

memtrans



Project N° : 518246

MEMTRANS

“Membrane transporters: In vitro models for the study of their role in drug fate”

STREP

Thematic priority 1: Lifesciences-Genomics and Biotechnology for Health

**PUBLISHABLE EXECUTIVE SUMMARY OF
PERIODIC ACTIVITY REPORT**

(2nd Period)

Period covered: from 01/04/2007 to 31/03/2008

Date of preparation: 15/05/2008

Start date of project: 01/04/2006

Duration: 36 months

Project coordinator name: Dr. Marival Bermejo

Project coordinator organisation name : UNIVERSITAT DE VALENCIA

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1. PUBLISHABLE EXECUTIVE SUMMARY

I) PROJECT OBJECTIVES

The goals of MEMTRANS project are to optimize and pre-validate validate in vitro cultured cell models to predict oral absorption and pharmacokinetics of efflux systems substrates (P-gp, MRP2, BCRX for instance), to establish an in vitro cut off for the experiments to study efflux processes; 2) the in vitro study of drug-drug (including phytopharmaca), drug-food, interactions related to secretion transporters; and 3) to obtain useful information for modelling transporter interactions in other normal and transformed tissues (blood brain barrier, lung mucosa, tumours).risk of secretion associated problems and to study the structure-affinity-transport relationships. That would allow 1) a reduction in the number of animal

The objectives of the project will be achieved by using a systems biology approach that involves modelling and simulating the complex dynamic interactions between proteins (transporters), metabolites (i.e substrates) and cells (lipoidal barriers). Computational and mathematical predictive models will be generated from the data based on the system parameters and drug characteristics. The experimental data generated in the project will be analyzed from a mechanistical point of view in order to split all the individual steps involved in transport. The mathematical models in combination with the right physiological, physicochemical and chemical information will be applied to predict drug transport in a wide range of membranes in the organism (blood brain barrier, liver, kidney, tumors etc) but especially in the gastrointestinal tract.

II) CONTRACTORS INVOLVED

Table 1. Contractors involved in MEMTRANS project

Partic. Role*	Partic. no.	Participant name/ Organisation	Participant Acronym	Country	Date enter project	Date exit project
CO	1	University of Valencia	UVEG	Spain	Month 1	Month 36
CR	2	Intervalece Biokinetics	INBIO	Spain	Month 1	Month 36
CR	3	Across Barriers GmbH	ACB	Germany	Month 1	Month 36
CR	4	Solvo	SOLV	Hungary	Month 1	Month 36
CR	5	Aukstieji Algoritmai	AA	Lithuania	Month 1	Month 36
CR	6	Hungarian Academy of Sciences/NMC	HAC	Hungary	Month 1	Month 36

*CO = Coordinator CR = Contractor

Table 2. Details of Participants in MEMTRANS project

Partner number	Acronym	Chief Scientist	e-mail	Phone	FAX
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3	ACB	E. Haltner	dr.haltner@acrossbarriers.de	+49 68195918800	+49 68195918802
4	SOLV	P.Krajcsi	krajcsi@solvo.hu	+36-23-503-940	+36-23-503-941
5	AA	P. Japertas	pranas@ap-algorithms.com	+370 5 2624032	+370 5 2623728
6	HAC	B. Sarkadi	sarkadi@biomembrane.hu	+3613724316	+3613724353

III) COORDINATOR OF PROJECT/SCIENTIFIC COORDINATOR

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IV) APPROACH AND METHODOLOGY

Prevalidation of different methods to predict gastrointestinal absorption of secretion transporters substrates.

Standard operation procedures for maintaining and working with the developed models in order to reduce inter-laboratory variability and to allow exchange of data obtained in different laboratories that might lead to a reduction of animal and human studies as showed by the validation of cell culture models for gastrointestinal absorption accepted by the FDA in its guidance about biowaivers based on the Biopharmaceutical classification system whose concepts are also included in the EMEA bioequivalence guidelines.

Mathematical models to predict from in vitro data the in vivo intestinal efflux characteristics and its impact on drug ADME.

V) RESULTS ACHIEVED SO FAR AND EXPECTED END RESULTS

With this improved validated in vitro methodology it would be possible to avoid extensive animal experimentation in preclinical phases to study efflux processes and to prevent failures of drug candidates due to poor absorbability. At the same time, an appropriate in vitro model with a level of P-glycoprotein similar to that found in experimentation animals and with less interlaboratory variability would allow the combination of data obtained in different laboratories and in this way will improve the statistical signification of the established relationships. All these facts will be reflected in faster development of new drugs for patients.

The oral route for drug administration is the most convenient and preferred by patients, and the prediction of drug absorption from the GI tract is a key issue for a potential new medication in the process of drug design and development. The early prediction of favourable pharmacokinetic properties is the new paradigm in the screening of drug candidates. Current in vitro models for the predictions of drug transport across biological membranes include cell cultures that reproduce physiological characteristics of different barriers, such as the intestine, the blood-brain barrier or the kidney and liver.

