A cartoon illustration of a woman shouting "MOTHER IS ALLERGIC TO BIODIVERSITY." and a child saying "BETTER NOT TO TELL HER ABOUT THE MAGGOTS..." in a garden setting. The woman is in the foreground, shouting with her mouth wide open. In the background, a group of people are gathered around a table with a question mark above them. In the foreground, a boy is holding a net over a jar, and a girl is sitting on the ground with a jar. The scene is set in a garden with various plants and flowers.

# Gut Microbiome and Hygiene Hypothesis On Explaining Allergic Diseases

George Hui (Year 2 MPhil student)

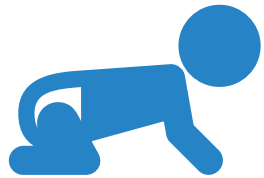
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07-12-2017

# Content

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## 1. The Birth of Hygiene Hypothesis

- Post-war allergy epidemic
- Original Hygiene Hypothesis
- Mechanisms for Hygiene hypothesis

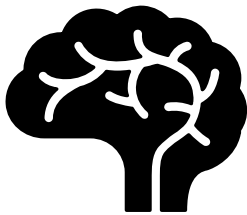
- Section One Summary
- 



## 2. Gut Microbiome and Hygiene Hypothesis

- Gut microbiome and Hygiene hypothesis
- Education in early immune system
- Immune Tolerance Overview

- Section Two Summary
- 



## 3. Conclusion

- The missing link in hygiene hypothesis
- Factors other than hygiene practices
- Summary

# Post-war Allergic Epidemic

After the second world war, allergic diseases (asthma, hay fever, food allergies) increased dramatically.

Many diseases are gone, but not allergic diseases.

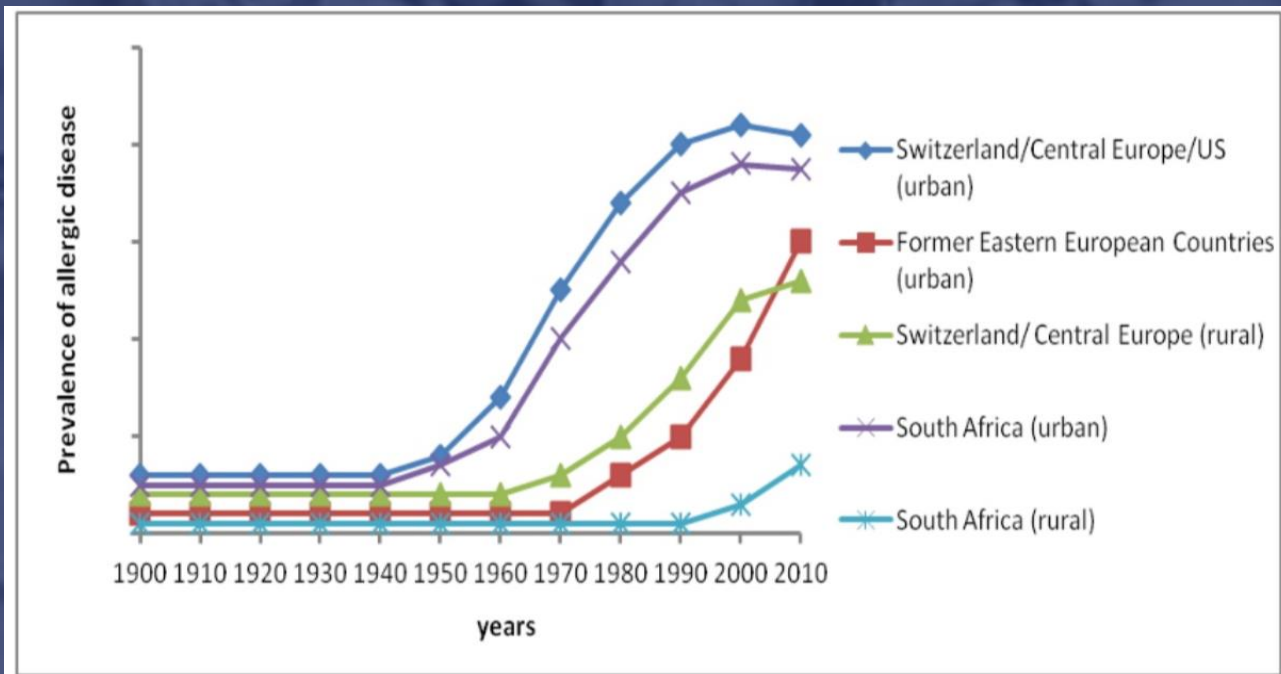
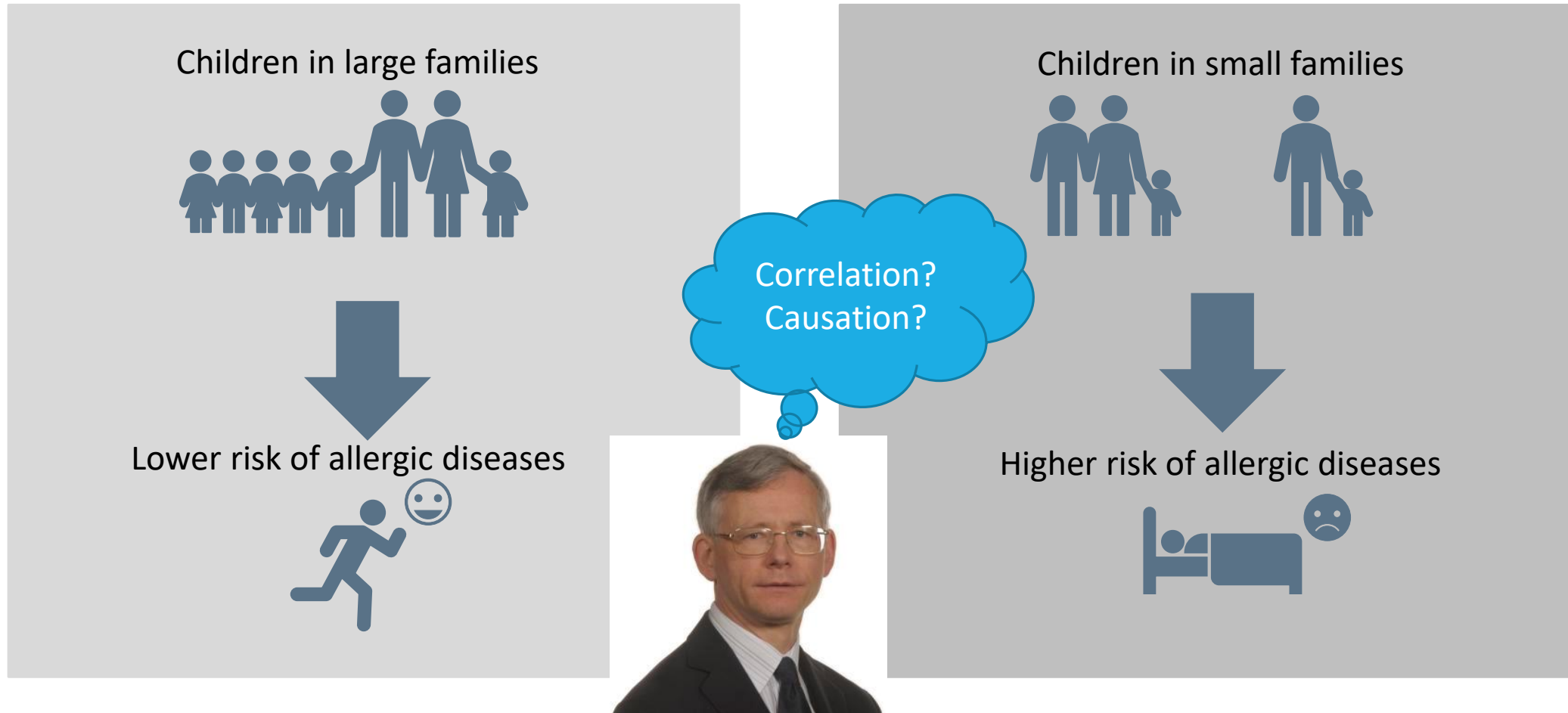


