After decades of drought, new drug possibilities flood TB pipeline

For the first time in decades, there are nearly 30 drugs for tuberculosis (TB) under development.

Most are still in preclinical testing—the earliest one might hit the clinic is 2010—but less than just five years ago, the pipeline was running empty. The newest drug used to treat the disease is 33 years old. There are a few others, but they are either too expensive or can't be used for children, pregnant women or HIV-infected individuals.

As HIV is driving a resurgence of TB, the old drugs are also losing their potency and drug resistance is spreading out of control. The current regimen, which is several pills taken for at least six months, is tough to stomach and even harder to monitor in remote locations. Most people abandon the course part way, contributing to the spiking rates of drug resistance.

1.7 million people died from TB in 2006

Scientists are urgently trying to come up with treatments that work faster, rely on new mechanisms to fight the infection and don't interact with AIDS medications. "The drug pipeline is larger than it has ever been in history," says Maria Freire, chief executive officer of the New York–based Global Alliance for TB Drug Development.

In August, a new Harvard University model suggested that a two-month drug course would dramatically cut TB's impact. If the shorter course were to be introduced in Southeast Asia by 2012, for instance, it could avert 13% of new cases and 19% of TB deaths (*PLoS Med.* **3**, e273; 2006). The impact might be even greater because the shorter course might free up resources, allowing health workers to spend more time detecting new cases.

Global agencies have spent much of their resources over the past decade scaling up existing treatments, but there also has to be a push to develop new ones, says lead investigator Joshua Salomon, assistant professor of international health at the Harvard School of Public Health. "That will produce a payoff over decades to come," he says.

Pharmaceutical giant Johnson & Johnson has been developing a new drug, a diarylquinoline, which stops the bacteria's energy production (*Science* **307**, 223–227; 2005). The compound has the potential to reduce treatment time to two months, seems to work against multidrug-resistant strains of TB and is in phase 2 clinical trials.

Apart from such examples, however, TB drug development has largely been left to the public sector. New public-private partnerships such as the Global Alliance for TB Drug Development are encouraging companies to get back into the field (see page 265).

For example, the Maryland-based biotechnology company Sequella is ushering into fast-track clinical trials a diamine drug dubbed SQ109, which was discovered at the US National Institutes of Health (NIH).

Still, these efforts are not nearly enough. Drug development is notoriously risky, and candidates can fail at every step.

TB kills nearly 2 million each year, compared with AIDS, which claims about 3 million lives. But the NIH's funding for AIDS is about 20 times higher than for TB.

"TB money is dismally poor," says Carol Nacy, Sequella's chief executive officer. "TB should get equivalent funding, but it doesn't and it hasn't as long as we've been in the business."

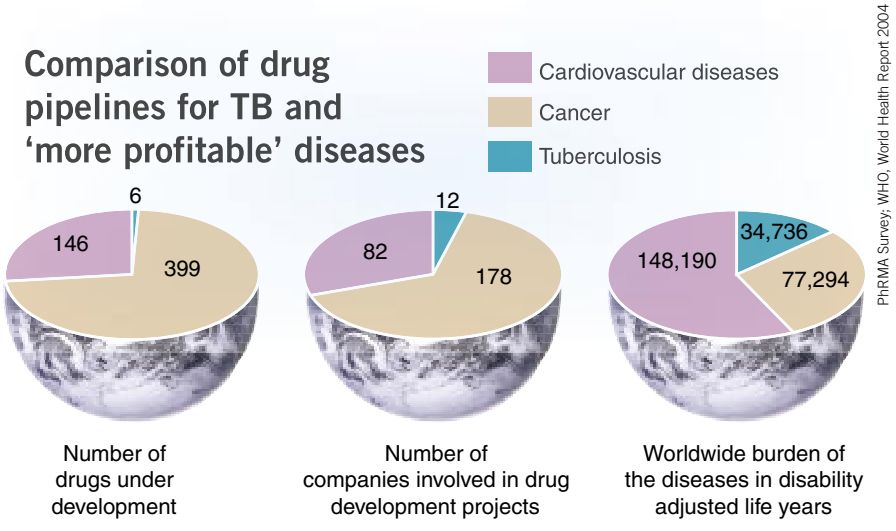
Erika Check, San Francisco

Tuberculosis drug candidates in development

Drug	Developers	Mechanism	Stage
Peptide deformylase inhibitors	GSK, TB Alliance	Inhibit cell growth	Discovery
Malate synthase inhibitors	GSK, Rockefeller University, Texas A&M	Inhibit carbon uptake	Discovery
Proteasome inhibitors	Cornell University	Inhibit cell maintenance	Discovery
Diamine SQ-109	Sequella	Inhibits cell wall biosynthesis	Phase 1
Diarylquinoline TMC207	Johnson & Johnson	ATP depletion and pH imbalance	Phase 2a
Nitroimidazoles	Otsuka, Chiron, Novartis, TB Alliance	Inhibit protein synthesis, cell wall lipid synthesis	Phase 2 / Phase 1
Fluoroquinolones (gatifloxacin & moxiflocacin)	NIH, WHO, Bayer, TB Alliance and others	Inhibit DNA replication and transcription	Phase 3 / Phase 2

Existing first-line drugs for tuberculosis

Drug	Year invented	Mechanism
Isoniazid	1952	Cell wall inhibitor
Pyrazinamide	1952	Membrane energy metabolism inhibitor
Ethambutol	1961	Cell wall inhibitor
Rifampin	1966	Nucleic acid synthesis inhibitor



Unequal burden: Tuberculosis is one of the biggest killers in the world but attracts little investment into development of new drugs or vaccines.