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# Update on activities ECVAM


## Thomas Hartung & ECVAM Team

*Institute for Health and Consumer Protection (IHCP)*
*Ispra (Va), Italy*


http://ecvam.jrc.it

# ECVAM Mission

**Directive 86/609/EEC**

- **Validation**
- **Database**
- **Research**
- **Communication**
- **ESAC**

**7th Amendment Cosmetics Directive + REACH**

**ECVAM Reorganisation**

# The ECVAM Business Plan

- A ten year program to meet the expectations from legislation
- Bundling of all stakeholder activities
- Combination of strategic and technical developments
- Estimated costs for test optimisation and (pre-) validation of 150 M€
- Adoption of ECVAM‘s services already initiated

# Reorganization of staff



**KEY AREAS**

- Systemic toxicity
- Topical toxicity
- Sensitisation
- Carcinogenicity
- Reproductive toxicity
- Toxicokinetics
- Ecotoxicology
- Biologicals

- SIS databases
- QSARs
- Strategic developments

(GLP, GCCP, HTS, toxicogenomics)

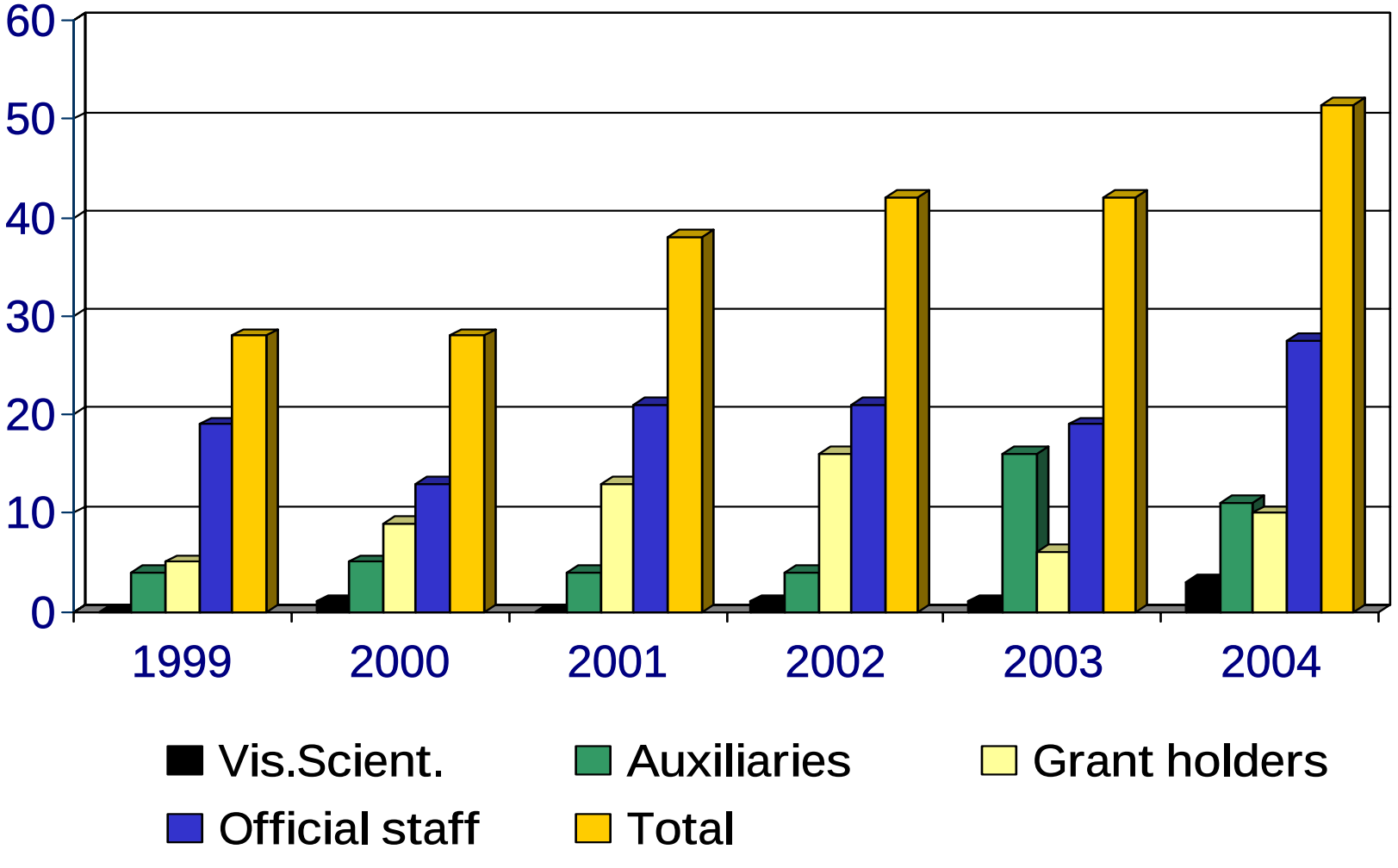
**ECVAM staff teams**

**(incl. 5 assistants)**

**plus laboratory activities**

**plus external experts**

# Staff 1999-2004



# *Foreseen New Permanent Staff*

## Published posts

- **Ocular Irritancy**
- **Biometry**
- **High-throughput Testing**
- **Biocompatibility**
- **QSAR**
- **Database (B)**

