

Antibiotic Incentives Helped Spero Get Where It Is Today

► By Joseph Haas

The progress made by antibiotic start-up Spero Therapeutics LLC offers a clear example of how the Generating Antibiotic Incentives Now provisions have helped reinvigorate research in the infectious disease space. In an interview with the Pink Sheet, Spero CEO Ankit Mahadevia noted that the GAIN incentives enabled his firm not only to raise about \$65m across Series A and B financings, but also will open up an accelerated approval pathway for the firm's novel drugs.

Approved in 2012 as part of the last Prescription Drug User Fee Act reauthorization, the GAIN provisions added regulatory clarity, additional exclusivity and faster regulatory reviews. (Also see "With GAIN In Place, Antibiotic Improvements Depend On FDA Implementation" - *Pink Sheet*, 13 Aug, 2012.) It has been used for products like Allergan Inc.'s *Avycaz* and The Medicines Co.'s *Carbavance*, and Spero anticipates its lead candidate, SPR741, will follow the same pathway. (Also see "Choice Of Regulatory Pathway Is Key Inflection Point In Drug Reviews" - *Pink Sheet*, 16 May, 2016.)

"What that pathway does is reduce the hurdle for us to get a novel lifesaving therapy to market and enables us to get that drug to patients who might most need it as soon as we can," Mahadevia said.

Mahadevia spoke effusively about the various incentives available now to encourage companies to develop novel antibiotics. For example, the GAIN Act provides a five-year extension of the exclusivity period for novel antibiotics that address serious or life-threatening infections. The expanded exclusivity offers the potential for increased profitability, providing an inducement for investment in companies developing novel antibiotics.

Based in Cambridge, Mass., and based on research conducted at Massachusetts General Hospital by Laurence Rahme, a company founder, Spero is working on novel class of antibiotics that not only will



Photo credit: Spero Therapeutics LLC

Spero CEO Ankit Mahadevia

address multi-drug-resistant Gram-negative bacteria but also enable drugs for Gram-positive infections to fight the Gram-negative spectrum.

The company's *Potentiators* disrupt the lipid outer membrane of Gram-negative bacteria, thus permitting entry to antimicrobial agents that previously were active only in Gram-positive infections. The disruption of what Mahadevia compared to a "raincoat" that protects Gram-negative bacteria allows the agent used in combination with the Potentiator access through the periplasm and cytoplasmic membrane.

"SPR741 is an agent that binds to a specific part of that raincoat and creates perturbations in it," he explained. "Think if you had a picket fence around your house and took some rails out – that allows a variety of Gram-positive agents to get through and do their work. So that's a combination paradigm that enables multiple therapies."

Spero unveiled preclinical data last month at the American Society for Microbiology's Microbe 2016 conference demonstrating SPR741's potential to work in combination with existing drugs such as rifampicin, azithromycin, meropenem and others, its ability to increase the potency of other antibacterial agents,

and confirming its mechanism of action, as well as its safety/tolerability profile and dosing range for human subjects. (Also see "Spero Therapeutics LLC" - *Scrip*, 23 Oct, 2014.) The biotech plans to file an IND and get initial clinical trials with SPR741 underway before year's end.

If approved, Potentiators will be the first novel class of antibiotics for Gram-negative infections since the first carbapenems in the 1980s, Mahadevia added. It also makes them eligible for the full suite of GAIN incentives.

The Qualified Infectious Disease Product classification and extended exclusivity allowed under the GAIN Act played important parts in making Spero viable, he said. It raised a Series A from Atlas Venture, SR One and Partners Innovation Fund in 2013, which was topped off to \$30m by investments from Lundbeckfond Ventures, Merck Research Ventures and Kraft Group in June 2015. All of those backers returned in a \$35m Series B round closed this past February.

Spero expects to conduct a Phase I safety and tolerability study for SPR741 that will provide "a deep understanding of pharmacokinetics of the drug, how it behaves in the body, where does it go and at what time and how long does it stick around," the exec said. Then, a moderately sized efficacy study in patients with complex urinary tract infections (cUTI) will be undertaken to show "741's effect in Gram-negative infections. The company would hope to use those studies as the basis for "a specific set of approvals," Mahadevia added.

