Determinants of Food Allergy Persistence and Severity

What determines sensitization?

Bert Ruiter, Wayne Shreffler

Immunology Institute and Jaffe Food Allergy Institute
Mount Sinai School of Medicine

Allergy-Immunology Research Conference
Northwestern University Feinberg School of Medicine

Why Food Allergy?

- important public health problem
- ‘clinically tractable’ phenotype presenting early in life
- paradigm of mucosal immune tolerance with highly variable expression

Variability of Both Allergen and Phenotype

- most children outgrow milk allergy, most do not outgrow peanut or shellfish allergy
- some children have much more persistent disease to the same allergen (*e.g.*, milk)

Our Research

- IgE and Effector Cell Function and Regulation
  - Characterization of Allergen-Specific IgE/ IgG Repertoire
  - Characterization of Basophil Reactivity and Its Regulation
- Allergen-specific T cell Repertoire
- Mechanisms of Allergenicity

Outline

The ‘Perfect’ Allergen

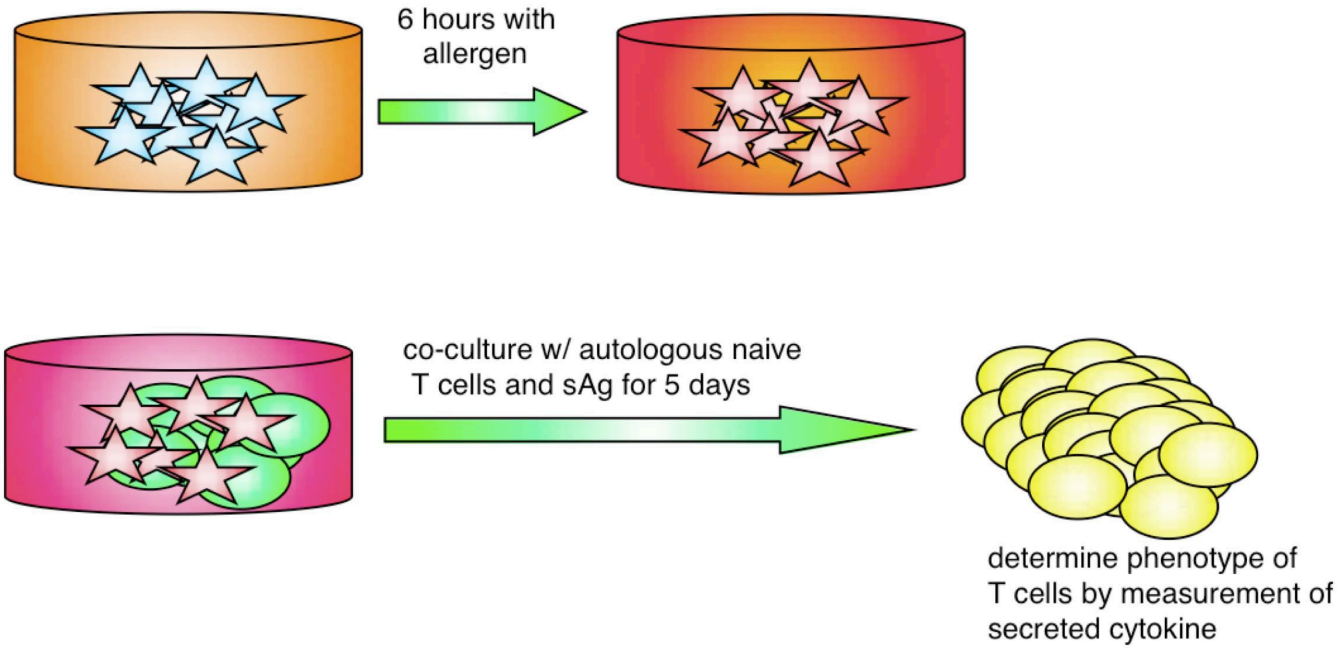
- common protein allergens are largely restricted to narrow group of protein families
- relative allergenicity coupled to innate immune activation

Examples

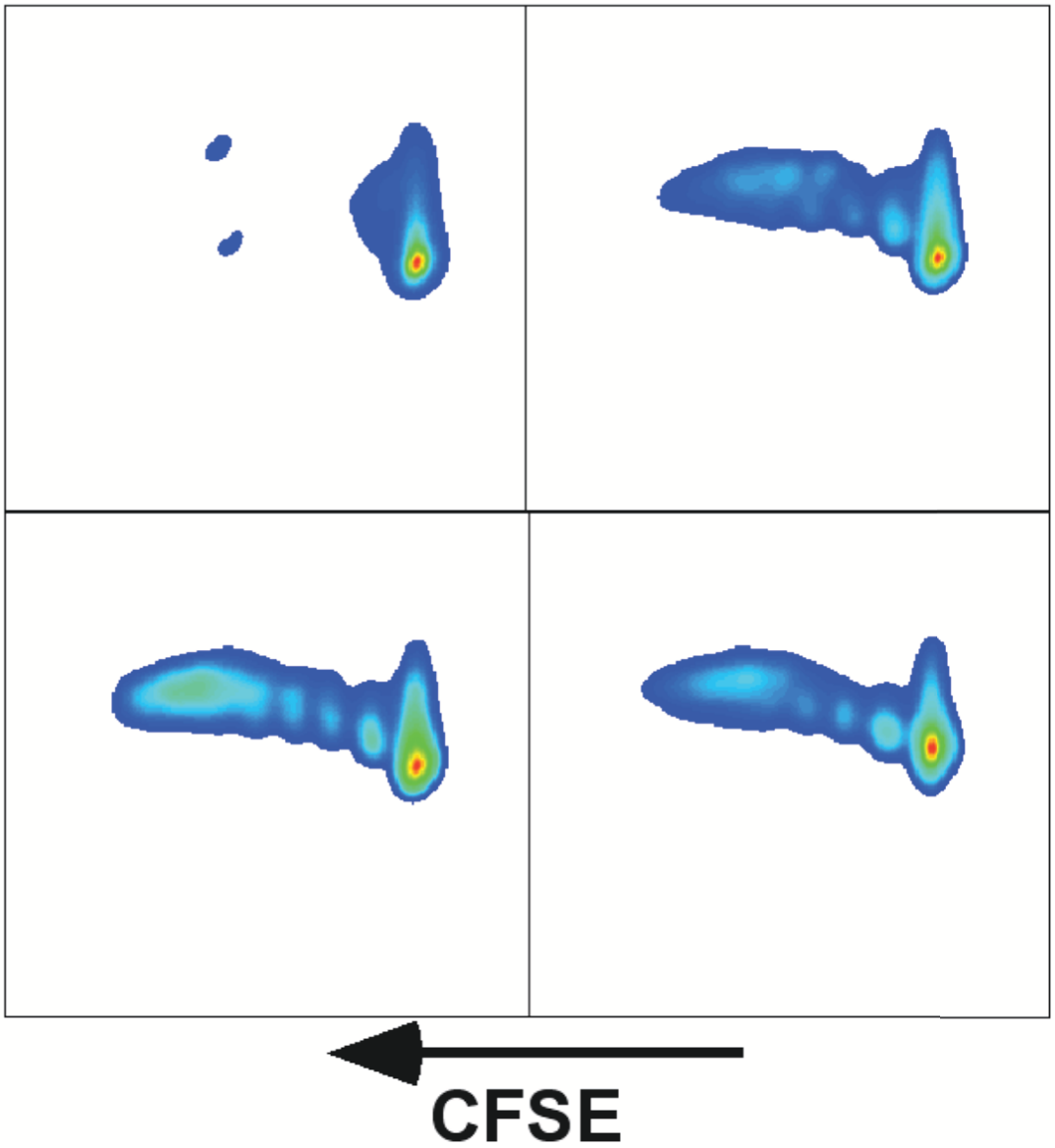
- protease (dust mite, papain): epithelium, dendritic cells, basophils
- C-type lectin engagement (peanut, dust mite): dendritic cells
- complement activation (hymenoptera, peanut): many potential targets

