



# HeCaToS

Hepatic and Cardiac Toxicity Systems modelling

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



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# About HeCaToS

Over the past decade the EU is dynamically moving towards the reduction of animal testing in research and screening and its replacement by alternative approaches. Alongside, there is a growing need for Suitability, Safety, Efficacy of Therapies efficiently addressing aspects of toxicology of innovative medical products, encouraging the employment of novel approaches that help to assess earlier, better and more cost-efficiently safety of novel drugs. In this context, an earlier report by the European Partnership for Alternative Approaches to Animal Testing, entitled The Chemistry of Life: Revolutionizing Toxicology, highlights that leading edge computational chemistry/ chemoinformatics and systems biology, when assembled in properly configured and validated computational systems, can revolutionize predictive toxicology and human safety assessment.

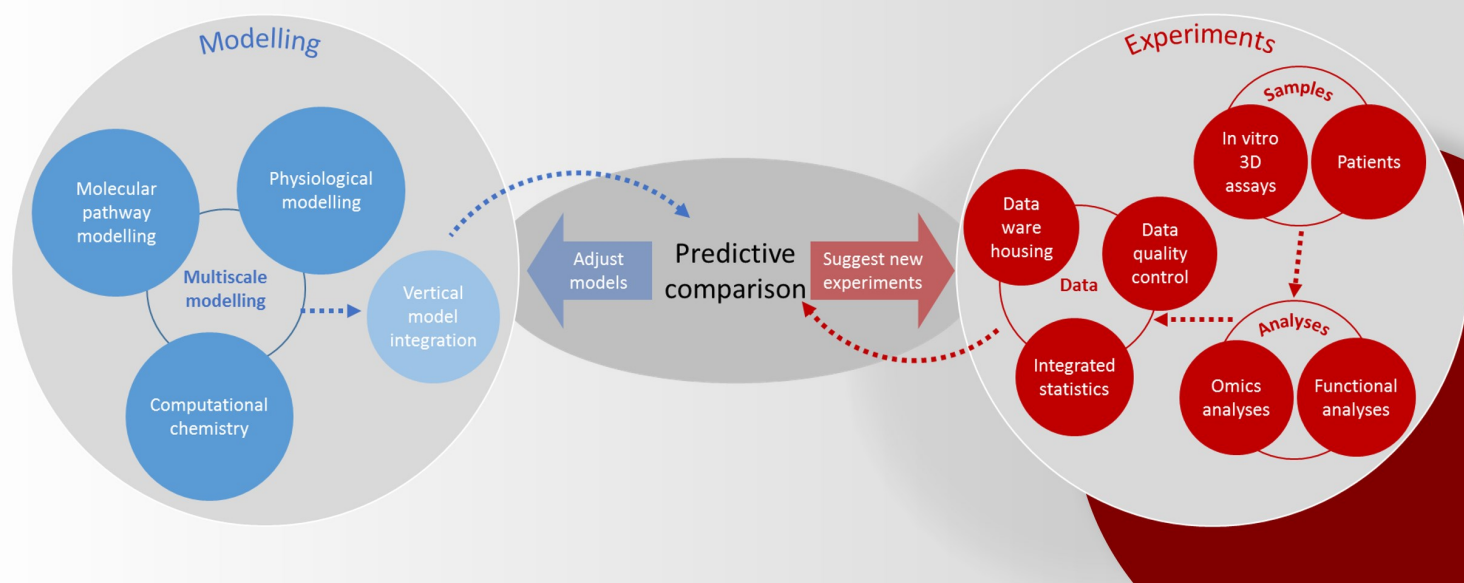
The HeCaToS project aimed at the establishment of a new integrative approach targeted towards highly predictive human safety assessment. Particularly, HeCaToS has contributed to the development of multi-scale *in silico* models for predicting repeated dose human liver and heart toxicity. This framework 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 hepatotoxic 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.

In order to achieve this challenging task, HeCaToS brought together leading research teams in the field of computational sciences, chemo- and bioinformatics, biostatistics, systems biology, molecular toxicology, molecular pathology, physiology, cell technologies, and 'omics' technologies. HeCaToS is a collaborative FP7 European research project which was launched in October 2013 and ran for five years.

