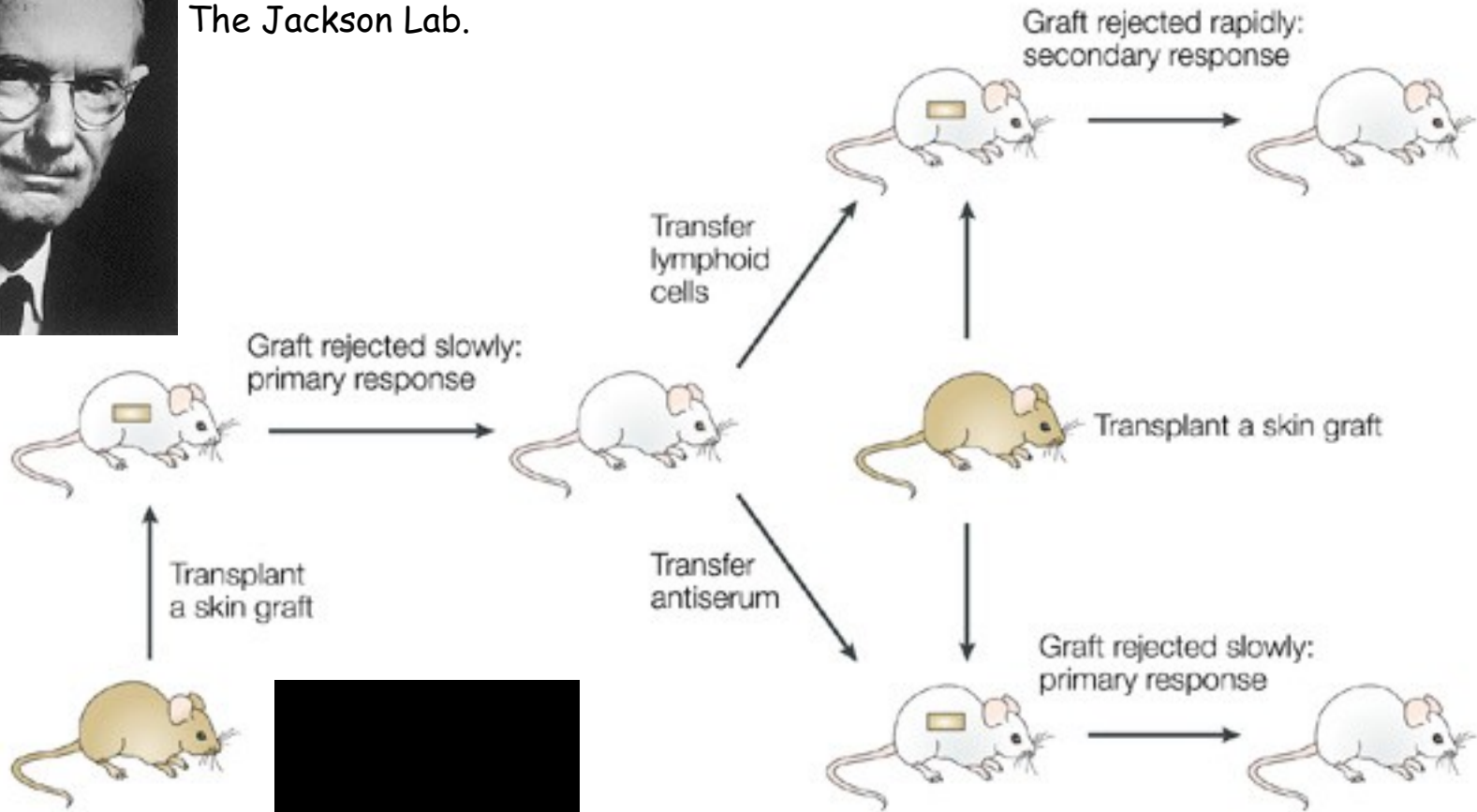
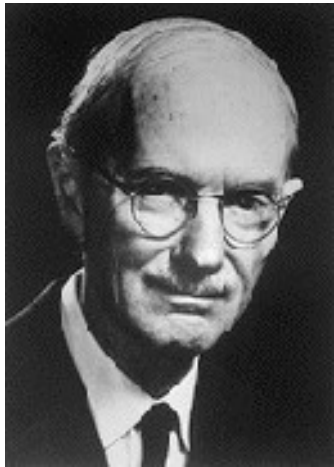


# Sixty years of immunology

Av Mitchison,  
University College London

# Life-long adoptive cellular immunity 1948

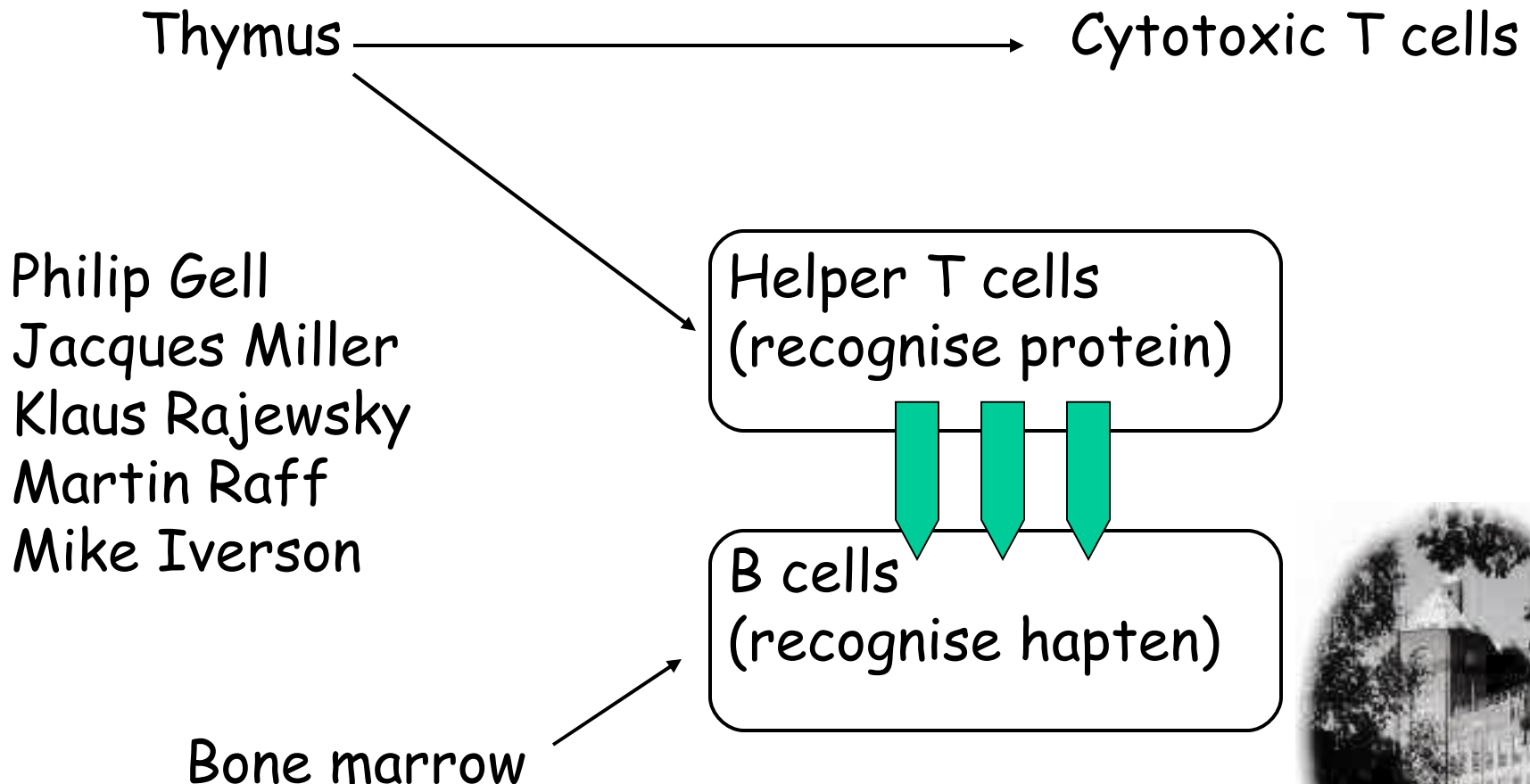
George Snell,  
The Jackson Lab.



