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Modelling toxic response in case studies for predictive human safety assessment

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Report on exploitation Plan of IP**

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RE	Restricted to a group specified by the consortium (including the Commission Services)	
CO	Confidential, only for members of the consortium (including the Commission Services)	

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Table of Contents

PUBLISHABLE SUMMARY	3
OBJECTIVES	3
1. INTRODUCTION	3
1.1. Purpose of the document	3
2. MANAGEMENT OF KNOWLEDGE, INTELLECTUAL PROPERTY AND OTHER INNOVATION RELATED ACTIVITIES	5
2.1. Likelihood of market uptake of project results.....	5
2.2. Exploitation of HeCaToS project results	6
2.3. Intellectual property management.....	8
2.4. Patents & protection.....	8

PUBLISHABLE SUMMARY

This is deliverable D14.3 Report on Exploitation Plan of IP of the FP7 project HeCaToS. This work was carried out as part of WP14 Management en WP13 Training and dissemination, specifically Task 14.6 Setting up ground rules for the management and exploitation of IP which might be generated by HeCaToS.

An important goal of the HeCaToS project is to develop integrative *in silico* tools for predicting human liver and heart toxicity, to ensure the sustainability of the project's outcomes through the Dissemination & Exploitation (D&E) activities to be developed during the project and will continue after it finishes. This first Exploitation Plan of IP sets the direction for all future actions and summarizes everything that needs to and will be done to ensure this.

OBJECTIVES

HeCaToS aims at developing integrative *in silico* tools for predicting human liver and heart toxicity. The objective is to develop an integrated modeling framework, by combining advances in computational chemistry and systems toxicology, for modelling toxic perturbations in liver and heart across multiple scales. This framework will include vertical integrations of representations from drug(metabolite)-target interactions, through macromolecules/proteins, to (sub-)cellular functionalities and organ physiologies, and even the human whole-body level. In view of the importance of mitochondrial deregulations and of immunological dysfunctions associated with hepatic and cardiac drug-induced injuries, focus will be on these particular Adverse Outcome Pathways.

Models will be populated with data from innovative *in vitro* 3D liver and heart assays challenged with prototypical hepato- or cardiotoxicants; data will be generated by advanced molecular and functional analytical techniques retrieving information on key (sub-)cellular toxic events. For validating perturbed AOPs *in vitro* in appropriate human investigations, case studies on patients with liver injuries or cardiomyopathies due to adverse drug effects, will be developed, and biopsies will be subjected to similar analyses. Existing ChEMBL and diXa data infrastructures will be advanced for data gathering, storing and integrated statistical analysis.

Model performance in toxicity prediction will be assessed by comparing *in silico* predictions with experimental results across a multitude of read-out parameters, which in turn will suggest additional experiments for further validating predictions. HeCaToS, organized as a private-public partnership, will generate major socioeconomic impact because it will develop better chemical safety tests leading to safer drugs, but also industrial chemicals, and cosmetics, thereby improving patient and consumer health, and sustaining EU's industrial competitiveness.

1. INTRODUCTION

1.1. Purpose of the document

The purpose of the Exploitation Plan (IP) is to provide guidelines to consortium partners in terms of establishing their individual Dissemination and Exploitation Plans for the HeCaToS outcomes. It also provides details for the Dissemination and Exploitation actions to be undertaken during the lifetime of the HeCaToS project, as well as after it finishes.

"Exploitation", in its positive meaning, is considered as "making use of and deriving benefit from a resource". Exploitation is associated with using the project outcomes at different levels, during the project and after its end.

Dissemination is linked to exploitation in the sense that efficient publicity is a facilitator of the exploitation of these results beyond the project lifetime. Dissemination allows to measure acceptance of the proposed concepts and reuse of them in other projects. While the Dissemination and Communication plan (WP13) defines strategy and planned activities, the Exploitation Plan presents in details the actual activities and how they support exploitation. It contains partners' intentions towards exploiting the project results to support their own business or activities.

