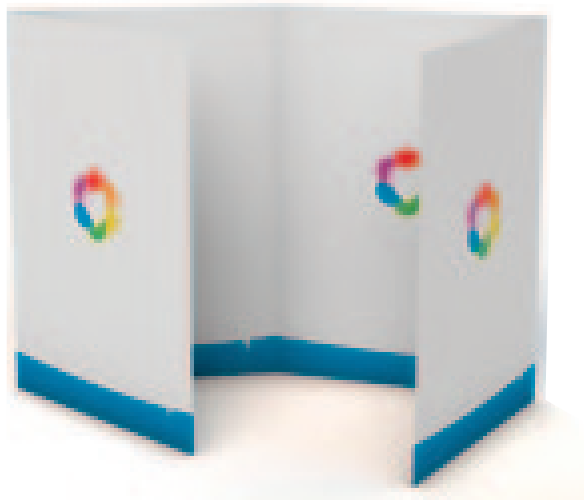


DETECTIVE

Detection of
Endpoints and Biomarkers

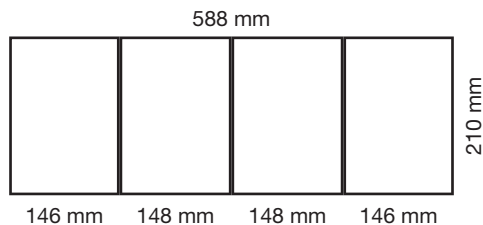
for Repeated Dose Toxicity Using In Vitro Systems



4x A5 'Window'-fold

format (plain) 588 mm x 210 mm

format (folded) 148 mm x 210 mm



Project approach

Development of human toxicity biomarkers for repeated dose toxicity testing in human-based *in vitro* systems by:

1. **Interfacing** with the other SEURAT-1 projects, in particular the ToxBank project to accumulate of existing biomarkers knowledge, toxicological data and relevant biological processes.
2. **Assessing** suitability and robustness of **existing cell systems** for biomarker development.
3. **Developing functional readouts** in human *in vitro* model systems for liver, heart, kidney and in embryonal stemcell-derived somatic cells.
4. **Developing “-omics” readouts** in these models.
5. **Developing concepts** for a standardised approach for identifying the best biomarker candidates in terms of sensitivity target specificity and reproducibility.
6. **Integration** of functional and “-omics” readouts in the *in vitro* models.
7. **Addressing biomarker qualification** by linking to clinical observations and taking the concepts for a standardised approach into account to ultimately obtain regulatory acceptance.
8. **Facilitating** online sharing of biomarker metadata using standardised nomenclature.
9. **Compiling** GLP-compliant SOPs of the most robust and predictive biomarkers.

Consortium partners

- Klinikum der Universität zu Köln (UKK)
- Commission of the European Communities – Directorate General Joint Research Centre (JRC)
- Universiteit Maastricht (UM)
- Roche Diagnostics GmbH (Roche)
- Vrije Universiteit Brussel (VUB)
- ProteoSys AG (PSY)
- Forschungsgesellschaft für Arbeitsphysiologie und Arbeitsschutz e.V. (IFADO)
- Imperial College of Science, Technology and Medecine (IC)
- Deutsches Krebsforschungszentrum (DKFZ)
- ARTTIC (ART)
- OÜ Quretec (QURE)
- Medizinische Universitaet Innsbruck (IMU)
- Leibniz - Institut für Analytische Wissenschaften (ISAS)
- Fraunhofer-Gesellschaft zur Förderung der Angewandten Forschung E.V. (ITEM)
- Universiteit Leiden (UL)

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the key
to the
development
of biomarkers
of long-term
toxicity in human
target cells

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Why Refinement, Reduction and Replacement to the use of animals in toxicity testing?

- Important for biotechnology, pharmaceuticals, cosmetics
- chronic exposure tests still require a high number of animals
- ethical considerations
- poor concordance between humans and animal models

What is SEURAT-1?

- European research initiative between European Commission and Colipa (European Cosmetics Association) “Safety Evaluation Ultimately Replacing Animal Testing”
- 6 collaborative research projects, supported by a coordination project.
- **General aim:** to replace repeated dose systemic toxicity testing, a standard regulatory test in human safety assessment of chemicals, including cosmetics.

What is DETECTIVE?

- One of the 6 research projects in the SEURAT-1 cluster
- **Specific aim:** to identify key biomarkers in human long-term toxicity

What is COACH?

- Coordination action supporting the integration of the results of the 6 projects to develop a novel human safety assessment strategy.

