payable and other liabilities</td>
<td>2,052,886</td>
<td>—</td>
</tr>
<tr>
<td>Accrued payroll and related liabilities</td>
<td>92,108</td>
<td>—</td>
</tr>
<tr>
<td>Deferred revenue</td>
<td>1,503,038</td>
<td>—</td>
</tr>
<tr>
<td>Deferred rent</td>
<td>(83,611)</td>
<td>—</td>
</tr>
<tr>
<td><strong>Net cash provided by operating activities</strong></td>
<td><strong>$ 3,321,014</strong></td>
<td></td>
</tr>
</tbody>
</table>

CASH FLOWS FROM INVESTING ACTIVITIES:

<table>
<thead>
<tr>
<th>Description</th>
<th>Program Services</th>
<th>Supporting Services</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purchase of investments</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Proceeds from sale of investments</td>
<td>3,000,000</td>
<td>—</td>
</tr>
<tr>
<td>Purchase of fixed assets</td>
<td>(23,947)</td>
<td>—</td>
</tr>
<tr>
<td><strong>Net cash used in investing activities</strong></td>
<td><strong>2,976,053</strong></td>
<td>—</td>
</tr>
</tbody>
</table>

Net increase in cash and cash equivalents $ 6,297,067
Cash and cash equivalents, beginning of year $ 45,021,624
Cash and cash equivalents, end of year $ 51,318,691

SUPPLEMENTAL DISCLOSURE OF CASH FLOW INFORMATION:

<table>
<thead>
<tr>
<th>Description</th>
<th>Program Services</th>
<th>Supporting Services</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cash paid for interest</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>
TB Alliance Stakeholders Association

American Lung Association
American Thoracic Society
Association of the British Pharmaceutical Industry
Bill & Melinda Gates Foundation
Community Representative, Francis George Apina
Eli Lilly and Company
European Commission
GBC Health
Global Fund to Fight AIDS, TB and Malaria
Global Health Advocates
Indian Council of Medical Research
Infectious Diseases Society of America
International Union Against Tuberculosis and Lung Disease
Irish Aid
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RESULTS
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Stop TB Partnership
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Treatment Action Group
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President, Pacers Sports and Entertainment

Mel Spigelman, M.D.
President & Chief Executive Officer, TB Alliance

Recognition of Support

Bill & Melinda Gates Foundation
European Commission
United Kingdom Department for International Development
United States Agency for International Development
United States Food and Drug Administration

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Skyelar Yaffie
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About the TB Alliance
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 Internal Revenue Code; 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: info@tballiance.org

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The TB Alliance wishes to thank its donors for their help in pursuit of our vision—a world without TB. Through this support, working with our partners worldwide, we can continue to cross scientific and other thresholds to ultimately transform our vision into reality.

The TB Alliance has also been able to deepen its impact and extract greater value from its funds due to the generous in-kind contributions from its partners. For instance, every dollar given to the TB Alliance produces roughly $2 worth of output. This leveraging of resources makes donors’ contributions go further and accomplish far greater impact than otherwise possible.

Thank you for your ongoing support of our mission to find better, faster-acting drugs to treat tuberculosis. With your help, we can transform lives.

More Support is Needed for a Better Cure

TB perpetuates the poverty cycle and is one of the world’s worst killers, yet it is among the most neglected and underfunded diseases in the world. The TB Alliance is working to stop this deadly pandemic and has created the largest pipeline of TB drugs in history. However, with this success comes the need for additional support to mount the late-stage clinical trials to bring promising new regimens through the final stages of development. New tools offer hope for transforming the epidemic—and for crossing the final threshold to create a world without TB.

Please support us in finding new and faster cures for TB.
The TB Alliance accelerates the discovery and development of faster-acting and affordable drugs to fight tuberculosis. Through innovative science and with partners around the globe, we aim to ensure equitable access to faster, better tuberculosis cures that will advance global health and prosperity.

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