## Planned early 2004

- **GLP / Labmanager**
- **E-learning**
- **Cell biology techn. (B)**

## 5 assistants

- **Cancer, endocrine disr., systemic tox., etc.**

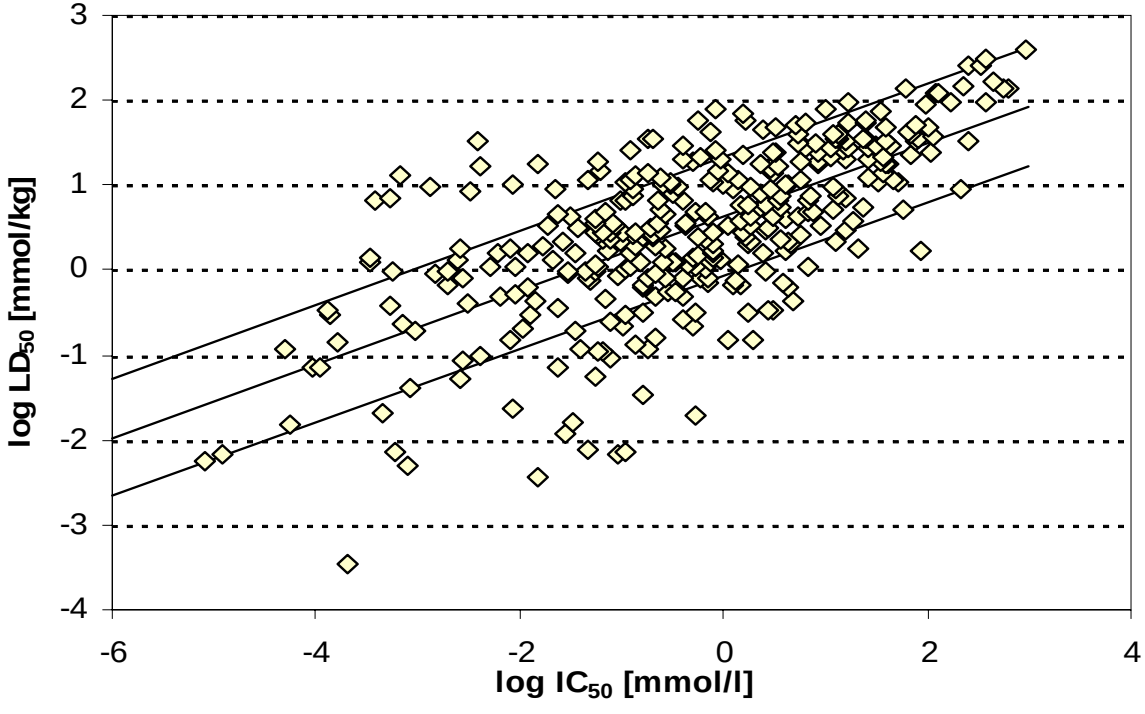
# *Topical Toxicity and Skin Sensitisation*

| | Development | Prevalidation | Validation | ESAC statement | Regulatory acceptance |
|---|---|---|---|---|---|
| **Skin Corrosion** | ✓ | ✓ | ✓ | ✓ | ✓ |
| **Phototoxicity** | ✓ | ✓ | ✓ | ✓ | ✓ |
| **Skin Irritation** | ✓ | ✓ | **2003** | | |
| **Eye Irritation** | ✓ | ✓ | **2004** | | |
| **Skin Sensitisation** | ✓ | | | ✓ | ✓ |
| **Percutaneous Absorption** | ✓ | | | | ✓ |