The HeCaToS project requires a coordinated dissemination and exploitation of results approach in order to exploit the possibilities within the current regulatory framework, to speed up the process of finding acceptance of its developed computerized prediction models for repeated dose toxicity, to support their implementation, and to communicate with institutions and parties involved in the introduction of predictive methods for chemical safety, and also to challenge a bit the politicians to feel responsible for the sequels of their demands in the context of the 7th Amendment and of REACH. The HeCaToS project will act correspondingly, through its active dissemination strategy, according to the EU FP7 Grant Agreement which requires project participants to communicate and engage with actors beyond the research community.

The dissemination and training Workpackage has been organised as a separate Workpackage (WP13) as an element of the coordinating activities, under the guidance of partner Imperial College, in close collaboration with the Coordinator, while the other HeCaToS partners (Table 1) and the international community of stakeholders will contribute.

Table 1: List of HeCaToS participants

Participant no.	Participant organisation name	Country
1 (Coordinator)	Maastricht University (UM)	Netherlands
2	Hoffmann-La Roche (Roche)	Switzerland
3	InSphero	Switzerland
4	University Hospital La Fe (HULAFE)	Spain
5	ETH Zurich-Functional Genomics Center (ETH)	Switzerland
6	Imperial College London (ICL)	United Kingdom
7	LuxCel	Ireland
8	European Molecular Biology Laboratory-European Bioinformatics Institute (EMBL)	Germany
9	Genedata (GD)	Switzerland
10	Max Planck Society/Max Planck Institute for Molecular Genetics (MPIMG)	Germany
11	King's College London (KCL)	United Kingdom
12	Rheinisch-Westfaelische Technische Hochschule Aachen (RWTH)	Germany
13	MicroDiscovery (MD)	Germany
14	Optibrium Ltd (OPT)	United Kingdom

Over the course of the project, HeCaToS will build and implement a clear intellectual property right strategy. Integrating many active participating consortium partners needs a clear and coherent policy for the management of knowledge, intellectual property rights and other innovations. The IPR policy of the HeCaToS project considers that each consortium partner contributes differently with regard to pre-existing know-how, knowledge generated during the period funded by the European Commission and beyond, and with regard to allocated funds and effort, procedures, systems, stakeholders and users, while knowledge newly generated under the HeCaToS project, will most probably be co-owned.

This policy will also consider that commercial interests of consortium partners, and the requirements of the patent filing process, may need to lead to postponing of:

- I. Publication, abstracts, posters, and
- II. Data sharing with global consortia for a grace period of 6-12 months.

In view of these challenges, the management of knowledge, IP and other innovations, in terms of both strategy and execution, will be a constant priority for the Executive Board.

2. MANAGEMENT OF KNOWLEDGE, INTELLECTUAL PROPERTY AND OTHER INNOVATION RELATED ACTIVITIES

Intellectual Property Rights (IPR) will be handled in conformity with the terms of the EC Contract. As a condition for proper management of knowledge, at the time of signing the HeCaToS Consortium Agreement all partners have been asked to list pre-existing know-how and knowledge already protected. Each methodology will identify every item sensitive to IPR, both internal and/or external of the consortium and considering background knowledge.

Each partner will have the property of his results, and thus will be free to patent and disclose results from research activities funded by the HeCaToS project, and will have the right to publish the results subject to prior approval of other consortium partners. Access rights of consortium partners to foreground and background IP has been laid down in the Consortium Agreement.

The consortium will actively explore opportunities for IPR. Workpackage leaders will be required systematically to file and report to the Executive Board new knowledge generated during the project period funded by the European Commission. The Executive Board will regularly evaluate opportunities of generating Intellectual Property and other innovations. The protection of the intellectual properties (IPs) of the project with patent applications will be reviewed continuously in the project as soon as results appear, and IP protection activities initiated. The knowledge management framework will thus enable real time analysis of output progress in the Workpackages, permitting the rapid deposition and licensing/commercialisation strategy of patents.

2.1. Likelihood of market uptake of project results

SME's play a pivotal role with their capacities to generate new innovations and drive them to the market. The HeCaToS project provides major opportunities for the involved SME, both to finance R&D and innovate products and services and to build strategic partnerships and operate in wider markets. The involved SMEs are notably in an area of high potential growth and will obtain a unique opportunity through this project to strengthen their position in the emerging market of *in vitro* toxicity testing with subsequent ranking.