These models have shown good performance for compounds that are transported by passive diffusion, but for drugs with a carrier-mediated mechanism, the predictions are less accurate, mainly due to the differences in expression levels and affinity for the carriers in vitro versus the in vivo situation. Several ABC transporters (ATP binding cassette), e.g. Pgp, BCRP and the MRP family are expressed in the intestine as well as in other tissues involved in drug distribution and elimination, such as the blood brain barrier, liver and kidney cells. It has been demonstrated that these proteins are responsible for the low and

erratic bioavailability of several drugs and these transporters have been pointed out as a major cause of the low access of some drugs, such as HIV protease inhibitors, to the central nervous system or as the cause of drug-drug interactions at the excretion and absorption level. Finally, the ABC-transporters are also expressed in tumor tissues, where they confer multidrug resistance to chemotherapeutic agents.

For these reasons it is of paramount importance to know already in the early stages of drug discovery whether a new compound is or is not a substrate and/or an inhibitor of an efflux pump in order to prevent absorption problems, drug-drug, drug-food interactions and to minimize pharmacological resistance.

The in vitro cell cultures currently used (Caco-2 cells) for high-throughput screening of absorbability-distribution of new drugs show good performance with passively absorbed drugs, but in the case of compounds absorbed by active mechanisms the predictability is still poor. The expression level of the transporters differs between clones and laboratories and it is highly dependent on the culture conditions. Standardised procedures and the use of quality controls to verify the functionality of the transporters are essential to achieve good predictive performance. On the other hand, stable cell lines with good expression of the transporter of interest are scarcely available.

VI) INTENTIONS FOR USE AND IMPACT

The MEMTRANS project will be coordinated -both at management and technical level- with the Network of Excellence BIOSIM. The proposed work in this project is directly related to workpackages 15 and 16 of the mentioned BIOSIM NoE. The BIOSIM was approved under the priority “Computer assisted modelling in drug discovery and development (LSH-2003-1.2.1-2)” The objective of the BIOSIM network is to take advantage of the benefits that can result from application of modern simulation techniques in the formulation of a dynamic and mechanism-based description of biological and pharmacological systems.

For that reason the potential impact of this STREP application is directly related to the impact of the BIOSIM NoE, as we shared the common objectives of:

- Integrate basic academic research with practical applications in the pharmaceutical and biotechnological industries
- Integrate a broad variety of biomedical research areas (bioinformatics, mathematical modelling, computer simulation, cell biology, physiology, etc.)
- Integrate different modelling approaches (pharmacokinetic/ pharmacodynamic modelling, mechanism-based modelling, etc.)
- Integrate national efforts in biosimulation into a coherent European network.

The main link between the MEMTRANS project and the BIOSIM network of excellence is WP15. There are clear differences in the approach and in the particular deliverables. BIOSIM WP15 has as main goal establishing relationships between in vitro and in vivo absorption models. The work is being focused in particular xenobiotics, for which in vivo animal experiments will be performed. On the contrary in MEMTRANS compounds with already existing in vivo human data will be assayed to prevalidate the in vitro models

On the other hand, the MEMTRANS project is a specifically targeted project on the prevalidation of in vitro methods with a clear focus on secretion transporters. The BIOSIM NoE, according to the type of instrument, is focused on enhancing the collaboration

among the partners to solve problems of common interest, but not the research itself. The MEMTRAS project will contribute to the BIOSIM objectives by providing knowledge on the influence of pharmaceutical excipients on the in vitro models, as the BIOSIM WP15 is intended to promote the collaboration among different European groups working on the absorption/pharmacokinetic-modelling. The BIOSIM WP15 focus for coordination of research is not only efflux but also absorption transporters and the simulation of other biological barriers as blood brain barrier.

The development of a new safe medicine needs a multidisciplinary approach that due to the problem size and complexity is more meaningful if it is addressed at European level. The MEMTRANS will improve the selection procedure of new drug entities with an in vitro methodology alternative to the pre-clinical use of animals, reducing the risk of failures in further phases of the development and reducing the numbers of candidates to be tested in animals. The work to be developed will improve the predicting ability about the biopharmaceutical properties of the new drugs. These high quality predictions would help to a smooth transition between the discovery of a new molecule and the introduction of the new drug for human use and would help to a better exploitation of the preclinical data.

The use on in vitro models, (once the in vitro model has been validated), allows reducing the use of animals: this will have a clear translation in lower development cost and less time-consuming processes. Moreover, the use of a good predictive model in the early phases of drug development could avoid non-optimum drug candidates reaching clinical development and to be withdrawn later with the wasting of time, resources and money that this fact implies. These later failures in clinical phase, drive usually to the use of more animal experimentation to assay novel drug formulations that could "save" the failing drug to its clinical use. Finally, all these advantages will translate in strengthening European competitiveness.

