



# Skin Sensitisation: Modelling the Human Adverse Response

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## Our Approach

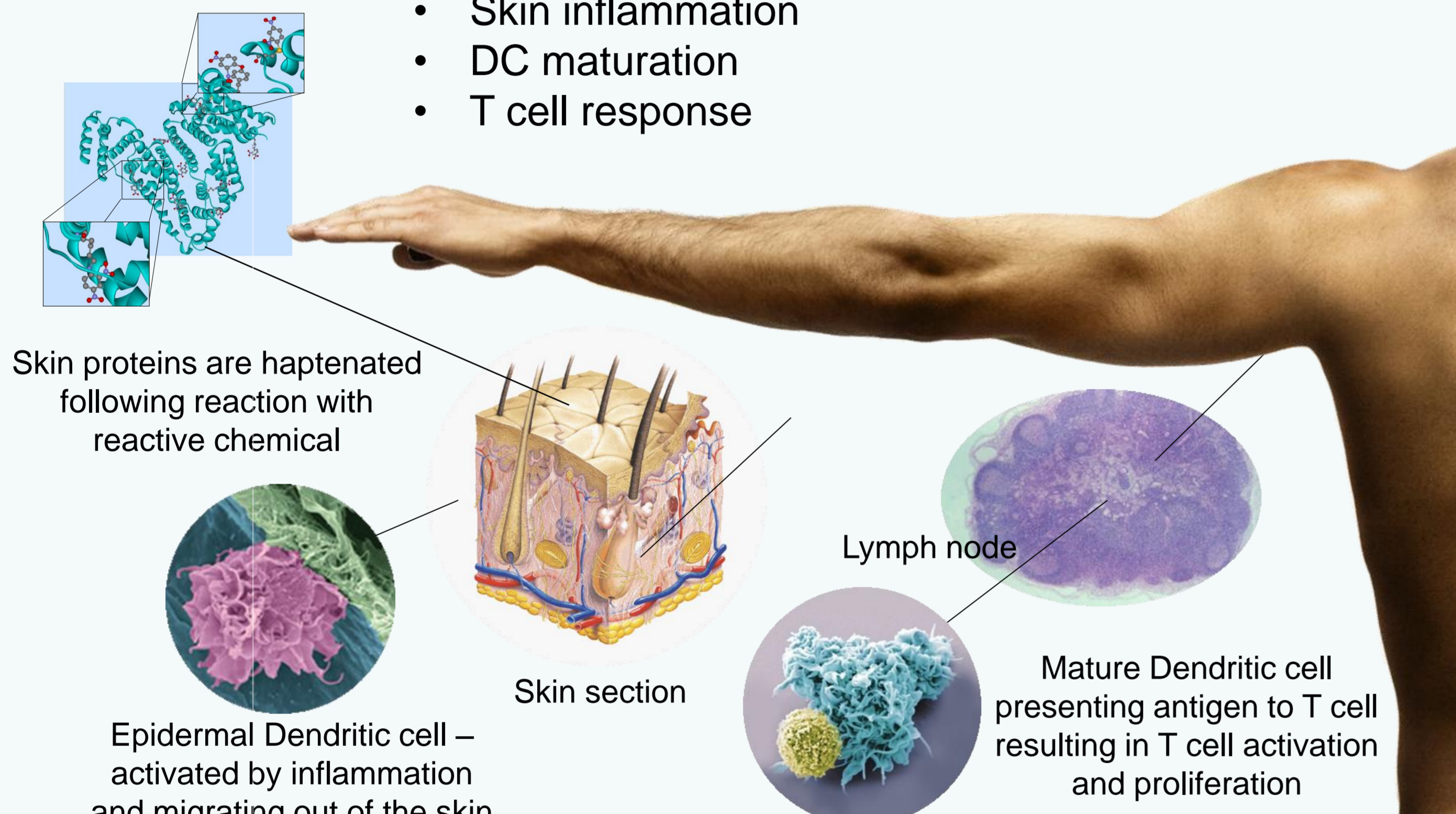
Assuring consumer safety without animal testing is a considerable challenge, however we remain confident it is ultimately achievable. A substantial research programme was initiated by Unilever in 2004, to critically evaluate the feasibility of a new conceptual approach for consumer safety risk assessment [1]. Here we demonstrate significant progress in developing a non-animal risk assessment approach for skin sensitisation.

