



# **A Snapshot of Ongoing Activities of the European Union Reference Laboratory for Alternatives to Animal Testing - EURL ECVAM**



*Patric Amcoff  
Operational Manager  
EURL ECVAM*

**THE EUROPEAN UNION REFERENCE LABORATORY  
FOR ALTERNATIVES TO ANIMAL TESTING**



# Outline

- **Introduction to EURL ECVAM**
- **EURL ECVAM's Networks and Tasks**
- **EURL ECVAM's Strategic Outlines for Endpoints of Special Regulatory Concern – Skin Sensitisation as an Example**



# INTRODUCTION TO EURL ECVAM

- **Duties and Tasks of the Union Reference Laboratory (EURL ECVAM's mission)**

**1. The Union Reference Laboratory referred to in Article 48 is the Commission's Joint Research Centre**

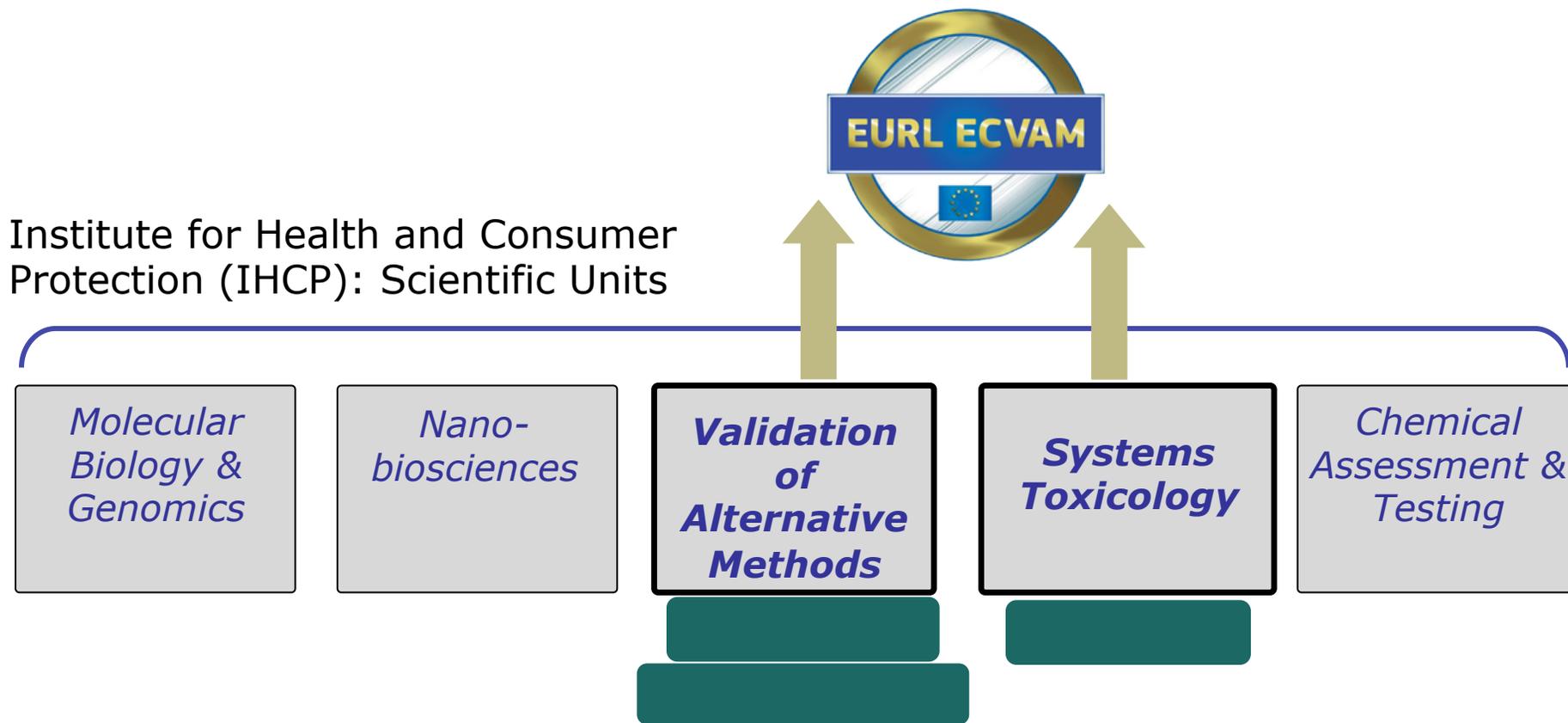
**2. The Union Reference Laboratory shall be responsible, in particular, for:**

- (a) coordinating and promoting the **development and use of alternative procedures** including in the areas of **basic and applied research and regulatory testing**
- (b) coordinating the **validation of alternative approaches** on Union level
- (c) Acting as a **focal point for the exchange of information** on the development of alternative approaches
- (d) Setting up, maintaining and managing **public databases** and information systems on alternative approaches and their state of development
- (e) **promoting dialogue between legislators, regulators, and all relevant stakeholders**, in particular industry, biomedical scientists, consumer organisations and animal welfare groups, with a view to the development, validation, regulatory acceptance, international recognition, and application of alternative approaches.

