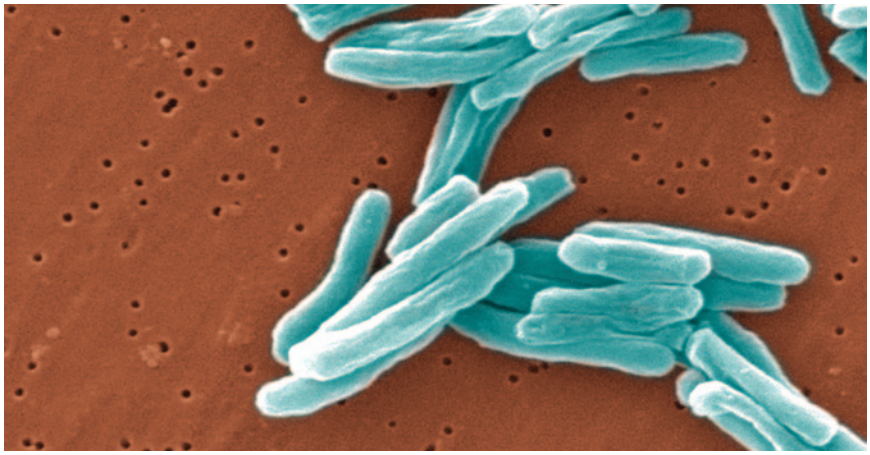
First novel anti-tuberculosis drug in 40 years

On the last day of 2012, the US Food and Drug Administration (FDA) approved a new drug to treat tuberculosis—the first anti-mycobacterial compound with a novel mechanism of action in 40 years. The agency's go-ahead is for Sirturo (bedaquiline), a diarylquinoline (DARQ) antibiotic, to be dispensed as part of combination therapy in cases of multidrug resistance tuberculosis (MDR-TB) when other alternatives are not available. The accelerated approval was based on phase 2 data from 394 patients (a follow-up phase 3 trial is slated for this year). It marks an important breakthrough for the treatment of MDR-TB and is the first of several other compounds with novel mechanisms progressing in the pipeline (**Table 1**).

Globally, 2 billion people are known to be infected with *Mycobacterium tuberculosis*, and 8.8 million develop active disease each year. Of any country, India bears the most severe TB burden—about 40% of the population is believed to be infected. Numbers for MDR-TB are less exact, but the rising prevalence is alarming (*Lancet* **380**, 1406–1417, 2012). "Everywhere you look, the problem is worse than people thought it was," says Mel Spigelman, president and CEO of The Global Alliance for TB Drug Development (TB Alliance). Although 95% of individuals with tuberculosis can be cured using a combination of four drugs, the rate drops as low as 50% in cases of MDR-TB, defined as cases resistant to isoniazid and rifampicin used in first-line treatment. MDR-TB can arise from lack of patient compliance with the full six-month course, inadequate treatment or a new primary infection with the MDR bacteria.

Sirturo stems from a collaboration between Janssen Pharmaceutics, formerly Tibotec, now a unit of Johnson & Johnson (J&J), and the TB Alliance, a not-for-profit product development organization, established in 2000 to boost research into TB drugs. Sirturo, unlike other antibiotics that attack the traditional weak points in the bacterium, such as cell-wall synthesis, protein synthesis, folate biosynthesis or nucleic acid replication, zeroes in on the mycobacterial ATP synthase's proton pump. It inhibits mycobacterial F_1F_0-adenosine triphosphate (ATP) synthase. Janssen scientist Koen Andries, also at the University of Antwerp in Belgium, who discovered Sirturo, says the discovery arose from testing a couple of thousand compounds against a relative of tubercule mycobacteria, *Mycobacterium smegmatis*. "The mechanism of action was discovered afterwards, a couple of years later, I must admit, by whole-genome sequencing of a few resistant mutants that we were able to raise *in vitro*." The Belgium researchers found that one gene was affected in all mutants—that encoding ATP synthase, which came as a surprise. "Back in time, nobody would advise you to work on that target because of the existence of the human homolog, the mitochondrial ATP synthase," says Andries. "But I think many people are not very familiar with the fact that a few amino acids' difference can make a huge difference in affinity. That's probably why the mitochondrial ATP synthase is so much less sensitive. We actually measured that; it's on the order of 10,000 times less, just because of a few amino acids at the right place, where the drug binds, that are different between mitochondrial and mycobacterial ATP synthases. That's how you get selectivity."

