

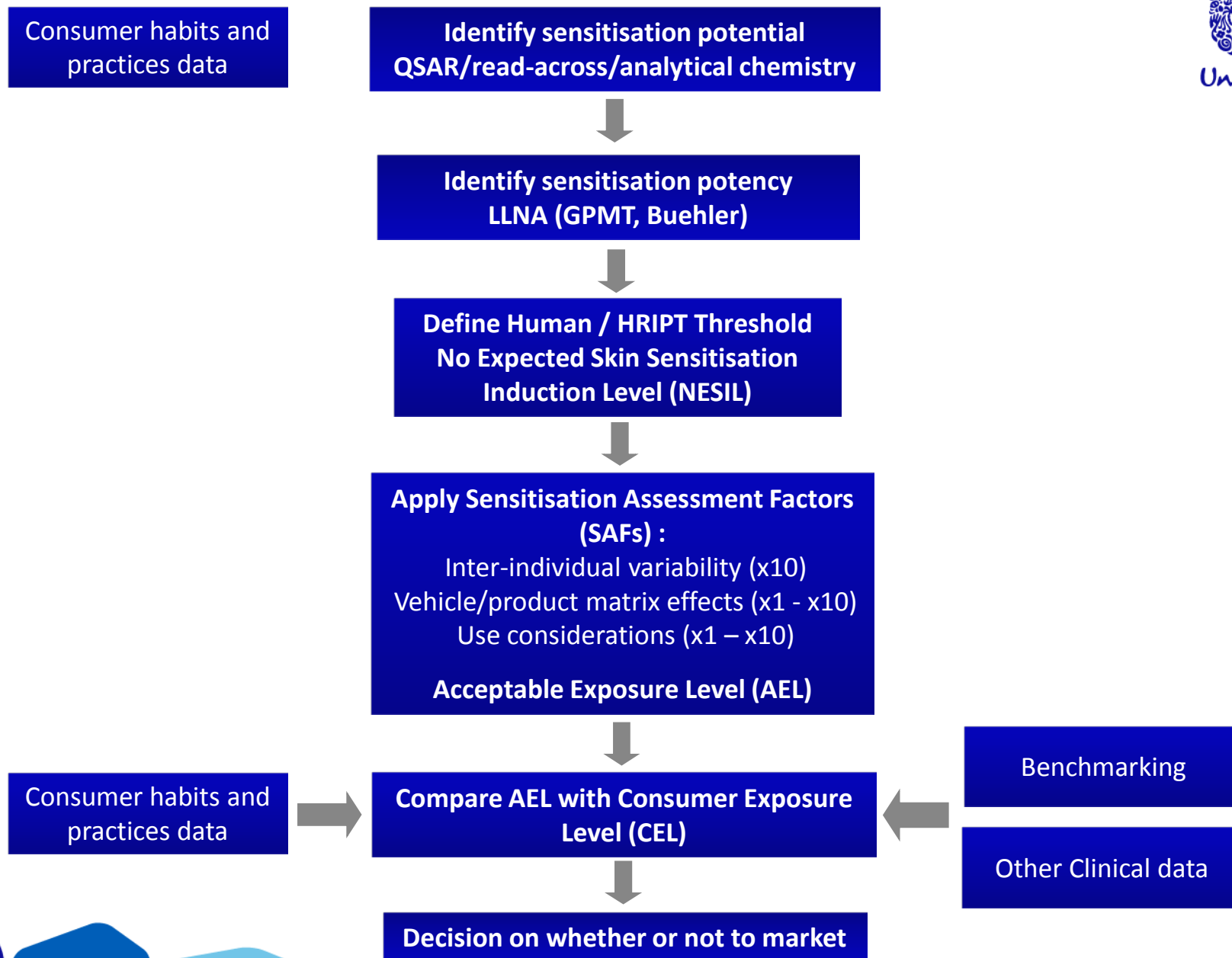


# **CASE STUDY PRESENTATION: A QUANTITATIVE AOP FOR SKIN SENSITISATION RISK ASSESSMENT**

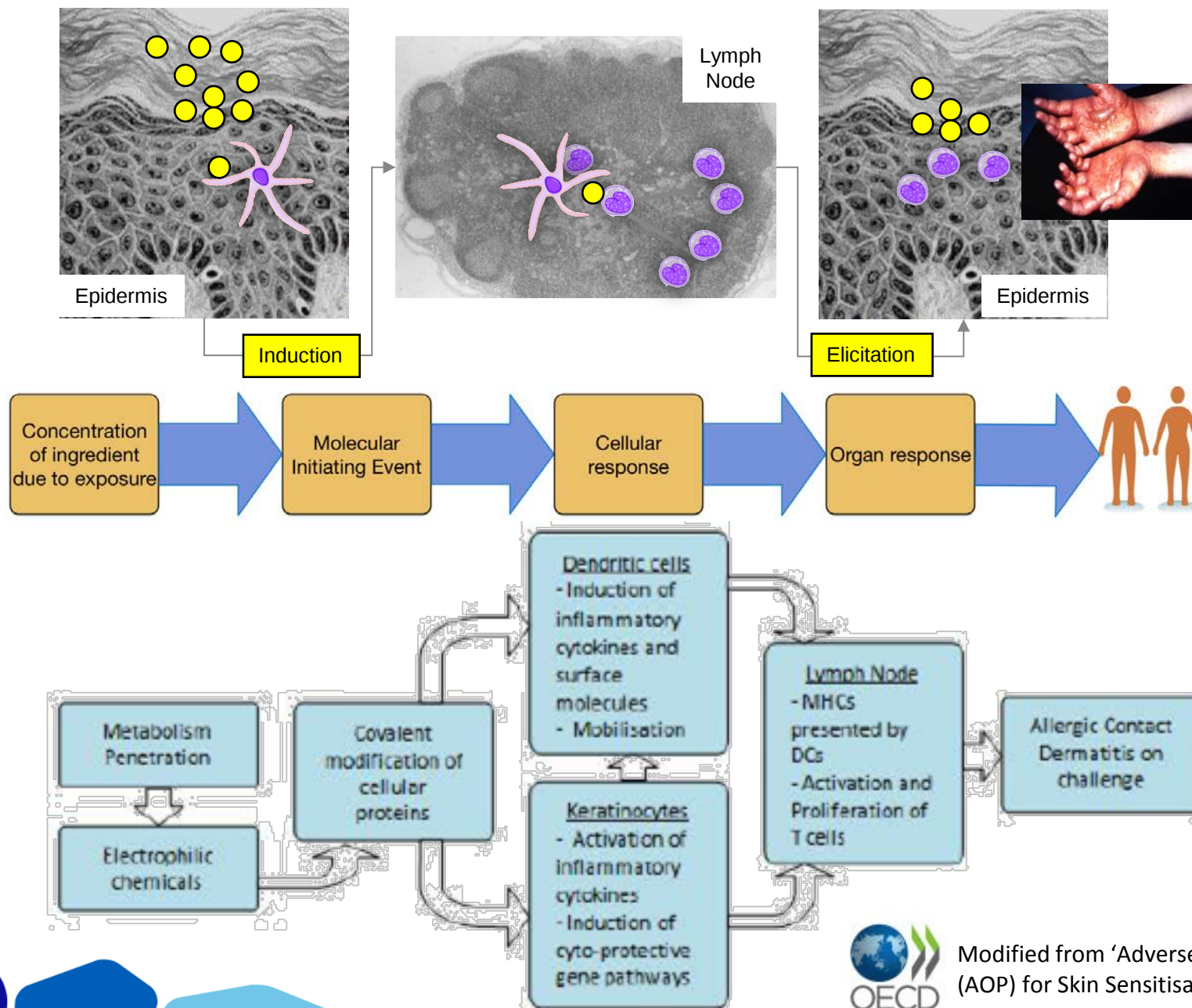
**GAVIN MAXWELL**, CATHERINE CLAPP, RICHARD CUBBERLEY, SERAYA DHADRA, NIKKI GELLATLY, STEPHEN GLAVIN, SARAH HADFIELD, SANDRINE JACQUOILLEOT, AMELIA JARMAN, IAN JOWSEY, SUE LOVELL, JACK MAYNE, CRAIG