**Titre de thèse :** ***Physiologically based pharmacokinetic modelling of drug combinations: case of immunosuppressive therapy in solid organ transplantation***

**Financement :** sous réserve AAPNA

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**Mots clés :** Physiologically based Pharmacokinetics/ Modelling and Simulations/ Immunosuppressants

**Profil et compétences recherchées :** Life Sciences (Medicine, Pharmacy, etc.), Statistics, computational sciences

**Description de la problématique de recherche :**

In several indications, more than one drug is needed to achieve the therapeutic effect with acceptable safety. In such situations, it is believed that the pharmacological (pharmacokinetic and pharmacodynamic) properties of these drugs permit expecting some added-value for the patient when they are combined as compared to when either of the combination components is used as monotherapy. Better understanding of these pharmacological interactions using quantitative tools such as physiologically based pharmacokinetic modelling and quantitative systems pharmacology methods offers an interesting opportunity for characterisation of the optimal doses for the different compounds included in the combination therapy.

Immunosuppressive therapy implemented after solid organ transplantation most often includes more than one drug. Most frequently drugs pertaining to different pharmacological classes such as calcineurin inhibitors (tacrolimus), antiproliferatives (mycophenolate), mTOR inhibitors (everolimus, sirolimus), and/or corticosteroids (methylprednisolone) are combined. However, the doses (or target exposures) for the different drugs are currently determined without taking into account the other(s) component(s) of the combination. There is currently very limited information available on the actual impact of the overall exposure to immunosuppressive drugs on the clinical outcome after solid organ transplantation and particularly graft rejection, drug toxicity, and patient survival. More optimal dosing of the drugs included in the combination would allow improving the patient quality of life and long term survival which are still considered as challenges in solid organ transplantation.

**Thématiques Domaine Contexte :**

Physiologically based pharmacokinetic modelling and simulations and quantitative systems pharmacology methods have successively be used to characterise drug-drug interactions in several other indications but their use in the field of transplantation is currently very limited. The working hypothesis for this thesis is that the use of these advanced tools will allow better understanding of the pharmacokinetic and pharmacodynamics interactions between the drugs included in immunosuppressive therapy in solid transplantation and therefore permit improving patient outcome thanks to optimal dosing of the different drugs included in the different combinations implemented after solid organ transplantation.

**Objectifs :**

The objective of this thesis will be to develop mathematical models to inform better dosing of drugs included in combination therapy in solid organ transplantation.

**Méthode :** Physiologically based pharmacokinetic modelling and simulations

**Résultat attendu :** Physiologically based pharmacokinetic models for different immunosuppressants and simulations of optimal dosing in different situations/contexts

**Références bibliographiques :**


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