

Northern Antibiotics presents new data on novel polymyxin compounds at the joint ICAAC/IDSA 2008

Helsinki, Finland - October 28, 2008 - Northern Antibiotics Ltd., the developer of novel polymyxin derivatives for the treatment of infections caused by multidrug-resistant Gram-negative bacteria, revealed today animal efficacy and pharmacokinetic data from their NAB compounds at the 48th Annual ICAAC/IDSA 46th Annual Meeting in Washington, DC.

Northern Antibiotics has developed two series of novel polymyxin (NAB) compounds (Vaara M. et al., 2008, *Antimicrob. Agents Chemother.* 52:3229). The compounds of the first series (lead compound, NAB739) are directly antibacterial against polymyxin-susceptible Gram-negative enteric bacteria such as *Escherichia coli*, *Klebsiella spp.*, and *Enterobacter spp.*, as well as against *Acinetobacter baumannii*. The representatives of the second series (lead compound, NAB7061) have only a weak direct action but sensitize in a very remarkable degree these Gram negative bacteria to antibiotics such as macrolides, rifampin, and others. The compounds of both series carry only three positive charges whereas the notoriously nephrotoxic old polymyxins (colistin, polymyxin B) carry a total of five positive charges.

The *in vivo* efficacy of NAB739 and NAB7061 was evaluated in a murine peritoneal infection model using the virulent, encapsulated *E. coli* strain IH3080 (K1:O18) as the challenge organism. As low a dose as 1 mg/kg (body weight) of NAB739, given at 1h postinfection and repeated at 3 h postinfection, displayed potent bactericidal effect. The bacterial counts in the treated animals were 4.8 log₁₀ lower in the mice treated with NAB739 than in the untreated control mice.

Furthermore, while NAB7061 (5 mg/kg) alone as well as erythromycin (20 mg/kg) alone were ineffective in the murine peritoneal model, the bacterial counts in mice that received their combination were 2.9 log₁₀ lower than in the untreated controls (dosing time schedule as above with NAB739). Accordingly, the *in vivo* efficacy studies corroborate the previous *in vitro* findings.

The pharmacokinetic studies, performed in Sprague-Dawley rats, showed that the serum half-lives of NAB739 and NAB7061 were close to that of colistin. However, both NAB compounds had much greater renal clearance and much higher urinary recovery than observed for colistin. Accordingly, and in contrast to colistin and polymyxin B, the NAB compounds are excreted into urine to a significant extent. This indicates that the reuptake of the NAB compounds in the proximal tubuli of the kidneys is less intense than that of colistin and polymyxin B.

The extensive reuptake is regarded to be the mechanism of the nephrotoxicity of polymyxins. Thus the reported findings suggest that NAB739 and NAB7061 are less nephrotoxic than colistin and polymyxin B. They are also in line with the previous finding (Vaara M. et al., 2008) that the affinities of NAB739 and NAB7061 for isolated rat kidney brush border membrane are significantly lower than that of polymyxin B.

These two studies were presented in the Poster Session #290 on Tuesday, October 28, 2008, 11:15 AM - 12:15 PM.

Poster F1-3966: "Novel Polymyxin Derivatives are Effective in Treating Peritoneal *E.coli* Infection in Mice", C. VINGSBO LUNDBERG¹, T. VAARA², N. FRIMODT-MØLLER¹, M. VAARA²; ¹Statens Serum Inst., Copenhagen, Denmark, ²Northern Antibiotics Ltd, Helsinki, Finland

Poster FI-3997: "Pharmacokinetics (PK) of Novel Anti-Gram-negative (G-) Antibiotics in Rats", F. E. A. ALI¹, G. CAO¹, A. POUDYAL¹, T. VAARA², R. L. NATION¹, M. VAARA², J. LI¹; ¹Facility for Anti-infective Drug Dev. & Innovation, Monash Univ., Melbourne, Australia, ²Northern Antibiotics Ltd, Helsinki, Finland

Professor Martti Vaara, CEO and co-founder of Northern Antibiotics Ltd., commented, "Multidrug-resistant enteric bacteria are emerging at an alarming rate. This is a serious concern, since enteric bacteria

are responsible for more than 80% of all the hospital infections caused by Gram-negative bacteria. Our NAB compounds have the potential to become a new treatment against these bacteria”.

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. The NAB compounds are polymyxin derivatives that have less cationic charges than the polymyxins currently in clinical use. This difference is believed to result in reduced nephrotoxicity of the novel compounds. For more information, visit www.northernantibiotics.com.

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