

Institut de
recherche
Centre universitaire
de santé McGill

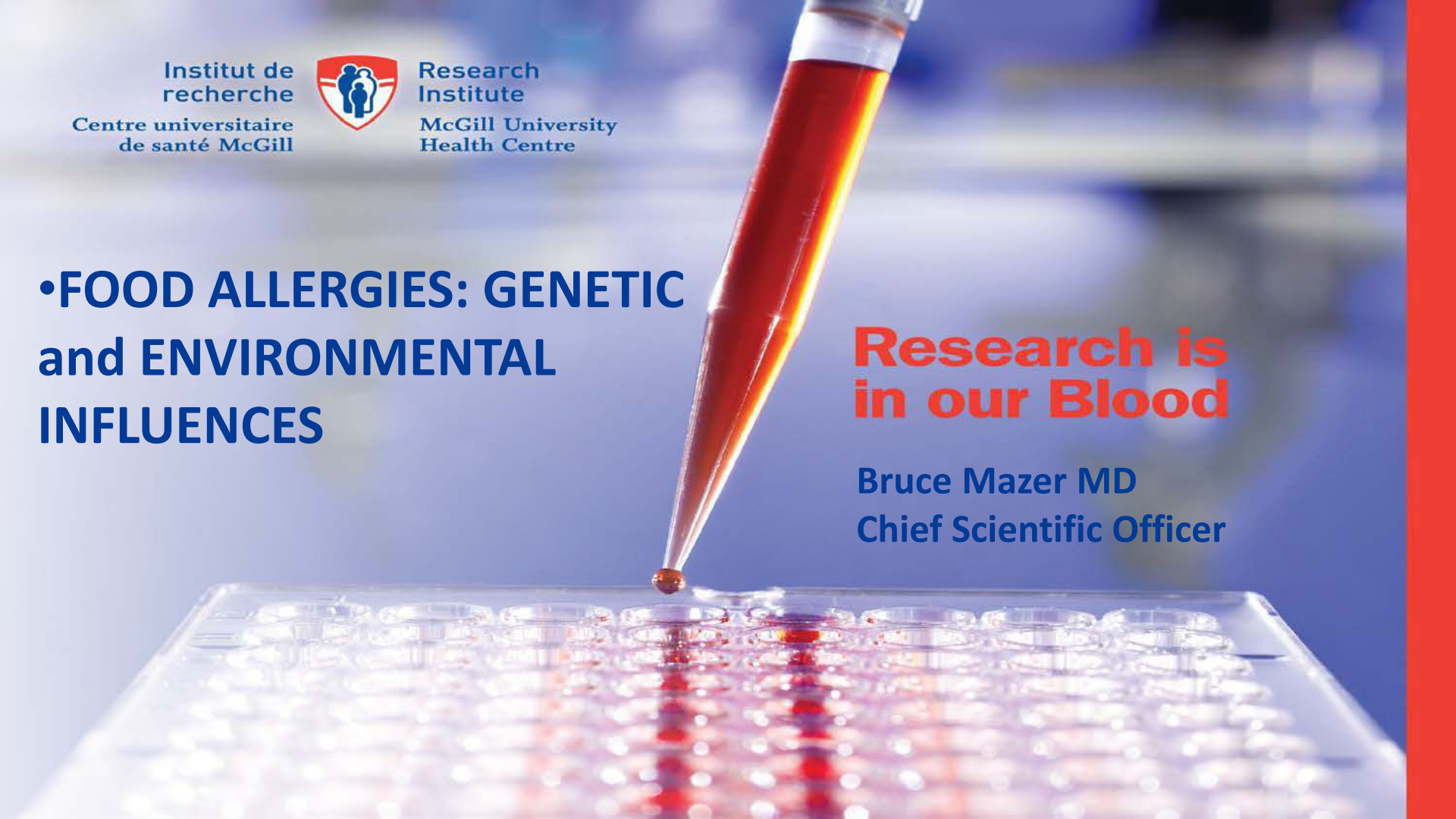


Research
Institute
McGill University
Health Centre

•FOOD ALLERGIES: GENETIC and ENVIRONMENTAL INFLUENCES

**Research is
in our Blood**

Bruce Mazer MD
Chief Scientific Officer



Disclosures

- No Conflicts of Interest to declare
- Funding for food allergy research
 - Canadian Institute for Health Research
 - Allergen-National Center of Excellence
 - Montreal Children's Hospital Foundation
- No corporate affiliations
- No contracts in food allergy



Food Allergy: A growing problem

- Food mediated chronic illness are increasingly important health issues in Western countries
- Food allergy is the atopic disease with the most rapid growth trajectory in the past 25 years
- Food allergy is divided into
 - IgE mediated food allergy
 - Non-IgE mediated food sensitivities/intolerances



IgE Mediated Food Allergy

- 2-8% of children
- Increasing in prevalence in adults
- Most common allergies are egg, milk, peanut, tree nuts, fish, shellfish, and sesame.
- IgE-Mediated food allergies are the only food related chronic illness with a risk of life threatening anaphylaxis