Analyst Josh Jenning, from investment bank Cowen & Co., thinks Sirturo could "define modern-day regimens" for MDR-TB. According to a research report by Cowen & Co., global sales for the new drug are forecast



Callista Images Cultura / Newscom

A close up of *Mycobacterium tuberculosis*, the most deadly bacteria in history.

IN brief

Citizen microbiome

uBiome has launched the first citizen science project to sequence and map the human microbiome. The San Francisco–based biotech startup, currently being incubated at the California Institute for Quantitative Biosciences (QB3), is funding the project exclusively through the popular crowdfunding website Indiegogo.com. People can pledge $69 to have their gut microbiome analyzed by high-throughput DNA sequencing technology, or donate larger amounts for multiple or repeat samples, to catalog their own microbes and see how lifestyle changes alter their microbial composition. The company sequences 16S ribosomal genes present in bacterial DNA to classify the microbial populations. "People pay us for the kits and also for access to the resulting data," says uBiome CEO and co-founder Jessica Richman. "We tell them what's in their gut and how they compare to others in our sample set and existing studies. As citizen scientists, they can also pose and answer questions of their data set." The microbial ecosystem colonizing humans is vast—the gut alone contains approximately 100 trillion bacteria. These gut microbiota play multiple roles in maintaining health, and their species composition changes in response to diet and drugs, and in conditions such as obesity and irritable bowel syndrome (*Nature* **488**, 178, 2012). Since launching in mid-November, uBiome has raised over $120,000, from more than 1,000 funders, towards its initial goal of sequencing the microbiomes of 1,000 people. *Moheb Costandi*

Gilead widens cancer focus

Gilead Sciences of Foster City, California, bolstered its oncology franchise in mid-December, with the $510-million cash purchase of Mississauga, Ontario–based YM Biosciences. Less than a month later, Gilead struck a deal potentially worth more than $1.1 billion with Rockville, Maryland–based antibody maker MacroGenics to develop and commercialize 'dual-affinity retargeting' products for four undisclosed targets. Although Gilead's past attempts to diversify beyond its anti-viral franchise have provided few returns, analysts are bullish about its current forays into cancer therapeutics. "Oncology is a very compelling area right now," says Richard Purkiss, an analyst at London-based Atlantic Equities. "Gilead has netted some interesting assets." YM's lead product is CYT387, an orally administered inhibitor of both the JAK1 and JAK2 kinases. Positive interim results were reported from a phase 1/2 trial of CYT387 in myelofibrosis. Jason Kolbert, analyst at New York–based Maxim Group, says that on the basis of available data, he thinks CYT387 has comparable efficacy to Wilmington, Delaware–based Incyte's Jakafi (ruxolitinib; currently approved for myelofibrosis) but may cause fewer side effects. Gilead's lead oncology compound is idelalisib, a phosphoinositide-3 kinase (PI3K) delta isoform inhibitor currently in phase 3 studies for lymphoma. *Malorye Allison*

Table 1 Selected drugs in development to treat *M. tuberculosis* infections

Company	Drug	Description	Status
J&J	Sirturo	DARQ that targets F_1F_0-ATP synthase	Approved for MDR-TB
Otsuka Pharma	OPC-67683 (delamanid)	Nitroimidazole derivative that causes intracellular release of lethal reactive nitrogen species	Phase 3 for MDR-TB
AstraZeneca	AZD5847	Novel linezolid analog	Phase 2
Global Alliance for TB Drug Development	PA-824	Nitroimidazole derivative	Phase 2
Pfizer	PNU-100480 (sutezolid)	Novel linezolid analog	Phase 2
Sequella	SQ109	Novel linezolid analog, inhibits cell wall synthesis	Phase 2

Source: BioMedTracker

to be between $400 and $500 million. The revenue opportunity is "likely to be capped by an expected low reimbursement rate in emerging markets," Jenning adds.

New regimens-to-be are already under investigation. Andries finds Sirturo especially compatible with two existing therapies, one of which is clofazamine, a leprosy drug sold by Novartis as Lamprene. "By far" the best match for Sirturo is pyrazinamide, Andries says, although its activity against TB "is controversial," he says. MDR-TB therapies are divided into five groups, according to their order of preference, and Lamprene falls in the last group. Paired with Sirturo, though, it shows "a strong additive effect," Andries says. The reason may have been pinpointed by Harvey Rubin at the University of Pennsylvania's Perelman School of Medicine. Rubin suggests that Lamprene is active against TB because it interacts with NADH dehydrogenase, an enzyme upstream from the ATP synthase in the respiratory chain. "If his hypothesis is true…this means clofazamine prevents electrons from coming down through the respiratory chain, feeding the ATP synthase, so you can see clofazamine as an indirect ATP synthase inhibitor," Andries says. "The same is true of pyrazinamide because it is supposed to break down the membrane potential, and membrane potential is of course driving the ATP synthase." If pyrazinamide decreases the difference in electron concentration inside and outside the cell membrane, then, again, it's indirectly inhibiting ATP synthase. The TB Alliance is conducting a trial that tests, among other combinations, Sirturo with Lamprene and Sirturo with pyrazinamide.

