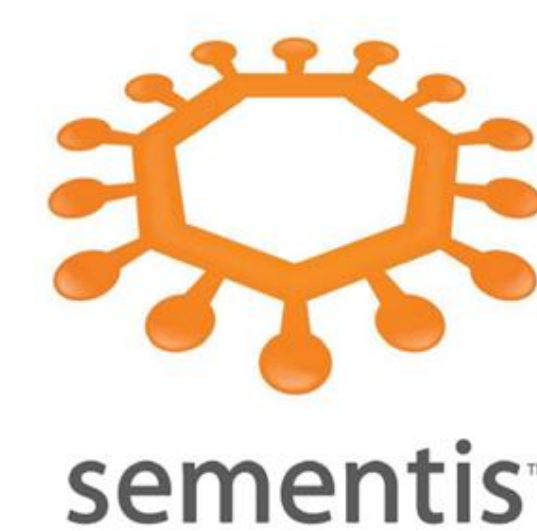


The Sementis Copenhagen Vector (SCV) system as an immunotherapeutic vaccine to modulate cytokine responses of antigen-specific T cells in peanut allergy



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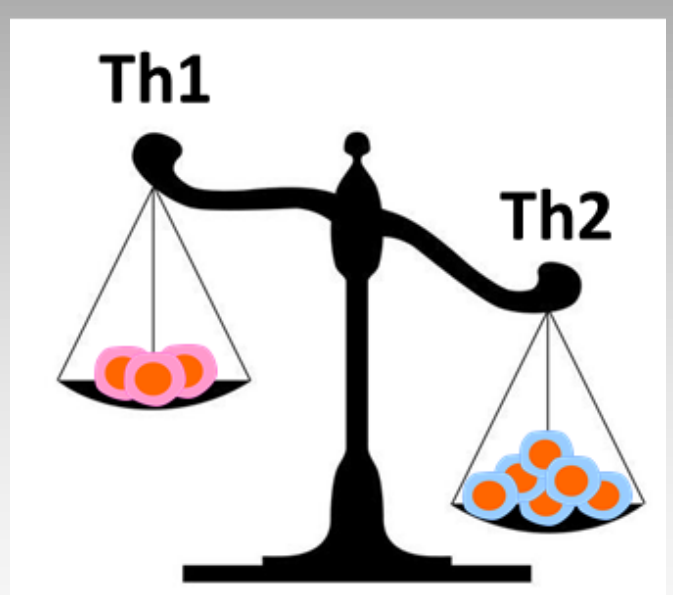
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SCV-Peanut Hypo-Allergy Vaccine (SCV-PHAV) Rationale

Peanut Allergy

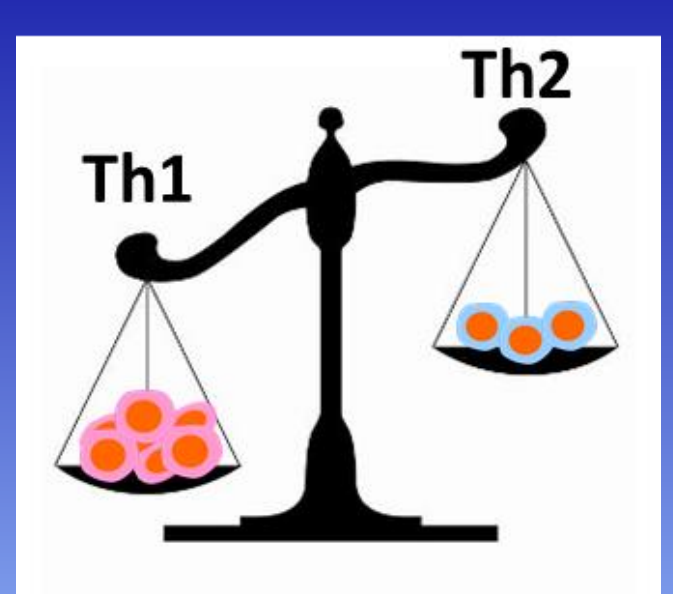


- Peanut allergy is the 2nd most common food allergy in children and most common cause of an allergic food reaction requiring emergency medical attention
- Only strict dietary avoidance is recommended to prevent fatal anaphylactic reactions
- Safe therapeutic options are needed to address the underlying pathogenic, allergen-specific, T helper-type 2 (Th2) biased CD4⁺ T cell responses.