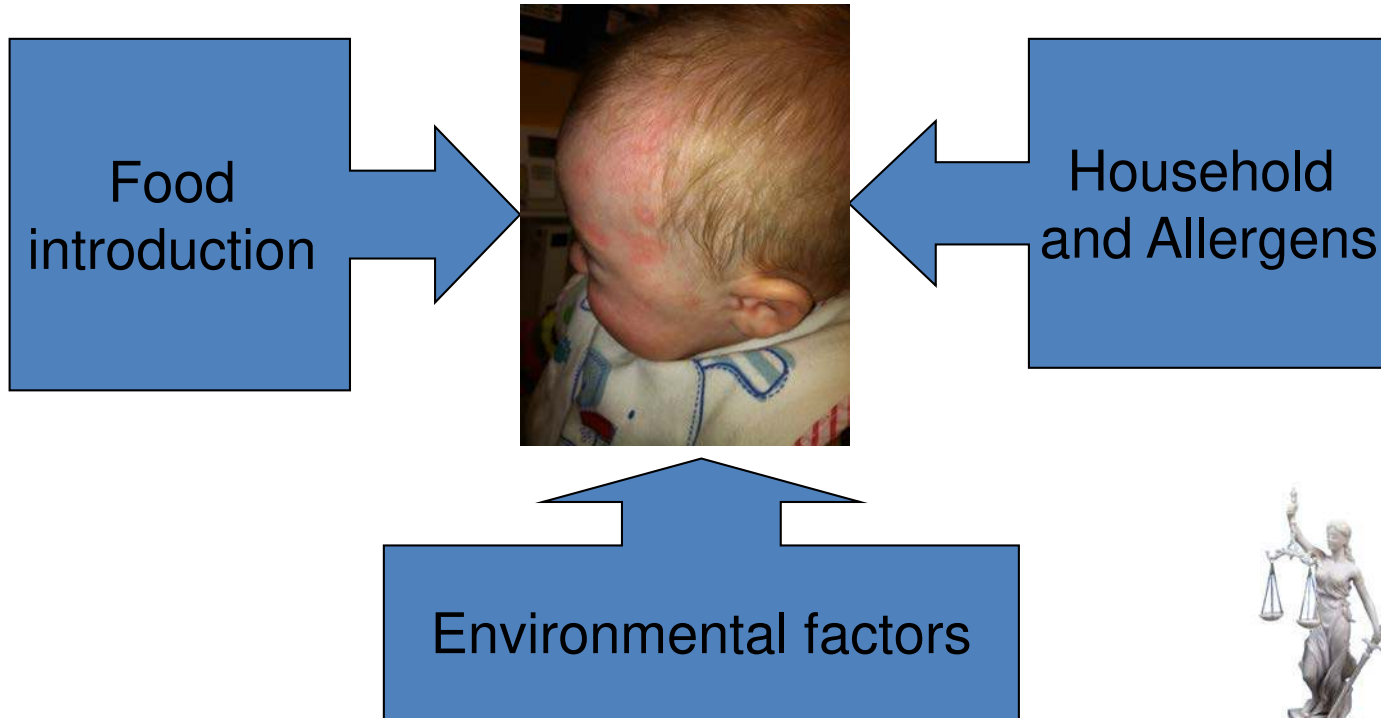


Objectives

- To understand the environmental factors that can influence food allergy
- To determine modifiable and non-modifiable environmental and genetic factors
- To review new findings in genetic risk factors for food allergy
- To understand possible mechanisms derived from new genetic findings



Environmental factors.



Environment and Food Allergy

- Aerosol allergen exposures
- Influence of the Microbiota
- Dietary exposures

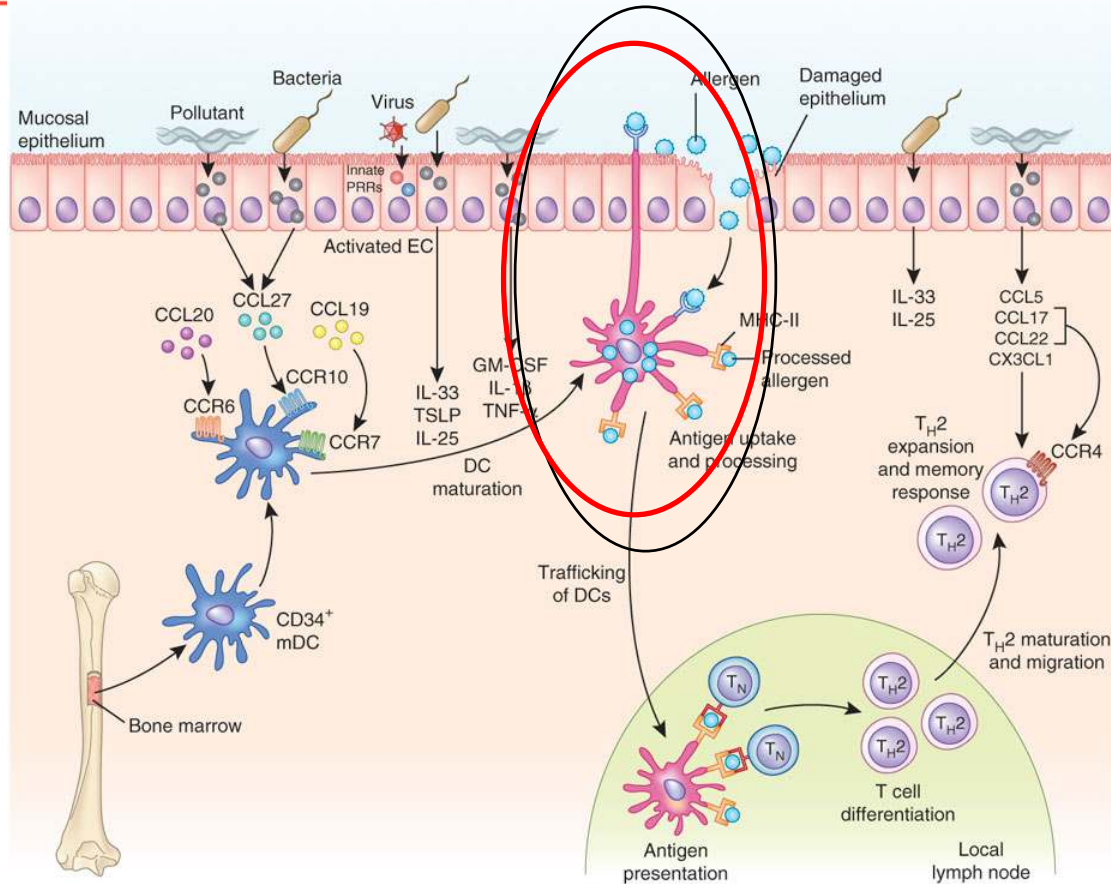


Aerosol Allergen Exposure

- Aerosol exposure via the skin or respiratory tract is a factor in development of allergic diseases
- Increased risk of food allergies in children with atopic dermatitis
- The high incidence of food allergy in children with eczema has been a major area of study



