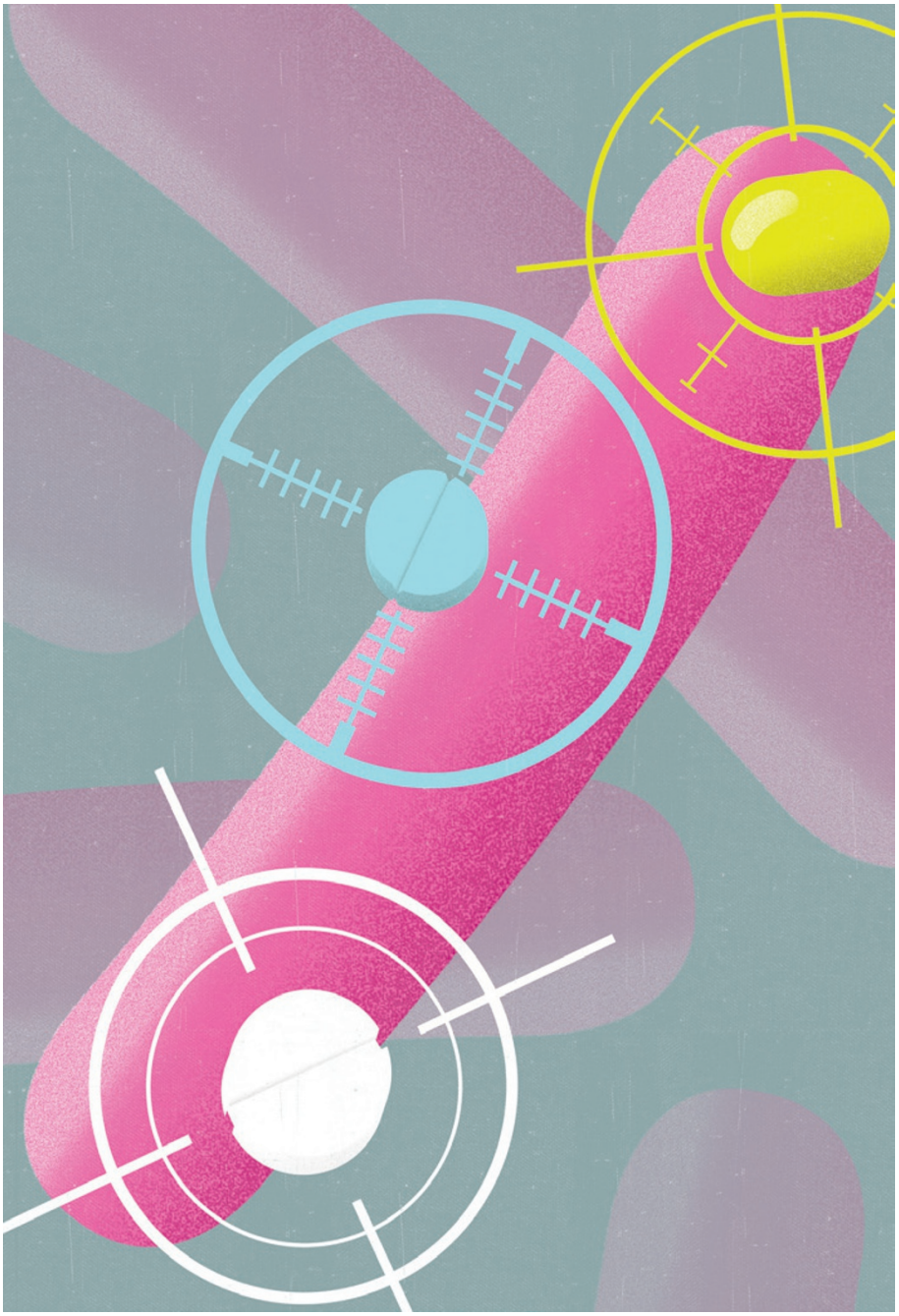


NEIL WEBB

DRUG DEVELOPMENT

A combined effort

Combinations of anti-TB drugs are difficult to overcome because they attack Mycobacterium tuberculosis *in different ways.*