SCV-PHAV

- SCV is multiplication-defective, vaccinia derived vector that can be manufactured using an engineered CHO cell substrate (Eldi *et al* 2017 Mol Ther).
- SCV is intrinsically a potent T helper-type 1 (Th1) adjuvant
- SCV-PHAV expresses a ubiquitinated, multi-peanut antigen fusion protein:
 - Ara h 1, 2, 3, 5, 6, 7, 8, 8.1, 9, 10, 11

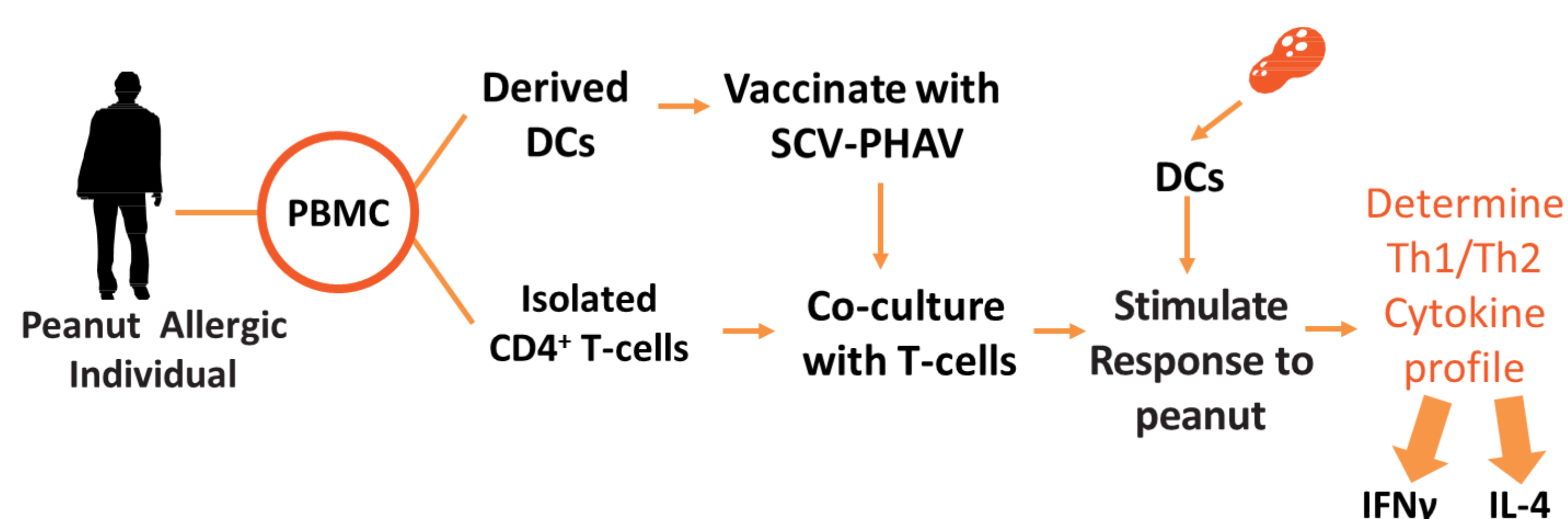
Vaccination



- SCV-PHAV vaccination produces peanut allergens in an environment of viral infection
- Peanut allergens are presented to the immune system generating Th1 T cells
- Th1 T cells secrete IFN γ that switch off IgE production and Th2 signals (e.g. IL-4)
- Blocking antibodies are produced
- Peanut-specific Th1 immune memory is created

An ex vivo human vaccination model to demonstrate therapeutic potential

1A



We established an *ex vivo* human DC: CD4 T cell culture system (Fig 1A) to investigate the capacity of SCV-PHAV instructed dendritic cells (DCs) to facilitate a peanut-specific Th1 switch in the CD4⁺ T cell response (Fig 1A).

Briefly, monocyte-derived immature DCs (iDCs) and CD4⁺ T cells were isolated from the blood of peanut allergic patients. Peanut-pulsed or SCV-PHAV vaccinated iDCs were incubated with CD4⁺ T cells, re-stimulated with peanut extract followed by labelling with proliferation dye and cytokine analysis of proliferating antigen-specific T cells by flow cytometry.

