

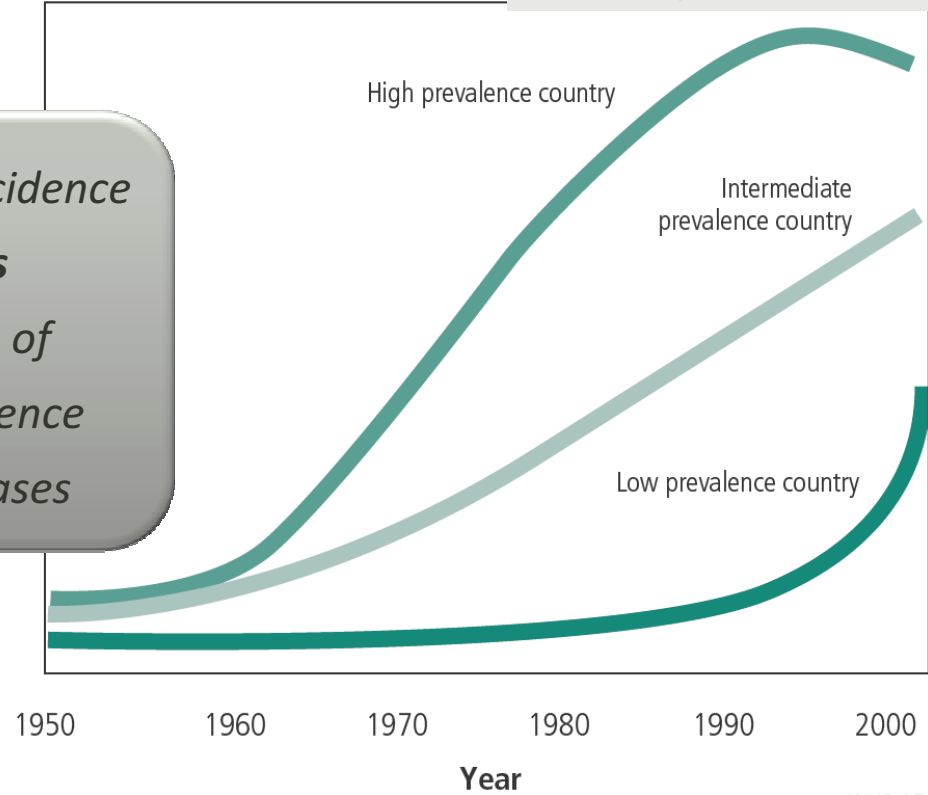
DP STRACHAN, HR ANDERSON, JM BLAND, C PECKHAM

Asthma as a link between chest illness in childhood and chronic cough and phlegm in young adults

Br Med J (Clin Res Ed) 1988; 296(6626): 890–893

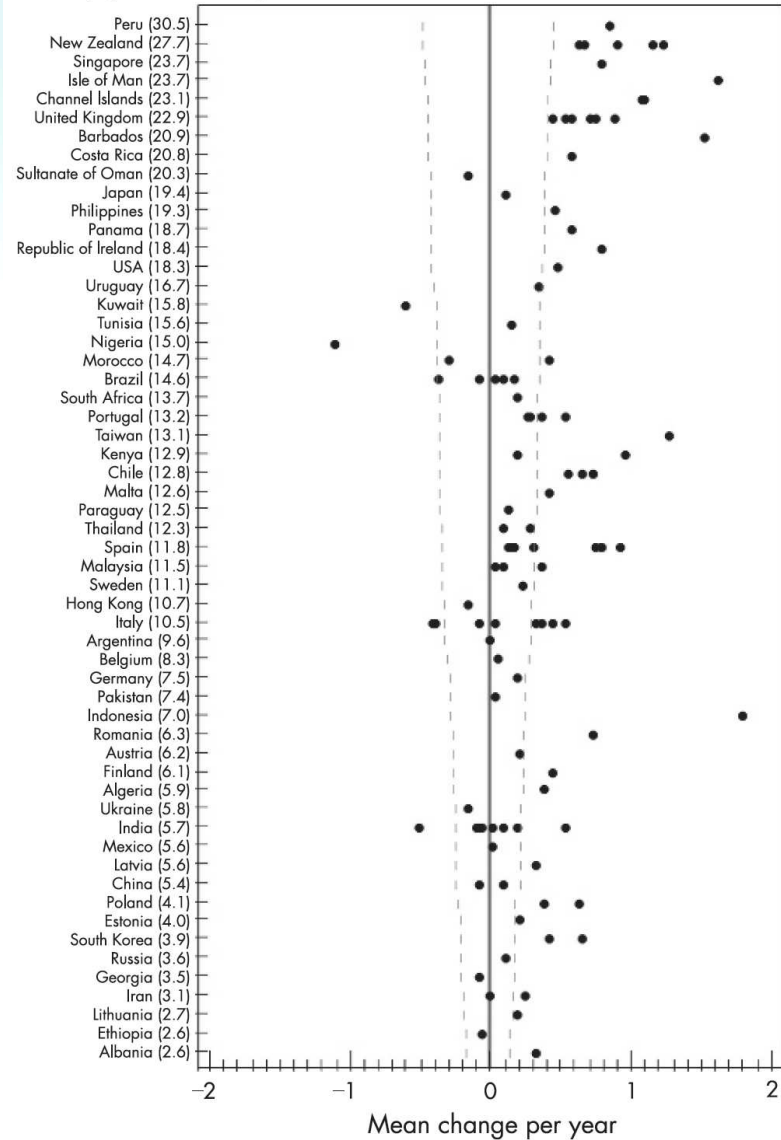
Trends in prevalence of asthma

*The decreasing incidence
of infections
is at the origin of
increasing incidence
of allergic diseases*



WHO 05.62

Country (prevalence %)

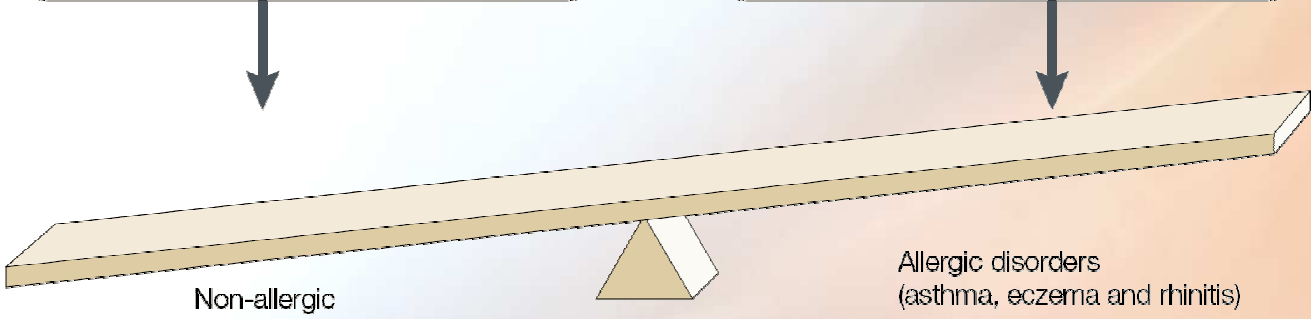


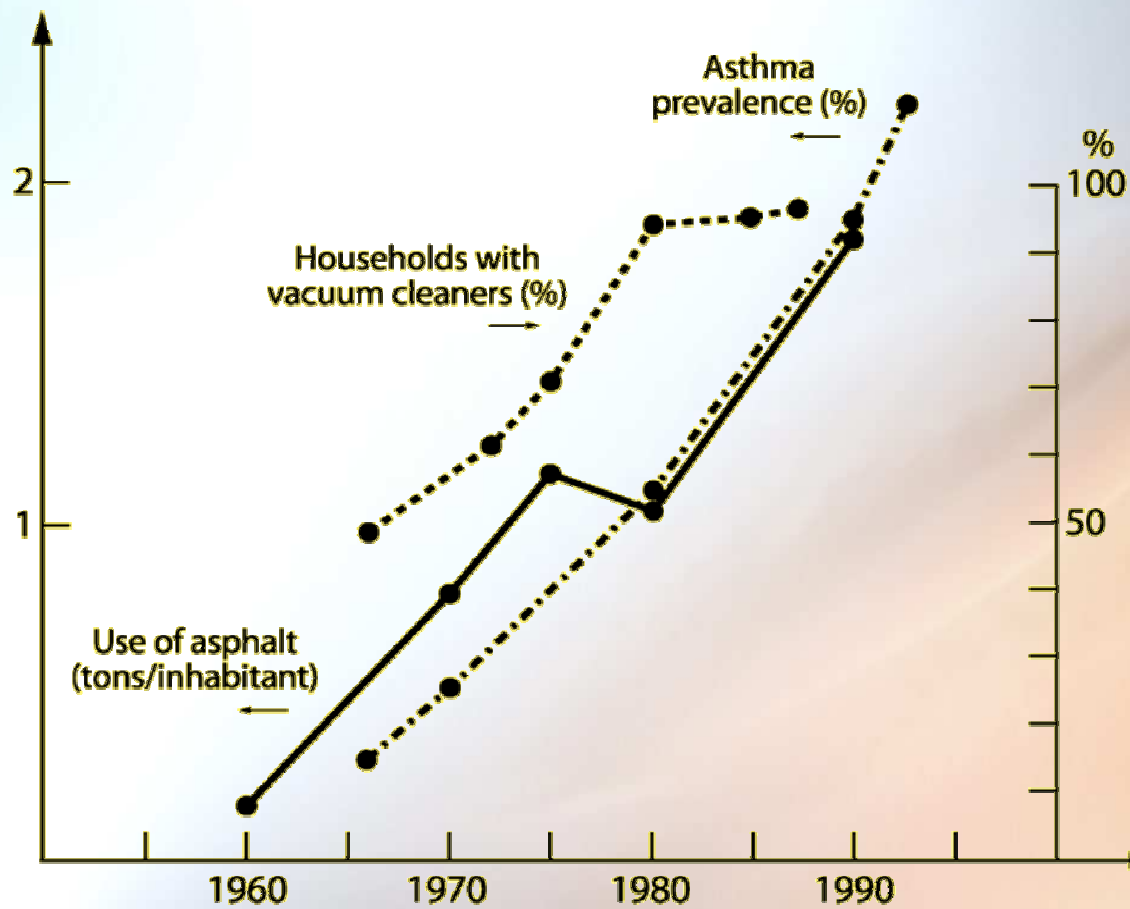
International Study of Asthma and Allergies in Childhood

The phase I survey was repeated after an interval of 5–10 years (phase III) in 106 centres in 56 countries in children aged 13–14 years (n = 304 679) and in 66 centres in 37 countries in children aged 6–7 years (n = 193 404)

'Developing' countries
Large family size
Rural homes, livestock
Intestinal microflora-variable, transient
Low antibiotic use
High helminth burden
Poor sanitation, high orofaecal burden

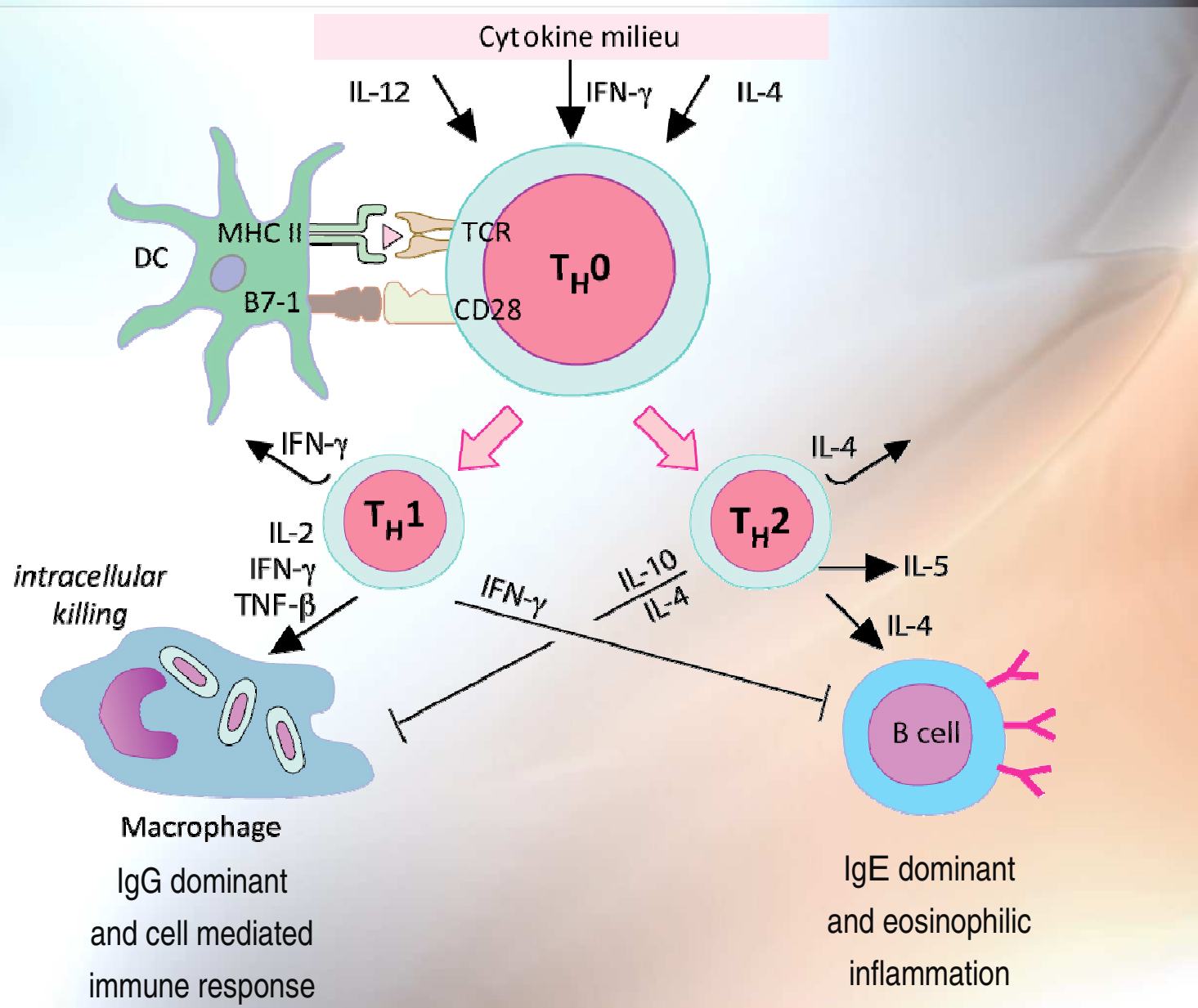
'Westernized' countries
Small family size
Affluent, urban homes
Intestinal microflora-stable
High antibiotic use
Low or absent helminth burden
Good sanitation, low orofaecal burden





