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

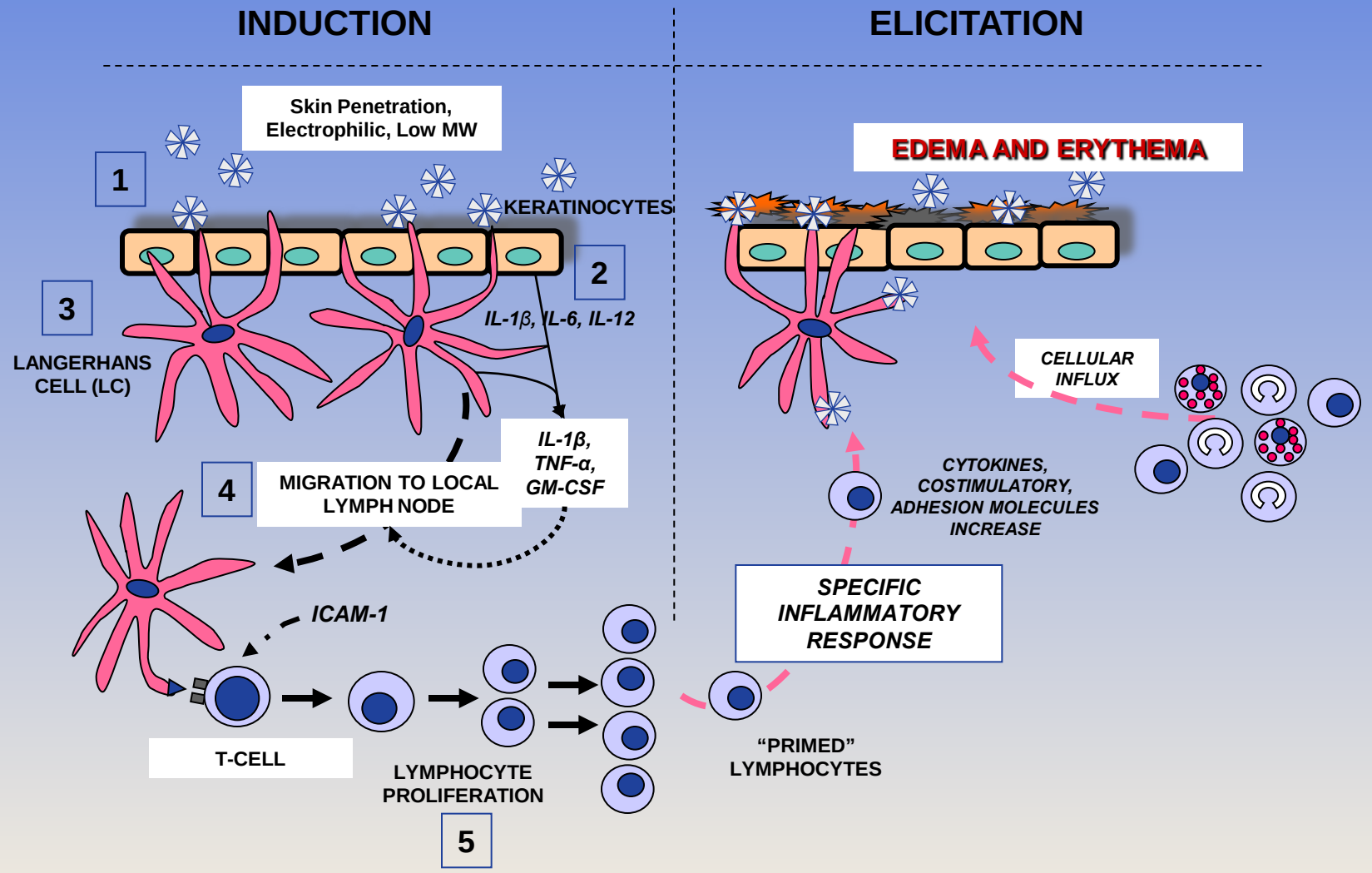
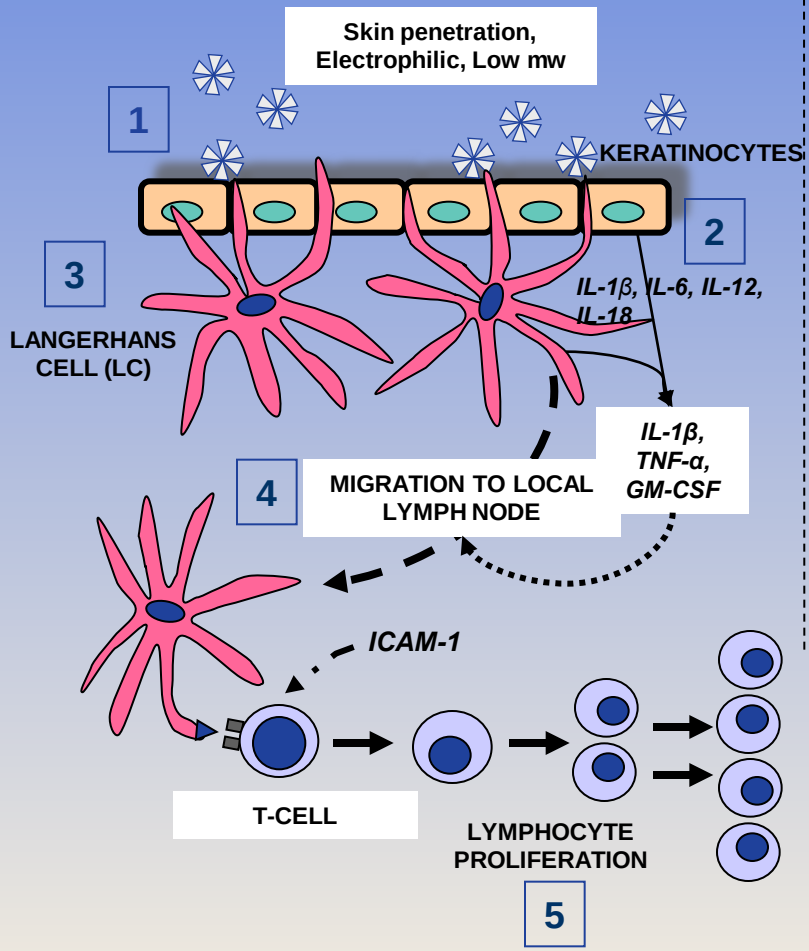