Peter Medawar, Oxford/Birmingham/UCL

# T cell - B cell cooperation 1969

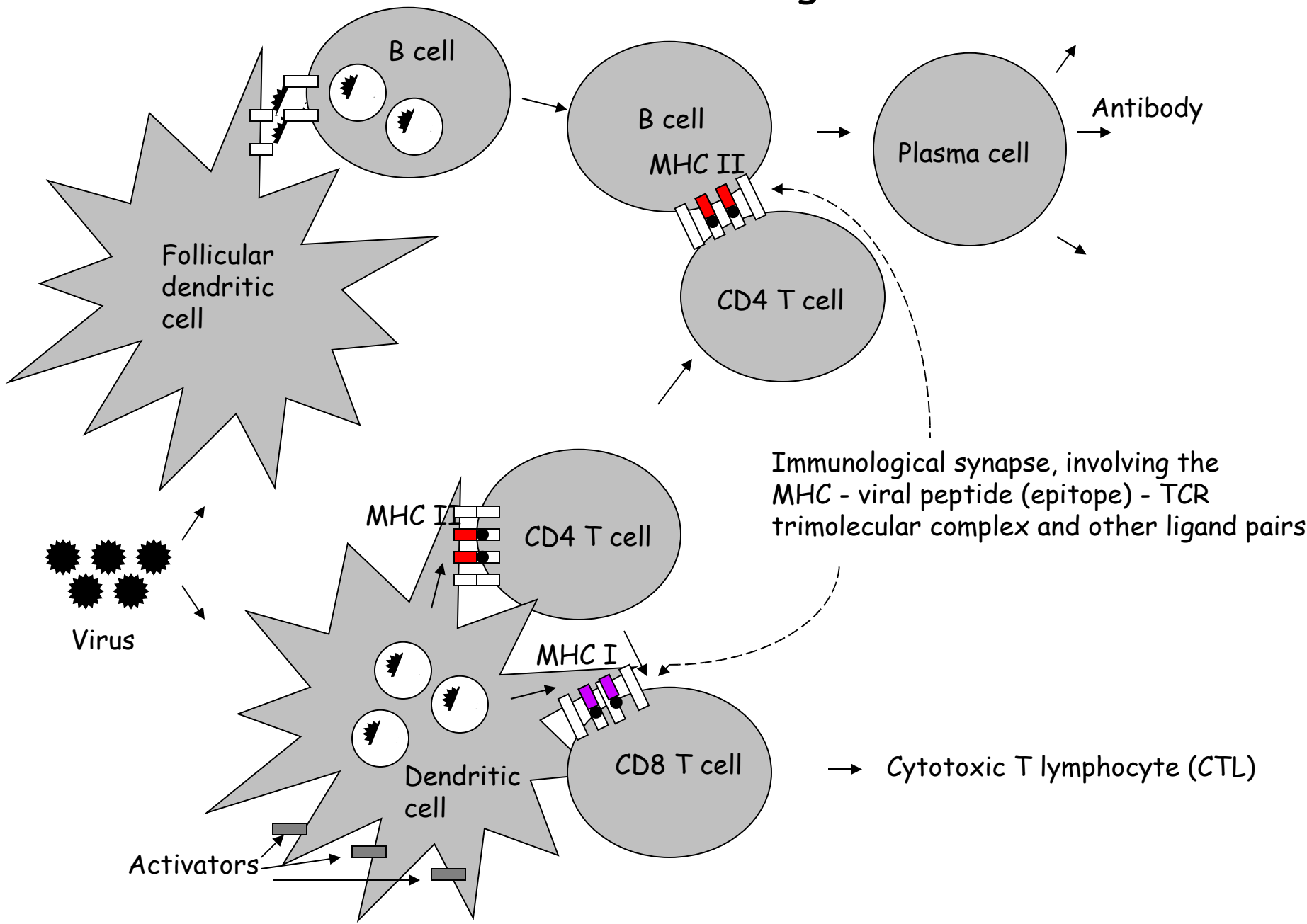
We learn that the "immune system" is composed not of autonomous cells, but of distinct cell populations that interact.



