Shionogi’s growing anti-infectives portfolio

With core competencies in small-molecule drug design and synthesis, Shionogi continues to achieve success in and expand its infectious disease portfolio of both antibacterials and antivirals, many of which are home-grown products.

Founded in 1878 and based in Osaka, Japan, Shionogi is a drug-discovery-based pharmaceutical company with more than 5,500 employees and operations around the globe, including offices in the US, UK, Italy, Spain, Germany, Taiwan, China, Singapore, and Hong Kong. Shionogi’s core therapeutic areas of focus are pain/central nervous system disease and infectious diseases. The company also maintains a focus on frontier therapeutic areas, including cancer and allergy immunotherapies, obesity, and geriatric metabolic diseases.

Over 60% of the company’s development projects are home-grown, noted Yoshinori Yamano, CSO for infectious diseases at Shionogi’s Pharmaceutical Research Division. “Shionogi’s drug discovery capabilities have been enhanced by colocating medicinal chemistry, toxicology, and pharmacology in one site, so that our researchers are in close communication with one another,” he said. This has heightened the company’s core competencies in small-molecule drug design and synthesis and early development, resulting in a rich pipeline.

Shionogi’s infectious disease portfolio of antibacterials and antivirals is emblematic of that success. In antibacterials, the company has demonstrated notable progress in particular in the rapid discovery of unique chemical structures for antibiotics against carbapenem-resistant Gram-negative bacterial strains. Several of these dangerous bugs feature on both the World Health Organization and the US Centers for Disease Control and Prevention global priority lists as critical threats, and the development of drugs to combat these pathogens is among the most serious challenges in modern medicine.

Most recently, Shionogi announced a pact with CARB-X, the public–private partnership devoted to antibacterial R&D. CARB-X and Shionogi will develop an antibiotic to treat infections caused by carbapenem-resistant Enterobacteriaceae (CRE). Shionogi received an initial award of up to $4.7 million and is eligible for $2.9 million more in potential milestone payments. In the US, up to half of all bloodstream infections caused by CRE result in death.

Leader in antibacterials

Antibiotic discovery has long been key to Shionogi’s success, and antibiotics have featured heavily in the company’s portfolio over the years. The company has launched more than a dozen antibacterials, including five drugs discovered by Shionogi. These include two oxacephem-class antibiotics that were launched in the 1980s. Even today, these drugs remain on the market without generic competition thanks to a difficult chemical synthesis mastered by Shionogi and the drugs’ continued utility in the treatment of certain Gram-negative bacterial infections.

Shionogi’s latest antibiotic advance is cefiderocol, a novel siderophore cephalosporin antibacterial with a unique mechanism of cell entry. The drug candidate has been granted the coveted Qualified Infectious Disease Product status by the US Food and Drug Administration (FDA) and has shown potent efficacy against a variety of priority Gram-negative pathogens, including carbapenem-resistant Acinetobacter baumannii, carbapenem-resistant Pseudomonas aeruginosa, and CRE. Global phase 3 studies are ongoing in subjects with hospital- and ventilator-acquired pneumonia and with carbapenem-resistant Gram-negative bacterial infections. Ultimately, successful development of cefiderocol would bring success to Shionogi where several large pharmaceutical companies have failed with siderophore compounds over the past decades. Yamano said that Shionogi plans to file its regulatory submission with the US FDA in 2018 and then move on to global submission, including in European countries and Japan. Though the company believes it can market the drug itself in some markets, Shionogi will look for a partner for rest-of-world territories, he said.

Success in antivirals

Shionogi’s antiviral platform has also enjoyed considerable success. The best-in-class HIV integrase inhibitor Tivicay (dolutegravir) was launched in 2013 and reached nearly $2 billion in global sales in 2017 (dolutegravir is also part of the triple-combination HIV therapy Triumeq). Tivicay provides a higher genetic barrier to resistance than competing molecules; a follow-on compound, cabotegravir, is in phase 3 trials for use as a long-acting injectable formulation. Tivicay’s high affinity for the HIV integrase arises from its unique binding mode, in which chelation via two metal ions is responsible for the binding of the compound.

That same two-metal binding concept was applied to the rational design of Shionogi’s promising new flu drug Xofluza (baloxavir marboxil), which was approved in Japan in February 2018 and continues to be developed elsewhere (Fig. 1). The drug is a cap-dependent endonuclease inhibitor that prevents mRNA synthesis, the first and necessary step in the life cycle of a flu virus once it enters a cell. This first-in-class drug prevents the expression of proteins required for flu to proliferate, and sharply reduces viral load. Xofluza has shown potent activity against both type A and type B seasonal influenza, as well as avian flu virus strains including H5N1 and H7N9.

“We believe we can apply our accumulated knowledge in designing two-metal chelating compounds in the future for the discovery of new antiviral compounds,” said Yamano.

Photo: Shionogi Pharmaceutical Research Center

Email: yoshinori.yamano@shionogi.co.jp

Shionogi Pharmaceutical Research Center

www.shionogi.co.jp/en

Yoshinori Yamano,
CSO for Infectious Diseases
Pharmaceutical Research Division
Shionogi Pharmaceutical Research Center
Osaka, Japan
Tel: +81 6 6331 6293
Email: yoshinori.yamano@shionogi.co.jp

In antibacterials

Influenza virus

Attachment

Release

Neuraminidase inhibitors (e.g., Tamiflu (oseltamivir))

Translation of transcribed mRNA

Polymerase inhibitor (Tivicay, dolutegravir)

Incorporation

Infection

mRNA synthesis

Replication of viral genome RNA

Membrane

infusion

Viral genome RNA

Cap-dependent endonuclease inhibitor, Xofluza

Fig. 1 | Novel mode of action of Xofluza (baloxavir marboxil). Xofluza is hydrolyzed in vivo to the active form that selectively inhibits cap-dependent endonuclease, a key enzyme involved in the initiation of influenza virus mRNA synthesis. Thus, proteins needed for the construction of new influenza virions cannot be synthesized in the presence of the drug.

Contact