

The HVN Immune Health Platform: Innovating for the Future of the New Zealand Food & Beverage Industry

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Leader Immune Health PRP

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Challenge Host



Challenge Collaborating Parties

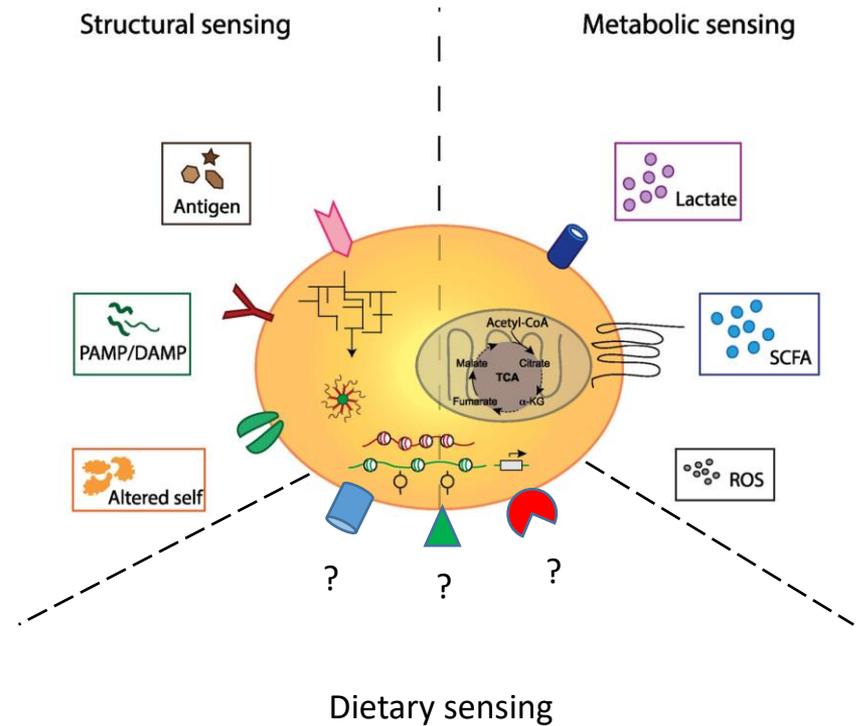
How to achieve innovation in nutritional immunology?

Biggest obstacle:

-> limited understanding of how food is being 'sensed' by (and can therefore influence) the immune system

The immune system

- **Well understood**: sensing of threats to homeostasis:
 - microbial or cancerous,
 - damage-associated, or
 - metabolic
- **Poorly understood**: sensing of pro-homeostatic signals from the:
 - diet
 - environment
 - ...



<https://doi.org/10.1111/cei.13291>

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NUTRITION

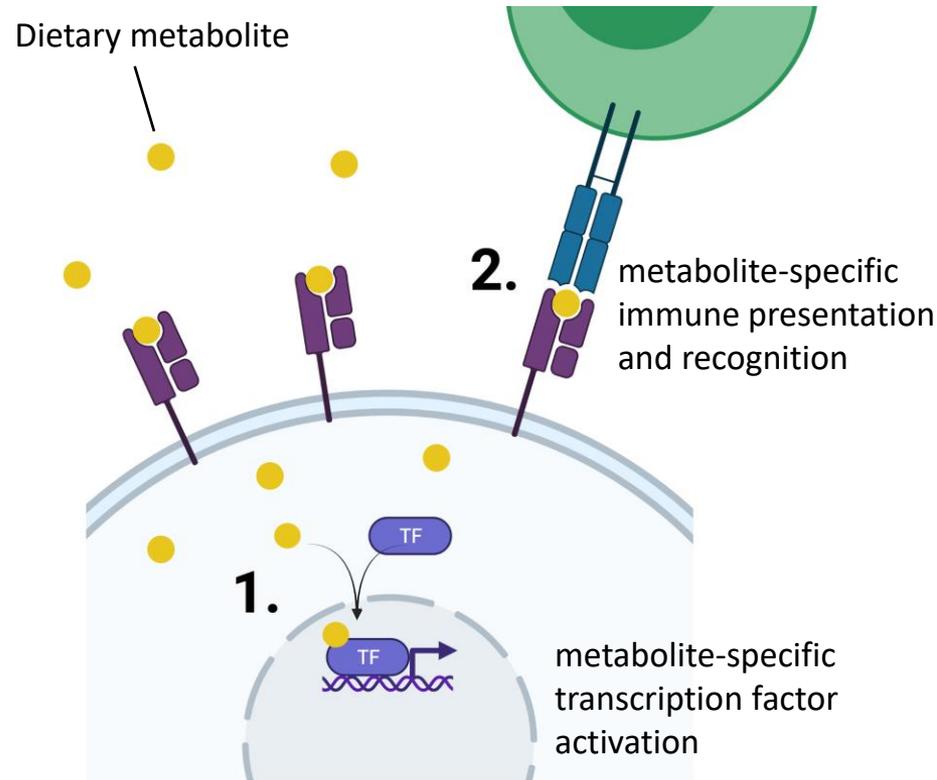
Ko Ngā Kai
Whai Painga

Dietary sensing

- Sensing through antigen- / metabolite-specific:

1. transcription factors (intracellular), or

2. cell surface receptors

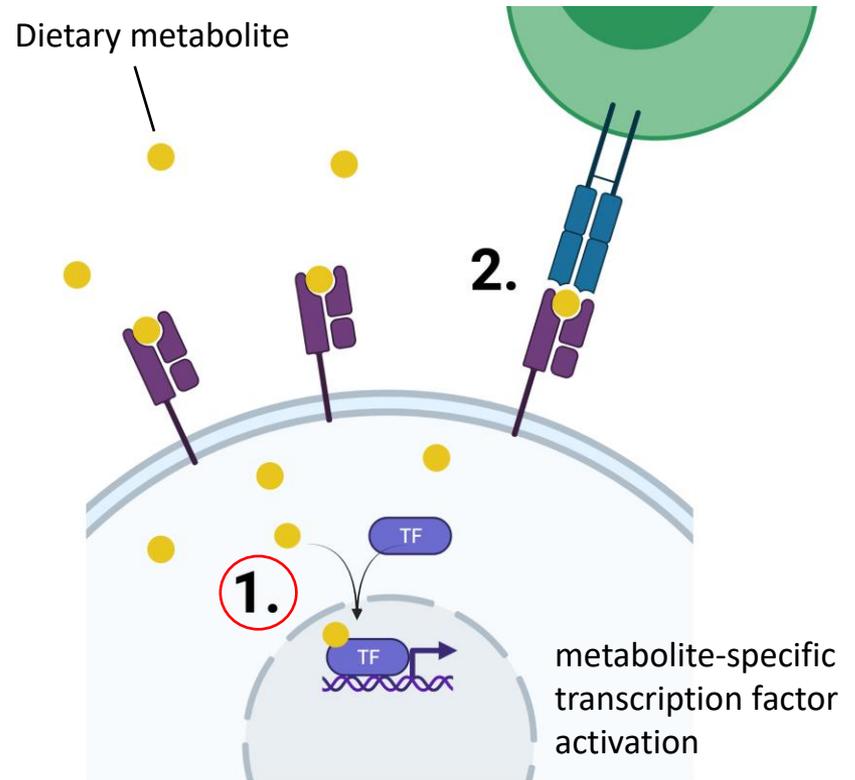
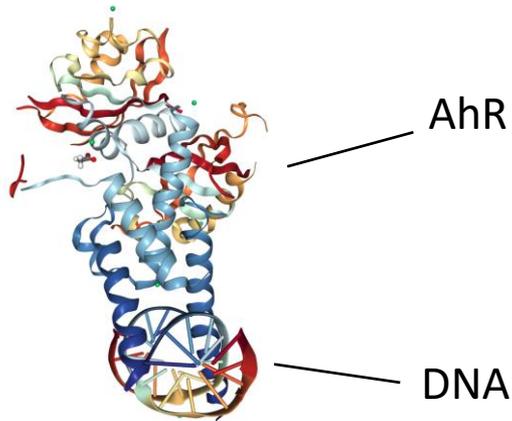


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Dietary sensing

- Sensing through:

1. the Arylhydrocarbon receptor (AhR)

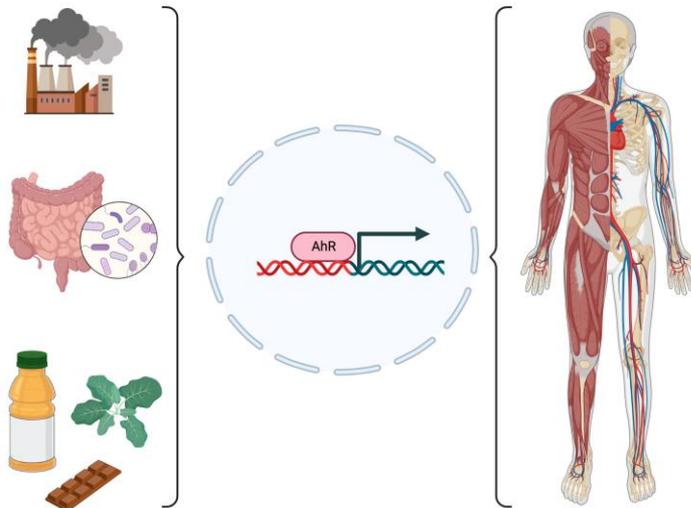


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1. AhR

- Why?

- mediates toxicity of environmental pollutants which impact the HVN target population (China)
- integrates environmental, dietary, microbial (including probiotic products) and metabolic signals
- impacts a very large number of physiological processes (developmental, metabolic, immune, gastrointestinal, ...)
- Food-bioactives: (poly)phenolic compounds



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1. AhR

- **How?**

- *in vitro* screening of dietary compounds with AhR reporter cell lines

- *in vitro* assessments of immunological impact using primary human blood cells (GI trafficking)

- Indigo naturalis dose escalation study (NZ-INDES study)

- analysis of clinical samples from HVN-funded studies

Practical Approach To Explore the Effects of Polyphenols on Aryl Hydrocarbon Receptor Regulated Immune Function

Jeffrey S. Tang,* Alissa Cait, Yanyan Li, Helena Abolins-Thompson, Katie Gell, Patries M. Herst, David O'Sullivan, and Olivier Gasser*

Cite This: <https://doi.org/10.1021/acs.jafc.1c02095>

Read Online

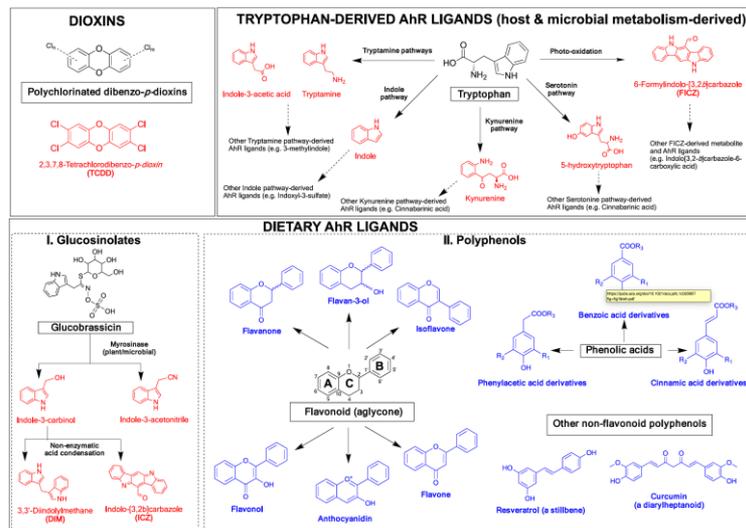


Figure 1. Classes of dietary compounds and environmental pollutants that are described to affect AhR signaling.