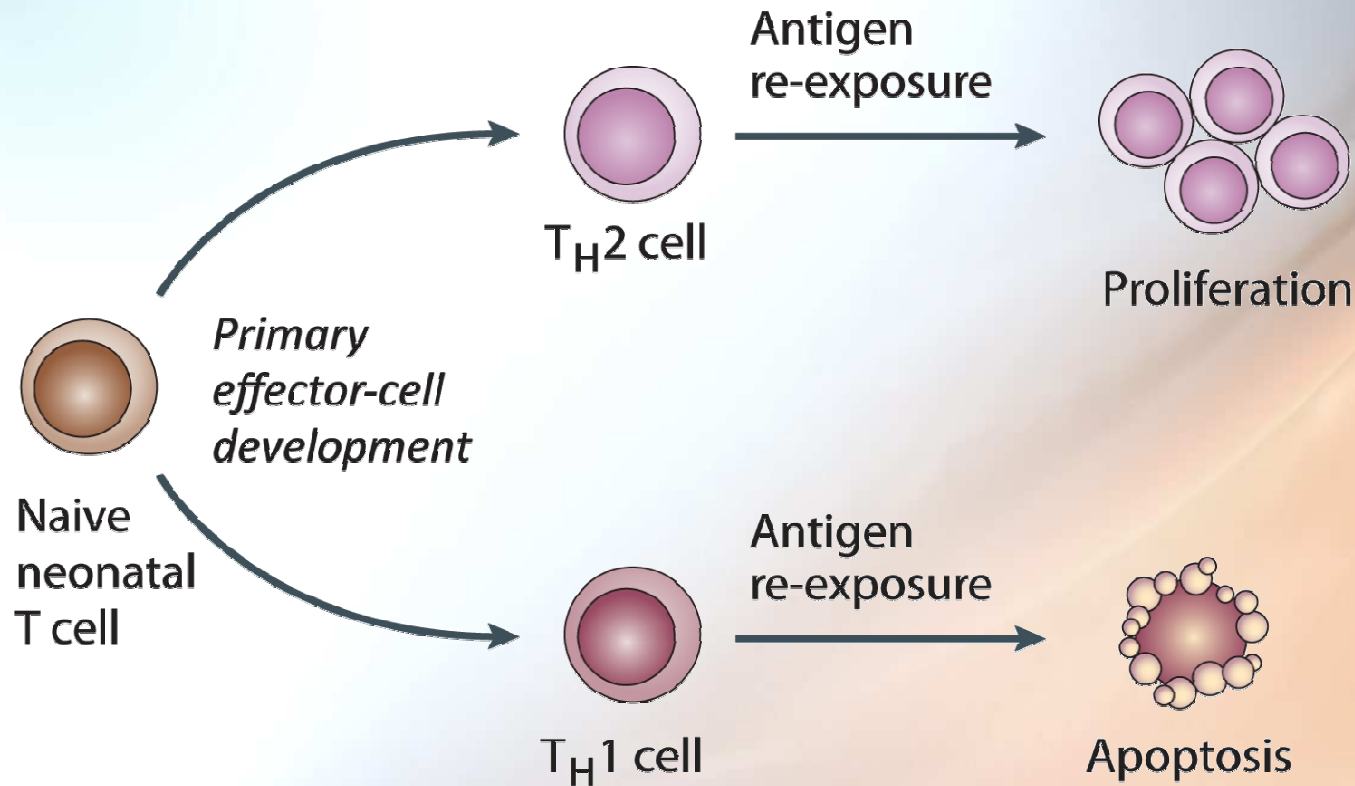
Finnish Allergy Programme 2008–2018

The T_H1/T_H2 paradigm



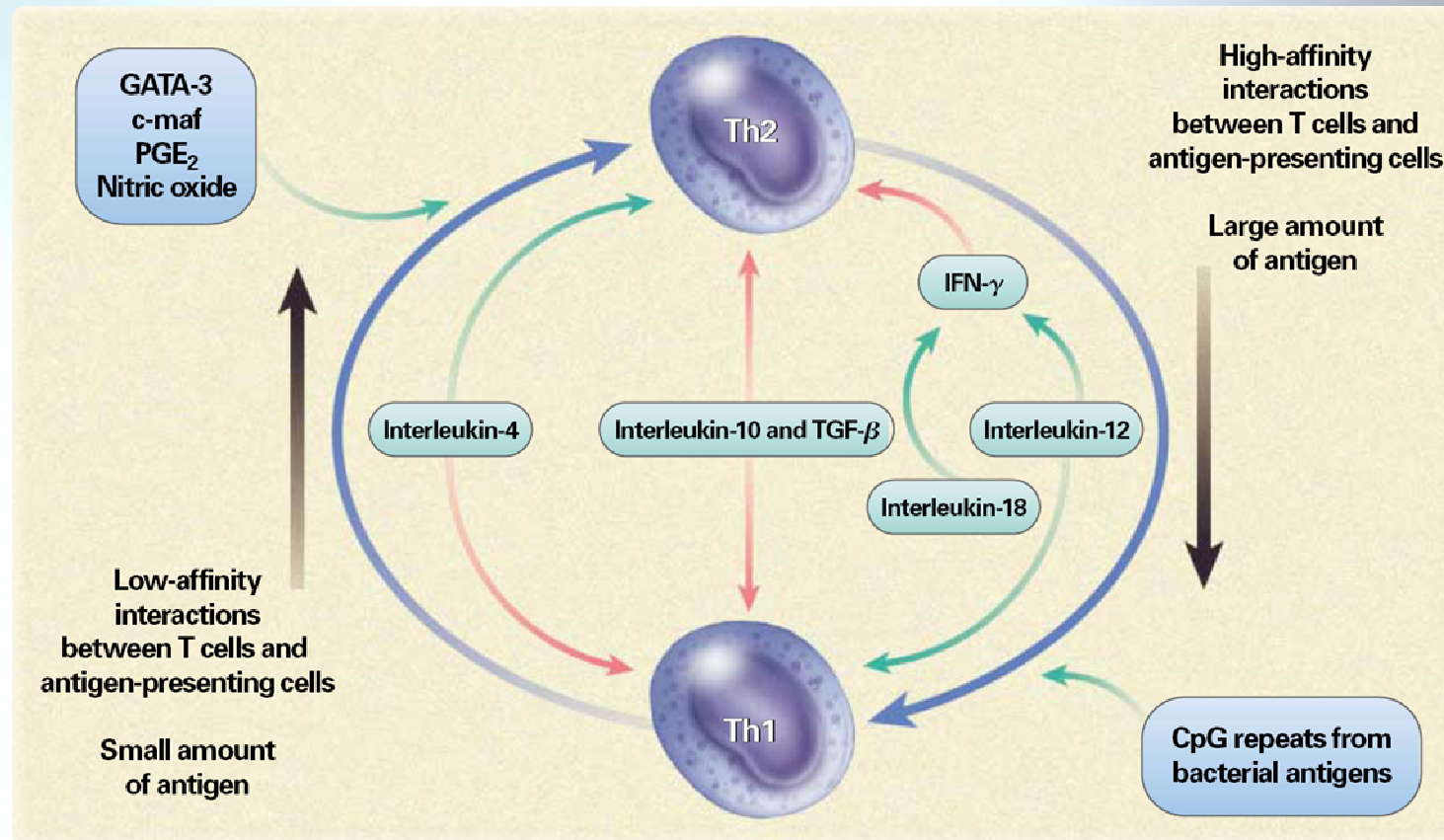
Unique properties of the neonatal T-cell compartment:

Selective apoptosis



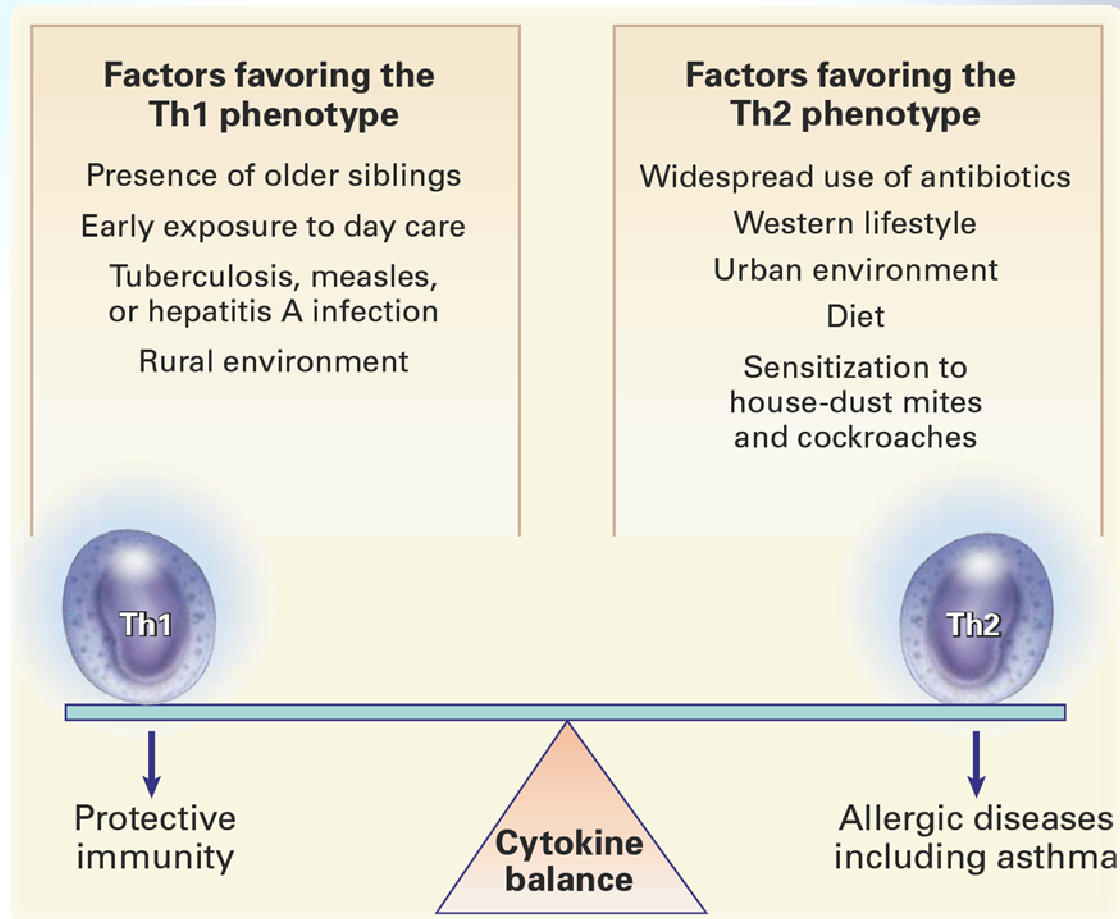
avoidance of harmful pro-inflammatory/T_H1-cell polarizing responses that can induce alloimmune reactions between mother and fetus