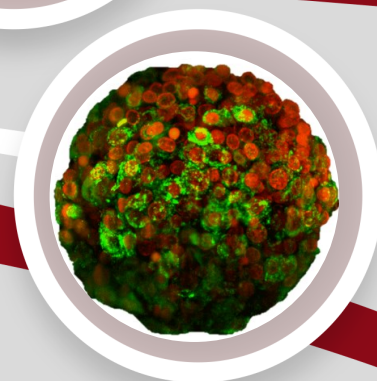
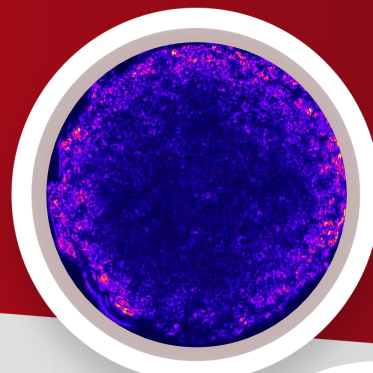
# Research Strategy

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:

- Multiscale modelling:** development of discrete mathematical models for heart and liver toxicity by integrating components and reactions  
**Molecular pathway modelling:** identification of AOPs for liver and heart toxicity by network analyses  
**Computational chemistry:** models for interaction of small molecules and macromolecules on an atomic level based on molecular dynamics simulations  
**Physiological modelling:** physiological liver and heart models for creating interfaces with molecular pathway models and computational chemistry models  
**Vertical model integration:** integration of different sub-modules describing functional endpoints at different scales of biological organisation
- Samples:** collection of experimental and clinical samples to provide relevant data for models  
**in vitro 3D assays:** establishment of 3D in vitro models that recapitulate human liver and heart function allowing monitoring of affected cell type, subcellular compartment and type of response over time upon treatment with liver and heart toxicants  
**Patients:** collection of liver and heart biopsies from drug-treated patients presenting relevant liver pathologies and cardiomyopathies to explore drug/disease related damage
- Analyses:** a combination of 'omics' and functional analyses using state-of-the-art methodologies to gain insights into molecular phenomena on multiple levels  
**Omics analyses:** multi-omics analysis (transcriptomics, proteomics, methylomics, and metabolomics) providing global information on systems biology events  
**Functional analyses:** innovative analyses of mitochondrial and immunological hepatotoxic & cardiotoxic endpoints
- 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  
**Data warehousing:** storage of data and support of data management in the BioStudies database  
**Data quality control:** quality control of 'omics' data and meta data using specifically designed software tools  
**Integrated statistics:** integrate the 'omics' data with functional data into AOPs using sophisticated cross-'omics' computational methods  
**Predictive comparisons:** assessment of model performance in toxicity prediction, by comparing *in silico* predictions with experimental results by performing simulations on parameter optimisation and by optimising whole organ simulations



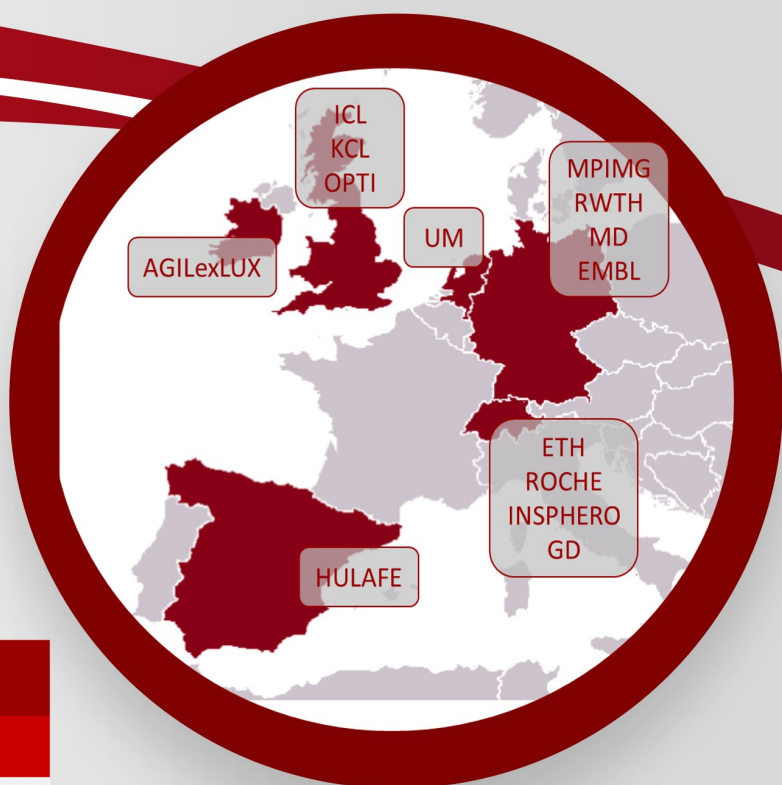
# Project Outcomes



- 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.



# Partners



## HeCaToS Consortium

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

The HeCaToS consortium combines the complementary expertise of fourteen internationally renowned research teams in the area of computational science, modelling, chemo-informatics, *in vitro* toxicology, molecular medicine, 'omics' technologies, bioinformatics and biostatistics. The consortium has recruited partners from eight academic institutions, four small and medium enterprises and two Large Enterprises around Europe.

## Project Coordinator

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For more information, please visit our website

**[www.hecatos.eu](http://www.hecatos.eu)**



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