End users of the technological platform and database developed within the HeCaToS project will be enabled to address the increasing need to further improve their drug development process.

Prior to dissemination, any protocols generated will be subject to an internal QMS procedure with is externally audited, thereby insuring a quality output. Within the consortium there is the possibility for close collaboration with relevant industrial partners, to maximise the impact of the data generated. There is the potential for the development of tools and measurement strategies which would be of particular interest to the safety assessment community within the pharmaceutical and biotech industries.

Where possible based on dissemination level, data generated will be discussed at relevant exhibitions and trade shows at which SME's participating in HeCaToS, will have a presence, such as Experimental Biology and the Annual Meeting of the Society of Toxicology. Where permissible, information will also be communicated to key industrial partners and opinion leaders.

This puts in particular InSphero (Partner 3) in position to provide new, systematically validated solutions for a first toxicological assessment already at an early stage in the development process, in which a high number of data points can be generated with primary liver and iPS-derived cardiac model. This complements the InSphero model portfolio derived from human donors for later stage testing focusing on aspects such as patient to patient variations or idiosyncratic toxicology.

For InSphero the technical knowledge and resulting product will have a substantial impact on the company growth and success in the years during and after the project. Together with its international competitors, InSphero has created a steadily increasing acceptance in the market place to use organotypic 3D cell models instead of assays based on 2D monolayers. However, whereas there is long time experience with traditional 2D models there is a high demand on generating data using novel more organotypic liver model systems which allow a better toxicological profiling than with conventional 2-dimensional cell models. The resulting data will provide in depth biological understanding of the model and significantly contribute to the acceptance and use of HepG2 microtissues for toxicity testing.

Regarding the assay development and the limited number of test compounds it is still valuable for modeling but to further validate the model for early stage applications more compounds would be required.

Genedata (Partner 9) is well established in the pharmaceutical market, especially also in toxicogenomics and biomarker research. HeCaToS is the next logical step for Genedata, since it makes use of the extensive experiences in application of bioinformatics solutions to toxicity assessment gained within numerous academic and industry collaborations, to develop a computational toxicity prediction platform. The project is driven by end user needs which are, at the same time, the most important customers of Genedata's bioinformatics solutions already. Through participation in this project, Genedata assures to stay on top of customer needs, further strengthens its expertise in the field of toxicity modeling, and proves once more the exceptional competitiveness of its solutions, especially in toxicogenomics applications.

2.2. Exploitation of HeCaToS project results

The HeCaToS project requires a coordinated and adequate dissemination approach on several levels:

- With the consortium to facilitate the transfer of knowledge and knowhow from RTD to SME's;
- With members of the SME's, to disseminate technological innovations widely within the toxicogenomics research society;
- With relevant stakeholders, Regulatory bodies, pharma-, cosmetic- and chemical industry.

HeCaToS can contribute to the increasing acceptance of more organotypic models for drug profiling and this allows developing “translational *in vitro* assays” which are characterized in depth. A translational *in vitro* assay means that we set up the testing conditions as physiologic as possible, applied on an organotypic model, use clinical relevant end points and complement that with computational modeling to make a risk assessment for the patient. As the modeling team around WP4 is working with open access software we can consider to open the software for the public to enable translational computational modeling to a broad user spectrum - imagine that open access concepts will find high appreciation by the EU.

	IP-POTENTIAL	DISSIMINATION
IN VITRO MODELS	Low	IS
TREATMENT MODALITIES (E.G. HOW TO MIMICK PHARMAKOKINETICS AND DYNAMICS)	Low	RO/IS
TRANSLATIONAL ASSAY DEVELOPMENT	Medium	LU
NOVEL BIOMARKERS	High	GE
TRANSLATIONAL ALGORITHM'S	High	GE

Furthermore the HeCaToS consortium intends to work as well on the ‘political level’ at the regulatory bodies to create awareness how translational *in vitro* assays (“physiological substance concentration’s and kinetics, organotypic model and clinical translational endpoints”) can benefit patient’s healthcare. In this perspective the discovery of “potential novel biomarkers/signatures” might improve toxicological predictions in the early stage of drug development.

