Arixa: Breaking resistance with oral beta lactamase inhibitors

BY SANDI WONG, STAFF WRITER

Arixa has made an IV antibiotic oral with prodrug chemistry. Arixa Pharmaceuticals Inc. is modifying diazabicyclooctanes, a class of beta-lactamase inhibitors that suffer from poor absorption across the GI tract, for use in combination with beta-lactam antibiotics to treat Gram-negative infections.

No oral beta-lactamase inhibitors have received FDA approval since the first in 1984: clavulanate. And, according to Arixa co-founder and CEO John Freund, many bacteria have become resistant to clavulanate.

Hospital IV administration of newer beta-lactamase inhibitors, including diazabicyclooctanes, increases patient costs compared with oral administration and introduces the risk of bloodstream infections from contaminated IV lines.

To solve this, Arixa co-founder and CSO Eric Gordon set out to make a prodrug of avibactam, a diazabicyclooctane that Allergan plc markets in combination with ceftazidime as Avycaz. According to Freund, medicinal chemists thought it was impossible to make a diazabicyclooctane prodrug that retained its prodrug structure until after absorption.

Freund is managing director of Skyline Ventures. He was chairman of XenoPort Inc., which specialized in prodrugs, and a director of antibiotics company Targanta Therapeutics Corp. He sits on the board of another antibiotics company, Tetraphase Pharmaceuticals Inc. Gordon, a Skyline partner, was a director of medicinal chemistry at Bristol-Myers Squibb Co. and co-founded Tetraphase and fellow anti-infectives company Vicuron Pharmaceuticals Inc.

In a paper published in October in the Journal of Medicinal Chemistry, a team led by Gordon described the synthesis of diazabicyclooctane prodrugs, which render the beta-lactamase inhibitors orally bioavailable without sacrificing activity. Following absorption, the prodrug structure self-cleaves itself, leaving the active compound behind. The company's IP covers the chemistry for creating prodrugs for all diazabicyclooctanes.

Arixa's lead compound, ARX-1796, is an oral prodrug of avibactam. Because ARX-1796's active ingredient has FDA approval, Freund said the program is greatly derisked.

He also said the prodrug's absorption rates in monkeys and dogs are 80% and 100%, respectively, which suggest ARX-1796 will be well absorbed in humans. Arixa is completing its toxicology studies and plans to complete a Phase I trial this summer.

Beta-lactamase inhibitors are paired with beta-lactam antibiotics to protect the latter from degradation. While Arixa is developing its own oral beta-lactam, regemonam (ARX-5986), Freund said the first ARX-1796 combination would probably be with the beta-lactam ceftibuten.

Arixa, a virtual company, has raised $12.5 million to date. Freund declined to disclose runway but said, "There's a strong possibility we'll sell the company assuming we have good toxicology results and good Phase I results."

Freund declined to name Arixa's competitors but noted that, in order to enable prodrug generation, one company developing an IV compound...
that inhibits three β-lactamase classes had altered the diazabicyclooctane scaffold in such a way that the resulting inhibitor only had activity against two classes. By contrast, he said Arixa’s prodrug chemistry did not decrease avibactam’s activity.

At least two companies are developing oral β-lactamase inhibitors. Entasis Therapeutics Inc.’s ETX0282 is an inhibitor of class A and C LACTB that is in Phase I testing. VenatoRx Pharmaceuticals Inc.’s VNRX-7145 is a preclinical LACTB inhibitor. Arixa declined to comment on Entasis’ and VenatoRx’s products.

COMPANIES AND INSTITUTIONS MENTIONED

Allergan plc (NYSE:AGN), Dublin, Ireland
Arixa Pharmaceuticals Inc., Palo Alto, Calif.
Bristol-Myers Squibb Co. (NYSE:BMY), New York, N.Y.
Entasis Therapeutics Inc. (NASDAQ:ETTX), Waltham, Mass.
Tetraphase Pharmaceuticals Inc. (NASDAQ:TTPH), Watertown, Mass.

TARGETS

β-lactamase (LACTB)