Emerging Company Profile

Adenium: Lugworms vs. superbugs

By Emily Cukier-Meisner
Senior Writer

Adenium Biotech ApS is developing derivatives of arenicin-3 to create a safer antibiotic than colistin to treat infections caused by multidrug-resistant Gram-negative pathogens.

Colistin is a broad-spectrum Gram-negative antibacterial first introduced in 1952. It was replaced by safer antibacterials in the 1970s due to its nephrotoxicity and neurotoxicity, yet it saw a resurgence in the late 1990s as the last line of defense against multidrug-resistant Gram-negative pathogens.

Arenicin-3 originally was identified at **Novozymes A/S** from a screen of more than 500 organisms that looked for novel antimicrobial peptides with broad Gram-negative activity. It is found in the marine lugworm *Arenicola marina*.

Because arenicin-3 binds promiscuously to human proteins, Novozymes generated variant libraries and screened them for reduced protein binding and equal or better activity against Gram-negative pathogens.

Novozymes spun out Adenium in 2011 to develop the resulting hits, while the parent company focused on bioethanol.

"Every generation we introduce a new antibiotic, with enough exposure to enough population, the bacteria will 'crack the code' and become resistant. So what is very important is not only that we develop new antibiotics, but that they have a clear, novel mode of action," said CEO Peter Nordkild.

"We have the same efficacy or better than colistin, but we don't have the side effects, and there's no cross-resistance between bacteria that are resistant to colistin," he said.

Both colistin and arenicins initially associate with the negatively charged outer membrane of Gram-negative bacteria. Colistin then induces cell death by permeabilizing the membrane through mechanisms that are not well understood, but requires a component called "Lipid A" for entry.

In contrast, arenicins disrupt both the outer and inner bacterial membranes without relying on the presence of a particular receptor.

Arenicins also may interfere with bacterial protein synthesis, although Nordkild said it is not yet known whether that mechanism occurs if membrane disruption is blocked.

Arenicins also may be less susceptible to resistance than other antibiotic targets. Nordkild said unpublished data show Adenium's AA139 and AA230 have a spontaneous frequency of resistance for select isolates of *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa* and *Acinetobacter baumannii* that is five to six orders of magnitude less than penicillin.

Across panels containing 55-120 multidrug-resistant strains for each of those bacteria, AA230 inhibited 90% of the species in each panel at concentrations of 0.5-4 µg/mL. AA139 did so at 1-8 µg/mL, and colistin at 0.25-8 µg/mL.

Arenicins also have demonstrated better activity than colistin in at least one animal model. In mice with pneumonia, aerosolized AA139 or AA230 reduced bacterial load after 48 hours by more than 10^4, compared to a $10^{1.75}$ reduction for colistin dosed equally by weight. Nordkild said a load reduction of at least 10^3 defines a bactericidal rather than bacteriostatic agent.

Nordkild said arenicins have a wide therapeutic window, as the half-maximal effective dose (ED50) and no observed adverse effect level in mice and minipigs differ by a factor of 25-150.

Nordkild said histamine release is the most likely side effect and should be manageable in a hospital setting.

This month Adenium selected AA139 as the clinical candidate because it had a more favorable pharmacokinetic profile than AA230. The company plans to submit a U.S. IND in 4Q14.

Adenium will develop the peptide in an IV formulation to treat urinary tract infections (UTIs) and an aerosol nebulized formulation for hospital-acquired and ventilator-acquired pneumonia.

Nordkild said UTIs and HAP/VAP are the two largest indications in which the multidrug resistant Gram-negative bacteria specified by the Generating Antibiotics Incentives Now (GAIN) Act predominate.

GAIN gives additional market exclusivity and Priority Review to qualified infectious disease products (QIDPs), including those that target pathogens specified by **FDA**. In July the agency published draft guidance on how to streamline clinical trials of pathogen-focused antibacterials, as required by GAIN (see *BioCentury, Nov. 19, 2012*).

Nordkild said the company is funded through the IND submission, and plans to tap current and two new investors for a $20 million series A round in 1Q14 to last through a Phase II proof-of-concept trial.

Adenium hopes to license the compound or be acquired by Phase II completion in 2Q17.

Novozymes does not hold any rights to Adenium's IP or programs, nor does it hold equity in the company.

Adenium Biotech ApS

Copenhagen, Denmark
Technology: Peptides based on arenicin to treat Gram-negative bacterial infections
Disease focus: Infectious
Clinical status: Preclinical
Founded: 2011 by Peter Nordkild
University collaborators: None
Corporate partners: None
Number of employees: 2
Funds raised: $9.5 million
Investors: Novo Seeds, Sunstone Capital
CEO: Peter Nordkild
Patents: 2 issued covering composition of matter and use of arenicin-3 variants

COMPANIES AND INSTITUTIONS MENTIONED

Adenium Biotech ApS, Copenhagen, Denmark
Novozymes A/S (CSE:NZYM B), Bagsvaerd, Denmark
U.S. Food and Drug Administration (FDA), Silver Spring, Md.

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