# *Example: Acute Systemic Toxicity*

## ICCVAM/ECVAM Validation

**Registry of Cytotoxicity**

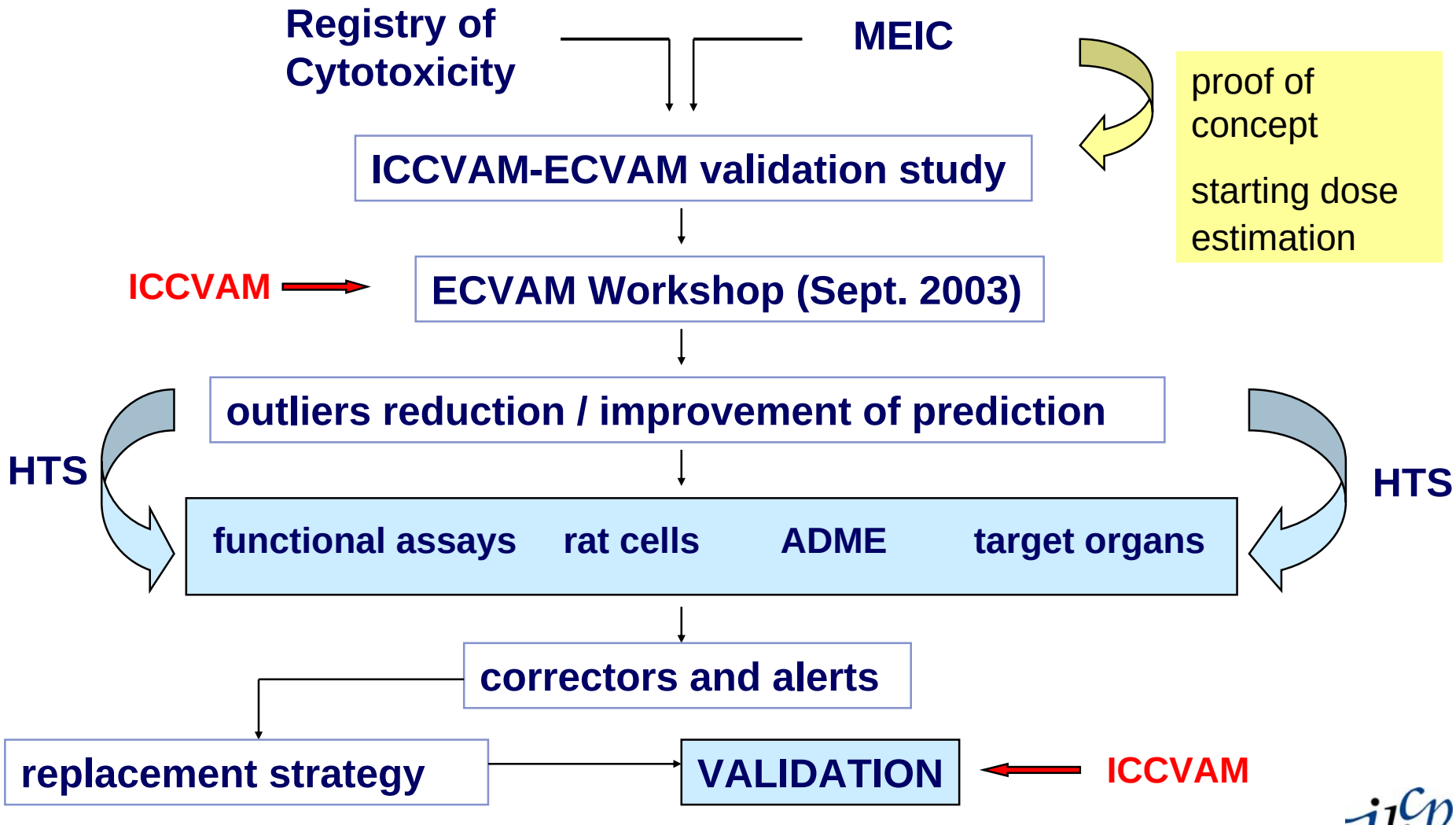



**ECVAM-ICCVAM**

**Joint Validation Study of two**

***In Vitro* Basal Cytotoxicity Assays**

# Strategy to Replace Acute Toxicity Testing



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# A-Cute-Tox

## Application for an R&D integrated project

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**Coordinator:**

Dr. C. Clemedson

**Steering Committee:**

Dr. L. Risteli

Prof. J.V. Castell

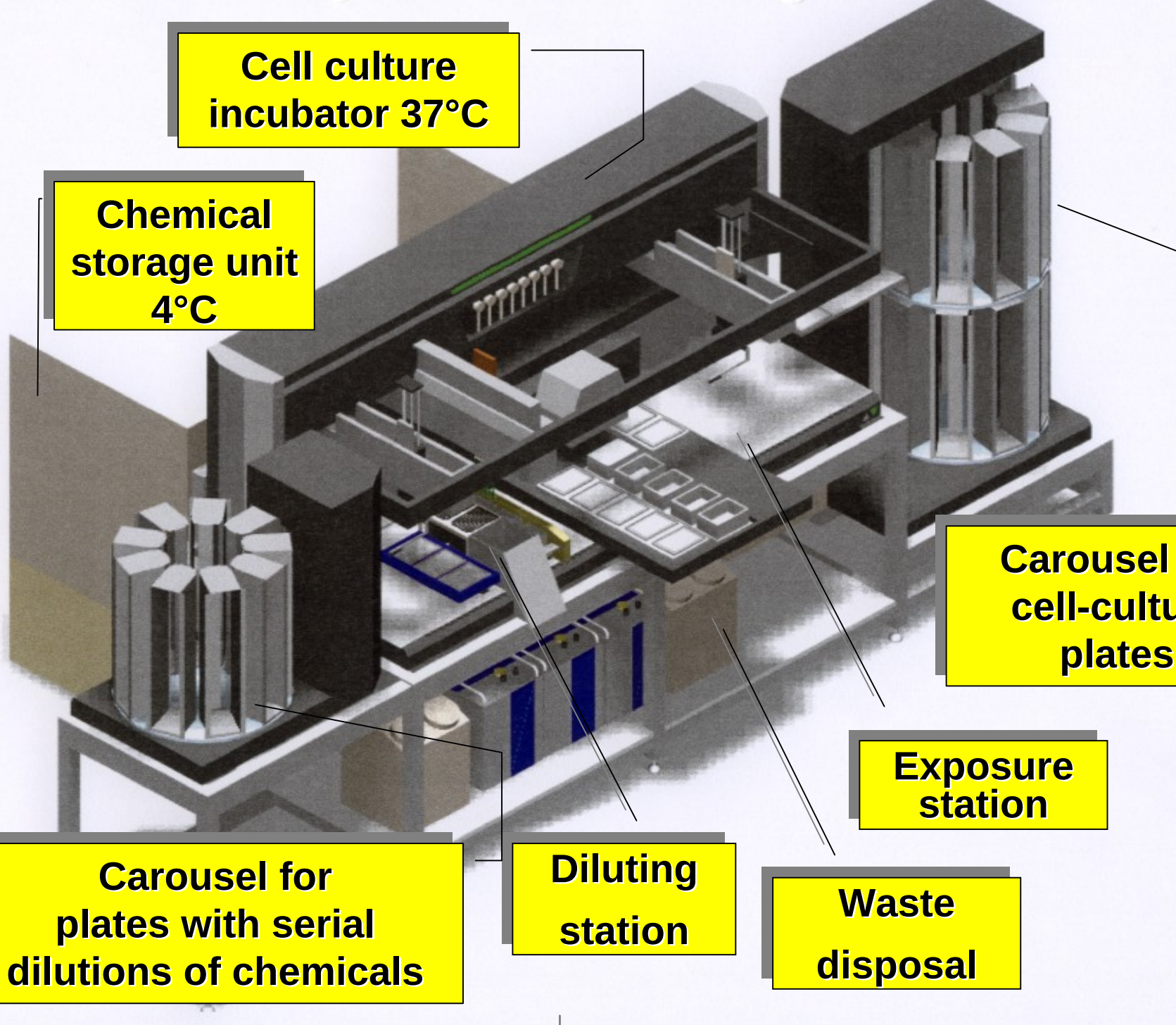
Dr. J.A Vericat

Prof. B. Blaauboer

Dr. P. Prieto

37 participants
14 States
17 Universities
10 SME
4 Research Institutes
2 Industries
2 Foundations
JRC

