

Summary of the last lecture:
DC & the initiation of adaptive immunity

- Signals required for initiating the adaptive immunity
 - *Ag recognition (Signal 1)*
 - *Co-stimulations (Signals 2, 3...)*
- Co-stimulations
 - *Cellular interactions or triggering other than Ag-specific stimulation*
 - *Cell surface-bound & soluble molecules*
- Models of T-B, DC-T-B cell cooperation
- DC – Initiator of the adaptive immunity
 - *Uniquely combined immunobiological properties*
 - *A link between the innate & the adaptive immune systems*
 - *The activator of naïve T cells*

T cell effector functions

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Outlines

- T cell phenotypic & functional heterogeneity
- Historical perspectives: *the Th1/Th2 paradigm*
- Essential factors driving T cell differentiation
- Effector T versus Regulatory T cells
- *DC: the master regulator of T cell responses*

T cell functional phenotypes

- *Helper T cells*
 - *Phenotypic marker: CD4⁺ (T4/L3T4)*
 - *Th1, Th2, Th3...Tfh*
- *Cytotoxic T cells:*
 - *Phenotypic marker: CD8⁺ (T8/Lyt-2)*
 - *Tc1, Tc2*
- *Regulatory T cells:*
 - *Phenotypic markers: CD4⁺Foxp3⁺ (CD25^{hi})*
 - *nTreg, Tr1...*

T helper cell functional heterogeneity

(Early findings)

- *Parish CR & Liew FY & (1971/2):*

Distinctive Th functions for humoral vs cellular responses to:

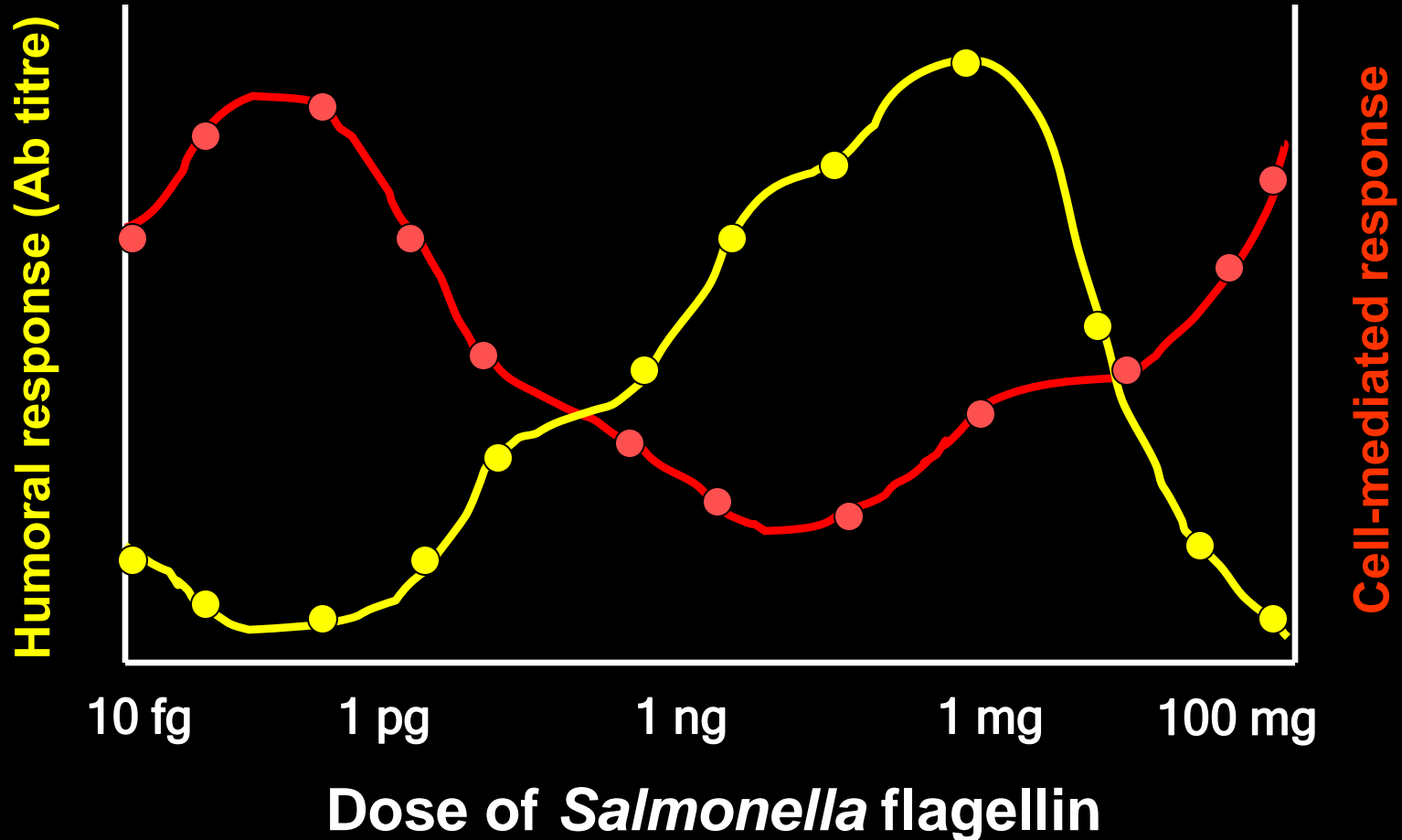
- *hapten-carriers*
- *bacteria (Salmonella)*

- *Tada T et al. (1978):*

Th types for Ab responses to different hapten-carrier conjugates

- *nylon wool non-adherent (Ia^-): Th1*
- *nylon wool adherent (Ia^+): Th2*

Birth of the T_H type/subtype paradigm



(Parish CR & Liew FY. JEM 1972, 135:298-311)

T_H clones distinctive in cytokine profiles

(Mosmann TR, Coffman RL et al., 1986, DYAX)

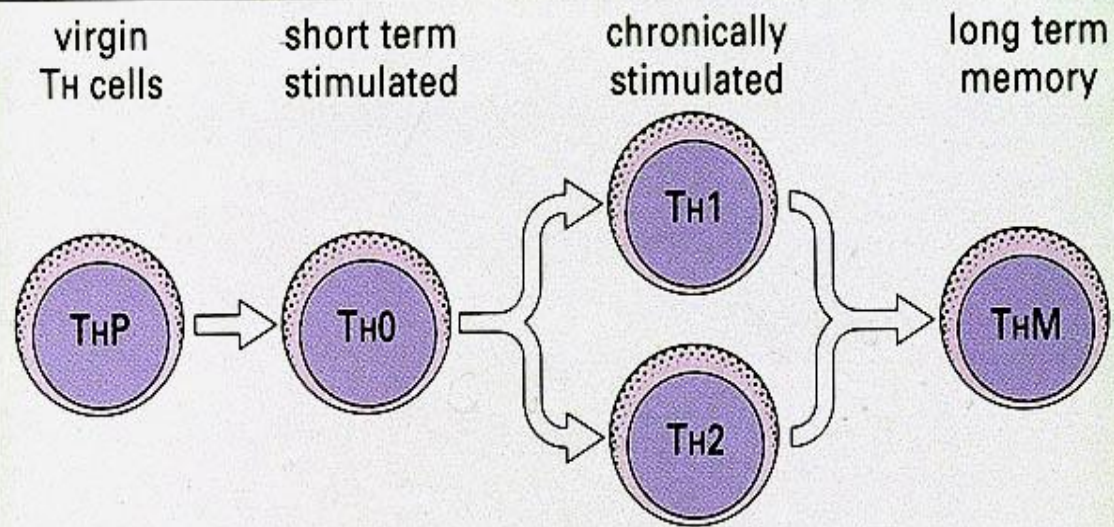
- **T_H1: IL-2, IFN- γ , IL-3...**
- **T_H2: BSF1 (IL-4), IL-3 ...**