Ex vivo therapeutic human T cell responses to vaccination

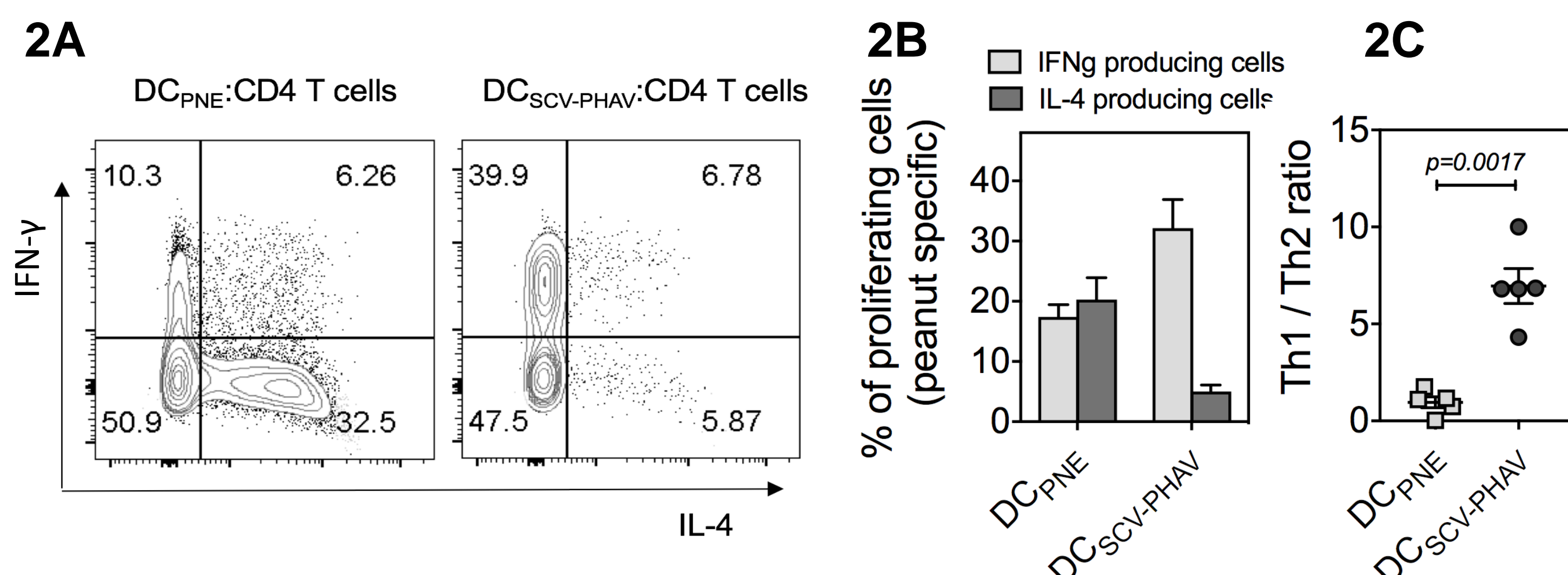


Figure 2: Antigen-specific CD4⁺ T cells in SCV-PHAV vaccinated cultures demonstrate higher Th1/Th2 ratio. (A) Representative intracellular cytokine analysis of peanut-pulsed (left) or SCV-PHAV vaccinated (right) iDCs from peanut allergic individuals. (B) IFN- γ (Th1 cytokine) and IL-4 (Th2 cytokine) producing antigen-specific CD4⁺ T cells detected in *ex-vivo* cultures (n=5). (C) Differences in Th1/Th2 ratio of peanut-pulsed and SCV-PHAV vaccinated cultures.