In addition to the DARQ class, where Sirturo stands alone, the TB Alliance identifies two more classes yielding new chemical entities that could work against drug-sensitive TB and MDR-TB. One is the nitroimidazole class, which includes Tokyo-based Otsuka Pharmaceuticals' OPC-67683 (delamanid), currently in phase 3, and PA-824, sponsored by the TB Alliance, in phase 2. Nitroimidazoles, which reduce nitro groups to hydroxylamines that then disrupt the DNA to fight infection, came to light in the 1950s, when the natural product azomycin (2-nitroimidazole) was isolated from a streptomycete. Researchers modified azomycin structurally to bring about the first-generation nitroimidazole known as metronidazole, today widely used against infection by protozoan and anaerobic organisms. PA-824 came to the Alliance in 2002 when the biotech firm Chiron (since taken over by Novartis) granted rights to the compound.

So far, data for both nitroimidazoles are good, says TB Alliance's Spigelman, but PA-824 requires once-daily dosing and OPC-67683 is given twice a day. "To have a major impact, we need to shorten and simplify therapy," thus ensuring compliance over the long haul of TB treatment, he says. The lack of compliance to six-month cocktail regimes plays a big part in causing the resistance problem in the first place, he points out.

The third promising new class comprises oxazolidinones, and is "a little more complicated," he says. Included in the class is the approved drug Zyvox (linezolid), manufactured by New York–based Pfizer for other infections. "It's being used on occasion for the treatment of TB, but it also has side effects and is extremely difficult for patients to tolerate over many months," Spigelman says. Other oxazolidinones are Pfizer's sutezolid (PNU-100480) and AZD5847 from London-based AstraZeneca. All are farther back in development than those in the other classes, but sutezolid turned up satisfying results in an early bactericidal activity test, a proof-of-concept experiment in which the drug is given for two weeks, and *M. tuberculosis* is then measured in sputum (such tests indicate efficacy against rapid-replicating, but not slow or nonreplicating, *M. tuberculosis*). AZD5847 was undergoing a similar test.

Commercial entities have been slow to come aboard the TB race until fairly recently, Spigelman says. "Some of the drug companies are putting resources behind [TB], such as Janssen with Sirturo and Otsuka with delamanid, but they are few and far between," Spigelman says. The first new chemical entity for TB to become the subject of a conventional licensing deal in decades was ethylenediamine (SQ109), developed by Sequella of Rockville, Maryland. In April 2011, ethylenediamine garnered an equity investment along with potential milestone payments and royalties from a syndicate of Russian venture capitalists, Maxwell Biotech Venture Fund, in exchange for the rights to develop the treatment in Russia. How much Maxwell invested upfront was not disclosed, but the deal could be worth up to $50 million to Sequella.

Alan Klein, executive vice president of corporate development at Sequella, says Sirturo's success "should engender a bit more activity" by companies that have stayed on the sidelines, and spur others "who may have had an inactive or semi-active TB program to get back into it, either through their own research and development efforts" or a deal with another firm. At the moment, the space is driven mainly by research collaborations between firms—Sequella has them with Janssen, Pfizer and Sanofi "to name a few," Klein says—and by agreements with not-for-profit groups.

Thanks to Sirturo, New Brunswick, New Jersey–based J&J may earn a priority review voucher, an incentive created by FDA in 2007 to reward companies developing drugs to treat neglected tropical diseases. The approval also provides other companies with the regulatory parameters for moving MDR-TB drugs towards approval (FDA also awarded the big pharma an accelerated approval for Sirturo). "We're taking the same tack that J&J is taking," Klein says. "We've completed our phase 2a, and we're moving into phase 2b." The next trial will be similar to J&J's trials, he says, serving as a phase 2b/3 study for registration globally. The exact mechanism for SQ109, Sequella's second-generation antibiotic is unclear, but research suggests that the compound (a 1,2-diamine related to ethambutol) could work by disrupting the microorganism's cell wall assembly.

