

ILSI HESI Workshop

Assessment of Respiratory
Sensitization

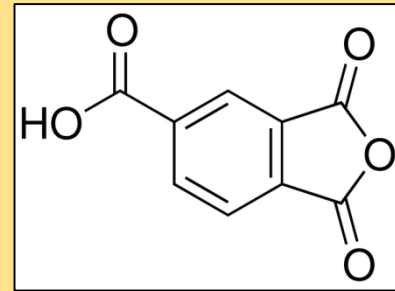
Toxicological Challenges:
Mechanisms and Routes of Exposure

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Chemical Respiratory Allergens

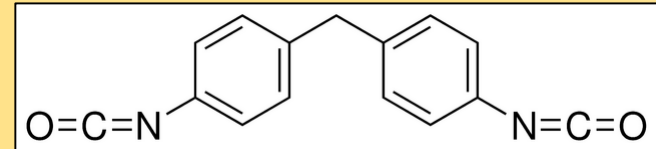
- Acid anhydrides

trimellitic anhydride (TMA)



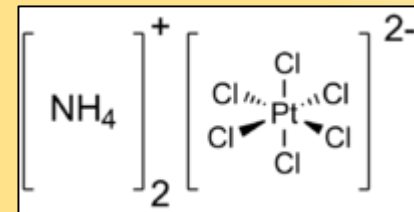
- Diisocyanates

diphenylmethane diisocyanate (MDI)



- Platinum salts

ammonium hexachloroplatinate (AHCP)