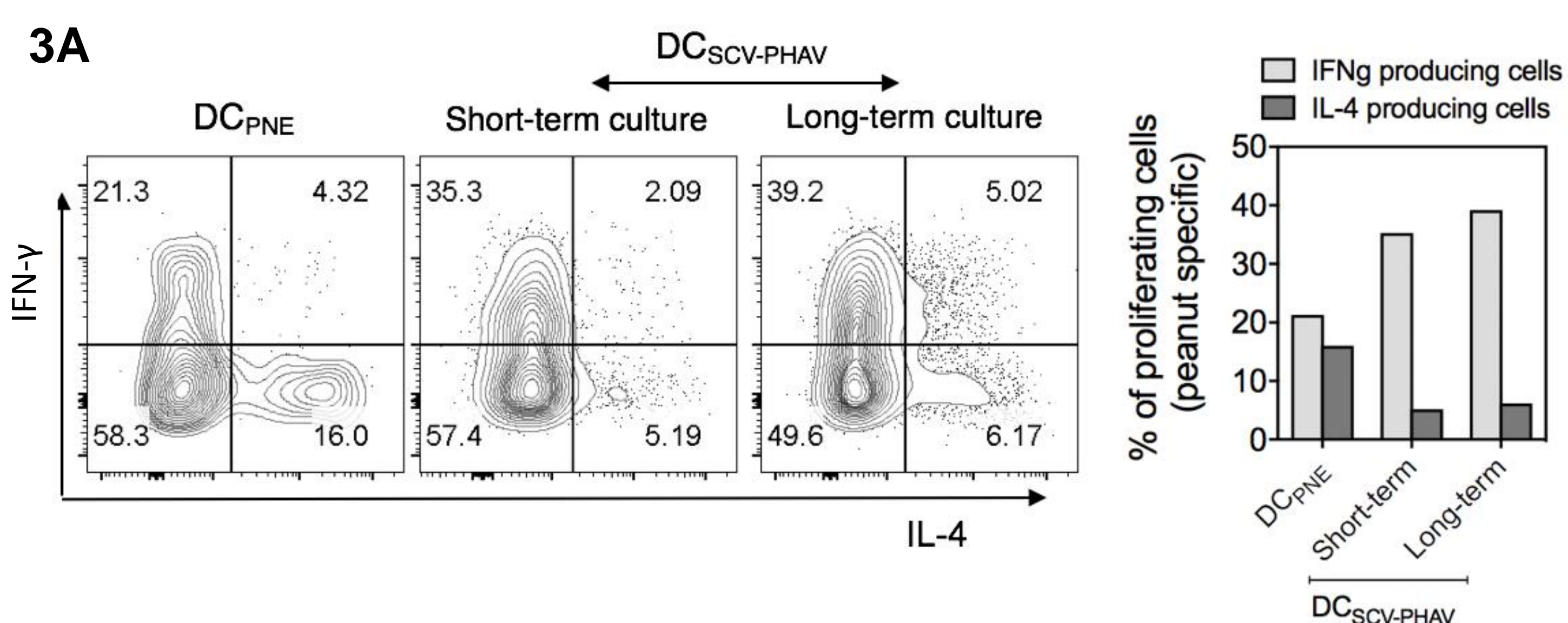


Figure 3: Maintenance of Th1 bias in SCV-PHAV vaccinated cultures following long-term, antigen-specific stimulation. (A) Cytokine profile of peanut-pulsed and SCV-PHAV vaccinated iDC: CD4⁺ T cell cultures following short-term expansion and long-term antigen-specific expansion.

