US ERA ARCHIVE DOCUMENT

# OECD Dermal Sensitization AOP Regulatory Perspective

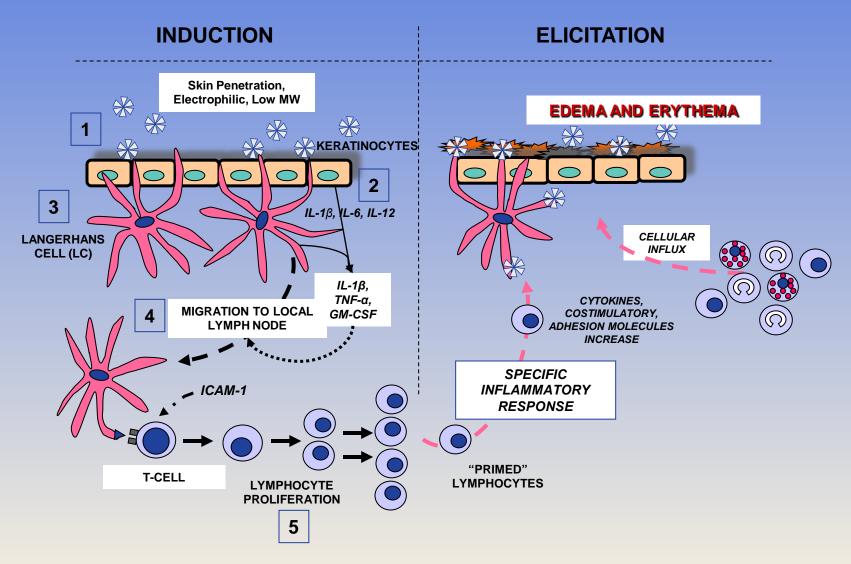
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## **Sensitization**

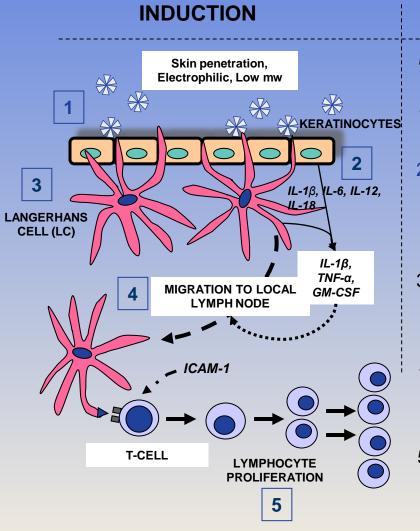
- ICCVAM: Interagency Coordinating Committee on the Validation of Alternative Methods, 15 Federal regulatory and research agencies
  - NICEATM: NTP Interagency Center for the Evaluation of Alternative Toxicological Methods
- EURL-ECVAM: European Union Reference Laboratory for Alternatives to Animal Testing
- ICATM: International Cooperation on Alternative Test Methods
  - ICCVAM, EURL-ECVAM, JaCVAM, KoCVAM
- Cosmetics Europe (COLIPA)
- U.S. regulatory agencies that have needs and/or requirements for sensitization testing:
  - EPA, FDA, OSHA, CPSC

# **Skin Sensitization Pathway**



<sup>\*</sup>Illustration by D. Sailstad

## **Key Events in the Skin Sensitization AOP**



#### **EVENTS AND ASSAYS**

In silico toxicokinetic model, QSARs, permeability methods

- 1. Haptenation: attachment of allergen to skin protein (DPRA, PPRA, EASA)
- Epidermal inflammation: release of proinflammatory signals by epidermal keratinocytes (KeratinoSens<sup>SM</sup>, AREc32, LuSens, SENS-IS, NCTC, SenCeeTox, Sensi-Derm, NCTC)
- 3. Dendritic cell (DC) activation and maturation (h-CLAT, MUSST, PBMDC, VITOSens, GARD)
- 4. DC migration: movement of DC bearing hapten-protein complex from skin to draining local lymph node
- 5. T-cell proliferation: clonal expansion of hapten-peptide specific T-cells (local lymph node assay [LLNA], hTCPA)

# Integrated Testing Strategy (ITS) for Skin Sensitization

- NICEATM developed a strategy that uses:
  - A structural assessment of reactivity (Safford et al. 2011)
  - Direct peptide reactivity assay (DPRA) data
  - rLLNA data
- NICEATM collaboration with UNC-CH: developed multiple QSAR models (using multiple 2D chemical descriptors and Random Forests) with 262 substances from the original rLLNA database.
- NICEATM collaboration with Dr. Joanna Jaworska (P&G)
  developing open-source Bayesian network that uses
  physicochemical, in silico, in chemico and in vitro inputs to
  predict skin sensitization.
  - Probabilistic graphical models
  - Probability of potency category

# Integrated Testing Strategy (ITS) for Skin Sensitization

- High throughput systems, Tox21 Assays
- Relevant assays which may predict skin sensitizing activity
  - EPA's ToxCast:
    - Evaluating activity signatures across the 700+ assays of EPA's ToxCast to determine the ability to predict reference immunotoxicity endpoints
    - 52 substances nominated by the NTP based on immunological relevance and correspondence to the AOP
  - NTP's High Throughput Screening program with the National Human Genome Research Institute's NIH Chemical Genomics Center (NCGC), with a library of 10,000+ compounds

# Tox21 Assays aligned to AOP key events

1. Skin Penetration

2. Electrophilic substance: directly or via auto-oxidation or metabolism

QSAR Model of skin permeability and penetration (*Tropsha*, et al.) 3-4. Haptenation: covalent modification of epidermal proteins

Novascreen enzyme activity biochemical cell-free assays (HDACs, EGFR, etc.) 5-6. Activation of epidermal keratinocytes & Dendritic cells

BSK\_hDF3CGF Human dermal fibroblasts

BSK\_KF3CT Human keratinocytes and fibroblasts

Attagene reporter gene assays HepG2 (Nrf2, LXR, RXR etc.)

Odyssey Thera oxid. Stress in U2OS (H2AFX)

BSK\_SAg and
BSK\_LPS
Human monocytes
and endothelial
cells

7. Presentation of

haptenated protein by

Dendritic cell resulting

in activation &

proliferation of

specific T cells

8-11. Allergic Contact
Dermatitis: Epidermal
inflammation
following re-exposure
to substance due to T
cell-mediated cell
death

QSAR Model built off NICEATM LLNA database (Tropsha, et al.)

Apredica oxidative stress in HepG2 (H2AFX)

Tox21 assay HepG2 bla (Nrf2/ARE)

## **Nomination Steps to ICCVAM**

Sponsor submits test method nomination to NICEATM and ICCVAM



**NICEATM** conducts preliminary evaluation of nomination to assess the extent to which it addresses prioritization criteria



ICCVAM considers NICEATM preliminary evaluation and drafts recommended review activity and draft priority



ICCVAM solicits additional relevant data and comments from public



Public meeting of SACATM: SACATM provides comments; another opportunity for public comment



Final ICCVAM recommendations on priority/activities by ICCVAM (workshops/evaluations) or stakeholder organizations with resources (validation studies)