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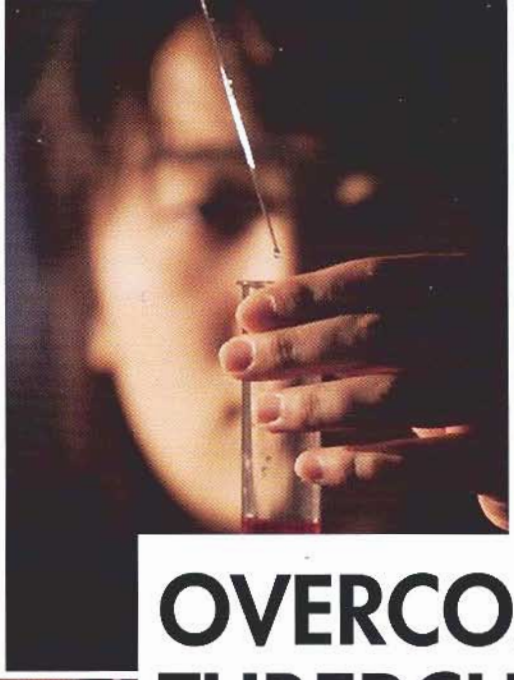

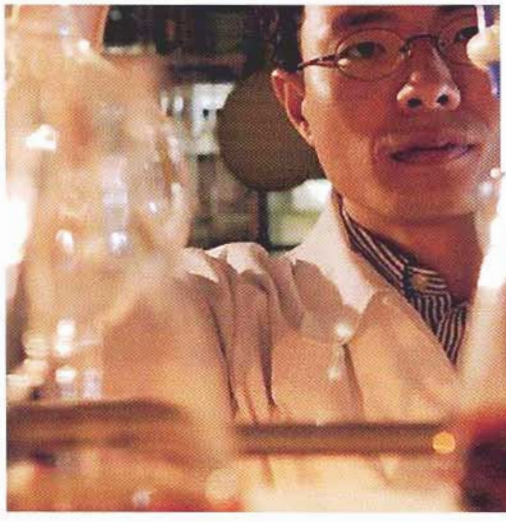




PHOTOS COURTESY OF THE GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

# OVERCOMING TUBERCULOSIS

## New Treatments on the Horizon

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Tuberculosis (TB) has targeted the world's vulnerable populations for centuries, striking people during their most productive years, undermining their health, economic well-being and the societies in which they live. In the industrialized world, TB is largely ignored, considered to be a disease of the past, even though it remains a global threat that kills nearly 2 million people a year, primarily in poorer nations. Fueling the international TB pandemic is the dramatic spread of HIV/AIDS in the last 25 years. Indeed, the TB-HIV co-epidemic is a startling wake-up call to any of us who may have thought that TB is no longer a major global health issue. Now, the increasing emergence of multi-drug resistant (MDR) TB in "hot spots" such as Eastern Europe, presents additional complex public health challenges. MDR-TB is also on the rise in the U.S., according to the U.S. Centers for Disease Control and Prevention; and even more ominous is the emergence of extensively drug-resistant TB (XDR-TB), which is untreatable with any existing antibiotics.

Global TB control efforts have continued to make important strides but have been hampered by the shortcomings of existing diagnostics, drugs and vaccines – the tools needed to fight TB. Today's cumbersome TB treatment regimens make compliance difficult, deprive patients of their livelihoods, burden health-care systems and drain economies. So the quest is to develop TB therapy that is as simple as those that cure common infections; time to cure TB needs to be measured in days, not in months and even years. In industrialized countries, medicines are constantly being improved, and the public expects nothing less. Unfortunately, the same standard does not always apply to diseases like TB that primarily affect the poor.

This is now changing. Thanks in large part to the attention and financial support of private foundations, there has been a resurgence in research and development, and TB is at the forefront of the fight against global diseases that must be conquered. The work now being done throughout the world to develop new TB drugs, vaccines and diagnostics is revolutionary and critical to the new Global Plan to Stop TB, which aims to eradicate TB by 2050.

The development and testing of powerful new antibiotics that shorten and simplify the current onerous therapy is making dramatic progress. When the TB Alliance began work five years ago, there were no novel TB drugs in development. Today, there is a vibrant new global drug pipeline, with six compounds in clinical development. As a public-private partnership focused on the development of new TB therapies, the Alliance has been an active participant in this revolution, collaborating, supporting and benefiting from the commitment of public and private organizations that share this goal. Because of these interactions and the activities of the multiple players, several drug candidates are in either in late discovery or preclinical

stages. If approved, this new generation of drugs will become the foundation for innovative shorter drug regimens. In the near term, these novel treatments will help reduce TB morbidity and mortality and, in the longer term, may help eliminate the disease altogether.