Outline

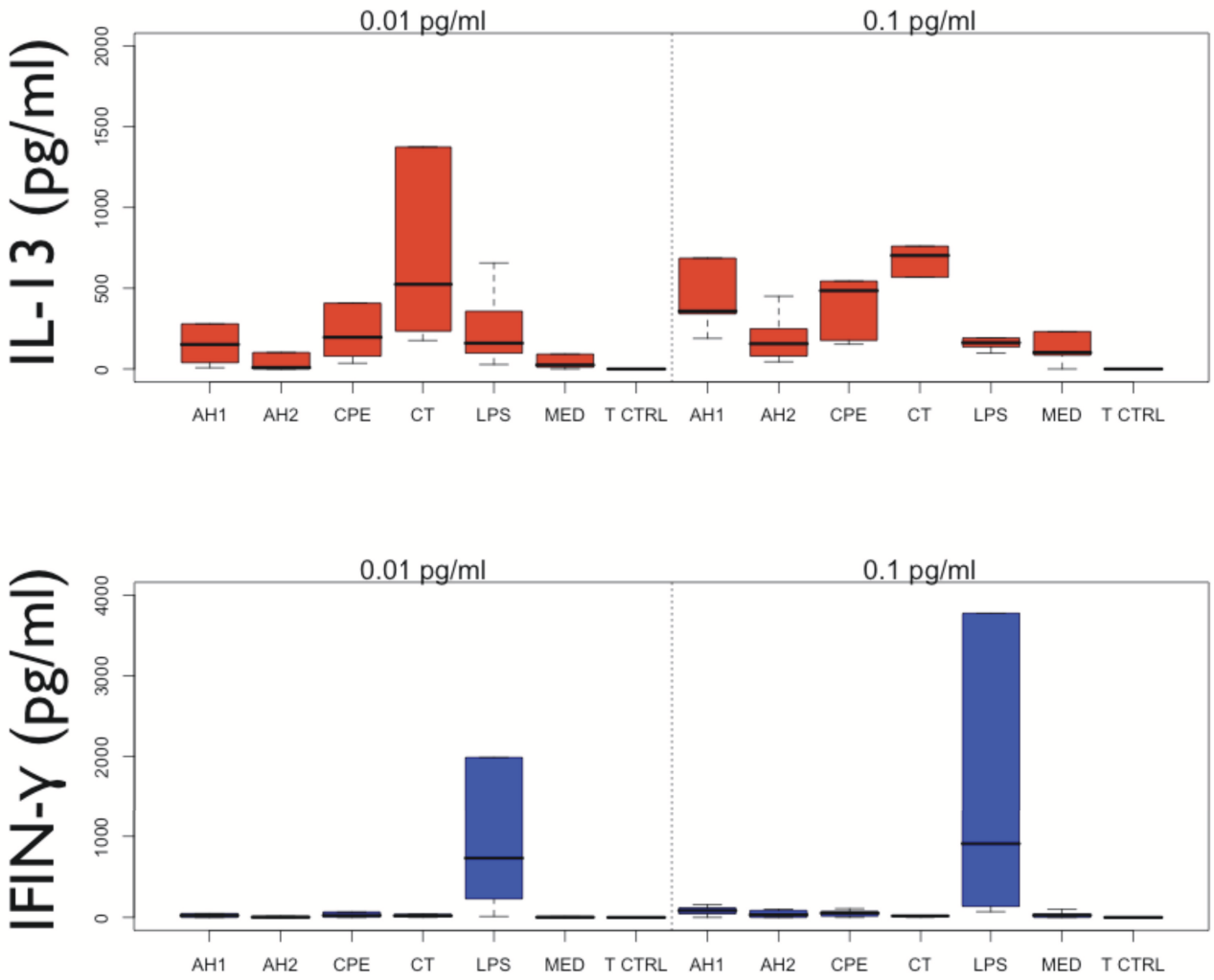
Method



Proliferation

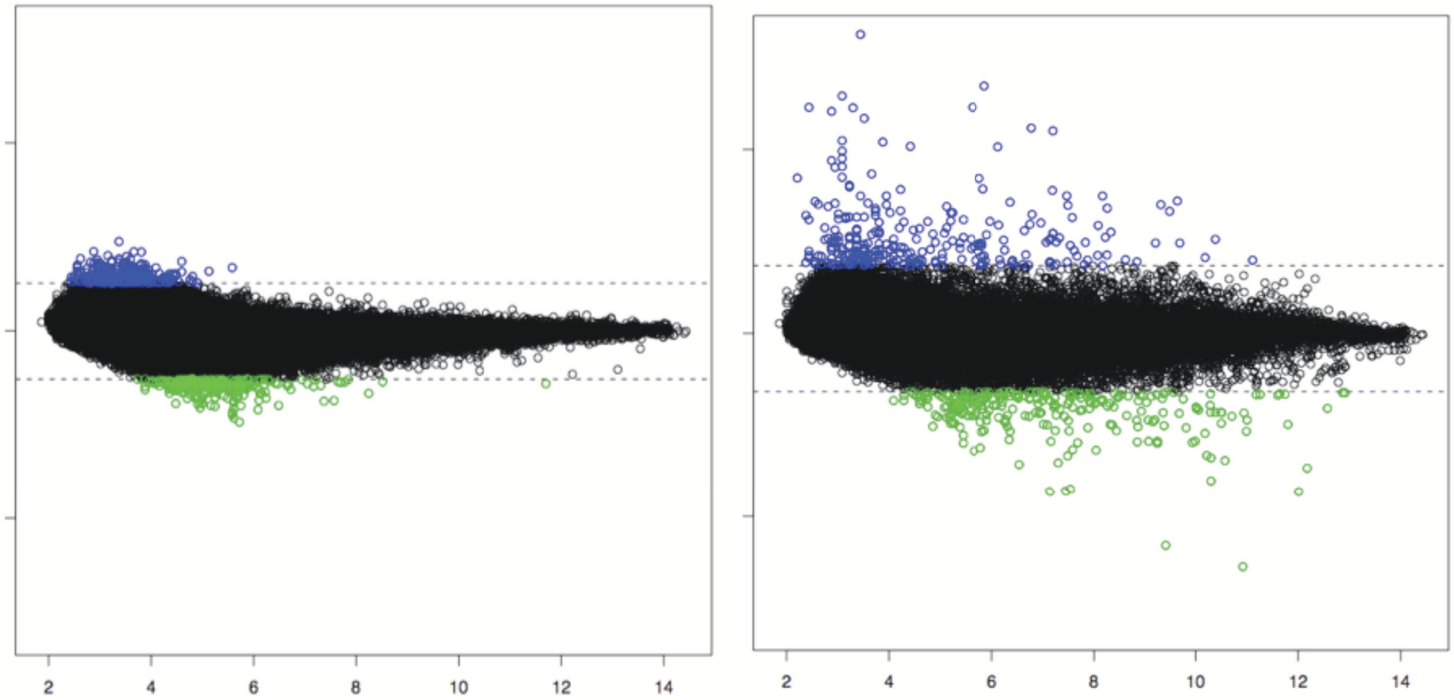


Differentiation

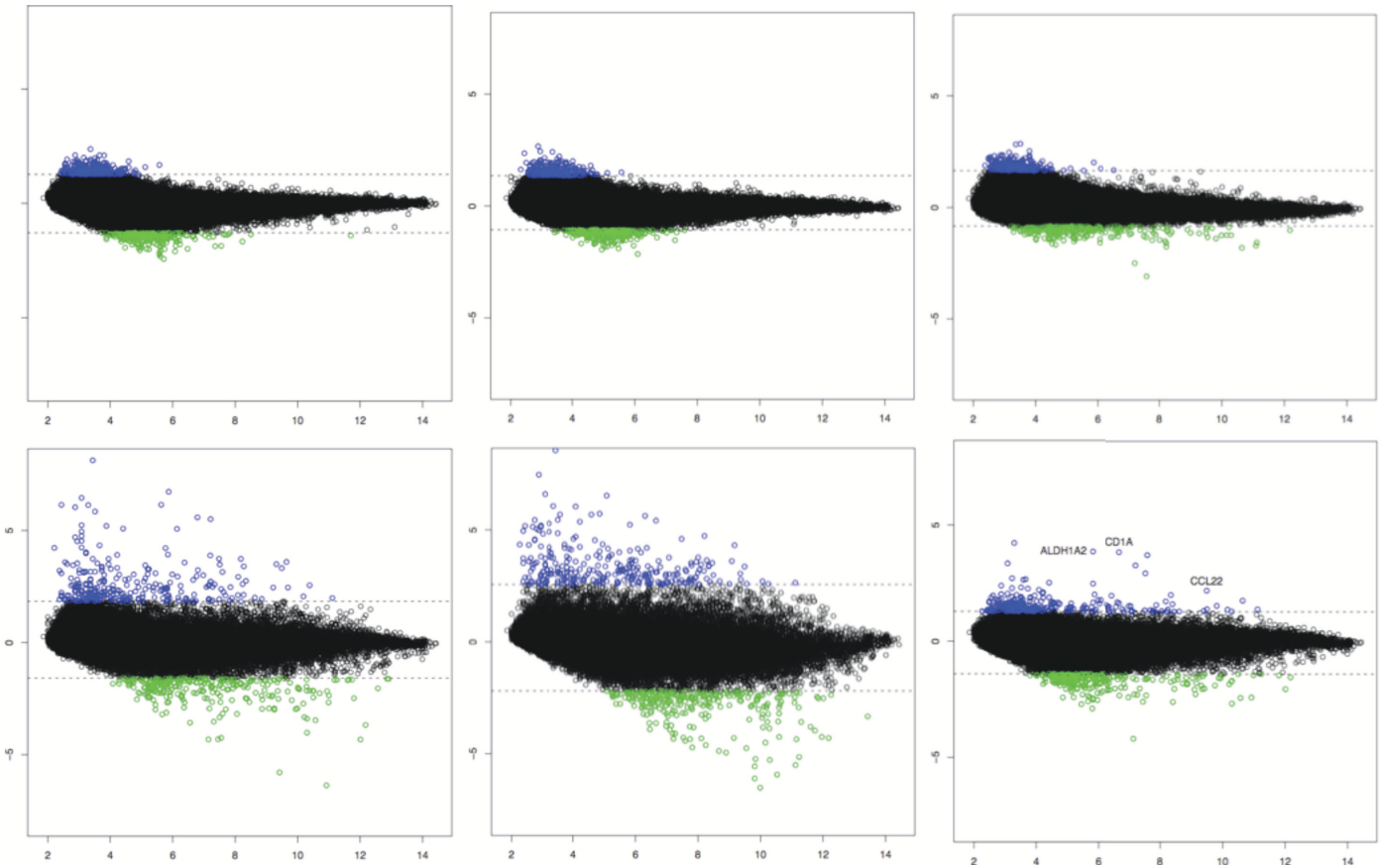


Outline

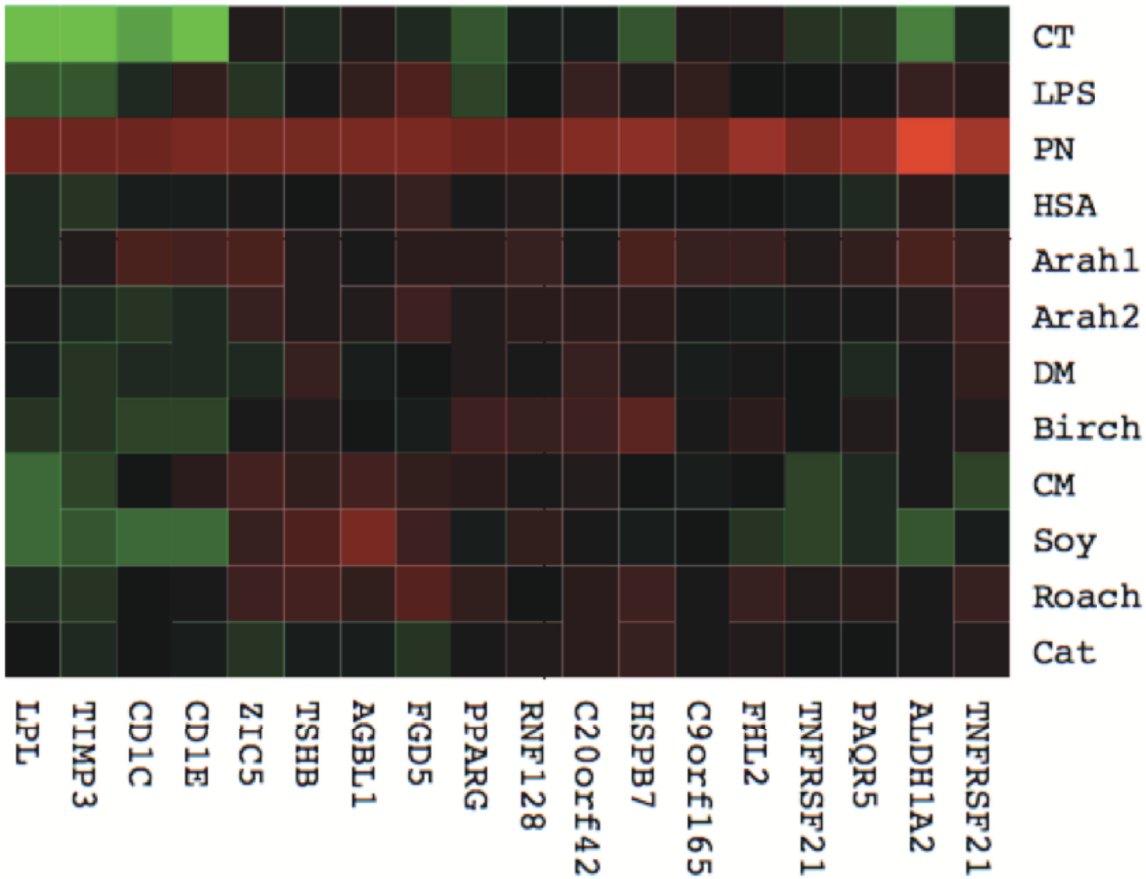
Microarray Expression Profiling



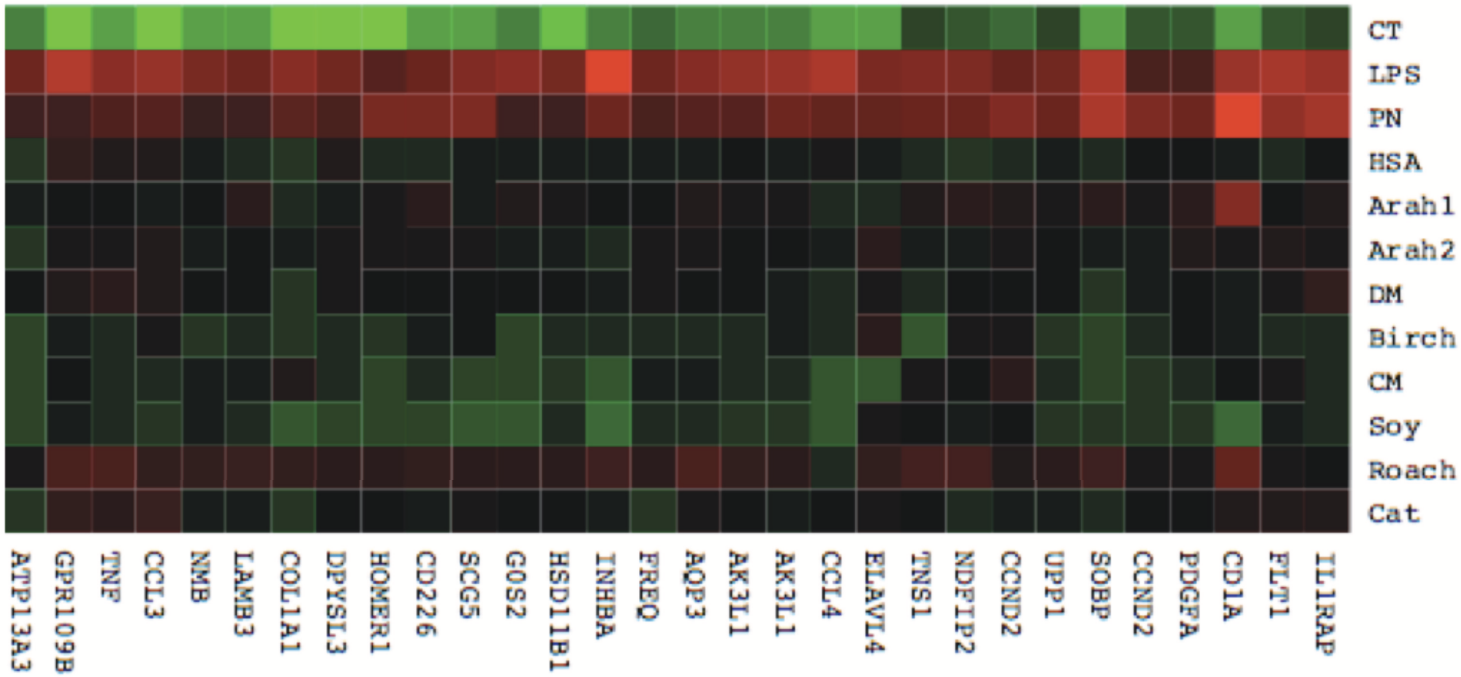
Microarray Expression Profiling



