

Spero Therapeutics: Remodeling Antibiotics

Like other companies investigating entirely new ways of treating bacterial infections, biotech start-up Spero is increasingly aware that novel antibiotics may need to travel new clinical and regulatory pathways to market.

BY DEBORAH ERICKSON

- If new antibiotics work differently than existing ones, they may not fit conventional approaches to drug development, regulatory assessment or clinical use. This challenge has enticed top talent to Spero.
- Spero aims to develop derivatives of powerful, but notably toxic, polymyxin antibiotics as “potentiators” that can help other drugs get inside gram-negative bacteria.
- The company also aims to inhibit bacterial virulence factors, to make microbes less toxic to the human host and less able to hide by going dormant. Its first such inhibitor is promised to Roche.
- Recent changes in the regulatory and commercial environment for antibiotics bode well for Spero, which is taking some unusual steps in the course of developing novel product candidates.

“*The old ways aren’t working any more.* Maybe the whole way we go about developing antibiotics needs to change.” So says John Tomayko, MD, the former senior director of clinical development in the Infectious Diseases Therapeutic Unit at **Glaxo-SmithKline PLC**, who at the start of September 2015 became chief medical officer of **Spero Therapeutics LLC**. Glaxo is one of the few big pharmaceutical companies to have continued investing in discovery and development of new antibiotics through recent decades. Spero is a start-up focused on developing new treatments for serious bacterial infections. Large or small, companies know that pursuing truly novel scientific approaches to fighting infection could prove disruptive well beyond the laboratory.

If new types of antibiotics work differently than existing ones, they won’t necessarily fit with the protocols by which antibiotics are currently developed by companies, evaluated by regulators and utilized by clinicians. For most organizations and investors, the idea of financing such an R&D excursion, where so much is unknown or undeveloped, is too radical to consider. Yet it is precisely

this chance to participate in a bold adventure that has attracted top talent to Spero’s leadership team.

Spero Therapeutics was founded in April 2013 with the specific intention of investigating promising but risky new approaches to treating people with serious bacterial infections. Initially, the company was focused on the concept of inhibiting a transcriptional regulator governing multiple virulence factors produced by *Pseudomonas aeruginosa* and potentially other gram-negative bacteria including *Escherichia coli* and *Klebsiella pneumoniae*. The intellectual property came out of the laboratory of Laurence Rahme, PhD, at **Massachusetts General Hospital**; she is named as a scientific founder of Spero. The Rahme lab and Spero’s data suggest that inhibiting this transcription regulator will not kill microbes directly, but instead will make them less toxic to the human host and less able to hide by going dormant. Spero thinks inhibiting this regulator, MvfR, could be a way of treating acute infections caused by *P. aeruginosa*. This organism is a frequent cause of pneumonia in ICU patients who need ventilators to assist their breathing, and a constant problem for people with cystic fibrosis.

Spero continues working on inhibition of virulence factors, which it believes are also linked to bacterial perseverance, and just recently complemented that effort with a project to commercialize chemical “potentiators.” In-licensed from **Northern Antibiotics Ltd.**, a small Helsinki-based company in June 2015, these potentiators are based on a potent but highly toxic class of antibiotics known as polymyxins. Spero says it has shown the chemicals are able to specifically create openings in the membranes of gram-negative bacteria, and so render the bugs more susceptible to drugs. If the phenomenon can be harnessed, existing antibiotics, even those now inactive or ineffective, might be revitalized by pairing them with a potentiator.

The kinds of combinations Spero envisions could help answer the call for better “stewardship” of approved drugs. Successful pairing of a potentiator with a known drug or drugs would have another upside: the process of developing a potent antibiotic combination could establish a clinical and regulatory foundation

that Spero might then build upon, to launch novel-novel combinations of treatment components.

“This is the right time to do something different,” declares Ankit Mahadevia, MD, CEO of Spero and a venture partner at Atlas Venture. He says Atlas moved to create Spero early in 2013, in part because the Generating Antibiotic Incentives Now (GAIN) title of the FDA Safety and Innovation Act became law in July 2012. The act was intended to help spur development of new antibiotics and antifungals for treatment of life-threatening infections caused by drug-resistant pathogens. It stipulates that “Qualified Infectious Disease Products” (QIDPs) are eligible for accelerated review by the Food and Drug Administration, and requires the regulatory agency to provide written guidance to drug developers. The act also extends patent exclusivity for QIDPs by five years.