In collaboration with Entelos Inc., we previously developed a computational model of skin sensitisation using the published literature [2]. Insights from this modelling exercise have allowed us to focus our subsequent non-animal test method development activities upon the identified toxicity pathways, namely skin bioavailability [3], protein binding [4], skin inflammation/Dendritic cell (DC) maturation and T cell proliferation. Guided by our previous work [2], we are now developing a pragmatic, mechanistic model of skin sensitisation capable of integrating non-animal datasets predicting these events (e.g. peptide reactivity) to allow risk assessment decision-making without animal test data. The aim is for the model to predict the dynamics of the emerging sensitizer-specific T cell response. Therefore, we are also further characterising the induction and maintenance of the human immune response to skin sensitizers.

## Skin Sensitisation

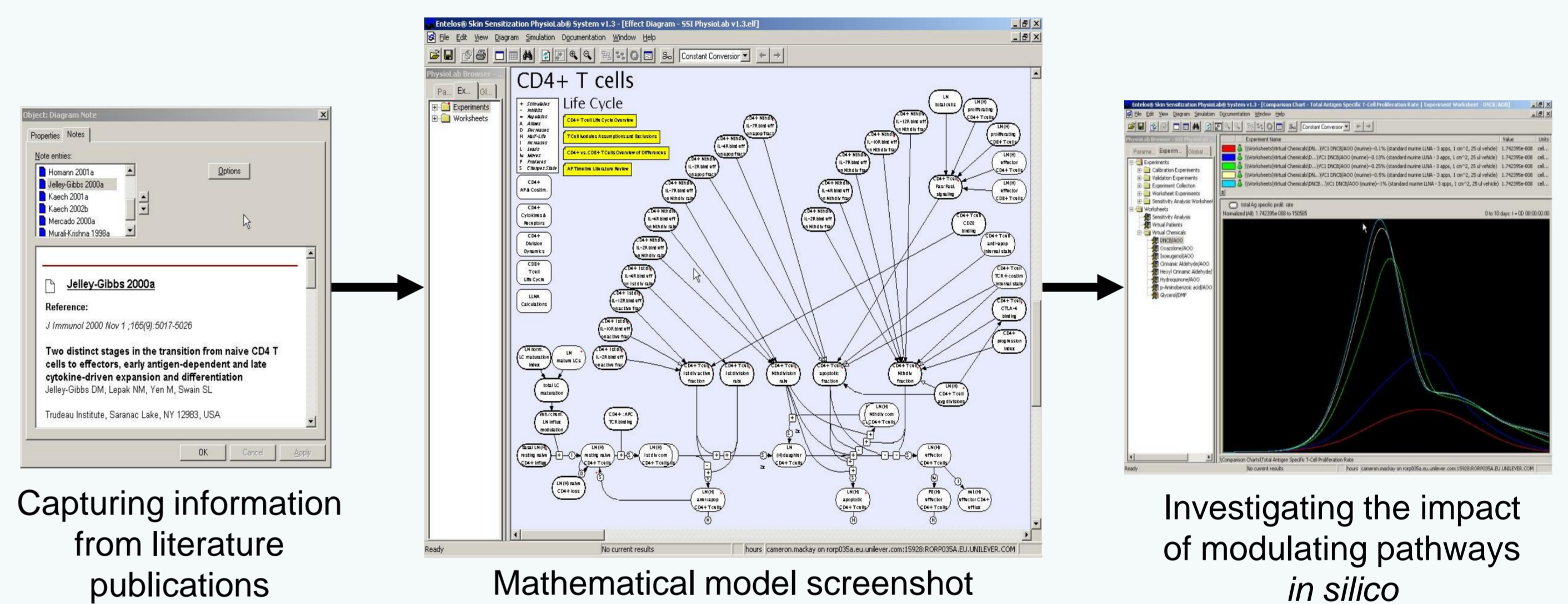
Induction of skin sensitisation (Allergic Contact Dermatitis) is a multi-stage process driven by several categories of toxicity pathway:

- Skin bioavailability (including skin metabolism)
- Protein binding
- Skin inflammation
- DC maturation
- T cell response



