H.F.R.I.
Hellenic Foundation for Research & Innovation

Description of the funded research project

1st Call for H.F.R.I. Research Projects to Support Faculty Members & Researchers and Procure High-Value Research Equipment

Title of the research project:
Optimizing drug development by Modeling and Simulation approaches

Principal Investigator:
Aristeidis Dokoumetzidis

Reader-friendly title:
Optimizing drug development by Modeling and Simulation approaches

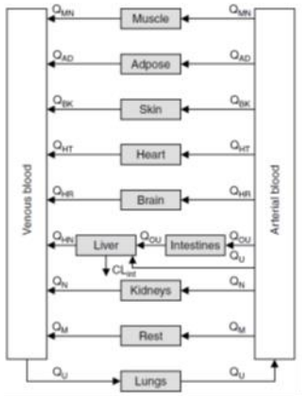
Scientific Area:
Life Sciences

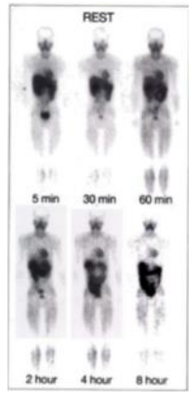
Institution and Country:
National and Kapodistrian University of Athens, Greece

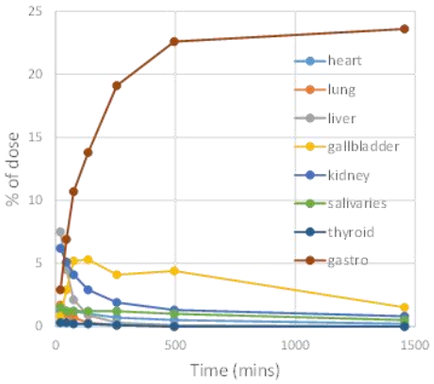
Host Institution:
“Athena” Research Center

Collaborating Institution(s):
National and Kapodistrian University of Athens

Project webpage (if applicable):
https://oddms.wordpress.com/







Budget: 180000 €

Duration: 36 months

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Research Project Synopsis

In a wide range of scientific and industrial applications, from weather forecasting to heavy industries, Modeling and Simulation (M&S) is an approach which uses computational models developed from scientific knowledge and collected data, in order carry out simulations for scenarios where data is sparse, or non-existent. In the last two decades M&S has found significant applications in all phases of drug development and has created the new field of pharmacometrics. Pharmacometrics relies on building mathematical models which describe the pharmacokinetics and pharmacodynamics of drugs, as well as the variability of the corresponding model parameters. Project ODDMS deals with the application of M&S methodologies in drug development, by focusing on 3 categories of products of particular interest to the Greek pharmaceutical Industry, and aims to produce (a) methodological advances in the way these products are developed by the industry and approved by the authorities and (b) produce specific new results for the application of the particular products studied. The proposed case studies are: (a) Absorption and pharmacokinetics of Long Acting Injectable products by Population pharmacokinetic modeling. (b) Gastrointestinal drug absorption by Physiologically Based Phaarmacokinetic (PBPK) models targeting in-silico bioequivalence studies. (c) Pharmacokinetics, efficacy and safety of radiopharmaceuticals by PBPK models developed from imaging data. For these studies specific pharmaceutical products will be used as case studies. The products studied are supported by significant amounts of quality datasets, which will be offered by Greek pharmaceutical companies. The main work will be undertaken by 3 PhD students, who will be trained at the highest level in the rapidly growing field of pharmacometrics with great career prospects and in collaboration with experts from Greece and abroad.

Project originality

In the project ODDMS modelling and simulation approaches will be utilized to develop novel methodologies and produce new results for in silico clinical trials.

Long Acting Injectables (LAI). The pharmacokinetics and absorption of LAI formulations will be studied, by the development of Population Pharmacokinetic models of the studied products to characterize in detail, their clinical performance, including the observed variability of all parameters. Also information from in vitro data will be incorporated explicitly in the models such that novel, model based, in vitro - in vivo correlations.

Virtual Bioequivalence studies. Physiologically Based Pharmacokinetic models (PBPK) can be used for gastrointestinal absorption of drugs for optimizing the formulation which is of particular interest to pharma companies developing generics. In the project ODDMS, retrospective clinical data from LAI products will be utilized, together with in vitro data, in order to predict retrospectively the clinical performance of these products with the intention of utilizing the methodology prospectively in the future. The ultimate goal of the project is to develop a novel platform for silico bioequivalence studies and greatly reduce generic drug development costs.

In silico dosimetry studies. An advantage of PBPK models is the ability to extrapolate. Usually such models are developed using either in vitro or preclinical data and then extrapolated to humans, since data from humans that offer mechanistic information (e.g. drug levels from individual tissues) are difficult or impossible to obtain. In the project ODDMS we will develop PBPK models from human imaging data. This is a novel approach which offers a way to develop PBPK models directly in humans using fewer assumptions and the potential to extrapolate to paediatrics or other special populations (e.g obese). The approach will be used to carry out in silico dosimetry studies to determine paediatric doses of radiopharmaceuticals.

Expected results & Research Project Impact

The proposed research is expected to provide results and have high impact in three main ways: (a) The optimization of the development of certain drug products, (b) regulatory impact in the way certain drug products are approved by the authorities, (c) the development of the M&S approach in the Greek Pharmaceutical Industry and (d) the training in pharmacometrics that 3 young scientists will receive.

These impacts have scientific, economic and social nature at the same time, since they mainly concern clinical aspects of drug therapies. These include new scientific knowledge, which optimizes and reduces the cost of drugs (economic impact), safer therapies to patients, such as recommendation of paediatric doses (social impact) as well as reduction of clinical studies (ethical and economic impact). In silico clinical trials are part of the EU strategy for the next 10 years as reported by the Avicenna Roadmap.

A more general impact comes from the development of M&S methodology in the Greek University and its adoption by the Greek industry, since this consists a competitive advantage. Also, training of young talented people in this rapidly growing field will have extremely positive influence in their career and may limit “brain drain”, an added benefit for the country.

The importance of this funding

The H.F.R.I. has offered our lab funding of 180000 € for 3 years. For me this grant is particularly important of a number of reasons. Especially in my field which is computational and it is considered relatively low budget this amount is very substantial, and it would be sufficient to fully fund our lab fully, for 3 years even if we did not have other funding. The grant is giving the opportunity to 3 talented young scientists to carry out their PhD. Unlike other, mainly EU projects, where each partner carries out a portion of a larger project, the H.F.R.I. grant offers the opportunity to a PI to do standalone research in a way that only the ERC offers, which is of course extremely competitive. It is therefore not surprising, that the H.F.R.I. grant is quite prestigious, which is yet another reason that makes it important for me.

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