**3. The Union Reference Laboratory shall participate in the validation of alternative approaches.**



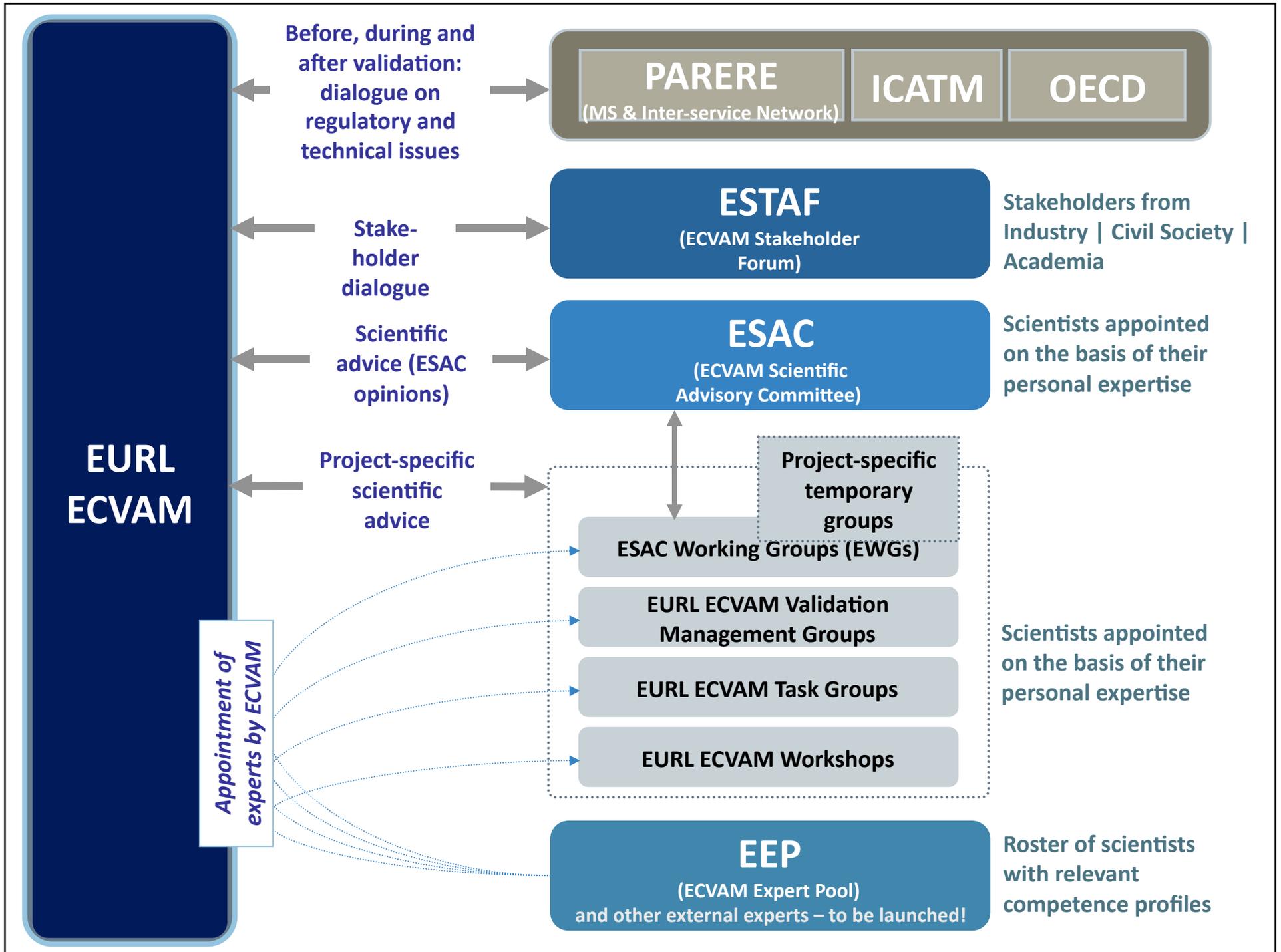
# EURL ECVAM - The European Union Reference Laboratory for Alternatives to Animal Testing