CD4⁺ T cell subsets induced during infection or immunization with *Leishmania Major* in mice

<i>Cells</i>	<i>Source</i>	<i>Protection</i>	<i>Ab</i>	<i>IL-4</i>	<i>IFN-γ</i>
• Tr	cured	+	+	-	+
• Ts	progressive	-	+	+	-
• Ti	i.v. immunized	+	+	-	+
• Tsc	s.c. immunized	-	+	+	-

Refs.: Liew FY. *Parasitol. Today* 1986; 2:264-270
 Liew FY. *Immunology Today* 1989; 10:40-45

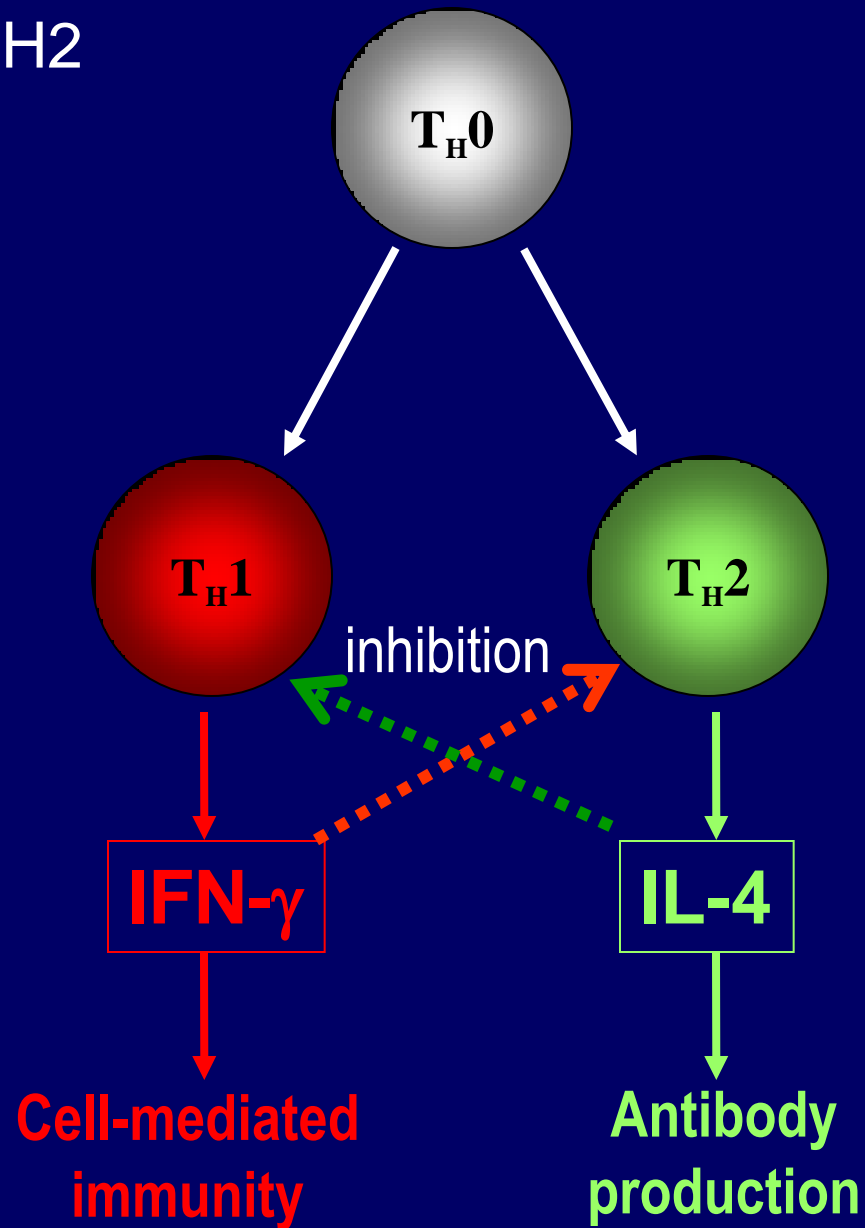
Differentiation of murine TH cells



cytokines released

ThP	Th0	Th1	Th2	ThM