Fig 1. Allergic Diseases Prevalance between 1900 and 2010

# A Bizarre Correlation: Family Sizes And Allergic Disease

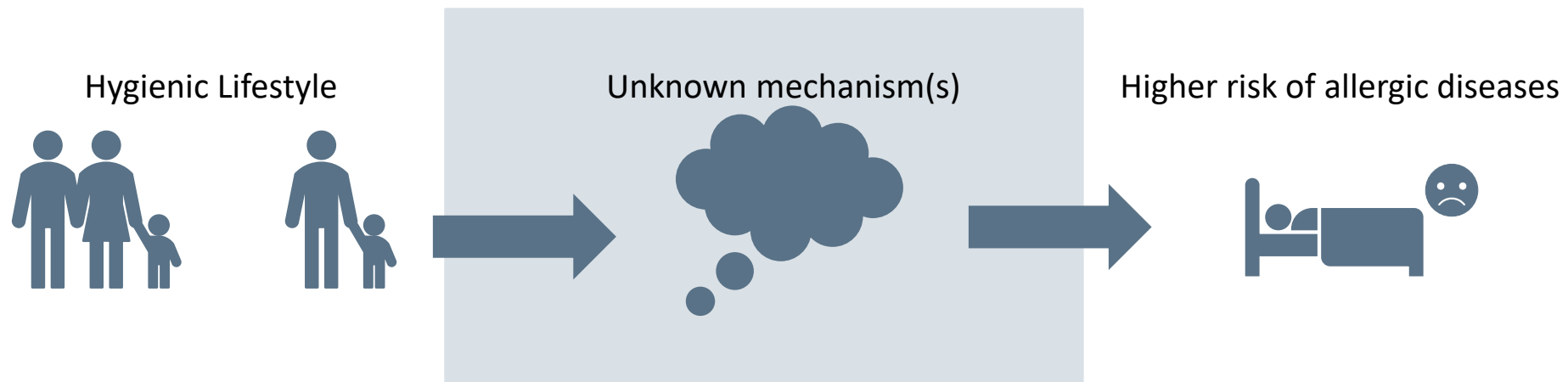


# The Birth of Hygiene Hypothesis

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- ① Smaller family, less unhygienic contact between siblings
- ② Modern homes are cleaner, personal hygiene improved
- Speculation: Both may have lead to reduced microbial burden in children

*A decreased childhood microbial exposure could be an explanation for the 20<sup>th</sup> century rise in allergic diseases”.*