Institute for Health and Consumer Protection (IHCP): Scientific Units

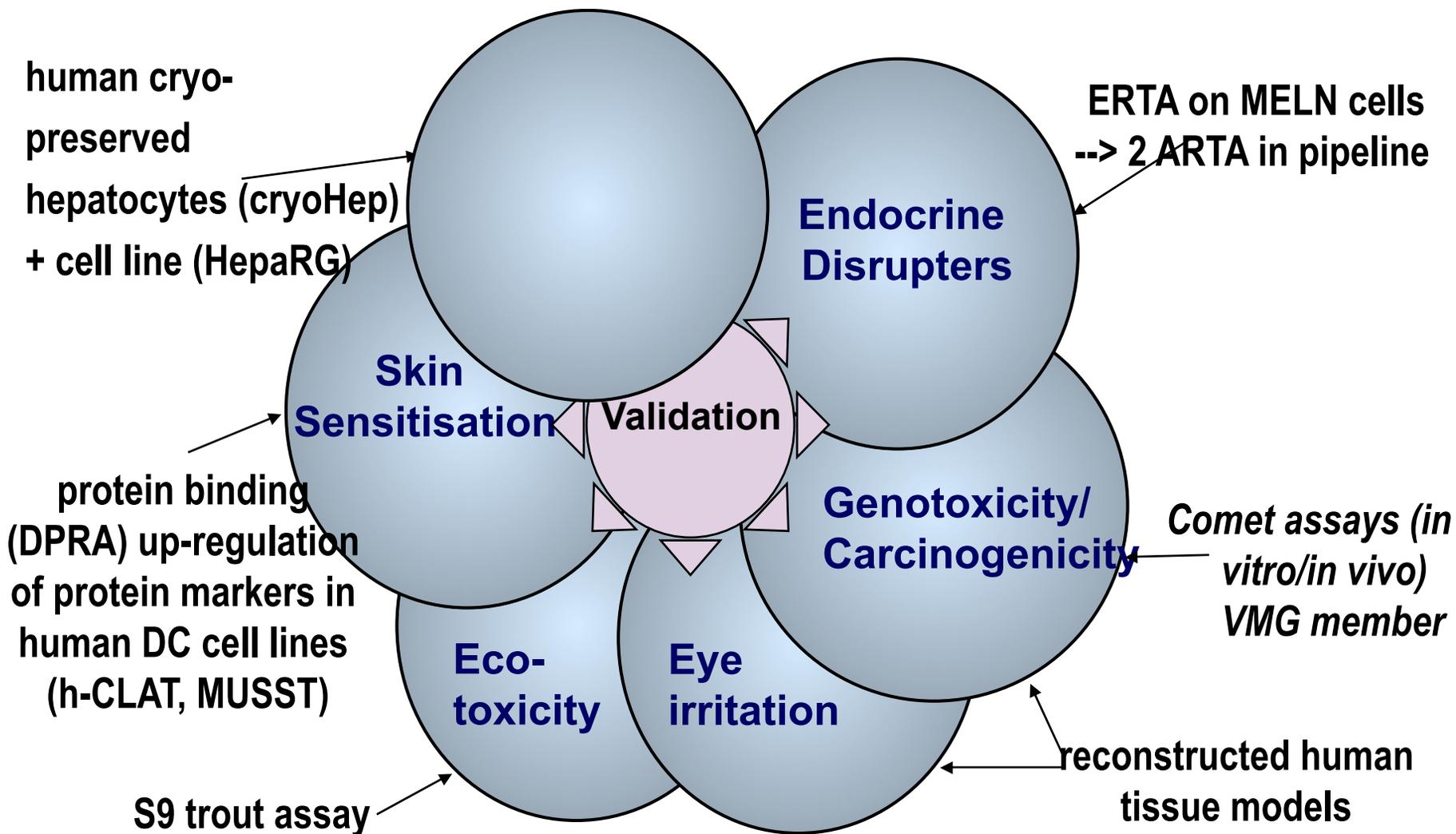


# **EURL ECVAM's NETWORKS AND TASKS**





## ONGOING 9 VALIDATION STUDIES / 14 TEST METHODS

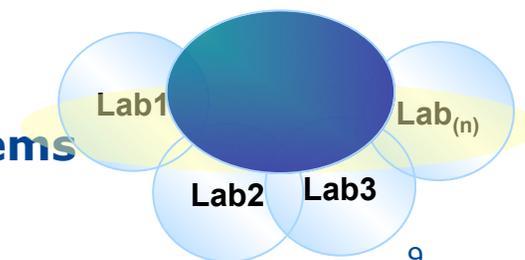




## Network of Laboratories for the Validation of Alternative Methods - NETVAL

### EURL ECVAM

- **Has invited Members States** to identify suitable laboratories (Oct-11)
- In accordance with the animal welfare Directive 2010/63
- On a case by case basis **laboratories** with the appropriate expertise and experience will be invited **to participate/coordinate validation studies**
- Will **select** those with the best balance of **cost** and **expertise**
- **38 nominated labs from 12 member states**
- **In general high quality of nominated labs covering a diversity of applications and competences**
- **Includes labs with GLP, ISO and other quality systems**



