New Direction & Transformation of ICCVAM and NICEATM

Warren M. Casey, Ph.D., D.A.B.T

Director, NICEATM

Agency for Toxic Substances and Disease Registry • Consumer Product Safety Commission • Department of Agriculture
Department of Defense • Department of Energy • Department of the Interior • Department of Transportation
Environmental Protection Agency • Food and Drug Administration • National Institute for Occupational Safety and Health
National Institutes of Health • National Cancer Institute • National Institute of Environmental Health Sciences
National Library of Medicine • Occupational Safety and Health Administration

Defining the respective roles of ICCVAM and NICEATM

ICCVAM does not..

- Validate methods
- Have authority over Federal Agencies
- Have a budget
- Have any physical infrastructure
- Have any full time staff

ICCVAM
Mandate and Legislative Context

- Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) was established with the "ICCVAM Authorization Act of 2000"

Public Law 106–545
106th Congress

An Act

To establish, wherever feasible, guidelines, recommendations, and regulations that promote the regulatory acceptance of new or revised scientifically valid toxicological tests that protect human and animal health and the environment while reducing, refining, or replacing animal tests and ensuring human safety and product effectiveness.

Dec. 19, 2000
[H.R. 4281]

ICCVAM
Mandate and Legislative Context

- Facilitate interagency and international collaboration to promote the development, regulatory acceptance, and use of alternative tests that encourage the reduction, refinement, or replacement of animal test methods
- Provide guidance to test method developers
- Consider results form expert peer reviews of alternative toxicological test methods that may be acceptable for regulatory use and make recommendations on their use to appropriate Federal Agencies (ICCVAM Recommendation)

ICCVAM Co-Chairs

Anna Lowit (EPA) and Abby Jacobs (FDA)

NICEATM

NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), organized as an office under the NTP Division, part of NIEHS

National Toxicology Program
NTP

NICEATM

- Is funded by NIEHS through the National Toxicology Program
- Two Federal employees, 12 Contract Staff (ILS, Inc.)
- Provides operational and scientific support to ICCVAM

New Vision and Direction for ICCVAM

ehp ENVIRONMENTAL HEALTH PERSPECTIVES

15 Years Out: Reinventing ICCVAM

February 1, 2013 Editorials Comments Off

Linda S. Birnbaum

Director, NIEHS and NTP, National Institutes of Health, Department of Health and Human Services, Research Triangle Park, North

"It has become clear that it is time to change our approach."

"..the interagency agenda will now be driven by the partner regulatory agencies—the agencies that will ultimately implement the ICCVAM-recommended methods."

http://ehp.niehs.nih.gov/2013/02/1206292/

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15 Years Out: Reinventing ICCVAM

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"Tox21 has the real potential to result in dramatic changes in the numbers and types of organisms used for toxicology testing. A stronger interface of NICEATM with Tox21 will better position ICCVAM for addressing how data from these new methods can be integrated into the existing regulatory framework."

http://ehp.niehs.nih.gov/2013/02/1206292/

New Vision and Direction for ICCVAM

- ICCVAM priority setting and current science focus areas:
  - Change in approach:
    - Streamline the number of active projects to those with a reasonable likelihood of success in the near future (1 to 5 years)
    - Maintain flexibility to reorient efforts to maximize potential progress towards use of alternative approaches
  - Short-term:
    - Biologics: *Leptospira* vaccine potency
    - Acute oral and dermal toxicity testing
    - Skin sensitization
    - **Acting on ECVAM Recommendations**

EURL-ECVAM

JOINT RESEARCH CENTRE

EURL ECVAM's mandate and activities cover the entire life cycle of alternative methods, i.e. development, validation, regulatory acceptance, international recognition and proper scientific use. At the core of these activities is the EURL ECVAM validation process.