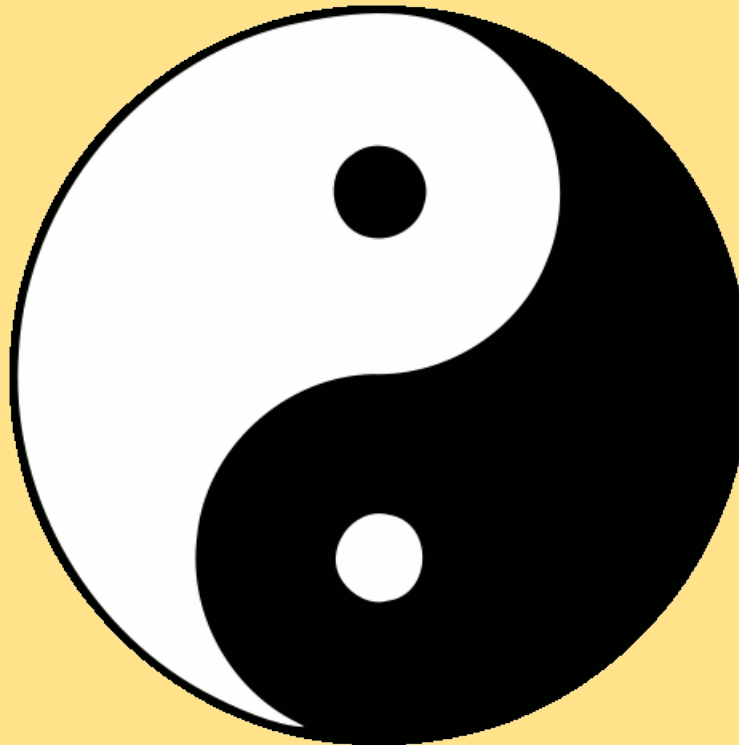


The yin/yang of chemical allergy

Sensitisation of the
respiratory tract



Chemical
respiratory allergy

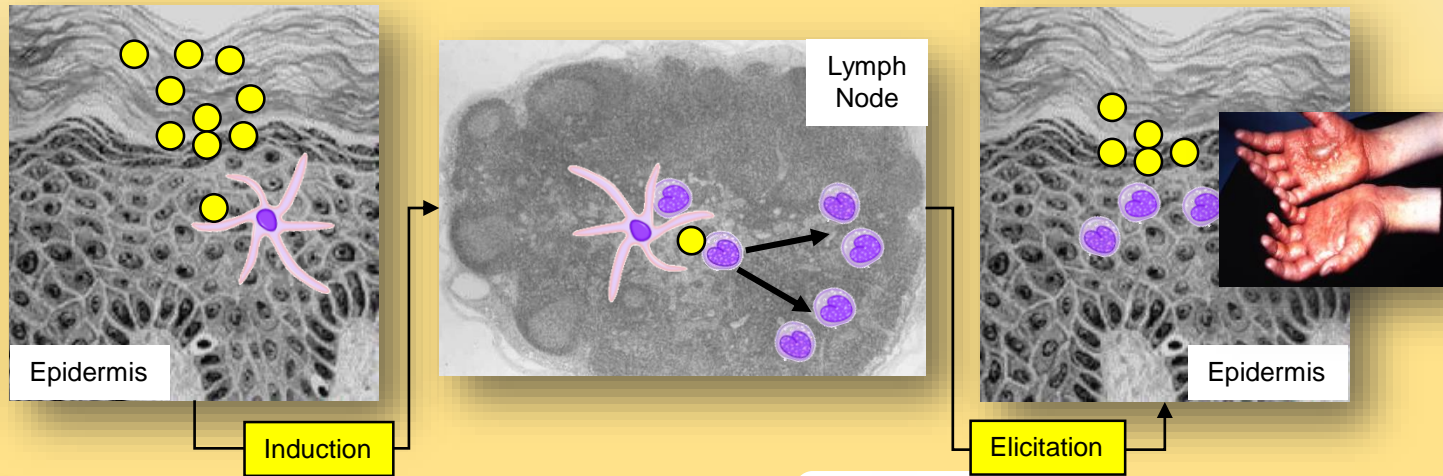


Skin sensitisation

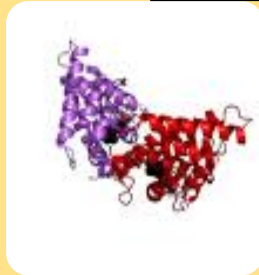


Allergic contact
dermatitis

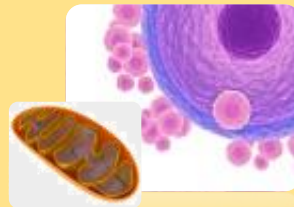
Skin Sensitisation AOP (G Maxwell)



1. Skin Penetration



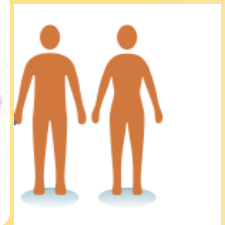
3-4. Haptenation: covalent modification of epidermal proteins



