VenatoRx Pharmaceuticals, Inc.
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Hunting down bacterial resistance

Anti-infective company VenatoRx Pharmaceuticals has developed injectable and orally bioavailable broad-spectrum antibiotics that could help curb the expansion of antimicrobial resistance. The company is now seeking clinical and commercial partnerships.

VenatoRx Pharmaceuticals, a private, clinical-stage pharmaceutical company, focuses on the discovery and development of new medicines to treat drug-resistant infections.

Founded in 2010 by three antimicrobial pharma research and development (R&D) veterans as a virtual company, with seed funding from a 3-year, multimillion-dollar grant from the National Institutes of Health, VenatoRx set out to implement an ambitious plan for developing novel molecules to treat drug-resistant infections. Today, with five projects in the pipeline, a workforce of fifty, a few rounds of venture funding, and the recent award of substantial US government drug discovery contracts from CARB-X and the US Defense Threat Reduction Agency (DTRA), VenatoRx is forging ahead with its plans.

VenatoRx (derived from the Latin word *venator*, meaning hunter, and Rx, the medical symbol for drugs) has two molecules in advanced stages of development—VNRX-5133 and VNRX-7145, injectable and orally bioavailable broad-spectrum lactamase inhibitors, respectively, with activity against all major subclasses of β-lactamases, including the well-established serine β-lactamases, the emerging metallo-β-lactamases, and different subtypes of serine carbapenemases.

VenatoRx is now seeking to expand its global footprint by entering into clinical and commercial partnerships.

Planning for the future

A wave of resistance has appeared in Gram-negative bacteria, which today account for more than 70% of intensive care unit-based infections. Over the last two decades, Gram-negative bacteria have accelerated their resistance to β-lactam antibiotics, the most widely prescribed class of antibiotic drugs (including penicillins, cephalosporins, monobactams, and carbapenems). What began as a handful of different β-lactamase subtypes now numbers more than 2,000 different variants. Despite the variations, all of these β-lactamase enzyme variants utilize either a serine-based or a metallo-based active site to inactivate their β-lactam targets.

To counter resistance, β-lactam antibiotics have been combined with protective β-lactamase inhibitors, but existing inhibitors such as clavulanic acid or tazobactam are no longer sufficiently effective against the emerging extended-spectrum β-lactamases (ESBLs), or the serine-based and metallo-based carbapenem-hydrolyzing β-lactamases (carbapenemases).

VenatoRx focuses specifically on shutting down these new β-lactamase variants, both serine-based and metallo-based. The company plans to develop its intravenous and oral broad-spectrum protective β-lactamase inhibitors to be ready for the next wave of resistance (carbapenem-resistant Enterobacteriaceae and *Pseudomonas*).

According to Christopher Burns, president and CEO of VenatoRx, "the trick in antibiotic R&D is to see and solve the next resistance problem while it is still percolating and then arrive into the market just as it explodes".

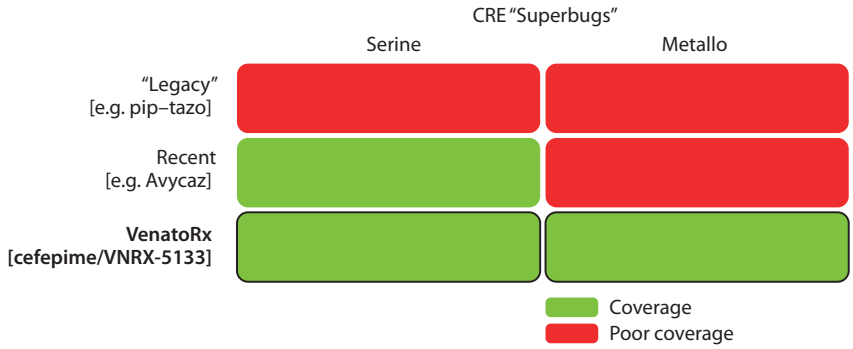

Fig. 1 | VenatoRx is developing broad-spectrum medicines to treat drug-resistant infections.

Broadest-spectrum β-lactamase inhibitors

Multidrug-resistant (MDR) Gram-negative bacteria have been spreading across the globe. Carbapenem-resistant Enterobacteriaceae (CRE) and carbapenem-resistant *Pseudomonas aeruginosa* (CRPA) in particular, including New Delhi metallo-β-lactamase-1 (NDM-1) and Verona integron-encoded metallo-β-lactamase-expressing 'superbugs', pose an unusually high public health risk, including increased mortality rates after infection.

VNRX-5133, VenatoRx's lead injectable β-lactamase inhibitor, which features potent and selective activity against both serine-β-lactamases and metallo-β-lactamases, has completed phase 1 clinical development in a fixed combination with the fourth generation cephalosporin cefepime. The company plans to start phase 3 pivotal trials in the second half of 2018. The VNRX-5133/cefepime combination has the potential to be best in class against MDR Gram-negative bacterial infections, including CRE and CRPA (**Fig. 1**).

VNRX-7145, VenatoRx's lead orally bioavailable β-lactamase inhibitor, which features potent activity against both extended-spectrum β-lactamases and serine carbapenemases, is in preclinical development and is expected to start human testing in early 2019. Oral, broad-spectrum treatments against MDR Gram-negative bacteria are urgently needed in the clinical setting to reduce hospitalization time or avoid hospitalization altogether.

PBP inhibitors, the next-generation antibiotics

In addition to the β-lactamase inhibitors, VenatoRx is developing a completely new class of antibiotics that could dramatically improve the treatment of MDR bacterial infections and turn back the Gram-negative resistance clock back by decades. β-lactam antibiotics kill bacteria by blocking the penicillin-binding protein (PBP), a key cell wall synthesis enzyme. VenatoRx is now developing novel PBP inhibitors that target the same mechanism—cell wall synthesis—but represent a new class of non-β-lactam molecules that are thus not susceptible to β-lactamases. With funding from both the DTRA and the aforementioned CARB-X public–private partnership program, this platform could deliver a new wave of standalone antibiotics.

VenatoRx's nimble structure allows it to quickly adapt to patient and regulatory needs and requirements as the threat of MDR bacteria intensifies globally. "We made a decision several years ago to step into the path of the coming hurricane while the sun was still shining," said Burns. "To address the coming storm, one needs to provide the best possible broad-spectrum antibiotic options to the clinician for when standard of care no longer works. We believe that VenatoRx is achieving that goal. With the right commercial partners, we can fight back against MDR bacteria both in the US and around the globe."

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