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 ₁ F 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 (del-

manid), 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.