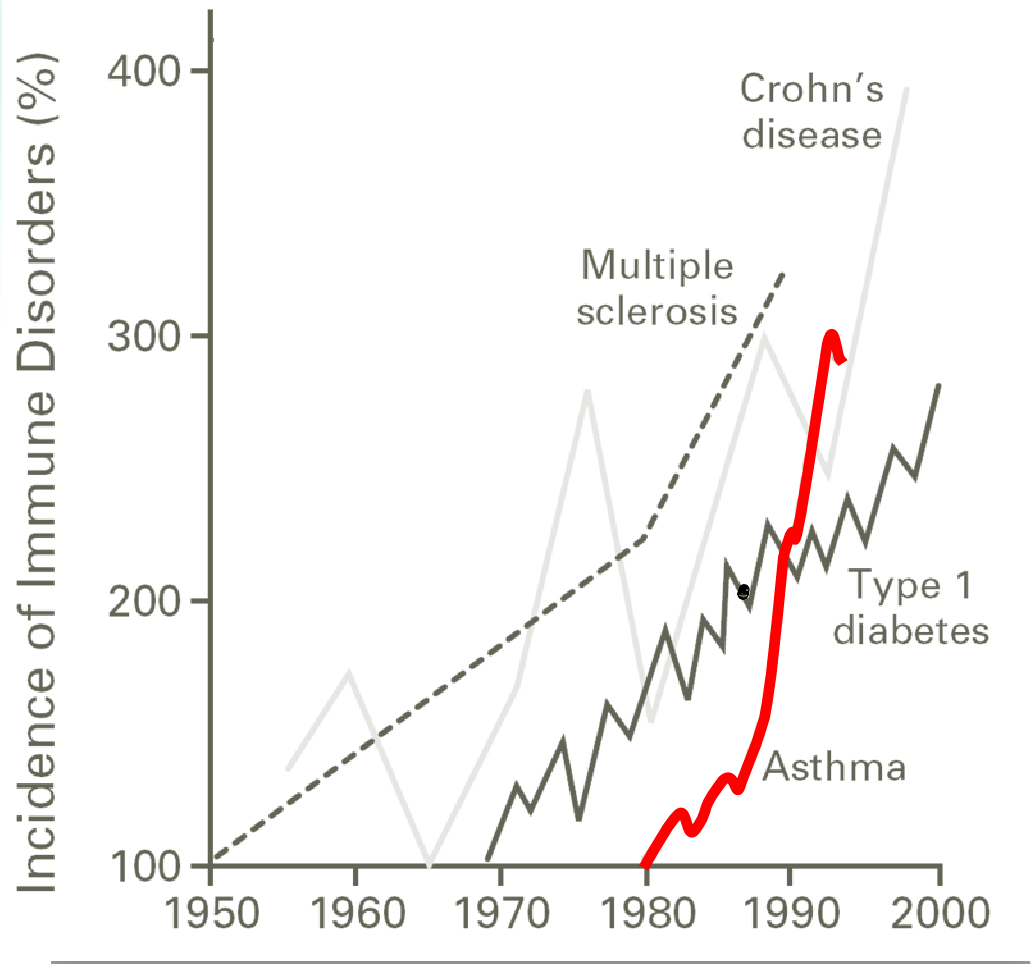
“Immunocalibration”



The Th2-skewed immune response of the newborn is progressively deviated towards a T_H1-response, achieving a mature equilibrium at the age of 5 years

The T_H1 to T_H2 shift theory

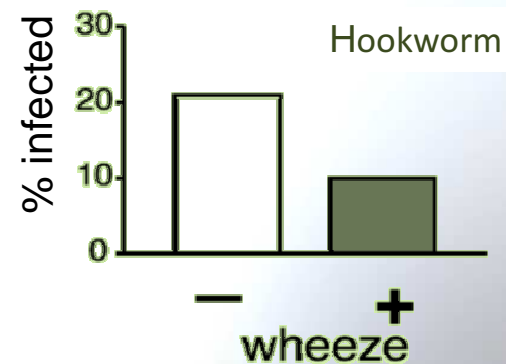
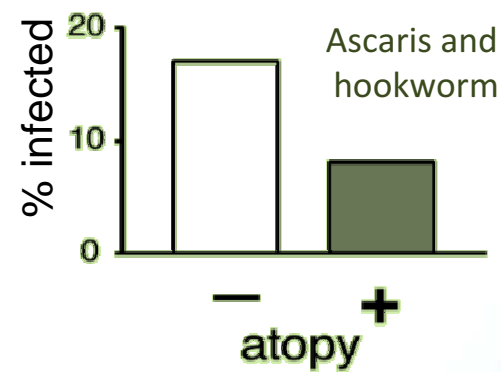
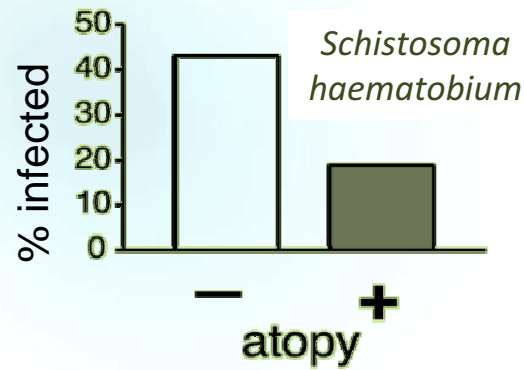




Coincidence of immune-mediated diseases driven by T_H1 and T_H2 subsets

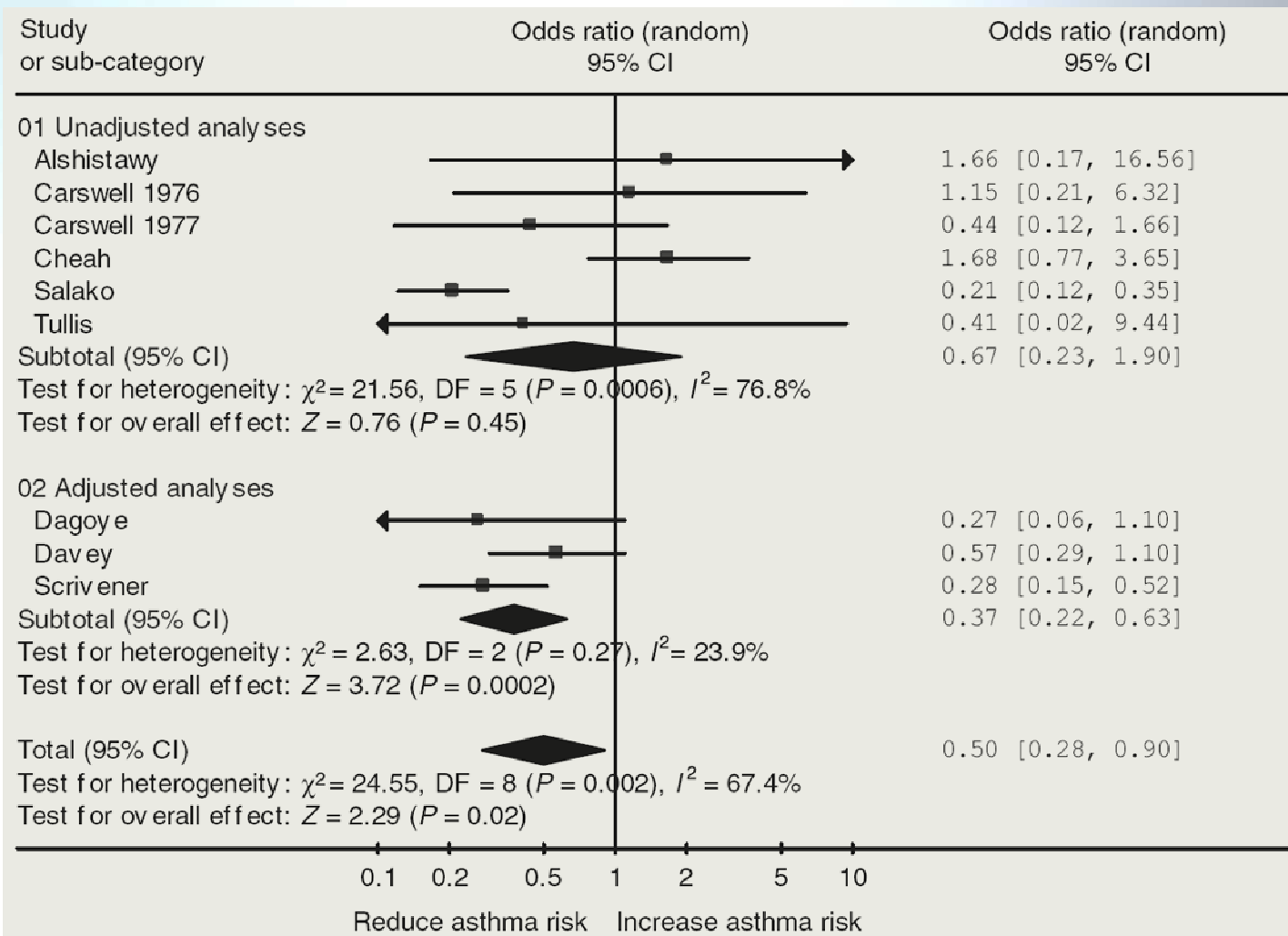
One year prevalence ratio of allergic diseases for subjects with T_H1 disease
(diabetes, psoriasis or rheumatoid arthritis)

	Standardized prevalence ratio	95% CI
Asthma	1.10	0.97 – 1.24
Eczema	1.67	1.48 – 1.87
Allergic rhinitis	1.22	1.02 – 1.44
All atopy	1.32	1.22 – 1.43



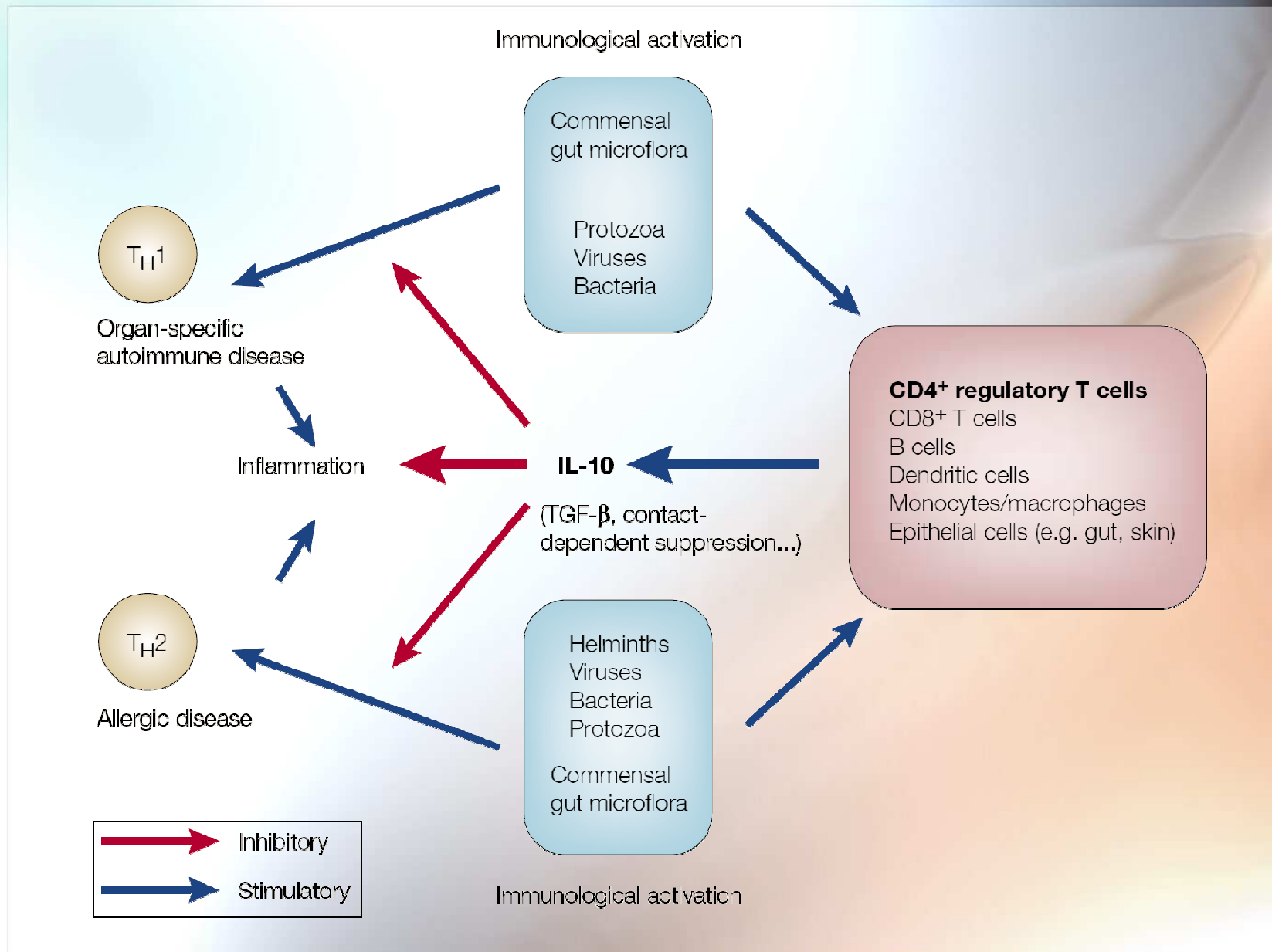
Helminth infections
and allergic diseases
do not overlap
despite both conditions
being accompanied
by strong T_H2 immune responses