The project results will also produce new knowledge by improving the understanding of the absorption, metabolism and elimination mechanism. The better knowledge of these mechanisms could bring new development opportunities using the carrier system as a novel target for new drugs. The possibility to determine in vitro whether a drug will or not be rejected in the intestine -and maybe in other tissues- would favour the design and development of novel improved therapeutics. On the other hand, the use of the in vitro model will help the study of drug-drug interaction and food-drug interaction and it will contribute to the design of the suitable clinical trials.

VII) PLAN FOR USING AND DISSEMINATION OF THE KNOWLEDGE

The dissemination of project results will be co-ordinated by the Management. The Consortium will generate a mechanism to protect the knowledge and to guarantee the exploitability and the dissemination of results.

The MEMTRANS project team will collaborate with the BIOSIM NETWORK of Excellence in the dissemination tasks. Therefore, the MEMTRANS results will be disseminated within the BIOSIM as a complementary channel.

The Dissemination activities will consist of:

- Publication of papers in scientific publications and congresses. Main targeted events are the meetings organised by EUFEPS, Eurotox and CRS, German

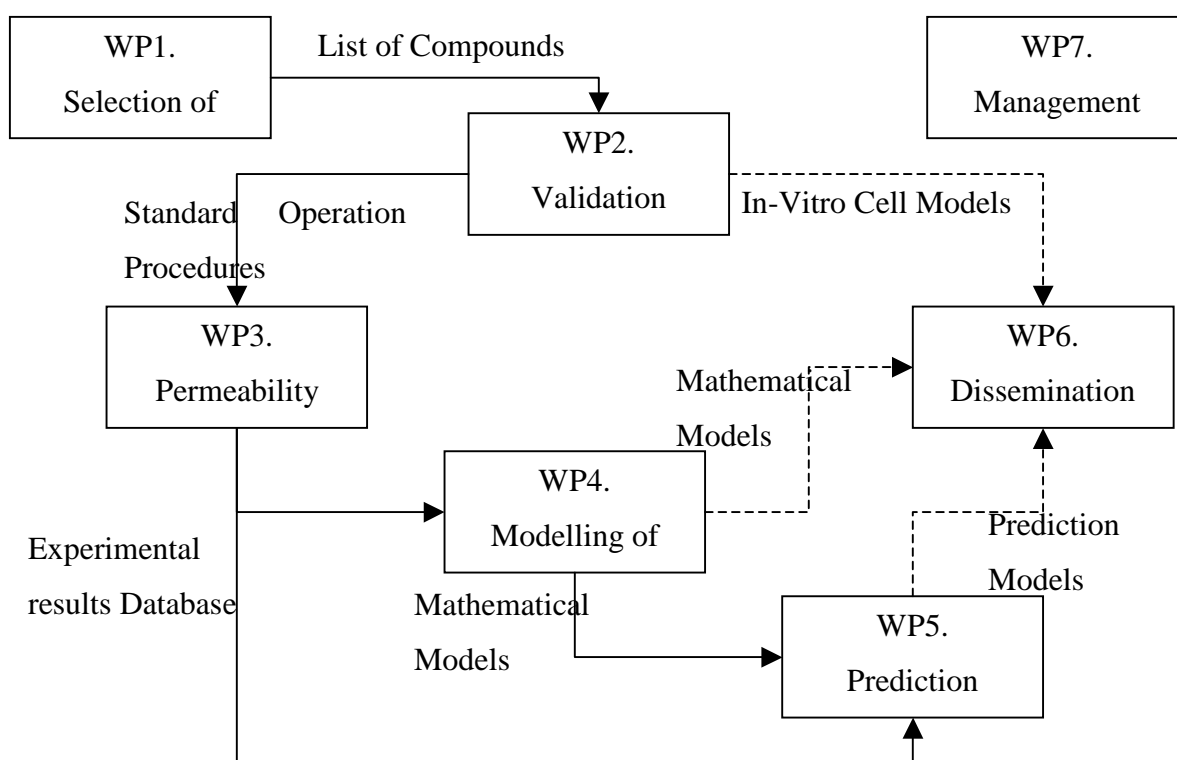
Pharmaceutical Society (DPhG), International Association for Pharmaceutical Technology (APV), Federation Internationale Pharmaceutique (FIP) and EFMC.

- Participation in the Biosim conferences and presentation of project results, targeting both industry and academia. Computerised material on project results will be distributed in CDROM to the attendants and to a wider audience by mailing.

The public area of the Project web site will allow access to updated information on project progress and generated material publicly available.

As individual partners dissemination tasks, the results shall be also disseminated through short training courses to customers, with the support of the computerised material developed for the conferences.

VIII) DIAGRAMS OR PHOTOS ILLUSTRATING THE WORK



IX) PROJECT LOGO

memtrans

X) REFERENCE TO THE PROJECT PUBLIC WEBSITE

<https://teamsite.intervallence.com:8443/internal/Memtrans/default.aspx>