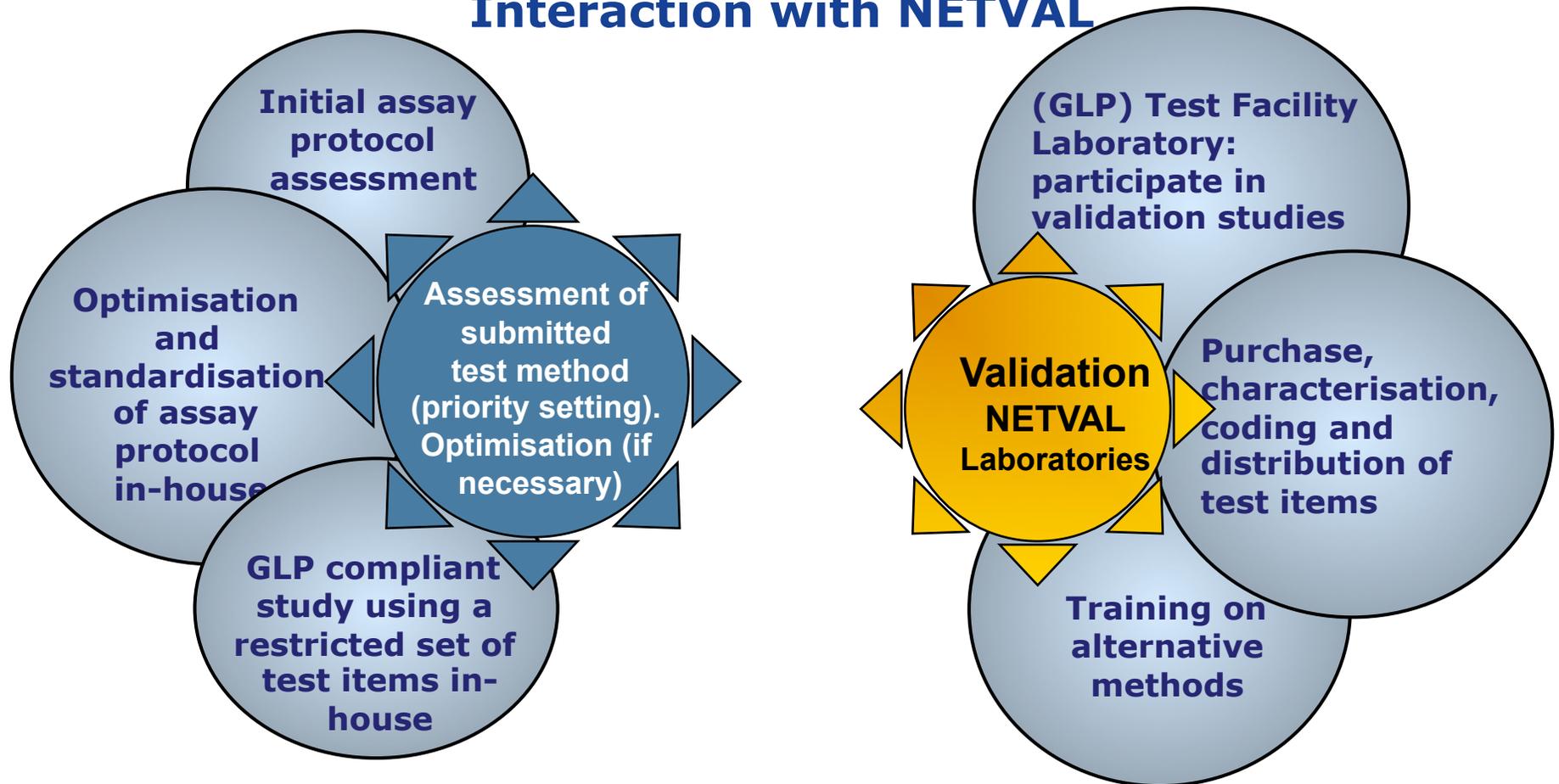


## **Network of Laboratories for the Validation of Alternative Methods - NETVAL Next step**

### **EURL ECVAM**

- **Make a first selection to assess the suitability of nominated labs by applying specific selection criteria, GLP requirements, leading capacity, etc.**
- **Open call for labs with specific competences needed by EURL ECVAM and possibilities for non-EU labs to participate**
- **The respective NCP will be consulted prior to any appointment of NETVAL compliant labs**
- **First planned full engagement with the AR TA validation study**

## New Strategy for In-house Validation and Interaction with NETVAL





## ESAC PEER REVIEWS

### *Ongoing in 2012*

- Keratinosens & DPRA: ESAC Opinion expected at ESAC37
- Bhas 42 Cell Transformation Assay: Peer review just initialized
- Performance Standards on Cytosensor Microphysiometer (eye irritation): Opinion expected at ESAC37
- ZFET - Zebrafish embryo acute toxicity test: Peer review just initialized