1. AhR

- How?

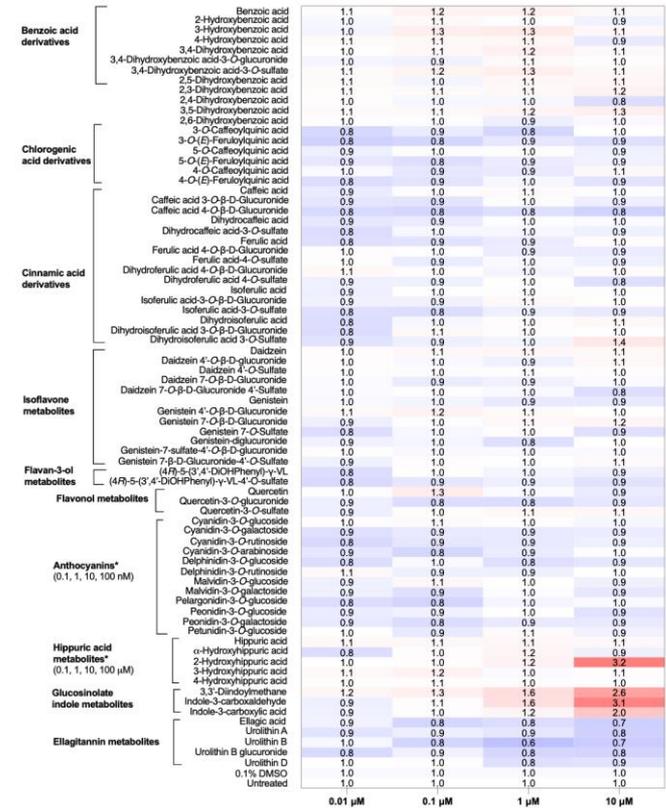
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inhibition ■ activation



Tang et al. submitted

1. AhR

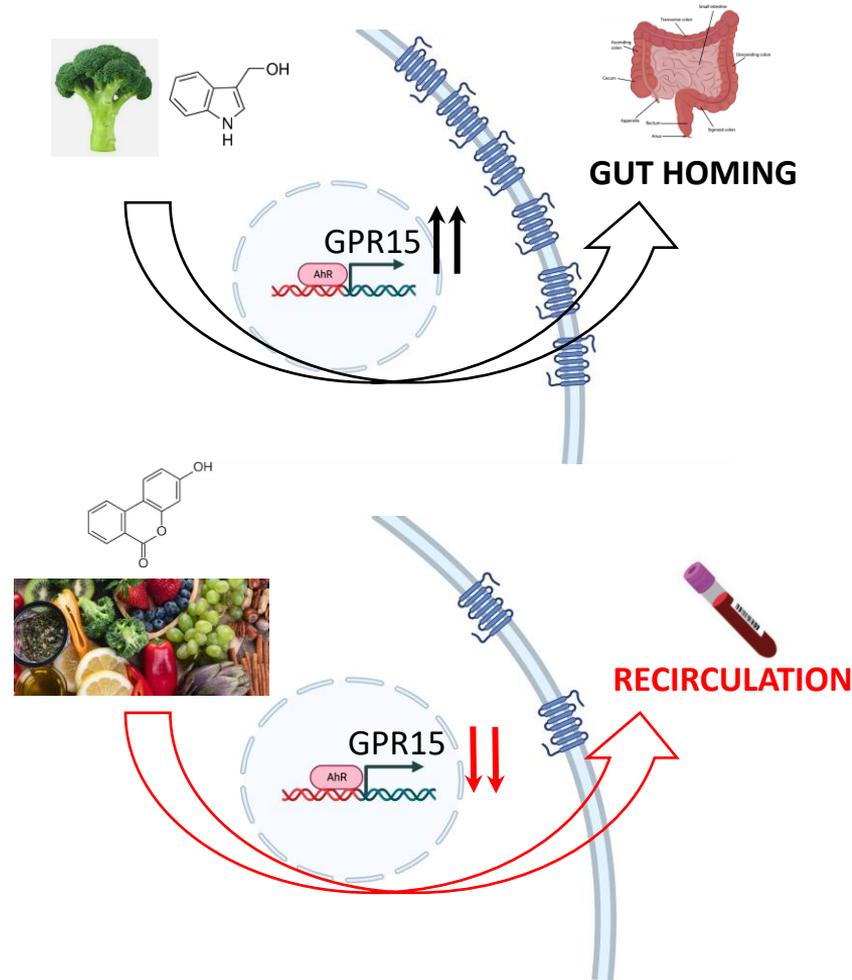
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1. AhR