Mucosal Immune responses



Debbie Maizels



Aeroallergen exposure

- In the Health Nuts cohort in Australia, dog exposure in early life with associated with diminished food allergies
- This association has been seen for asthma as well
- Decreased sensitization if there are increased siblings in home



Aeroallergen exposure to Foods

- Egg sensitization is also linked to aerosol exposure, especially in children with poor skin barriers
- High levels of environmental peanut exposure are associated with sensitization
- Current data suggests improved outcomes in some food allergies if oral exposure is started early (between 6 and 11 months of age for egg and peanut; thus dietary exposure may decrease the risks



Influence of microbiota

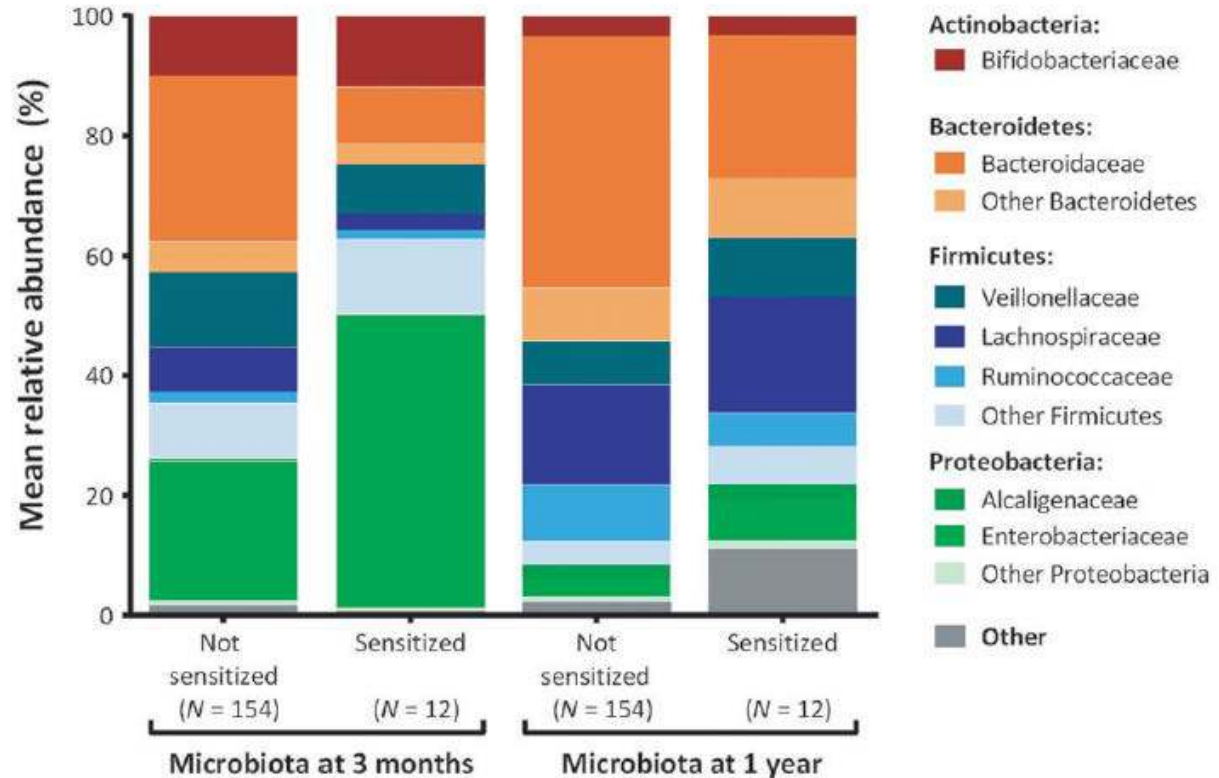
- Food Allergy is a GI problem
- Oral tolerance has been shown to be influenced by GI flora especially Clostridium species
- Few good studies
- Factors that may influence microbiota
 - Cesarean section
 - Breast feeding
 - Early maternal or child antibiotic exposure
- Results are inconsistent

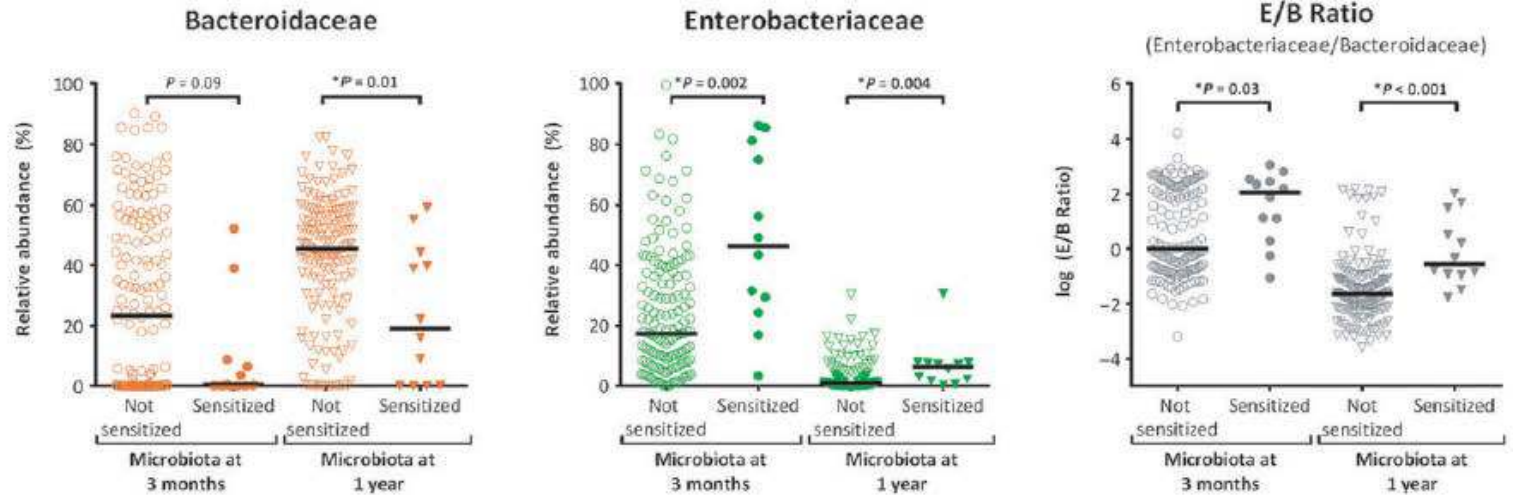


- Azad et al showed that children with food sensitization had lower GI flora richness (Chao1 score) at age three months than those who were not sensitized but this difference was not apparent at 12 months
- Small sample size (166 infants, 12 with sensitization)