Validated Methods

1. Test submission handling, scientific/relevance assessment. Optimisation (if necessary)

2. *Planning, conduct of Validation Studies (VS). >> VSR for ESAC (VMG)*

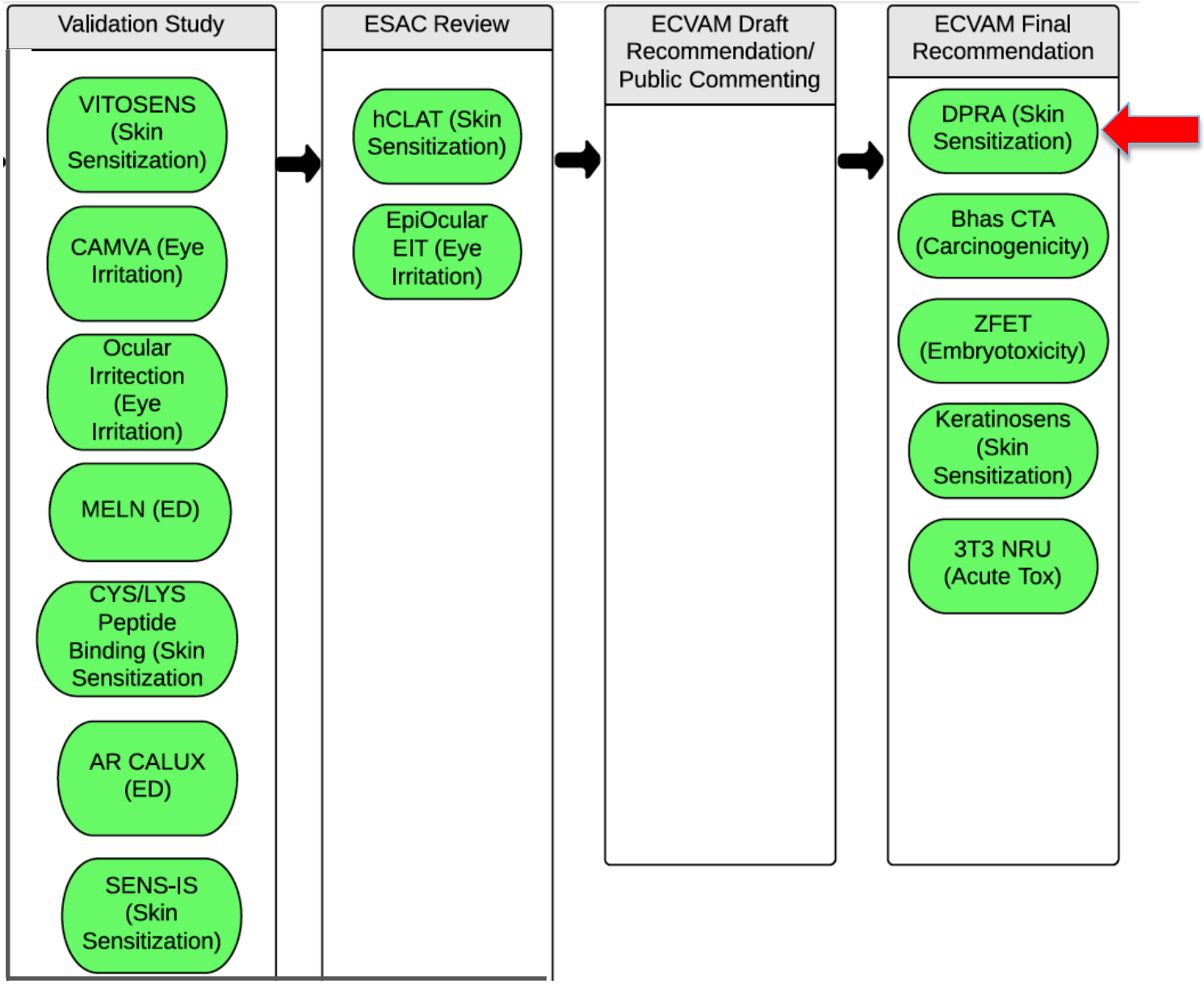
3. *ECVAM request to ESAC & ESAC review & opinion on (a) VS conduct, (b) VMG conclusion (c) ESAC opinion on validity*

4. *Draft ECVAM Recommendation*
5. *'Right to be heard' process*

6. *Public Commenting*

7. *Finalisation and publication of ECVAM recommendation, incl. ESAC opinion & VSR.*

→ **ECVAM Recommendation**


Validation Study
VITOSENS (Skin Sensitization)
CAMVA (Eye Irritation)
Ocular Irritection (Eye Irritation)
MELN (ED)
CYS/LYS Peptide Binding (Skin Sensitization
AR CALUX (ED)
SENS-IS (Skin Sensitization)
ESAC Review
hCLAT (Skin Sensitization)
EpiOcular EIT (Eye Irritation)
ECVAM Draft Recommendation/ Public Commenting
ECVAM Final Recommendation
DPRA (Skin Sensitization)
Bhas CTA (Carcinogenicity)
ZFET (Embryotoxicity)
Keratinosens (Skin Sensitization)
3T3 NRU (Acute Tox)

Exploring New Paradigms

- ICCVAM has recognized the need for an evolving concept of validation that is responsive to new technologies and on-going paradigm shifts in toxicity testing

