EMERGING COMPANY PROFILE

EYEING NEW ANTIBIOTICS

BY STEPHEN PARMLEY, SENIOR WRITER

Traditional antibiotics kill bacteria by inhibiting protein, DNA, or cell wall synthesis but require multiplying cells to be effective. SinSa Laboratories Inc.'s peptide antibiotics kill slow- and fast-growing bacteria by direct disruption of the cell membrane, and could have reduced risk of susceptibility to resistance mechanisms compared with existing antibiotics for antibiotic-resistant eye infections.

SinSa's antimicrobial peptides were created with its SpearHead technology, which incorporates positively charged amino acids and lipophilic groups to specifically disrupt negatively charged bacterial cell membranes regardless of their growth state.

According to CSO Robert Beuerman, "It doesn't make any difference whether the cells are in log or stationary phase, we see rapid killing." Beuerman also is senior scientific director of the Singapore Eye Research Institute (SERI), from which SinSa has exclusive rights to the SpearHead technology, plus antimicrobial compounds AM218 and B2088.

Beuerman said another benefit of the compounds' mechanism is a low likelihood of resistance emerging quickly because the compounds target polymers in the cell wall and cell membrane, not proteins.

"Our drugs target the membrane in several different ways, and they don't depend on one biosynthetic step," he said. "Since these polymers do not mutate, bacteria cannot acquire resistance by simply mutating the target."

Beuerman said his group synthesized the SpearHead antimicrobials by modeling them after natural antimicrobial peptides, like polymyxin B and human defensins, but he added that the compounds should have better drug-like properties.

The group screened for compounds that disrupted bacterial cell membranes but did not affect mammalian cell membranes.

According to Beuerman, while compounds like polymyxin B work directly on bacterial membranes, they lack therapeutic potential because the concentration required to kill bacteria in an active infection is too high. "At a therapeutic dose you see a terrible amount of inflammation," he said.

SINSA LABORATORIES INC.
Montreal, Quebec

Technology: Synthetic peptide antimicrobials that target pathogen membranes

Disease focus: Infectious

Clinical status: Preclinical

Founded: 2014 by Roger Beuerman, Magnus Precht and Urban Olson

University collaborators: Singapore Eye Research Institute (SERI)

Corporate partners: None

Number of employees: 2

Funds raised: Not disclosed

Investors: Not disclosed

CEO: Magnus Precht

Patents: 5 issued covering small molecules, peptides and pharmaceutical antimicrobial compositions

In 2012 the SERI team reported preclinical data for B2088 in the *Journal of Biological Chemistry*. The SpearHead antimicrobial is a dimeric cationic peptide that was synthesized based on the human beta defensin 3 C-terminus.

B2088 killed Gram-negative bacteria, *Pseudomonas aeruginosa*, *Escherichia coli* and *Klebsiella pneumonia* with a minimum inhibitory concentration (MIC) of 2.75 µg/mL. It did not lyse red blood cells at concentrations as high as 2 mg/mL. The selectivity for bacterial cells versus mammalian cells was significantly higher than reported values for Lytix Biopharma A/S's Lytixar (LTX-109), a synthetic antimicrobial peptide in Phase II testing for skin infections, and Dipexium Pharmaceuticals Inc.'s Locilex pexiganan acetate, a linear peptide in Phase III for infections of diabetic foot ulcers.

B2088 killed more than 99.99% of gentamicin-resistant *P. aeruginosa* in 10 minutes at 2x MIC. The study also showed it was possible to passage *P. aeruginosa* more than 17 times in B2088 with no resistance. Resistance emerged with gentamicin or norfloxacin by passage 15.

The combination of B2088 with gatifloxacin was more effective than gatifloxacin alone at treating an existing *P. aeruginosa* corneal infection in mice. In a rabbit corneal wound-healing model, topical application of B2088 did not interfere with wound closure and showed no clinical signs of toxicity.

President and CEO Magnus Precht said SinSa has started manufacturing B2088 and will combine it with fixed doses of gentamicin — a combination the company calls Dorzidin — to treat antibiotic-resistant *Pseudomonas* eye infections that lead to keratitis in contact lens wearers.

The company's second candidate is AM218, a SpearHead antimicrobial that was synthesized by modifying a hydrophobic xanthone core with cationic arginine and lipophilic isoprenyl groups. Data published in the *Journal of Medicinal Chemistry* last month showed AM218 killed a wide range of Gram-positive bacteria. In studies similar to those performed on B2088, AM218 killed *Staphylococcus aureus* with a MIC of 0.5 µg/mL, lysed red blood cells with an EC50 of 277 µg/mL and showed less resistance than generic gatifloxacin or norfloxacin.

SinSa plans to begin Phase I testing of Dorzidin within a year and a half of series A funding. It is seeking a $10 million in series A.

The company plans to start Phase I testing of AM218 for Gram-positive eye infections after obtaining clinical proof of concept with B2088.

COMPANIES AND INSTITUTIONS MENTIONED

Dipexium Pharmaceuticals Inc. (NASDAQ:DPRX), New York, N.Y.
Lytix Biopharma A/S, Tromso, Norway
Singapore Eye Research Institute, Singapore
SinSa Laboratories Inc., Montreal, Quebec

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