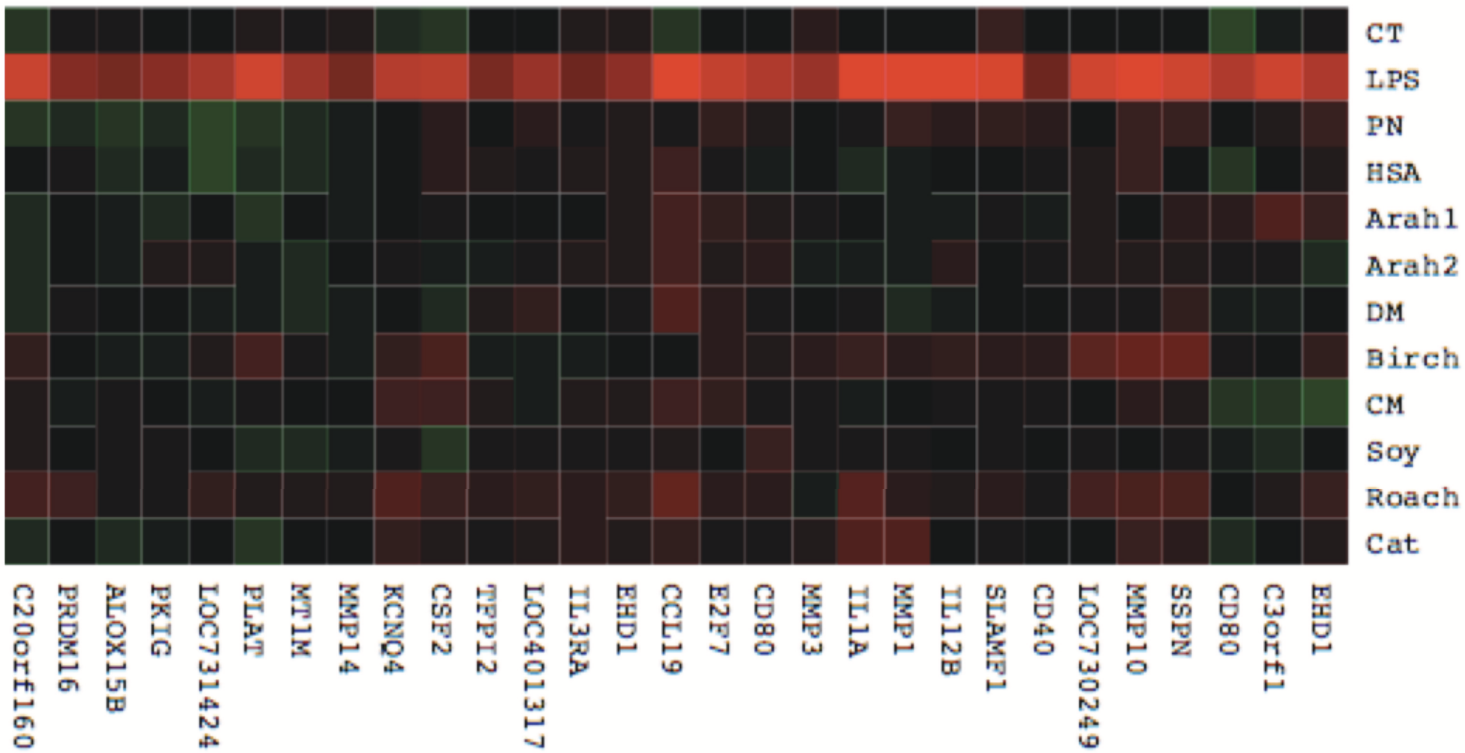
Transcriptional Changes Uniquely Induced by Peanut



Targets Shared with LPS



Targets Uniquely Upregulated by LPS



Outline

RALDH2 and Retinoic Acid

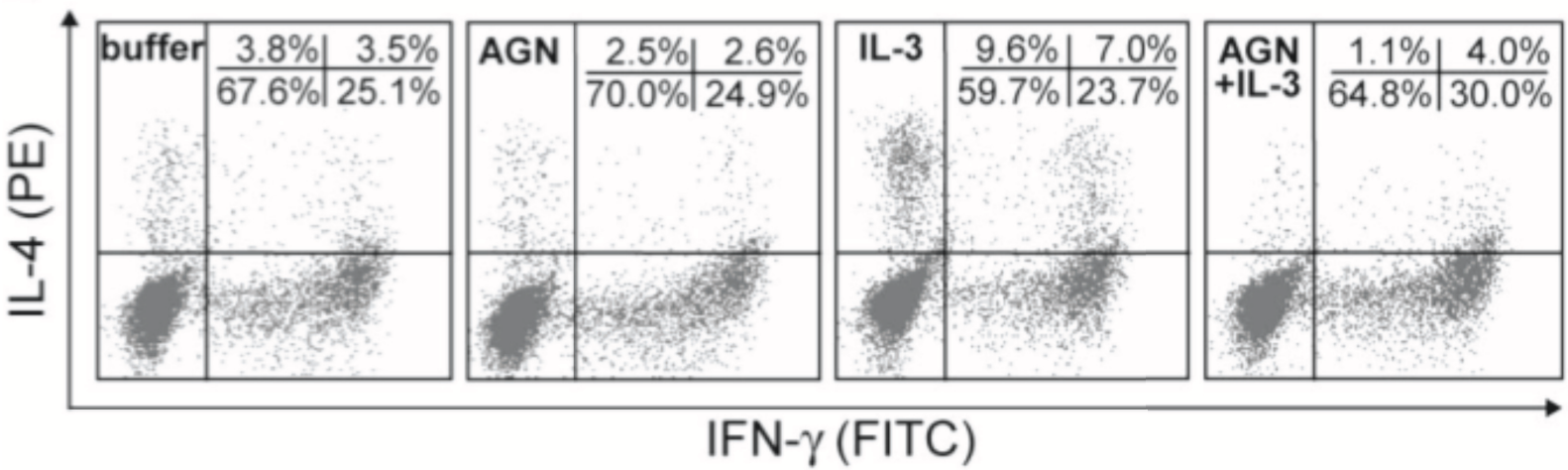
- Retinoic Acid (RA) is derived from Vitamin A by two oxidation reactions.
- The first-step conversion of vitamin A (retinol) to retinal is catalyzed by ubiquitously expressed alcohol dehydrogenases.
- RALDH2 (ALDH1A2) is the inducible and rate-limiting catalyst for the second step conversion of the aldehyde form, retinal to retinoic acid that determines cell-specific expression of RA, which can exist in two isomeric forms – ATRA and 9-*cis*-RA.

RALDH2 and Retinoic Acid in the Immune System

- Vitamin A deficiency has been long associated with Th2 developmental impairment and overproduction of IFN-γ.
- More recently, RA has been shown to suppress Th17 in favor of FoxP3^{+} Treg by antagonizing IL-6 induced RORγt.