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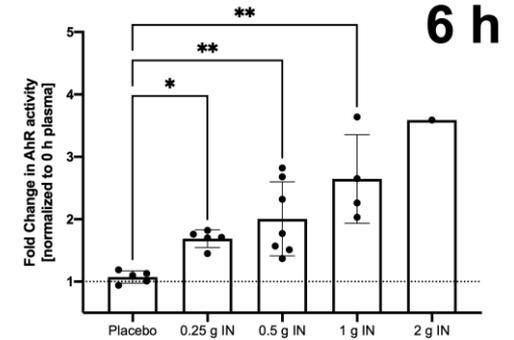
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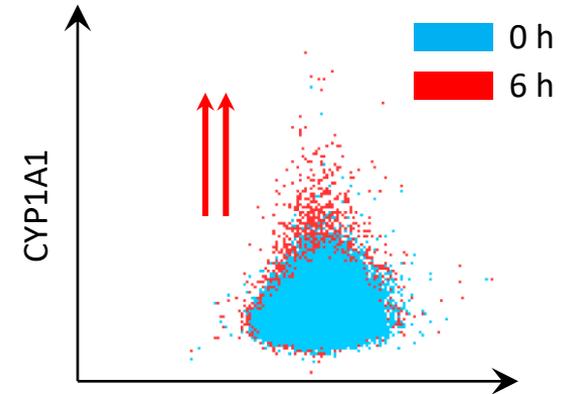


How does the acute ingestion of a known AhR agonist influence the peripheral immune system?

Dose-dependent AhR activity



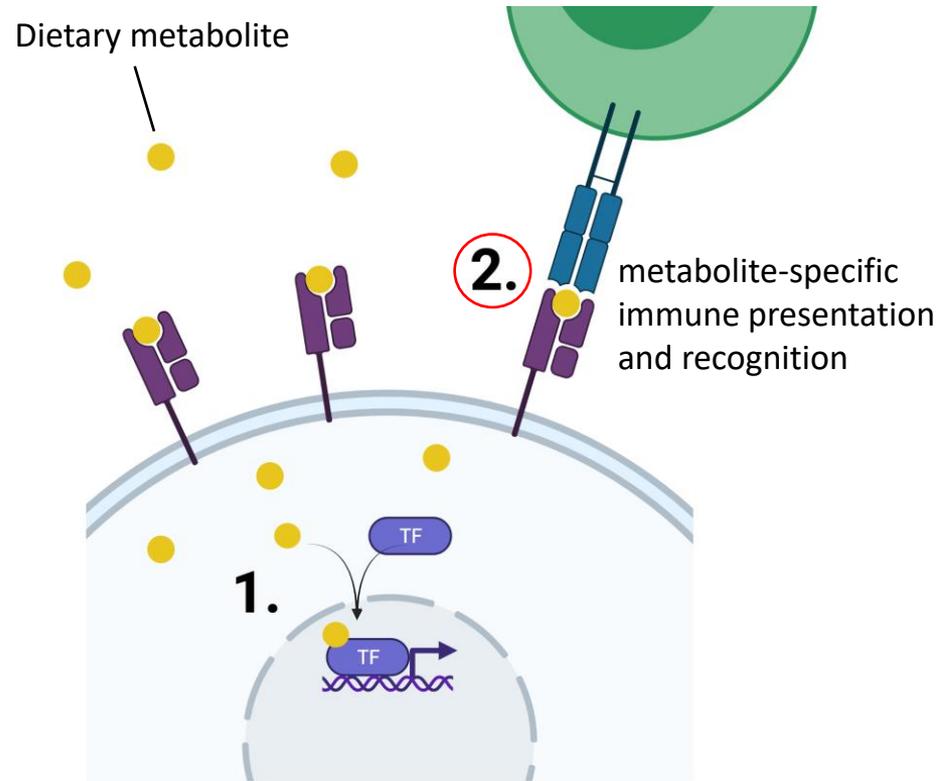
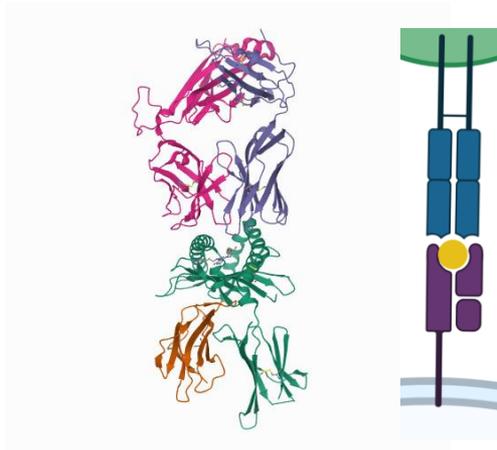
Changes in gene expression



Dietary sensing

- Sensing through:

2. MHC-class 1 related molecule (MR1)



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2. MR1

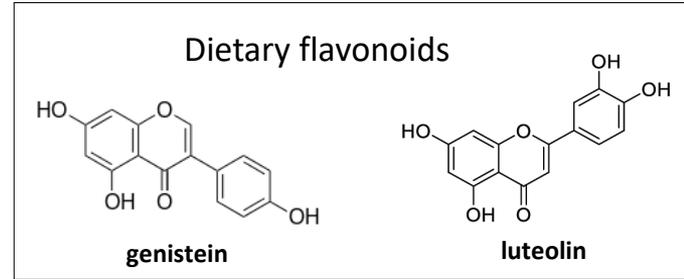
- Why?

- overlap between dietary metabolites binding AhR and MR1

- MR1 restricts the largest T cell subset in humans (mucosal associated invariant T – MAIT cells)

- MR1 immunobiology linked to gastrointestinal, metabolic, pulmonary, skin, liver health as well as antibacterial and antitumoral immunity.