	IFN _γ	IFN _γ		
IL-2	IL-2	IL-2		IL-2
	IL-4		IL-4	
	IL-5		IL-5	
			IL-6	
	IL-10		IL-10	

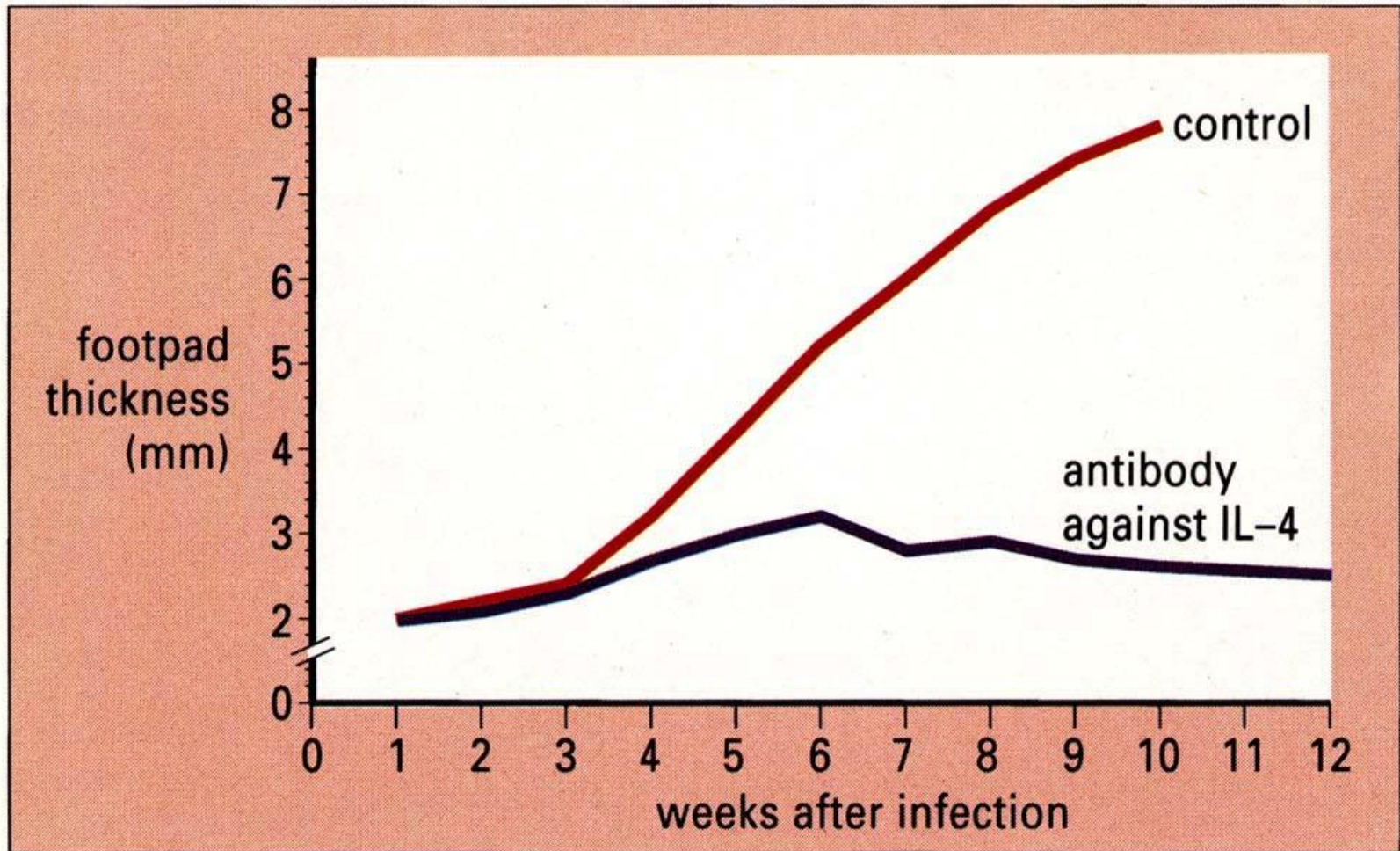
T_{H1} vs T_{H2}



Type of Th effector mechanism induced
may determine the outcome of an infection

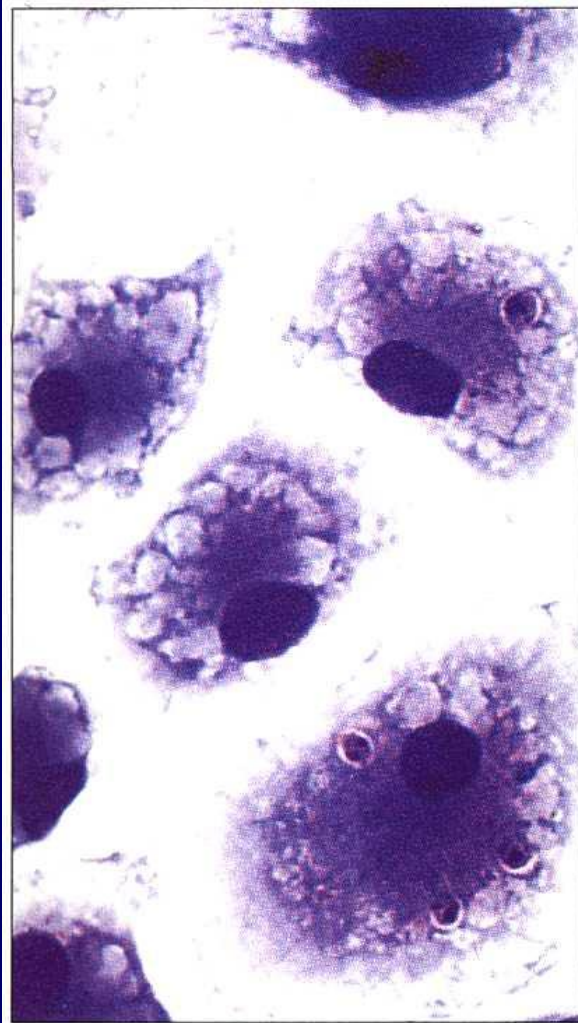
Role of IL-4 in *L. major* infection

Cytokine production and the spread of infection



Killing of Leishmania by lymphokine-activated macrophages

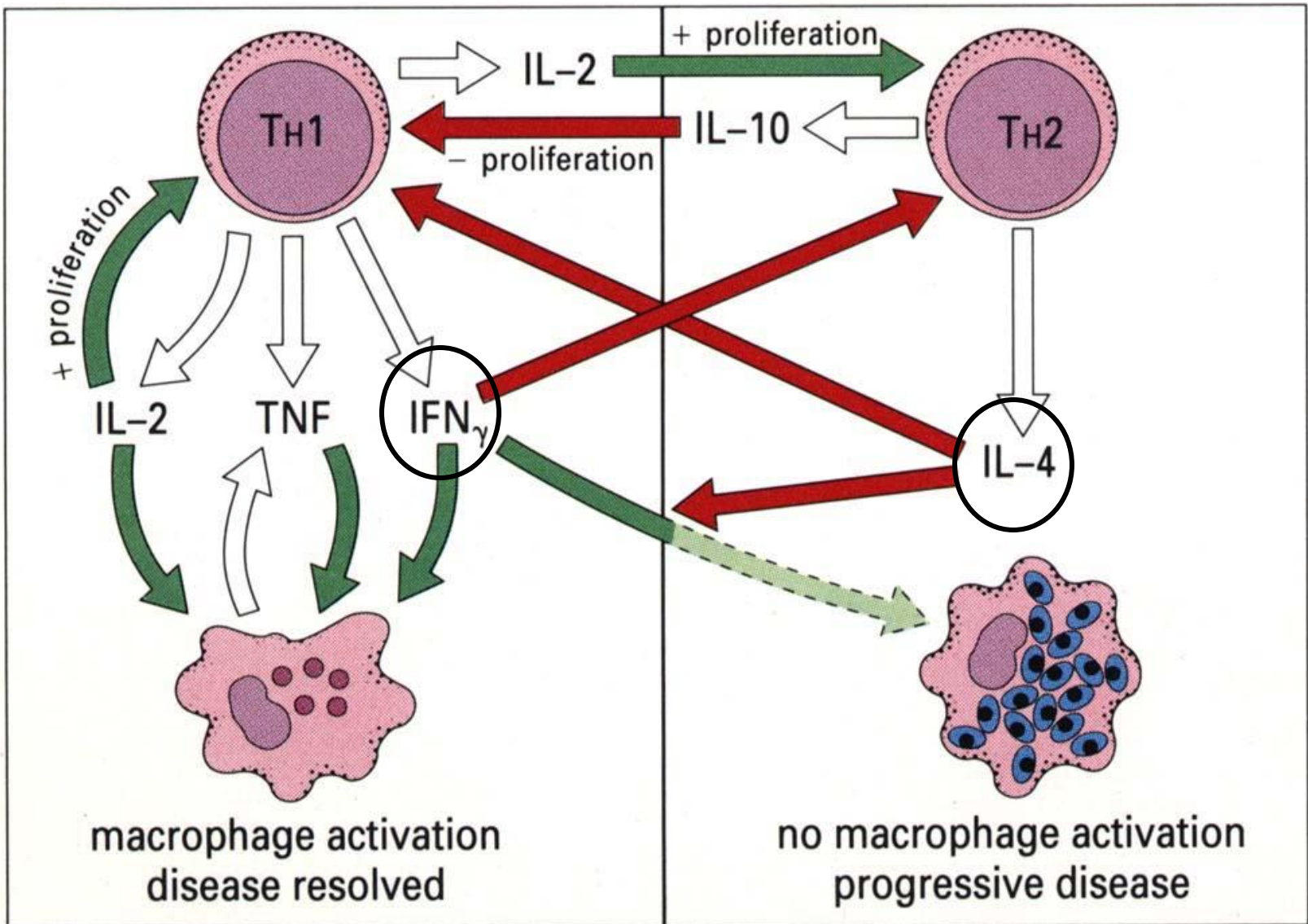
Activated (IFN- γ)