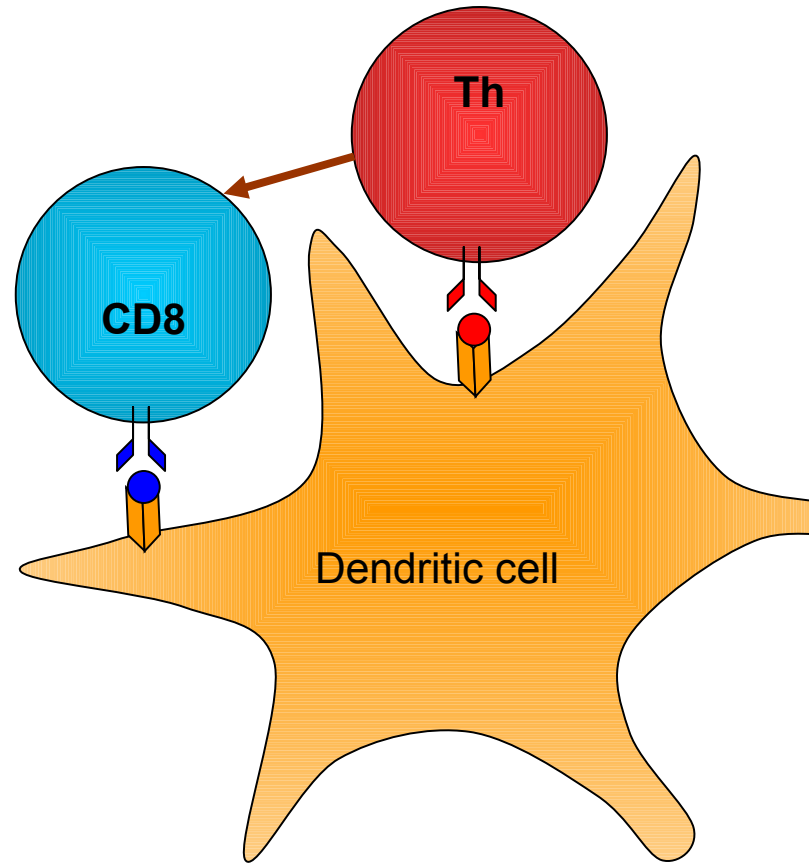
NIMR



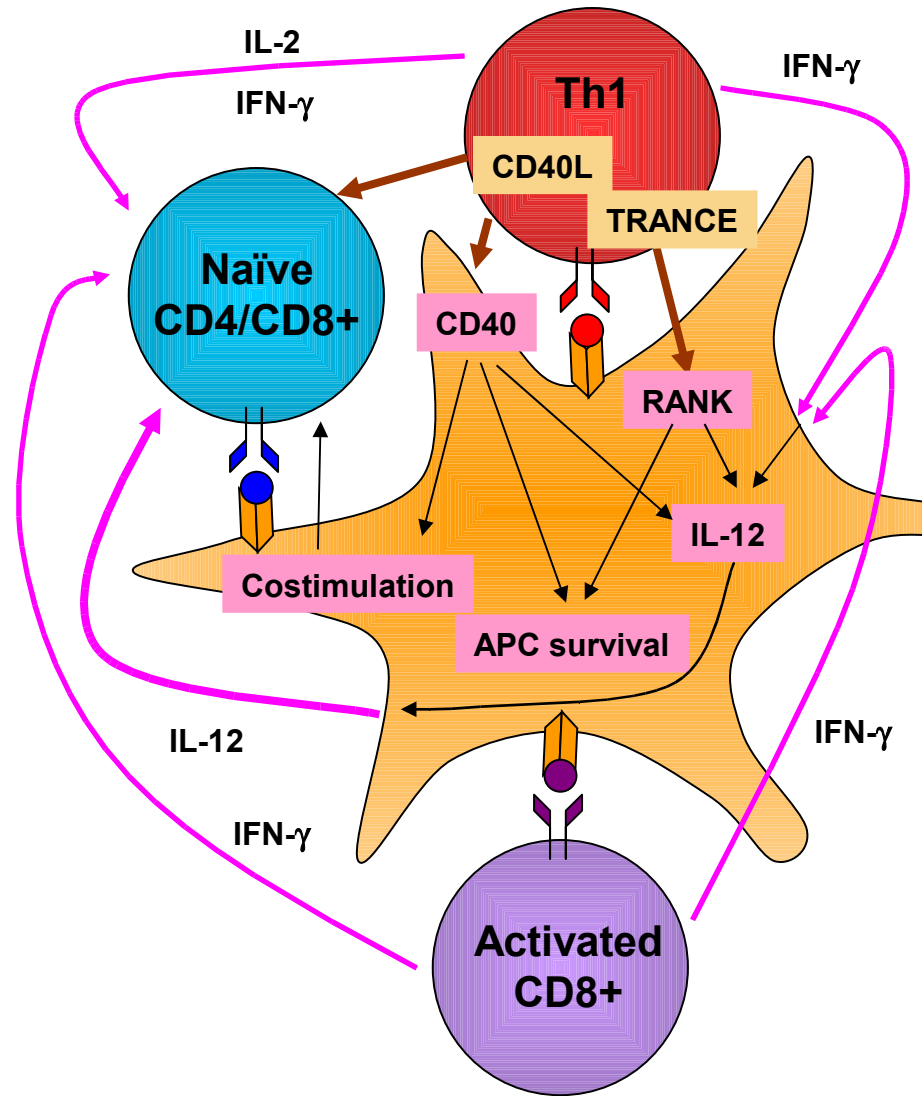
# Current view of immunoregulation



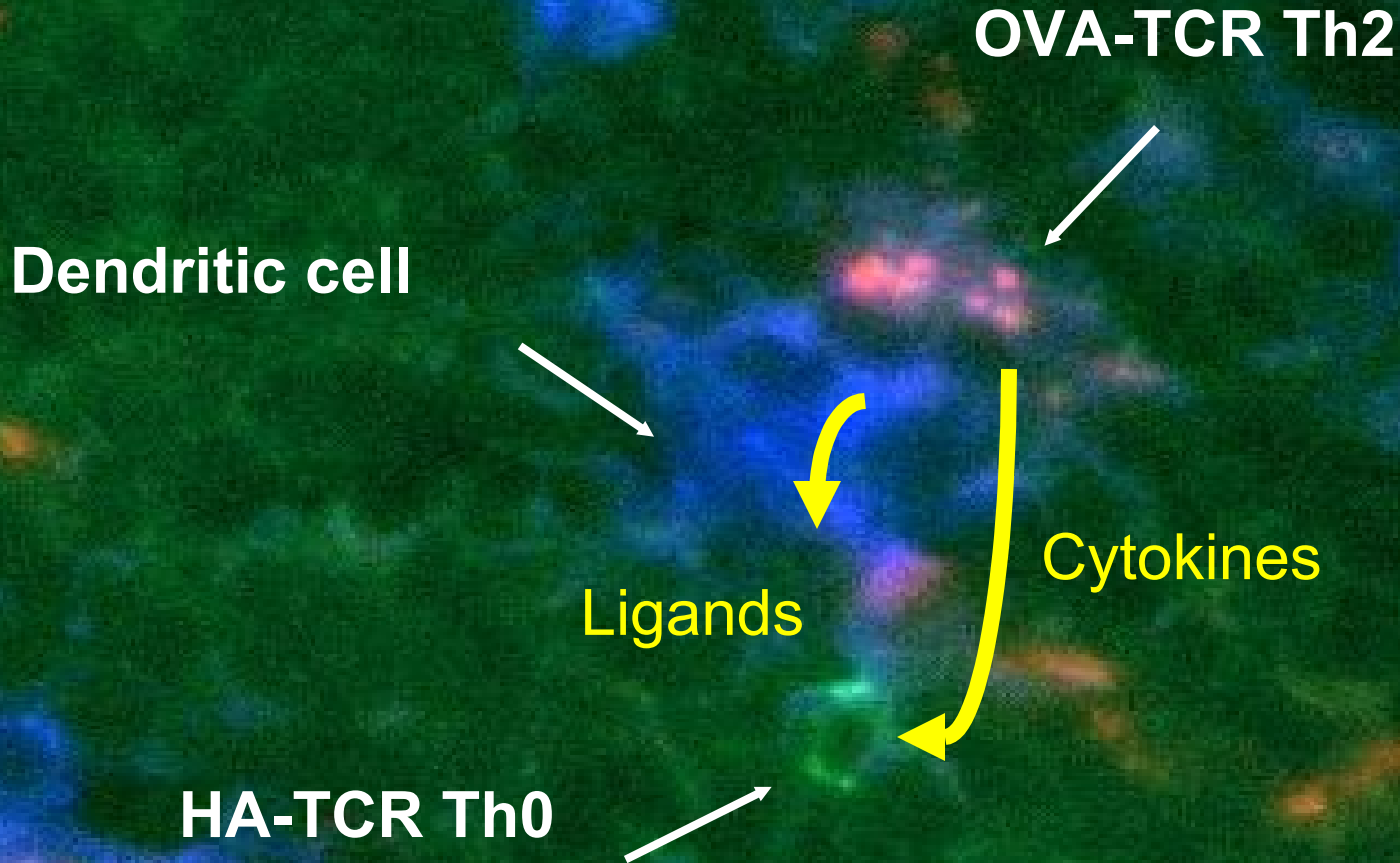
# T cell - T cell cooperation 1987



# T cell - T cell cooperation today



# Th1/Th2 polarization within a dendritic cell cluster



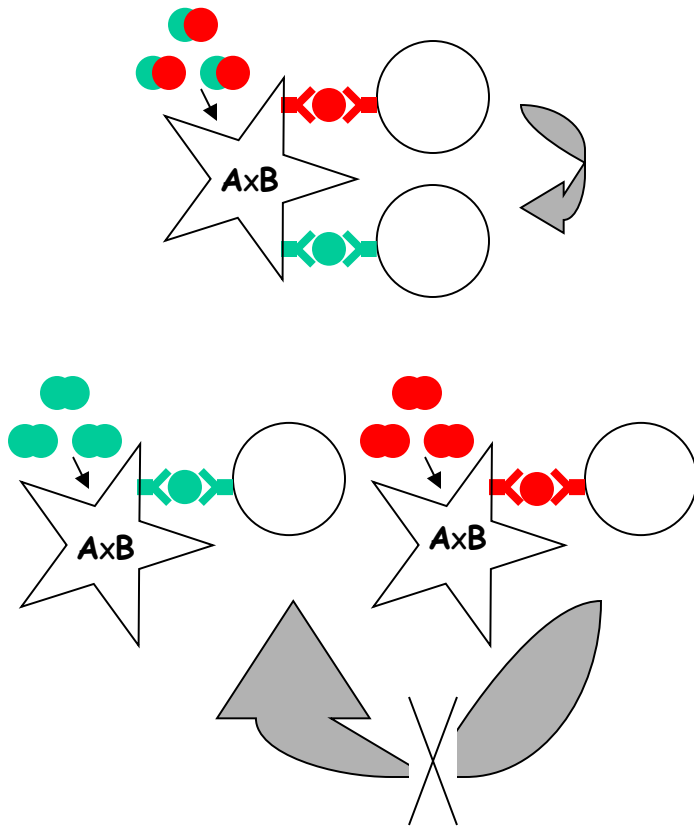
# Gene Gun



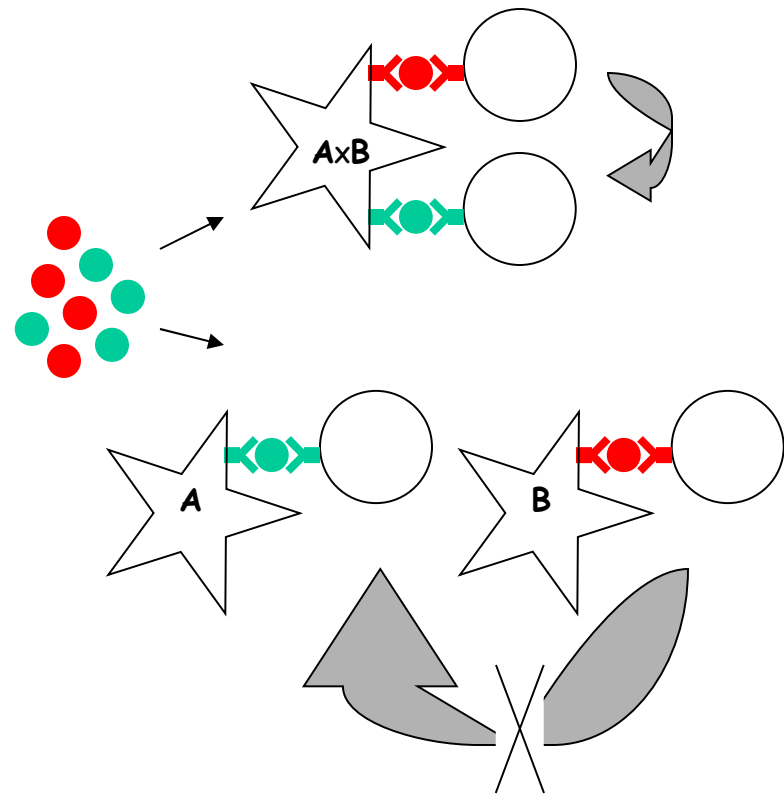


# Each cluster around a dendritic cell is autonomous

Demonstrated by particle immunization  
(Creusot et al 2003)