(a) All infants [N = 166]





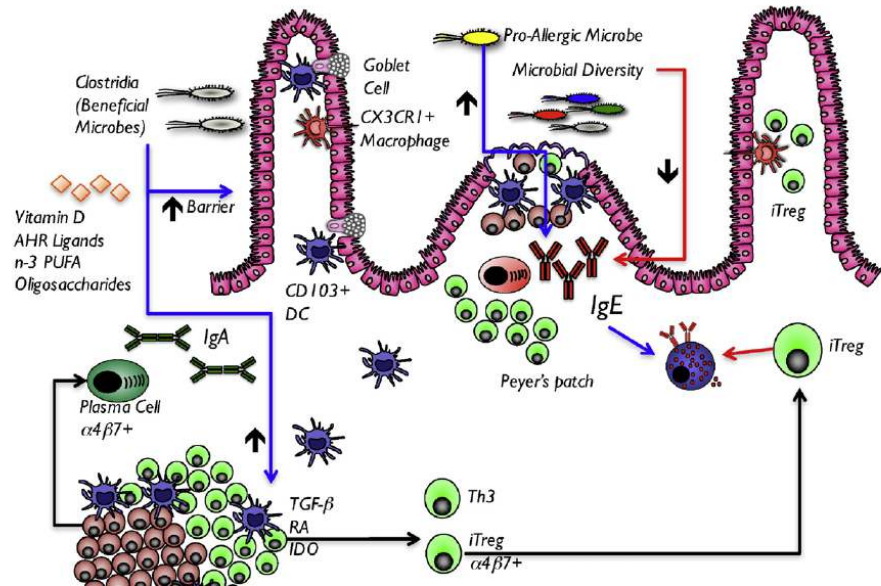
Influence of the microbiome

- Correlation with siblings and dogs?



Microbiome

- Timing may be everything!
- Difficult to study in humans
- Modifiable factors in mice may lead to better probiotics



Environmental impact on functional and immunological tolerance to foods

- Early mucosal exposures appear to influence the development of immune responses
 - Tolerance vs. Allergy?
- Timing of exposures
- Co-incident exposures: gut flora, innate immune agonists, viral infections
- Pattern recognition proteins



Genetics of food allergy

- Incidence of food allergies are increased in children of atopic individuals
- Higher concordance of food allergy in siblings
- Slowly we are finding other genetic risk factors using large population cohorts and better techniques



McGill Peanut Allergy Cohort

- Clarke, Ben-Shoshan, Asai, Daley (UBC)
- Collected data on Peanut Allergy patients (primarily Quebec and Ontario) since early 2000
- Several longitudinal studies
- Basis for genetic cohort

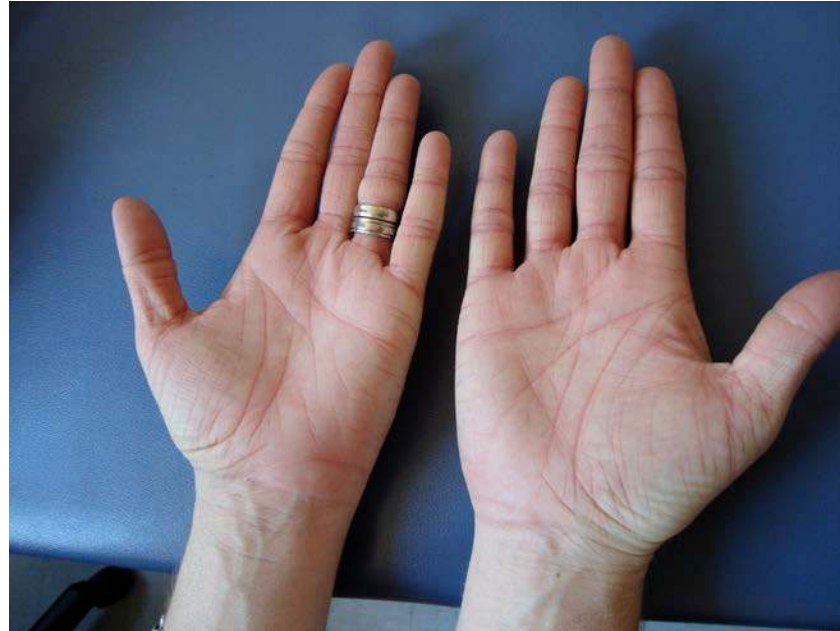


Genetics of Peanut allergy

- Highly heritable:
 - 64% concordance rate monozygous twins
 - 7% concordance rate dizygous twins
 - OR risk in relative of peanut allergy person is 6.7-13.5
- Many candidate genes proposed, but very little found