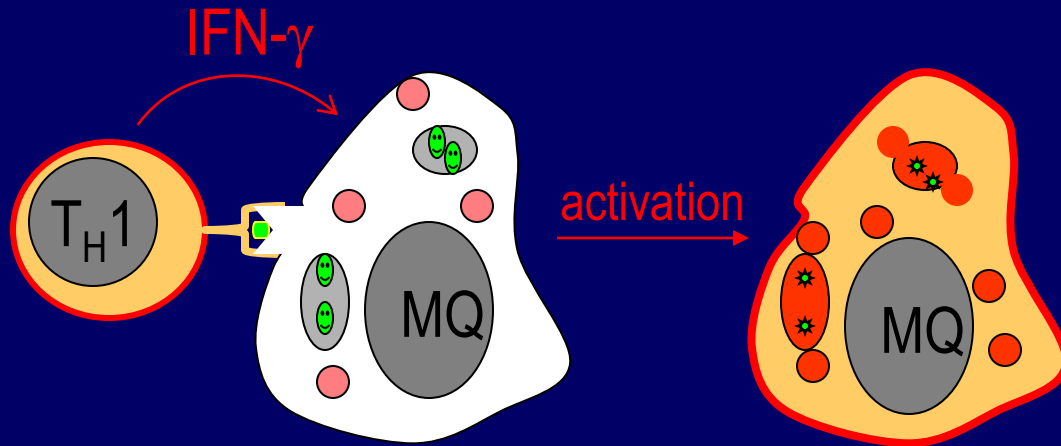
Control



Action of TH1 and TH2 cells in *Leishmania* infection



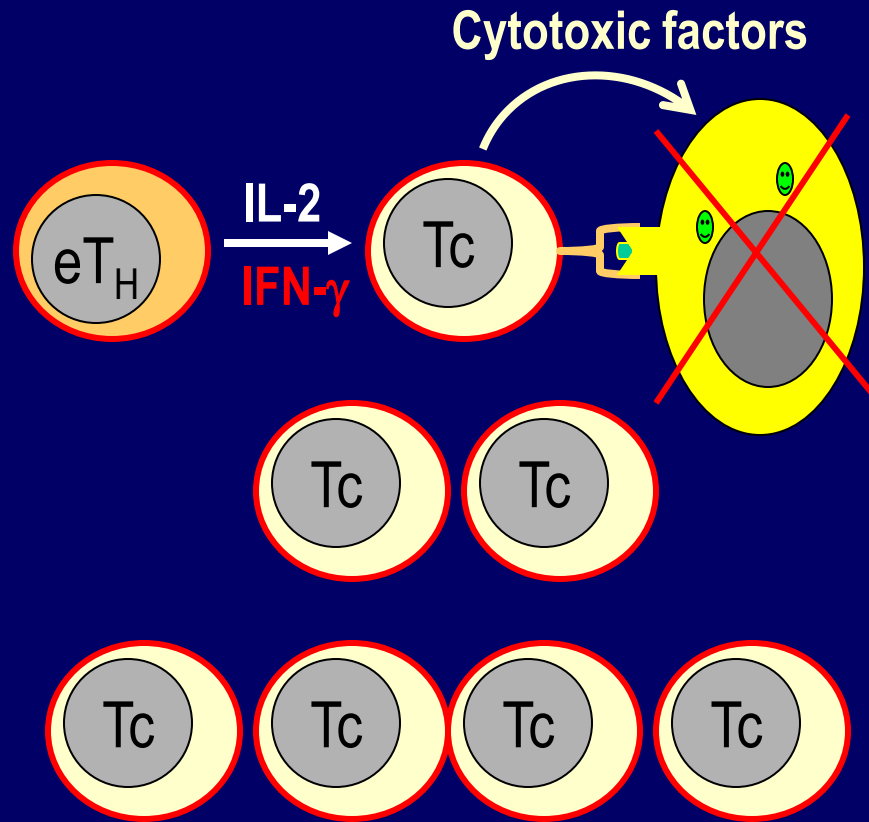
T-dependent macrophage activation



MHC expression
phago-lysosomal fusion
inducible NO synthase (iNOS)