MOORE, RUTH PENDLINGTON, JULIETTE PICKLES, JOE REYNOLDS. OUARDA SAIB, DAVID SHEFFIELD, RICHARD STARK, WENDY SIMPSON, VICKI SUMMERFIELD. DAWEI TANG, SAM WINDEBANK & CAMERON MACKAY

**SAFETY & ENVIRONMENTAL ASSURANCE CENTRE (SEAC),  
UNILEVER R&D**

# TRADITIONAL SKIN SENSITISATION RISK ASSESSMENT

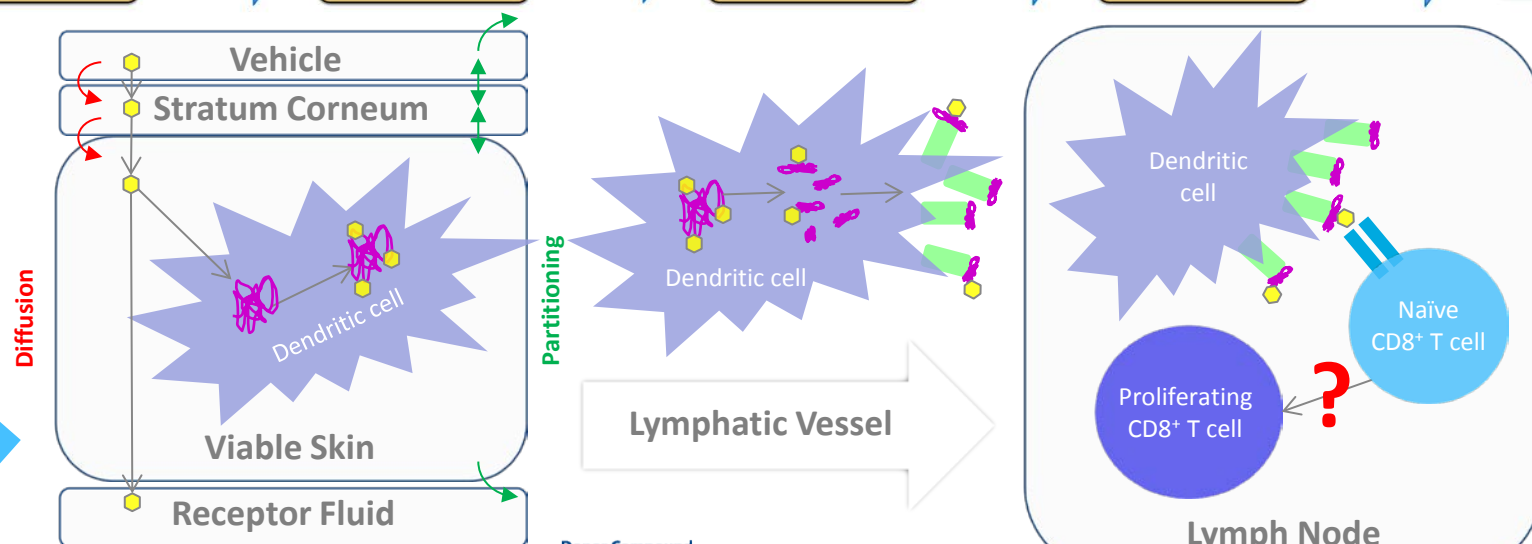
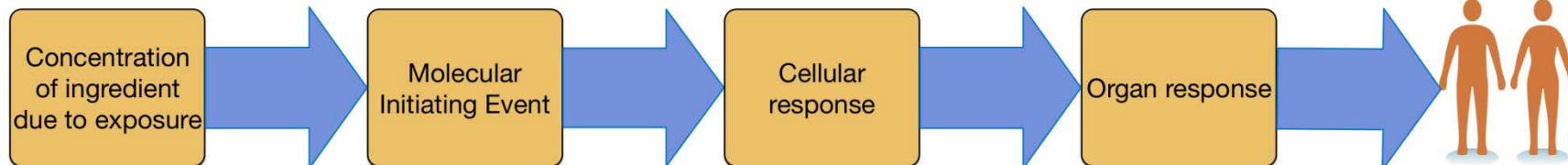


