

Determinants of Food Allergy Persistence and Severity

What determines sensitization?

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Allergy-Immunology Research Conference
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Why Food Allergy?

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

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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)

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- ▶ 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

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The 'Perfect' Allergen

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

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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

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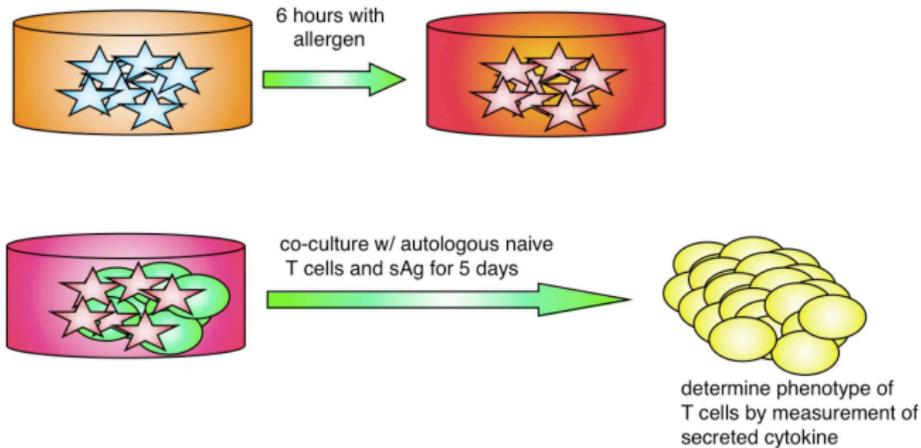
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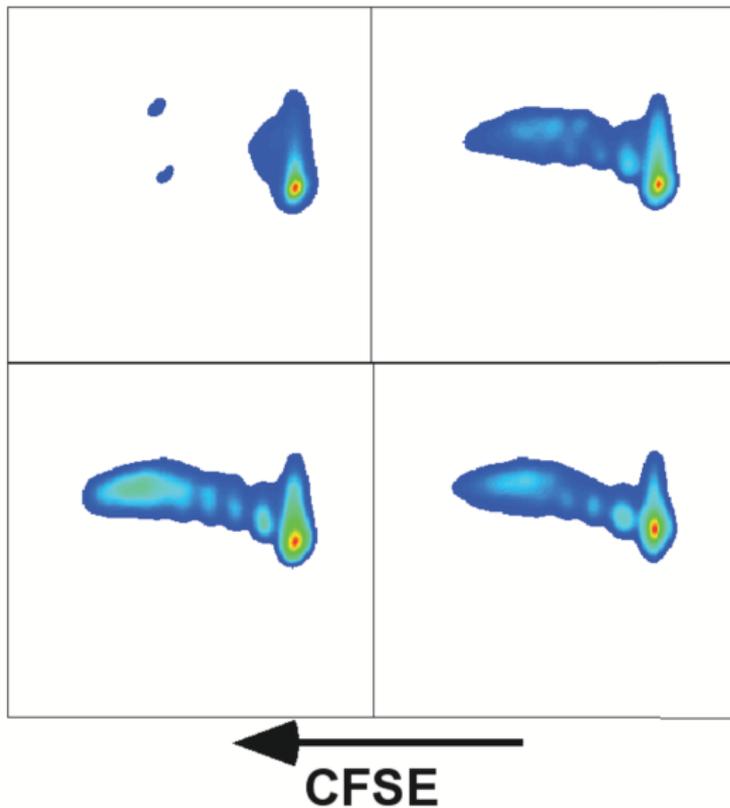
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Proliferation



