New Paradigms for skin sensitisation potency: scientific perspective

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[*Thinking outside the box*]

Ian Kimber, Emeritus Professor of Toxicology
University of Manchester

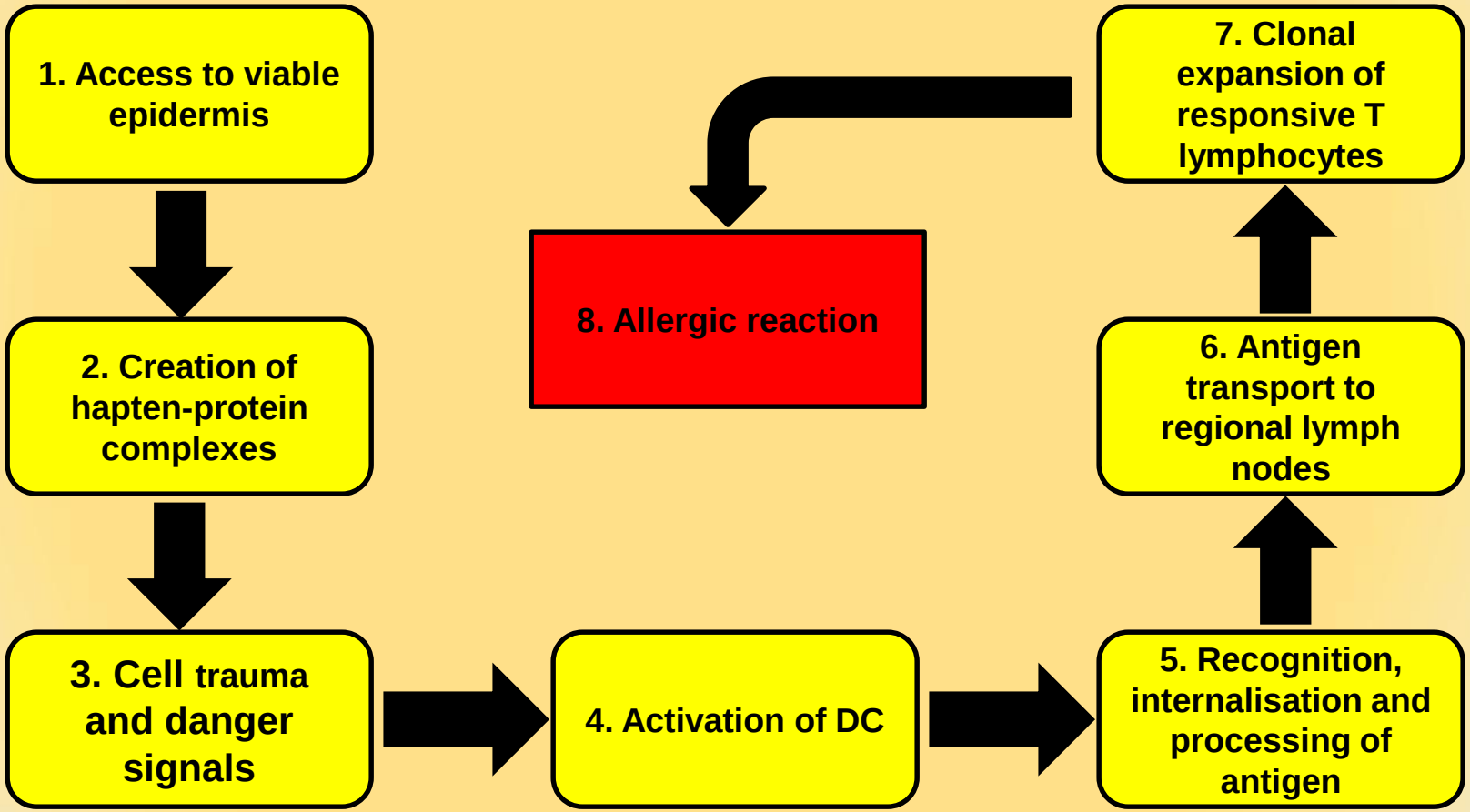
What is potency?

- **Vigour of response** *Immunology*
- **Concentration/dose required to give biologically/clinically meaningful effect** *Toxicology*

What drives skin sensitisation potency?

- **VIGOUR** of T lymphocyte responses
- **QUALITY** of T lymphocyte responses
- **BREADTH** of T lymphocyte responses

Skin sensitisation: Adverse Outcome Pathway (AOP)



In Vitro Tests:
The current paradigm

KE1: Haptenation of skin proteins [OECD TG 442C]

DPRA

KE2: Generation of danger signals [OECD TG 442D]

KeratinoSens; LuSens

KE3: Activation of dendritic cells [OECD TG 442E]

H-CLAT; U-SENS; IL-8-Luc assay

The Challenge

Markers of potency should be causally AND quantitatively associated with the relevant end-point

(acquisition of skin sensitisation)

Threshold or Continuous Variable?

- Covalent interaction with protein [KE1]
- Elicitation of danger signals [KE2]
- Activation of DC [KE3]

Threshold or Continuous Variable? Considerations

- **Covalent interaction with protein [KE1]**

  Kinetics of interaction, repertoire of proteins haptenated, amino acid selectivity?

- **Elicitation of danger signals [KE2]**

  Extent of DG production, quality of DG elicitation, longevity of DG response?

- **Activation of DC [KE3]**

  Type of DC activation, populations of cutaneous DC affected, impact on migration, differentiation and or survival?

Options and Opportunities?

- Anti-hapten antibody responses
- Holistic assessment of biological responses to sensitising chemicals (gene expression/epigenetic/proteomic signatures) [+/-machine learning/AI]
- Detailed qualitative evaluation of protein haptenation (kinetics/amino acid selectivity/orientation of hapten expression)
- More exhaustive characterisation of the response of cutaneous DC to sensitising chemicals (quality and quantity)
- Qualitative/quantitative aspects of danger signal responses