BY AMY MAXMEN

The ringing in Dalene von Delft's ears had become unbearable. The inescapable noise was caused by the drug amikacin, which von Delft — a doctor at Vergelegen Mediclinic hospital in Cape Town, South Africa — was taking to treat her drug-resistant tuberculosis (TB). But von Delft's biggest fear was that the ringing would go silent; in certain studies, up to half of those injected daily with amikacin for the two-year regimen were found to go deaf[1]. She wanted to cure her disease, but losing her hearing seemed like too high a price. As a doctor, "you need to be able to use a stethoscope", she says. "It would have ended my career." But stopping treatment altogether would have been an even more dangerous option. Without proper treatment, up to two-thirds of people ill with TB will die[2].

von Delft learned of a new anti-TB drug that was performing well in clinical trials. Although its safety had not been established, she pleaded with the drug's maker, Janssen Pharmaceuticals, based in Titusville, New Jersey, and the South African Medicines Control Council, and managed to switch to the unapproved drug, called bedaquiline. And although it made her heart palpitate temporarily, the remote danger of a heart attack seemed more bearable than losing her hearing. "You weigh the risks against the benefits," she admits. After two years, the TB was gone and her hearing remained. "I was very lucky," she says.

A new drug for TB has been a long time coming. Bedaquiline, approved by the US Food and Drug Administration (FDA) at the close of 2012, is the first novel anti-TB drug since rifampicin was introduced nearly half a century ago. With TB killing approximately 1.4 million people each year, industry, academic institutions and public-health organizations are having to collaborate like never before to stem the rise of drug-resistant TB.

NOT GOING QUIETLY

Rates of TB in the United States and Europe began to decline at the turn of the twentieth century because of sanatoriums built to isolate TB patients, along with improvements in overcrowded tenements that slowed TB transmission. Then, from the 1940s to the 1960s came antibiotics — streptomycin, isoniazid, rifampicin and 4-aminosalicylic acid (PAS) — that could effectively treat the disease. The arrival of these drugs led many to believe that TB would soon disappear altogether. "We were convinced in the 60s that we would end TB," recalls Jacques Grosset, a professor at the Center for Tuberculosis Research at the Johns Hopkins School of Medicine in Baltimore, Maryland, who is himself a victim of TB (he had a portion of his lung removed during a bout with the disease in the 1950s).

But those expectations failed to materialize. Many patients, lacking careful supervision, would stop midway through the one- to two-year-long course of treatment. When this

happened, or when the drugs were given singly rather than in combination, naturally drug-resistant strains of the TB pathogen thrived and overtook the more sensitive population. People feel better after a few months and stop taking their pills, says Grosset. Once a patient acquired drug-resistant disease, they could spread their resistant pathogens directly to their neighbours.

Then came the HIV epidemic, which made people acutely vulnerable to TB. Developing countries, which had never managed to fully suppress the disease, experienced skyrocketing TB rates, and Western countries saw a resurgence. In 1993, the World Health Organization (WHO) in Geneva, Switzerland placed the disease back on the public-health agenda by declaring TB a global emergency. New drugs were needed with different mechanisms of action, which would suppress resistance and shorten treatment times. And yet pharmaceutical companies had little incentive to invest the massive amounts of money necessary for drug development — TB predominantly affects people from low-income countries, who cannot afford expensive treatments. Without a business case for TB drug development, progress stalled.

In the wake of the WHO declaration, the Bill & Melinda Gates Foundation, headquartered in Seattle, Washington, along with other non-governmental organizations and government agencies, including the National Institutes of Health in Bethesda, Maryland, got together to convince drug developers across the public and private sectors to work together. In response, the pharmaceutical giants GlaxoSmithKline (headquartered in Brentford, UK), Novartis (Basel, Switzerland), AstraZeneca (London) and Sanofi (Paris) agreed to collaborate with each other and with universities to pick up where TB drug developers had left off in the 1960s.