## ESAC PEER REVIEW

***Upcoming in 2013:***

- SkinEthic, EpiOcular** (eye irritation)
- MUSST, hClat** (skin sensitisation)
- cryoHepRG, cryoHep** (toxicokinetics/CYP1, metabolism)



# OECD Projects

## **New projects WNT24 (lead):**

- SPSF on AOP for skin sensitisation
- SPSF on in vitro skin sensitisation test methods (Keratinosens and DPRA)
- SPSF on Transcriptional assay for the detection of estrogenic and anti-estrogenic compounds using the MELN Cells and inclusion of an HTS lab as part of the validation study
- SPSF for use of BCOP for unclassified chemicals

## **Draft SPSFs for WNT25**

- MUSST and hCLAT for skin sensitisation, cryoHepRG and cryoHep for CYP1 metabolism, in addition to an AR TA PBTG



# ECVAM DataBase service on ALternative Methods to animal testing (DB-ALM)

## Main Features

- Required by European Commission and Parliament as a **major objective of ECVAM** (SEC-91-1794; Directive 2010/63/EU art.46; Annex VII [2] [d])
- Public online service covering animal alternatives at **any** stage of development, validation and/or regulatory acceptance with emphasis on **toxicity assessments**
- **TSAR tracking system** under further development (ECVAM will host the ICATM tables)

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• **INVITTOX** Protocols for all ECVAM validated protocols  
**DB-ALM** <http://ecvam-dbalm.jrc.ec.europa.eu>

SACATM Meeting 6 September 2012, NTP, RTP, NC, USA

Joint  
Research  
Centre





# **EURL ECVAM's STRATEGIC OUTLINES FOR ENDPOINTS OF SPECIAL REGULATORY CONCERN – SKIN SENSITISATION AS AN EXAMPLE**



## **Defining EURL ECVAM Outline Strategies**

- **Develop EU strategy documents by mapping regulatory requirements and needs in addition to inventories of test methods available for potential validations**
- **DG RTD Framework Programmes, e.g. ACuteTox, ReproTect, SensiTive**
- **Overall aim to base the strategies on internationally accepted AOPs or other agreed frameworks**
- **Get endorsement on the draft strategies by our advisory networks**
- **Serves the purpose of communicating the EURL ECVAM strategies and intentions for validations to our DG customers, stakeholders and to the public, and provide the basis for priority settings among test method submissions**