# NEW SKIN SENSITISATION RISK ASSESSMENT PARADIGM?



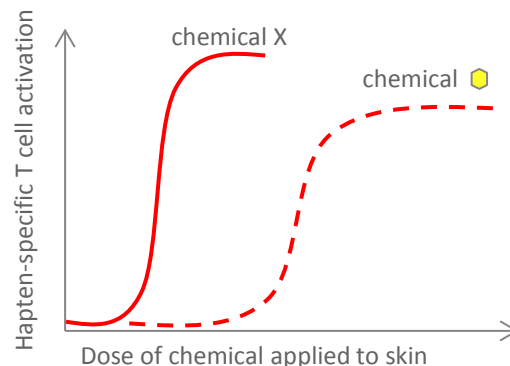
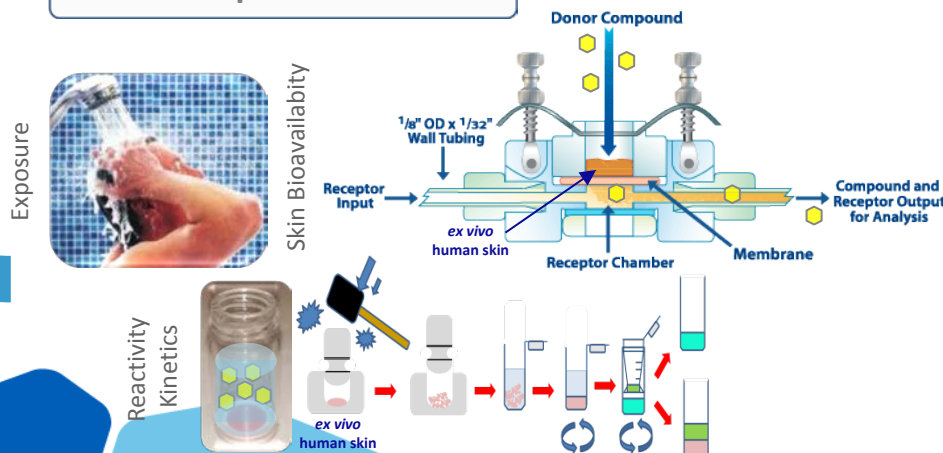
Modified from 'Adverse Outcome Pathway (AOP) for Skin Sensitisation', OECD

# DEVELOP A MATHEMATICAL MODEL OF ALLERGIC CONTACT DERMATITIS TO ENABLE RISK ASSESSMENT DECISION-MAKING FOR NEW CHEMICALS