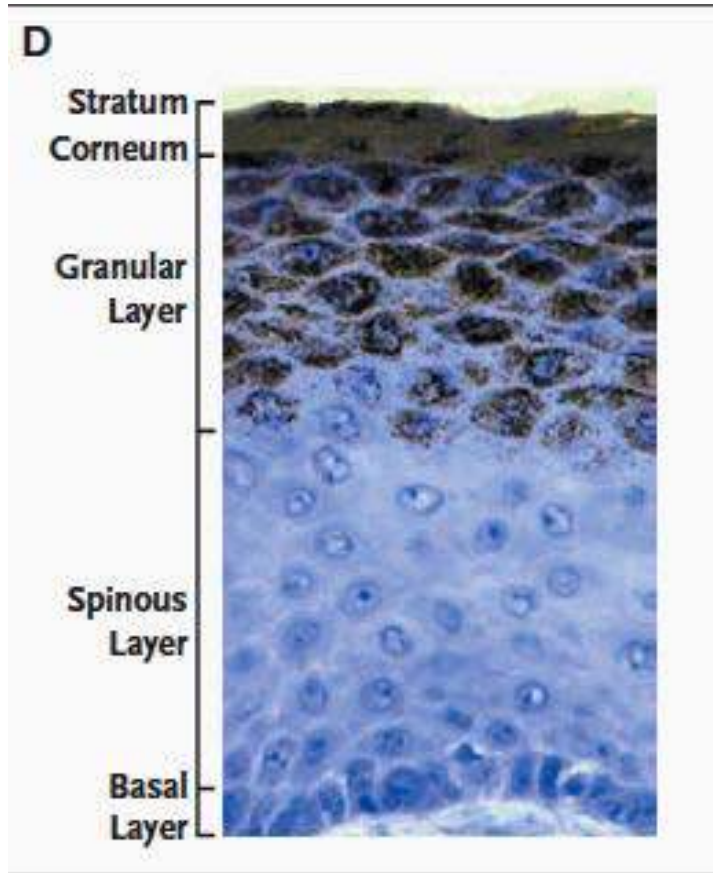
Genetic determinants of food allergy and tolerance



What genetic condition gives you very dry, very scaly skin?



Filaggrin



Filaggrin breakdown products

- become NMF (natural moisturizing factor)
- protect against staphylococcus
- Keep proteases inactive

Irvine et al, NEJM 2011



Original Study Question:

- Since *FLG* mutations are associated with many other atopic conditions, could they also be involved in peanut allergy?

Loss-of-function variants in the filaggrin gene are a significant risk factor for peanut allergy

Sara J. Brown, MD,^{a,c,d,*} Yuka Asai, MD,^{e,f,*} Heather J. Cordell, DPhil,¹ Linda E. Campbell, MSc,^a Yiwei Zhao, MD, PhD,^a Haihui Liao, MD, PhD,^a Kate Northstone, PhD,^k John Henderson, MD,^k Reza Alizadehfar, MD,¹ Moshe Ben-Shoshan, MD,^{f,1} Kenneth Morgan, PhD,^h Graham Roberts, DM,¹ Laury J. N. Masthoff, MD,^m Suzanne G. M. A. Pasmans, MD, PhD,^m Peter C. van den Akker, MD,ⁿ Cisca Wijmenga, PhD,ⁿ Jonathan O'B. Hourihane, PhD,^o Colin N. A. Palmer, PhD,^b Gideon Lack, PhD,^p Ann Clarke, MD, MSc,^{f,g} Peter R. Hull, MD, PhD,^q Alan D. Irvine, MD,^{d,r} and W. H. Irwin McLean, PhD, DSc^a *Dundee, Newcastle-upon-Tyne, Bristol, Southampton, and London, United Kingdom, Dublin and Cork, Ireland, Montreal, Quebec, and Saskatoon, Saskatchewan, Canada, and Utrecht and Groningen, The Netherlands*



Impact of the study

MailOnline



Home | News | U.S. | Sport | TV&Showbiz | Femail | **Health** | Science | Money | RightMinds

[Health Home](#) | [Health Directory](#) | [Health Boards](#) | [Diets](#) | [MyDish Recipe Finder](#)

Gene defect 'triples risk of peanut allergy in children'

By DAILY MAIL REPORTER
UPDATED: 13:43 GMT, 11 March 2011

[Comments \(11\)](#) | [Share](#) [+1](#) [0](#)

Scientists have found a gene defect which can triple the risk of a child developing a peanut allergy.

It could lead to new treatments for the most common cause of death from food aversions.

An international team, led by researchers at the University of Dundee, studied defects in the Filaggrin protein, which are carried by more than 10 per cent of people.



king up ad.uk.doubleclick.net...

CBCnews | Health

Home | World | Canada | Politics | Business | **Health** | Arts & Entertainment | Technology

Health

Peanut allergy linked to gene defect

CBC News | Posted: Mar 11, 2011 5:03 PM ET | Last Updated: Mar 14, 2011 1:38 PM ET | 32



Novel Genes in Peanut allergy

- Using target gene approaches and small populations, gathering consistent data on associations between food allergy and specific gene defects were frustrating
- More recently, evaluation of snps (Single Nucleotide Polymorphisms) and CNV (Copy Number Variations) has been more elucidative



Evidence of genes that increase the risk for food allergy

- Most work is in peanut cohorts
- **Madore et al (2013)** found an association between the *HLA-DQB1* gene and this disease
- Used a candidate gene approach but based on GWAS for asthma; however as 2/3 of the cohort with PA had asthma, this needed independent verification using larger cohorts.



Genes that increase the risk of developing Peanut allergy

- Hong et al GWAS 2015
- 2100+ cases of food allergy from Chicago Food Allergy Study
- 316 peanut allergy cases, plus 144 “hypercontrols” and 1700 “unclassified” controls
- HLA-DR and DQ on Chr 6 p21.32
- Differential DNA methylation of the HLA-DQB1 and HLA-DRB1 genes partially mediate the identified SNP–PA associations rs7192 and rs9275596



Genes in Peanut Allergy

- Peanut GWAS Martino and Ferrero 2016
- **Variance at Position 71** within the peptide-binding groove of HLA-DRB1 (replication of study) 73 patients, 148 controls



GET-FACTS GWAS (Asai, Clarke, Ben-Shoshan, Daley)

- 880 children with peanut allergy
- >1000 controls from two different sources
- Results submitted to JACI



Modifiable and Non-modifiable risk factors



What have we learned?