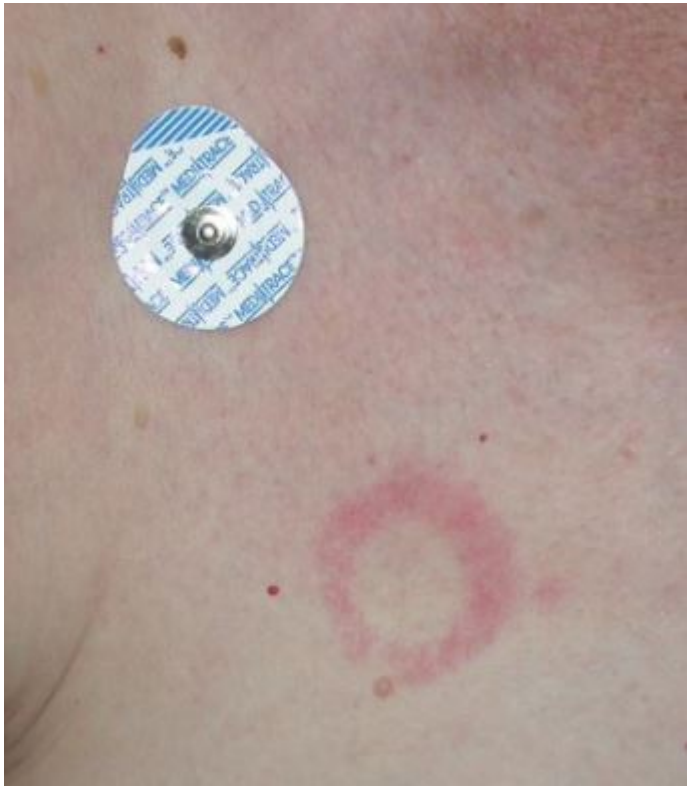
"Validation"

A determination of the usefulness and limitations of a test method for a specific purpose

Exploring New Paradigms

- ICCVAM has recognized the need for an evolving concept of validation that is responsive to new technologies and on-going paradigm shifts in toxicity testing
- Evaluate predictive, integrated test strategies that combine *in silico* approaches, multiple *in vitro* assays, and limited targeted testing in laboratory animals