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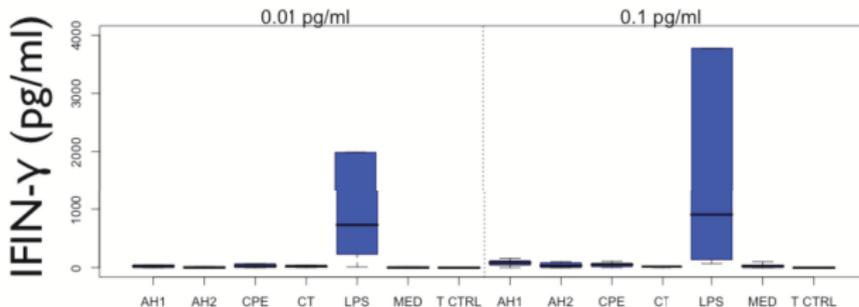
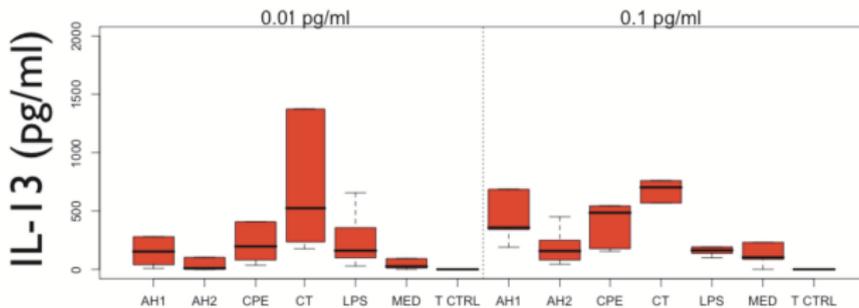
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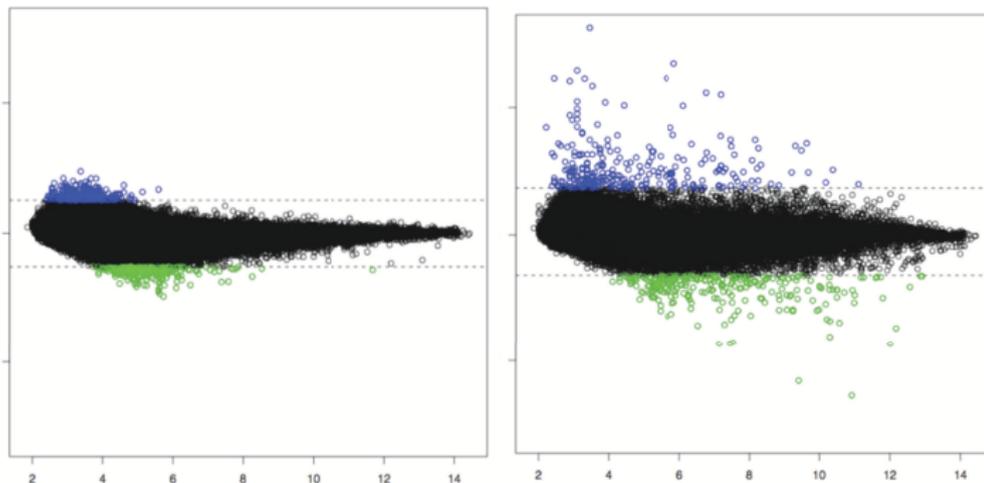