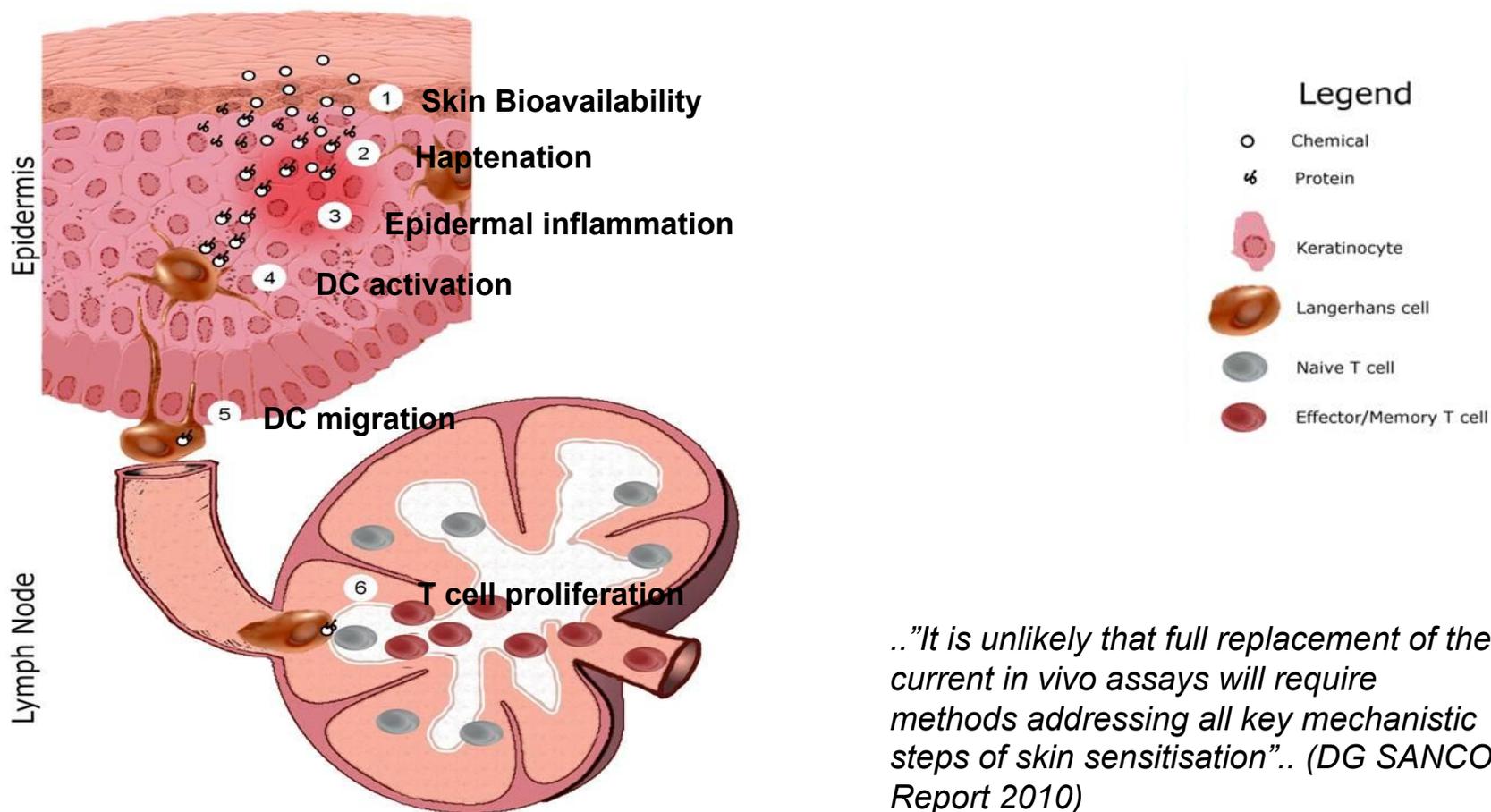


## **Defining EURL ECVAM Strategies**

- **At presently 5 endpoints under development**
  - **Skin sensitisation, ED, vaccine safety testing, carcinogenicity and toxicokinetics**
- **Skin sensitisation the most advanced so far**
  - **SPSF for an OECD AOP**
  - **13 test methods submitted or in validation (Sensitive)**
  - **First ECVAM Workshop by invitation planned early 2012**
  - **Interim target is replacement for hazard identification for the 2018 REACH deadline for the 1 tonnage and above level**
  - **Potential saving of ~200.000 mice by 2018**
- **Final product: a GD for full replacement and implementation at EU and OECD level**