Health Nuts

Non-modifiable risk factors for food allergy

Having parent/s born in East Asia (compared with Australian-born parents):

OR 2.8, 95% CI 1.9-4.0

Koplin et al. Allergy 2014

Family history of allergy:

OR 1.4, 95% CI 1.1-1.7

Koplin et al. IJERPH 2013

Filaggrin loss of function mutations

OR 3.2, 95% CI 1.2-8.5

Tan et al. JACI 2012

Prenatal

Not associated with food allergy

Maternal consumption of egg during pregnancy

Koplin et al. JACI 2010

Caesarean section delivery

Koplin et al Allergy 2012

(examined for egg allergy outcome)



Potentially modifiable factors

Decreased risk: Factors associated with the 'hygiene hypothesis'
Presence of siblings: **OR 0.7, 95% CI 0.6-0.8**
Dog exposure: **OR 0.7, 95% CI 0.5-1.0**
Koplin et al. Allergy 2012

Increased risk: Later introduction of egg
(compared to at 4-6 months of age)
At 10-12 months: **OR 1.6, 95% CI 1.0-2.6**
After 12 months: **OR 3.4, 95% CI 1.8-6.5**
Koplin et al. JACI 2010

(all examined for egg allergy outcome only)

Birth

Not associated with food allergy

Duration of breastfeeding
Age at first introduction of solids
Maternal consumption of egg during breastfeeding
Koplin et al JACI 2010

Child care attendance
Cat exposure
Use of antibiotics in infancy
Koplin et al Allergy 2012

(examined for egg allergy outcome)



From Health Nuts

Potentially modifiable risk factor

Vitamin D insufficiency
OR 3.1, 95% CI 1.1-8.6
Allen et al. JACI 2013

(Among infants with Australian-born parents)

12 months

Infant eczema:
Potential risk factor (may be modifiable)
or co-manifestation

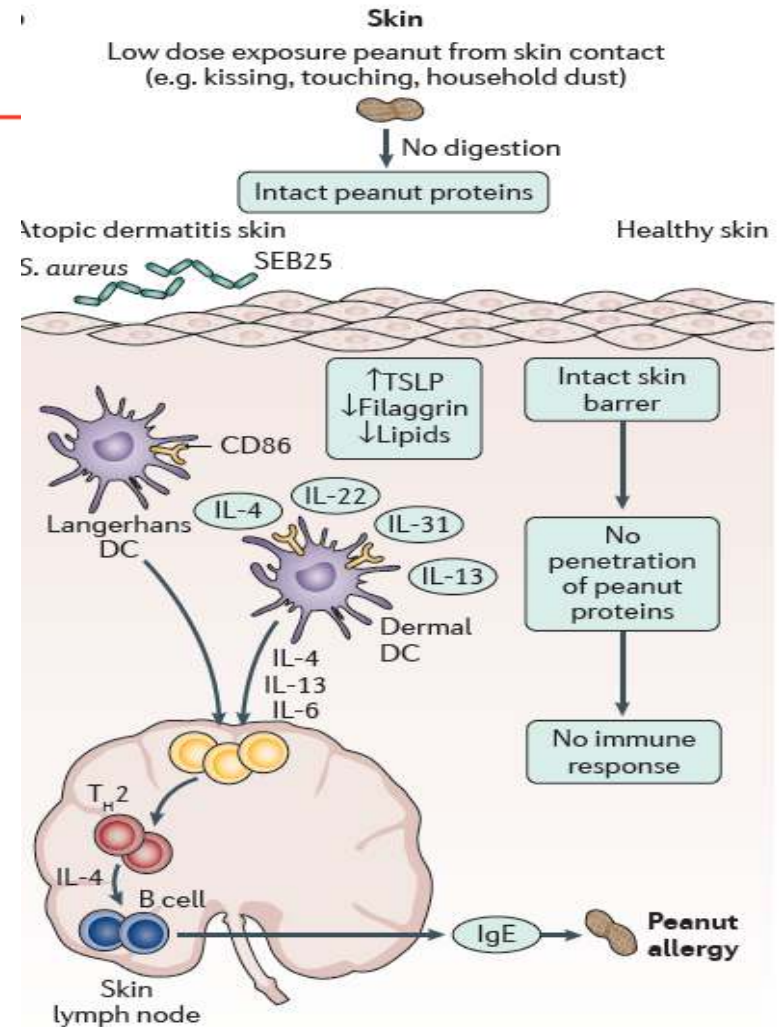
OR 6.2, 95% CI 4.9-7.9
Martin et al. CEA 2014

(Risk factors for eczema are described in Martin et al. CEA 2013)



Fillagrin and Food Allergy

- In Health Nuts, the prevalence of FLG null mutations was similar in those with asymptomatic food sensitization and those with symptomatic food allergy.