In vivo prophylactic mouse antibody responses to vaccination

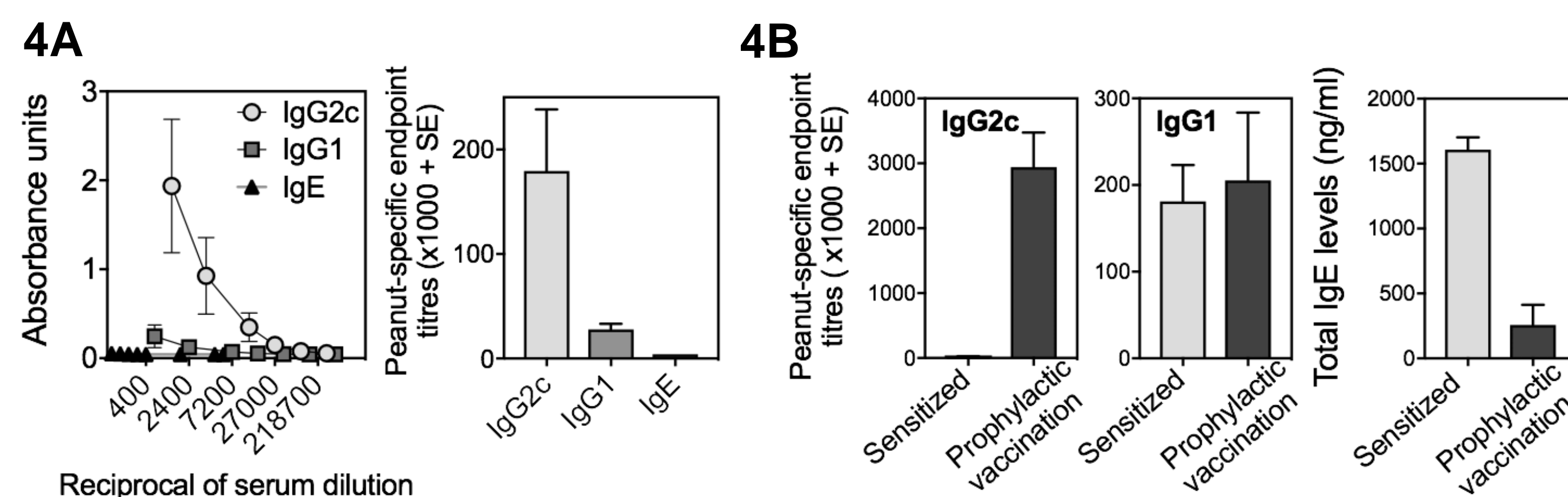
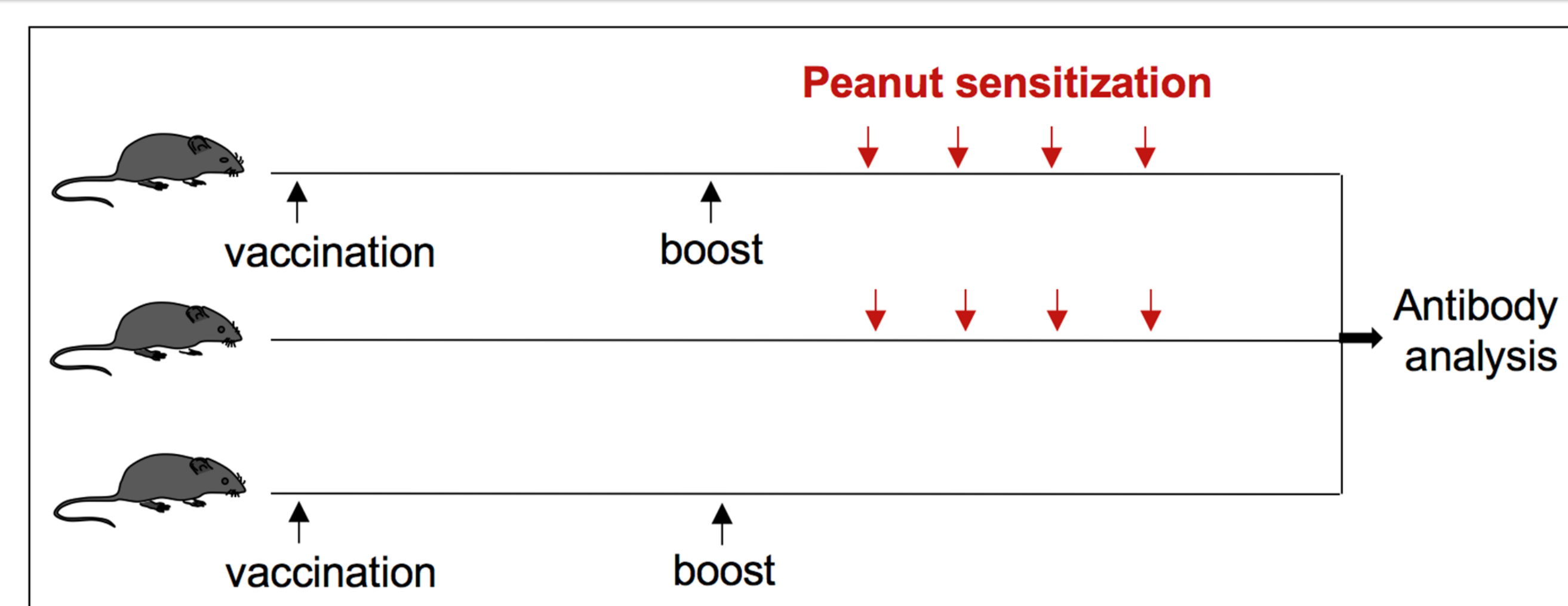


Figure 4: Antigen-specific antibody profile following prophylactic vaccination and sensitization to peanut in mice. (A) Vaccination with SCV-PHAV generates a Th1 (IgG2c) biased peanut specific antibody response without IgE. (B) Allergen sensitization following vaccination induces a significant boost in the IgG2c response

Conclusions

- In a human peanut allergic background, dendritic cells vaccinated with SCV-PHAV *ex vivo* mediated a Th1 switch in the CD4 T cell response; IL-4 producing T cells decreased while IFN γ producing T cells increased in response to peanut.
- Vaccination of mice with SCV-PHAV produced a Th1 biased antibody profile and did not induced IgE. Subsequent peanut sensitisation of vaccinated mice boosted IgG2 antibodies.

Therapeutic mouse models of vaccination are in progress to further demonstrate that vaccination can cause a shift from a pro-allergic Th2 bias to a Th1-biased profile that has potential to alleviate allergic conditions.