

**ACRONYM: CO-ACTION****Title: Developing combinations of CO-ACTIVE antimicrobials and non-antimicrobials****Keywords: synergy; screening; PKPD; combinations; Polymyxin B; Gram-negative bacteria****Consortium composition:**

Type	Name	Institute	Country
C	MOUTON Johan	Erasmus University Medical Center / Dept. of Medical Microbiology and Infectious Diseases [ER]	Netherlands
P	FRIBERG Lena	Uppsala University / Biopharmaceutical Sciences [UUF]	Sweden
P	Van BAMBEKE Françoise	Université catholique de Louvain / Pharmacologie cellulaire et moléculaire [UCL]	Belgium
P	TANGDEN Thomas	Uppsala University / Dept of medical sciences [UUT]	Sweden
P	COUET William	University of Poitiers / Pôle Biologie Santé Inserm U1070 [UP]	France
P	BOUSQUET-MELOU Alain	INRA - UMR1331 Toxalim / National Veterinary School [INRA]	France

**Abstract:**

The CO-ACTION project aims to develop and provide a framework for evaluating and validating the effectiveness of antibiotic- and non-antibiotic combinations (COMs) in the preclinical setting based on pharmacokinetic/pharmacodynamic (PK/PD) principles, with a specific emphasis on Neglected and Disused AntiBiotics (ND-AB) as well as COMs with non-antibiotics (NA) both for human and veterinary medicine. To fulfill this ambitious goal, 6 work-packages with 6 interacting partners were developed involving several steps in the development of useful COMs and are executed partly sequential, partly in parallel: screening for CO-ACTION between ND-AB and NA in a collection of strains with well described resistance mechanisms, selecting potential synergistic COMs, subsequent validation using PK/PD experiments and modelling and finally testing COMs in animal models. A full PK/PD work-up and analyses form an important part of the process. The interaction between ND-AB from at least 6 different classes, including Polymyxin B will be determined using checkerboard experiments in 10 well characterized Gram-negative (e.g. *P. aeruginosa*, *K. pneumoniae*) multidrug resistant strains and analysed by surface response modelling. In parallel, a high throughput system (the oCelloscope) will be applied to allow efficient screening for large numbers of COMs.

The CO-ACTION of clearly synergistic COMs will be quantified using kill-curves both in medium as well as intracellularly and PK/PD modelling will be used to predict effective dosing regimens vivo. Effectiveness of the most promising 3-6 COMs will be determined in up to 4 different available animal model systems : a neutropenic mouse thigh and lung model, a rat model and effectiveness in a pig model to evaluate emergence of resistance in the gut of different COMs. A full PK/PD evaluation, including in vivo checkerboards will be performed and assessment of concentrations in ELF and microdialysis. The potential of the COMs in patients will be evaluated by Monte Carlo Simulations of the COMs both using plasma as well as ELF concentrations and derived PK/PD relationships and PD targets. The development of useful COMs requires a high level of interaction between specialized partners. This international collaboration of six partners in CO-ACTION will lead to synergistic antibiotic COMs useful in patient care by bringing together specialists that each have significant expertise in their own field.