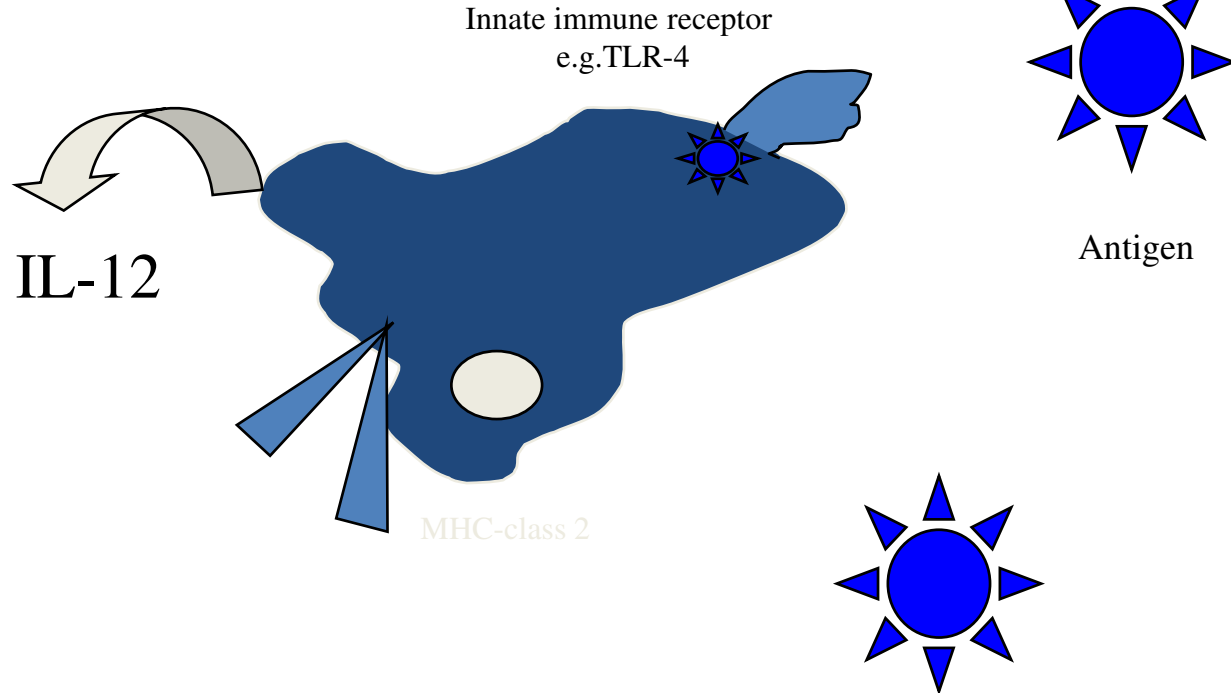
FLG and Food Allergy

- This discordance suggests that other factors might play a role in the development of true food allergy following initial sensitization to foods.