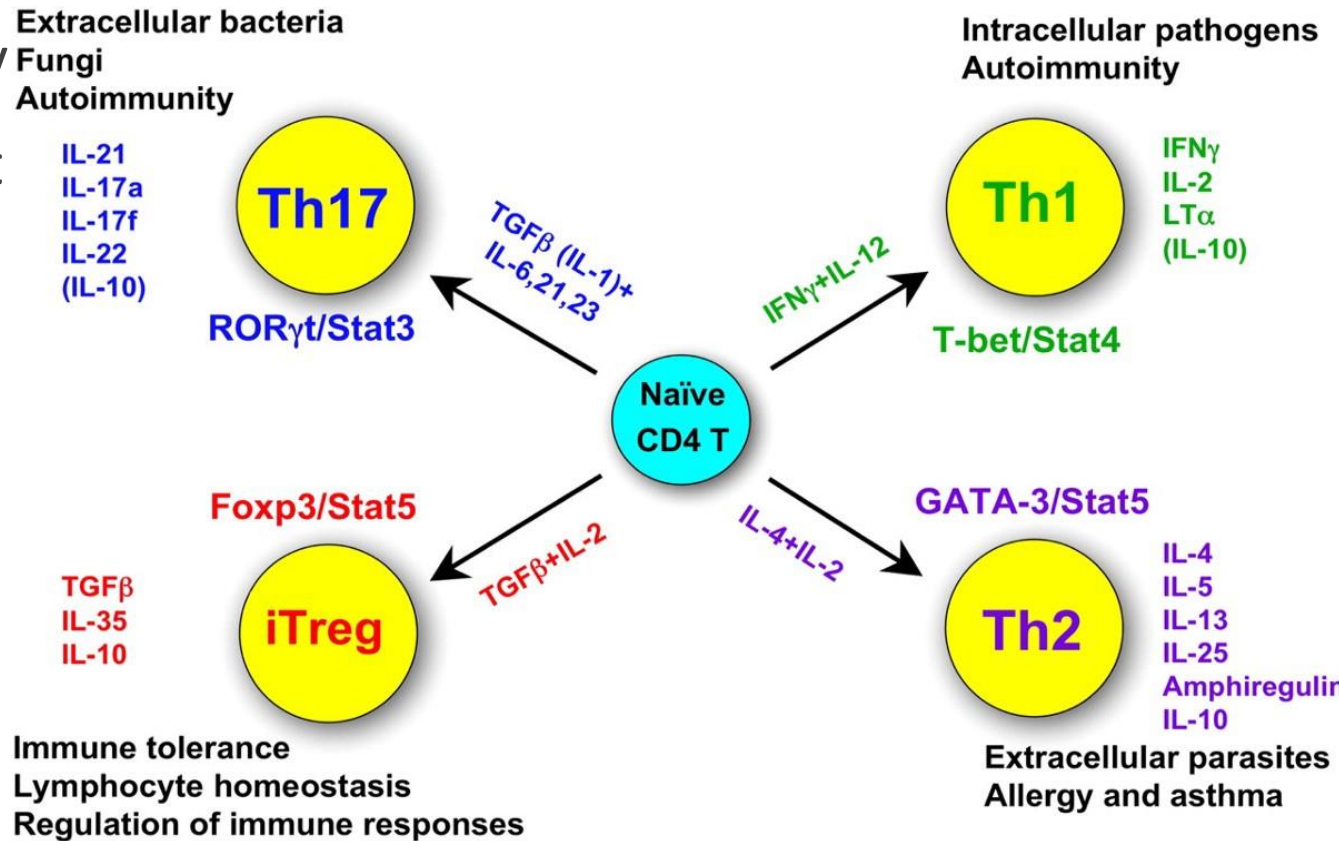
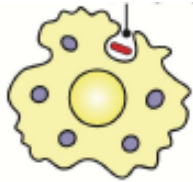
# Two Possible Mechanisms for Hygiene Hypothesis

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- ❑ Early Immunologists were skeptical, it only states an association without plausible mechanisms.
- ❑ Later, immunologists discovered two mechanisms:
  - ①  $T_H1 / T_H2$  Homeostasis
  - ② Immunoregulation through  $T_{reg}$  Cells
- Let's take a look at them

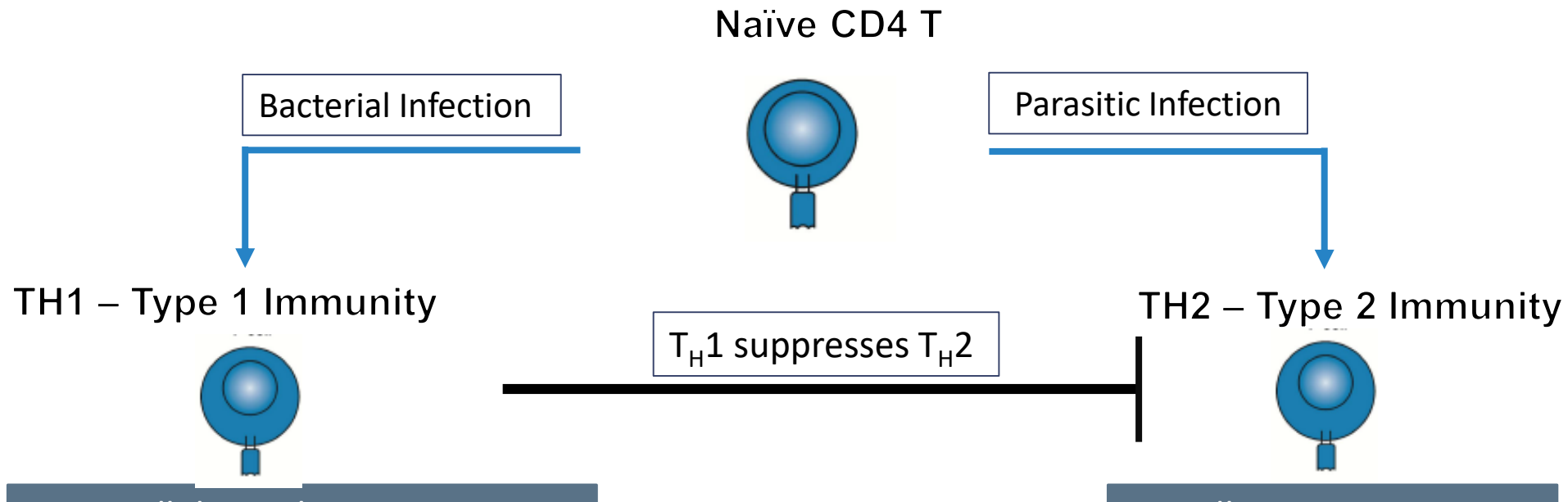
# CD4+ T<sub>H</sub> Cell Differentiation

- Cellular arm of adaptive immunity
- Different populations for different immunity
- Naïve CD4 T requires input from antigen presenting cells (APC):



# ① Loss of $T_H1$ Population

□  $T_H1$ - $T_H2$  Homeostasis /  $T_H1$ - $T_H2$  Polarization



Reduced microbial exposures lead to a loss of  $T_H1$  population, by  $T_H1$ - $T_H2$  Homeostasis,  $T_H2$  population increases and an allergic immunity profile resulted



## ② Immunoregulation through $T_{reg}$ Cells

- Natural regulatory T cells ( $T_{reg}$ ) promote tolerance towards allergens and self-antigens.