### The Need for New TB Therapies

Modernizing TB treatment will yield a number of public health and socio-economic benefits. Despite several recent important regional successes with Directly Observed Treatment Short-Course (DOTS), the current best method of delivering drugs and ensuring patient compliance, the trends in deaths and spread of the disease reflect the limitations of the drugs themselves. The emergence of multi-drug resistant and extensively resistant strains as well as the symbiotic interaction between TB and HIV/AIDS is increasing the incidence of TB worldwide. Shorter therapies designed to work more quickly and also be easily administered alongside antiretrovirals will help reverse current trends of this deadly co-infection. By speeding time to cure, novel therapies will increase compliance, treat and prevent drug resistance, and enable marked improvements in the care of TB-HIV co-infected individuals.

TB's financial consequences are dramatic. TB costs the world $16 billion annually – $4 billion for diagnosis and treatment and $12 billion from lost income. The need for extended, intensive monitoring of TB patients by health-care workers puts enormous strains on already overstretched health-care systems in the developing world. Research suggests that shorter therapies could reduce this burden by as much as 65 percent.

Drug Development Process

### A Revolutionary Concept for TB Drug Development

For reasons that are not yet fully understood, successfully treating and curing TB – even of standard, drug-susceptible disease – requires a complex treatment course. Four drugs must be taken in combination for the first two months followed by four months of treatment with two drugs. The conventional strategy to improve current therapy would substitute new drugs, one at a time, within the current combination. Using that approach, dramatic improvements in today's treatment would take several decades to complete for two reasons. First, clinical drug development in TB is a lengthier process than other infectious diseases; and second, each substitution must be fully tested before it can be approved for use. The good news is that the TB Alliance has conceived a strategy to streamline and shorten this process by developing several new drugs simultaneously and designing "smart" combinations of the best drugs now in the pipeline. In this fashion, we can envision replacing today's entire four-drug regimen with a new package of superior drugs in as a few as six to eight years.

This strategy calls for each potential drug in the pipeline to advance in the traditional way through Phase I, establishing its unique preclinical efficacy, safety and pharmacokinetic profile while simultaneously beginning preclinical evaluations of potential novel combinations. Successful new preclinical combinations will be designed that can then be brought into later stage clinical development. By examining individual drug profiles and looking for complementary targets, we can devise optimal combinations for ethical preclinical and clinical evaluation.

In this manner, we can design multiple, novel combinations that will first improve, then expand and ultimately transform TB control. The new combinations will remove some of the most pressing public health obstacles in TB treatment, such as multi-drug resistance and the difficulty of simultaneous TB-HIV therapy. They also will expand the scope of TB control by redefining public health targets. For example, it is expected that new therapies will enable treatment of a larger pool of TB patients before they become contagious. When combined with other new interventions in development, such as improved diagnostics, new drugs will have an even greater impact.

### 'AAA' – From Pipeline to Patient

No new therapy will be effective if it doesn't reach the people who need it – primarily those who can least afford to pay for live-saving medicines. The TB Alliance's response to this challenge is an explicit commitment to Affordability, Adoption and Access – its "AAA" strategy.

The Alliance engages the best minds and institutions to work on every aspect of R&D and to assure that the cost of the drugs developed are kept as low as possible. Toward this end, the TB Alliance optimizes TB drug development by partnering with pharma, academia and industry; in-licenses new technologies; and leverages intellectual property for negotiating rights, fields of use and royalties in a manner that assures access and affordability of treatments that are developed under the TB Alliance banner. In addition, the Alliance establishes innovative partnerships that share the potential returns as well as the risks of antimicrobial drug development to speed the advancement of potential TB drugs.

The successful introduction of new tools for TB depends on acceptance by broad constituencies, including governments, international health organizations, health-care providers, patients and their advocates. The TB Alliance works closely with these groups to secure their support for its work and to seek their assistance for new and harmonized regulatory guidelines to accelerate the approval of new TB therapies. In addition, the Alliance works to leverage the contributions that the growing production capacities of developing countries can make to help assure affordable pricing of new TB drugs.

To facilitate the prompt adoption of new drugs in national TB control programs, the TB Alliance is engaging patients, care providers and health networks in endemic countries and maintains close working relationships with the Stop TB Partnership and the World Health Organization. Vehicles such as Memoranda of Understanding encourage cooperation with endemic countries and the TB Alliance currently has agreements in place with Brazil, India, Peru, the Philippines and South Africa.

The impact of TB is clear. Without new medicines, TB's global threat will intensify, driven by its deadly synergy with HIV/AIDS, complicated by multi-drug and super-resistant strains, and amplified by the consequences of poverty. But there is good reason for hope. Thanks to the vision and support of donors such as the Bill & Melinda Gates and Rockefeller Foundations, the U.S. Agency for International Development and the British, Dutch and Irish governments, organizations like the TB Alliance are tapping and strategically advancing the scientific discoveries, capacity and know-how of their partners and helping to lower the hurdles for others to join this effort. To succeed, the TB community needs the commitment of public, private and governmental sources throughout the world. We are in this battle together – we must be in it to win.

*For more information on the Global Alliance for TB Drug Development, visit www.tballiance.org.*