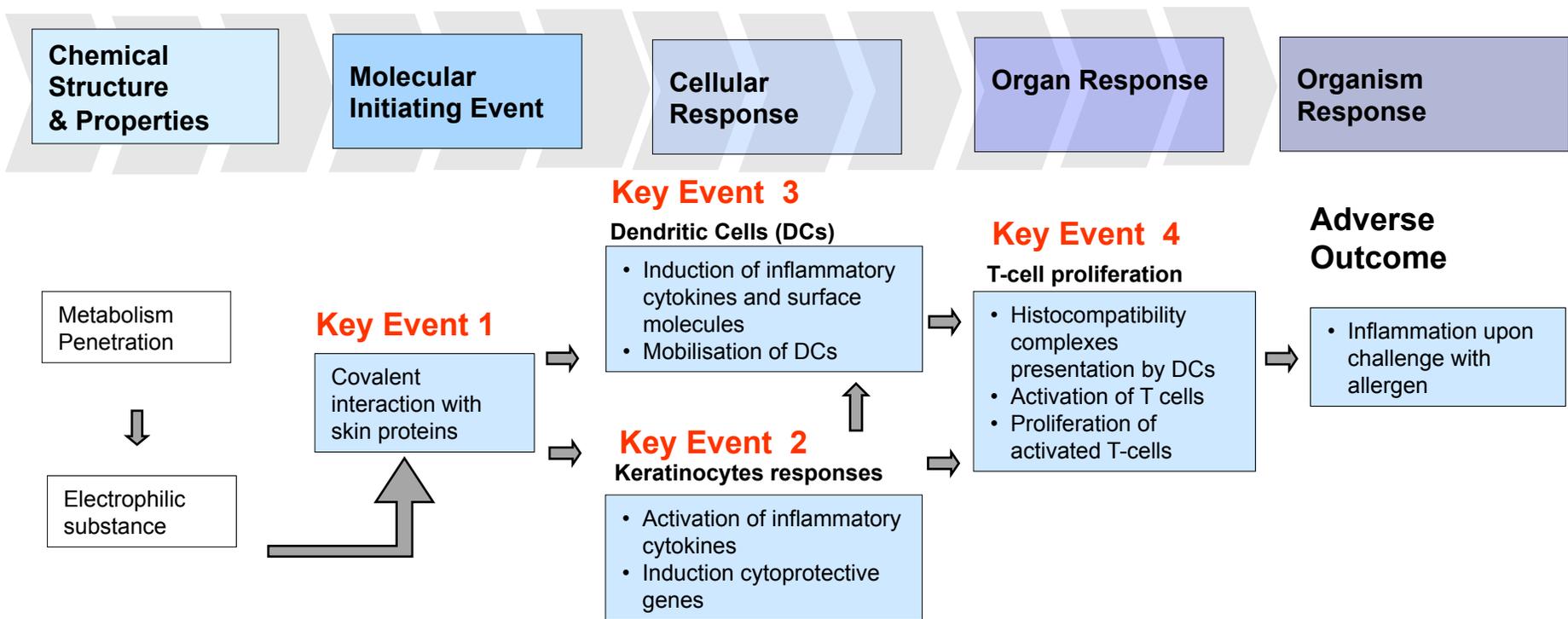
# Skin Sensitisation

Key events considered for the purpose of the Cosmetics Report (DG SANCO)



..”It is unlikely that full replacement of the current *in vivo* assays will require methods addressing all key mechanistic steps of skin sensitisation”.. (DG SANCO Report 2010)

# OECD AOP for Skin Sensitisation





## Mapping of Test Methods According to Key Event(s) – OECD (13 submitted test methods)

Test Method	Skin Bioavailability	Key Event 1	Key Event 2	Key Event 3		Key Event 4
		Haptenation	Epidermal inflammation	DC activation/maturation	DC migration	T cell proliferation
1		Direct reactivity towards synthetic peptides (lysine and cysteine)				
2		ARE/EpRE pathway mediated gene-expression (indirect measurement of reactivity towards cysteine)				
3		ARE/EpRE pathway mediated gene-expression (indirect measurement of reactivity towards cysteine)				
4		Direct reactivity towards synthetic peptides (glutathione) ARE/EpRE pathway mediated gene-expression				
5			Expression of a gene signature in reconstituted epidermal models			
6			IL-18 production in keratinocytes			
7			Cytotoxicity and IL1 $\alpha$ release in reconstituted epidermal model			
8				Expression of a protein signature in a dendritic cell line		
9				Expression of a gene signature in a dendritic cell line		
10				Dendritic cell surface protein expression		
11				Dendritic cell surface protein expression		
12					Dendritic cell migration	



# **EURL ECVAM OUTLINE STRATEGY FOR SKIN SENSITISATION**

- **Short-term goals 2013-14**
  - **Promote the validation of test methods**
  - **Promote OECD AOP work**
  - **Establish an EURL ECVAM database on skin sensitisation to support ITS development and evaluation**
  - **Expert consultation meeting by invitation in early 2013 to focus on replacement of the LLNA for hazard identification**
  - **Identification of data gaps, and recommendations for further studies for international regulatory implementation of the ITS at EU and OECD level.**



# **EURL ECVAM OUTLINE STRATEGY FOR SKIN SENSITISATION**

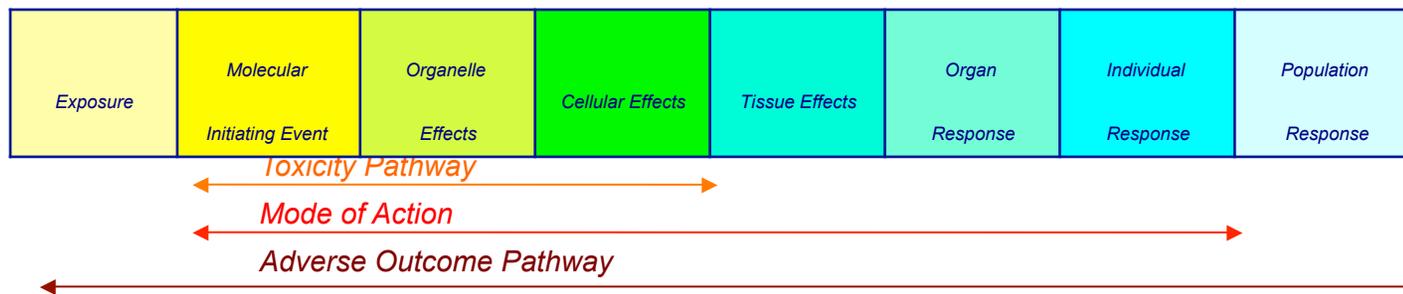
- **Medium-term strategy 2014-15**
  - **Exploitation of the data in the EURL ECVAM database for predicting reactivity and sensitisation, as well as prediction models/ITS for hazard identification predictions.**
  - **Definition of requirements for international regulatory acceptance and implementation of the ITS at EU and OECD level.**
  
- **Long-term strategy 2016 and beyond**
  - **Focus on regulatory acceptance and implementation, including the need for ITS suitable for risk assessment**
  - **OECD Guidance Document for replacement of LLNA for hazard identification by 2018, followed by a more thorough strategy for full replacement for RA**