Relationship between hookworm infection and asthma

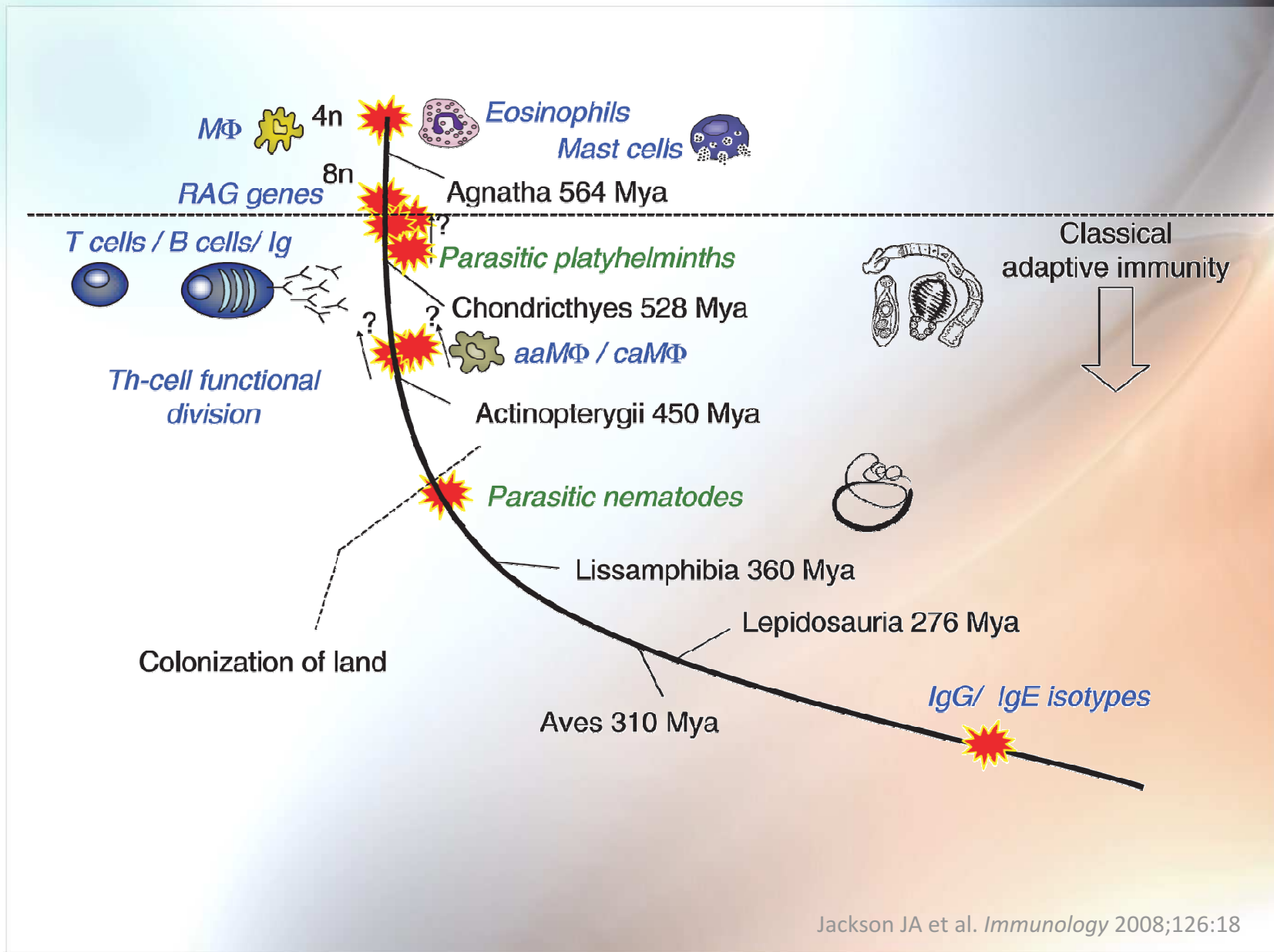


- ❑ The clear skewing towards T_H2 -type responses that can be observed in mice is not readily apparent in humans. In human neonates, T_H -cell responses are often diminished in magnitude, but this can affect T_H1 - or T_H2 -cell function or both.
- ❑ The reciprocal negative regulation by T_H1 and T_H2 effector cells is most often seen *in vitro* or during the **initiation** of immune responses, with most laboratory work done in naïve, clean laboratory mice.
- ❑ IL-10 is a product of various types of cell with regulatory functions, and its secretion is regulated independently of the secretion of the T_H2 cytokines (IL-4, IL-5, IL-13). If the presence of IL-10 secreting regulatory cells was not specifically excluded, the effect is more likely to have been due to Tregs of which the researchers were unaware.

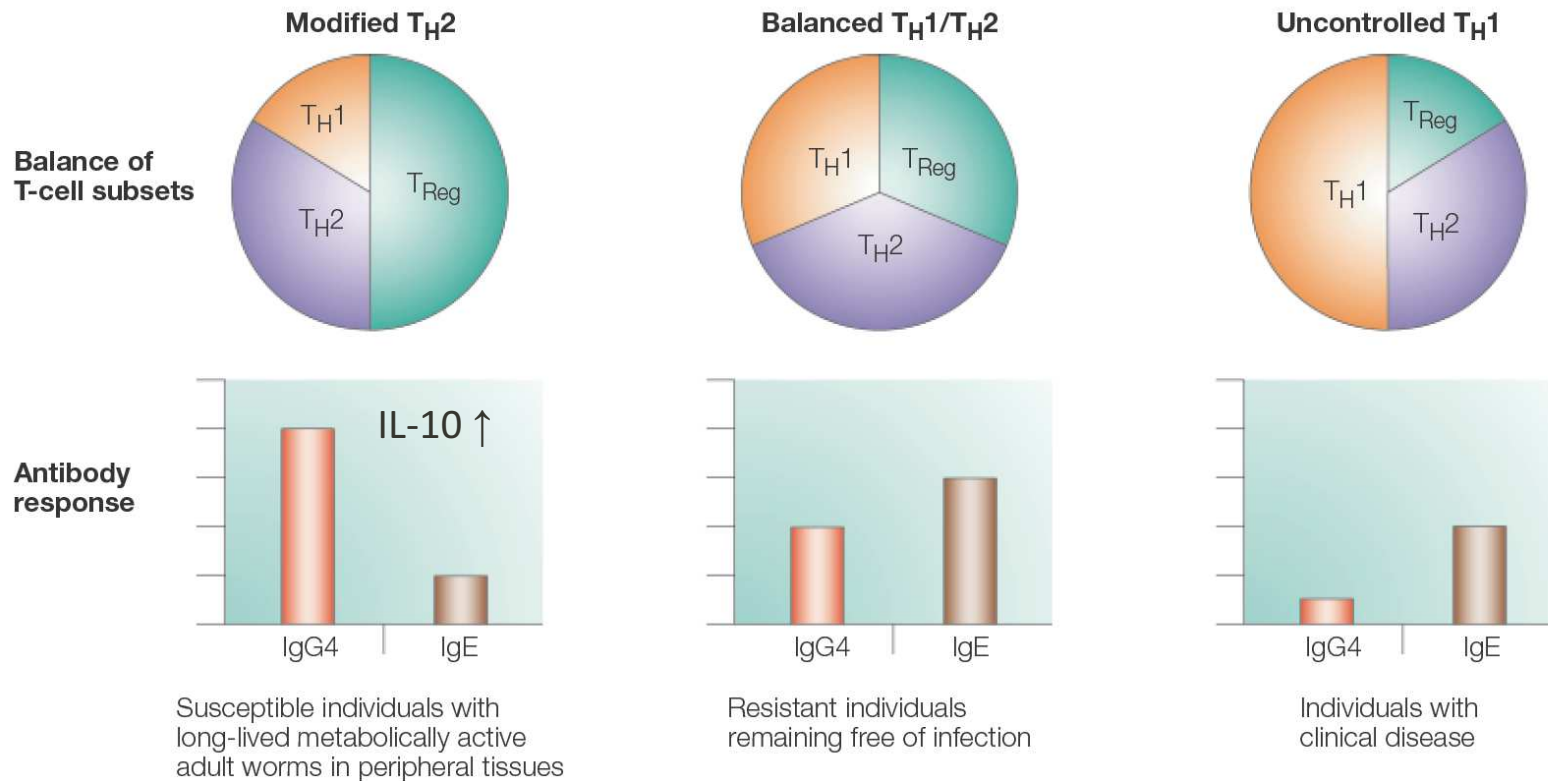
The counter-regulation hypothesis



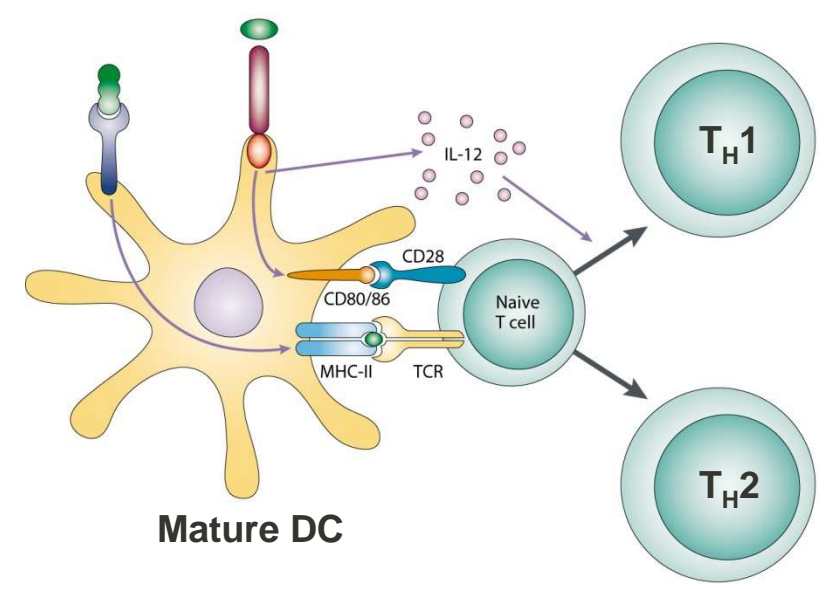
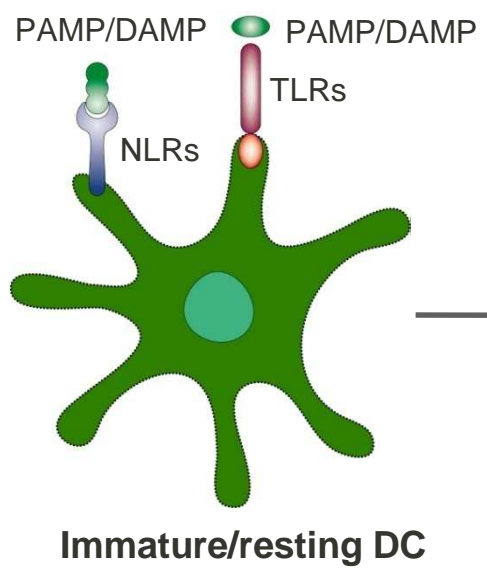
The immune system evolved in the presence of helminths