5-6. Activation of epidermal keratinocytes & Dendritic cells



7. Presentation of haptened 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



Modified from 'Adverse Outcome Pathway (AOP) for Skin Sensitisation', OECD

Allergic contact dermatitis

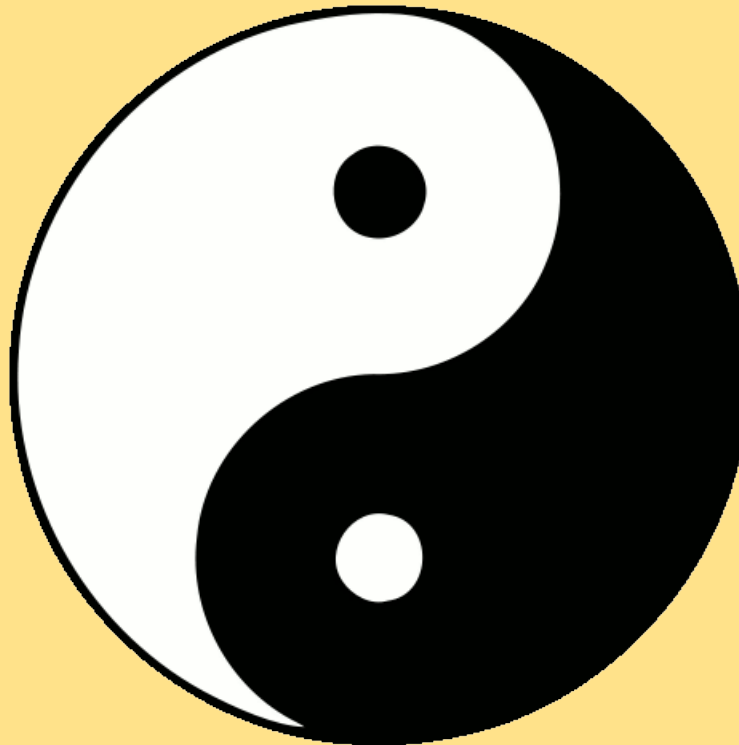


The yin/yang of chemical allergy

Sensitisation of the
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Chemical
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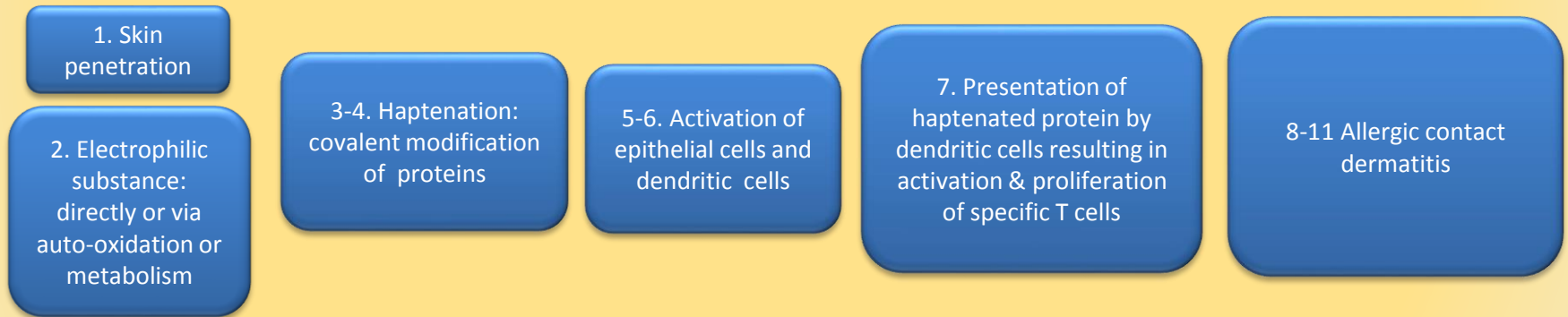