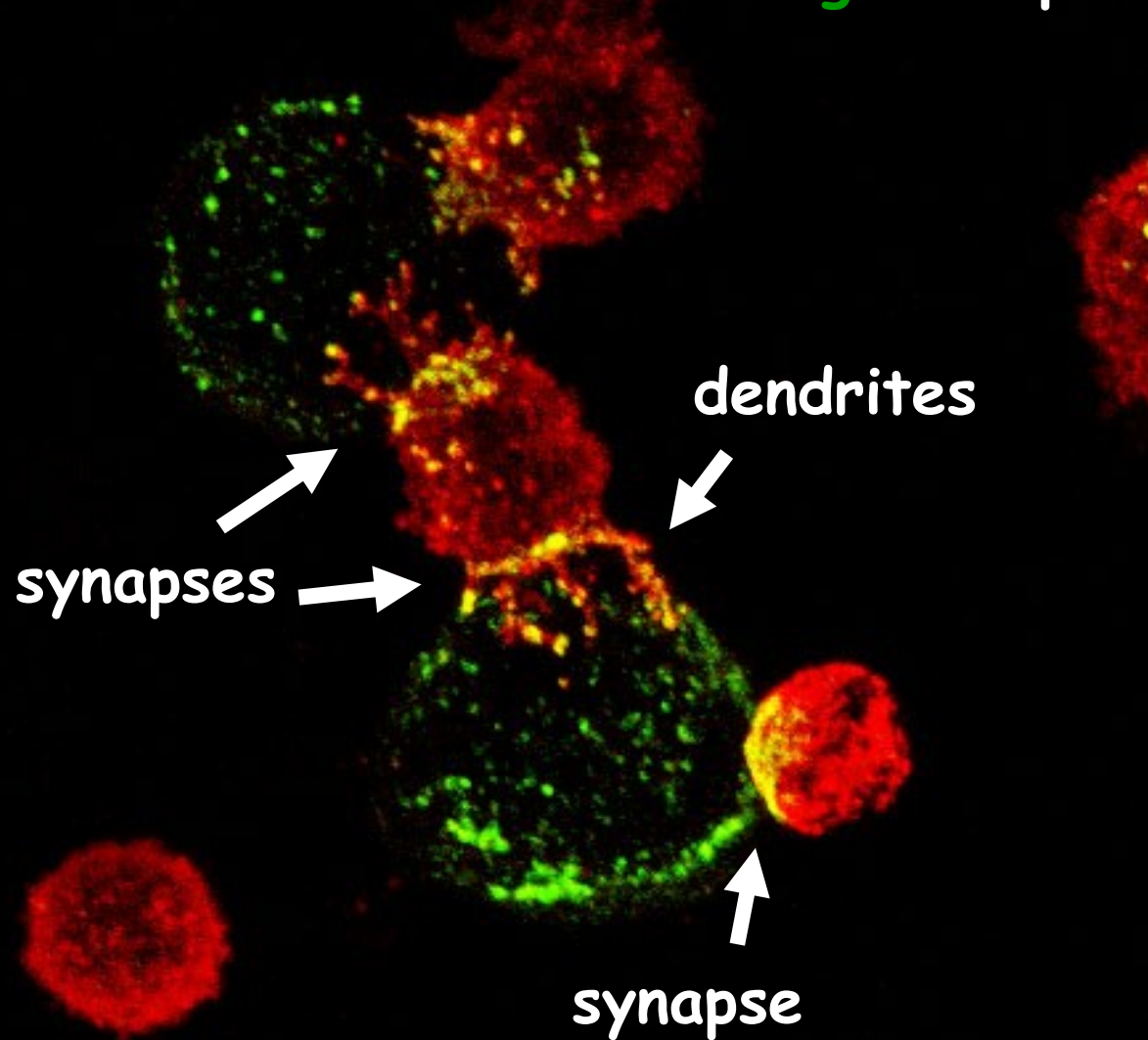


Demonstrated by bone marrow chimeras  
(Matzinger et al 2004)



A and B are allelic MHC II's

B cells stained for **IgM** synapse with FcR+  
myeloid cells stained with **HEL-IgG** complexes



(Jo Edwards - rituximab)

*FC Batista*

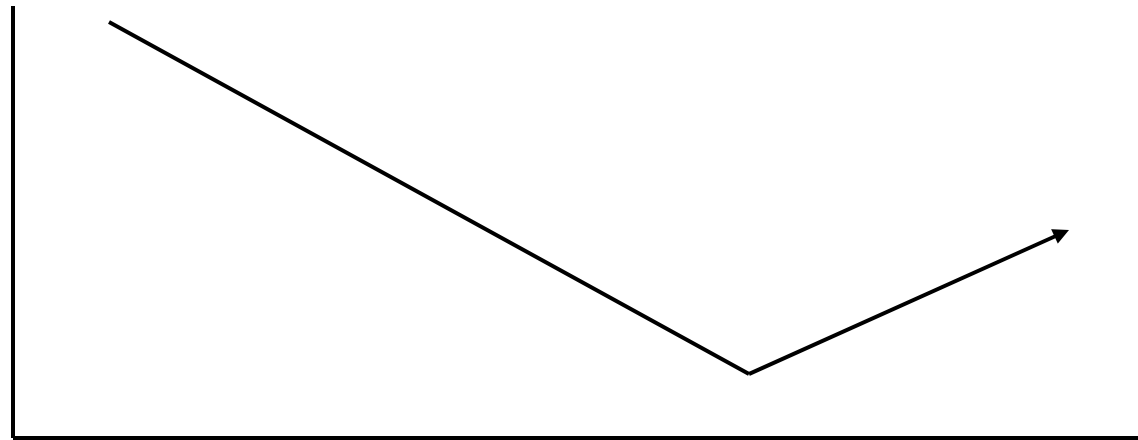
# Vaccination

## Conjugate vaccines 1985-

- Hib (Haemophilus influenzae type b - diphtheria toxoid)
- MenC (Neisseria meningitidis Group C - diphtheria toxoid)
- Pneumococcal (Streptococcus pneumoniae - diphtheria toxoid)
- Malaria (circumsporozoite protein - S antigen of hepatitis B virus, HBsAg)

1965: when Otto Westphal & I missed out.

# Cancer vaccines



1950

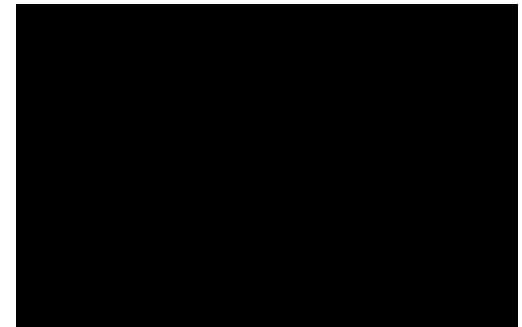
Immune surveillance

1980

Defined,  
genome-based antigens\*

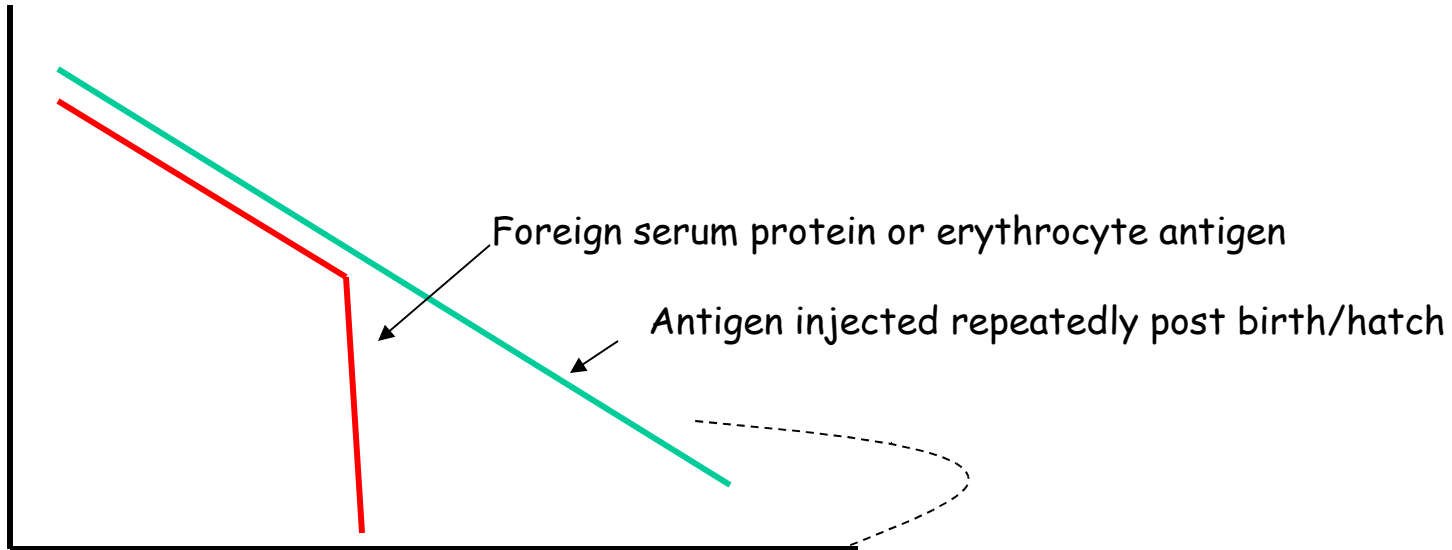
\*we estimate 27,000 possibilities  
per epitope, allowing for choice of  
adjuvant molecules!

