Northern Antibiotics Ltd.
www.northernantibiotics.com

# Building on 30 years of experience to fight AMR

**Northern Antibiotics is developing improved versions of polymyxins to help fight against resistant Gram-negative bacteria and has three parallel programs in development.**

Founded in 2003, the Finnish company Northern Antibiotics was created to fight the rise of antimicrobial resistance (AMR) and provide new options for physicians and patients. The company was co-founded by Martti Vaara and his brother Timo, and is based on Martti's lifetime of work in antibacterial agents, including polymyxins.

The company is owned by its founders and by the University of Helsinki, venture capital company Biothom, and 123 private and corporate investors. Development work is carried out through collaborations with academic groups, contract research organizations and antibiotic companies across the world. Northern Antibiotics is one of the founding members of BEAM Alliance (Biotech companies in Europe combating AMR).

## Revisiting polymyxins

Polymyxins are effective antibiotics that kill Gram-negative bacteria by attacking their membranes. The polymyxins were largely abandoned in the 1960s because of their nephrotoxicity and narrow therapeutic window, and these drugs are now only used as an antibiotic of last resort in infections with extremely drug-resistant bacteria. While many antibiotics currently in use are fourth- or fifth- generation, polymyxins are still in their first iteration. Based on Martti Vaara's work, Northern Antibiotics is developing improved versions of polymyxins to help to defeat resistant bacteria. The company has three parallel development programs: direct acting compounds, sensitisers and compounds for the treatment of haemolytic uremic syndrome (HUS).

## The direct route to new antibiotics

Northern Antibiotics has a pipeline of direct acting antibiotics derived from polymyxin B that aim to retain the antibiotic activity, but with a much broader therapeutic window. In preclinical trials, the two lead compounds, NAB739 and NAB815, were around three-fold less nephrotoxic than polymyxin B, as shown in animal studies. They also were able to sensitise pathogens that had acquired resistance to polymyxin B and other antibiotics.

NAB739 (Fig. 1) and NAB815 are secreted into urine at up to ten-fold higher concentrations than polymyxin B, and have been shown to be very effective in treating *Escherichia coli* (*E. coli*) urinary tract infection in mouse models. Combined with the lower nephrotoxicity, this means that these second-generation polymyxins could potentially be used at much lower doses than polymyxin B.

"Multidrug resistance, while it may seem to be falling overall, is still growing in enteric bacteria such as *E. coli* and *K. pneumoniae*, and these are the most common causes for complicated urinary tract infections," said Timo Vaara, co-founder and vice president of business development at Northern Antibiotics. "Complicated urinary tract infections, which can lead to life-threatening bloodstream infections, are the biggest indication for hospital antibiotics. Ours are the only polymyxins actively secreted into urine."

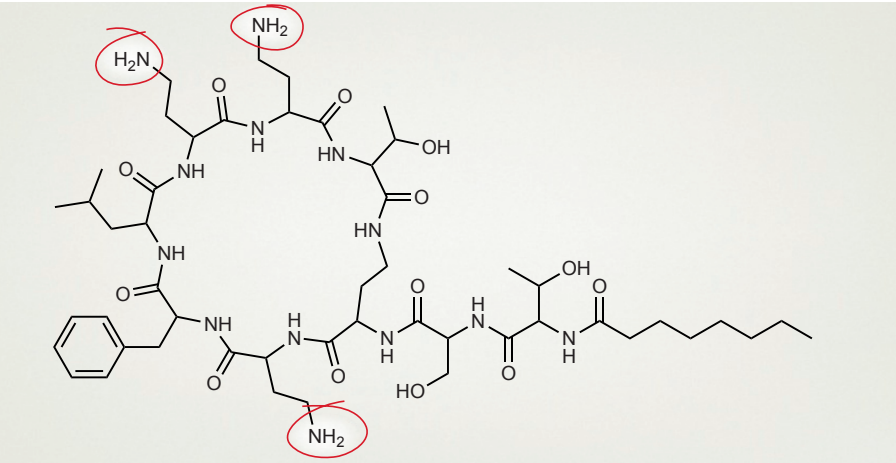


**Fig. 1 | The chemical structure of NAB739.** The lead compound at Northern Antibiotics is derived from polymyxin B.

NAB739 and NAB815, should they reach the market, are likely to be antibiotics of last resort.

## The sensitiser approach

Polymyxin B nonapeptide (PMBN) is a derivative of polymyxin B that does not have antibacterial activity, but sensitizes bacteria to other antibiotics. However, it is still nephrotoxic. Northern Antibiotics has created a series of molecules that are much less toxic and significantly increase the sensitivity of resistant bacteria to antibiotics. The lead compound, NAB741, was licensed to Spero Therapeutics in 2015. In preclinical trials, NAB741 increased the potency of antibacterial agents, including against common drug-resistant pathogens, such as *E. coli* and *K. pneumoniae*. In a phase 1 trial carried out by Spero Therapeutics in 2017, NAB741 was safe and well-tolerated at doses higher than those to be used in a planned phase 2 trial. Development ceased after phase 1 following a strategy change at Spero Therapeutics. Northern Antibiotics is seeking collaborators to create combination products that partner NAB741 with new antibacterial agents.

## Focusing on HUS

Northern Antibiotics and Maurizio Brigotti's group of researchers at the University of Bologna, Italy, are developing NAB815 for the treatment of haemolytic uremic syndrome (HUS) caused by foodborne infections with Shiga toxin-producing *Escherichia coli* (STEC). HUS causes kidney damage, and can be fatal. Dosing patients with antibiotics can cause increased release of the toxin into the body, so patients are given only supportive treatment, including dialysis, blood transfusions and hyperhydration.

NAB815, a polymyxin B derivative, interacts with Shiga toxins and could be used to treat and prevent HUS caused by STEC at concentrations ten-fold lower that bactericidal levels. The next step is to test NAB815 in STEC HUS animal models.

As there is no toxin-specific treatment for STEC HUS, NAB815 may be designated as an orphan drug. STEC is also listed as a potential bioterrorist agent by the US Department of Homeland Security.

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