Skin Sensitization



Skin Sensitization Pathway

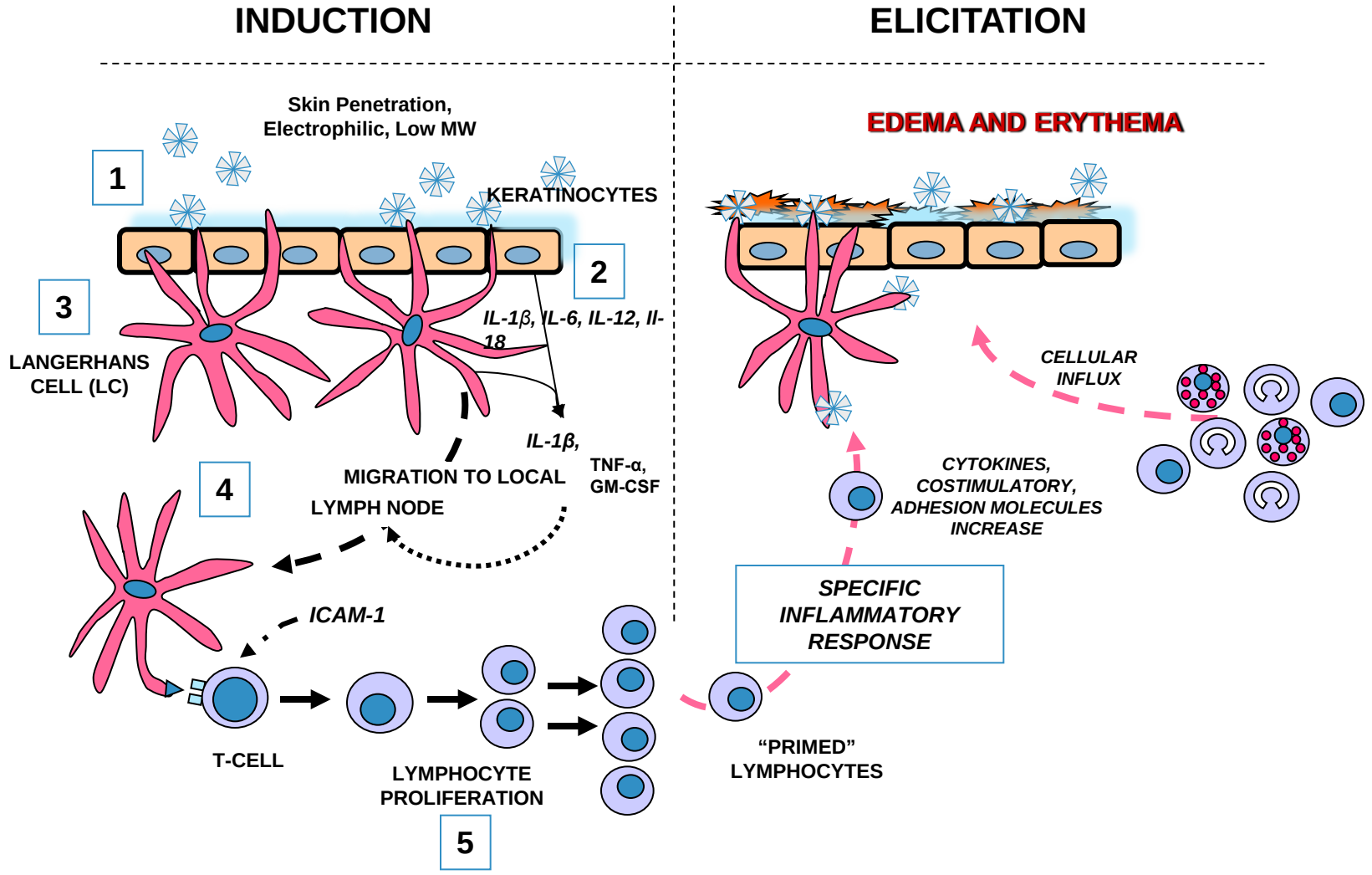
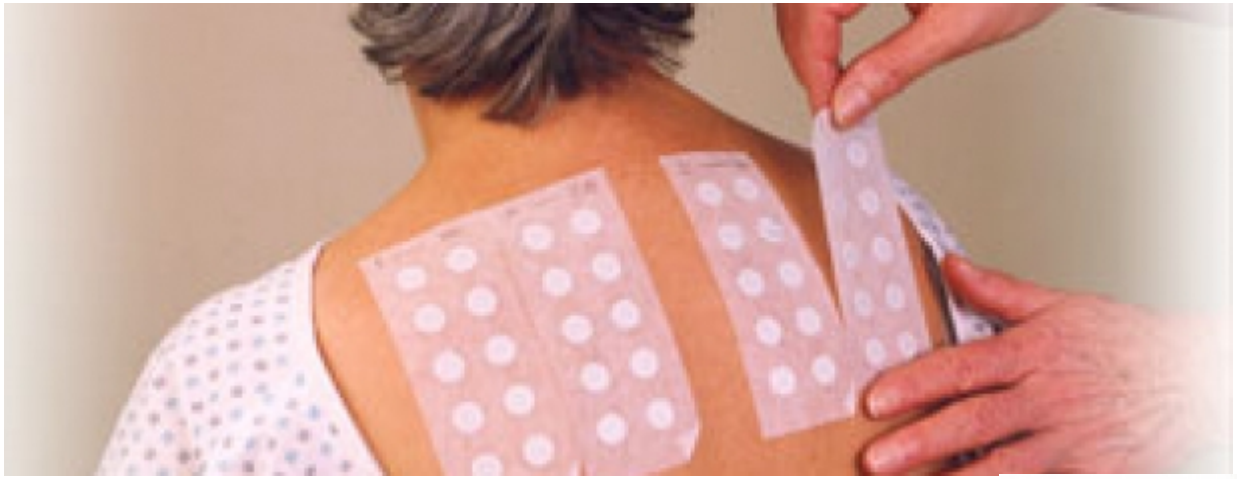
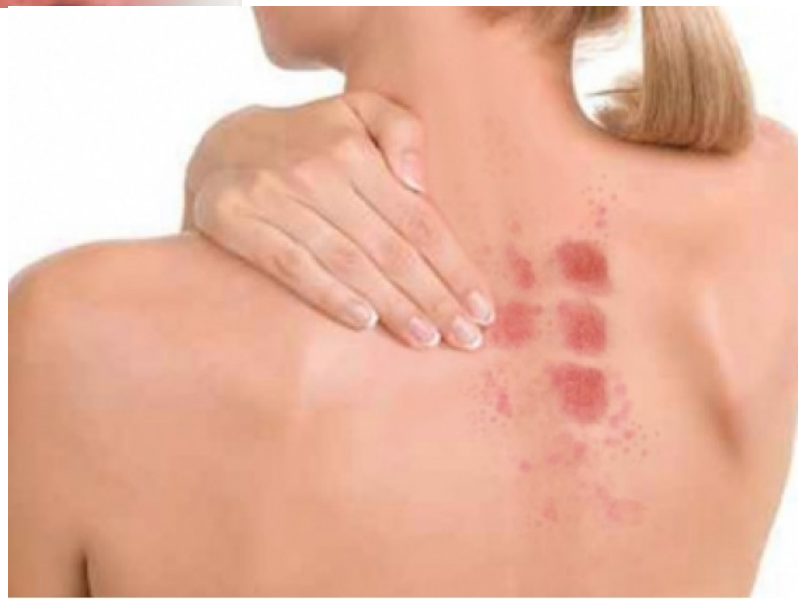