Hans Stauss



1960-

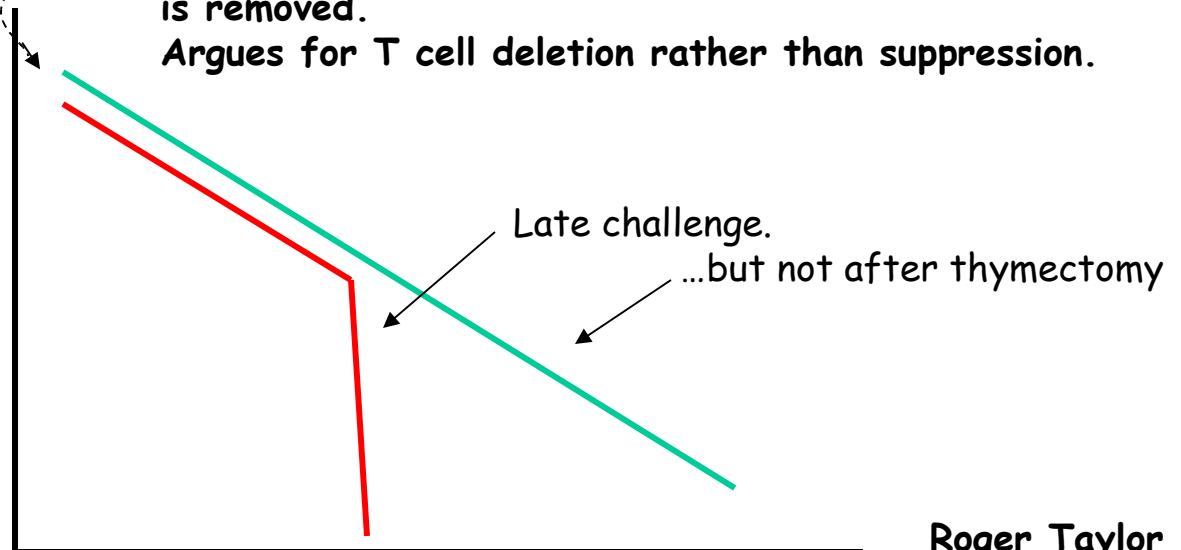
# Tolerance - of - self



University of Edinburgh

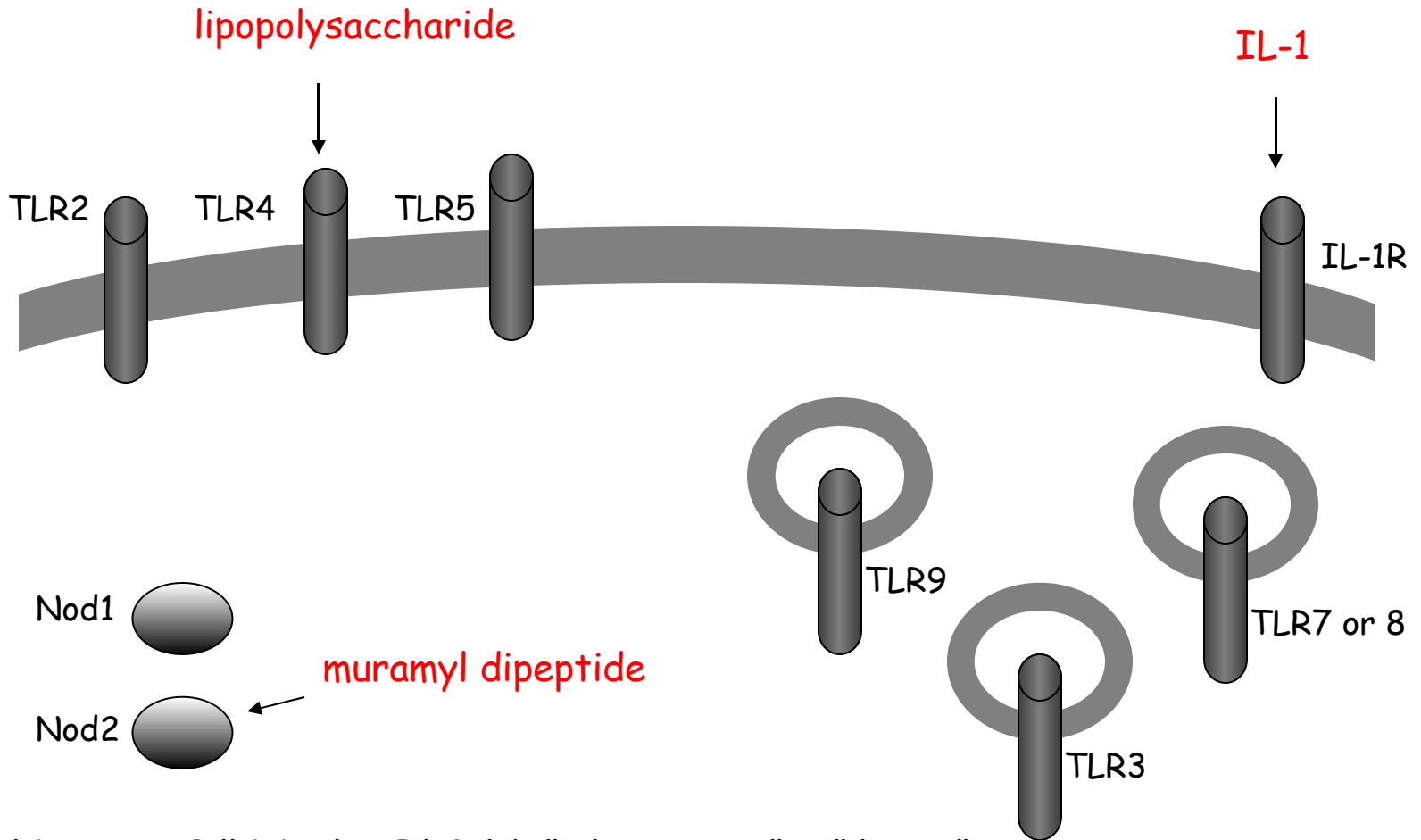


**Without antigen tolerance wains, unless the thymus is removed.  
Argues for T cell deletion rather than suppression.**



Roger Taylor

# "Sentinels": triggering inhibits tolerance induction



David Dresser, Bill Weigle, Ed Golub "adjuvanticity" ~ "danger"