- **WP1:** In vivo database
- **WP2:** In vitro database
- **WP3:** Testing strategy
  Iterative amendments
- **WP4:** New endpoints
  New cell systems
- **WP5:** Correctors - ADE
- **WP6:** Correctors - metabolism
- **WP7:** Correctors – target organ
  7.1 Neurotoxicity
  7.2 Nephrotoxicity
  7.3 Hepatotoxicity
- **WP8:** Technical optimisation of the test startegy
- **WP9:** Prevalidation
- **WP10:** Management, dissemination and exploitation of results

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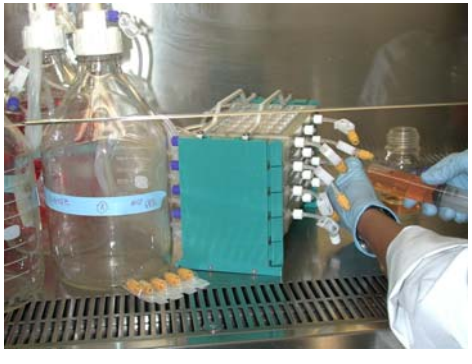
# Conclusions

- **A-Cute-Tox represents an extension of the ICCVAM/ECVAM validation and MEIC study approach towards a full replacement test strategy**
- **It is piloting strategies for systemic toxicities**
- **Similar strategies will have to be developed for other systemic toxicties**

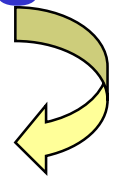
# Chronic Toxicity

- **Workshop on Long-Term Toxicity Testing (1999)**
- **Pilot study (flow-cell bioreactor, static-cell bioreactor)**



- **Evaluation of a new perfusion system developed in FP4**
  **- ongoing prevalidation**
  **- PREDICTOMICS**
  **- Workshop 2004**

# PREDICTOMICS



## Development of in vitro systems predicting long-term toxicity in humans

- **Development of advance cell culture systems: liver and kidney**
  - ✓ **co-cultures**
  - ✓ **targeted cell transformation**
  - ✓ **stem cell technology**
  - ✓ **organotypic cell cultures**

- **To identify specific early mechanistic markers of toxin induced cell alterations: genomic, proteomic and cytomic analysis**

- **To establish and prevalidate a screening platform predictive of toxin induced chronic liver and renal diseases.**

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# PREDICTOMICS

**Coordinator:**

**Prof. Jose V. Castell**

**Executive board:**

**Prof. Jose V. Castell**

**Prof. Walter Pfaller**

**Dr. Bernt Garthoff (ECOPA)**

**Prof.Thomas Hartung (ECVAM)**

**14 participants**
- **8 States**
- **6 Universities**
- **2 SME**
- **4 Industries**
- **1 Foundation**
- **JRC**

**WP1: Liver cell model developments**
- Innovated 3D culture technology
- Hepatocyte cell differentiation
- Stem cell technology

**WP2: Kidney cell system developments**
- Primary cultures, mono- and co-cultures
- New perfusion culture techniques
- Molecular biology studies on kidney differentiation

**WP3: Optimisation of analysis tools**
- Genomics
- Proteomics
- Cytomics

**WP4: Mechanistically based gene markers identification (liver)**
- Exposure to model toxicants
- Analysis of effects related to the mechanisms of toxicity
- Identification of marker genes

**WP5: Mechanisms of nephrotoxicity and identification of toxicity markers**
- Exposure to toxins and co-factors
- Analysis of activated genes
- Identification of mechanistically relevant marker genes and novel endpoints