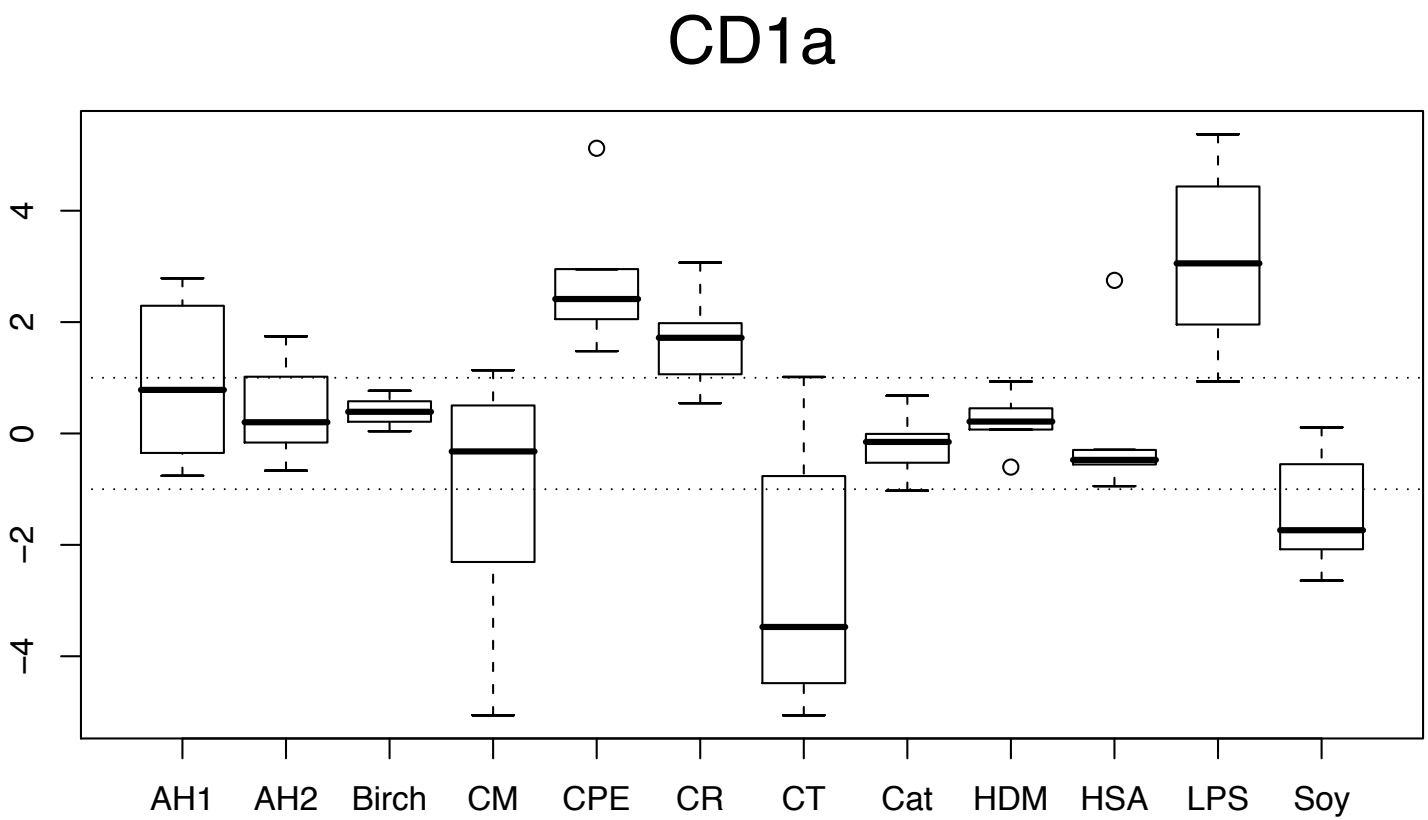
RALDH2 and Retinoic Acid in the Immune System

- Spiegel et al. recently demonstrated that human basophils could be induced to express RA (by induction of RALDH2), which induced Th2 differentiation on co-culture with naïve T cells. *Blood 2008 vol. 112 (9) pp. 3762-71*