SHAKY START

Developing a new drug for TB is a complex process. It involves screening thousands of compounds to find any that might kill the bacterium, *Mycobacterium tuberculosis*; adapting these compounds into substances that work as a drug; testing for efficacy in animal models; and finally testing how effective and safe the drug is in human patients.

Various labs were able to identify compounds that inhibited metabolic pathways and other vital processes occurring within the bacterium; unfortunately, it became apparent that many compounds selected through these screens had trouble penetrating the membrane of whole mycobacteria and subsequently failed tests in mice. So researchers changed their screening protocols to look for the effects compounds had on whole mycobacteria — even so, it has not been smooth sailing.

In 2009, a team at the Novartis Institute for Tropical Diseases in Singapore landed on a new class of compound, pyrimidine–imidazoles, which killed *M. tuberculosis in vitro* but had no effect on infected mice. In 2010, the researchers figured out why: the drug only blocked the ability of the mycobacteria to survive in its glycerol suspension — leaving it with little relevance in the world beyond the test tube[3]. "That was not fun," recalls Thomas Dick, who led the project at Novartis, and now directs the Antibacterial Drug Discovery Laboratory at the National University of Singapore after Novartis dropped out of TB drug discovery. "It was the failure of a two-year project that took a lot of investment."

"My fear is that what is really needed is orders of magnitude more funding."

Despite such disappointments, candidates for new anti-TB drugs are continuously being identified. In May 2013, for example, researchers reported that high doses of vitamin C wipe out cultures of *M. tuberculosis* by triggering a DNA-damaging reaction[4].

TB survivor van Delft took a chance on a new drug.

In July, a team at the Institute Pasteur Korea in Seongnam-si discovered a compound labelled Q203 that cuts off the energy supply to mycobacteria by blocking ATP synthesis both in culture and in mice[5].

Indeed, in the past decade, six types of compound that target *M. tuberculosis* in new ways have progressed to trials in humans. However, these trials face their own set of problems. Foremost among them is phase 2a testing, which checks whether a drug decreases the mycobacterial load in patients' sputum within two weeks of starting treatment. Because some drugs act slowly, the short timeframe of this trial can be misleading. In fact, a number of people at Janssen wanted to shut down the bedaquiline programme after it performed poorly in a phase 2a trial, says Myriam Haxaire-Theeuwes, who is developing bedaquiline at Janssen's research and development branch in Beerse, Belgium. Spectacular results in cell culture and in mice convinced the team of bedaquiline's worth. "You need to have strong product champions," she says, "and senior management that will listen."

NATURE.COM
For a review of tuberculosis drug discovery, visit:
go.nature.com/ruw6so

Phase 2b trials are problematic for a different reason. For drug-resistant TB, such a trial needs to run for at least two years to determine whether the new treatment works: it can take that long to cure the disease. In the meantime, at least 310,000 patients with drug-resistant TB are taking potentially toxic medicines each year[2].

To address the urgent need for new treatments for TB, the FDA announced in 2009 that in some cases they would grant 'accelerated approval' for promising drugs. For example, treatment success could be measured by no detectable mycobacteria in a patient's sputum after six months of treatment, rather than ensuring that patients fully recover from drug-resistant TB at the end of a 2.5 year study.

It was under these new guidelines that bedaquiline was approved for multidrug-resistant TB in late 2012. Shorter clinical trials, however, leave more unknowns, including rates of cure and the incidence of side effects. "In situations where patients have few treatment options, healthcare providers will accept greater risk," explains Edward Cox, the director of the FDA's Office of Antimicrobial Products.