THE P-WORD: PARADIGM SHIFT?

The GAIN Act is helping to instigate a paradigm shift, Mahadevia asserts. The P-word should never be used lightly, he acknowledges, but it is appropriate given the way commercial and regulatory factors pertaining to antibiotics have begun changing. “The FDA has shown it is serious about getting drugs on the market for treating gram-negative infections,” Mahadevia declares, pointing to the February 2015 approval of Allergan PLC/Actavis’ Avycaz (ceftazidime-avibactam) for complicated intra-abdominal and urinary tract infections. (See “Actavis’ Avycaz Approval Shows How FDA Handles Limited-Data, Limited-Use Antibiotic” — “The Pink Sheet,” *March 2, 2015*.) This new, fixed-combination drug pairs a familiar cephalosporin antibiotic, ceftazidime, with a novel beta-lactamase inhibitor, avibactam. It was the fifth QIDP approved as such.

“[The example of] Avycaz makes us feel that we were right to make the bet and establish Spero when we did,” Mahadevia says. He explains that under the GAIN Act, FDA agreed to consider for approval QIDPs tested in just 300 to 500 patients. Other antibiotics tested recently began Phase II clinical efficacy trials aiming for a safety database of 2,000 patients, requiring a far greater investment of time and money. The FDA did even better by Avycaz than it had to, granting marketing approval after reviewing clinical data from just 200 patients. That is a heartening precedent for drugmakers. It is also evidence, Mahadevia asserts, that FDA realizes it has been too strict on antibiotics and is now willing to relax its thinking around those antibiotics addressing the unmet need of resistance.

The regulatory schema for antibiotic development tightened up significantly about 2007, when FDA began requiring more clinical trials than ever before. That was the year FDA withdrew approval from the second of three indications for Sanofi’s first-in-class antibiotic *Ketek* (telithromycin). Originally approved by FDA in January 2004 for three indications, the drug was found to

cause liver damage in some patients. The problem had not been fully appreciated in the data FDA reviewed; it became obvious once the drug was in a large population.

The *Ketek* incident was a wake-up call for industry and the FDA alike because until the 1990s, antibiotic development was considered easy to do and of no special import or concern. Bacterial infections were a problem solved. Proof of that mind-set exists in the language of the Drug Price Competition and Patent Term Restoration Act of 1984, also known as the Hatch-Waxman Amendments, for the legislators who sponsored it. The act eased the flow of generic drugs to market, while it also established special market protections for brand-name “innovator” drugs. Antibiotics were deliberately excluded from protection.

But that was then and this is now. In the meantime, bacterial resistance to antibiotics has gotten worse and the production of new drugs has dwindled. In the 1980s, 29 new antibiotics were approved and another 23 in the 1990s. By the 2000s, just nine new antibiotics came to market. Now, the problem is serious enough to be gaining attention at the highest levels of government, in the US and abroad.

In September 2014, President Barack Obama ordered the National Security Council to collaborate with at least a dozen other agencies, to develop and implement policies for combating antibiotic-resistant bacteria (CARB). Government money has been freed up to support research addressing specific, listed organisms. In the UK, the “Longitude Prize” fund established

to help solve problems of global concern is now offering a £10 million prize for a diagnostic tool that can either rule out antibiotic use or help identify an effective antibiotic to treat a patient. In July 2015, the US House of Representatives passed the 21st Century Cures Act, which aims to speed the development of antibiotics and give drugmakers incentive to create drugs for small populations. The US Senate won’t consider the act until 2016.

NARROW-SPECTRUM DRUGS ON THE WAY

All of this action on commercial and regulatory fronts bodes well for companies in position to develop novel antibiotics that can do what is needed: defeat bacteria responsible for the most lethal infections, extend the utility of existing antibiotics and replenish the pipeline. But the climate for new antibiotic development is clouded by the fact that many truly excellent drugs have long been available as low-cost generics. From penicillin to azithromycin to ciprofloxacin, the ubiquity of powerful and inexpensive drugs that are still able to fight *most* infections creates the expectation that all antibiotics ought to be cheap. Great drugs of the past are almost all “broad-spectrum” agents able to kill many kinds of organisms. They work well, until they don’t.