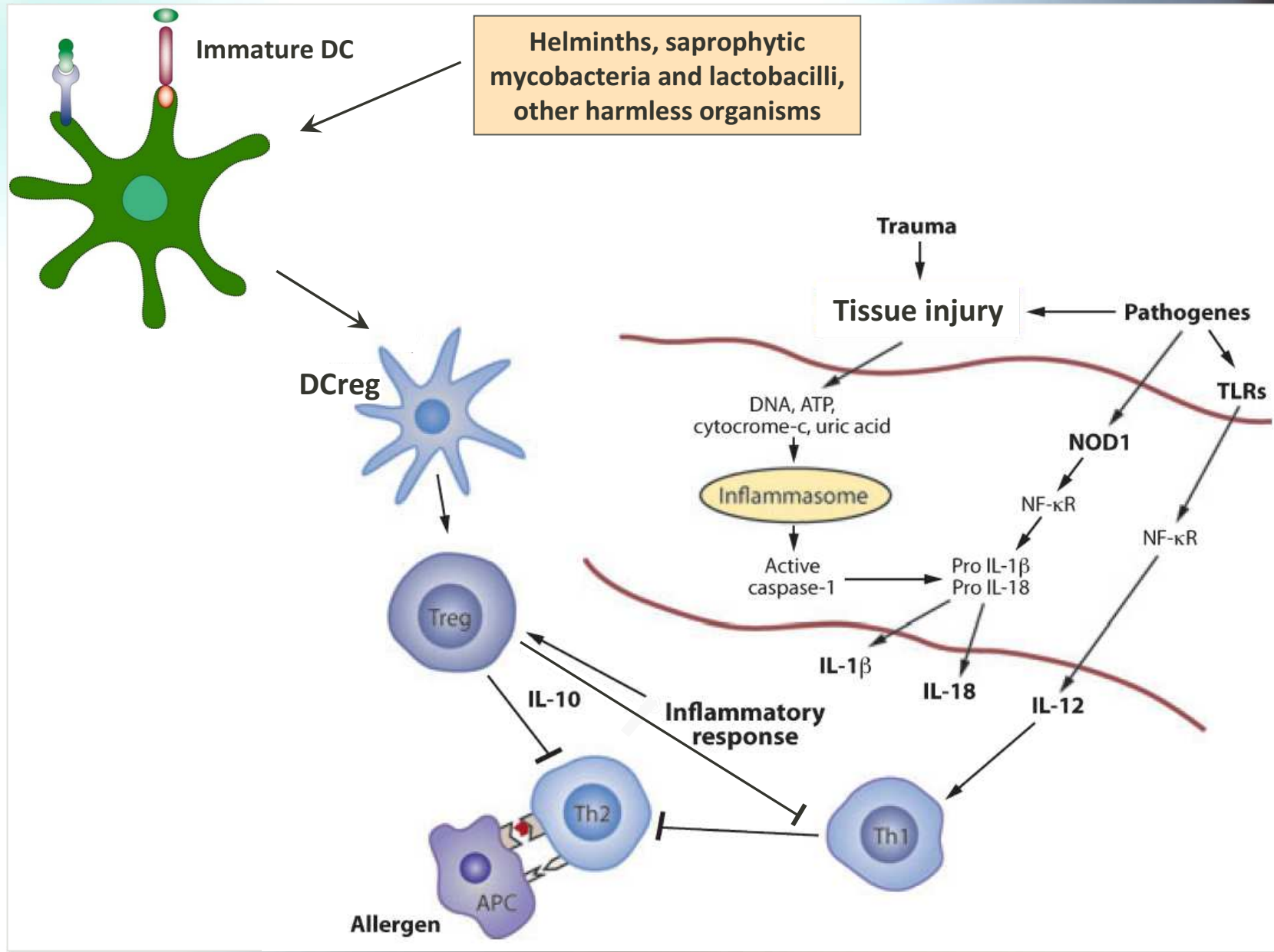


The immunotolerance hypothesis

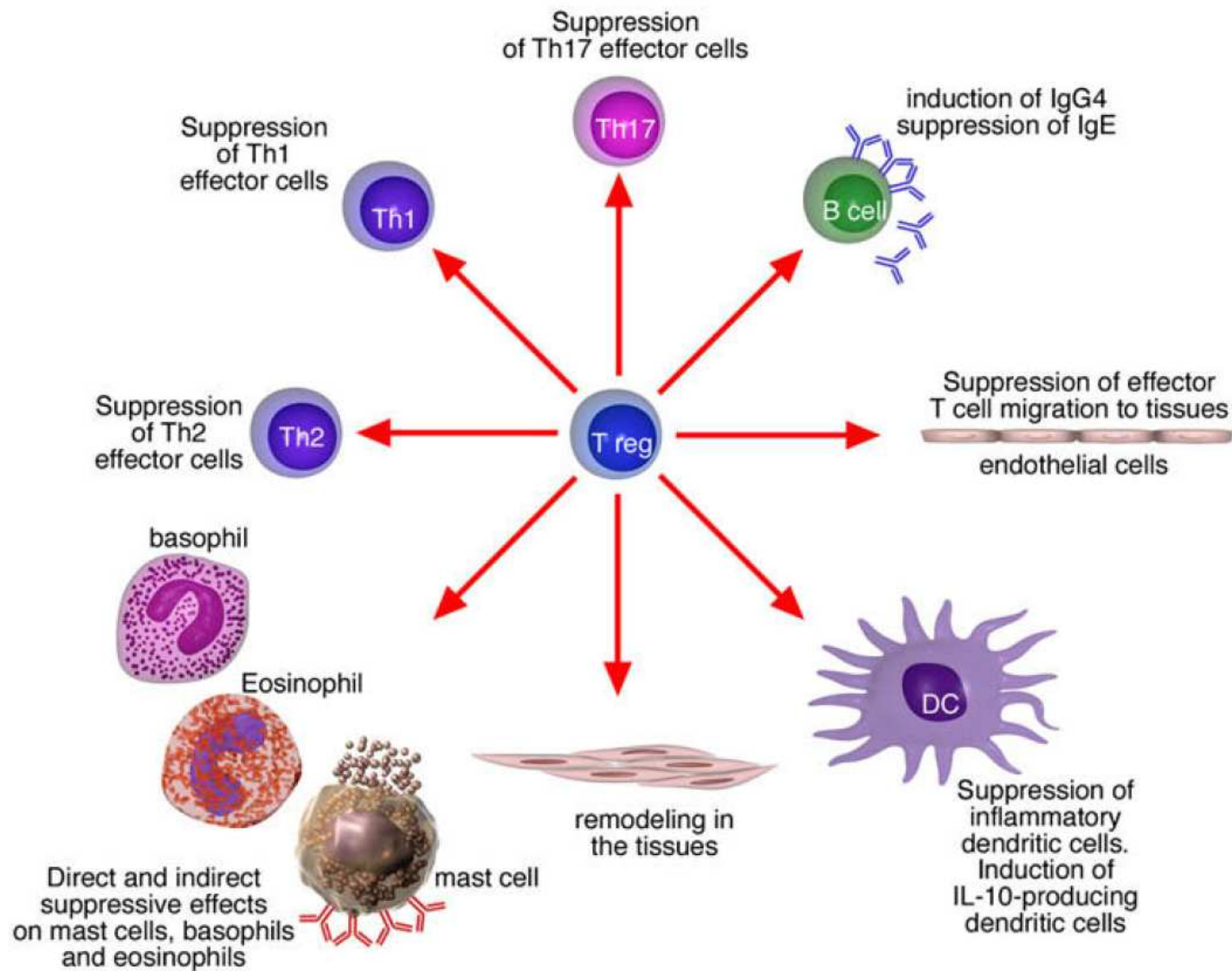


Whilst helminths are handled with gentle immune responses, with a strong regulatory component, that may take weeks, months or even years to reach their peak effectiveness, microbes represent an imminent threat and are usually countered by rapid, relatively violent inflammatory responses

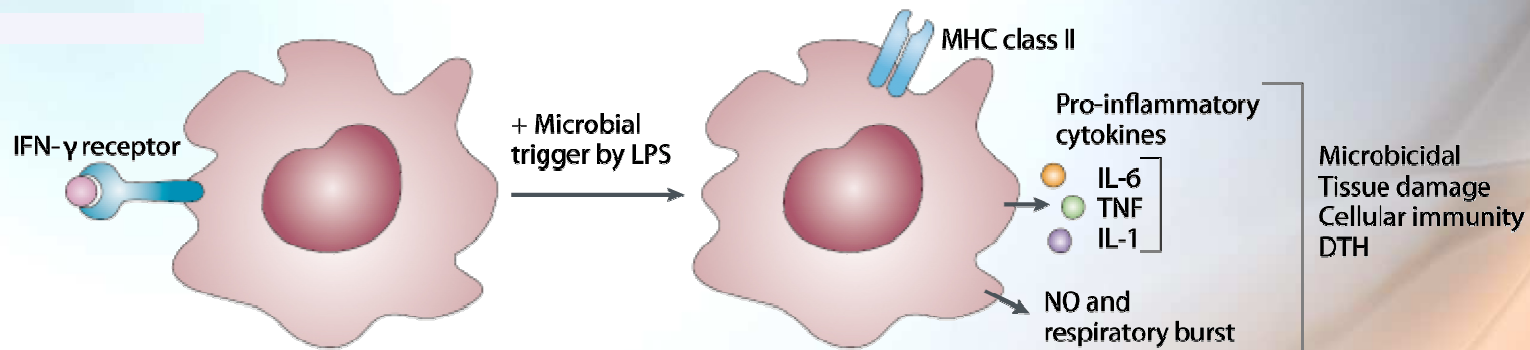




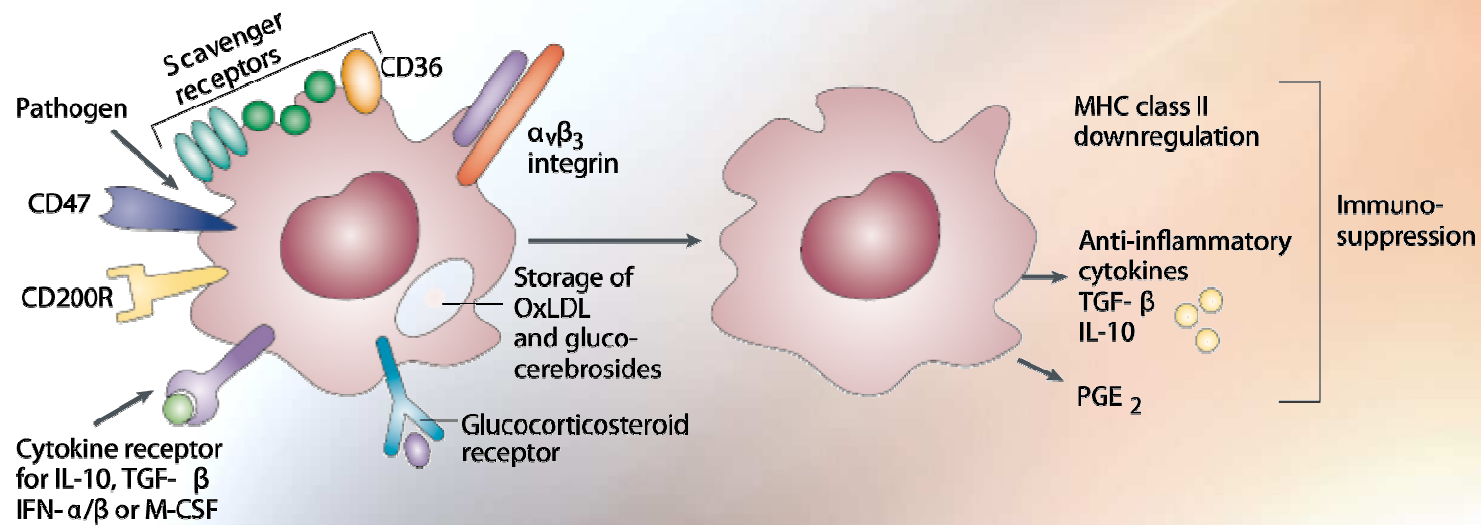
FoxP3⁺CD4⁺CD25⁺ and T_R1 cells contribute to the control of allergen-specific immune responses in several major ways



