

FEATURES

THE DRUG PUSH

As fears of drug-resistant bacteria loom, governments try to coax companies back to the field

By Kelly Servick

This past January, microbiologists Kim Lewis and Slava Epstein reported the discovery of teixobactin, a compound that in lab dishes kills several antibiotic-resistant strains of bacteria. Media outlets heralded the discovery, announced in *Nature*, as a new solution to the growing problem of antimicrobial resistance. A White House press release mentioned teixobactin, which Lewis and Epstein, both of Northeastern University in Boston, had isolated from soil bacteria, as the “kind of innovative research” it aims to promote with a \$1.2 billion antibiotics budget initiative. And Lewis and Epstein were repeatedly asked: “When will this be in the clinic?”

Now, after years of encouraging wild, hard-to-culture microbes to fill a lab dish so he could harvest their chemical weapons, Lewis and the company he co-founded, NovoBiotic Pharmaceuticals, must engage in a different kind of coaxing. “In order to go into the clinic, we either need major investment or a big pharma partnership,” he

says. Someone has to bankroll studies that can turn their natural compound or a derivative of it into something that is soluble, potent, and likely to be safe—ready to try out in people.

“Those kinds of funding are really hard to come by in academia, not just for antibiotics,” says June Lee, director of early translational research at the University of California, San Francisco’s Clinical and Translational Science Institute, “[but] in antibiotics, you’re less likely to find partners who are willing to invest that early on. ... There just isn’t a lot of money going into antibiotics.”

That may seem counterintuitive, given recent projections of what will happen if harmful microbes continue to evolve resistance to our current drugs. A particularly ominous review commissioned by U.K. Prime Minister David Cameron lays out a worst-case scenario of 10 million deaths per year due to antimicrobial resistance by 2050. But the economics are stacked against new antibiotics. They must compete with a

variety of cheap generic ones that (for now) still work for most infections. The short course of a typical antibiotic treatment makes it harder for drugmakers to turn a profit. And because using an antibiotic increases the selective pressure on bacteria to evolve resistance, doctors typically reserve newly approved treatments for the few cases where everything else has failed.

Today, only a handful of large pharmaceutical companies are willing to play those odds, and a slew of startups and academics are competing for the attention of skeptical investors. “For years, we’ve been starving the whole bacteria side of R&D,” says Kevin Outterson, a health law professor at Boston University. As a result, “lots of ideas, both good and bad, just don’t get followed up.”

Recently, though, those watching the field are heralding new signs of life. Their excitement centers mostly on signals from industry superpowers. In December, pharmaceutical giant Merck announced that it would pay \$8.4 billion to acquire Cubist Pharmaceuticals, a company focused on de-





veloping drugs for serious infections. A few other large firms, including Roche and Actavis (soon to be Allergan), are also building up their antibiotics programs.

Meanwhile, the United States and the European Union are discussing policies to make antibiotic development more attractive to companies. A U.K. report released last week calls for the founding of a global organization that would make multibillion-dollar lump-sum payments to firms that manage to introduce a new drug. Governments are also taking a more direct role in funding and overseeing antibiotic projects than ever before, fearing that resistant infections are evolving faster than our knowledge of how to kill them. “For the past 7 decades, we’ve known that this is a problem,” Outterson says. “The ability to act and the willingness to act, I think, are strongest now.”

BUT LEWIS AND OTHER RESEARCHERS with potential new antibiotics face an industry still deeply skeptical that developing such drugs can be profitable. That

caution is fueled by recent scientific and financial disappointments.

In the late 1990s, researchers hoped that the growing field of genomics, combined with the screening of much larger chemical libraries, would help identify new antibiotics. Many companies tried sequencing bacterial DNA, then searching their libraries for compounds that could inhibit the

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products of key bacterial genes. But they came up empty-handed. Part of the problem was that these libraries excluded natural products isolated from plants and soil, which had been rich sources of antibiotics in the past, but are harder to work with and more expensive to manufacture, says

Gail Cassell, a visiting scholar at Harvard Medical School in Boston who was vice president of infectious diseases at Eli Lilly when the company dropped its antibiotics research in 2002.

In place of antibiotics, industry pursued highly profitable drugs for chronic conditions such as heart disease and high blood pressure. As Cassell puts it, “This was the age of the blockbuster.” Meanwhile, the U.S. Food and Drug Administration (FDA), spurred in part by safety issues with the already-approved antibiotic telithromycin, moved to tighten the requirements for any new antibiotic to win approval. Roche, Sanofi, Pfizer, Johnson & Johnson, Bristol-Myers Squibb, and Wyeth all joined Lilly in abandoning the field.

