HeCaToS

Hepatic and Cardiac Toxicity Systems modelling

Integrative *in silico* tools for predicting human liver and heart toxicity

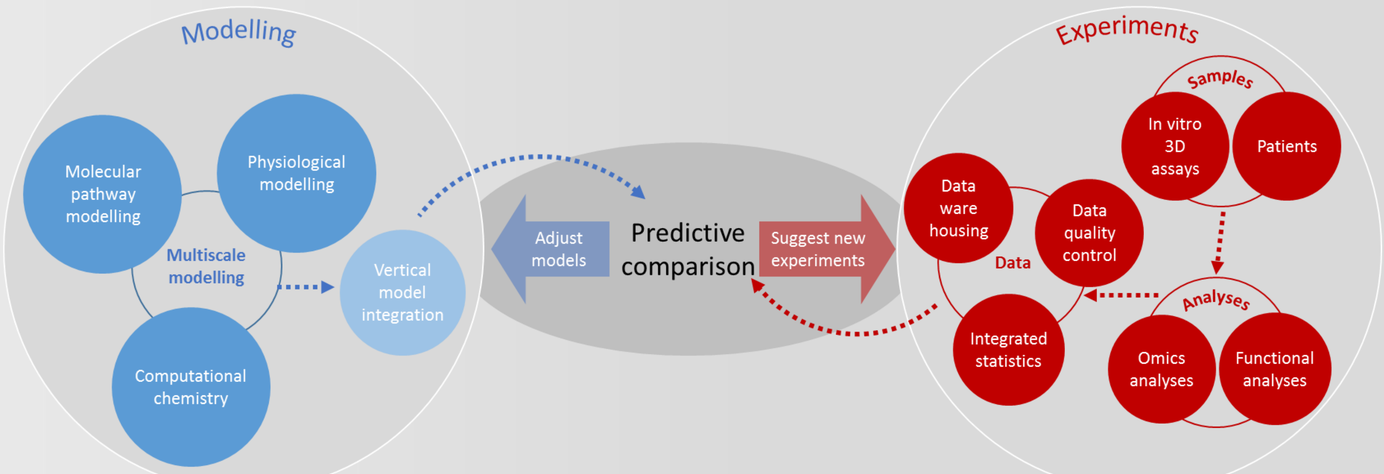
About HeCaToS

The HeCaToS project aimed at the establishment of a new integrative approach targeted towards highly predictive human safety assessment. Particularly, HeCaToS has contributed to the development of multi-scale *in silico* models for predicting repeated dose human liver and heart toxicity. This framework includes 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 dysregulations and of immunological dysfunctions associated with hepatic and cardiac drug-induced injuries, focus was given on these particular Adverse Outcome Pathways. Innovative *in vitro* 3D liver and heart assays have been developed and challenged by a panel of hepatoxic and cardiotoxic drugs with data collected by state of the art molecular and functional analytical techniques used to build integrated in silico models. Molecular data generated through these *in vitro* systems have subsequently been benchmarked against data collected from biopsies from patients expressing the relevant heart and liver disease phenotypes.

Research Strategy

Our goal is to develop integrated models, combining advances in computational chemistry and systems toxicology, to predict toxic perturbations in liver and heart across multiple scales. To achieve this HeCaToS is divided into interdependent Workpackages grouped within dedicated sub-projects:

1. **Multiscale modelling**: development of discrete mathematical models for heart and liver toxicity by integrating components and reactions (divided in **Molecular pathway modelling**, **Computational chemistry**, **Physiological modelling**, **Vertical model integration**)



2. **Samples**: collection of experimental and clinical samples to provide relevant data for models (divided in in vitro **3D assays**, **Patients**)
3. **Analyses**: a combination of 'omics' and functional analyses using state-of-the-art methodologies to gain insights into molecular phenomena on multiple levels (divided in **Omics analyses**, **Functional analyses**)
4. **Data infrastructure**: creation of a data hub of HeCaToS data, generated through 'omics and functional experiments combined with sample information, and quality controlled, stored, and analysed in an integrated fashion to identify Adverse Outcome Pathways (AOPs) and Hallmarks of Toxicity (divided in **Data warehousing**, **Data quality control**, **Integrated statistics**, **Predictive comparisons**)

Partners

HeCaToS Consortium		
COUNTRY	**PARTNER**	**GROUP LEADER**
NETHERLANDS	Universiteit Maastricht (**UM**)	***Jos Kleinjans*** ***Stephane Heymans***
SWITZERLAND	Eidgenoessische Technische Hochschule Zurich (**ETH**)	***Ralph Schlapbach***
	InSphero AG (**INSHERO**)	***Jens M. Kelm***
	Hoffmann- La Roche AG (**ROCHE**)	***Adrian Roth***
	Genedata AG (**GD**)	***Hans Gmuender***
SPAIN	Fundacion Para La Investigacion Del Hospital Universitario La Fe De La Comunidad Valenciana (**HULAFE**)	***José Castell*** ***Pilar Sepúlveda***
UNITED KINGDOM	Imperial College Of Science, Technology And Medicine (**ICL**)	***Hector Keun*** ***Ian Gould***
	King's College London (**KCL**)	***Steven Niederer***
	Optibrium LTD (**OPTI**)	***Matthew Segall***
IRELAND	Agilent Technologies INC. formerly Luxcel Biosciences LTD (**AGILexLUX**)	***James Hynes***
GERMANY	Max Planck Gesellschaft Zur Foerderung Der Wissenschaften E.V. (**MPIMG**)	***Ralf Herwig***
	Rheinisch-westfaelische Technische Hochschule Aachen (**RWTH**)	***Lars Kuepfer***
	European Molecular Biology Laboratory (**EMBL**)	***Ugis Sarkans***
	MicroDiscovery GMBH (**MD**)	***Johannes Schuchhardt***

Project Outcomes

- Proven suitability of *in vitro* 3D assays (human iPSC cardiac and primary liver microtissues) recapitulating human heart and liver tissue function for the assessment of repeated dose toxicity in humans
- Generation of a unique resource of multi-omics dataset (transcriptomics, metabolomics, methylomics, and proteomics) in 3D human *in vitro* and in patient samples upon exposure to cardiac and liver toxicants
- Proven relevance of a cross-omics based systems biology approach to identify which molecular pathways independently or in combination are responsible for anthracycline-induced cardiotoxicity
- Establishment of physiologically based pharmacokinetic (PBPK) models to predict *in vivo* drug response of perturbed biological pathways and cellular processes in liver by integrating *in vitro* toxicity data on the cellular level and clinical markers
- Development of biophysical computational models to simulate drug effects at cellular and organ scale allowing prediction of different toxicity mechanisms in a unified framework

SEVENTH FRAMEWORK PROGRAMME

HeCaToS is funded by the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 602156

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