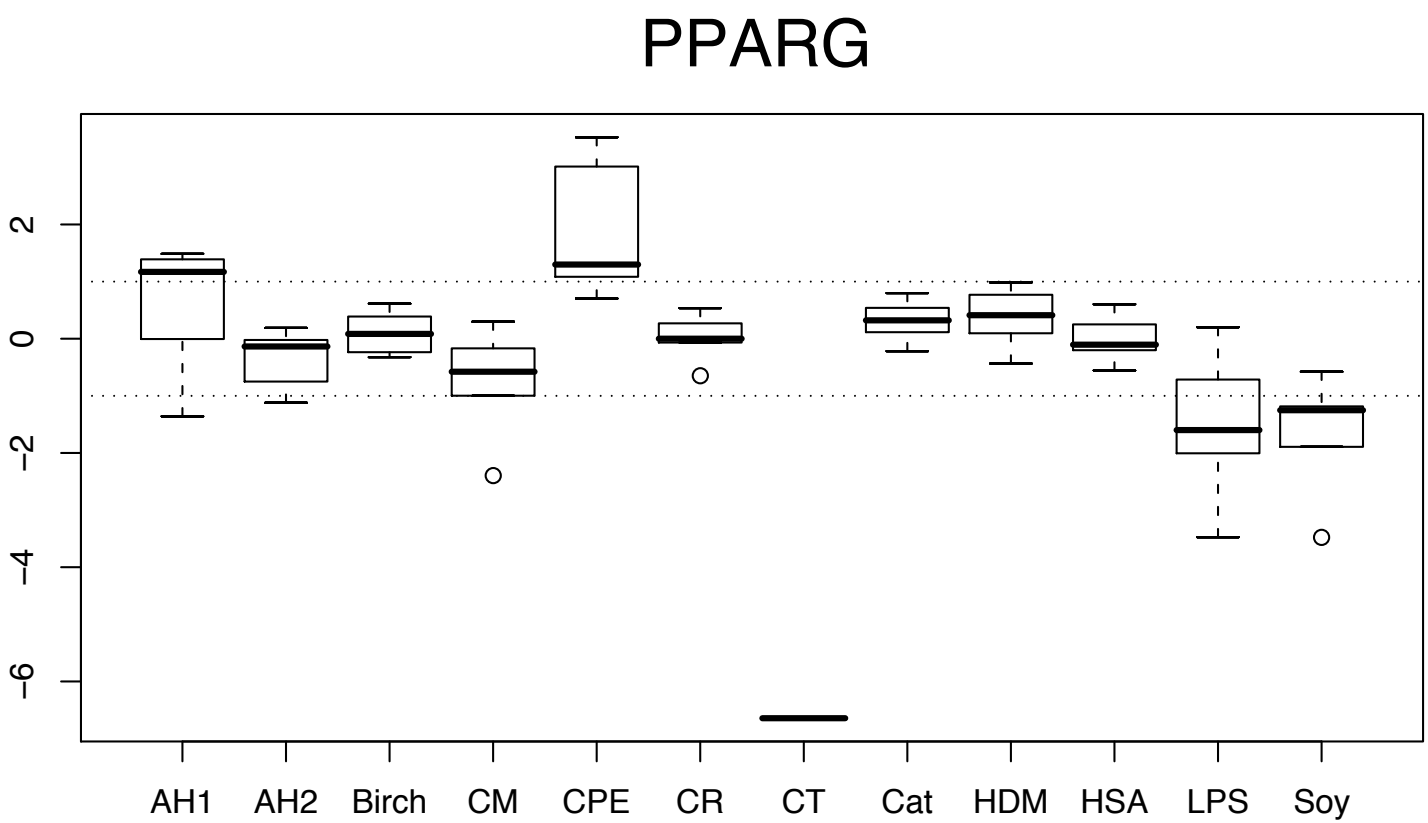


Outline

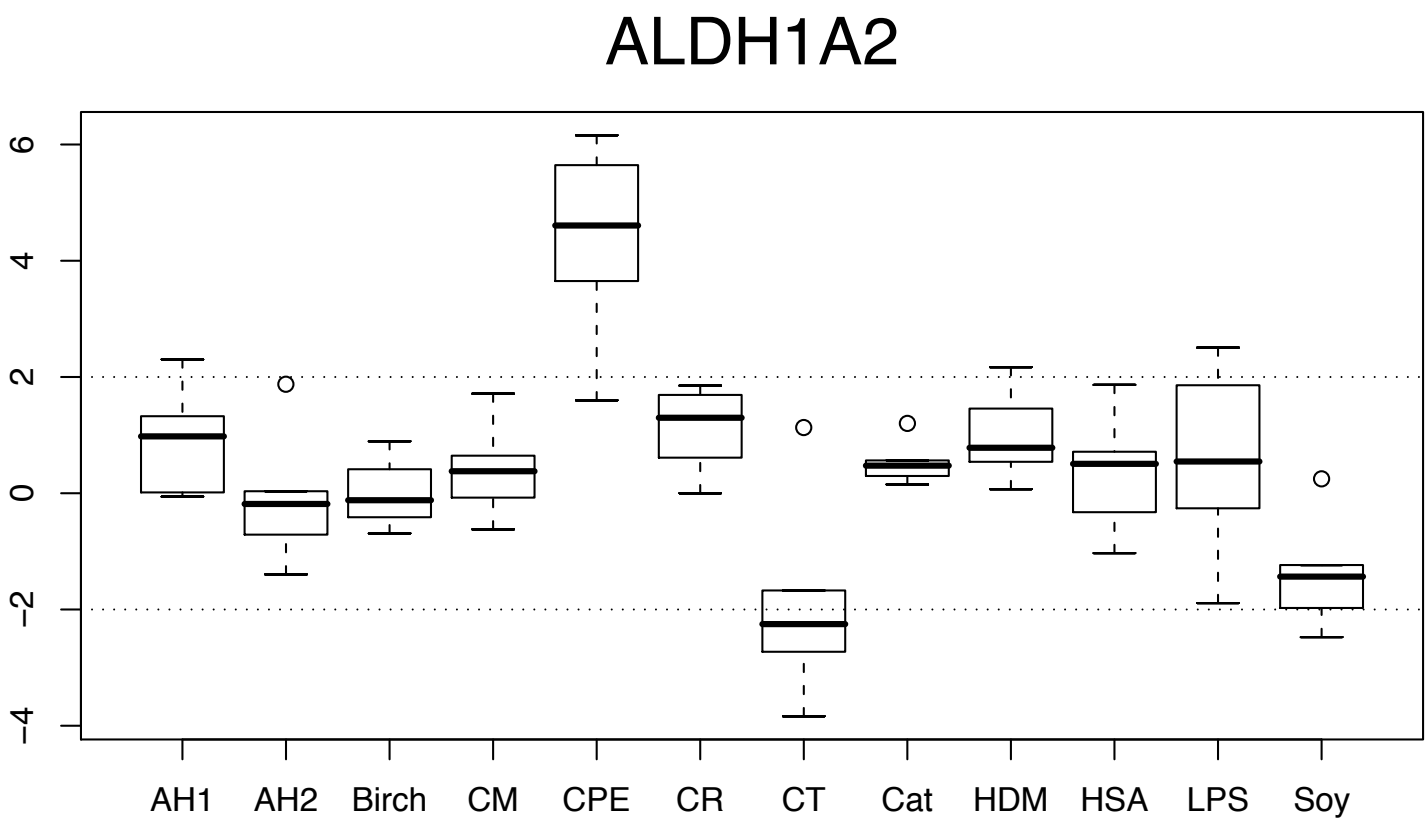
qPCR confirmation



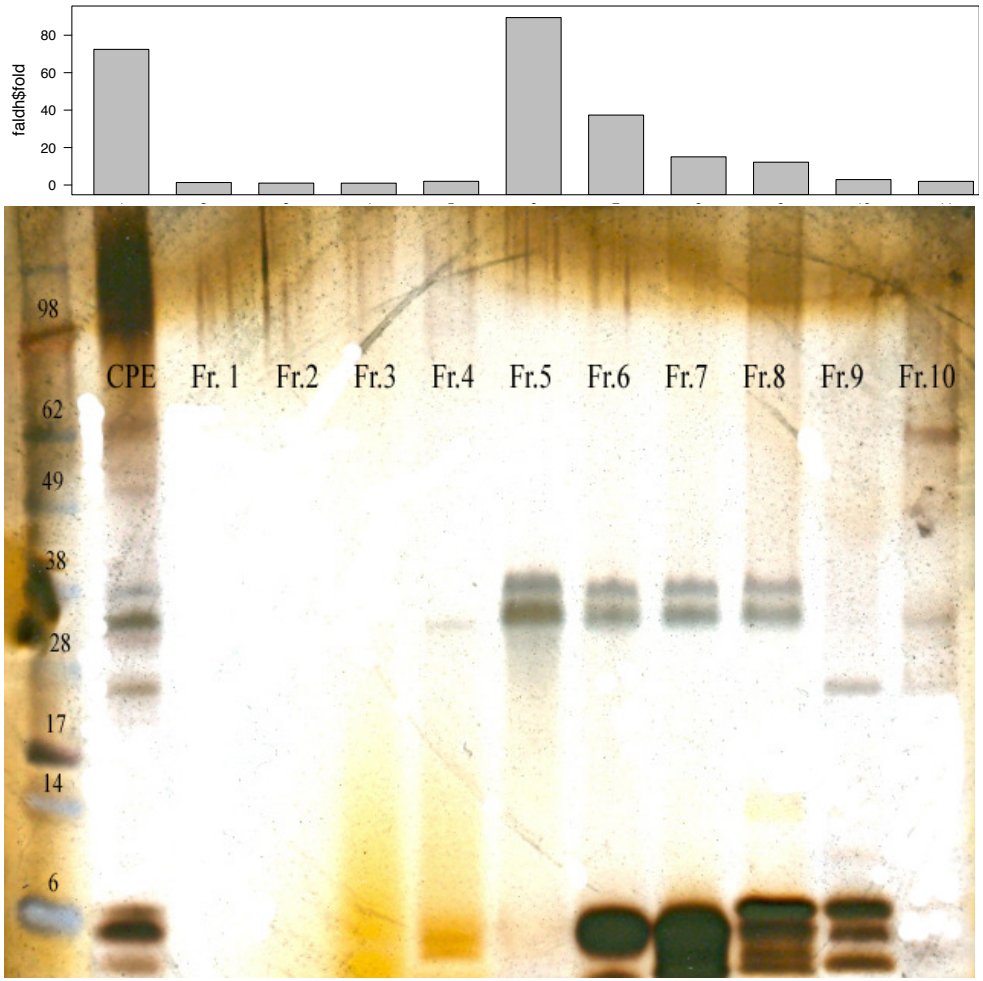
qPCR confirmation



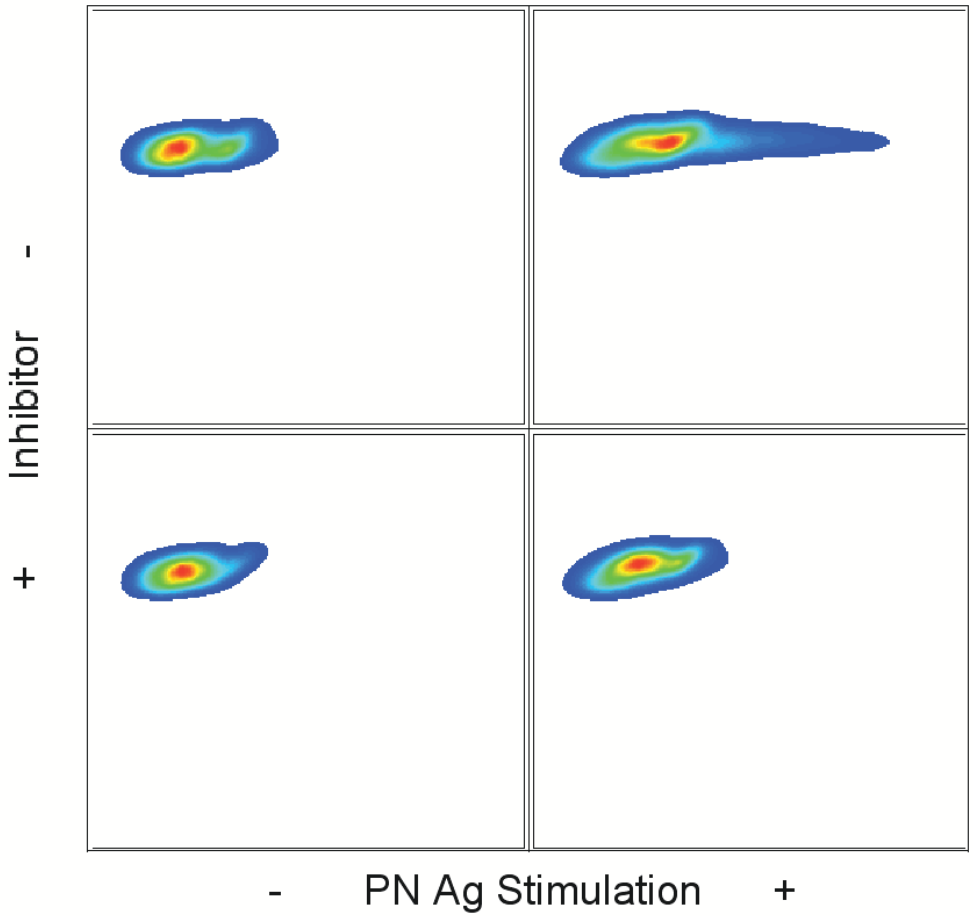
Reproducibility of RALDH2 Induction



Fractionation of RALDH2 Inducing Activity



Induction of Retinal Oxidation



Summary

- Peanut extract activates myeloid DCs to induce proliferation and differentiation of naïve T cells.
- Peanut extract induces a distinctive transcriptional program in DCs.
- A fraction of peanut extract induces the rate-limiting enzyme for the production of RA in (a subset?) of human DCs.

Future Work