Now that it's approved, it is unclear how soon Sirturo might reach patients in the countries where it's most needed. "Any new bedaquiline-containing regimen for MDR would have to be adopted by the government, and only then can we start using it," says Shelly Batra, co-founder and president of New Delhi–based Operation ASHA, which provides TB treatment, education and compliance monitoring in 2,053 slums and villages in six Indian states, as well as two provinces in Cambodia.

Meanwhile, Andries hopes Sirturo will change how experiments are done to find new MDR-TB candidates. "We lost a lot of time in the search for new antibiotics by taking the wrong strategy, which is target-based research," he says. "If you work as a researcher in a university, or at a place where you do not have access to a big library of original compounds, then that is obviously the only thing you can do. But if you have access to such a library, it would be a shame to test them for single targets only."

Randy Osborne *Atlanta*

IN their words

"I had allowed myself to slip into a world of relativism, where the ends justify any means. It's very hard to imagine how I became that kind of person." Joseph Skowron III, a former fund manager at FrontPoint Partners, on being sentenced to a five-year prison term for insider trading. The firm collapsed after illegal transactions involving a Human Genome Sciences' hepatitis C drug. (*Bloomberg News*, 27 November 2012)

"The GE salmon has no socially redeeming value. It's bad for the consumer, bad for the salmon industry and bad for the environment. FDA's decision is premature and misguided." Andrew Kimbrell, executive director of the Center for Food Safety, a Washington, DC–based advocacy group, following the FDA's >16-year assessment of AquaBounty's genetically engineered salmon. (*New York Times*, 21 December 2012)

"We're through many cost-cutting programs, restructurings and portfolio arrangements. When you put that together with record levels of cash available and improving, but still moderate R&D productivity, we think there will be more big pharma M&A activity in 2013." Henry Gosebruch, managing director of health-care mergers and acquisitions at JPMorgan Chase & Co. Biotech analysts predict $10-billion-plus deals in 2013. (*Bloomberg News,* 7 January 2013)

IN brief

Isis inks two antisense deals

Isis Pharmaceuticals of Carlsbad, California, ended 2012 with two noteworthy deals, one with Cambridge, Massachusetts–based Biogen Idec and another with London, UK–based AstraZeneca around five cancer targets. Under the Biogen Idec deal, Isis receives an upfront payment of $30 million, and up to $200 million in license fees, plus milestone payments per program, to develop and commercialize Isis' antisense drugs against three undisclosed neurologic targets. These new programs expand a previously established collaboration to develop antisense drugs for spinal muscular atrophy and myotonic dystrophy type 1. The AstraZeneca deal nets Isis $31 million in the near term plus potential milestone payments. That deal includes an Isis compound targeting STAT3. In October, a US Food and Drug Administration (FDA) advisory panel meeting for the company's antisense drug, Kynamro (mipomersen), turned into a "proxy [discussion] on antisense technology," says Stephen D. Willey, an analyst at St. Louis–based Stifel Nicolaus. The recent deals indicate that "Clearly, potential partners know that Isis has been refining and improving that technology," he adds. Isis CEO Stanley Crook concurs. "Our second-generation antisense drugs have much higher affinity, increased potency and are more stable," he says. The company has 28 drugs in development. "Investors are particularly interested in the spinal muscular atrophy program now," says Willey. The FDA's decision on Kynamro was due January 29. *Malorye Allison*

Forty fight rust and rot

More than 40 institutes around the world are teaming up to use biotech tools to improve food security in sub-Saharan Africa and India. The Sustainable Crop Production Research for International Development (SCPRID) will provide a total £16 ($25.5) million for 11 projects aimed at developing crops that will resist pests or survive in harsh environments. Each project will include at least one UK-based partner and another from a developing nation. Grants will be funded by the UK Biotechnology and Biological Sciences Research Council (BBSRC), the Department for International Development, the Bill and Melinda Gates Foundation and India's Department of Biotechnology and will be administered by the BBSRC. Geneticist Cristobal Uauy at the John Innes Centre in Norwich, UK, will lead a five-year sequencing project on wheat rust spread and evolution. His team, including collaborators in Kenya, Ethiopia and India, will screen germplasm from the open-access Watkins Landrace Wheat Collection. Uauy's collaborator, pathologist Ruth Wanyera of the Kenyan Agricultural Research Institute in Njoro, aims to develop new rust-resistant wheat varieties adapted to local conditions. Although SCPRID grant holders' intellectual property resides with their host institutions, which can conduct commercial development, they have agreed to offer BBSRC a royalty-free license to distribute technologies "at reasonable cost to people most in need in developing countries." *Lucas Laursen*