Skin sensitisation

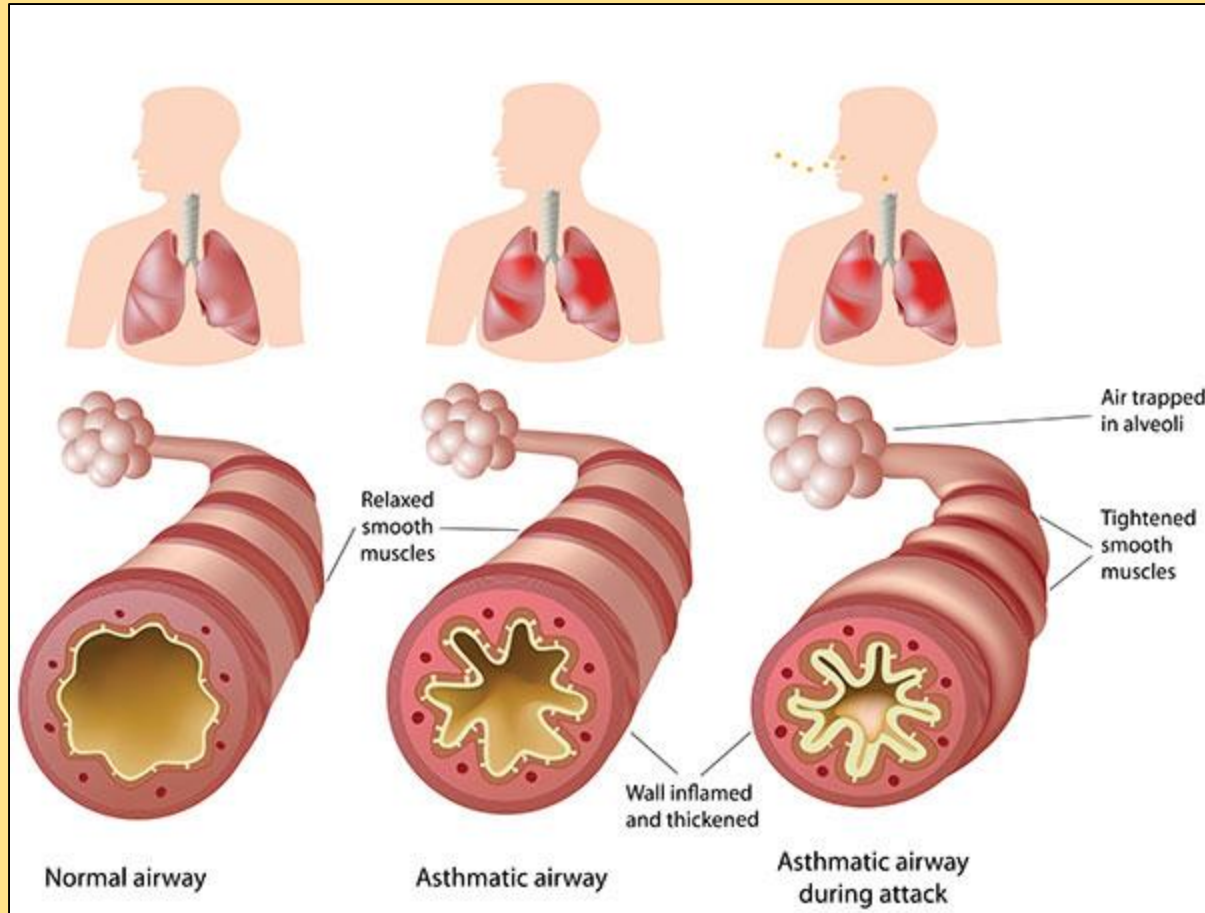


Allergic contact
dermatitis

Skin Sensitization OR Sensitization of the Respiratory Tract ?



Asthma



The Toxicological Challenge

There are currently available no validated or widely accepted methods for the identification and characterisation of chemical respiratory allergens.

Areas of Uncertainty

1. Route of exposure:

- Inhalation or skin exposure?

2. The role of IgE antibody

The Importance of Skin Exposure



Areas of Uncertainty

1. Route of exposure:

- Inhalation or skin exposure?