*Illustration by D. Sailstad

Patch Test





Skin Sensitization Pathway

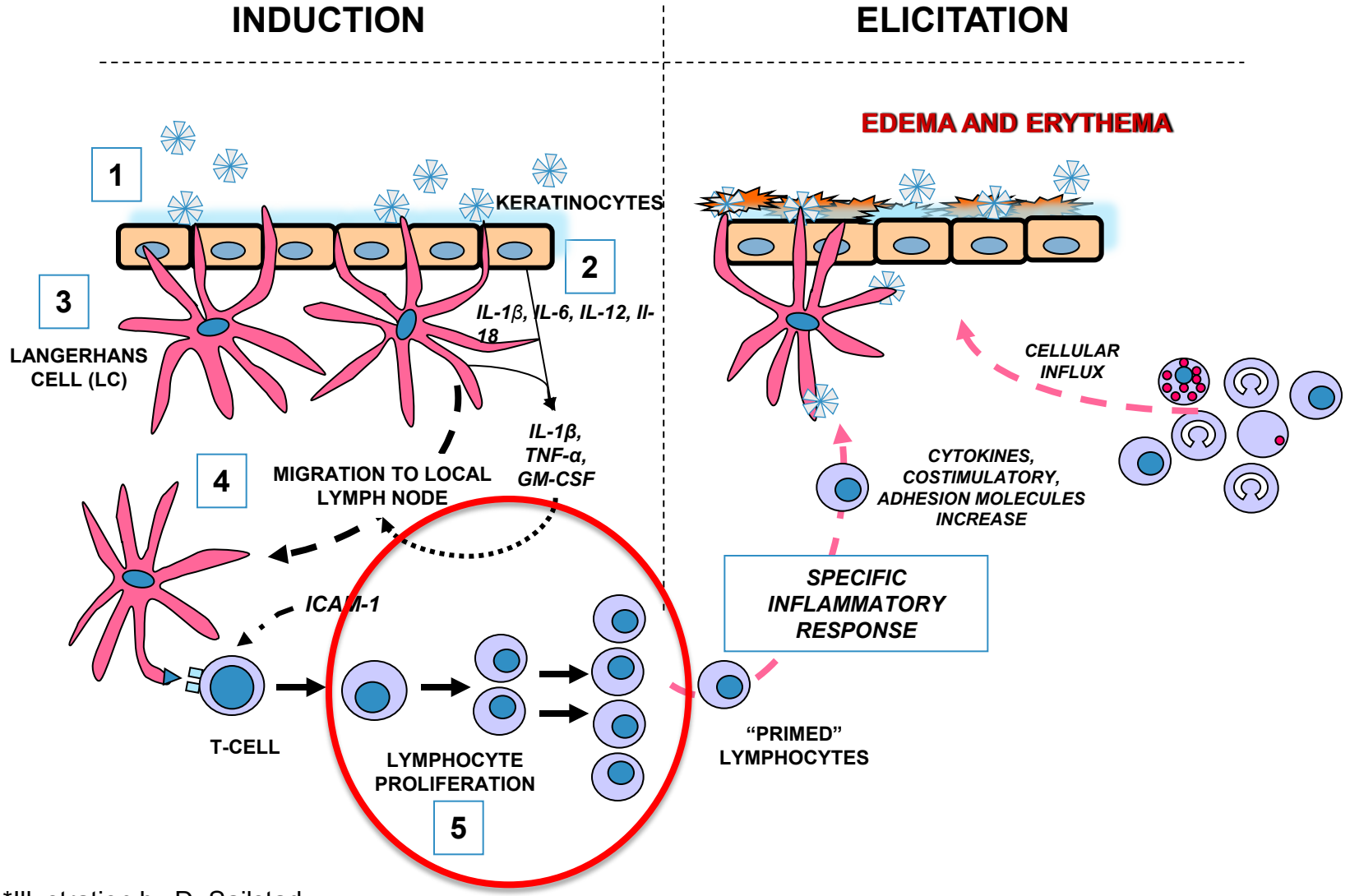
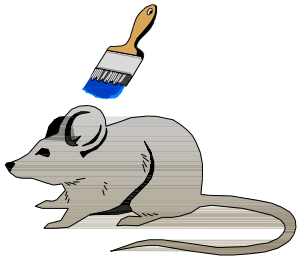
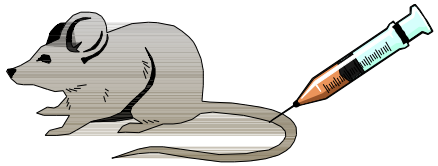


*Illustration by D. Sailstad

LLNA Test Method Protocol

Apply 25 µl Test Substance → **No Treatment** → **Administer Radioisotope (^{3}H or ^{125}I)**