Fresh science is leading researchers toward “narrow-spectrum” antibiotics able to kill specific strains of organisms without harming others, and diagnostics are a key part of the vision. That is

From penicillin to azithromycin to ciprofloxacin, the ubiquity of powerful and inexpensive drugs that are still able to fight most infections creates the expectation that all antibiotics ought to be cheap.

hardly surprising. In a growing number of diseases, there is desire and increasingly the requirement by payers that treatments be accompanied by “companion diagnostics” capable of distinguishing who is likely to benefit from a given product *before* it is administered. Big change is coming for diagnostics paired to anti-infectives, insiders say, but they’re not yet sharing details publicly. Spero and others are, however, talking openly about what kinds of data can determine whether a given molecule is a good candidate for treating a given infection, and how much if any of this can be accurately forecast from animal or early human data.

It’s likely that companies and regulators will be paying increasing attention to pharmacokinetics and pharmacodynamics (PK/PD) – understanding of how a molecule moves through the body, and what impact it has there. Developers of anti-infective drugs look at such things as whether a molecule can enter the cells or tissues where the problem is occurring, and whether it is the drug concentration or exposure time that kills the bacteria.

John Tomayko says he first started learning about PK/PD when he was training in infectious diseases, soon after the first fluoroquinolone antibiotics like **Johnson & Johnson’s** *Levaquin* (levofloxacin) came to market. He recalls his attention was captured by a paper that looked “under the curve” of data charting drug concentration against time. If a patient achieved an exposure of a certain level, it predicted they would get well, and if they didn’t achieve that level, it was equally predictive that the patient would fail that round of treatment and need another drug. Tomayko says he aims to help Spero develop some predictive assays that will be acceptable to regulators, and he knows it won’t be easy.

To correlate a drug’s effect with a clinical endpoint, a researcher must understand what an antibiotic does, what its pharmacodynamic driver is, how the endpoint is achieved and whether patients achieved an adequate exposure level. “It’s a lot harder than you’d think,” Tomayko points out. “The drug exposure of a healthy subject can change dramatically after, say, a traumatic injury where bleeding is involved, ICU-level care is required, and drug clearance is unpredictably altered.” He says Spero is taking all of this into account.

“We expect to be able to titrate doses to achieve better dosing in patients; that is the way we are heading,” Tomayko declares. Host defense, what the body does to prevent bacteria from thriving, is also important, and very much of interest to Spero and to other companies developing antibiotics, he says. “This is where we’re going: boosting host defense and minimizing collateral damage caused by infection-triggered toxins, and yet still finding novel ways of inhibiting or killing difficult and resistant pathogens.”

UNIQUE TALENTS JOIN TO BATTLE DOOM

“Somebody is going to be the first company to bring truly novel antibiotics before FDA, and test new regulatory pathways, and we hope it will be Spero,” Mahadevia declares. The company’s leadership now includes individuals of notably high pedigree. Chief Sci-

entific Officer Thomas Parr, PhD, who assumed this role at Spero in April 2014, has been presenting drug candidates to the FDA for over 25 years and is highly respected in the field of antibiotics research. He has worked on marketed antibiotics representing numerous drug classes, from macrolides to glycopeptides, aminoglycosides, beta-lactams and more. Frequently involved with big pharma firms, he held executive positions at Targanta (now part of The Medicines Co.) and Fedora Pharmaceuticals before joining Spero.

Parr will contribute expert knowledge about what regulators want and need to see in new treatments for infection. He was also the one to connect Spero with Northern Antibiotics, which licensed to Spero intellectual property covering new understanding of polymyxin derivatives, the “potentiators” that are now Spero’s lead project.

Spero’s first employee was Mike Pucci, PhD, hired as executive director, early drug discovery. He previously held jobs in antibacterial drug discovery at Achillion Pharmaceuticals Inc. and Bristol-Myers Squibb Co. Pucci has been helping Spero identify non-equity sources of funding. Like others in the antibiotics space, Spero intends to take full advantage of the cash that the federal government has put up for projects linked to combating specific pathogens. Head of Biology Aileen Rubio, PhD, worked at antibiotic specialty pharmaceutical firm **Cubist Pharmaceuticals Inc.** for over nine years, in antibacterial drug discovery. **Merck & Co. Inc.** acquired Cubist in January 2015, and announced the first layoffs in March. Rubio joined Spero in May.