Th1 & CTL effector functions



Dysregulated Th functions in autoimmunity

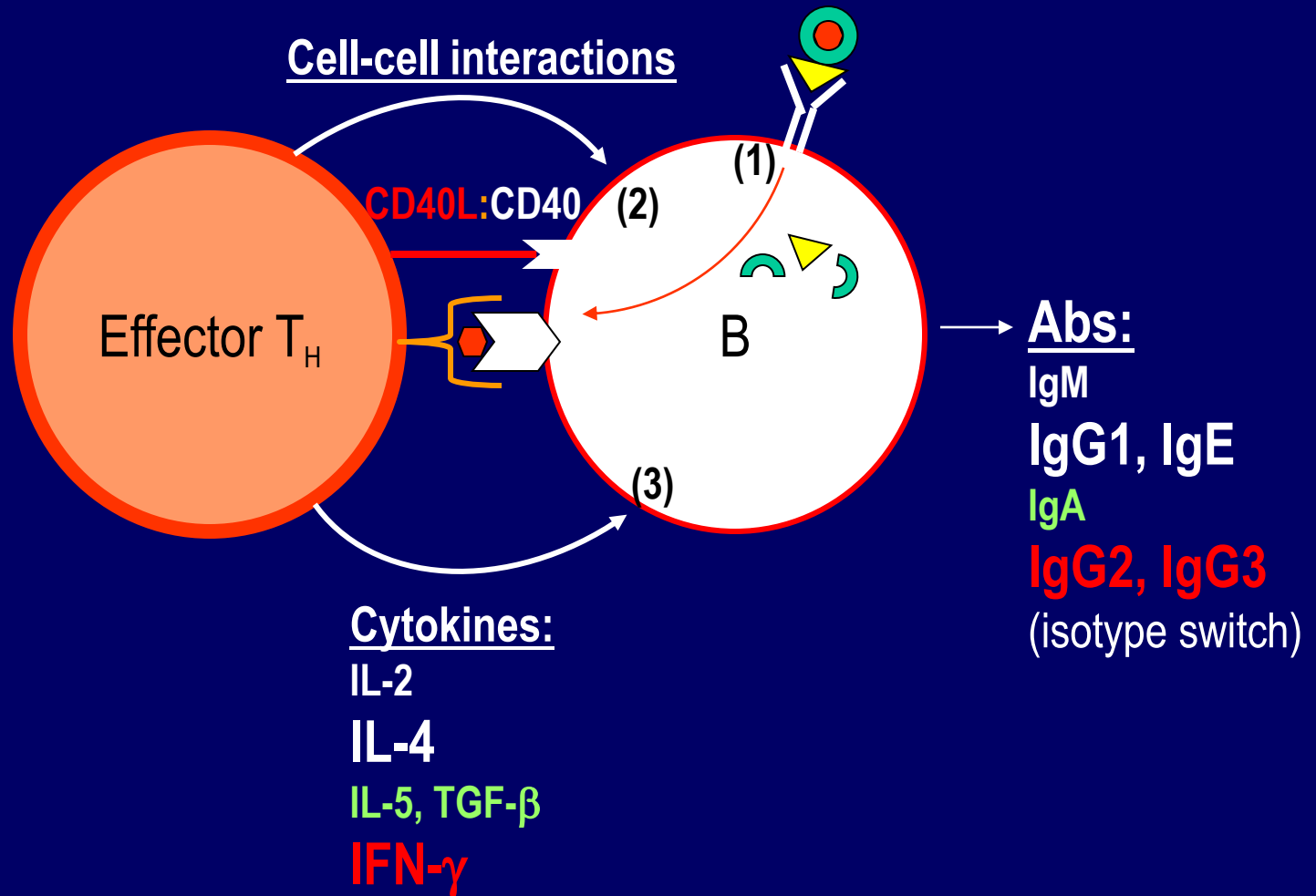
- Autoimmune diseases associated with polarization of T cell responses *in vivo*:
 - **Th1**: IBD, RA, type I diabetes mellitus
 - **Th2**: allergy, asthma
 - **Th2 & Th1**: SLE
- Modulation of immune system may have therapeutic benefit.

Lupus disease induction & the Th1-mediated pathogenic autoantibodies



Systemic autoimmune disease induced by dendritic cells that have captured necrotic but not apoptotic cells in susceptible mouse strains

T-B cell cooperation



Factors driving Th1 & Th2 cell differentiation

- Factors important for **Th1** differentiation
 - **IL-12** (*DC*, MQ)
 - **IL-18** (MQ, Kupffer cells, *DC*)
 - **IFN- γ** (T, NK, *DC*)
- Factors important for **Th2** differentiation
 - **IL-4** (T, *DC*, NK-T/mast cells?)
 - **IL-6** (T, MQ...)
 - **IL-10** (T, MQ, *DC*)
 - **IL-33** (HEV, *DC* ...)

The questions:

DC heterogeneity?

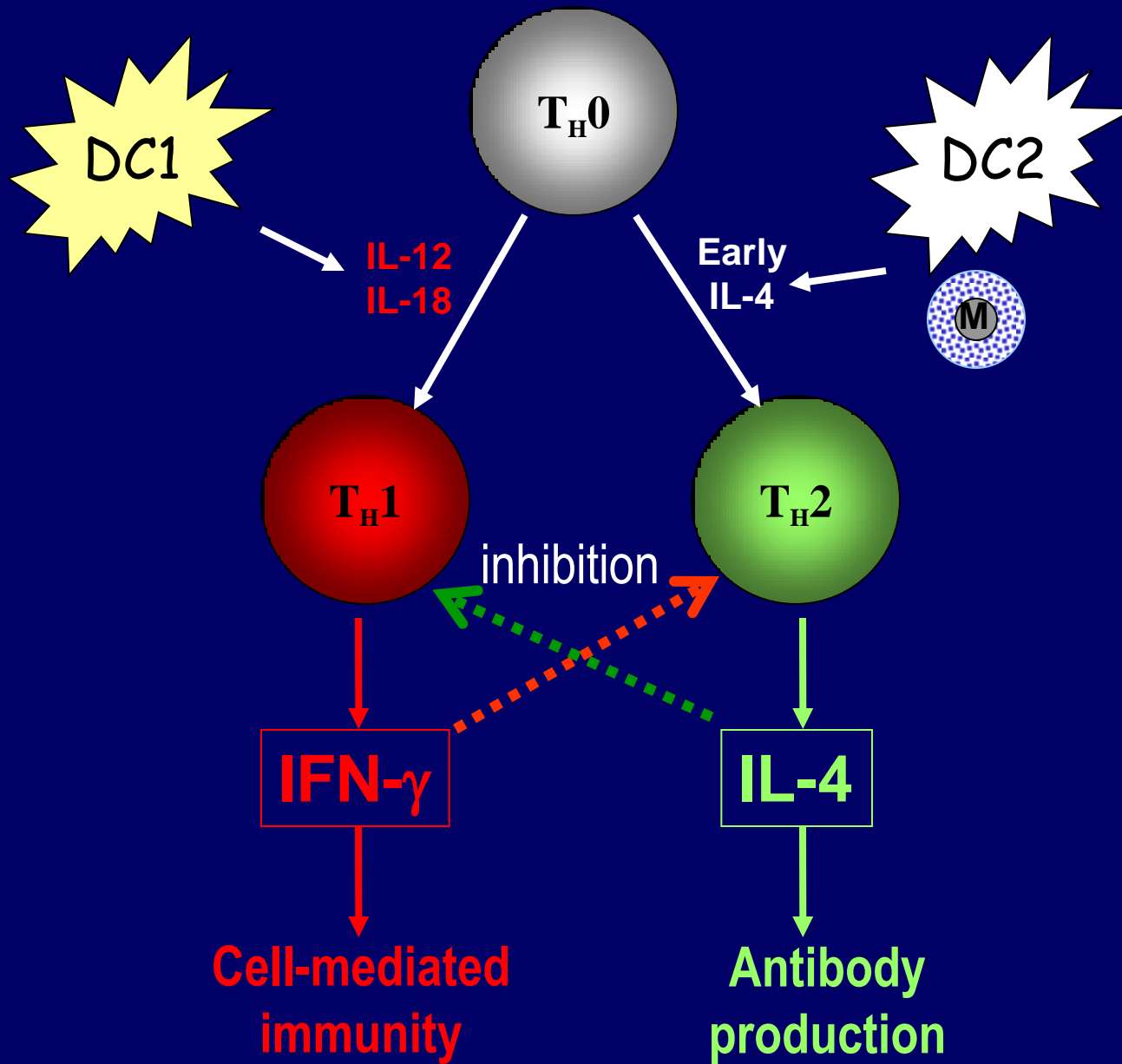
How DC may induce immunity, & tolerance?