Healthy Individuals



- ①  $T_{reg}$  and  $T_H1$  dominate
- ②  $T_{reg}$  target harmless aeroantigens

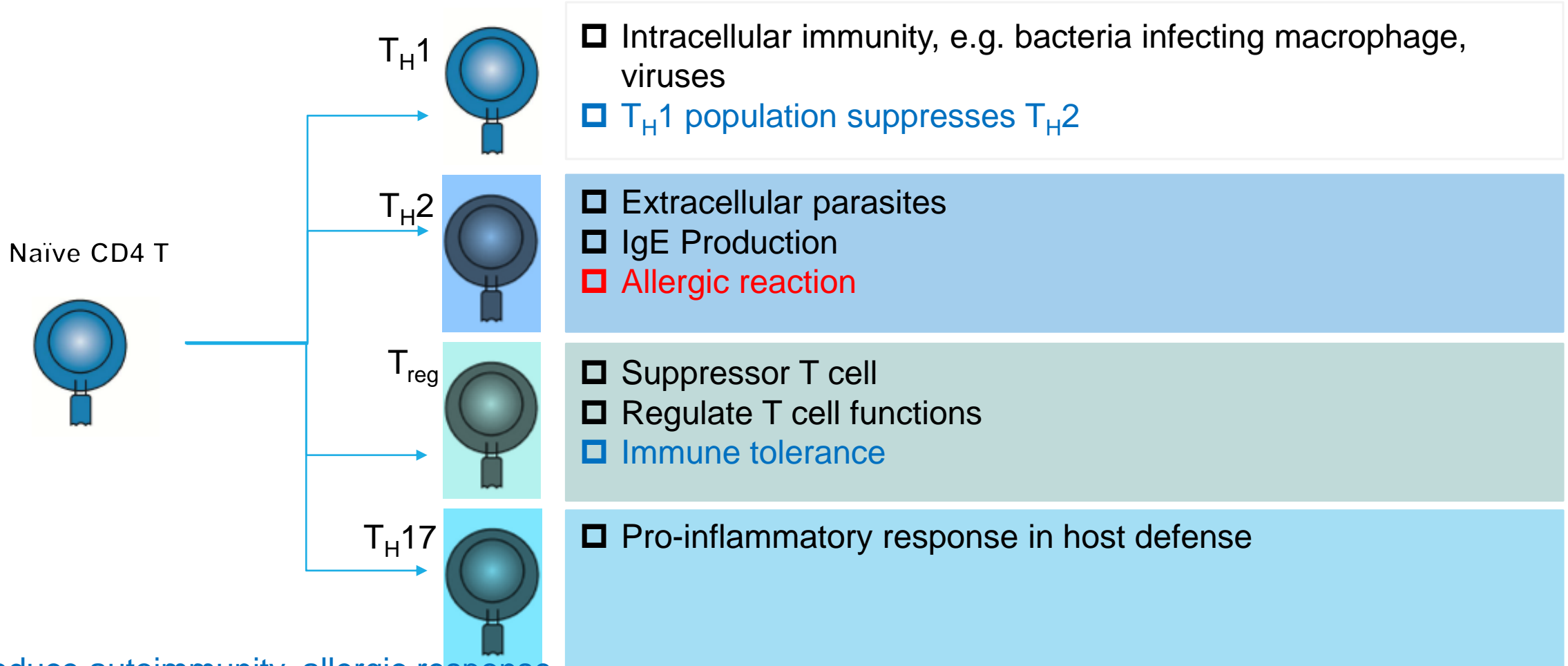
Allergic Individuals



$T_{reg}$  and  $T_H2$  population coexists  
\*\* $T_H2$  response escaped  $T_{reg}$  control

Individuals with a disruption in  $T_{reg}$  populations are prone to allergy

# Quick Summary on CD4+ T<sub>H</sub> Lineage

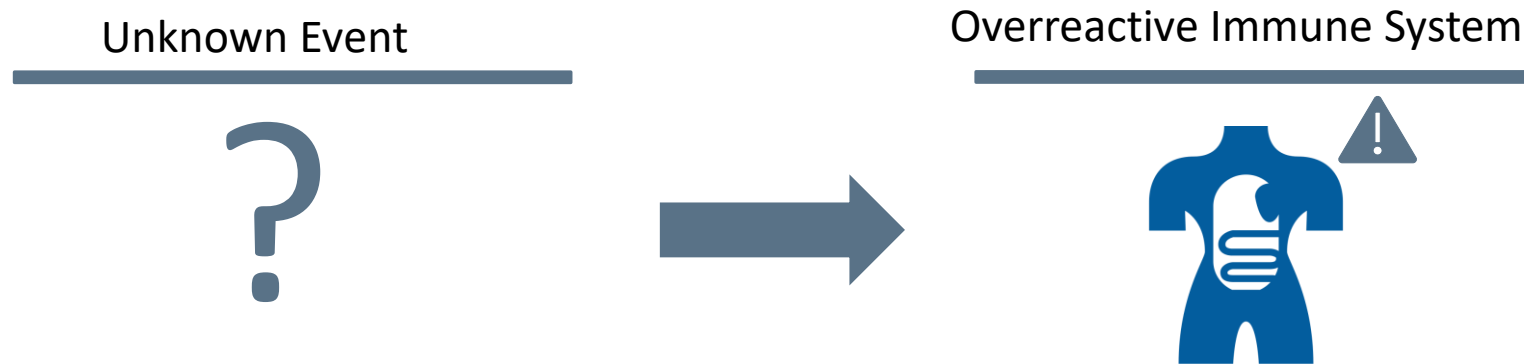


- ☐ Reduce autoimmunity, allergic response
- ☐ Promote auto immunity, allergic response

# What Triggered Our Immune System

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- From above, allergies are a result from a maldeveloped immune system.
- But how may this overreactive immune system exist in the beginning?