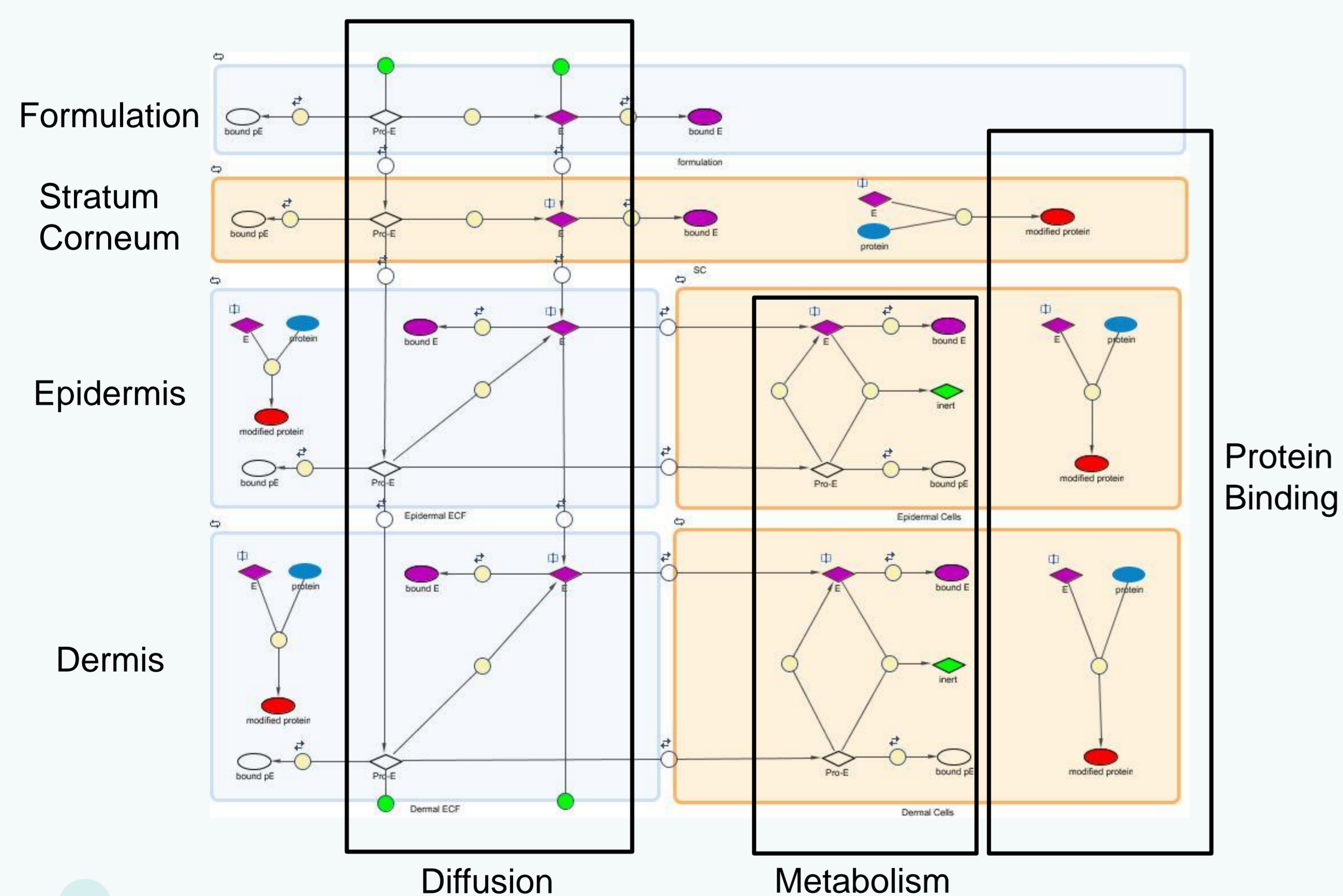
## Mathematical modelling

In collaboration with Entelos Inc. we previously developed a computational model of skin sensitisation using the published literature [2]. Modelling the disease process enabled us to characterise the relative role that different toxicity pathways play in the induction of skin sensitisation & consequently has provided us with a mechanistic rationale for the interpretation/integration of non-animal datasets for risk assessment decision-making.