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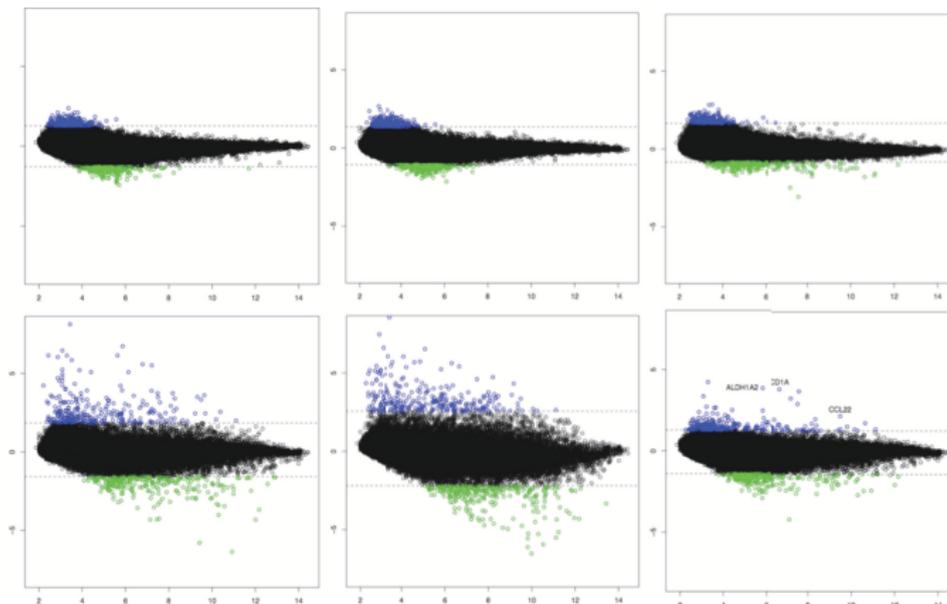
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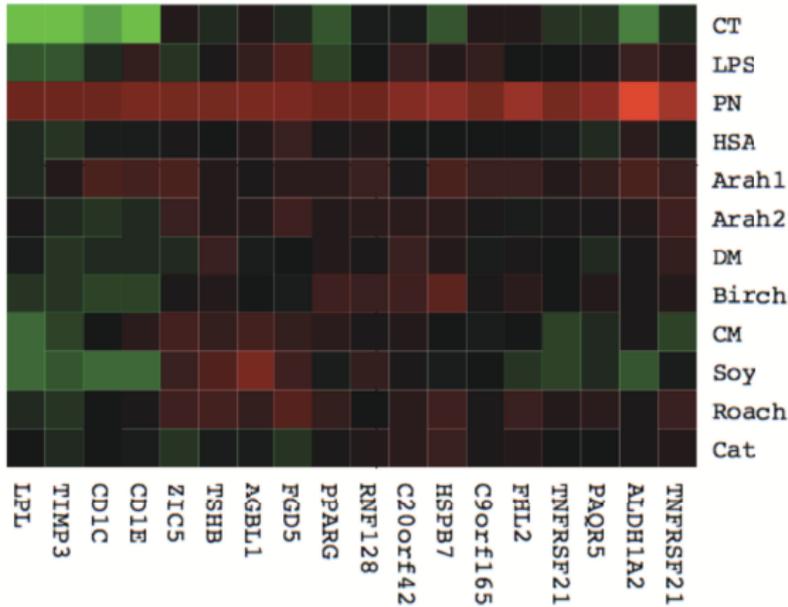
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Transcriptional Changes Uniquely Induced by Peanut