*Illustration by D. Sailstad

Key Events in the Skin Sensitization AOP

INDUCTION



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EVENTS AND ASSAYS

In silico toxicokinetic model, QSARs, permeability methods

1. Haptenation: attachment of allergen to skin protein (DPRA, PPRA, EASA)
2. Epidermal inflammation: release of pro-inflammatory signals by epidermal keratinocytes (KeratinoSens^{SM}, 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)

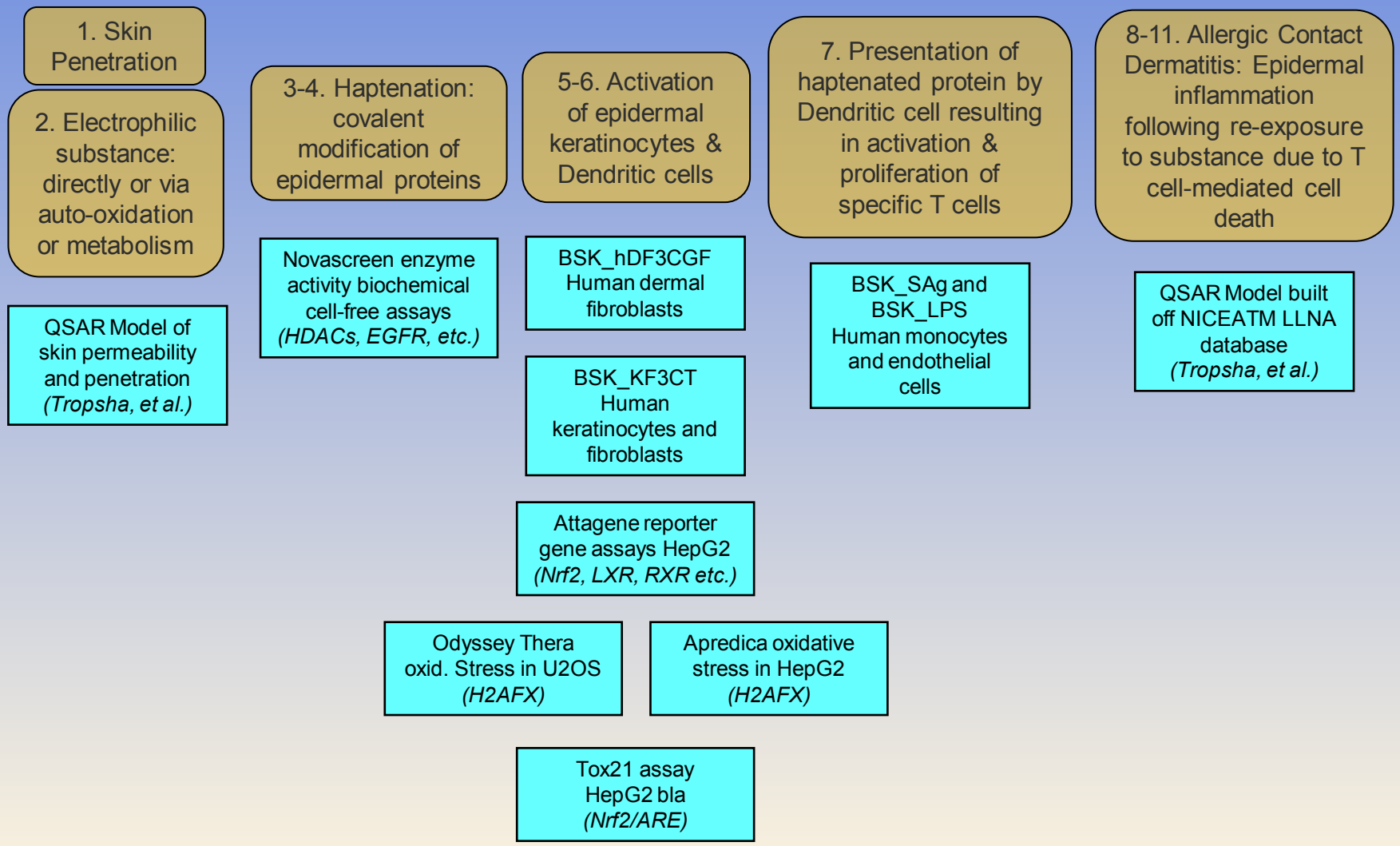
Integrated Testing Strategy (ITS) for Skin Sensitization

- 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



Nomination Steps to ICCVAM