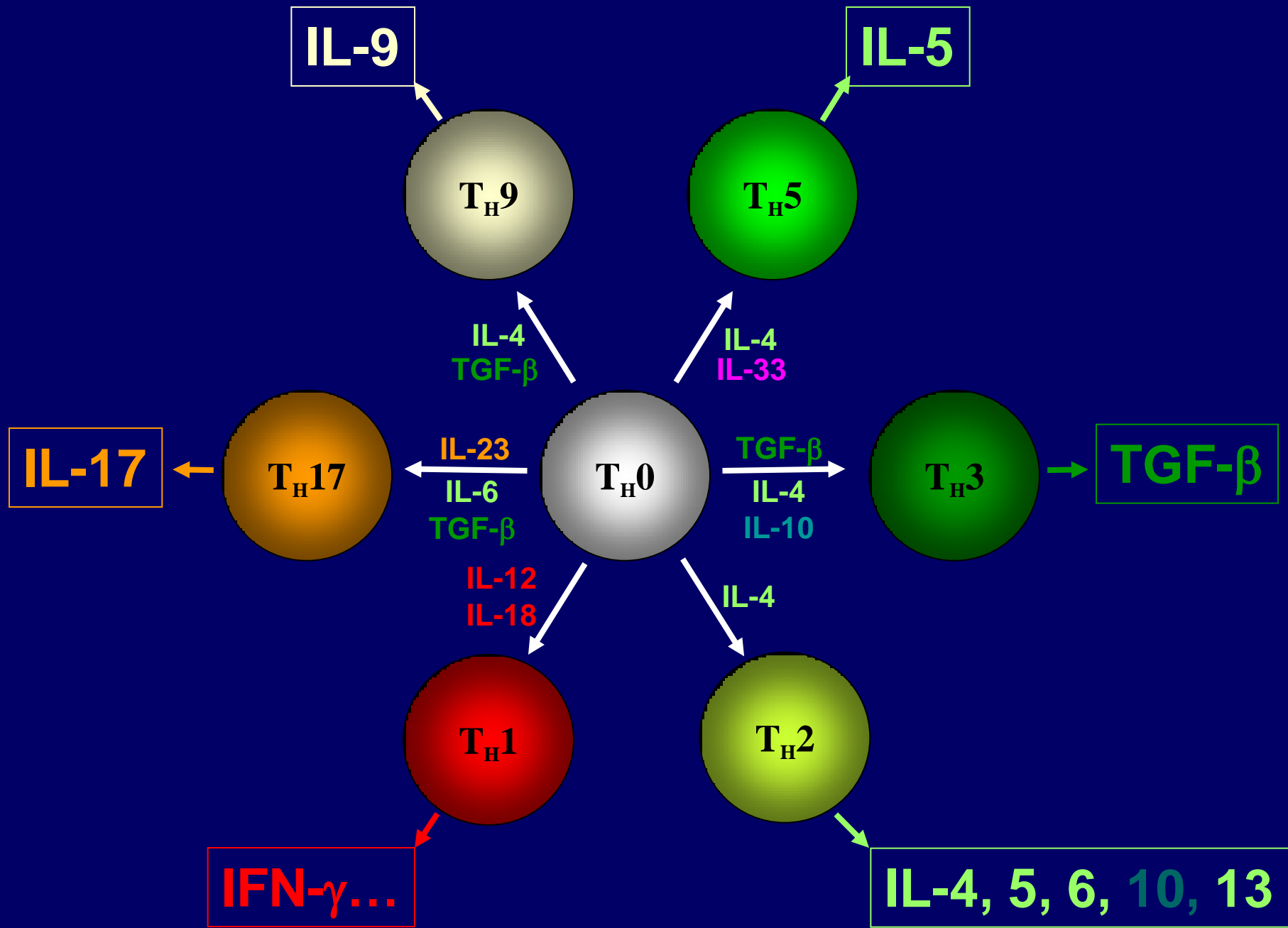
Dendritic cells (DC) & follicular dendritic cells (FDC) are two very different cell types

	<u>DC</u>	<u>FDC</u>
Origin:	Bone marrow-derived Haematopoietic	Non-BM derived Stromal cells?
Where:	T areas, & peripheral tissues	B follicles
Nature:	endocytic & migratory	resident
Life-span:	days	years
Present Ag:	as peptide to T cells by MHC	as IC to B cells by Ig-Fc

DC subsets & lineage origins

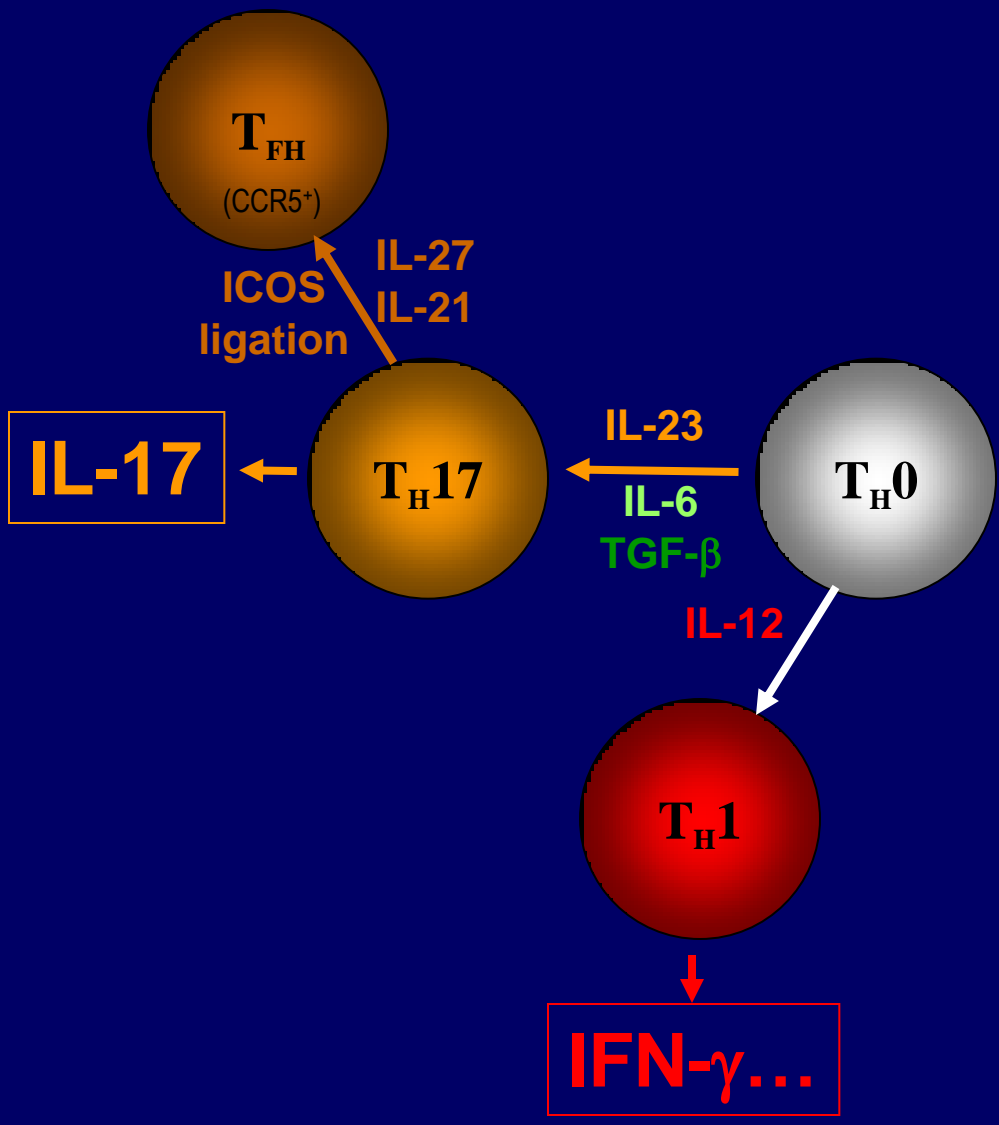
- *Mouse:*
 - $CD8\alpha\alpha^-$ ($CD11c^+$, myeloid)
 - $CD8\alpha\alpha^+$ ($DEC205^+$, lymphoid)
- *Rat:*
 - $OX41^-$ ($CD4^-OX62^+$, myeloid?)
 - $OX41^+$ ($OX41^+OX62^+$, lymphoid?)
- *Human:*
 - cDC ($CD11c^+$, myeloid): **DC1**
 - pDC2 ($CD11c^-CD123^{++}$, lymphoid?): **DC2**