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Targets Shared with LPS

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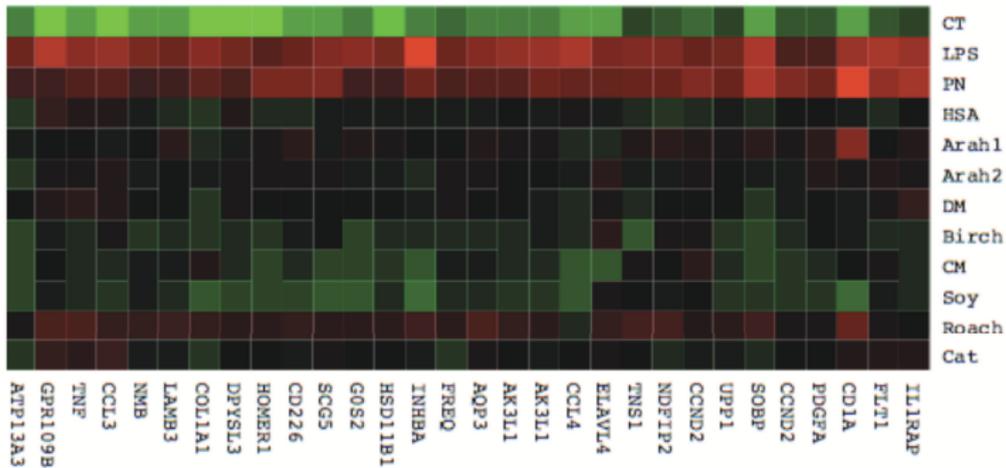
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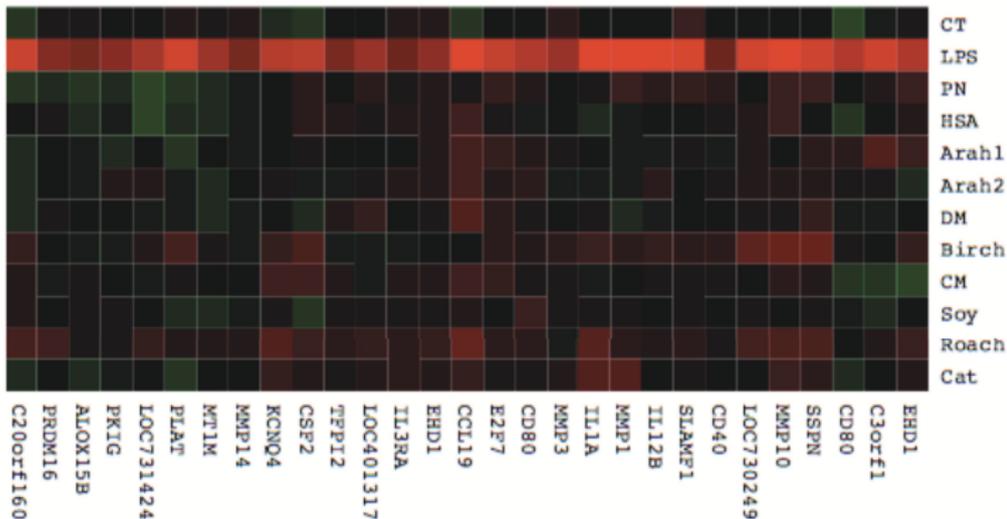
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- ▶ Retinoic Acid (RA) is derived from Vitamin A by two oxidation reactions.
- ▶ The first-step conversion of vitamin A (retinol) to retinal is catalyzed by ubiquitously expressed alcohol dehydrogenases.
- ▶ RALDH2 (ALDH1A2) is the inducible and rate-limiting 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.

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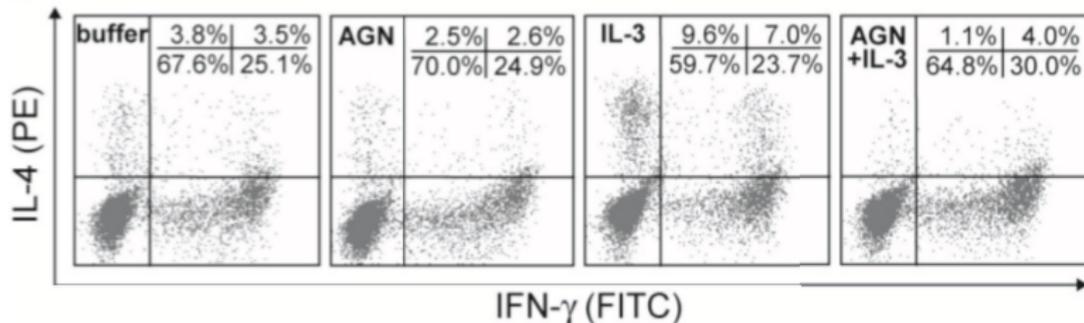
RALDH2 and Retinoic Acid in the Immune System

- ▶ 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 ROR γ t.

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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