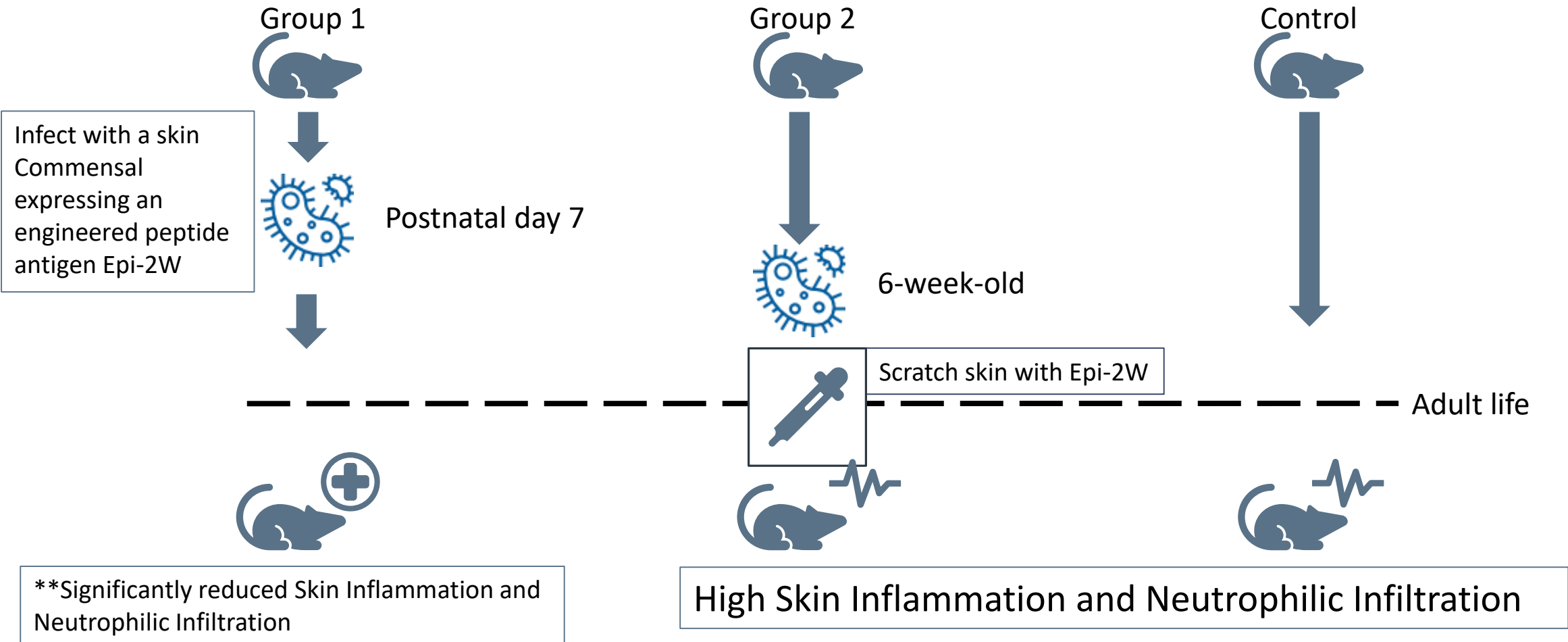
# Gut Microbiota Predicts Allergy

- Intestinal microbiota could be biomarkers in allergic diseases
- Among allergic individuals' gut microbiota:
  - Smaller diversity of bacteroidetes
  - Larger diversity of clostridiaciae