The Th17 cell

- Important role in host defence against certain pathogens:
 - Bacteria, eg. *Klebsiella pneumoniae*
 - Fungi, eg. *Candida albicans*
- Involved in tissue inflammatory responses, including recruitment of neutrophils
- Implications in autoimmune diseases:
 - Rheumatoid arthritis (RA)
 - Experimental autoimmune encephalomyelitis (EAE)

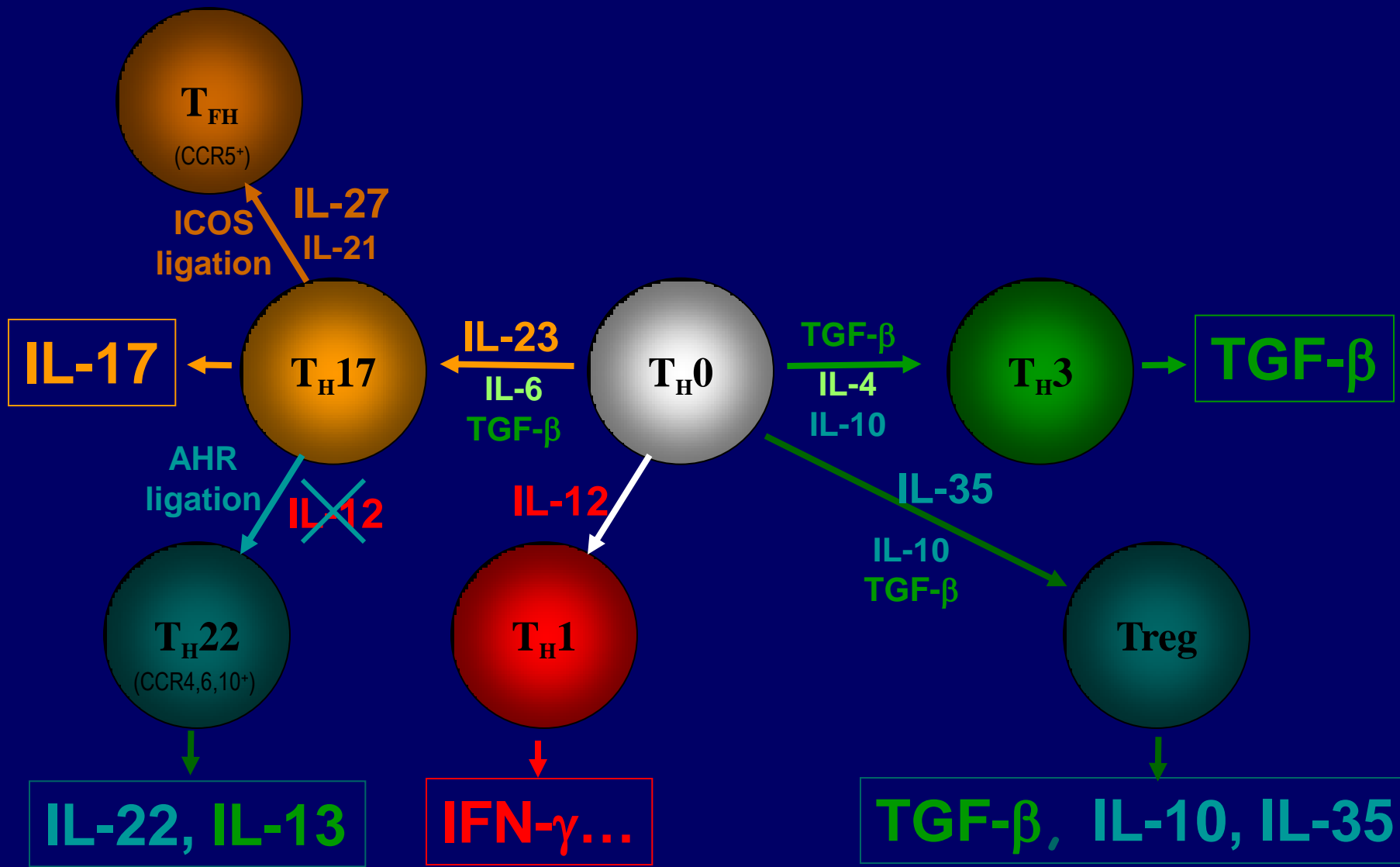


T_{FH} : Cognate help for B cells

- Play crucial roles for B cell selection in the germinal centre.
- Express ICOS & interact with follicular B cells (ICOSL⁺).
- Express CXCR5⁺ (ligand: CXCL13).
- Development mediated by IL-6, IL-21, IL-27, ICOS, Bcl6.