Today, the signs of a turnaround are ambiguous. “You’ll see in a lot of newspaper articles ... that pharma may be getting back in,” says Alan Carr, a biotechnology analyst at Needham & Co. in New York City. “That’s still somewhat questionable.” AstraZeneca, which had continued to develop antibiotics after many companies bailed, announced earlier this year that it will spin out its anti-infectives projects into a separate company. And shortly after Merck’s eye-catching purchase of Cubist, the pharma giant revealed that it would lay off 120 of the biotech’s researchers and close its early-stage research and development arm.

“There’s a big fascination with these large pharmaceutical companies, but they are not the drivers of innovation,” says Ramanan Laxminarayan, an economist who directs the Center for Disease Dynamics, Economics & Policy in Washington, D.C. “The model is, let the little guys come up with it, and then the big guys can eat them.” Many hope that renewed involvement by big pharma in antibiotic development will bring in deeper pockets to fund trials, broader drug development expertise, and more influence with policymakers and regulators. But Laxminarayan is adamant that smaller companies can—and should—bring drugs to market themselves.

One company making a go of it is Tetraphase Pharmaceuticals, a spinout of Andrew Myers’s Harvard University chemistry lab. Instead of hunting for new antibiotics in nature, Myers builds known natural antibiotic compounds from scratch, using cheap industrial chemicals. The approach lets him tweak their structures to thwart resistance to the original drugs. “The power of the approach is indisputable,” he says.

In 2005, he and colleagues hit on a synthetic route to making a class of broad-spectrum antibiotics known as tetracyclines, the first of which was isolated from a soil bacterium in 1948. These compounds act on Gram-negative bacteria—microbes

Dwindling breakthroughs

After a flurry of serendipitous discoveries of antibiotics—largely from plants and soil—researchers have struggled to identify new classes of the bacterial killers.

				1959 Metronidazole							
				1957 Rifamycin							
			1948 Cephalosporin	1956 Novobiocin							
			1948 Chlortetracycline	1955 Cycloserine							
			1947 Polymyxin	1953 Streptogramin	1969 Fosfomycin						
			1947 Chloramphenicol	1953 Vancomycin	1961 Fusidic acid	1978 Oxazolidinone					
			1946 Nitrofurans	1952 Isoniazid	1961 Lincomycin	1976 Carbapenem					
			1945 Bacitracin	1952 Erythromycin	1961 Trimethoprim	1975 Fidaxomicin	1987 Daptomycin				
1908 Salvarsan		1928 Penicillin	1932 Sulfonamide	1943 Streptomycin	1950 Pleuromutilin	1961 Nalidixic acid	1971 Mupirocin	1981 Monobactam	1997 Bedaquiline		
1900s	1910s	1920s	1930s	1940s	1950s	1960s	1970s	1980s	1990s	2000s	2010s

with hard-to-penetrate outer membranes that are increasingly becoming resistant to available treatments. With a potentially valuable new antibiotic in hand, he faced a decision: Form a company to develop the drug, or license his discovery to a large pharma. Despite interest from “what conventional wisdom would call an outstanding suitor,” Myers says he was reluctant to sign away the work to a large pharma, which might jettison the project if it hit a snag. Instead, he founded Tetrphase. (The suitor, he says, abandoned the field of antibiotics soon thereafter.)

Now that Tetrphase has brought one of the new tetracycline variations into phase III clinical trials, Myers wants to repeat the feat with another class of antibiotics called macrolides. But this time around, despite a flood of investor money going into many other biomedical sectors, he found it harder to drum up enthusiasm from venture capitalists. “After the third meeting, we had one VC turn to us and say, ‘Well, you know, antibiotics aren’t valued in the marketplace.’” Another, whom Myers describes as “a fairly famous young wunderkind,” wasn’t as patient. “We had just made introductions and then he began to ridicule us, [saying] ‘You antibiotics people don’t even think about how to make money.’”