The investment incentives under GAIN enabled about \$150m in venture capital and public funding to be raised for antibiotic developers over the past year, the CEO said.

While GAIN has been a success, he now looks to additional incentives to be established in order to create a "sustainable ecosystem" for the development of novel antibacterial drugs, Mahadevia said.

"The second step is will we be able to build on the positive momentum that GAIN has created for this field and for patients by executing on one of several, I think, well-written programs within Congress under

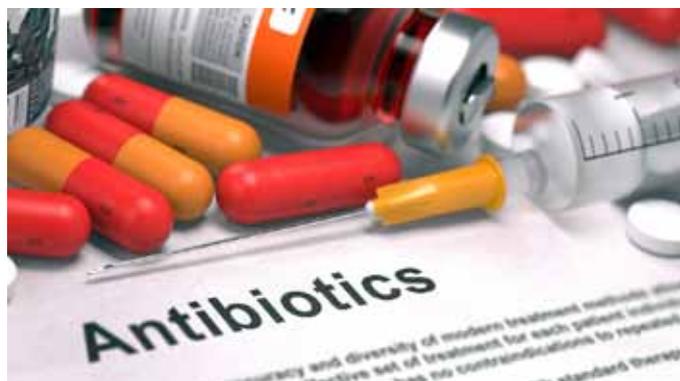


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21st Century Cures to enabled to us to create a sustainable market," he said.

The 21st Century Cures package includes the Promise for Antibiotics and Therapeutics for Health Act (S. 185), which is intended to shorten the development of new treatments to combat life-threatening superbugs. The bill is under consideration by the Senate; the House of Representatives passed its 21st Century Cures legislation in July 2015, including similar provisions for accelerated antibiotic development. (Also see "Senate 'Cures' Companion Advances; Funding Unclear" - *Scrip*, 7 April, 2016.)

"A lot has been said about push incentives ... that have helped us push drugs to the market because they reduced the capital burden that is required to get a drug to patients and enabled a broader range of firms to be able to do that," Mahadevia continued. "The next thing that we're working on - which is under discussion in Europe as well as the US - are so-called pull incentives, which means once we get a drug approved, how do we ensure that when a larger company looks ahead to developing and launching multiple antibiotics, they see a sustainable ecosystem."

Push incentives, which provide mechanisms to reduce research and development costs for new drugs, and pull incentives, which ensure future revenues for drugs that successfully complete the development and regulatory process, were featured in the UK's Review on Antimicrobial Resistance, which will come to final conclusions this summer. (Also see "Global Fund For Antimicrobial Resistance Proposed, Financing Unclear" - *Pink Sheet*, 6 Feb, 2015.)



Since Potentiators will work in tandem with antibacterials, Spero has a pair of strategies for finding agents to pair with its candidates, the exec said. Earlier this year, the biotech signed deals with Promiliad Biopharma Inc. and Vertex Pharmaceuticals Inc. to bring in assets to pair with its Potentiators.

The Promiliad deal in-licensed R&D, manufacturing and commercial rights to dihydrofolate reductase (DHFR) inhibitors, while the Vertex deal conferred global rights to the preclinical gyrase inhibitors VXc486/VXc100 as well as a portfolio of antibacterials targeting bacterial gyrase and/or topoisomerase IV. Specific terms for both were not disclosed.

"The first [strategy] is to combine 741 with generic partners that already have physician experience

but couldn't get through that outer membrane," Mahadevia said. "We've also found very interesting combinations with novel agents that other pharmas designed originally for Gram-positive applications but as Gram-positive applications largely had been met, these molecules had limited commercial value until we were sort of able to reinvigorate them and add spectrum."

The latter strategy was applied in the Vertex transaction, where combination with a Potentiator dramatically increased the in-licensed agents' spectrum, he added. Spero continues to assess other possible collaborations with companies that have approved antibacterials, or candidates nearing approval and even earlier in development, he said.