In addition to John Tomayko, in September 2015, Spero announced the hiring of Head of Chemistry Troy Lister, PhD, formerly team leader of infection chemistry at AstraZeneca PLC, and VP of Development Timothy Keutzer, formerly VP, program and portfolio management for Cubist.

Like the Avengers in Marvel Comics’ tales, each member of Spero’s leadership team contributes a unique talent to the fight against an enemy threatening the entire world with doom. But the team members have things in common, too, such as feeling fed up with bureaucracies, hierarchies, risk-reduction strategies and confining limits. Rubio explains, “At Cubist, we had guardrails in place to limit the number of high-risk projects such as anti-virulence. Cubist also didn’t prioritize these types of projects at that time.” Troy Lister says he decided to step out of big pharma and into this tiny outfit, after concluding that, “Spero has the ambition to not just push the market one tick farther along, but to start taking quantum leaps.”

INTENSE COLLABORATIONS

It is not uncommon for top-tier venture capital firms to build companies around “all-star” teams of scientists, but it is unusual for 15 such stars to crowd into a 300-square foot room to work in direct contact with each other. Spero will move into new space in Cambridge’s Central Square in early January 2016, but for now the company works in a team room within the offices of Atlas Ventures. “The atmosphere we’ve got in these close quarters is hugely

“Somebody is going to be the first company to bring truly novel antibiotics before FDA, and test new regulatory pathways, and we hope it will be Spero.”
– Ankit Mahadevia, MD

collaborative,” says Troy Lister, adding, “We’re constantly breaking out into discussion of our programs and what we can do for all of them.” Beyond potentiators and MvfR he says there is a third, as yet secret project.

An investment syndicate headed by Atlas Ventures put up only \$3 million at Spero’s founding, then a larger group including all the original investors closed a \$30 million Series A financing in June 2013. But Spero also obtained an unspecified financial contribution from Roche, in return for a claim on the lead compound out of the MvfR project. The agreement calls for Spero to transfer the asset once it is ready to file for the FDA’s marketing approval. Because Spero is a limited liability corporation, this should be an easy hand-off, even if it is down the road a ways. Spero is not saying anything right now about clinical time lines.

The relationship between Roche and Spero is a real working partnership, Lister explains, “not just a give money and let them do their thing arrangement.” Roche has been actively involved in integrating its expertise in computer modeling, CMC, toxicology and more into Spero’s MvfR development program, he says. “We have a small team and advisory board, but Roche has a huge medicinal chemistry group with extraordinary expertise. We’ve had many face-to-face interactions, where break-out teams of medicinal chemists sit down, talk about molecules, do modeling, and figure out which avenues are worth pursuing.”

“We are aware that there are not that many companies that we or other developers of new antibiotics can sell to,” Rubio acknowledges. So the relationship with Roche is helpful in that regard too, enabling Spero to “get a sense of what data are going to drive value for the partner.” But gathering data about limiting the virulence of bacteria is no simple matter, she points out, because “all the standard models are geared to seeing the burden on the bug, and we are looking for different things up front.”

Rubio says Spero has developed assays that show the virulence-limiting effect of an MvfR inhibitor, or the pathogen-weakening power of a potentiator, as a measurable incident distinct from the antibacterial effect of a drug.

Troy Lister is confident that Spero’s in-licensed potentiator program can produce good results from the polymyxin class of drugs, which have been known since 1950 for being as nephrotoxic (damaging to the kidney) as they are potent against bacteria. Instead of trying to change key safety and efficacy qualities of molecules in the class, like several other pharmaceutical companies have done, Spero decided to work with the compounds as they are – disruptors of the outer membrane barrier of gram-negative bacteria. Spero doesn’t need its compounds to act as antibiotics; it only asks the compounds to help other drugs get past the membrane and into the bacteria.

“We ran this polymyxin project upside-down from how anyone else would have run an R&D effort,” Lister declares. Spero

decided not to follow standard drug-discovery protocols, which entail spending a lot of time up front extensively assessing microbiology, pharmacology and PK/PD before picking the best candidate to take into animal toxicology studies. Instead, Lister says, “We agreed to go for the jugular, and find out if our compounds were ‘clean,’ [not nephrotoxic] or not, because if not, forget about it. We knew if we didn’t have safety, we didn’t have a program.”

