Bad news to Bad bugs: Northern Antibiotics develops novel polymyxins with reduced toxicity

Helsinki, Finland – July 1, 2008 - The emergence of multidrug-resistant Gram-negative bacteria has necessitated the use of polymyxins as the agents of last resort despite their known nephrotoxicity. Now Northern Antibiotics Ltd, a Finnish biotech company, has developed novel polymyxin derivatives which in early preclinical studies show signs of lower nephrotoxicity.

The derivatives contain three positive charges only, while polymyxin B and colistin have five. They bind to the isolated brush-border membrane of rat kidney at an affinity which is only 1/5-1/7 of that for polymyxin B. *In vivo* rat studies also show remarkable differences in parameters that are considered to indicate early kidney damage, such as serum urea nitrogen, albuminuria and cylindrouria.

The derivatives fall in to two groups that differ in their mode of action. The lead compound of the first group, NAB 7061, sensitizes enteric bacteria to other antibiotics. For example, it reduces the minimum inhibitory concentration (MIC) of clarithromycin for ESBL-producing strains of *Escherichia coli* by a factor of 250-750. NAB 739, the lead compound of the second series, acts directly against enteric bacteria. For *E. coli* (including ESBL-producing strains) the MIC_{90} is identical to that of polymyxin B. While NAB 739 is already alone highly active against multidrug-resistant strains of *Acinetobacter baumannii*, it also at very low subinhibitory concentrations sensitizes this bacterium to other antibiotics. A paper entitled "Novel polymyxin derivatives carrying only three positive charges are effective antibacterial agents" was published ahead of print on June 30, 2008 (Antimicrob. Agents Chemother., doi:10.1128/AAC.00405-08).

"The efficacy of both lead compounds has been verified using an experimental *E. coli* peritonitis model in mice, and we are now talking to potential partners to further develop and eventually commercialize these two lines of novel compounds", says **Professor Martti Vaara**, CEO and co-founder of Northern Antibiotics Ltd.

"The need for well-tolerated antibiotics that are active against multidrug-resistant Gram-negative bacteria is urgent. Enteric bacteria are responsible for more than 80% of all the hospital infections caused by Gram-negative bacteria, and now they are rapidly becoming resistant to most antibiotics that are currently used to treat them. Plasmid-mediated carbapenemases, probably transferred from *Klebsiella pneumoniae*, have now been found in *E. coli*, the clinically most important species of Gram-negative enteric bacteria. Also plasmid-mediated methylases that cause resistance to all aminoglycosides have been encountered. Finally and quite alarmingly, a single genetic element conferring transferable resistance to carbapenems, aminoglycosides and fluoroquinolones has been reported in *K. pneumoniae*. One does not need to be very smart to guess what follows when these plasmids become more common and the resulting extremely multidrug-resistant strains start to spread."

About Northern Antibiotics Ltd.

Founded in 2003 and headquartered in Helsinki, Finland, Northern Antibiotics Ltd is engaged in the discovery and development of novel antibiotics against multidrug-resistant Gram-negative bacteria. For more information, visit www.northernantibiotics.com.

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