**WP6: Database generation. Analysis of model predictivity. Prevalidation**

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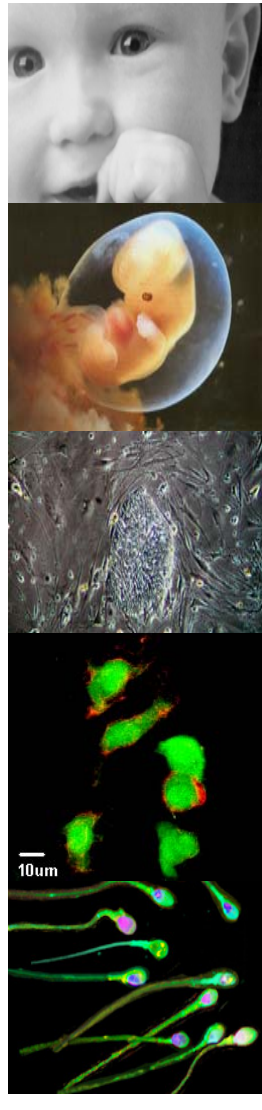
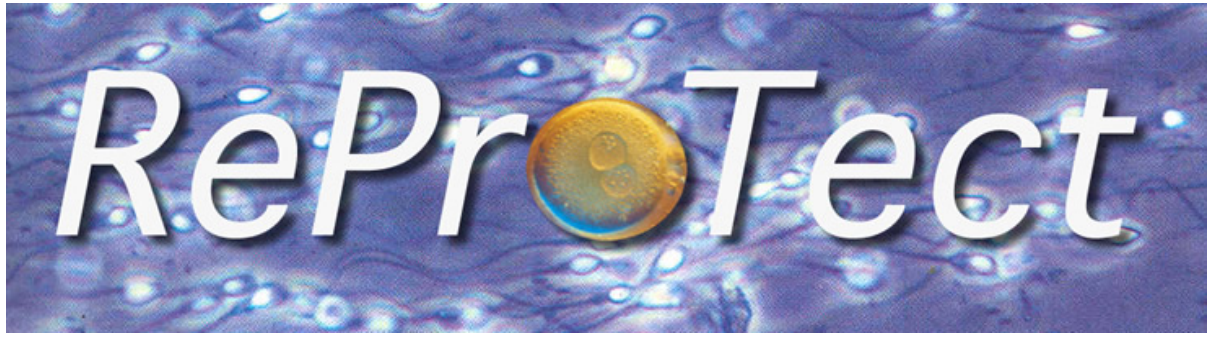
ihcp

# *Reproductive Toxicology*

- **2002 Validation of three embryotoxicity tests**
  **2003 Workshop Regulatory Use**
- **Human embryonic stem cells in ECVAM**
- **2003 Prevalidation Leydig cells**
- **Integrated project ReProTect**
  **(35 partners, granted 9 M€)**
- **Review tests for endocrine disrupters (OECD)**
  **Taskforce (Inventory, 2004: Prevalidations)**






# “Reproductive Toxicology”

# “Protection of Animals”

# “Detection of reproductive toxicants”

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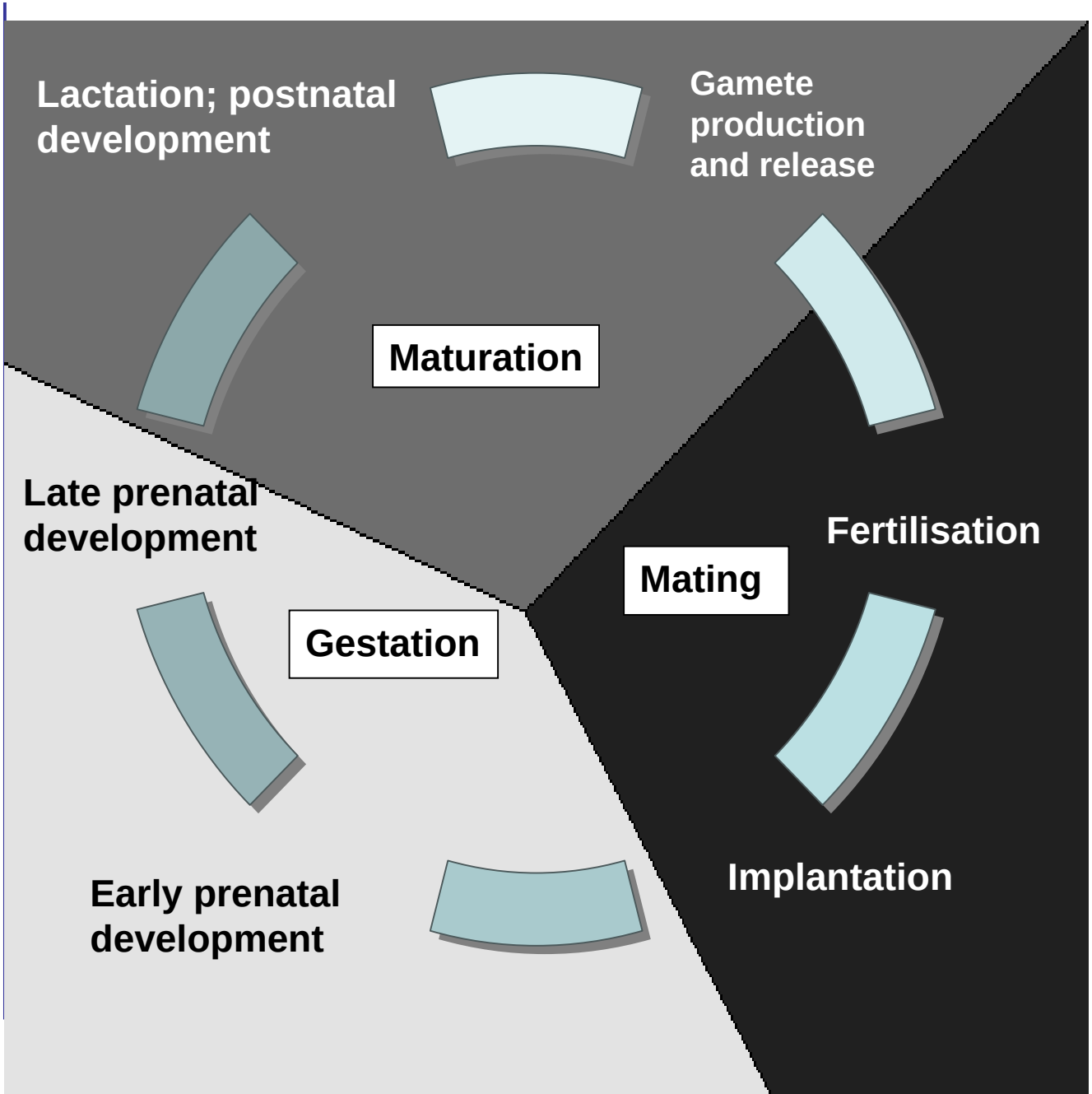
# Guidelines to be replaced