Model Inputs

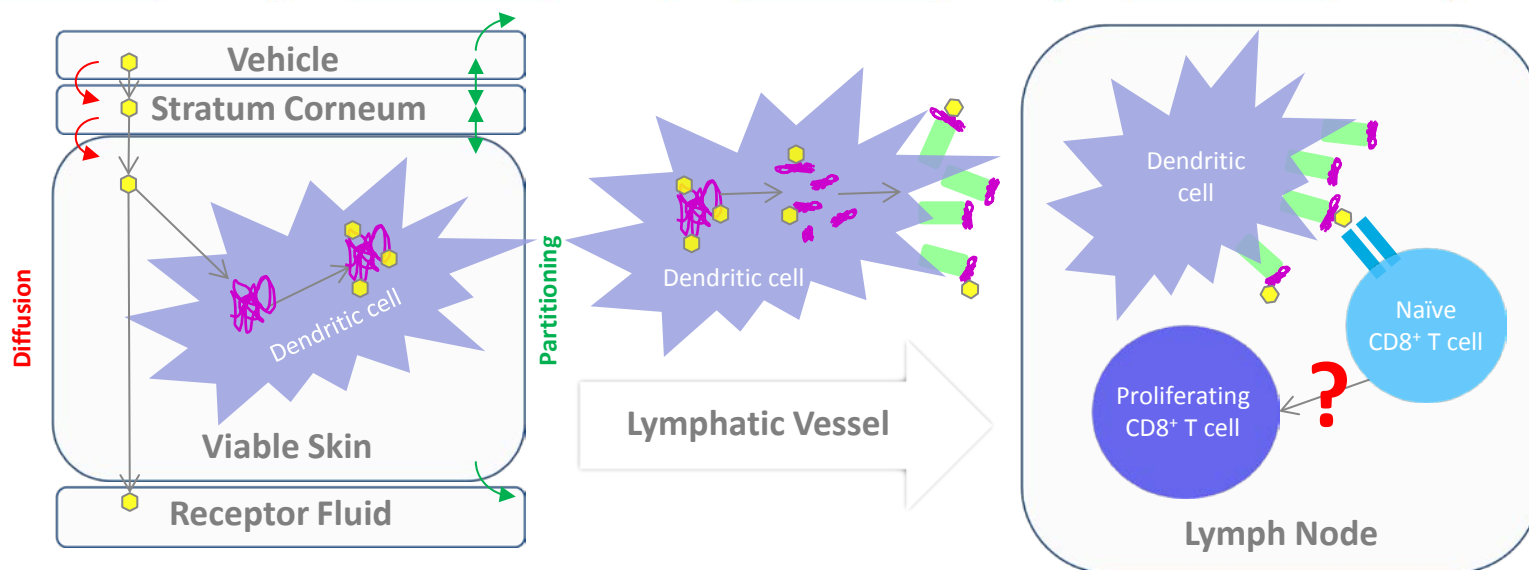
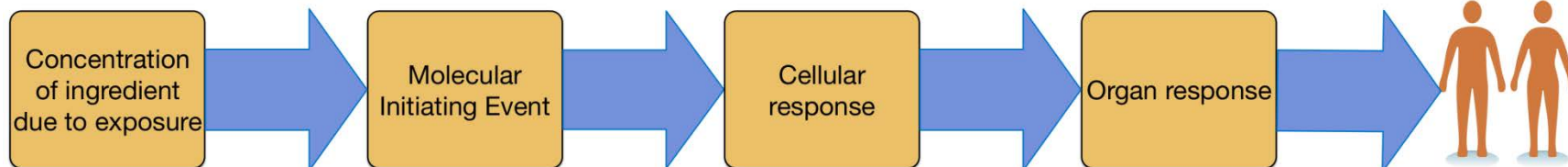
Model Output



# DNCB CASE STUDY – BENCHMARK MODEL PREDICTION USING DATA FROM FRIEDMANN *ET AL.* 1983



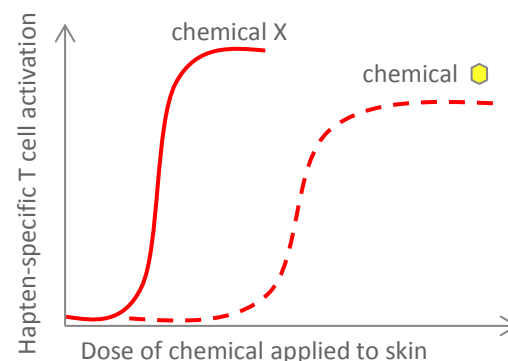
Unilever



*Clin. exp. Immunol.* (1983) 53, 709–715.

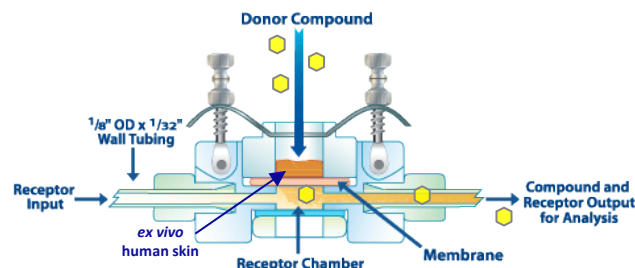
## Quantitative relationships between sensitizing dose of DNCB and reactivity in normal subjects

P. S. FRIEDMANN, CELIA MOSS, S. SHUSTER & JUDY M. SIMPSON\* *Department of Dermatology and \*Department of Medical Statistics, University of Newcastle upon Tyne, Newcastle upon Tyne, UK.*