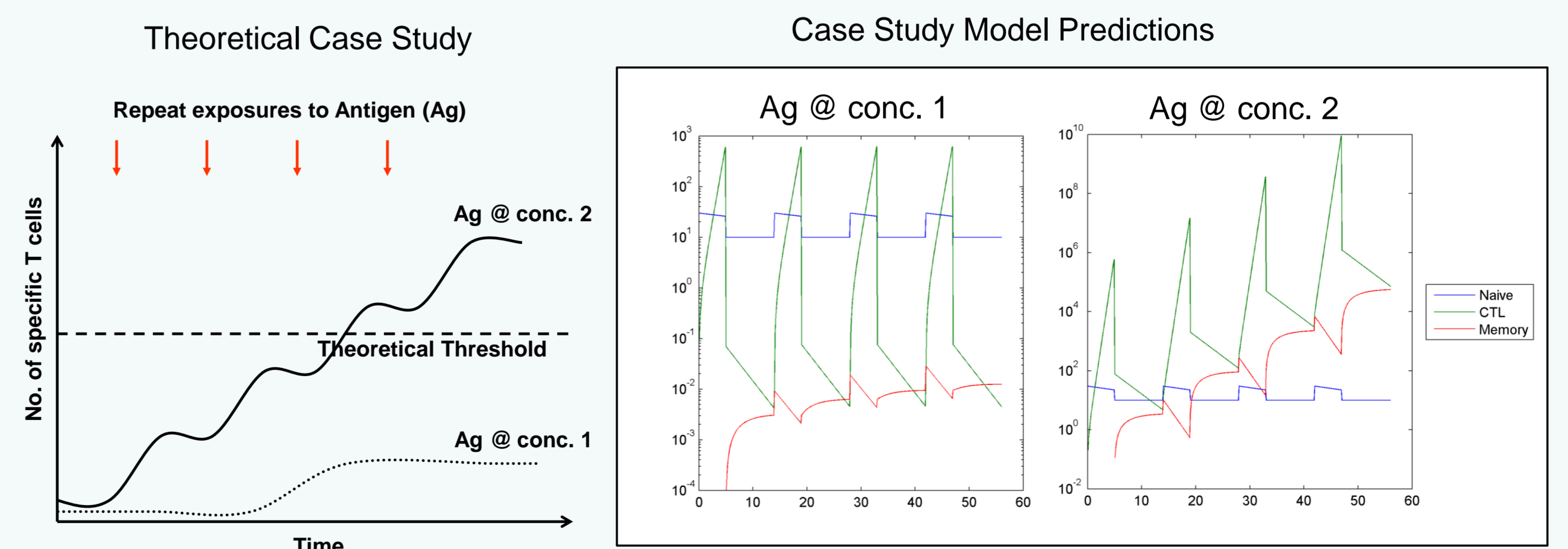
## Skin Bioavailability & Protein Binding model

We are currently developing a mathematical model (draft model overview below) to integrate (non-animal) data on skin diffusion, skin metabolism & protein binding to allow a 'total modified skin protein' metric to be predicted for a given sensitizer & consumer exposure scenario. At present we are exploring whether data generated using existing test method protocols (for example those detailed in refs 3 & 4) can be used to inform model predictions or whether further method development/optimisation is required.



## Sensitizer-induced T cell response model

In May 2010, we held an expert workshop in London to discuss the T cell response characteristics that reflect skin sensitizer potency? The consensus was that the Magnitude (volume, kinetics & duration), Quality (balance of different T cell sub-types) & Breadth (proportion of T cell clonal repertoire) of the T cell response could all have an impact on human sensitizer potency. Furthermore it was acknowledged that our current understanding of how these parameters varied across the human immune response to different sensitizers was limited. Consequently in addition to developing a pragmatic T cell model that will predict the magnitude of the sensitizer-induced CD8<sup>+</sup> T cell response (using the 'total modified skin protein' metric to represent antigen load), we are also exploring to what extent the quality & breadth of the T cell response impact the induction of skin sensitisation in humans.



## Summary & Next Steps

We are currently developing a mathematical model of the induction of skin sensitisation by using non-animal test data to predict a 'total modified skin protein' metric for a defined ingredient & consumer exposure scenario, which can be used to predict the magnitude (volume, kinetics & duration) of the sensitizer-induced CD8<sup>+</sup> T cell response. This goal is supported by a long-term research programme that has been scoped to address key gaps in our understanding of skin sensitisation (e.g. skin metabolism, reactivity & detoxification, human T cell response) and to apply this new understanding to improve model predictions.

### References:

1. Fentem, J. et al. (2008). AATEX; 14. 15-20;
2. Maxwell & MacKay (2008). ATLA 36:521-56;
3. Davies, M. et al. (2011). Toxicol. Sci. 119. 308-318 ;
4. Aleksic, M. et al. (2009). Toxicol. Sci. 108. 401-411