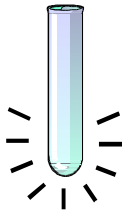




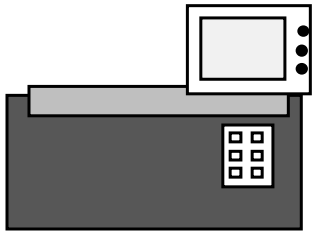
Days 1 - 3 — **Days 4 - 5** — **Day 6**

Day 6 (5 hours)

Collect Draining Auricular Lymph Nodes



Prepare Single Cell Suspension



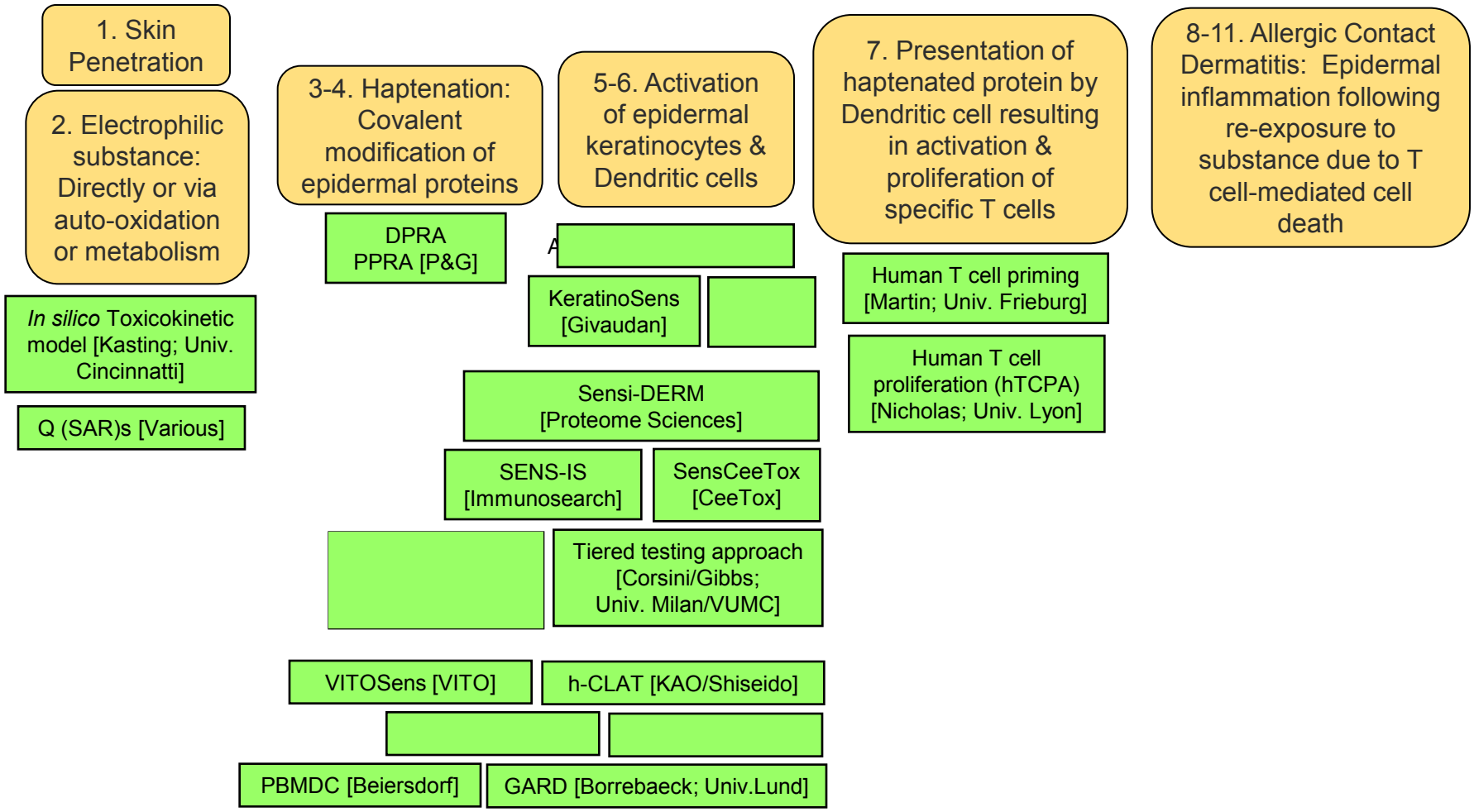
Measure Proliferation (Scintillation Counts)

$$SI = \frac{\text{Mean DPM of Treatment Group}}{\text{Mean DPM of Vehicle Control Group}}$$

SI ≥ 3 = Sensitizer (Positive)
SI < 3 = Nonsensitizer (Negative)