Classical activation of macrophages

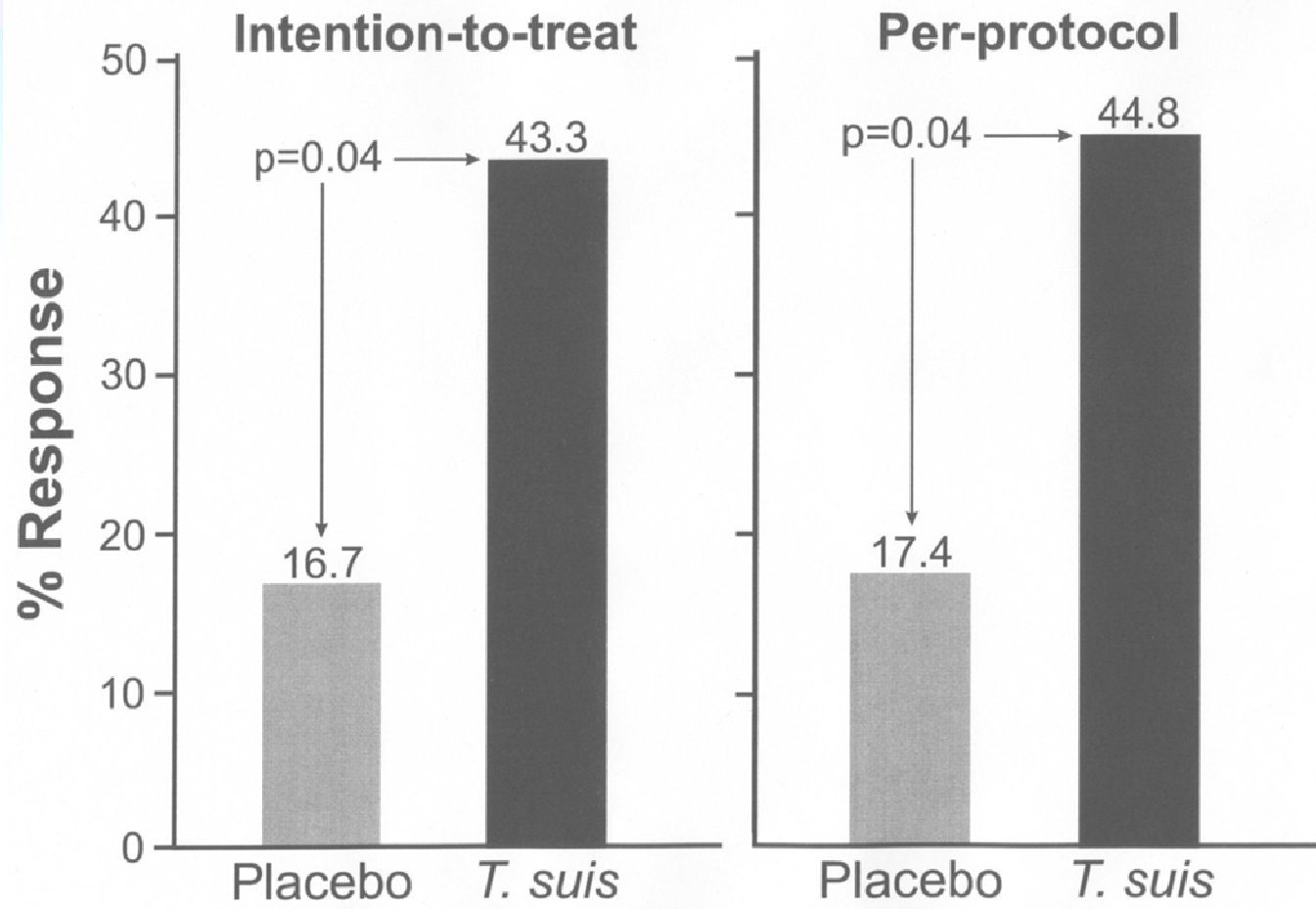


Alternative activation of macrophages



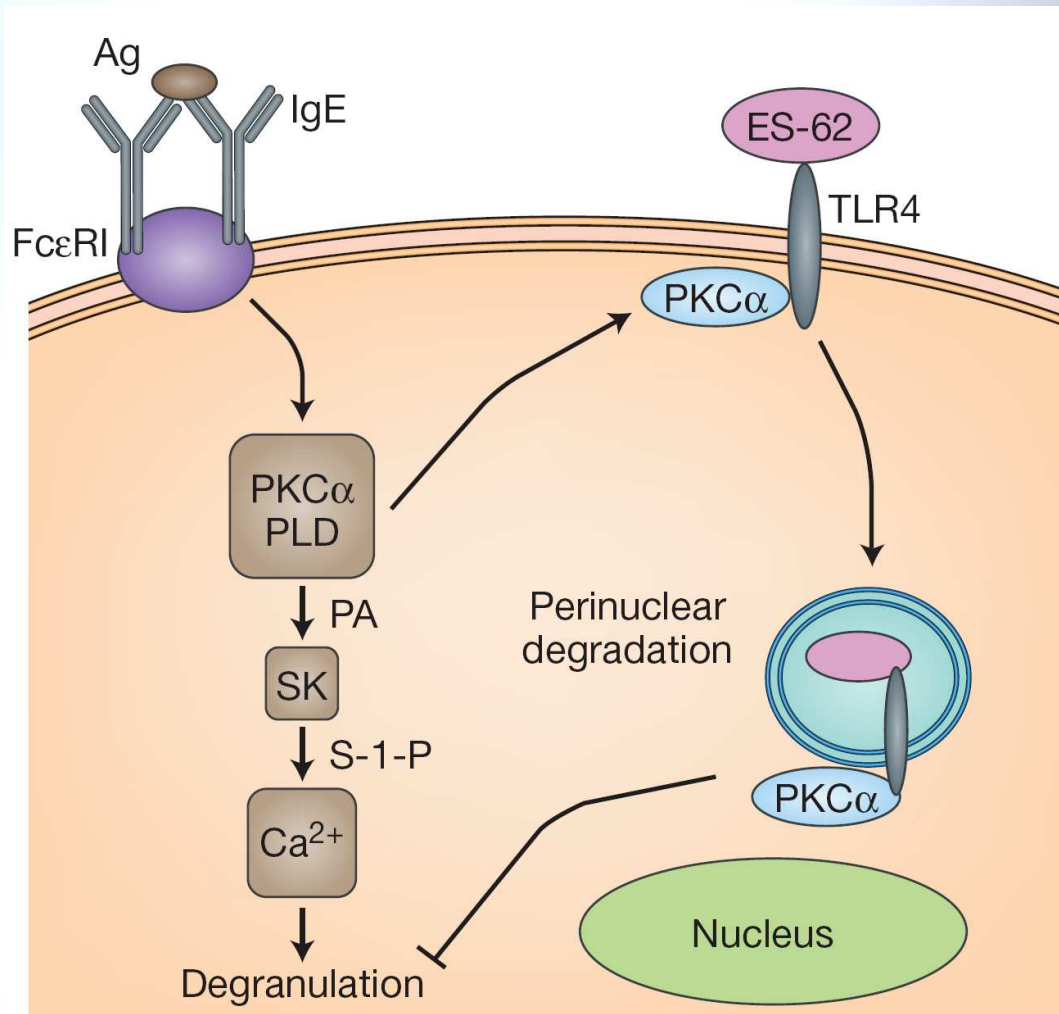
- ❑ The immunodysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome
- ❑ MS patients developing parasite infections induce Tregs that specifically responded to MBP and have significantly fewer exacerbations
- ❑ ASIT has been the only treatment that induces specific Treg cells in human subjects
- ❑ Microorganisms that are currently 'missing' from the environment in rich countries treat allergy, autoimmunity or intestinal inflammation (experimental models and clinical trials)

Trichuris suis therapy for active ulcerative colitis

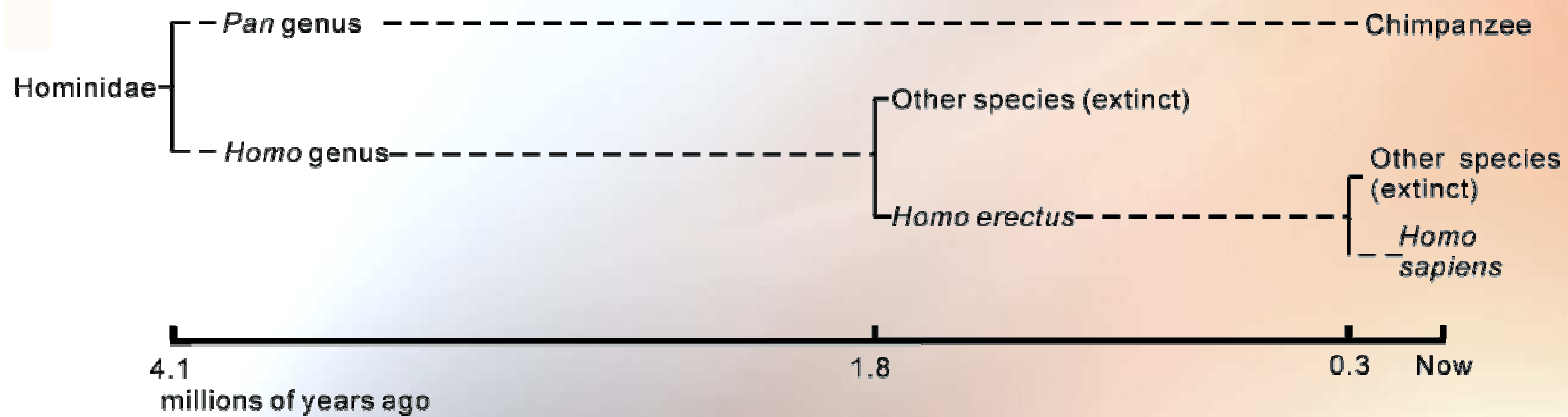
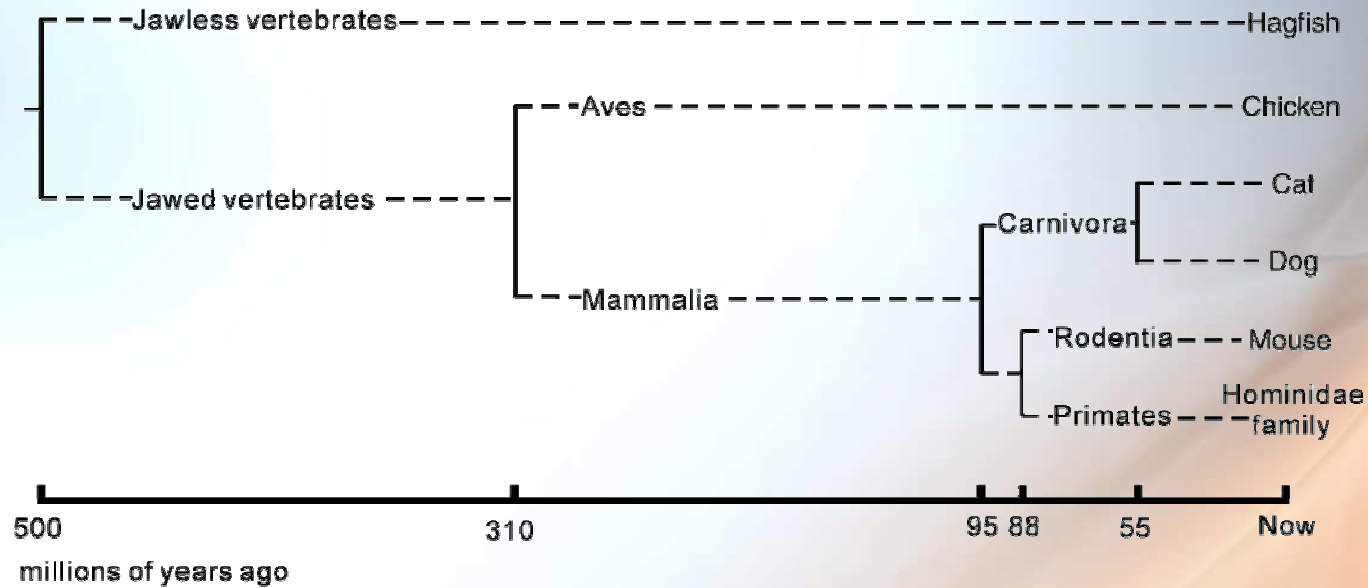


Summers RW et al (University of Iowa)

Filarial nematode-derived ES-62 induces hyporesponsiveness of mast cells by disrupting Fc ϵ RI signalling



The hygiene hypothesis: Macroevolutionary evidence



Summer catarrh... only occurs in the middle or upper classes of society, some indeed of high rank. I have made inquiry at the various dispensaries in London and elsewhere, and I have not heard of a single unequivocal case occurring among the poor.

BOSTOCK J. *On the catarrhus aestivus or summer catarrh.*

London: Medico-Chirurgical Transactions;

1828; p. xiv:437-446.1

It would seem that hay-fever has, of late years, been considerably on the increase. The persons who are most subjected to the action of the pollen belong to a class which furnishes the fewest cases of the disorder, namely, the farming class.