- Food-bioactives: (poly)phenolic compounds (quinones, flavones, isoflavones) and likely others



2. MR1

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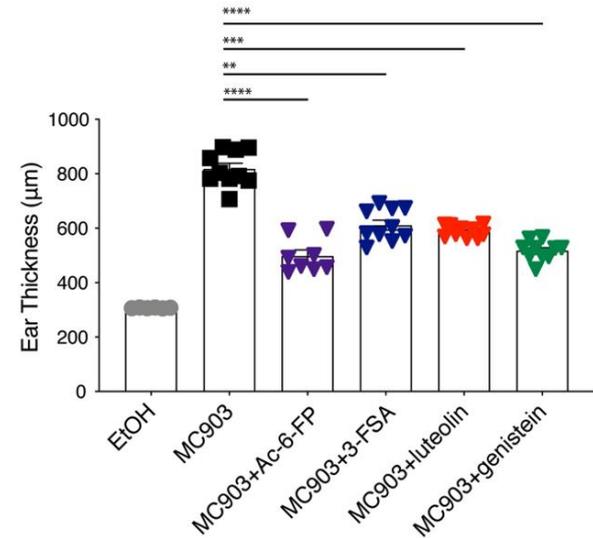
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MR1-dependent immune surveillance of the skin contributes to pathogenesis and is a photobiological target of UV light therapy in a mouse model of atopic dermatitis

Karmella Naidoo¹ | Katherine Woods¹ | Christophe Pellefigues¹ | Alissa Cait¹ | David O'Sullivan^{1,2} | Katie Gell¹ | Andrew J. Marshall³ | Regan J. Anderson³ | Yanyan Li^{1,2} | Alfonso Schmidt¹ | Kef Prasit¹ | Johannes U. Mayer¹ | Aurelie Gestin¹ | Ian F. Hermans¹ | Gavin Painter³ | Elizabeth A. Jacobsen⁴ | Olivier Gasser^{1,2}



Allergy. 2021;00:1–16.

2. MR1

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MR1-dependence of unmetabolized folic acid side-effects

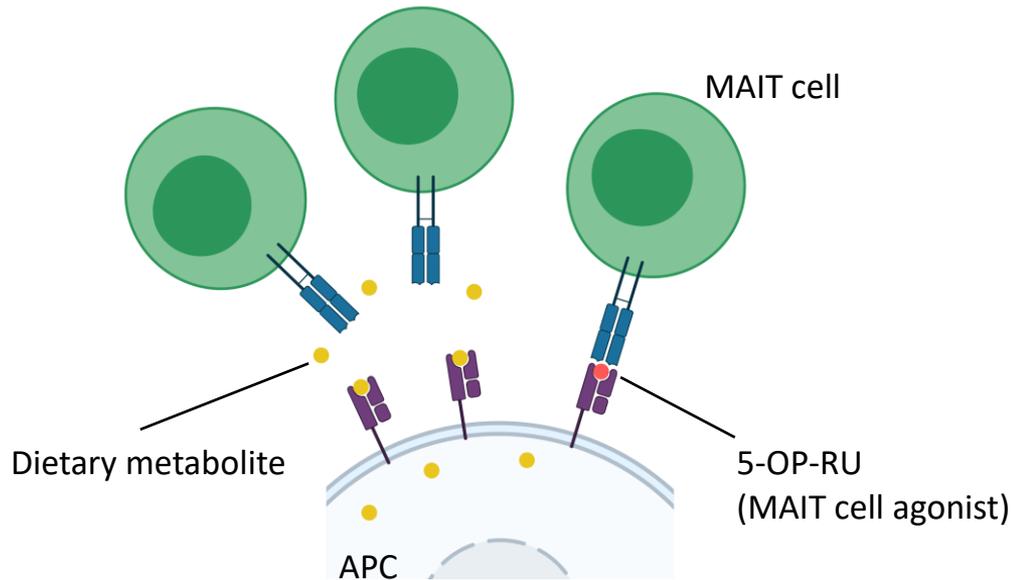
Jeffrey S. Tang^{1,2}, Alissa Cait¹, Reuben M. White³, Homayon J. Arabshahi³, David O'Sullivan^{1,2} and Olivier Gasser^{1,2*}

TYPE Hypothesis and Theory
PUBLISHED 09 August 2022
DOI 10.3389/fimmu.2022.946713

2. MR1

- **How?**

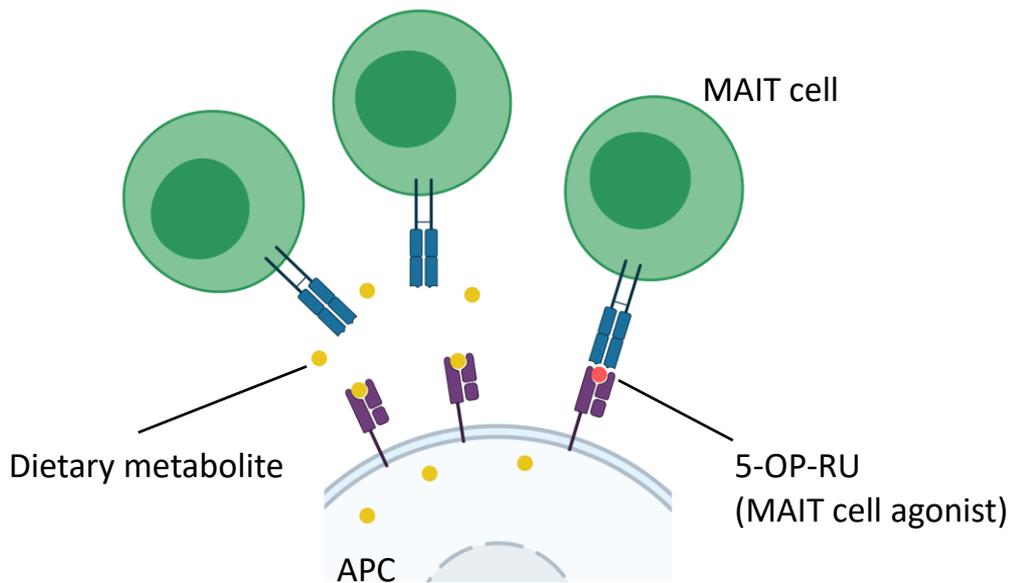
- *in vitro* screening of dietary compounds with MAIT cell competition assay



