Meropenem loaded liposomes as nanotherapeutics to treat antibiotic resistant Gram-negative pneumonia infections

Y.M. te Welscher[1], H. van der Weide[2], J. Kalb[1], I. Loinaz[3], S. Wronski[4], J. Knebel[4], M. Niehof[4], I.A.J.M. Bakker – Woudenberg[2], G. Storm[1], C.F. van Nostrum[1]

[1]Utrecht University, Utrecht, The Netherlands
[2]Erasmus University Medical Center, Rotterdam, The Netherlands
[3]CIDETEC, San Sebastián, Spain
[4] Fraunhofer ITEM, Hannover, Germany
E-mail: Y.M.teWelscher@uu.nl

Meropenem is a broad-spectrum antibiotic and belongs to the subgroup of carbapenems that inhibit bacterial cell wall synthesis. This project makes use of liposomes that have the antibiotic meropenem encapsulated. By using liposomes we aim for prolonging the exposure of the bacteria in infected lung tissues to high meropenem concentrations, by preventing antibiotic escape into the bloodstream as well as prohibiting antibiotic degradation, in this way minimizing emergence of meropenem resistance. The goal of this project was to optimize the liposomal lipid composition, which results in maximal loading of meropenem with high antibacterial activity and low toxic side effects. This liposomal formulation will then be used for therapy through inhalation in animal models of bacterial lung infections.

Bilayer fluidity and permeability of the liposomes were varied by using different mixtures of (phospho)lipids containing EPC, DPPC, EPG, DPPG, DOTAP and cholesterol. The optimum diameter for the highest loading of meropenem in liposomes was determined to be around 400 nm. Liposomes with different compositions were characterized and their stability tested. Near neutral liposomes and positively charged liposomes showed aggregation, while all other negatively charged formulations were physically stable in time. Meropenem encapsulated in the liposomes was stably retained in time when the formulations were stored at +4°C. In addition, preliminary release studies of the formulations performed under physiological conditions showed differences in meropenem release rates. All formulations with high loading of meropenem showed *in vitro* antibacterial activity as determined by minimal inhibitory concentration and time kill kinetics against the Gram-negative model organism *Klebsiella pneumoniae*.

From these results one liposomal formulation with the best anti-bacterial activity, stability and release profile was selected for further studies on cytotoxicity with two cell lines of the respiratory tract (A549 and Calu-3) and will be further investigated in an *in vivo* animal model of *Klebsiella pneumoniae* lung infection.

More information: For more information visit: http://www.pneumonp.eu/