**OECD TG 414**
**OECD TG 415**
**OECD TG 416**
**OECD TG 421**
**OECD TG 422**
**OECD TG 426**
**OECD TG 478**
**OECD TG 483**

**Directive 67/548/ EEC B22**
**Directive 67/548/ EEC B23**
**Directive 67/548/ EEC B31**
**Directive 67/548/ EEC B34**
**Directive 67/548/ EEC B35**
**Directive 67/548/ EEC B22**
**Directive 67/548/ EEC B23**

**Fertility segment I**
**Embryotoxicity/ Teratogenicity segment II**
**Pre-postnatal Toxicity segment III**

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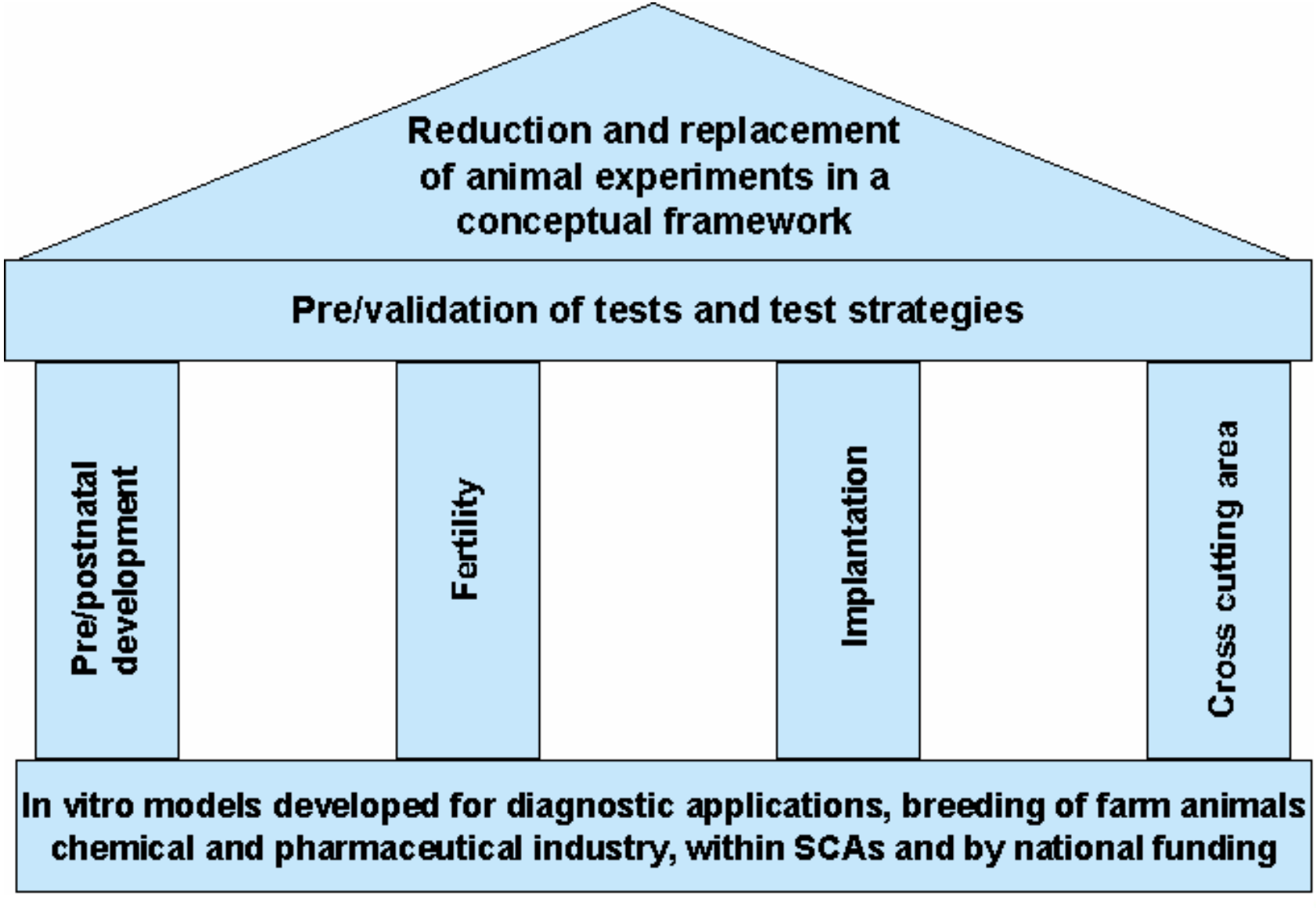
# Structure of the ReProTect