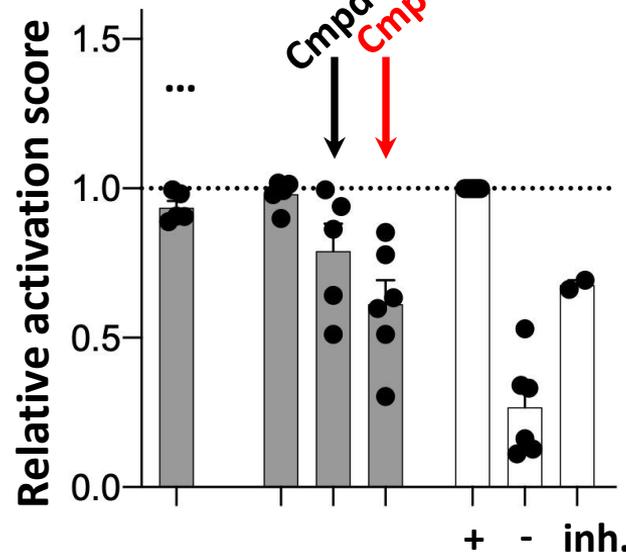
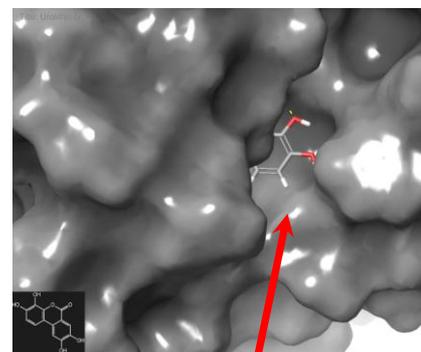
2. MR1

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John Arabshahi, UoA

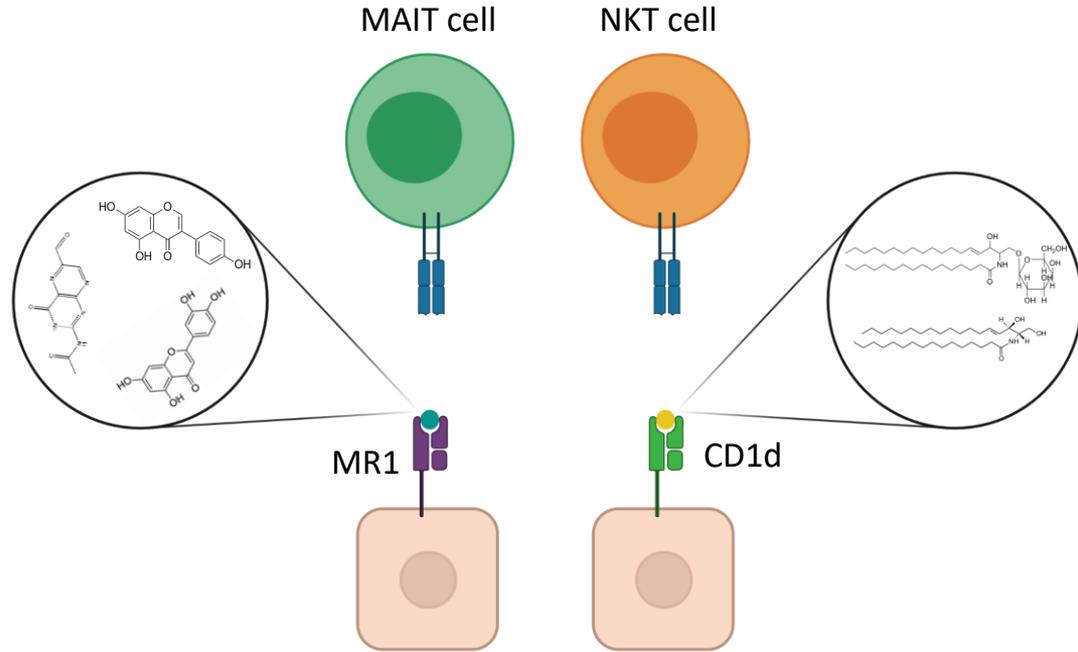


Aligned project: CD1d

- **Why?**

- CD1d is, like MR1, a non-classical MHC molecule, but binds **lipids**

- CD1d is known to bind dietary lipids and thereby influence the immunological activity of **NKT** cells



Aligned project: CD1d

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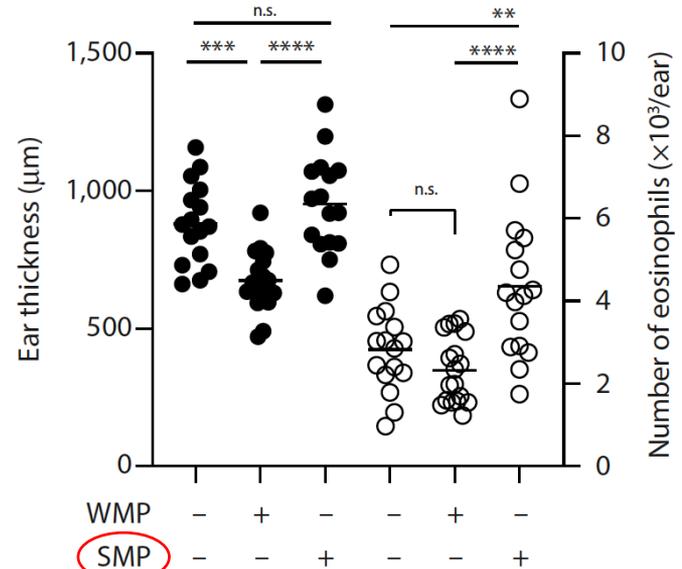
- CD1d is known to bind dietary lipids and thereby influence the immunological activity of **NKT** cells