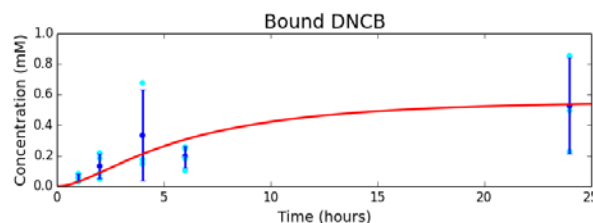
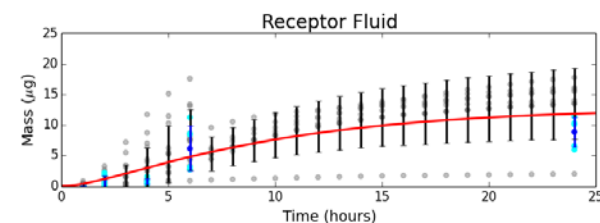
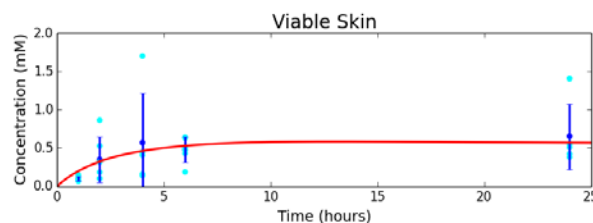
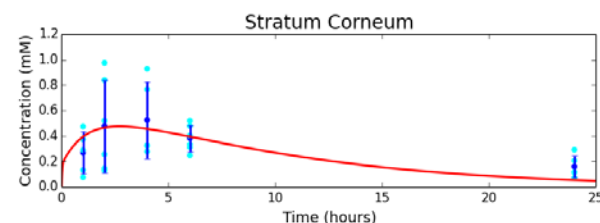
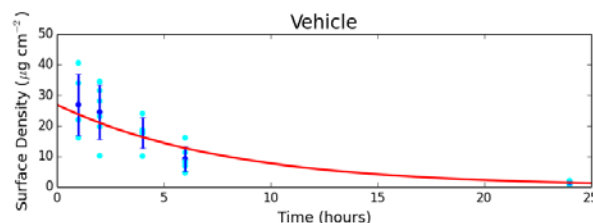
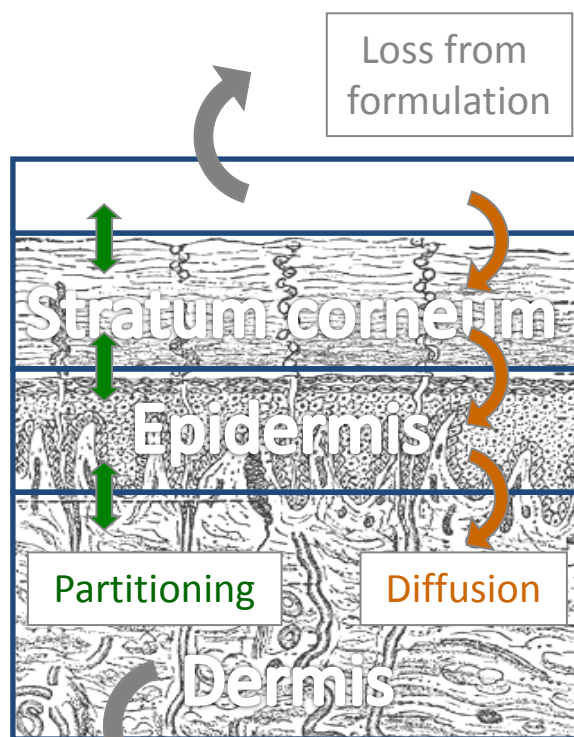


Model Output

# MODELLING SKIN BIOAVAILABILITY OF EXPERIMENTAL SENSITISER 2,4-DI-NITRO CHLOROBENZENE (DNCB)



| Exposure Scenario | <i>in vitro</i> skin pen        |
|-------------------|---------------------------------|
| Dose              | 38.25 $\mu\text{g}/\text{cm}^2$ |
| Vehicle Volume    | 20 $\mu\text{L}$                |
| Surface area      | 0.64 $\text{cm}^2$              |