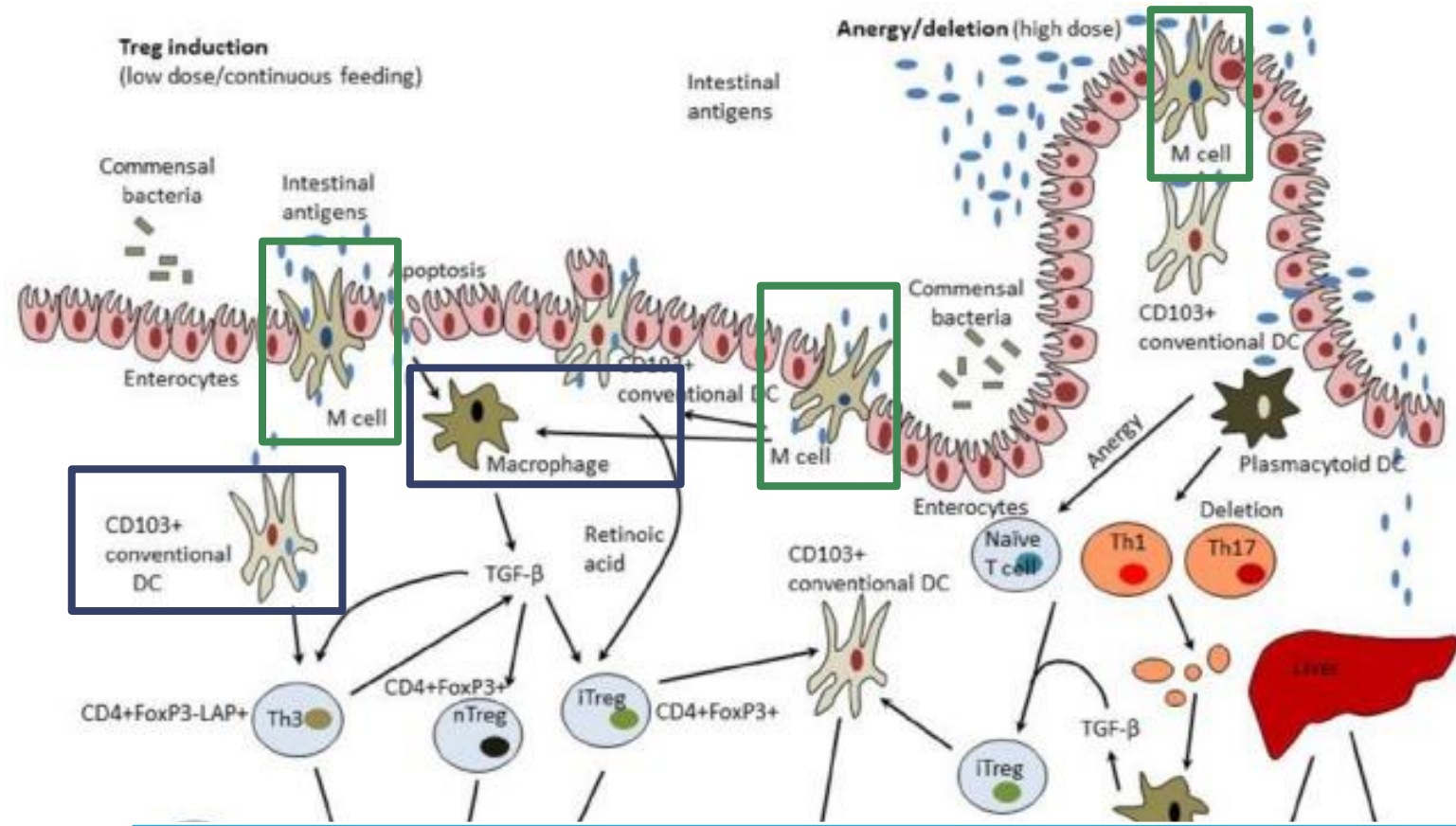


Gut microbiota change is linked to allergy

# Immune System Needs To Learn Through Microbiota



# An Interface: Mucosa-Associated Lymphoid Tissue



Microfold (M) cells:  
 □ Transfer of colon material from gut lumen to cells of immune system

Antigen presenting cells (APCs):  
 □ Dendritic cells (DCs), Macrophages  
 □ Performs phagocytosis  
 □ Present antigen to lymphocytes

Immune system learns what to tolerate and what not to at MALT



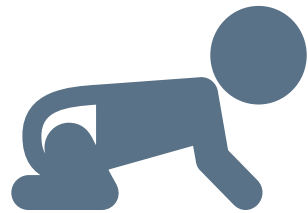
# Reduced Microbial Diversity in Gut May Leads to Overreactive Immune System

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- Chronic microbial exposure is required to induce immune tolerance during early childhood
- Hence, reduced microbial exposure in early childhood may lead to an overreactive immune system.

Reduced Microbial Exposure

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Overreactive Immune System

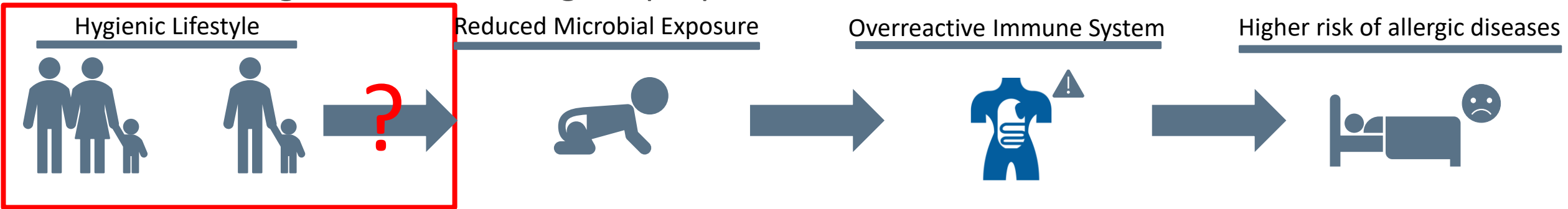
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# The Final Puzzle – Hygienic > Microbial Exposure

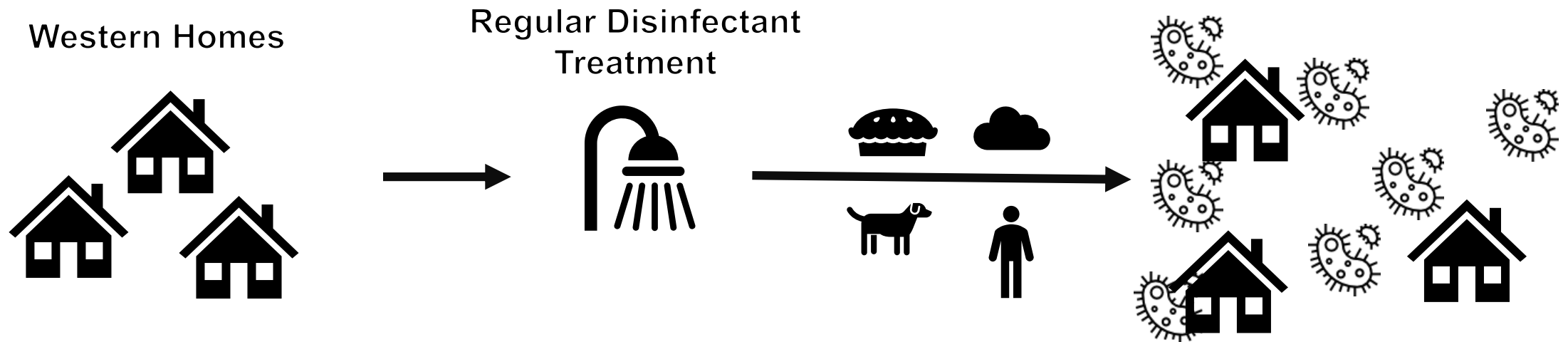
① Let's go back to the original proposal from Dr. Strachan:



- ① Smaller family, less unhygienic contact between siblings
- ② Modern homes are cleaner, personal hygiene improved

Modern homes = Cleaner, more hygienic?