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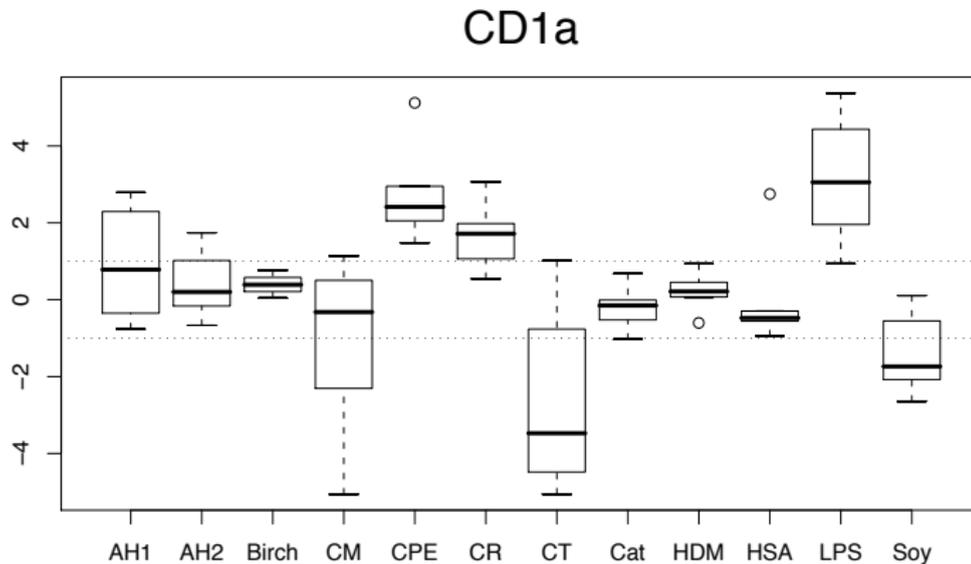
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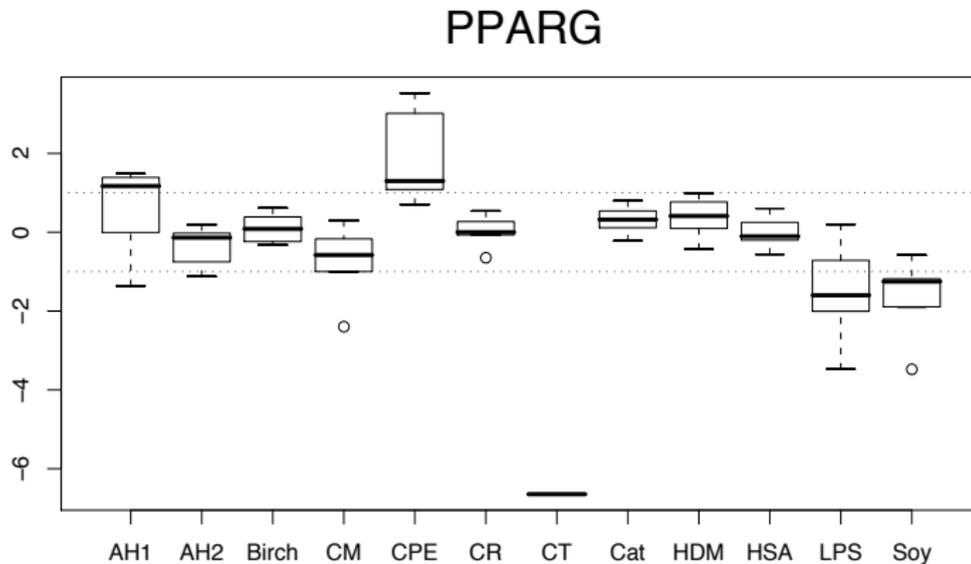
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Reproducibility of RALDH2 Induction

