Pharmacology of anti-infectious drugs - Inserm U1070

Post-Doc profile
Inserm UMR 1070 – Poitiers- France

Job: Post Doctoral Student

Titile: Antibiotic Distribution and Recovery in Tissue (AB-DIRecT)

Project Duration: September 1, 2019 – May 30, 2021

Manager: William Couet (william.couet@univ-poitiers.fr)

Location: UMR INSERM 1070. University of Poitiers. Health Biology Pole. 1 Rue Georges Bonnet. TSA 51106. 86073 Poitiers Cedex (http://phar.labo.univ-poitiers.fr/)

Financing: IMI (Innovating Medicine Initiative)

Objectives: Gepotidacin is a novel antibiotic currently under development. Its distribution into peripheral tissues following systemic administration has not been fully characterized. The objective of the project is to explore a potential new option for the treatment of pharyngeal *Neisseria gonorrhoeae* infections or prostatitis caused by *Escherichia coli* by demonstrating adequate penetration of a novel antibiotic intonsillar and prostate tissues. This workplan consists in:

- Conducting *in vivo* rat microdialysis in healthy and infected prostatis (*E. coli* prostatitis) and refine existing physiologically based pharmacokinetic (PBPK) models to predict human exposure of gepotidacin in prostatis, and compare them with results of the proposed clinical study;
- Measuring gepotidacin (GSK2140944) levels in tonsillar and prostatic tissue by *ex vivo* microdialysis (and whole organ homogenates for comparison) following single oral dose of gepotidacin in subjects undergoing elective tonsillectomy or prostatectomy;
- Refining the PBPK and the population pharmacokinetic (PopPK) models based on the generated clinical data to describe gepotidacin penetration into human tonsillar and prostate tissue;
- Developing a pharmacokinetic-pharmacodynamic (PKPD) model that relates the gepotidacin tissue exposure (PK) with the effect (PD) from time-kill curves using *E. coli* and *N. gonorrhoeae*;
- Determining the probability for target attainment for 90% of the subjects in plasma, prostatis and tonsils based on data from microdialysis ex-vivo study to support the evaluation of dosing regimens for each disease;

Objectives of Inserm U1070 in this project will be to build PKPD, PBPK and PKpop models to predict tonsil and prostate distribution of gepotidacin levels determined in *ex vivo* experiments, other data on gepotidacin (e.g. existing time-kill curves) and information from the rodent prostatis model

Objective 1: Development of rat E. coli prostate infection model, microdialysis analysis of

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gepotidacin levels in rat prostate and analysis of the data using physiologically-based pharmacokinetic (PBPK) modelling to project the human exposure in the plasma and prostate tissue over time
Objective 2: Non-compartmental analysis using plasma samples obtained in clinical ex-vivo microdialysis study
Objective 3: Population pharmacokinetic model and PBPK models will be built with the simultaneous modelling of plasma and tissue concentrations
Objective 4: PKPD model and Monte Carlo simulations to evaluate different doses and the impact of the tonsil and prostate exposures on eliminating microorganisms

Activities:

- Preclinical protocol writing for submission to the ethics committee
- Work in a level 2 confined environment
- Animal experimentation
- Participation to the *ex-vivo* microdilaysis clinical study
- Analytical assays of gepotidacin in biological rat matrices (plasma, dialysates) by LC-MS/MS in an ISO 9001 environment
- Non-compartmental analysis of *ex-vivo* clinical data
- PBPK modelling of plasma and tissue pre-clinical data
- PKPD modeling of *in vitro*, pre-clinical and *ex-vivo* clinical data and Monte Carlo simulations
- Communications: writing articles, poster and oral presentations....

Aptitudes:

- Rigor and organization
- The ability to work in a team
- Autonomy

Required degree level: PhD in pharmacology and/or pharmacokinetics

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