# Infection and autoimmunity

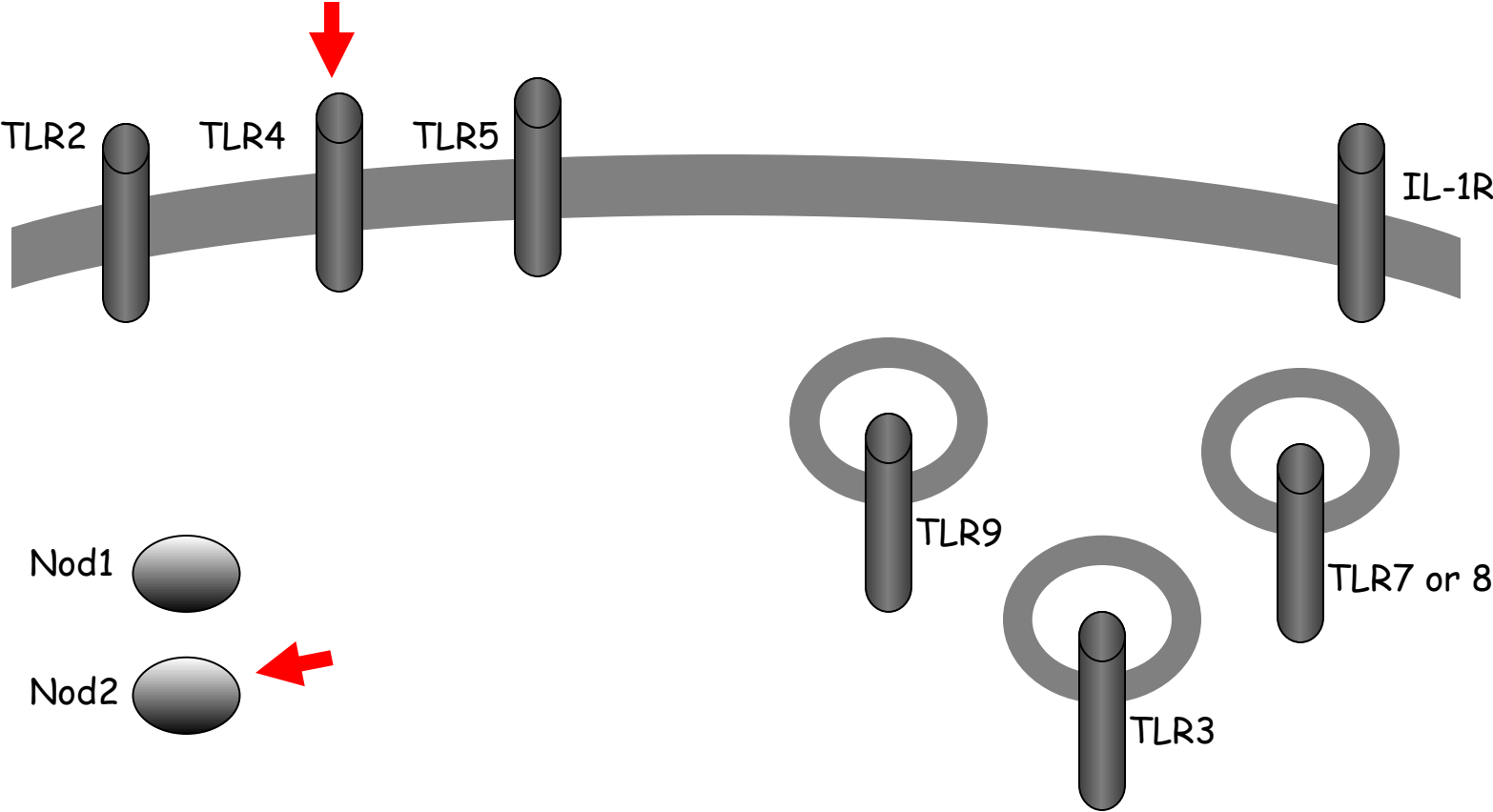
☹️ hygiene hypothesis

☹️ inappropriate triggering

☹️ molecular mimicry

☹️ disregulation

# Defective triggering associated with Crohn's disease





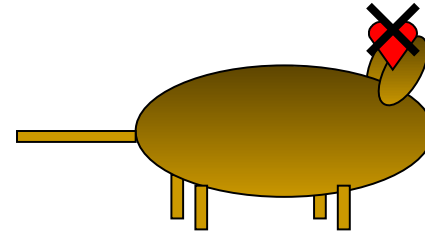
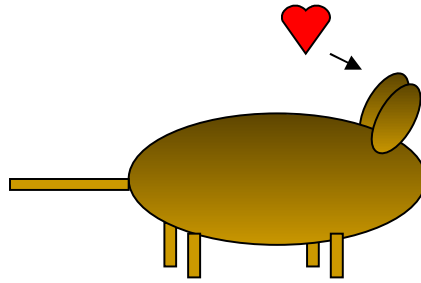
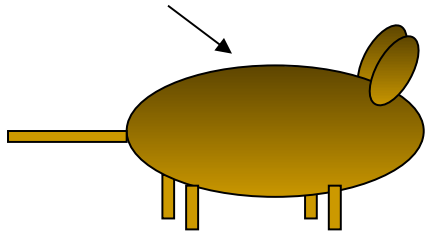
Chronic infection triggers inflammation, but little convincing evidence of autoimmunity triggered by molecular mimicry

Disease	Target organ
Chagas	Heart, gut
Herpes simplex keratitis	Cornea
Malaria	Red blood cell
Onchocerciasis	Eye
Onchocerciasis	Skin (SOWDA)
B3 coxsackievirus-associated cardiac	Heart
Rheumatic fever	Heart
B4 coxsackievirus-associated T1D	Pancreas
Spondylarthropathy*	Joints
Crohn's disease	Gut
Lyme disease (antibiotic resistant)	Joints

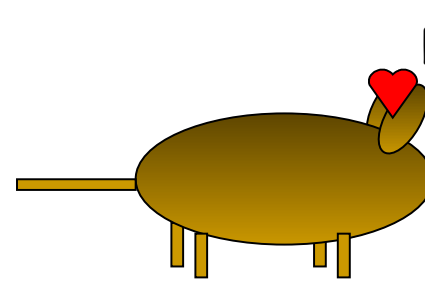
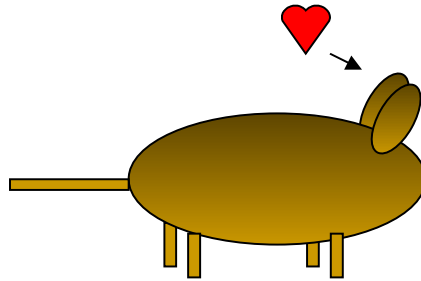
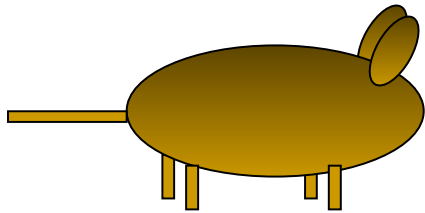
\* the best case for autoimmunity

# Pontes-de-Carvalho's heart transplant experiment

Trypanosoma cruzi



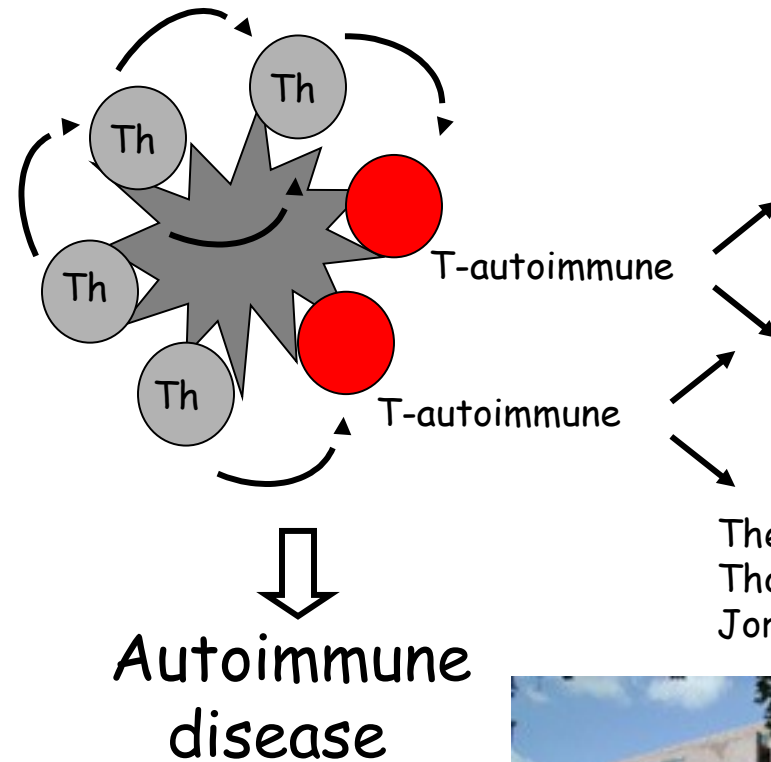
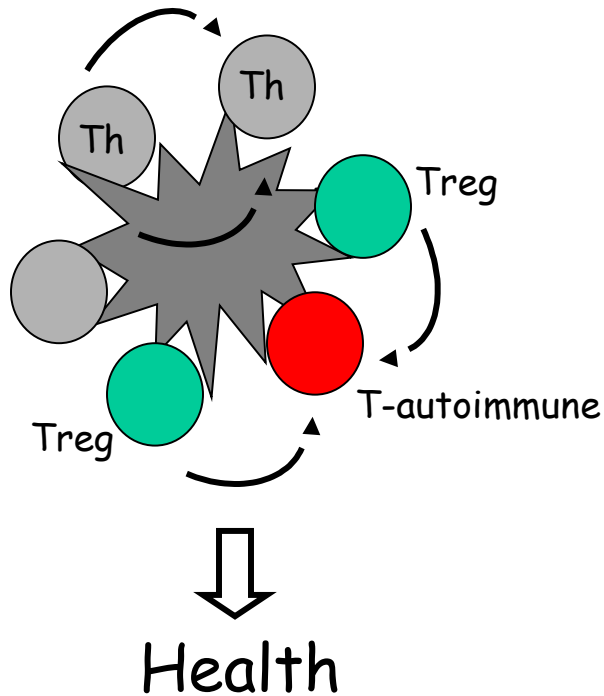
Control



beat beat

But: the rejected heart may well have acquired the parasite; this mistake can halt efforts to build a vaccine (as also with MenB).