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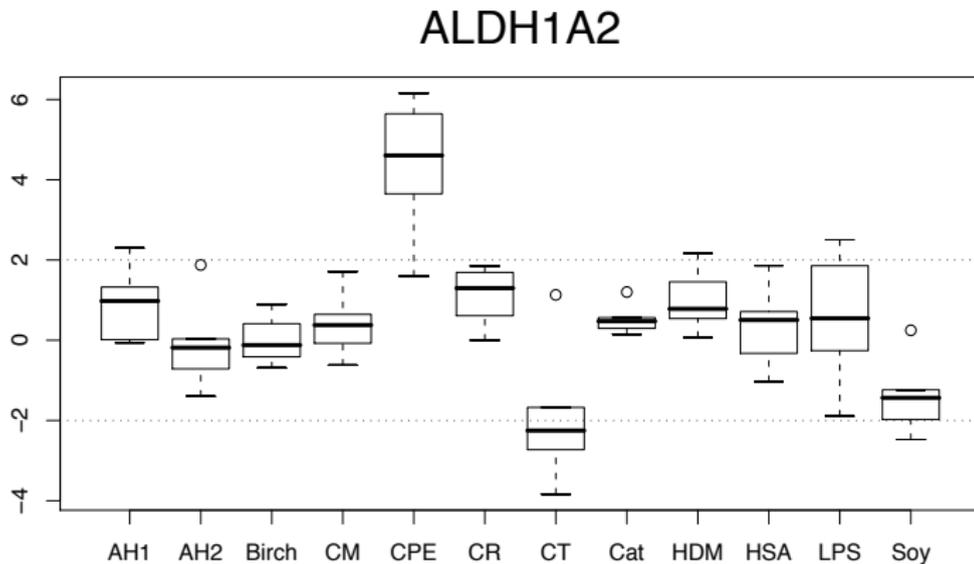
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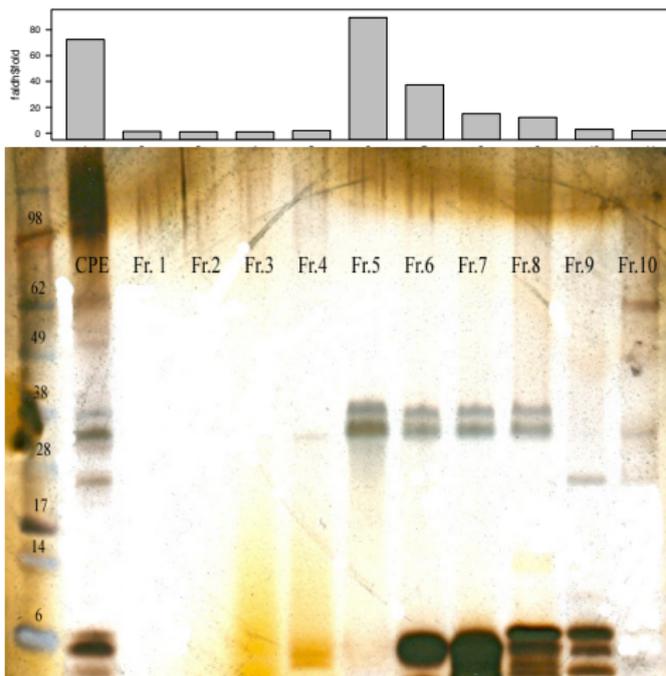
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Fractionation of RALDH2 Inducing Activity



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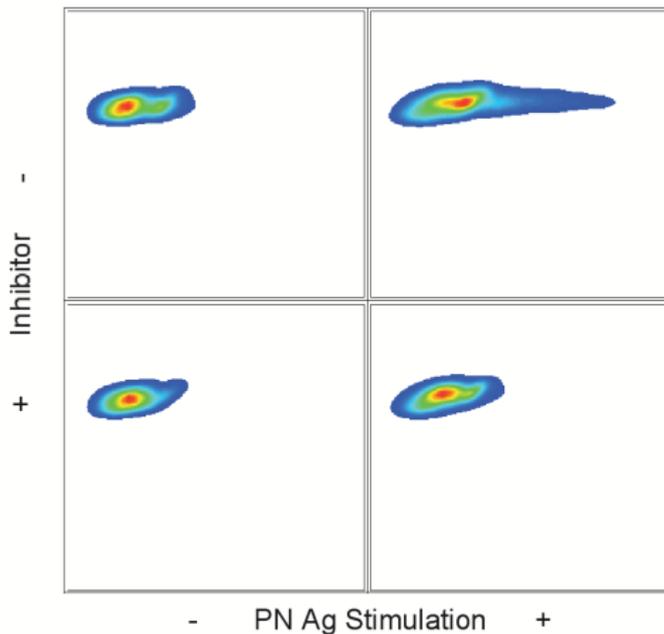
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Induction of Retinal Oxidation



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- ▶ 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.

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- ▶ 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.

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 - ▶ Mayer Lab
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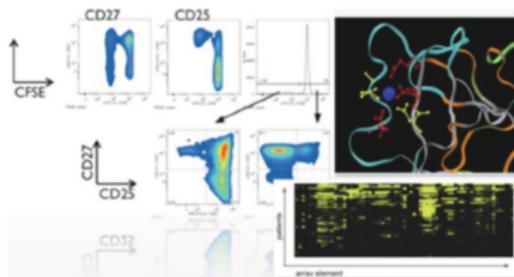
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