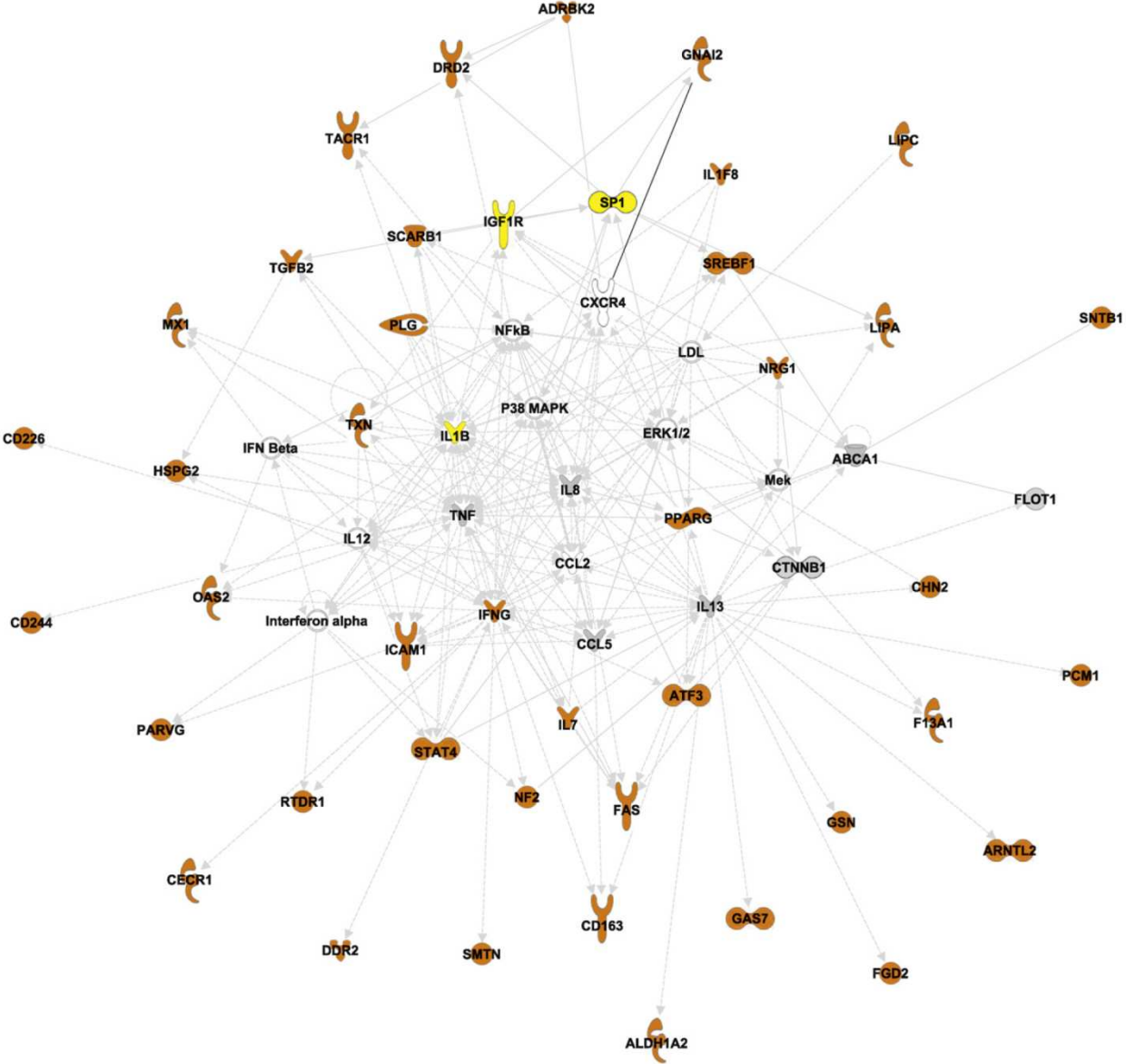
BLACKLEY CH. *Experimental researches on the causes and nature of Catarrhus aestivus (hay-fever or hay-asthma).*

London: Balliere, Tindall & Cox; **1873**

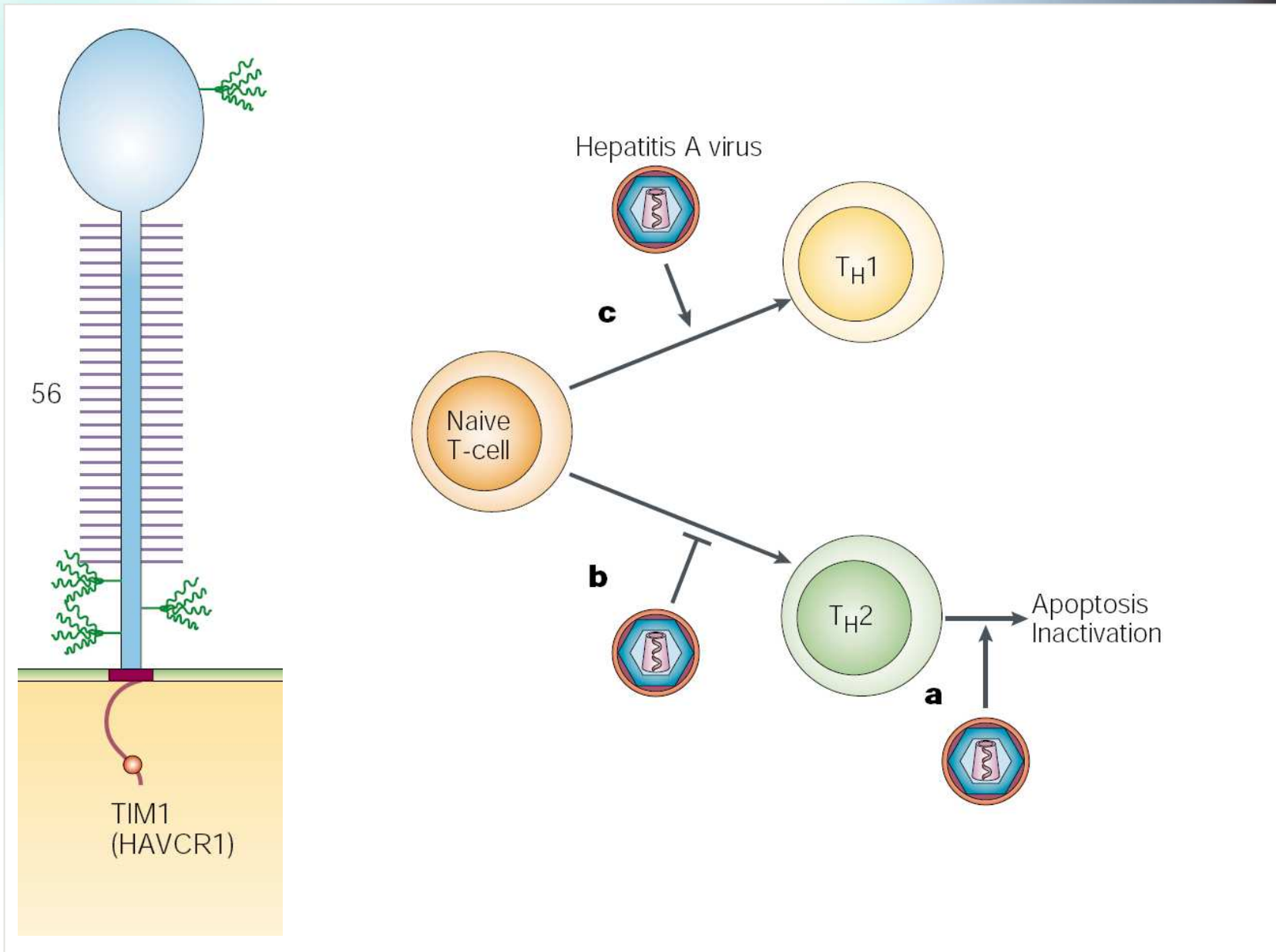
The hygiene hypothesis: **supporting evidence**

- ❑ Epidemiological evidence
- ❑ Immunological evidence
- ❑ Therapeutic evidence
- ❑ Macroevolutionary evidence
- ❑ Genetic evidence ?

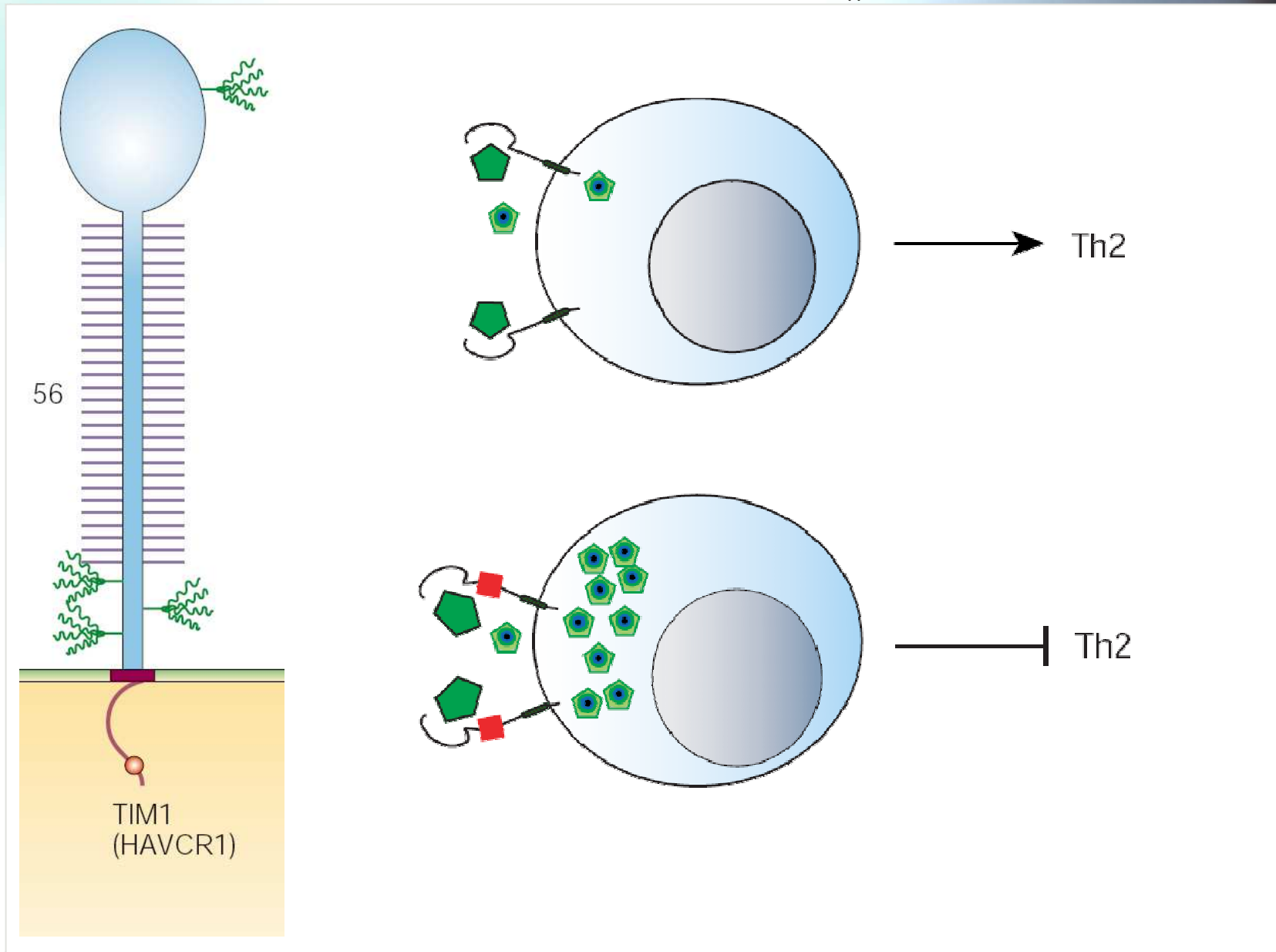
Network analysis of immune genes associated with protozoa diversity



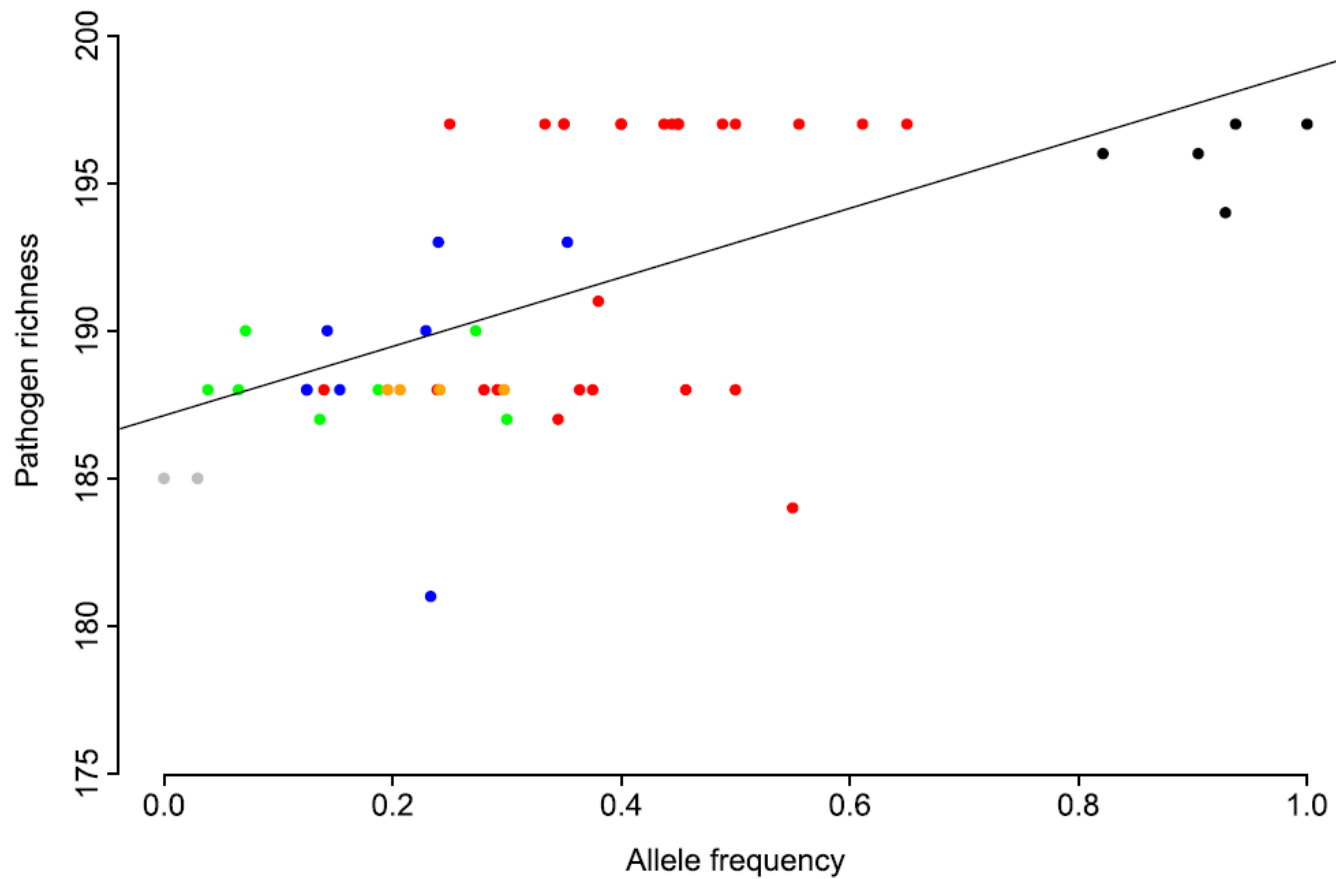
Mechanisms by which HAV affect the development of helper T cells