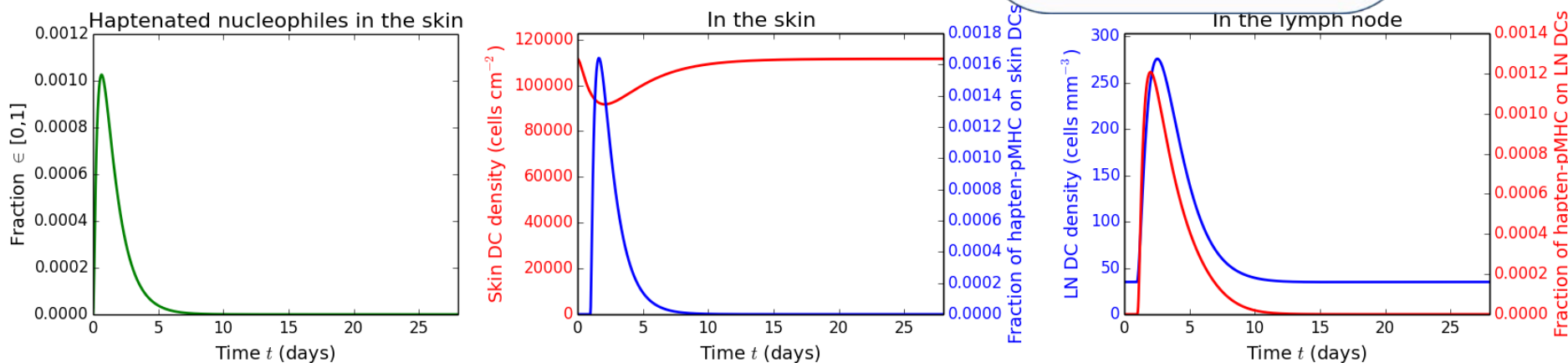
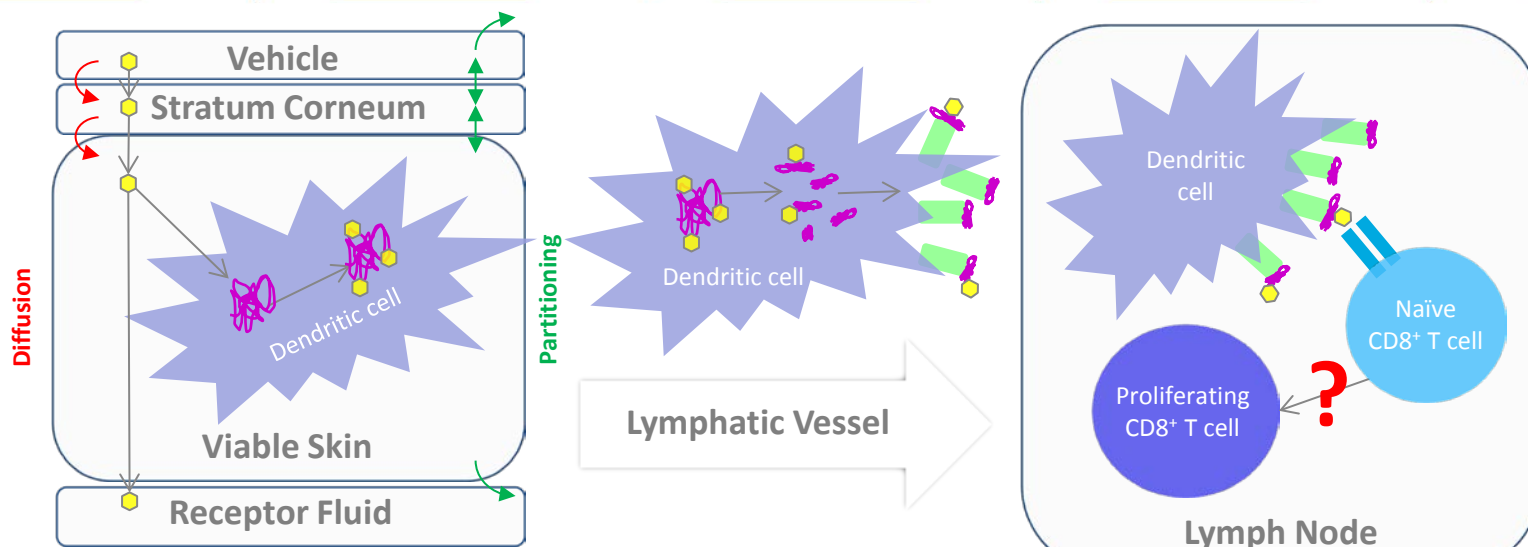
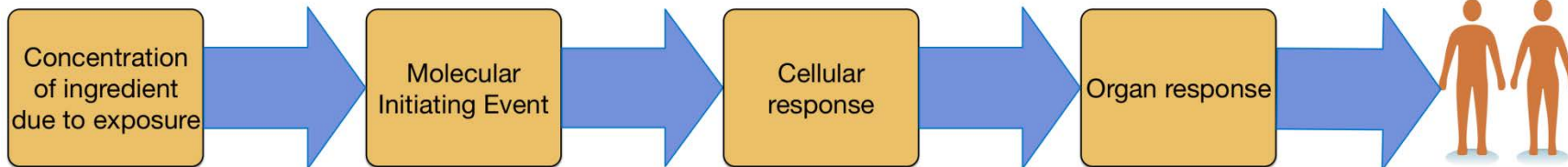
## Estimation of Bioavailability in Skin - based on OECD Test Guideline 428

- DNCB & ex vivo human skin - Pendlington et al 2008 [Cutan. Ocul. Toxicol.](#) 27, 283-94.
- Penetration system modelled and partitioning and diffusion rates determined by fitting - Davies et al 2011 [Toxicol. Sci.](#) 119, 308-18

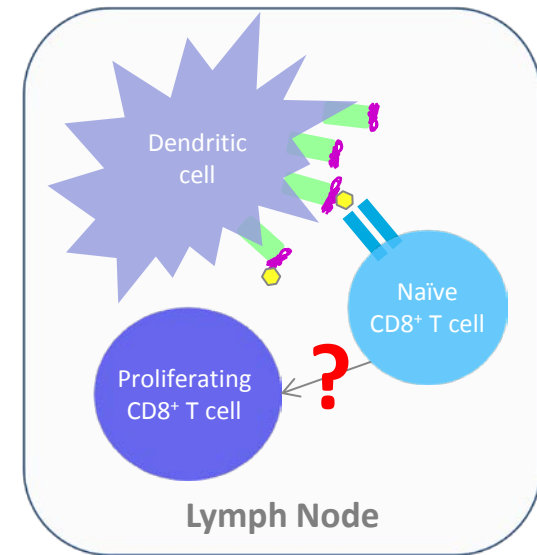
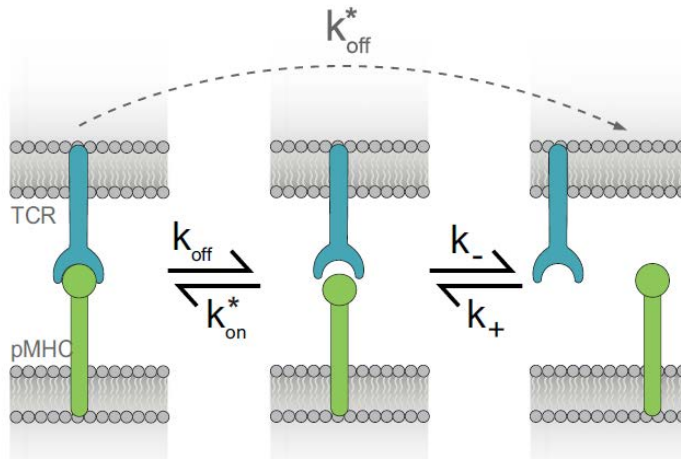
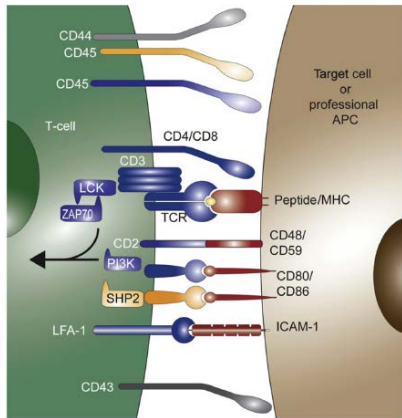
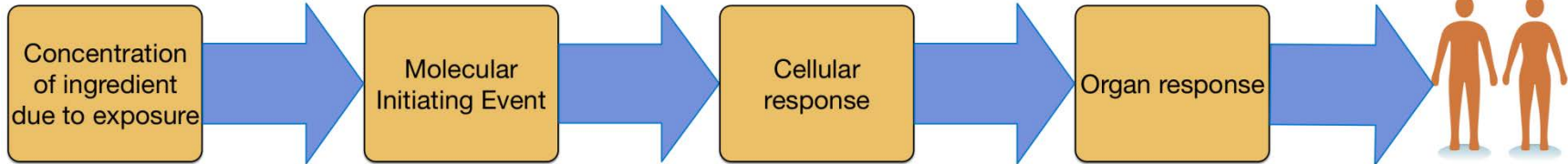
# MODELLING OF SKIN PROTEIN HAPTENATION → SKIN DENDRITIC CELL ANTIGEN PROCESSING, PRESENTATION & MIGRATION TO DRAINING LYMPH NODE