Goat Milk-Derived Lipids Restrain NK T Cell-Dependent Eosinophilic Inflammation in a Murine Model of Atopic Dermatitis

JID Open

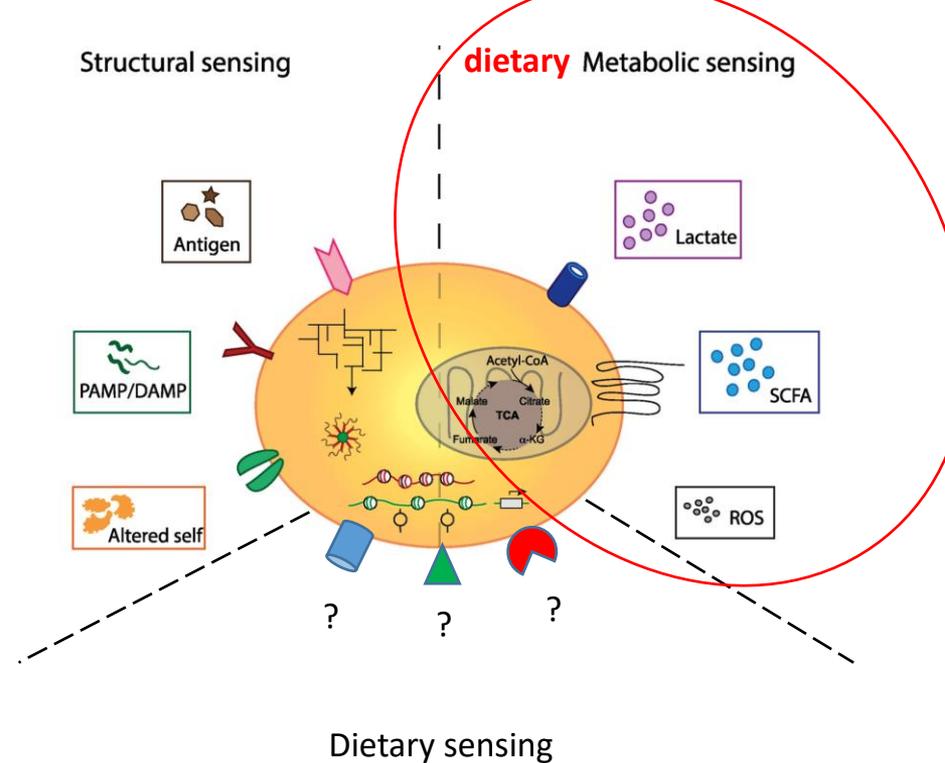
Journal of Investigative Dermatology (2022) ■, ■-■; doi:10.1016/j.jid.2022.03.006



Skim milk doesn't work!!

The immune system

- **Well understood**: sensing of threats to homeostasis:
 - microbial or cancerous,
 - damage-associated, or
 - metabolic
- **Poorly understood**: sensing of pro-homeostatic signals from the:
 - diet
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<https://doi.org/10.1111/cei.13291>

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3. Immunometabolism

- Why?

- has rapidly become an essential part of immunology but never applied to nutrition

- obvious relevance for immunophenotyping of dietary intervention samples

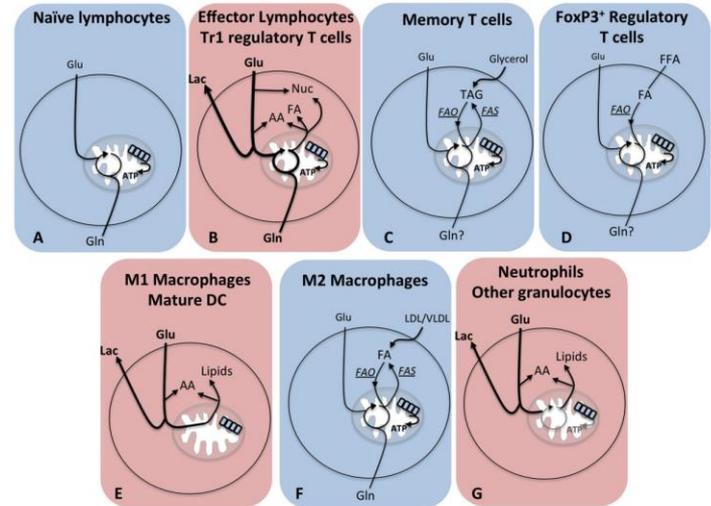
- impacts virtually every aspect of immune function

- Food bioactives: probably most ...

Immunometabolism: Cellular Metabolism Turns Immune Regulator*

Published, JBC Papers in Press, November 3, 2015, DOI 10.1074/jbc.R115.693903

Róisín M. Loftus[‡] and David K. Finlay^{‡§1}



THE JOURNAL OF BIOLOGICAL CHEMISTRY VOL. 291, NO. 1, pp. 1–10, January 1, 2016
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3. Immunometabolism

- Why?

Basic concept: if the ingestion of a food can induce a metabolic shift in a cell, it can change immune function.