Yet Myers eventually did pull together a consortium of investors, and Macrolide Pharmaceuticals launched in March with \$22 million in funding. Its support comes from a young venture firm called Gurnet Point Capital and, somewhat ironically, the investment arms of three large pharma: SR One, the venture capital outfit for

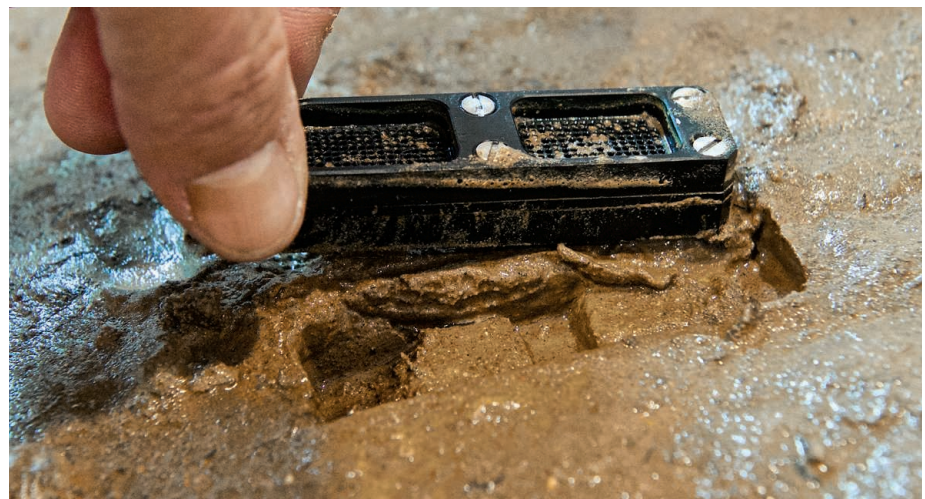
GlaxoSmithKline; Novartis Venture Fund; and Roche Ventures.

Roche in particular seems to have renewed its commitment to antibiotic development. The company was among the first big players to flee the field, in 1999, but in 2013, the company began shopping around for promising antibiotic projects to beef up its programs addressing “future unmet medical needs,” says Janet Hammond, head of infectious diseases discovery in Roche’s Pharma Research & Early Development team in Basel, Switzerland. And unlike large companies that focus exclusively on late-stage projects, Roche plans to license preclinical antibiotic projects and develop them in-house.

A small firm called Spero Therapeutics caught Hammond’s eye, and last year, Roche generated media buzz when it chipped in

an undisclosed amount for the company’s preclinical research, in exchange for the option to buy it down the road. Hammond says that Spero has “a completely novel approach” that “com[es] at bacteria from an unexpected angle.”

Microbiologist Laurence Rahme, whose lab at Harvard Medical School produced the idea behind Spero, is tickled when people call it “innovative” or “novel.” She is pursuing compounds that interfere with how bacteria signal one another to produce virulence factors—molecules that help them attack and colonize a host. For years, she says, “nobody has been paying attention.” But Rahme attracted the attention of her school’s portfolio managers in 2012, and they connected her with Ankit Mahadevia, an entrepreneur at the venture capital firm



Soil chambers that can grow previously uncultivable soil bacteria have revealed new potential antibiotics.

CREDITS: (DATA) SILVER ET AL., CLIN MICROBIOL REV, JAN 2011. (PHOTO) SLAVA EPSTEIN

Atlas Venture in Cambridge, Massachusetts, who would become the CEO of Spero.

To Mahadevia, antibiotic development is a delicate bud ready to burst into bloom, nurtured by what he calls “a regulatory renaissance.” A key reason he decided to build Spero was a 2012 U.S. law known as Generating Antibiotic Incentives Now, which gives drugs designated as “qualified infectious disease products” a faster review process at FDA and an additional 5 years of marketing exclusivity once they are approved. Another idea under discussion in the House of Representatives would allow FDA to approve drugs for rare, life-threatening infections based on smaller clinical trials than normally required for an antibiotic meant for the masses.

Such changes could be a particular boon to companies such as Spero, which is now focused on making a narrow-spectrum drug to treat *Pseudomonas aeruginosa*—a major cause of hospital-acquired blood and lung infections that is particularly common in lungs of people with cystic fibrosis. Narrow-spectrum antibiotics offer a company a smaller pool of patients, meaning it’s harder to recruit for large clinical trials and harder to make back the cost of development before a company’s marketing exclusivity period runs out. But they are appealing from a scientific perspective because they are less likely to exert selective pressure on other microbes, fostering the spread of resistance genes. Hammond says the regulatory changes under way make it “feasible to contemplate” developing a drug aimed at a single, high-priority pathogen.