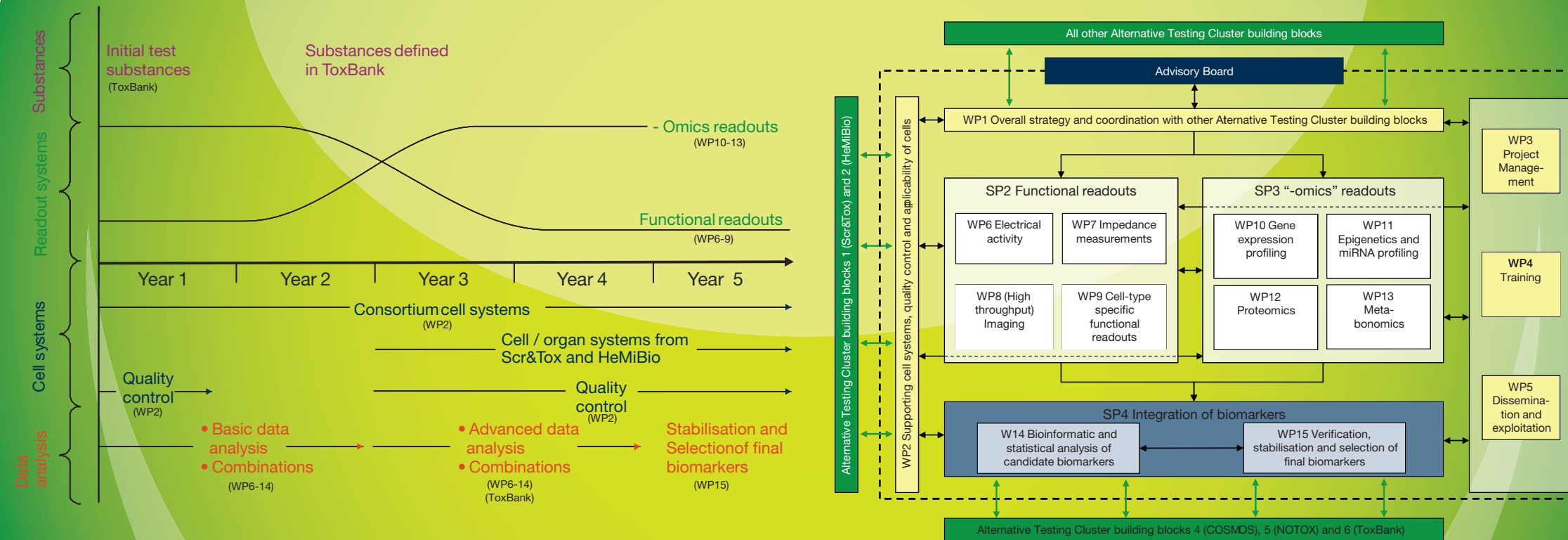
Project workplan phases

The DETECTIVE work plan is divided into different phases according to the availability of test substances, cell systems and readout systems used. These will have impact on the type of data analysis to be carried out.

- The consortium starts working with the cell systems currently in use within the consortium (heart, liver and kidney). Quality control of the applicability of these cell systems is carried out in the first months.
- Once additional cell systems and organ-simulating devices become available from other projects (1, 2), these will also be used after quality control of robustness and reproducibility.
- Relevant test substances will be selected from the substance library provided by project 6.
- For the development of biomarkers, functional readouts (SP2) will be used.
- “-Omics” technologies (SP3) will be limited to investigating basic questions (budgetary constraints).
- Once stable cell systems and organ-simulating devices are provided (projects 1 and 2), the “-omics” technologies will be fully applied to generate comprehensive data for selected compounds and exposure protocols (until end of year 4) to leave sufficient time for thorough data analysis (SP4).
- Functional readouts will be used also in the last year of the project to relate the results of the “-omics” readouts to the physiological status of the cells to aid qualification of “-omics” markers. Stabilisation, selection of final biomarkers and verification of in another laboratory or using a second method will be done in the last project year.

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DETECTIVE



Overall, DETECTIVE will lead to a major breakthrough in the field of *in vitro* toxicity testing, moving toxicology beyond descriptive science and towards mechanism-based prediction

Research areas

4 sub-projects (SPs) exist, each composed of several workpackages (WPs):

SP1: Central work packages

These address transversal topics:

WP1: coordination of the research, identification of overlaps and agreement on an overall time table for inputs and outputs from the SEURAT-1 cluster; overall scientific coordination and strategy.

WP2: Quality control and verification of the applicability to readout technologies, stability and reproducibility of all cell systems. Comparison of various exposure protocols to select the most appropriate treatment scheme to be used consistently throughout the project.

WP3 Project management, WP4 Training and WP5 Dissemination and exploitation.

SP2: Functional readouts

To identify biomarkers of repeated dose toxicity for multiple target organs *in vitro*. The dose-response curves obtained in SP2 will provide a better understanding of thresholds of concern leading to functional failure of various cell types. The following technologies are used: electrical activity and impedance measurements, (high throughput) imaging and cell-type specific readouts.

SP3: “-omics” readouts

To improve traditional biomarkers of toxicity by gathering and integrating data on transcriptomic, proteomic, metabonomic and epigenomic responses to exposure in human *in vitro* models. As such a novel set of mechanism-based intermediate biomarkers of repeated dose toxicity applicable to evaluate the safety of different substances will be developed.

SP4: Integration of biomarkers

To evaluate significance of putative *in vitro* biomarkers for heart, liver and kidney toxicity by data integration obtained of all partners.