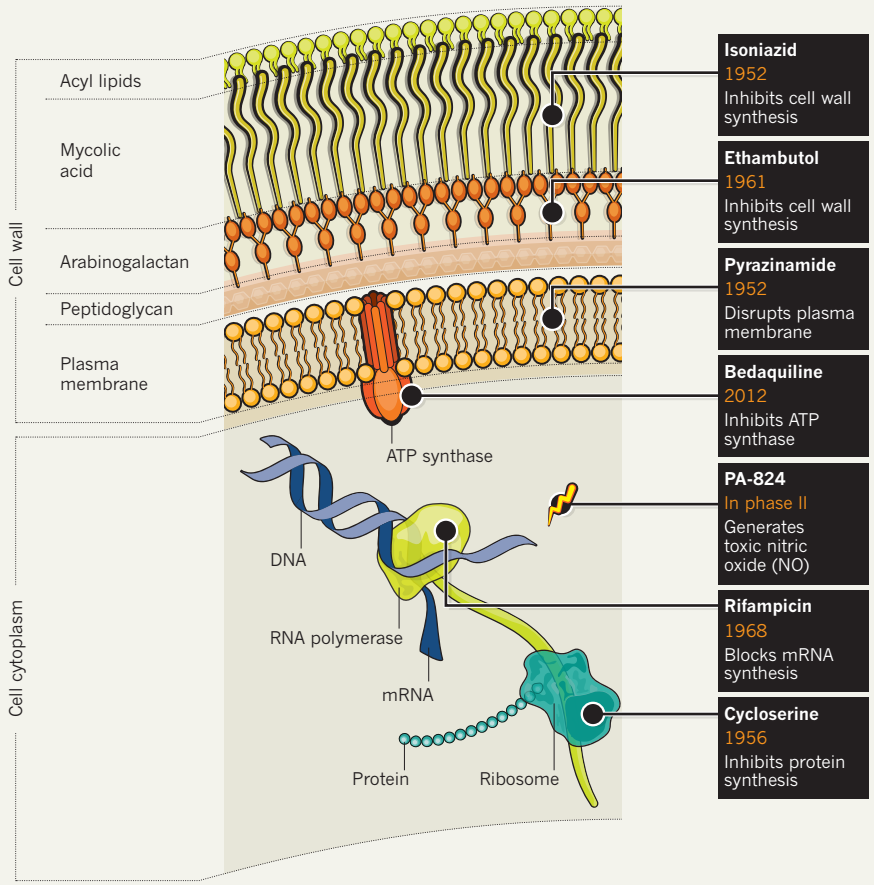
In June 2013, Janssen began to sell bedaquiline in the United States, and approval is pending in several other countries. In the meantime, the drug is undergoing a phase 3 trial to assess with greater certainty its effects on drug-resistant TB. The Global Alliance for TB Drug Development (the TB Alliance), a non-profit organization based in New York, is also running a trial on bedaquiline — this time in combination with a leprosy drug, clofazimine, and another novel anti-TB agent, PA-824, in hopes of reducing the duration of the current six-month course of treatment for drug-susceptible TB.

JOINING FORCES

Although they are often used as a marker of how well a drug is doing in trials, sputum bacterial counts are far from ideal. Counts can vary from day to day in a single patient, making the measure rather messy, says Clifton Barry, a TB researcher at the National Institute of Allergy and Infectious Diseases in Bethesda, Maryland, and at the International Tuberculosis Research Center in Masan, South Korea. In his Korean laboratory, Barry scans patients' lungs with computed tomography (CT) and positron emission tomography (PET) to see

HIT LIST

Anti-TB drugs attack *Mycobacterium tuberculosis* in different ways, so combining different drugs helps combat the bacterium developing ways to overcome a drug.



how drugs alter the state of *M. tuberculosis* inside the patient. Because the bacteria lurk in patients' lungs long after they leave their sputum, he says this method is far more precise.

Scans may also help reveal complementary drug combinations. Thomas Dick in Singapore says that the ideal drug combo would include medicines that quickly kill *M. tuberculosis* replicating in the lung fluid, along with slower acting drugs that hit hard-to-reach mycobacteria hiding out in lesions in the lungs.