But to make a business case for antibiotics, companies will also need confidence that they will be able to charge more for antibiotics than they have in the past, say many in the industry. A course of doxycycline, a commonly prescribed broad-spectrum tetracycline, averages less than \$20 in the United States. A newer antibiotic called daptomycin, which is among the most expensive on the market, can cost as much as \$1800. Meanwhile, Sovaldi, a new treatment for the hepatitis C virus, runs \$84,000 a course.

“The other renaissance coming is going to be the reimbursement renaissance,” Mahadevia declares. House lawmakers are now considering a bill that would increase levels of Medicare reimbursement for newer antibiotics. And a new E.U.-funded consortium involving industry and government is mulling a more dramatic step: separating a drugmaker’s revenue from the number of pills prescribed. Governments would reward the maker of a drug for “the mere existence of it in the pharmacy, ready to go, not expired, because ... when you need it, you need it right away,” explains John Rex,

senior vice president of infection for global medicine development at AstraZeneca in Waltham, Massachusetts, who helped set up the consortium.

That “de-linkage” approach last week gained the support of a U.K. government-appointed commission, chaired by former Goldman Sachs economist Jim O’Neill. The commission’s new report on how to refill the antibiotics pipeline suggests a “single global body,” whose member countries would pay a company between \$2 billion and \$3 billion for the rights to sell a new antibiotic and carefully manage its supply.

These discussions are still in the early stages, and many are skeptical that the approach would gain support in the United States. But even the conversations are enough to inspire confidence in some. “We see the tea leaves turning,” Mahadevia says. “There’s some folks that are waiting on the sidelines until we get an appropriate reimbursement picture. We see it. It’s not explicit yet, but we’re hoping and planning that it will be.”

GOVERNMENTS ARE ALSO trying to supply a final element missing from the antibiotics field: drug development experience. With the departure of big pharma, “all the expertise that they had before they got out is long gone,” says David Shlaes, a retired consultant specializing in antibiotic discovery and development, based in Stonington, Connecticut. Many smaller companies and academic labs don’t have the knowledge or resources to optimize potential drugs for clinical trials, he says.

One U.S. program aims to inject drug development knowledge—along with a large chunk of cash—into new antibiotic projects. The Broad Spectrum Antimicrobials Program at the U.S. Biomedical Advanced Research and Development Authority (BARDA) hands out 5-year contracts of \$50 million to \$85 million for clinical-stage research and offers the recipients access to its team of drug development experts. In an unusual move, it made a \$200 million agreement with GlaxoSmithKline in 2013 to fund a broad portfolio of projects, some still in preclinical stages. BARDA hopes to

expand the model, provided that the president’s proposed antibiotics budget initiative is funded, says program head Joseph Larsen, who is based in Arlington, Virginia. Other companies dipping a toe into antibiotic research have expressed interest in a similar partnership, he adds.

Additional initiatives are also trying to kick-start antibiotic development projects. The European Gram-negative Antibacterial Engine (ENABLE), another arm of the partnership between the European Union and the European pharmaceutical industry, has assembled a team of 32 companies and academic institutions and given them €85 million to bring one drug candidate for Gram-negative infections through a phase I clinical trial by 2019. “We’re essentially a virtual pharmaceutical company,” says Diarmaid Hughes, a microbiologist at Uppsala University in Sweden, which manages ENABLE. Small companies and academic labs can submit drug candidates, and if the experts are interested, ENABLE will pay for and help manage their development.

Hughes concedes that asking taxpayers to fund drug development by companies is bound to draw some critics. “At one level, it maybe smacks of desperation, you know—if companies won’t do it themselves, let’s pay them to do it.” But he also sees long-term value in exposing academics to the realities of drug development. Several of the applicants, he says, have had strong chemistry background, but no knowledge of microbiology or how to test for resistance to the drugs they’re developing.

Like the small cohort of investors and companies taking a risk on antibiotics, Hughes and his ENABLE colleagues

are playing the long game, hoping the market will be friendlier by the time their projects reach expensive clinical trials. If not, Hughes says the work will at least help create a stockpile of potential antibiotics. “If a project is killed for economic reasons, it can just be left in a freezer,” he says. “You could imagine this like discovering an oil field in the deep ocean. It may not be economical to develop it, but if the price of oil goes up, you know where it is.” ■

Antibiotic stats

23

thousand

Annual U.S. deaths from antibiotic-resistant infections

2.05

million

Annual U.S. illnesses caused by antibiotic resistance

41

Estimated number of antibiotics now under development

23

Estimated years, from start of development, to turn a profit on an antibiotic