2. The role of IgE antibody

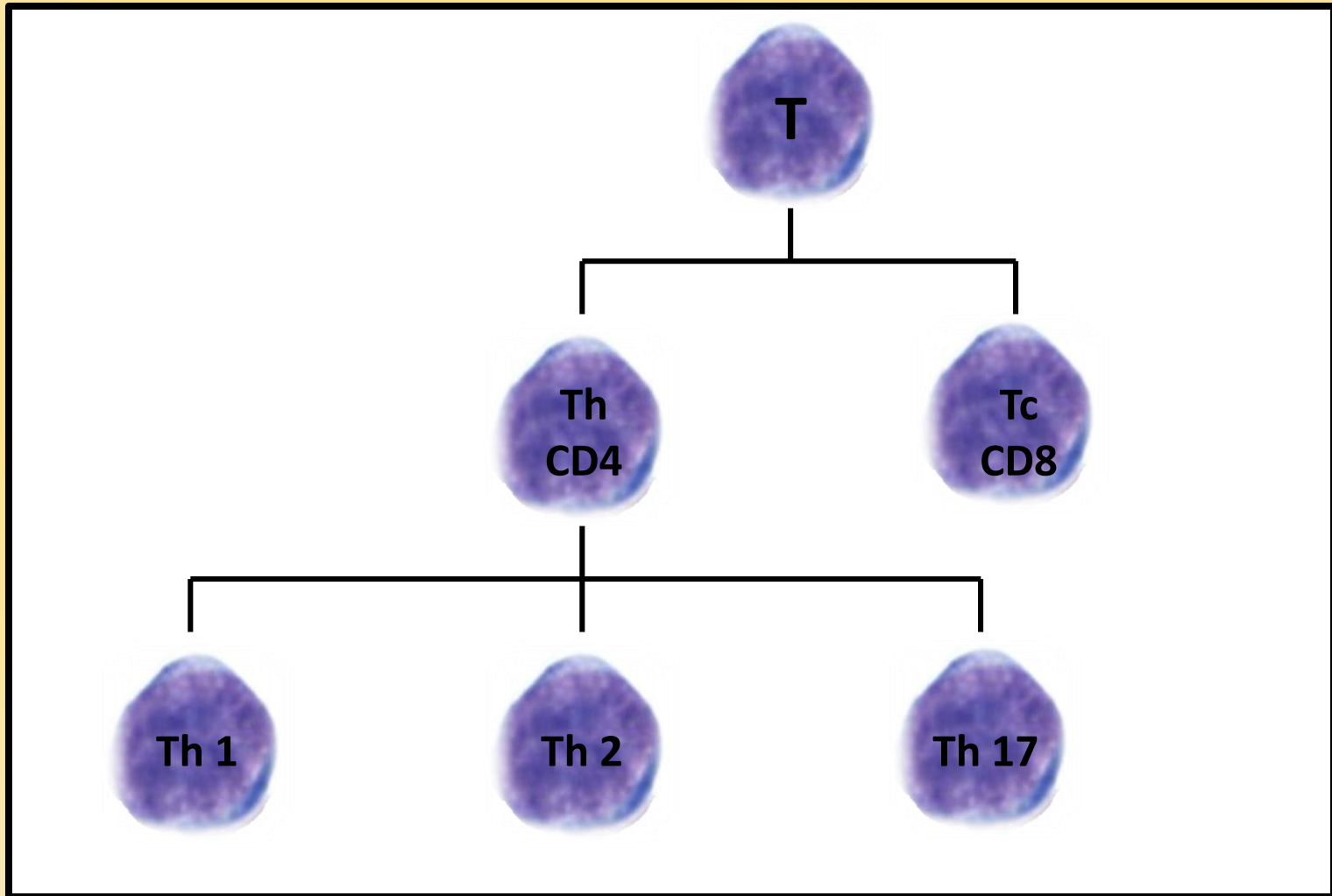
The Debate

The role of IgE antibody

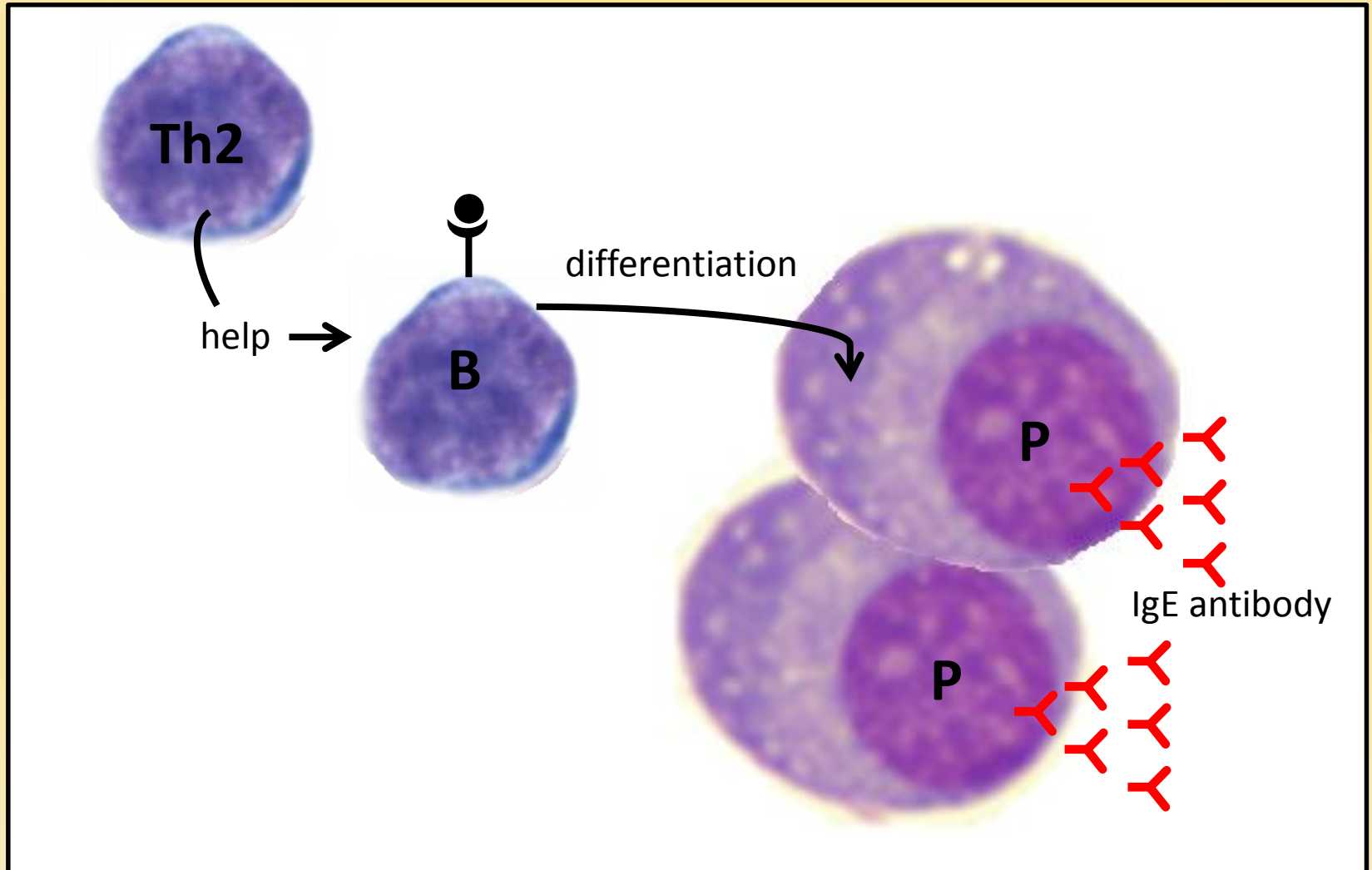
EITHER: There are immunological mechanisms other than/in addition to IgE antibody that cause sensitisation of the respiratory tract to chemicals and occupational asthma

OR: IgE antibody plays a mandatory universal role in sensitisation of the respiratory tract to chemicals and occupational allergy