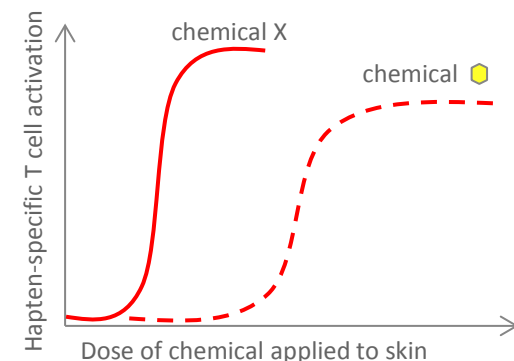
Unilever



# PREDICTING THRESHOLD OF T CELL ACTIVATION VIA MODELLING OF DC: T CELL IMMUNE SYNAPSE



Explore effect of pMHC surface density and  $k_{on}/k_{off}$  on probability of T-cell triggering with the available models (Zarnitsyna & Zhu, 2012). Simulations generated using 'confinement time' model of Dushek, et al, 2009.



Model Output

# DNCB CASE STUDY – MODEL OUTPUT & CLINICAL DATA



*Clin. exp. Immunol.* (1983) 53, 709–715.

## Quantitative relationships between sensitizing dose of DNCB and reactivity in normal subjects

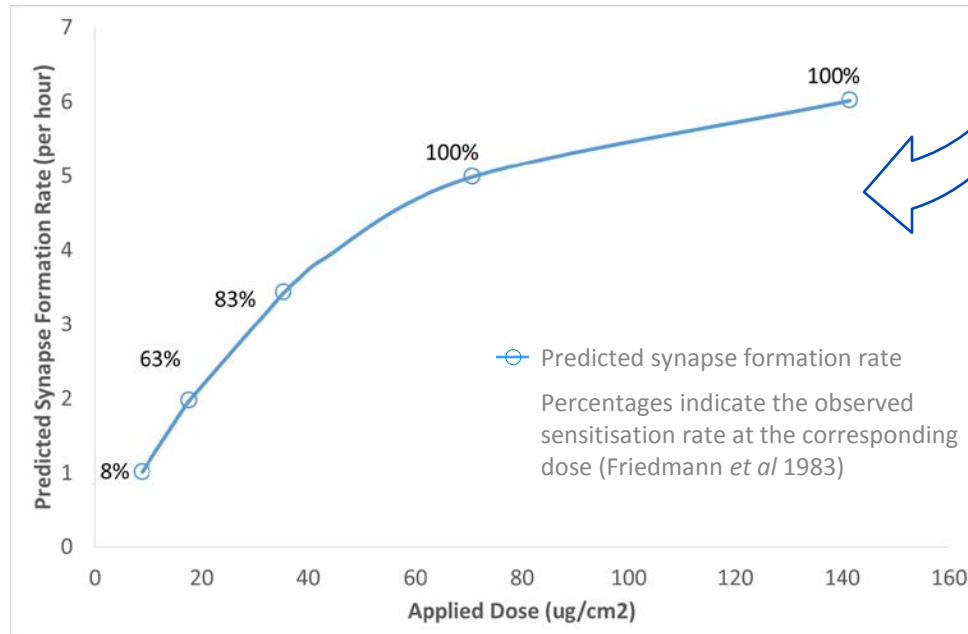
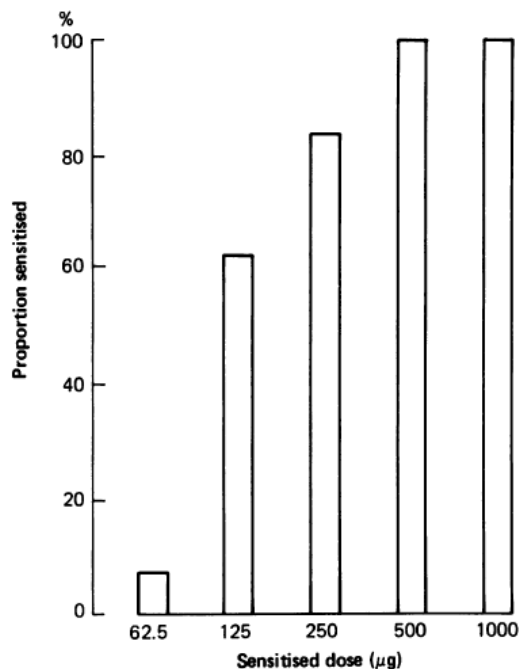
P. S. FRIEDMANN, CELIA MOSS, S. SHUSTER & JUDY M. SIMPSON\* *Department of Dermatology and \*Department of Medical Statistics, University of Newcastle upon Tyne, Newcastle upon Tyne, UK.*