The IL-12 family members

- **IL-12** (p35:p40):
 - **Th1**/NK driving factor
- **IL-23** (p19:p40):
 - **Th17**/NK driving factor
- **IL-27** (p28:EBI3):
 - Promotes **Th1/TFH**/NK but suppresses **Th17**
- **IL-35** (p35:EBI3):
 - Suppresses **Th1** & **Th17**
 - *Induces, & expressed by, Treg*



AHR: aryl hydrocarbon receptor

Regulatory T cells

- Generated in thymus
 - Naturally occurring (nTreg)
 - Expanded in periphery upon Ag stimulation (iTreg, Tr1, iTR35)
- IL-2 dependent
- Phenotypic markers
 - CD4⁺CD25^{hi}
 - **Foxp3⁺**
 - **CTLA-4⁺**
- Suppress immune responses by:
 - Release of immunosuppressive cytokines: IL-10, IL-35, TGF- β ...
 - Cell-cell contact

Co-stimulations

- Cellular interactions/triggering other than Ag-specific stimulation

- **B7 (CD80, CD86)**

- **B7:CD28** interaction delivers a positive signal to T cells
- **B7:CTLA-4** interaction delivers a negative signal to T cells

- **CD40/CD40L, ICOS/ICOSL (B7H)**

- Crucial for B cell growth & differentiation

- **Cytokines & cytokine receptors**

- **Adhesion molecules...**

Tolerogenic / Regulatory DC

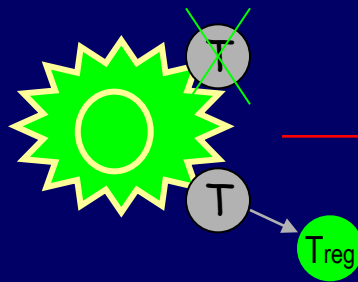
- DC associated tolerogenic molecules
 - Cytokines: IL-10, TGF- β
 - IDO (Indoleamine 2,3-dioxygenase)
- DC “licensed to kill”
 - Thymic medullary DC mediated negative selection
 - *CD8 $\alpha\alpha$ ⁺ DC in mouse (Fas/FasL mediated killing?)*
 - OX41⁻CD4⁻ DC in rat (NKR-P1)
- *Immature DC induces Tregs*
 - *DC confers tolerogenic memory and specificity through the induction of regulatory T cells?*

DC maturity & immuno-adjuvanticity

Immature DC

(Ag uptake mode)

Low surface MHC
Low B7

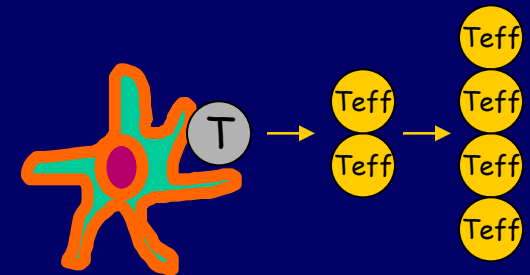


'Tolerogenic'

Mature DC

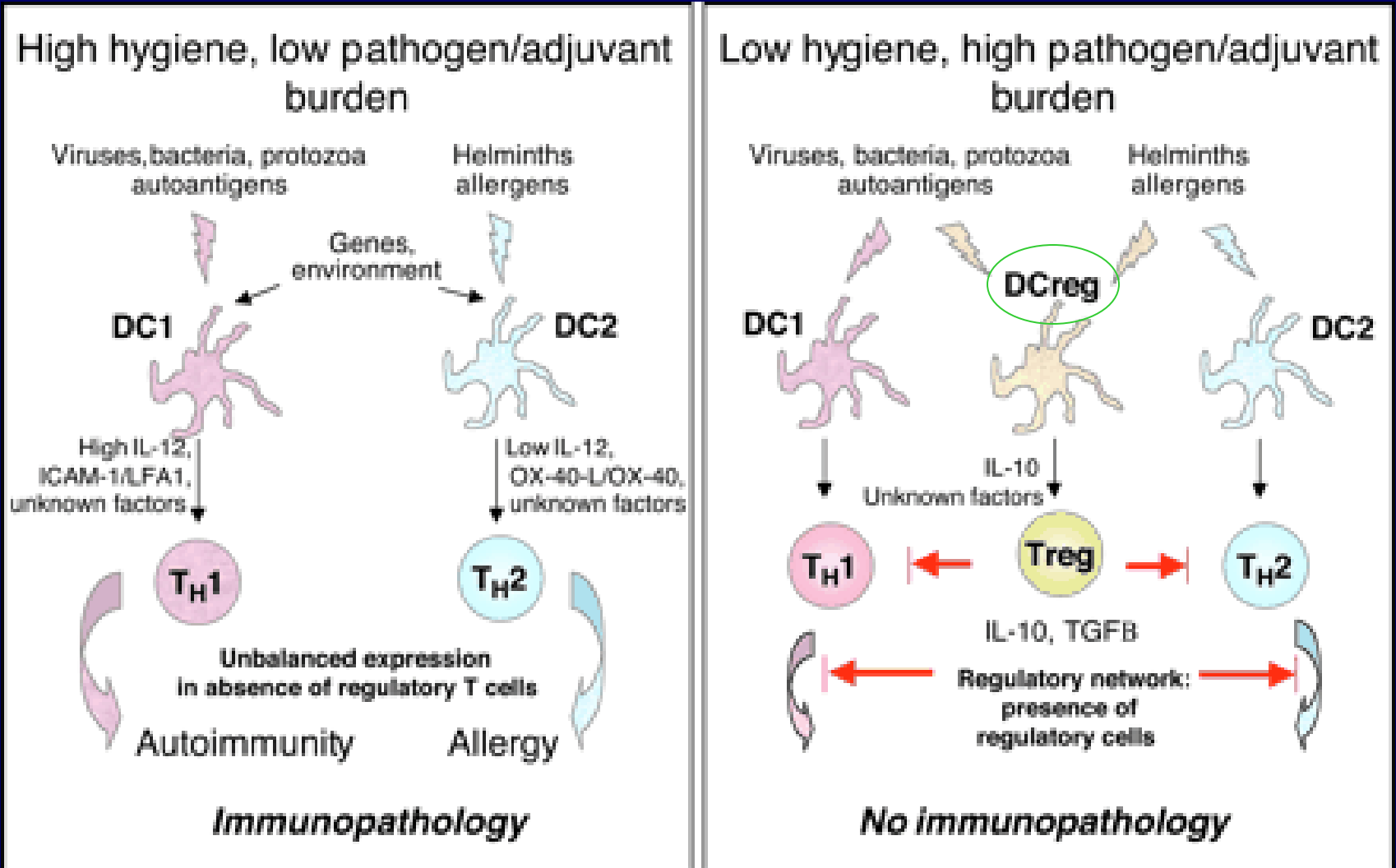
(Ag presenting mode)

High surface MHC,
High B7, cytokines



'Immunogenic'

The Hygiene Hypothesis explained by regulatory T-DC network?



Further questions:

Do DC need to be activated to induce immunity?

What then activates DC?

Vaccination: why adjuvant?

Summary : *T effector functions*

- T cell phenotypic & functional heterogeneity:
 - Th1: important for cell-mediated immunity.
 - Th2 : important for humoral immunity.
 - Tc, Th...
 - Th17: immunity against infections, cancers, & autoimmune diseases.
 - Tfh: Crucial roles for B cell selection in the germinal centre.
 - Treg: Suppress immune responses via cellular interactions & cytokines.
- Cytokines - key functional molecules of T effector cells.
- DC: the master modulators of T effector functions.
- A self-regulated & balanced immune system is important in health, & in its fight against diseases.