In fact, continuous interaction with end-users will allow both a fast and capillary diffusion of HeCaToS strategies and a direct access of HeCaToS outcomes to the research community. On the other hand, the end-users allows the active participation of expert end-users that is very useful in suggesting and driving the requirements and the needs in order to improve the effectiveness and the suitability of the final results developed in the HeCaToS project.

Workpackage leaders will systematically file and report new knowledge generated during the project period funded by the European Commission. Each methodology has identified every item sensitive to IPR, both internal and external of the consortium and considering background knowledge.

Each partner has the property of his results, and thus is free to patent and disclose results from research activities funded by the HeCaToS project, and has the right to publish the results subject to prior approval of other partners. In case of joint ownership of the results, the ownerships share of each of the joint owners shall be determined in good faith, taking into account each owner’s relative intellectual contribution to the joint results. They will enter into negotiations to conclude a joint ownership agreement.

The HeCaToS consortium will actively explore opportunities for IPR. The Executive Board has regularly evaluated opportunities of generating IP and other innovations. The protection of the IP of the project with patent applications is reviewed continuously in the project as soon as results appear and IP protection activities are initiated.

The knowledge management framework will enable real time analysis of output progress in the Work Packages, permitting the rapid deposition and licensing/commercialisation strategy of patents.

The Executive Board will see to it that potential IP will not inflict on the general progress of the HeCaTos project

Potential IP that is identified during the described process can be submitted to the patent attorney of Maastricht University, who will take care for the initial checks and any filings of the patents. In addition, in case the data should be anonymized, then this is a competence/responsibility which has to be specifically recorded in a separate document.

2.3. Intellectual property management

The Consortium Agreement is a very important document when it comes to ownership and sharing of Knowledge or project result, as it sets out or further defines how the consortium agrees on the use and dissemination of the project results.

The background that is brought into the project will always remain the property of the partner(s) involved. Those partners making available pre-existing know-how during the course of the project will specify any conditions for access thereto in the Consortium Agreement.

The Consortium agreement will dedicate one section or one appendix to define which access rights to the background may be granted. Also background to be excluded from access rights in any event will be specified in another dedicated section or appendix. All other background will be considered as unnecessary and excluded from the access rights.

In the case of the foreground, i.e. the project results and any IPR that can be attached to them, typically it is owned by the participant that carried out the work from which it resulted. Nevertheless, the intention of the consortium is to strive for a maximum of openness in the design and operation of the Transport and Mobility Internet. This platform will facilitate the pooling of data and services and could thus lead to maximum growth of the eventual market. Also, any genuine service or information provider should be freely able to join the network and add to the choices on offer to customers.

Partners working in the same WP shall have Access Rights to all foreground and background needed for the execution of the WP, from all WP Partners. Participants from other WPs will enjoy the same access to foreground and background, if these form part of a deliverable or are necessary for the execution of the sub-project.

Bilateral agreement between the Contractors participating in the same WP or in other WPs may be set if Contractors believe that foreground or background forms part of a deliverable of the other WPs or is necessary to carry out activities in the other WPs. These access rights can be extended to affiliates that are participating to the project, but these rights will expire at the end of the project.

2.4. Patents & protection

Publication and dissemination of foreground are granted with the approval of the Consortium, making sure that the period of secrecy needed for a successful patent application is respected.

Any patent applications relating to foreground filed shall be reported in the plan for the use and dissemination of foreground, including sufficient details/references to enable the Commission to trace

the patent (application). Any such filing arising after the final report must be notified to the Commission including the same details/references.

Contractors have to inform the HeCaToS Consortium and the Commission of its intention to publish on its foreground. Publication can be impeded if another contractor can show that the secrecy of the foreground is not guaranteed.

Where the foreground is capable of industrial or commercial application and its owner does not protect it, the Union may, with the consent of the beneficiary concerned, assume ownership of that foreground and adopt measures for its adequate and effective protection.