To find drugs that penetrate lesions, Dick proposes that researchers switch some of their animal studies to rabbits because, unlike in mice, *M. tuberculosis* forms lesions in their lungs. "It allows for a more rational selection of compounds that will work well in combination," Dick says.

One new drug with a novel mechanism is probably not enough to fight *M. tuberculosis* drug resistance. To tackle this, the Bill & Melinda Gates Foundation funds the TB Drug Accelerator programme, which partners seven drug companies with several laboratories at publically funded institutions. "We want at least one combination of three agents that every TB patient is sensitive to so that the current notion of drug resistance just goes away," says Ken Duncan, deputy director of drug discovery at the Gates Foundation.

The companies involved in the programme share their compound libraries and their results. Barry, who is a participant, says that sharing tools and information at each step of drug development eliminates the redundancy that can occur in more secretive and independent drug development programmes where higher profits are at stake.

The FDA is also looking at ways to speed up the development of combination therapies. In 2010, they issued draft guidelines for testing combinatorial treatments in urgent situations. These guidelines will permit researchers to skimp on data about the effects of individual components within new combinations in cases where the drugs are for the treatment of life-threatening diseases for which there are no satisfactory alternatives.

"You need to have strong product champions."

The coming decade looks bright for TB drug development. By 2014, the European Medicines Agency in London is expected to approve delaminid, a novel drug from the Japanese drug company Otsuka, based in Tokyo. This compound, a nitroimidazole, poisons mycobacteria by releasing nitric oxide once it is metabolized. In July 2013, Pfizer, headquartered in New York, sold a novel drug candidate — sutezolid — that was sitting on its shelf to Sequella, a small pharmaceutical company in Rockville, Maryland, for development and commercialization. Sutezolid, a drug that prevents mycobacteria from making proteins, looked promising in mouse studies, but Pfizer had frozen its development at that stage[6].

MONEY MATTERS

Early results from the TB Alliance trial on bedaquiline, clofazimine, PA-824 and pyrazinamide also look encouraging. Trials like this are exceptional in the drug development world because they involve compounds owned by multiple companies. Khisimuzi Mduli, a drug development project leader at the TB Alliance, suggests that the strength of the TB Alliance is that they have nothing to gain financially from drug development. This means that "our partners in pharma allow us to use their compounds in long clinical trials", he says.

Even as such collaborations bring hope to the TB research community, uncertainty looms. As the founding director of the new KwaZulu-Natal Research Institute for Tuberculosis and HIV, Durban, South Africa, William Bishai is both thrilled with the recent infusion of money for TB research and filled with dread that it is not enough. "My fear is that what is really needed is orders of magnitude more funding rather than slight increases of 10 to 20 per cent per year," says Bishai, who recently stepped down from the position to return to Johns Hopkins in Baltimore, Maryland.

Working in South Africa put Bishai at the heart of the TB epidemic. As well as giving his team access to a large pool of patients, he also made a happy discovery: there is no shortage of people willing to go after the disease. Like Dalene von Delft and Jacques Grosset, their personal experience of TB is motivation enough. "When I give a lecture here, two-thirds of the room has had TB or knows someone who has died from TB," he says. "So there's a real fire in the belly of the young people here, and they want to be part of the next generation of scientists fighting TB." ■

Amy Maxmen *is a science writer based in Brooklyn, New York.*

1. Frymark, T. *et al. Evidence-Based Systematic Review: Drug-Induced Hearing Loss—Amikacin* (American Speech-Language-Hearing Association, 2010).
2. World Health Organization. *Tuberculosis Factsheet No. 104* (World Health Organization, 2013).
3. Pethe, K. *et al. Nature Commun.* **1,** 57 (2010).
4. Vilchèze, C. *et al. Nature Commun.* **4,** 1881 (2013).
5. Pethe, K. *et al. Nature Med.* **19**, 1157–1160 (2013).
6. Lessem, E. *The 2013 Pipeline Report* 22–261 (i-Base/TAG, 2013).