Friedmann *et al* 1983

- Single exposure to DNCB
- 7.1cm<sup>2</sup> volar forearm
- 100μL acetone vehicle

Sensitisation assessed by challenge with DNCB 4 weeks after application

**Prediction of maximum immune synapse rate in the 4 weeks following application**



# DNCB CASE STUDY – MODEL OUTPUT & CLINICAL DATA



REVIEW ARTICLE

DOI 10.1111/j.1365-2133.2007.08162.x

## The relationships between exposure dose and response in induction and elicitation of contact hypersensitivity in humans

P.S. Friedmann

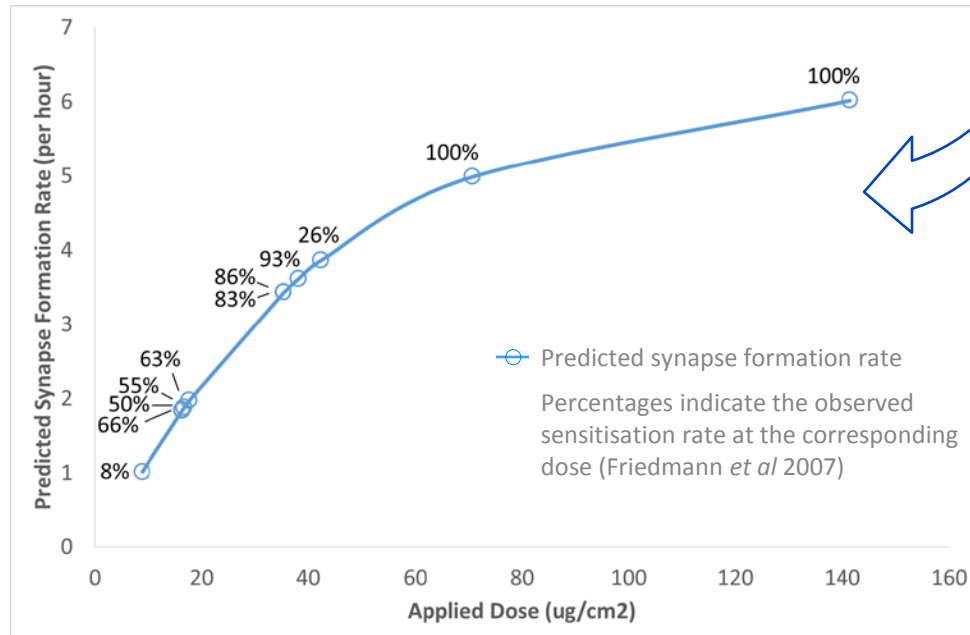
Friedmann 2007

- Single exposure to DNCB
- Various exposure areas, sites, vehicles & volumes

Sensitisation assessed by challenge with DNCB 4 weeks after application

**Prediction of maximum immune synapse rate in the 4 weeks following application**

| Diameter (cm) | Area (cm <sup>2</sup> ) | Total (µg) | Concentration (µg cm <sup>-2</sup> ) | Number of subjects | Percentage sensitised |
|---------------|-------------------------|------------|--------------------------------------|--------------------|-----------------------|
| 3             | 7.1                     | 1000       | 142                                  | 24                 | 100                   |
| 3             | 7.1                     | 500        | 71                                   | 40                 | 100                   |
| 3             | 7.1                     | 250        | 35.4                                 | 30                 | 83                    |
| 3             | 7.1                     | 125        | 17.7                                 | 30                 | 63                    |
| 3             | 7.1                     | 62.5       | 8.8                                  | 24                 | 8                     |
| 1.5           | 1.8                     | 62.5       | 35.4                                 | 7                  | 86                    |
| 2.1           | 3.5                     | 58         | 16.4                                 | 22                 | 55                    |
| 3             | 7.1                     | 116        | 16.4                                 | 34                 | 50                    |
| 4.25          | 14.2                    | 232        | 16.4                                 | 15                 | 66                    |
| 1 cm paper    | 0.8                     | 30         | 38                                   | 28                 | 93                    |
| 3 mm paper    | 0.08                    | 3          | 38                                   | 15                 | 26                    |



## OVERALL SUMMARY

- We have developed a mechanistic, mathematical model of DNCB-induced CD8<sup>+</sup> T cell activation in humans with the purpose of informing skin sensitisation risk assessment
- The model predicts various measures of sensitiser-induced CD8<sup>+</sup> T cell activation for different DNCB exposure scenarios using a combination of chemical- & exposure-specific non-animal data on skin bioavailability and reactivity

## NEXT STEPS

1. Progress human CD8<sup>+</sup> T cell response model development to allow mechanistic prediction of allergic contact dermatitis
2. Determine the uncertainty in our model predictions through characterising parameter & model uncertainty

# ACKNOWLEDGEMENTS

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## University of Leeds

Sheeja Krishnan, Grant Lythe & Carmen Molina-París

UNIVERSITY OF LEEDS

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Jason Williams



## University College London

Benny Chain & Theres Oakes