# Management of the ReProTect

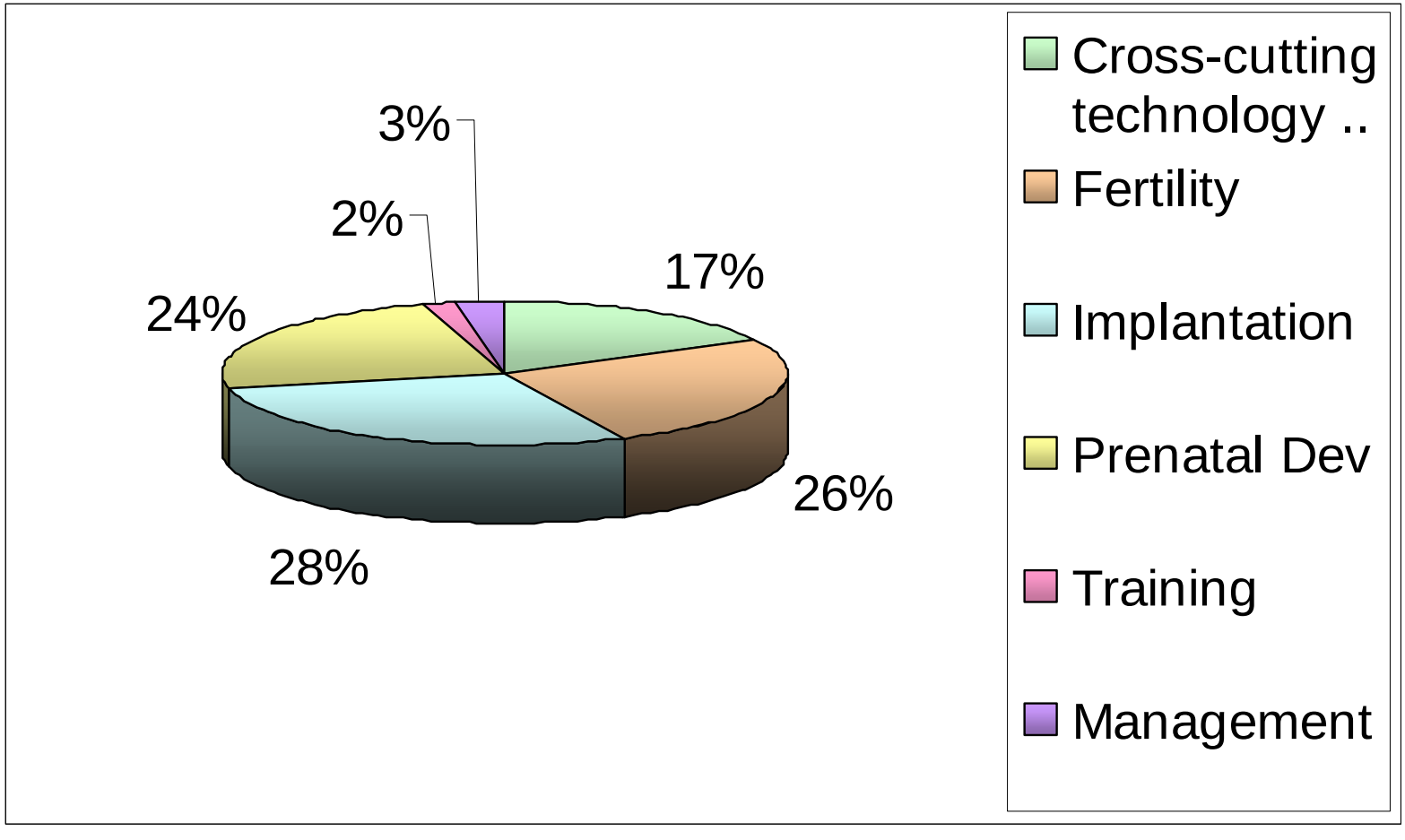


| Advisory Board |
| --- |
| Chair: ECOPA<br>Industry, Regulators |

| Coordination: | ⟷ | Scientific and Technical Management: |
| --- | --- | --- |
| Univ. Tuebingen/ Germany | | JRC/ Institute for Health and Consumer Protection |