Abbreviations: DPM = disintegrations per minute; SI = stimulation index

Non-animal Methods for Skin Sensitisation: Aligned to AOP Key Events



Slide courtesy of Gavin Maxwell (Unilever/Cosmetics Europe)

Creating an Open Source Model for Probabilistic Skin Sensitization Hazard Prediction

Research Article

Journal of Applied Toxicology

Received: 14 January 2013, Revised: 4 February 2013, Accepted: 4 February 2013 Published online in Wiley Online Library

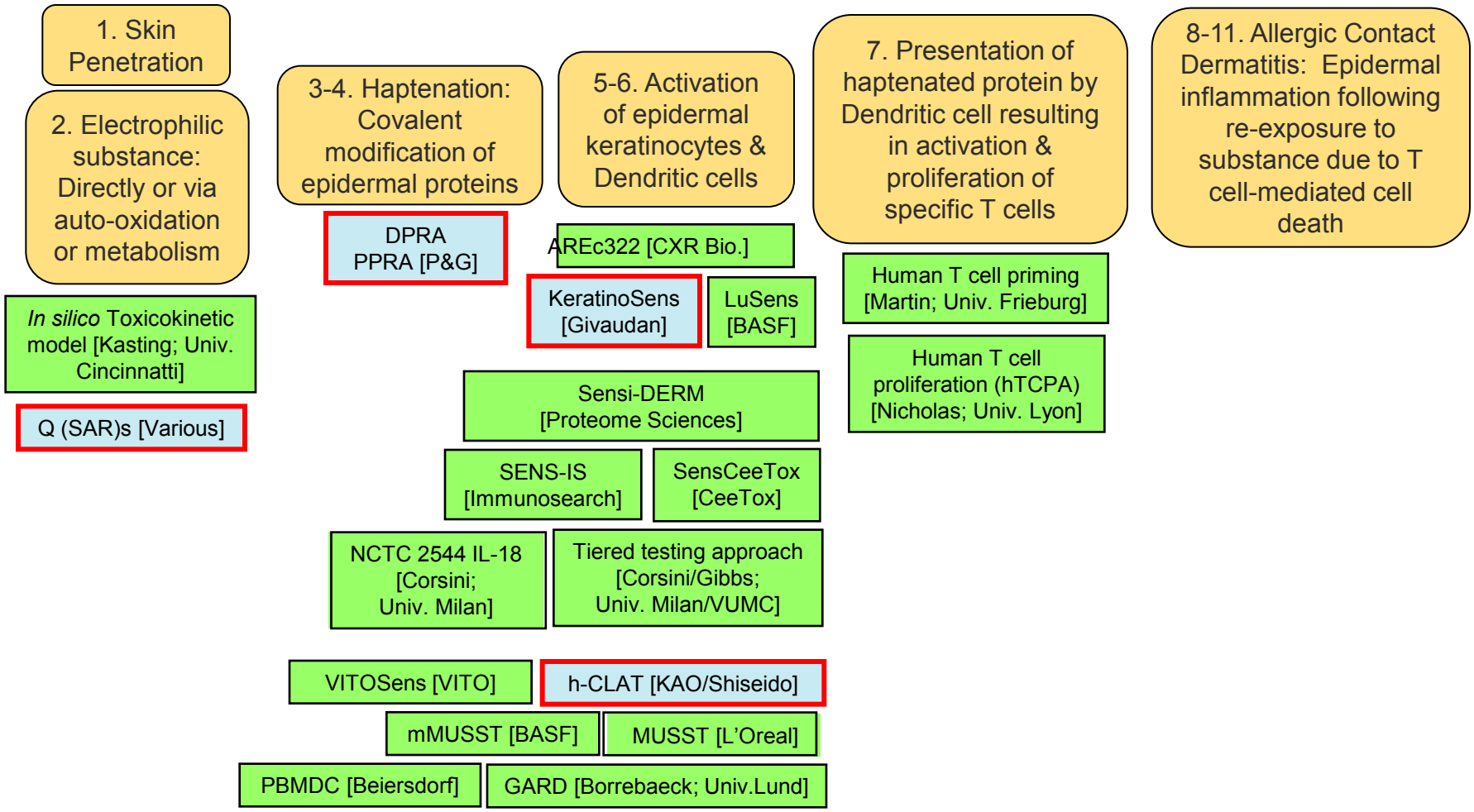
(wileyonlinelibrary.com) DOI 10.1002/jat.2869

Bayesian integrated testing strategy to assess skin sensitization potency: from theory to practice

Joanna Jaworska[a]*, Yuri Dancik[a], Petra Kern[a], Frank Gerberick[b] and Andreas Natsch[c]

Open source software  http://www.r-project.org/

Non-animal Methods for Skin Sensitisation: Aligned to AOP Key Events



Slide courtesy of Gavin Maxwell (Unilever/Cosmetics Europe)

Skin Sensitization

- What model system for assessing performance: Guinea pig, Mouse LLNA, human patch test?
- What are the endpoints: Yes/No, potency/category (which category system), susceptibility?