3. Immunometabolism

Ahl et al. *Commun Biol.* 2020
Hartmann et al. *Nat Biotechnol.* 2020
Levine et al. *Immunity* 2021
Artyomov et al. *Cell Metab.* 2020

- **How?**

- metabolic flow cytometry

Phenotypic & Metabolic Targets

MCT1: Monocarboxylate transporter moves lactate across cell membrane

PKM: Pyruvate kinase is a key ATP producing step in glycolysis

GLS1: Glutaminase is required for glutamine utilisation in the TCA cycle

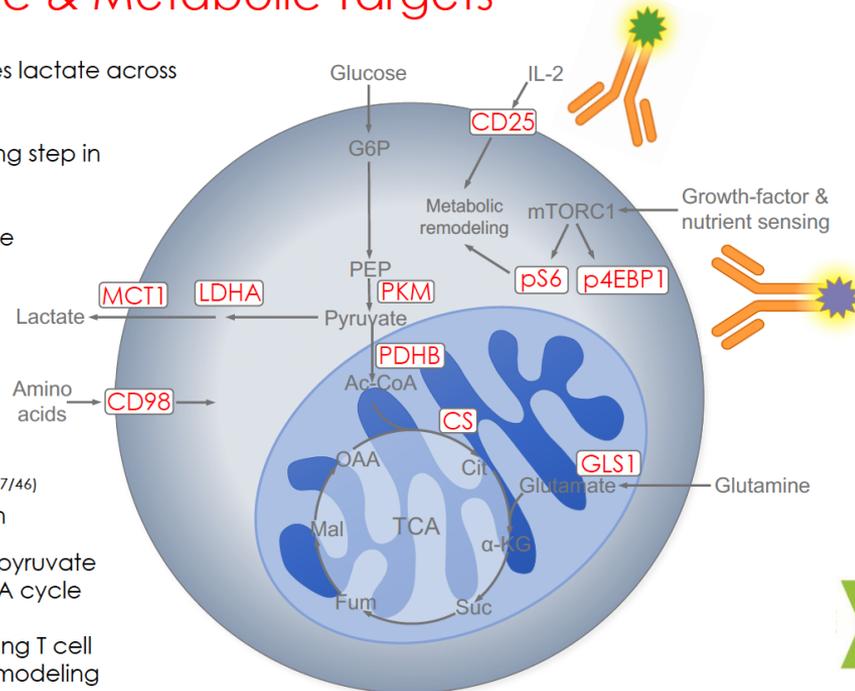
CD98: transporter of branched chain and aromatic amino acids

Citrate synthase: rate limiting enzyme of the tricarboxylic (TCA) cycle

p4EBP1 & pS6: phosphorylation of 4EBP1 (Thr37/46) or S6 (Ser235/236) induces increased translation

PDHB: pyruvate dehydrogenase converts pyruvate to acetyl-CoA to link glycolysis and the TCA cycle

CD25: IL-2RA receptor upregulation following T cell activation is associated with metabolic remodeling



O'Sullivan et al.
NZASI 2022 poster

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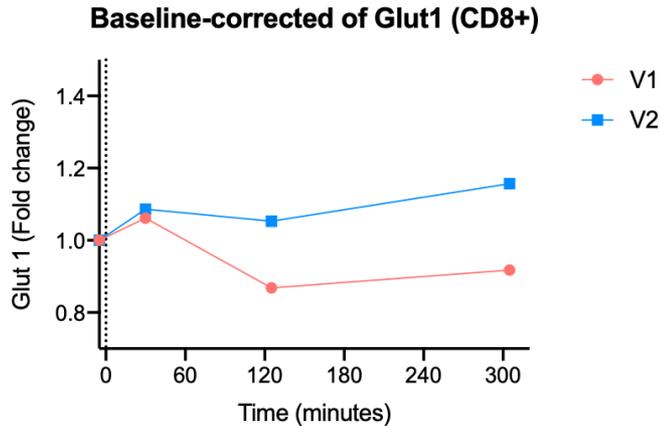
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3. Immunometabolism

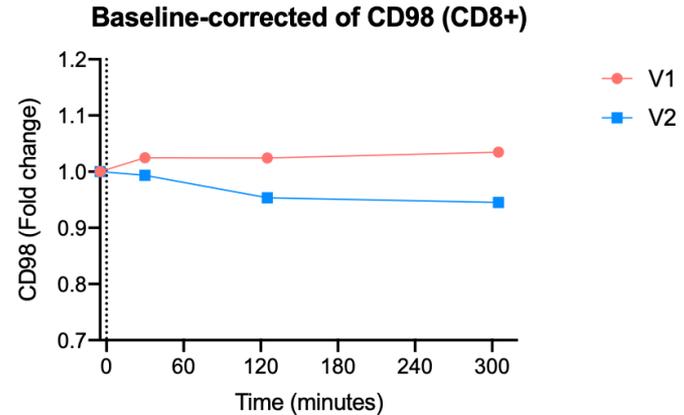
- How?

- metabolic flow cytometry: acute changes upon ingestion of equicaloric foods with different glycemic index (preliminary data; Metabolic Health PRP sample)

Glucose transporter



Amino acid transporter



O'Sullivan et al.
unpublished

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Summary

- Diet is fundamentally linked to human health via immune sensing. The underlying mechanisms are poorly understood
- The characterization of novel and specific interactions between immune receptors and dietary ligands can lead to innovation and is commercially valuable
- Compositional analyses of (your) products is very important (NZ-origin can be leveraged)
- Immune-phenotyping approaches are, and always will be, customized to the clinical outcome and the interventional product
- **!!** Receptors are not necessarily conserved across species (implications for preclinical models of disease)

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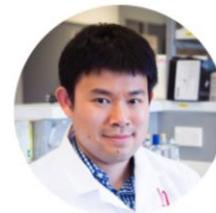
Ruby Barker-Thomson

Malaghan Core Facilities

Malaghan Fundraising



Dr David O'Sullivan



Dr Jeffry Tang

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