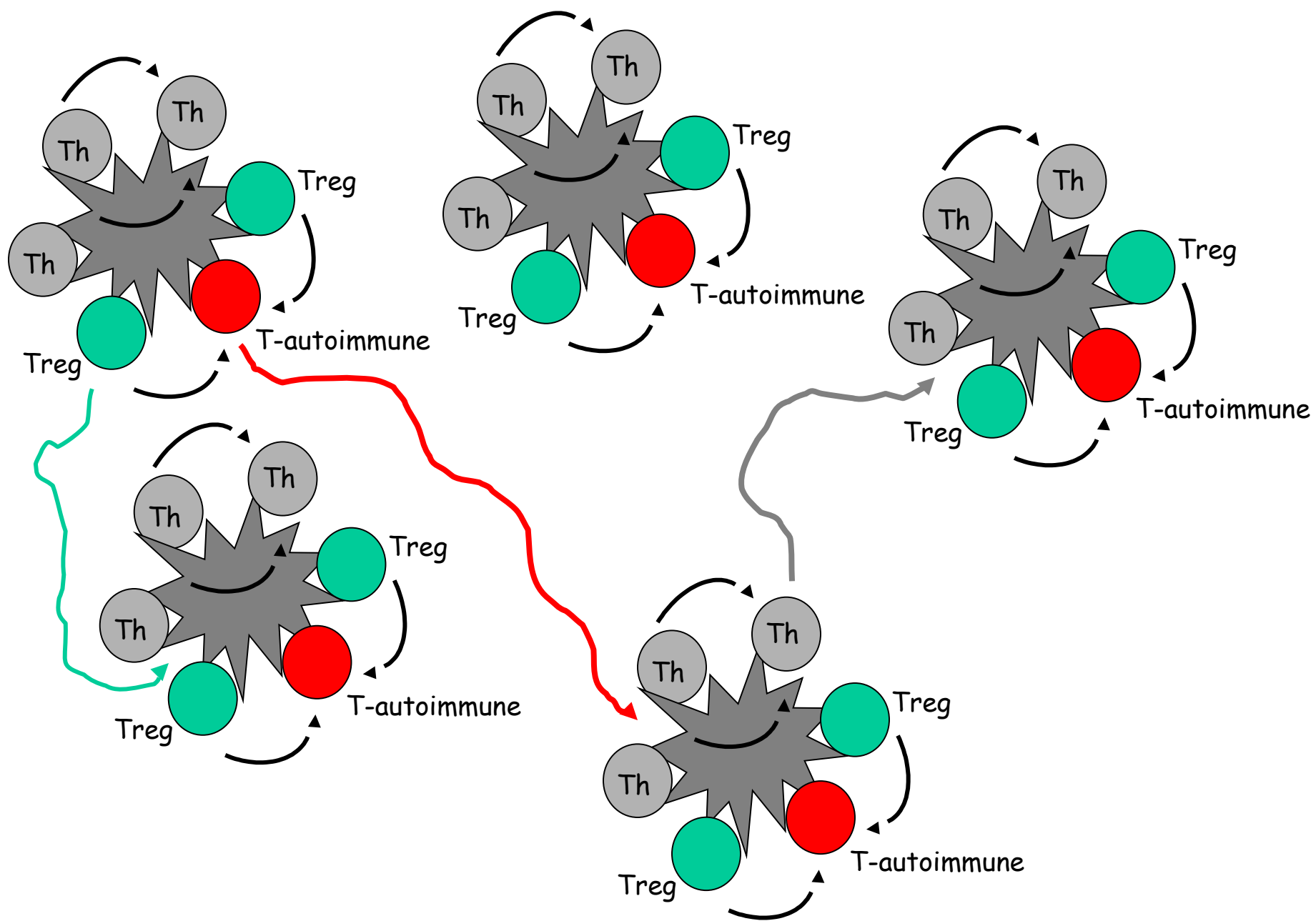
# Disregulation by a rogue parliamentary majority?



The theoreticians:  
Thomas Höffer,  
Jorge Carneiro

DRFZ Berlin





But the restless voters wander between constituencies - Ron Germain

Further insights into  
immunoregulation:  
signal strength at the  
immunological synapse



AJ717755B10PH2p  
AJ717754C3HNBH2p

AJ717753w14  
AJ717767w18

AJ492963TIRANO  
X86154b

AJ717760w16  
AJ717758w17

AJ717772w11  
AJ717768w5

AJ492958CALB  
AJ717756w25  
AJ717757w21

AJ717770w3  
Y13072NZW

IV k  
Y13075MSMF47.1  
AJ492960PERA/Ei

X86155k  
M35677f  
Y13076MSMF47.2  
AJ717771w8  
AJ492962SK  
AJ492961PERA/Rk

X00777d

AJ717763w23  
AJ717776PWK  
AJ717761w20  
AJ717765w19  
AJ493005MOR  
AJ493002CAST  
X86156q  
AJ493008WSB  
AJ493007SKIVE  
AJ493006PERC  
AJ493004LEWES  
AJ493003CZECHII  
AJ493001CASA  
AJ717751w10  
AJ717762w22  
AJ717766w15  
AJ717764w1  
AJ717759w24