# Domestic and Personal Hygiene

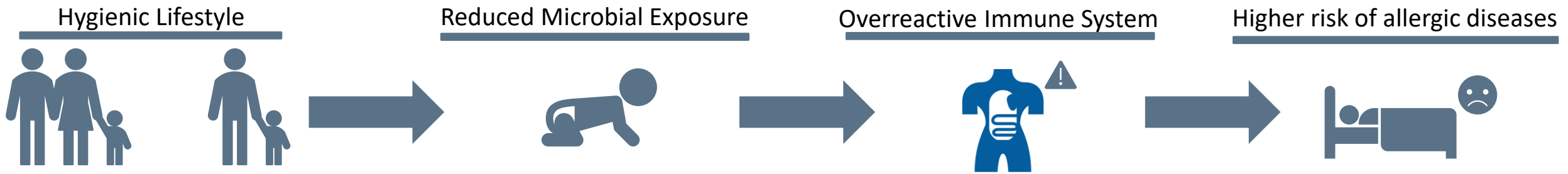


- Bacterial Contaminants repopulate western homes very soon (~ half an hour)
- Regular or irregular use of disinfectants in homes is unlikely to reduce bacterial contaminants for long period

“Sterile” environment cannot be created easily in home, modern homes are “teeming with microbes”

# Hygiene Hypothesis Is Still Under Debate

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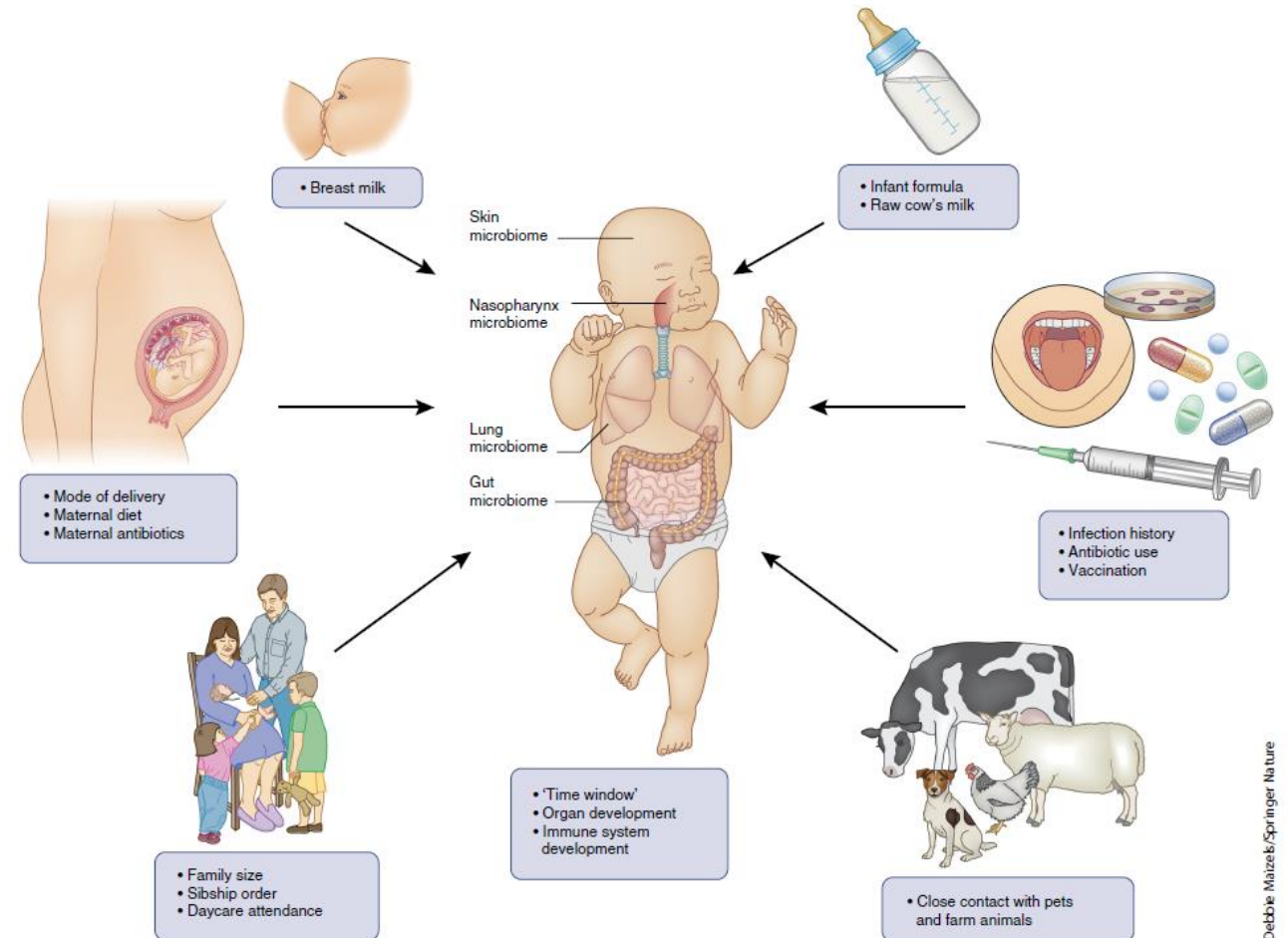


- Having a more “hygienic lifestyle” may not be indicative of reducing microbial burden
- We have a better understanding from reduced infectious pressure to higher allergy prevalence, many immunologists skewed towards the “Old friend hypothesis”.