Spero skipped the usual step of optimizing its potentiator molecule for safety in kidney cells and rodents, and spent a lot of time and money on primate nephrotoxicity studies. The data came back positive: it appears to be safe, as well as efficacious, Lister reports. He says the company has already begun pairing the potentiator with various antibiotics and testing the combinations. This too is a bold move, or would have been just a few years ago, when intentional combination therapies for bacterial infections were exceedingly rare. Recently, however, the FDA has shown with the approvals of Avycaz and Zerbaxa (another beta-lactam/beta-lactamase inhibitor product from Cubist [Merck]) that it can appreciate combinations. Lister says Spero believes it is constructing a story and a data set that regulators, clinicians and patients alike will understand.

Some people try to relate Spero’s concept of pairing a known antibiotic with its potentiator as similar to new drugs like Avycaz, which link an old beta-lactam antibiotic to a beta-lactamase inhibitor that can stop bacterial enzymes from eroding the drug and diminishing its potency. “Ours is sort of like that,” Lister says, “but what we have is more powerful.” Adding a beta-lactamase inhibitor to a beta-lactam removes only a

single target of inhibition, and bacteria will inevitably evolve resistance to that, he explains. Spero figures its drug candidate will fare better, by operating at more of a macro scale – interacting with lipopolysaccharides (LPS) on the surface of the bacteria. The company envisions developing a fixed ratio of components based on its understanding of PK/PD, which can be co-formulated with assorted antibiotics in possibly different ratios as long as they together create the desired picture “under the curve.”

The FDA does not explicitly require drugmakers to understand the mechanism of action of their products, but Spero is advancing this understanding for its potentiator. The company wants to substantiate its claim that what it is doing is fundamentally different from the way that any other antibiotic until now has been groomed to work. That will be necessary to obtain patents. “We believe our molecules are interacting with the LPS explicitly, not on the inner membrane or the cytoplasm like ordinary polymyxins that cause intracellular damage,” Lister asserts.

The fidelity of microscopy has gotten so good, Lister says, that it is possible to watch molecules localize on the cell surface and observe the extent and rate at which they enter gram-negative bacteria. So Spero scientists can see, for example, that a macrolide

Heavy-duty preclinical science is often under-appreciated as important in antibiotic drug discovery, and perhaps it was not so vital in the past when the primary question was only, are the bacteria dead or not?

antibiotic cannot get into a cell on its own. But then when the drug is labeled and given with a potentiator, it can be seen to get inside. Lister says this research approach devised and carried out by **Linnaeus Bioscience Inc.** in San Diego, CA, “really helps you understand the phenotype of the bacteria, and what morphological change your compounds are causing.”

Heavy-duty preclinical science is often under-appreciated as important in antibiotic drug discovery, and perhaps it was not so vital in the past when the primary question was only, are the bacteria dead or not? But now that treatment approaches are becoming more precise, experts predict that preclinical science is something that drugmakers’ customers will want to know about. Jeffrey Stein, PhD, the president and CEO of antifungal drug developer **Cidara Therapeutics Inc.** since 2014, and one of the most experienced biotech executives in the anti-infective space, believes that the customer chain starts with potential licensing and acquisition partners, extends to regulators and stretches on to include clinicians and patients.

As a scientific advisor to Spero, Stein thinks the start-up is taking the right approach by delving deep into preclinical research. He points out that Spero has its own small internal lab where scientists on staff perform experiments, sometimes devising them

from scratch because the company’s work is so fresh. Maintaining any such infrastructure has been frowned upon by venture capitalists for the past decade or so, he notes. But contract research organizations typically cannot do the kinds of hard-core scientific research that Stein believes Spero and other successful companies need at every stage of their evolution.

A top executive in two anti-infective firms that were acquired by larger companies (**Quorex Pharmaceuticals** by Pfizer, **Trius Therapeutics** by Cubist), Stein declares, “Doctors want to see strong preclinical data to understand how your drug works. If you wish to partner or to be acquired, you also need that data, because your negotiating partners will want it. If you don’t have it, they will use that fact to drive down your price.” Stein insists that the anti-infection companies he leads and advises have the data they need, particularly peer-reviewed journal articles, to prove the value of their approaches. The fact that Spero employs a slew of talented individuals should make this part of fortifying the start-up a snap. **SU**

[\[A#2015900197\]](#)

COMMENTS?

EMAIL THE EDITOR: NANCY.DVORIN@INFORMA.COM

©2016 Informa Business Information Inc., an Informa company. No reproduction without the written consent of the copyright owner.