Skin Sensitization

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- What are the endpoints? **Yes/No**, potency/category (which category system), susceptibility

Skin Sensitization

- Pilot Project: Validate IDTS using Bayesian network to classify chemicals as sensitizers / non sensitizers, using mouse LLNA as the reference

Improving Communications Role of ICCVAM

Achieve broader engagement with the scientific community and stakeholders (e.g., the regulated community, public interest groups) though a number of different mechanisms, such as:

- Face-to-face forums
- Community of practice webinars
- ICCVAM Website as a repository of 3R activities
- Focused workshops with well-defined objectives

NIH National Institute of Environmental Health Sciences

Collaborative Workshop on Aquatic Models and 21st Century Toxicology

May 5-6, 2014
James B. Hunt Jr. Library
North Carolina State University
Raleigh, North Carolina, USA

Presented by:
The National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM)
North Carolina State University

To register, visit the workshop webpage at http://ntp.niehs.nih.gov/go/41308
For more information contact NICEATM:
919-316-4668 – niceatm@niehs.nih.gov

Individuals with disabilities who need accommodation to participate in this event should contact Dr. Elizabeth Maull at 919-316-4668 or maull@niehs.nih.gov. TTY users should contact the Federal TTY Relay Service at 800-877-8339. Requests should be made at least 5 days in advance of the event.

NIH National Institute of Environmental Health Sciences

NC STATE UNIVERSITY

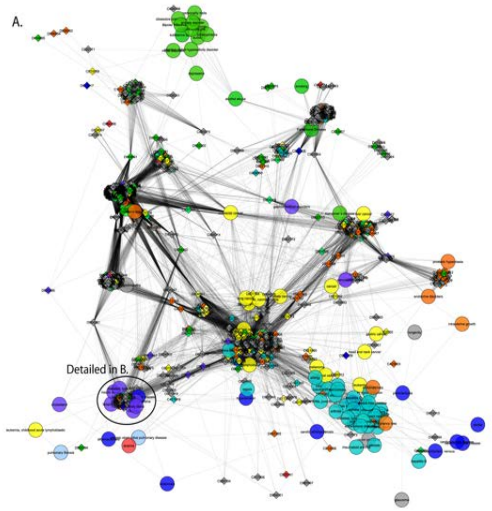
Summary

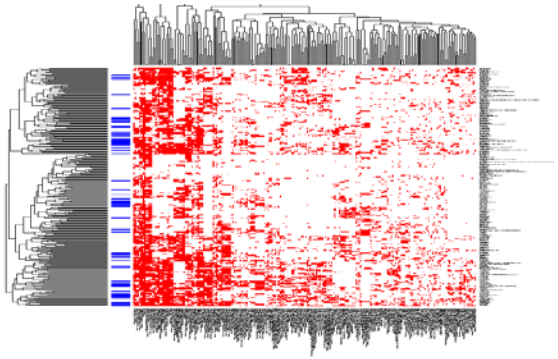
- ICCVAM and NICEATM are distinct entities but work together to promote the validation and acceptance of alternative methods
- Both have new direction and focus on collaboration, not control.
- There are many challenges ahead. We need to aggressively pursue “realistic” goal, while investing in “stretch” goals.

Questions / Comments?

Tox21 Goals

- Prioritize compounds for more extensive toxicological evaluation
- Develop predictive models for biological response in humans
- Reduce reliance on animal models





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 Primary human dermal fibroblasts

BSK_KF3CT Primary human keratinocytes and fibroblasts

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

Odyssey Thera oxid. stress in U2OS *(H2AFX)*

Apredica oxidative stress in HepG2 *(H2AFX, MitoMem)*

Tox21 assay HepG2 bla *(Nrf2/ARE)*

7. Presentation of haptenated protein by Dendritic cell resulting in activation & proliferation of specific T cells

BSK_SAg, 3C, 4H and BSK_LPS Primary human monocytes and endothelial 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.)*

Local Lymph Node Assay (LLNA)

Tox21 Summary

- Phase I (2800 Chemicals x 100 Assays, 320 Chemicals x 550 Assays) is completed and data are publically available.
- Phase II (~10,000 Chemicals x 30 assays/year) is ongoing, data available via pubchem.
- Phase III (follow up in Low/Med throughput systems) is ongoing, data available as projects are completed and published.

Workshops

- Adverse Outcome Pathways, Fall 2014 (NIH Campus, Bethesda MD)
- Alternatives to HIST w/NC3R Aug 2014 (Prague, CR); Oct 2014 (London, UK)