CO-ACTION

Prof.dr. J.W. Mouton

Note : some technical and all results slides were removed

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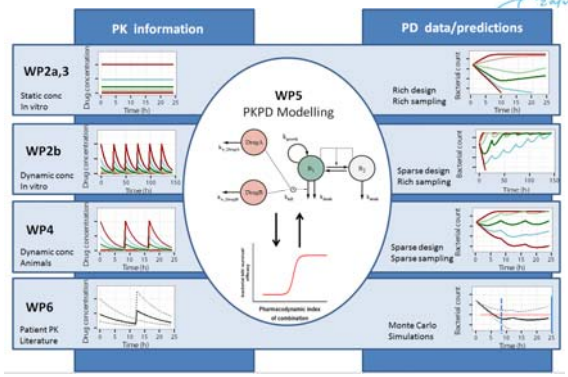

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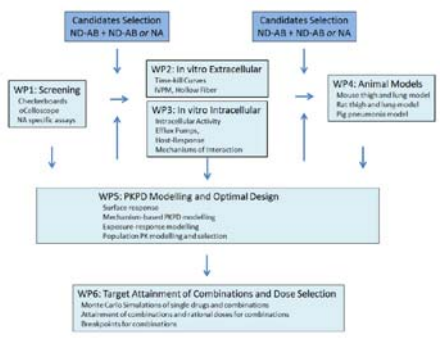

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Clinical Development of (old drug) combinations : essentials

Potency of combination — CoAction

↓

PK profiling — CoAction

↓

Dose

Partners and participants involved in the realisation of the project

Partner Number	Country	Institution/ Department	Name of the Principal Investigator (PI)[1]	Other participant
1 Coordinator	Netherlands	Erasmus University Medical Center / Dept. of Medical Microbiology and Infectious Diseases [EMC]	Mouton Johan	Meletiadis Joseph; post-doc1; PhD1
2	Sweden	Uppsala University / Pharmaceutical Biosciences [UUF]	Friberg Lena	Nielsen Elisabet; Jansson Britt; post-doc1; post-doc2
3	Belgium	Université catholique de Louvain / Pharmacologie cellulaire et moléculaire [UCL]	Van Bambeke Françoise	Tulkens Paul ; Khandekar Shaunak; Peyrusson Frederic; post-doc1
4	Sweden	Uppsala University / Dept of Medical Sciences [UUT]	Tängdén Thomas	Cars Otto; post-doc1; labengineer1; labtechnician1.
5	France	Université de Poitiers / UFR Médecine-Pharmacie [UP]	Couet William	Marchand Sandrine; Grégoire Nicolas
6	France	INRA - UMR1331 Toxalim / National Veterinary School [INRA]	Bousquet-Mélou Alain	Toutain Pierre-Louis; Ferran Aude; Concordet Didier; post-doc1

Drug selection

Antibiotic combinations, AB + AB (≥ 6 classes)

1. **Polymyxins**
   Polymyxin B, colistin
2. Aminoglycosides
   Gentamicin, amikacin, plazomicin
3. Beta-lactams
   Penicillins: temocillin, mecillinam
   Cephalosporins: ceftazidime, ceftolozane
   Carbapenems: meropenem
   Monobactams: aztreonam
4. Fluoroquinolones
   Ciprofloxacin, levofloxacin
5. **Chloramphenicol**
6. **Tetracyclines**
   Minocycline
7. Tigecycline
8. Fosfomycin
9. Rifampicin

Antibiotic combinations Non-AB examples

- **Anti-inflammatory**
- **Efflux pump blockers**
- **Immunomodulators**
- **Beta-lactamase inhibitors**
  - Tazobactam
  - Sulbactam
  - Clavulanic acid
  - Avibactam

Drug selection

- Phenotypical
- Different Assay systems

Overview: oCelloScope

- Microscopy and image analysis.
- Real time monitoring and analysis of microorganisms over time.
- Analysis options:

1. **Growth kinetic analysis (GKA)** –monitor growth of microorganisms using different algorithms *i.e.*
   - Background corrected absorption (BCA)
   - Segmentation extracted surface area (SESA)
   - Total absorption (TA)
   - Segmentation Extraction of Average Length (SEAL)
2. Segmentation –segmentation all objects (bacteria) in a scan area
   - Segmentation parameters e.g. area, circularity, thinned length
   - Segmentation kinetics analysis
3. Cell proliferation and migration analysis *(new version)*

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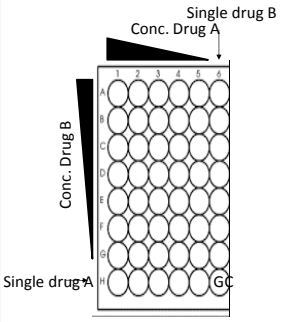
Checkerboard assay



- Serial dilution in horizontal and vertical direction
- Concentrations based on MIC results
- 4x highest MIC and 0.25x lowest MIC

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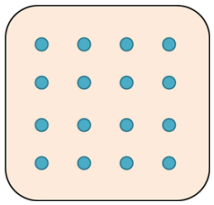
Combination with non-antibiotics

1. Synergy test



17 drugs with antimicrobial activity previously described and available in injectable /oral formulations

First round candidates

NAC Acetylcysteine
Omeprazol
Esomeprazol
Zuclopentixol
Verapamil
Propanolol
Chlorpromazine
Paracetamol
Diazepam
Fenobarbital
Acid acetylsalicilic
Ibuprofen
Haloperidol
Clonazepam
Nifedipine
Lidocaine
Promethazine

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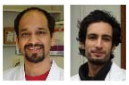
Developing combinations of CO-ACTIVE antimicrobials and non-antimicrobials - intracellular

Pharmacologie cellulaire et moléculaire
Louvain Drug Research Institute
Université catholique de Louvain,
Brussels, Belgium

Supervision:
Françoise Van Bambeke
Paul M. Tulkens

Post-doc in charge:
Emilien Drouot



Intracellular team :
Shaunak Khandekar
Frédéric Peyrusson

Technical staff:
Marie-Claire Cambier
Katia Santos Saial

Task 5.2 and 5.3

PKPD-modelling to…

- Describe time-courses
- Understand interactions
- Predict bacterial killing at 24h as well as at other time points
- Naturally integrate all available information
- Propagate information (translate) from one step to the next
- Design new experiments

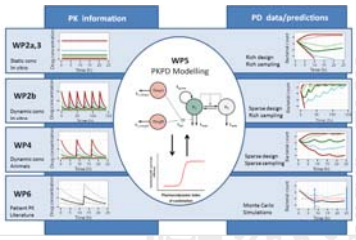
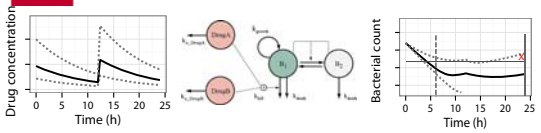


Fig. 2 Illustrates the central position of modelling, prediction and validation after intial screening



- Simulate from
  - Human (patient) population PK from literature
  - Mechanism-based models incorporating both in vitro and in vivo information
- Suggest dosing regimens of combinations based on
  - Proportion of patients
    - Reaching a certain magnitude of bacterial killing at 24h
    - Reaching a certain magnitude of bacterial killing at e.g. 6h (rate)
  - Possibility minimize emergence of resistance
  - Known concentration-toxicity relationships

Animal studies – dose finding

- Major challenge : animal welfare regulations
- Combinations that show synergism in vitro
- Modelling for optimal dosing

Conclusion

- Phenotypical screening assays set up
- Some interesting combinations have come up