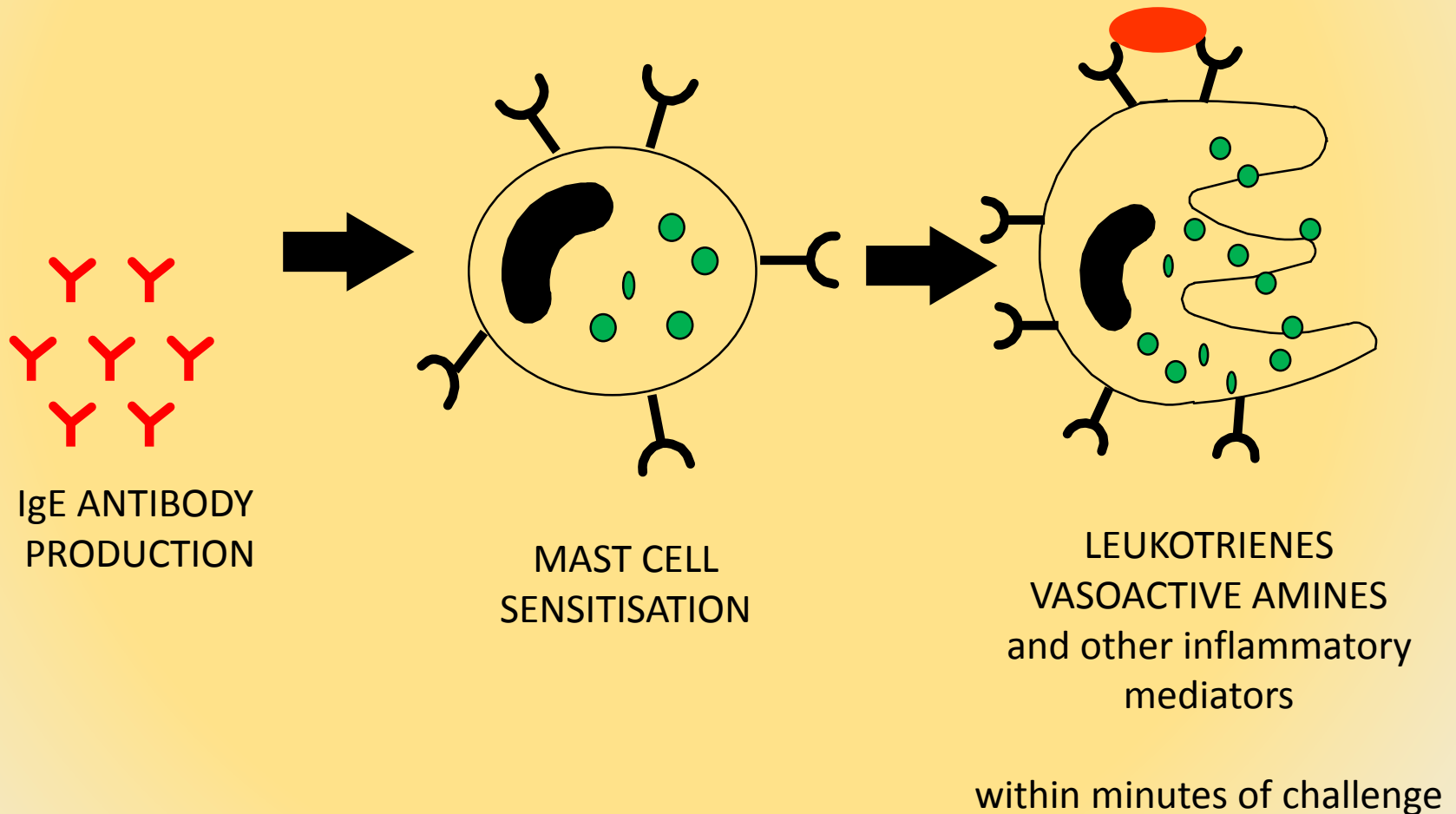
T lymphocyte heterogeneity



Th2 cells drive IgE antibody production



IgE antibody and inflammation



Is IgE antibody important?

NO

Plasma IgE antibody not detected
in many subjects with diisocyanate
asthma

Yes

- IgE antibody has 'previous' in respiratory allergy
- IgE antibody has been associated with all known chemical respiratory allergens
- IgE antibody is very difficult to detect
- IgE antibody levels drop following last exposure

The Debate

The role of IgE antibody

EITHER: There are immunological mechanisms other than/in addition to IgE antibody that cause sensitisation of the respiratory tract to chemicals and occupational asthma

OR: IgE antibody plays a mandatory universal role in sensitisation of the respiratory tract to chemicals and occupational allergy

BIG CHALLENGES

- Mechanistic master switch
- Relevance of routes of exposure
- Role of IgE antibody