- Demonstrate whether RA is produced in co-culture and plays a role in naïve T cell differentiation.
  - RARE reporter construct in T cell line to demonstrate *trans*-activation.
  - Substrate dose response and RAR antagonists effect on T cell differentiation.
- Characterize DC population that is responsive to peanut.
- Define and purify the fraction of peanut extract to determine its sufficiency for DC and T cell activation.
- Replicate RA induction by peanut allergen in murine model.

Acknowledgments

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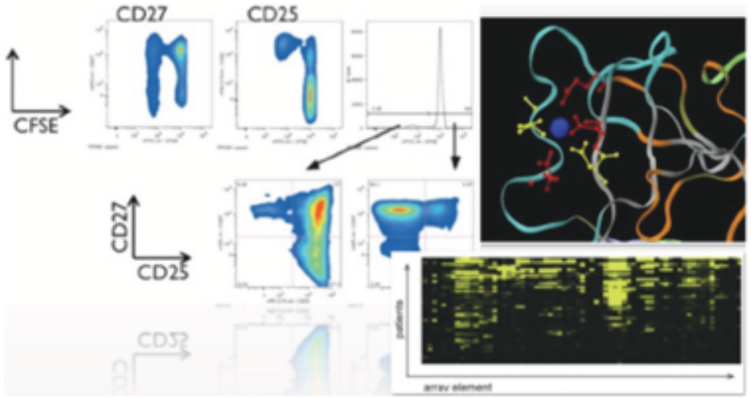

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