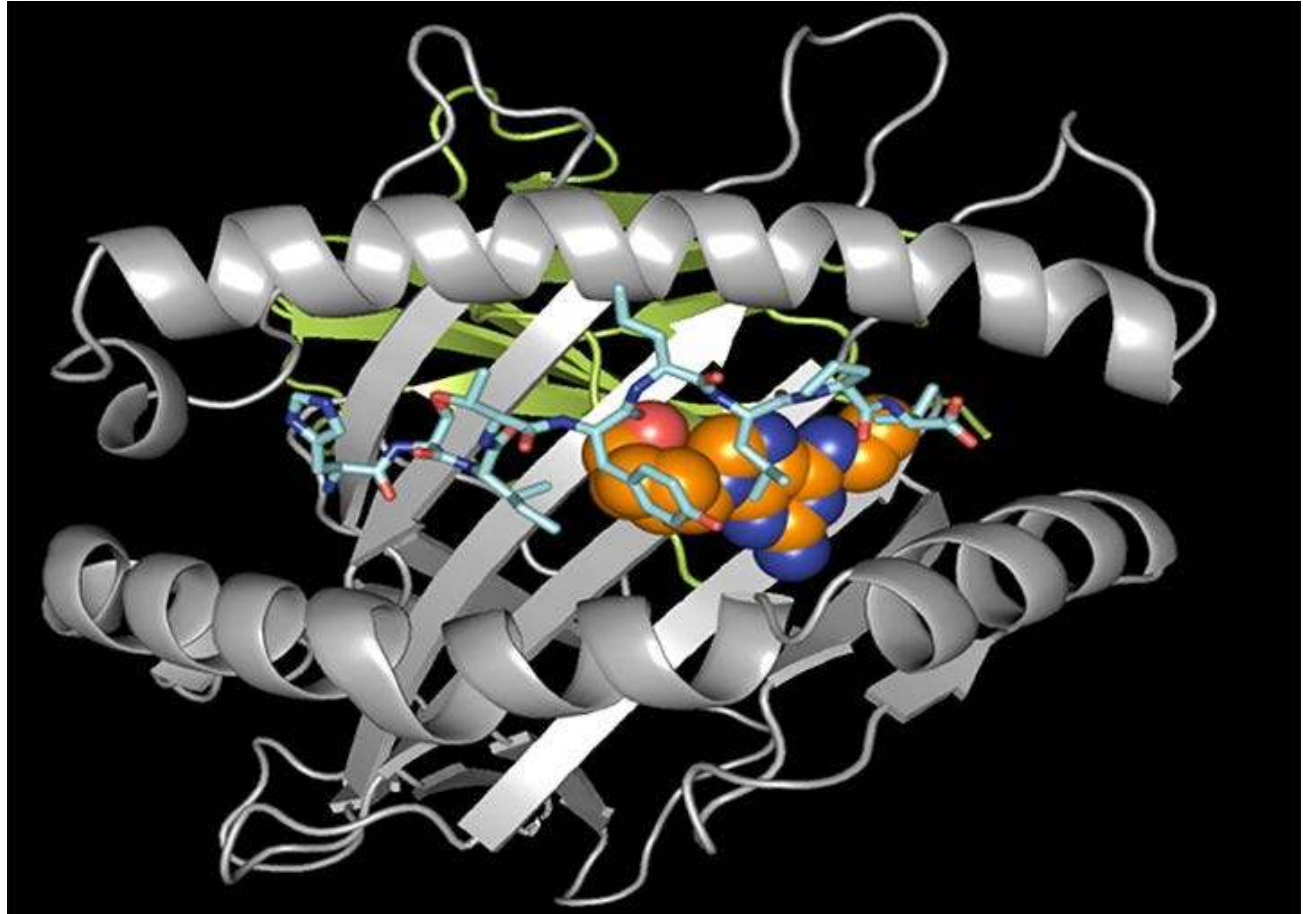


Why HLA genes? Lessons from antigen recognition and processing

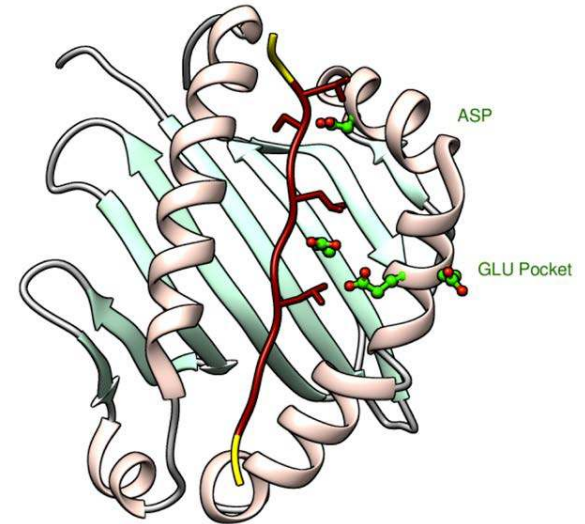
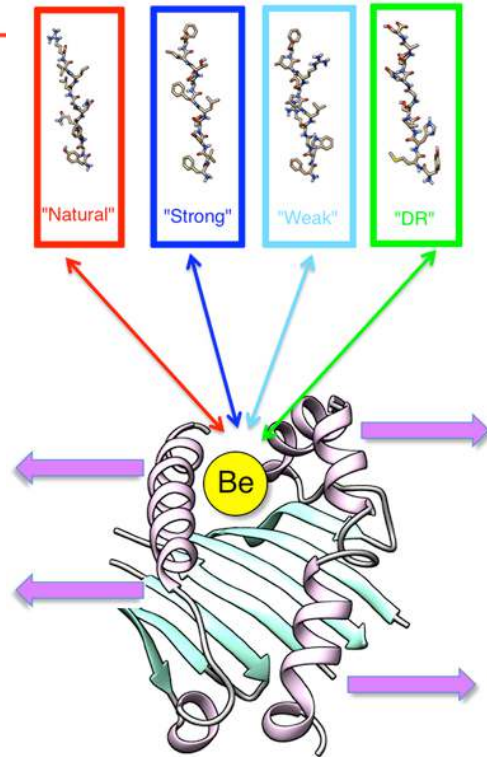
Dendritic cell



Lessons from Drug Allergy



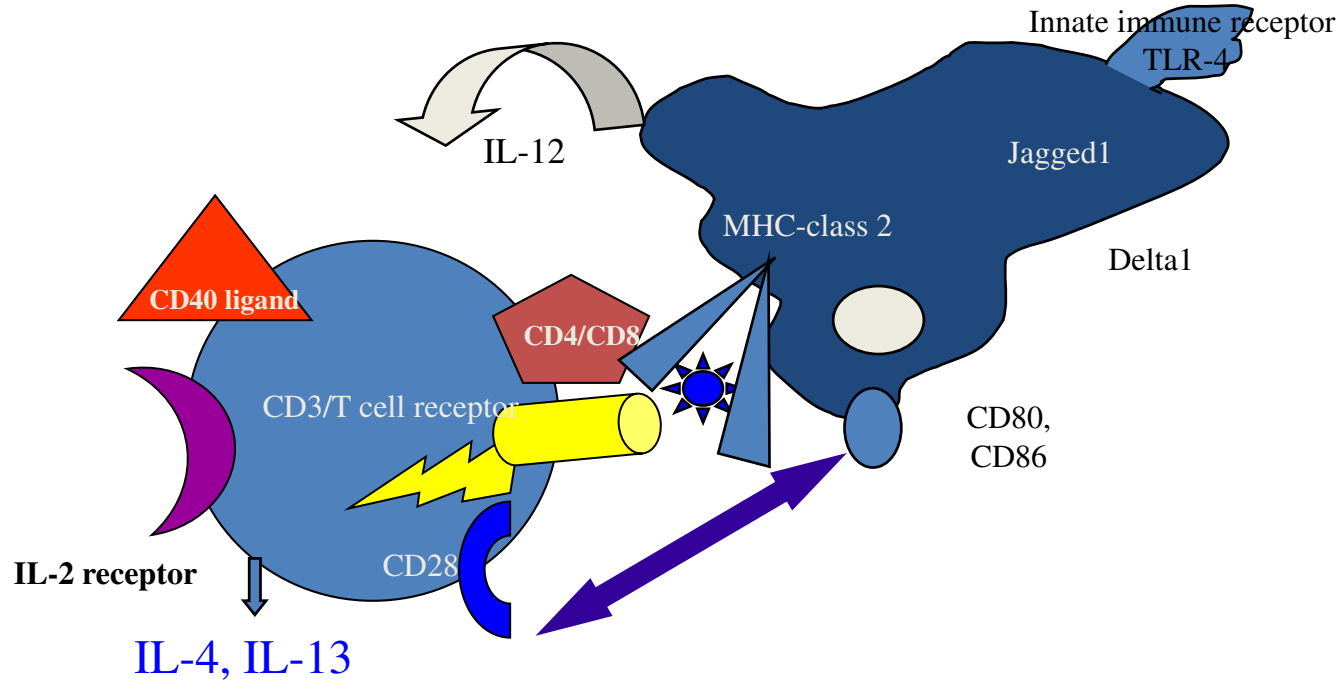
Lessons from Beryllium Sensitization



Petukh M, Wu B, Stefl S, Smith N, Hyde-Volpe D, et al. (2014) Chronic Beryllium Disease: Revealing the Role of Beryllium Ion and Small Peptides Binding to HLA-DP2. PLOS ONE 9(11): e111604. doi:10.1371/journal.pone.0111604
<http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0111604>



Antigen Presentation influences the T-cell response!



Summary and Take Home Points

- The risk food allergies may be influenced by environmental and dietary exposures
- Antigen handling and antigen presentation are important genetic risk factors
- Many of these factors, especially diet and skin barrier are modifiable
- More understanding of gut microbiota is required although the studies are complex



Is food allergy prevention possible?



Institut de
recherche
Centre universitaire
de santé McGill



Research
Institute
McGill University
Health Centre

Thank you



The Information contained in this document is proprietary to
the Research Institute of the McGill University Health Center.

©2016
Research Institute of the McGill University Health Center
All rights reserved.