# SEURAT-1 – the strategy



DG RTD EU FP  
& Cosmetics EU

- 50 million euro joint project
- The SEURAT strategy is to adopt a toxicological mode-of-action framework to describe how any substance may adversely affect human health, and to use this knowledge to develop complementary theoretical, computational and experimental (in vitro) models that predict quantitative points for safety assessments of repeat dose toxicity testing

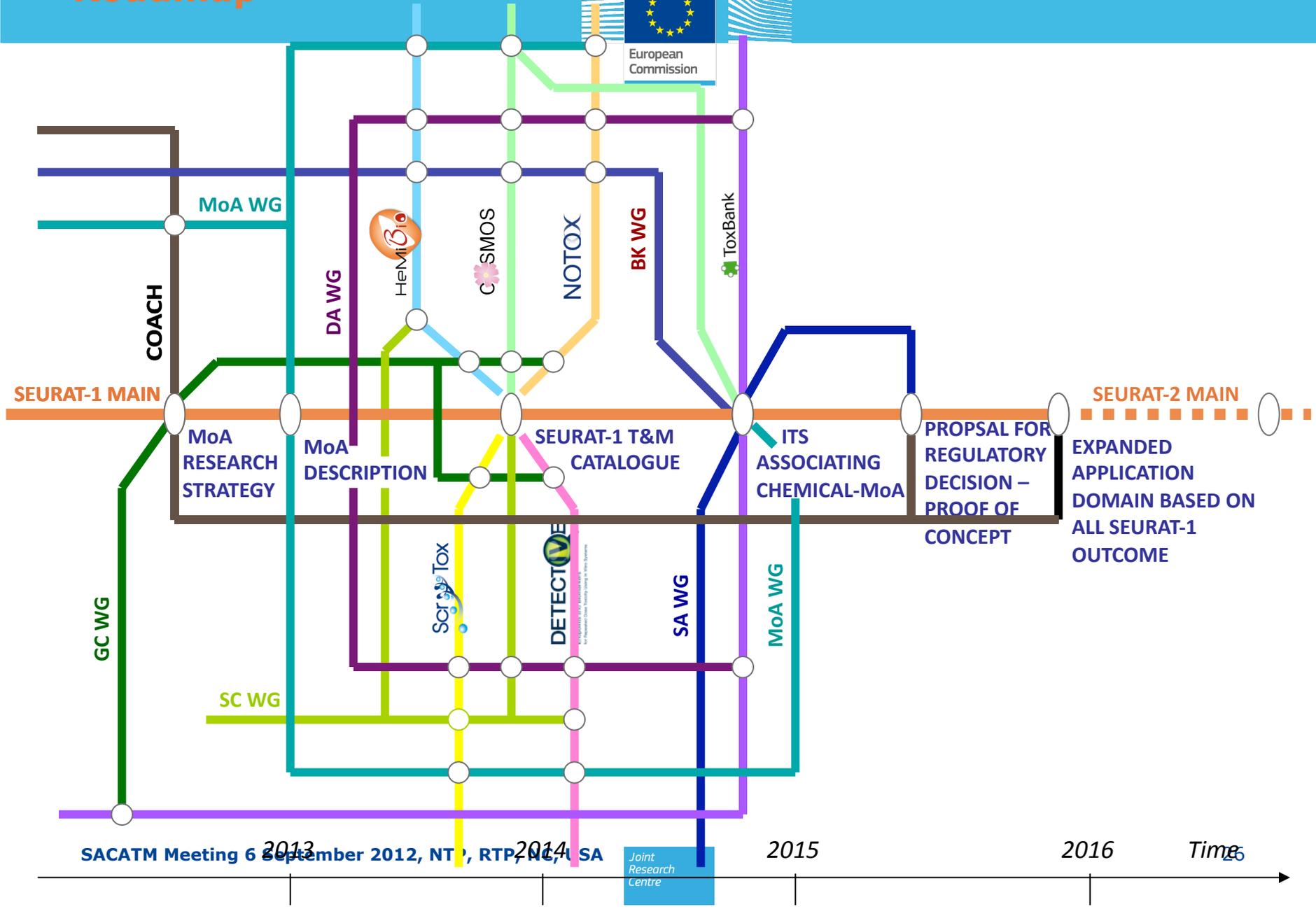


# SEURAT-1 – the cluster



Seurat-1 is designed as a cluster of seven projects: five complementary research projects, a central data management and servicing project (ToxBank), and a coordination and support action (COACH).

# First draft SEURAT-1 Roadmap



SACATM Meeting 6 September 2012, NT, RTP, SA, Joint Research Centre, 2013, 2014, 2015, 2016, Time



**Thank you for your attention!**

**[patric.amcoff@ec.europa.eu](mailto:patric.amcoff@ec.europa.eu)**

**<http://ihcp.jrc.ec.europa.eu/>**