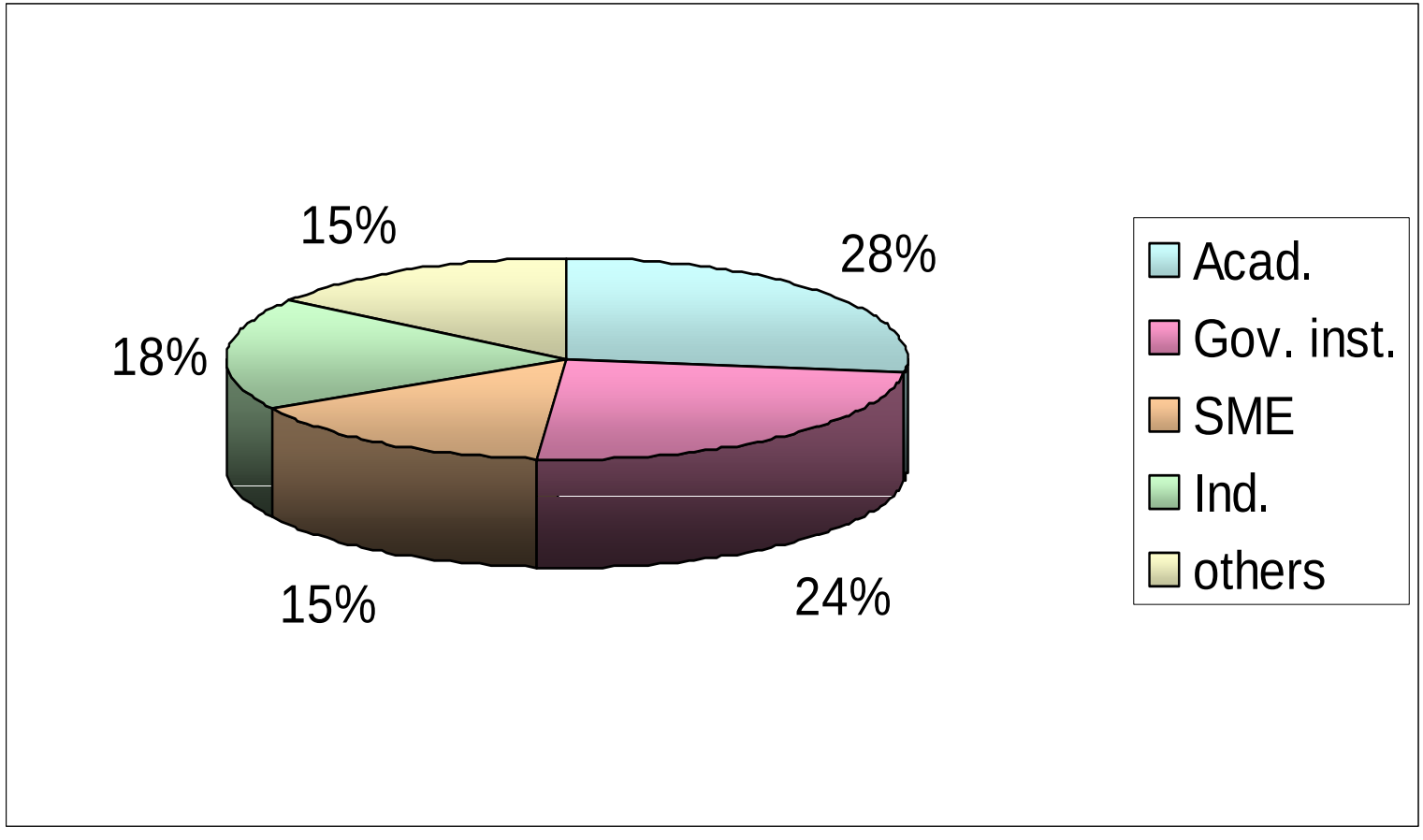
| Science | Technology | Strategy | Exploitation |
| --- | --- | --- | --- |
| Fertility<br>Prenatal development<br>Implantation | QSAR<br>Array technology<br>Sensor technology<br>Biometry | Conference Workshops<br>Task forces<br>Regulators<br>Industry | Training<br>Train the trainer<br>e-learning |

# Breakdown of costs




**Total costs: > 16 Mio Euro**
**Requested funding: 12 Mio Euro**

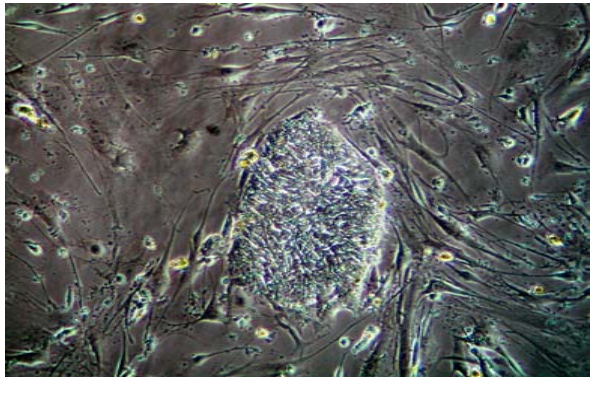
# The consortium




**35+ partners with complementary expertise**

# First EU sponsored project using human embryonic stem cells

- **The used embryonic stem cell line has been established more than 5 years ago**
- **No additional human embryos need to be used**
- **Advice of the European group on Ethics in Science and New Technologies:**
  **…..Culturing of specific cell lines to be used for pharmacological studies and toxicological testing is the most likely immediate biomedical application, making possible the rapid screening of large numbers of chemicals……"**

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In Vitro Testing
Industrial Platform
ProteoSys
Innovation in Functional Proteomics
ECVAM
Joint Research Centre
LTR
Imperial College
London
BAYER
Bayer
VITO
rivm
Rijksinstituut
voor Volksgezondheid
en Milieu
Pfizer
LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY
syngenta
DH
Department
of Health
UPPSALA
UNIVERSITET
OECD
Erasmus Universiteit Rotterdam
BASF
VRIJE UNIVERSITEIT BRUSSEL
SCIENTIA VINCERE TENEBRAS
liverpool
JMU
Johnson&Johnson
PHARMACEUTICAL RESEARCH
& DEVELOPMENT
IAM
ENEA
Centro Ricerche Casaccia
ENTE PER LE NUOVE TECNOLOGIE, L'ENERGIA E L'AMBIENTE
IT University of Copenhagen
zebet
NOVARTIS
TNO
BDS
BioDetection Systems
ISTITUTO SUPERIORE DI SANITÀ

## Further ECVAM-ICCVAM efforts not covered today:

**OECD GLP draft guidance document**

**Validation skin irritation & ocular irritancy**

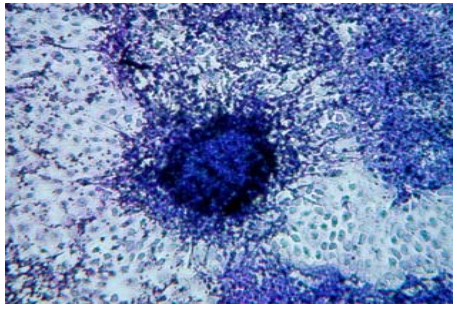
**Workshops toxicogenomics & metabolism**

# *Carcinogenicity*

**(Animal test: 1 M€)**

**Focus on non-genotoxic agents**

**Establishment of Cell Transformation Assay**



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**2004: (Pre)validation**

**2003: Toxicogenomics (Pilot study, Workshop)**