# Factors other than “Hygiene”

- ① Mode of delivery
- ② Domesticated animals/pets
- ③ Antibiotic use in early childhood
- ④ Diet etc.

All have major influence on microbial burden and alternation in microbiota

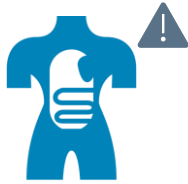


# Conclusion

Reduced Microbial Exposure



Overreactive Immune System



Higher risk of allergic diseases



Hygiene hypothesis  
Childhood microbial exposure offer protection to allergic diseases

Hygiene hypothesis Mechanism  
①  $T_H1 / T_H2$  Homeostasis  
② Immunoregulation through  $T_{reg}$  Cells

Immune Tolerance  
① When - Childhood  
② Where - MALT

Allergic Disease  
① Hygiene lifestyle  $\neq$  reduced microbial burden  
② Multiple factors

# Q&A

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# Can $T_H1$ - $T_H2$ Homeostasis Explains Hygiene Hypothesis?

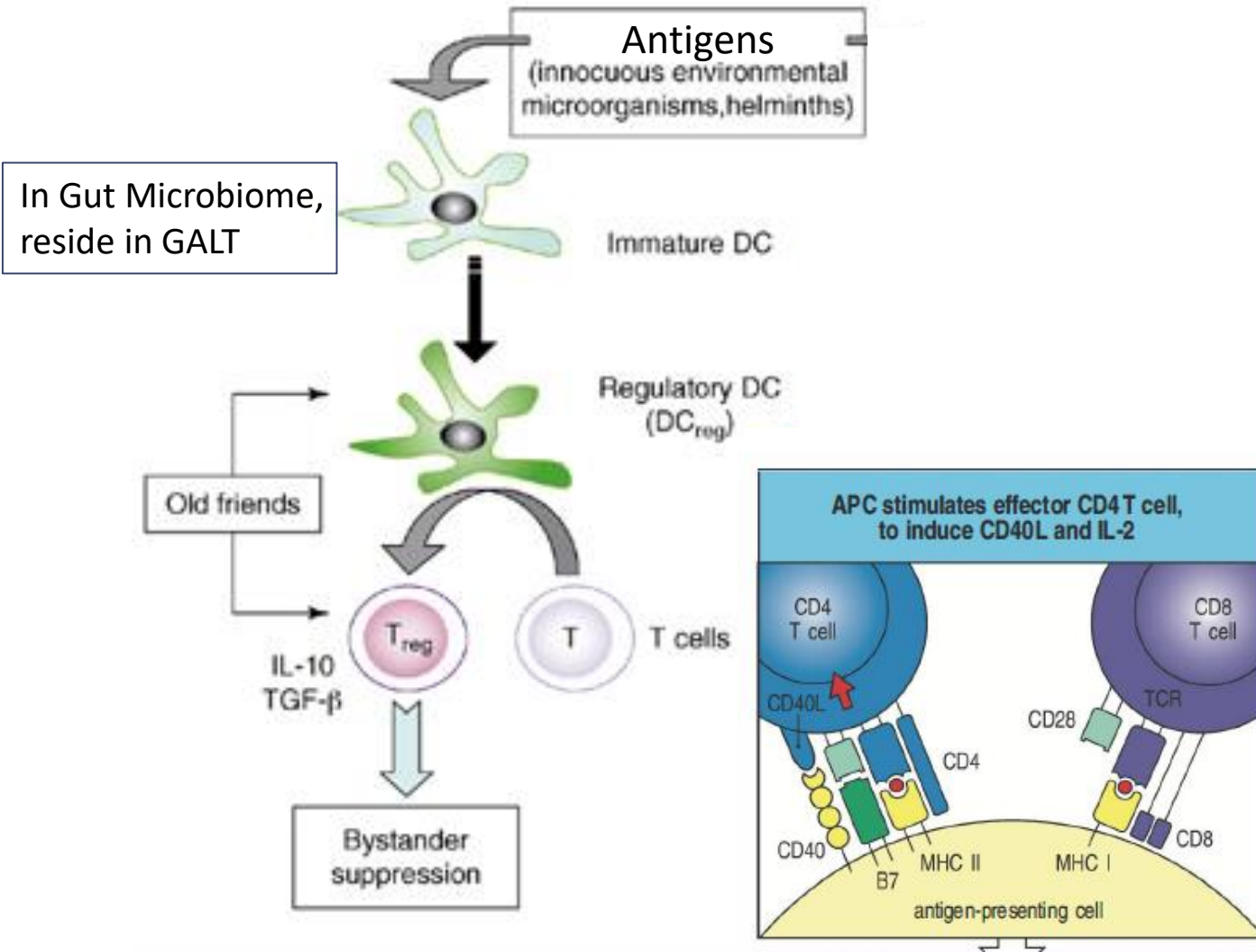
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As simple as the  $T_H1$  counterbalance might be, the following observation seem to be contradictory:

- ① Among healthy individuals, allergen-specific  $T_H1$  population is not particularly dominant.
- ② Parasite infections which triggers  $T_H2$  immunity are protective to allergic disease too.

It seems unlikely that loss of  $T_H1$  alone is responsible for the allergic response

# Immune tolerance Relies on DC<sub>reg</sub>



DC<sub>reg</sub> picks up allergens

↓

Present antigens to T cells

↓

Allergen specific T<sub>H</sub>1 and T<sub>reg</sub> inhibits T<sub>H</sub>2 response

↓

Allergic response is a suppressed/avoided