I b,d,q,

AJ492959MOLE

AJ717752w4

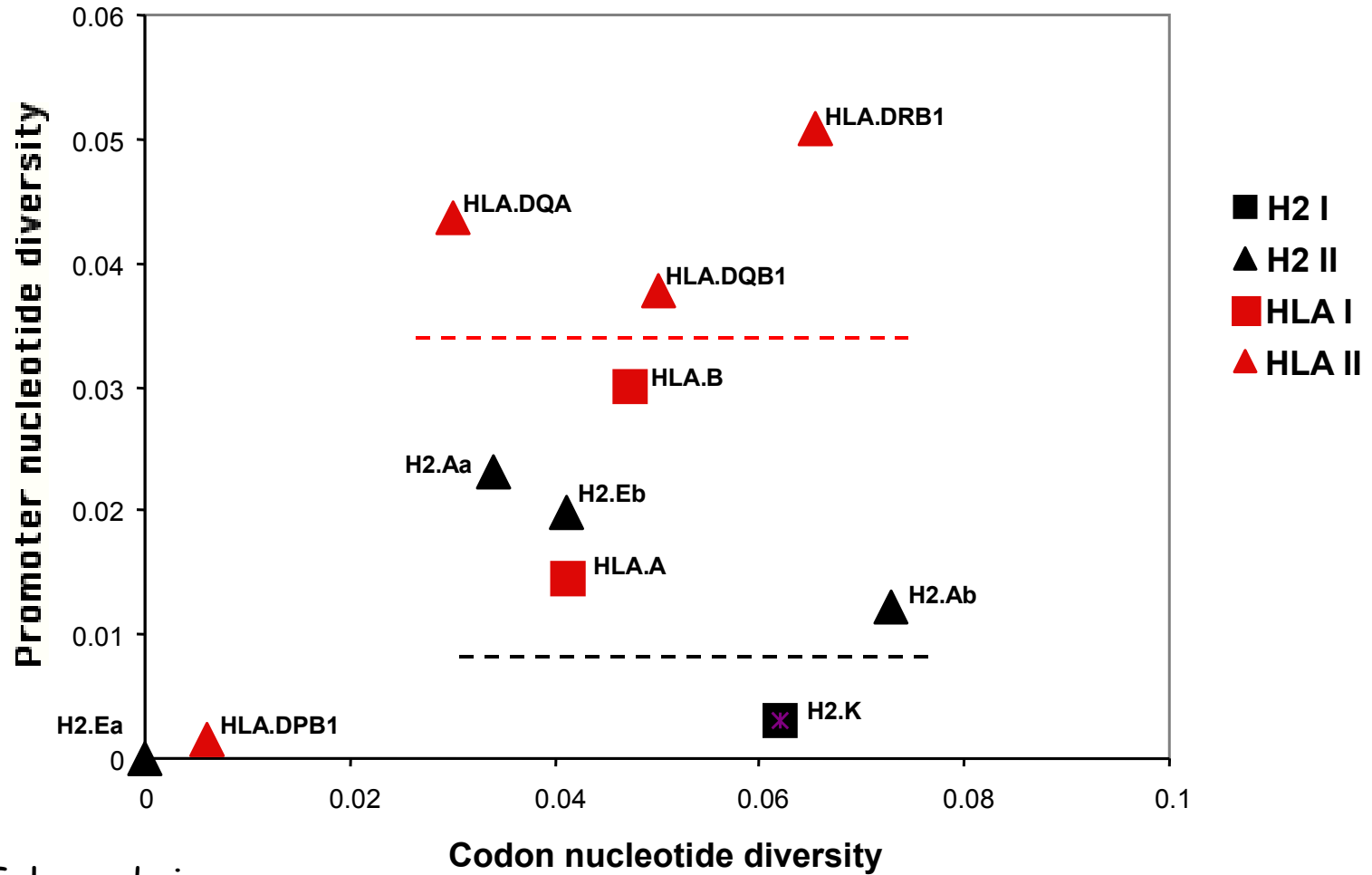
II z

AJ717769w6  
AJ492964ZALENDE  
AJ717775MSM/JAX

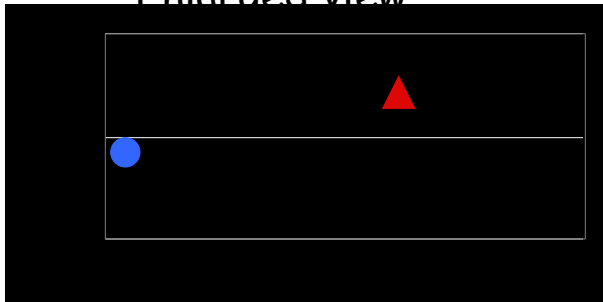
AJ493012SF  
AJ493009MOLC  
AJ493011MOLF  
AJ493010MOLD  
AJ717773MOLG/JAX  
AJ717774JF1/JAX

III f

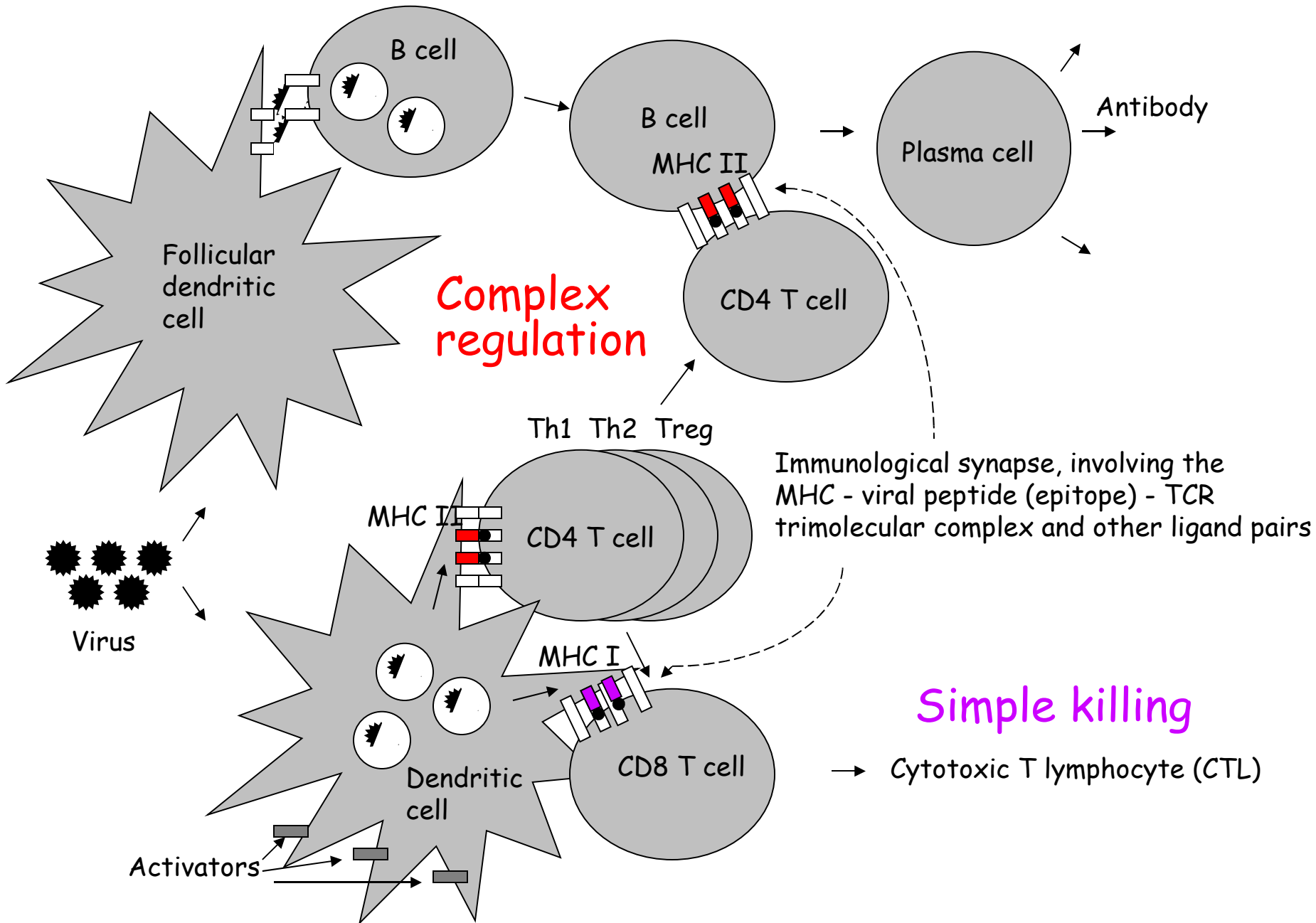
# Greater promoter diversity among MHC class II genes



Enlarged view



# MHC I and MHC II have different tasks





## Two interesting substitution in the B27 promoter

-270                      -260  
CGAAGTCC**A**AGGcCCCGGgCG**C**GGCTCT    3 HLA.B27 promoters  
CGAAGTCCCAGGcCCCGGgCGGGGCTCT    54 other HLA.B promoters

← IK2                      GC →

# Functional activity of MHC promoter polymorphisms?

- RT-PCR
- Reporter constructs (<1kb) ✓
- Transduction (<10kb)
- BAC (~100kb)
- Homologous recombination ("knock-in")

# BAC spanning the mouse classical MHC

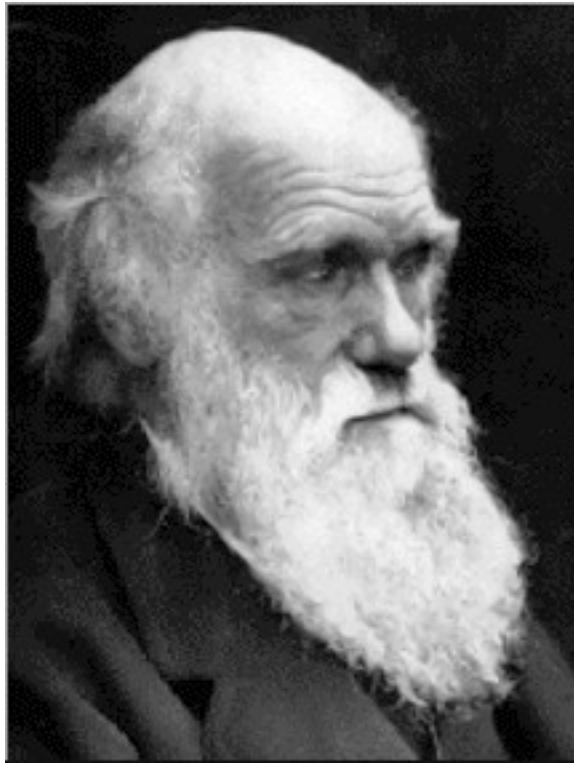
10 kb



QUICKTIME® AND A  
NONE DECOMPRESSOR  
ARE NEEDED TO SEE THIS PICTURE.



neodarwinism



Shall we ever crack regulatory DNA?

# Summary

## We like...

Genome based vaccines.

Regulation based on signal strength at the immunological synapse.

In-and-out around dendritic cells.

Systems biology (expression arrays) applied to T & B cells development.

## We don't like...

The holistic approach: "strengthening" the immune system or "weakening" it.

The asthma "epidemic"  
Environmental pollution "damaging" the system.

Molecular mimicry.

Auto-antibodies as cause of disease.

Cancer surveillance.