A variant of TIM-1 (157insMTTTPV) increase binding of HAV to the receptor leading to deletion and reduction of differentiation of T_H2 cells

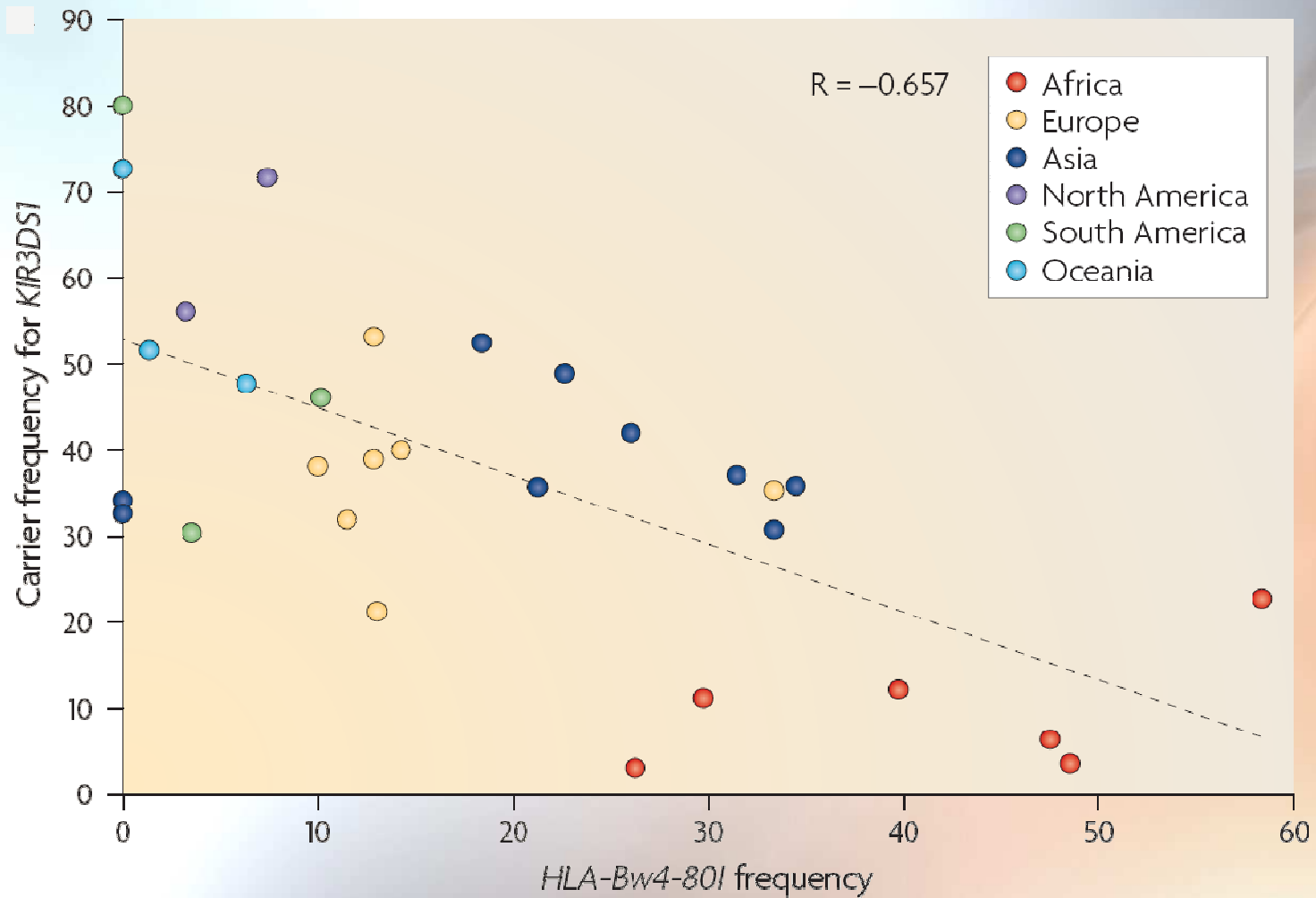


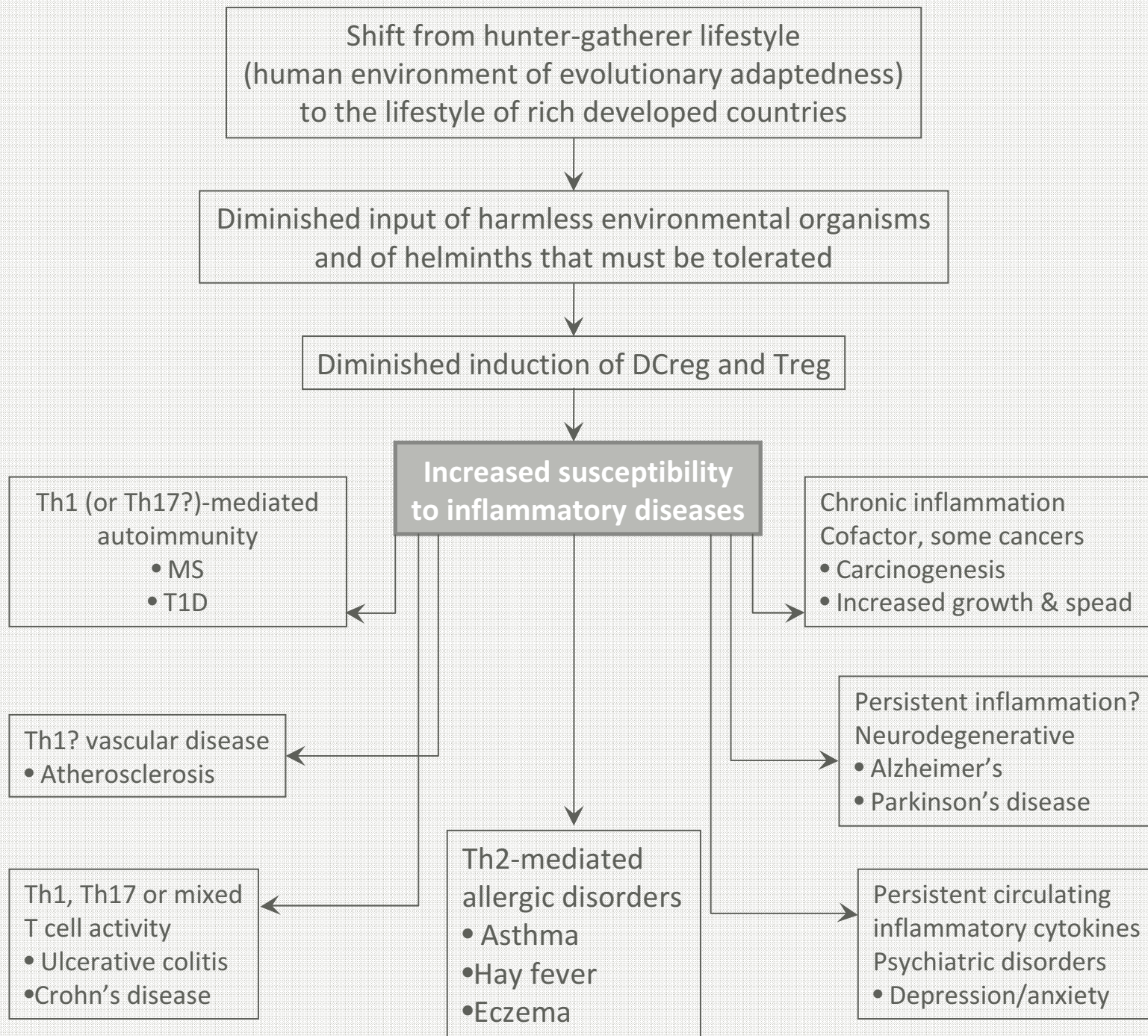
Correlation between pathogen richness (a measure of pathogen-driven selection) and allele frequency in 52 human populations distributed worldwide for rs917997 in *IL18RAP*, an IBD/CeD risk allele

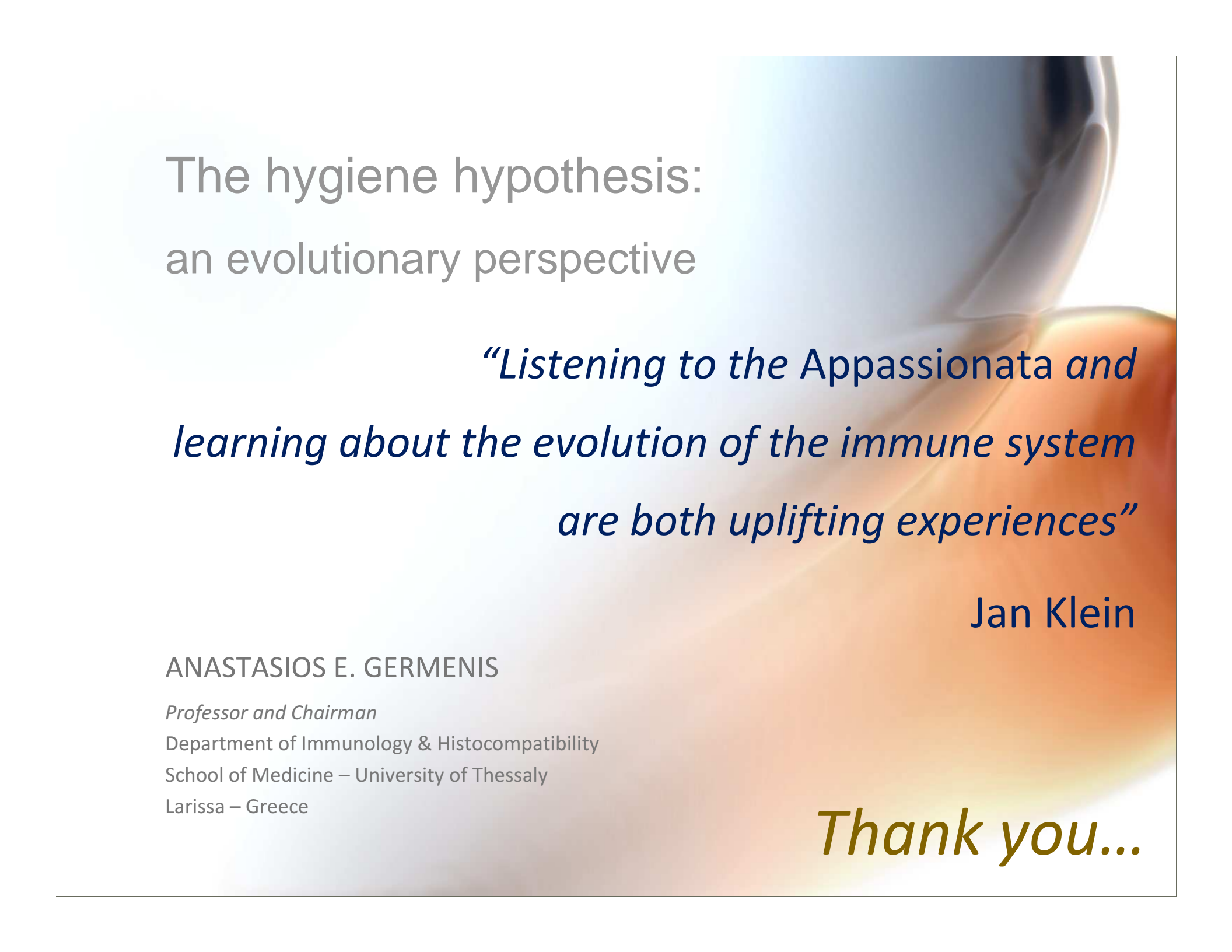


Epistatic selection: co-evolution of immune players

KIR3DS1 and *HLA-Bw4-80I* increase susceptibility to autoimmunity







The hygiene hypothesis:
an evolutionary perspective

*“Listening to the Appassionata and
learning about the evolution of the immune system
are both uplifting experiences”*

Jan Klein

ANASTASIOS E. GERMENIS

Professor and Chairman

Department of Immunology & Histocompatibility

School of Medicine – University of Thessaly

Larissa – Greece

Thank you...