Adaptive immunology continued
CD4 T cell activation and functions

Viral peptides
usually by infection

Bacterial peptides usually
by phagocytosis

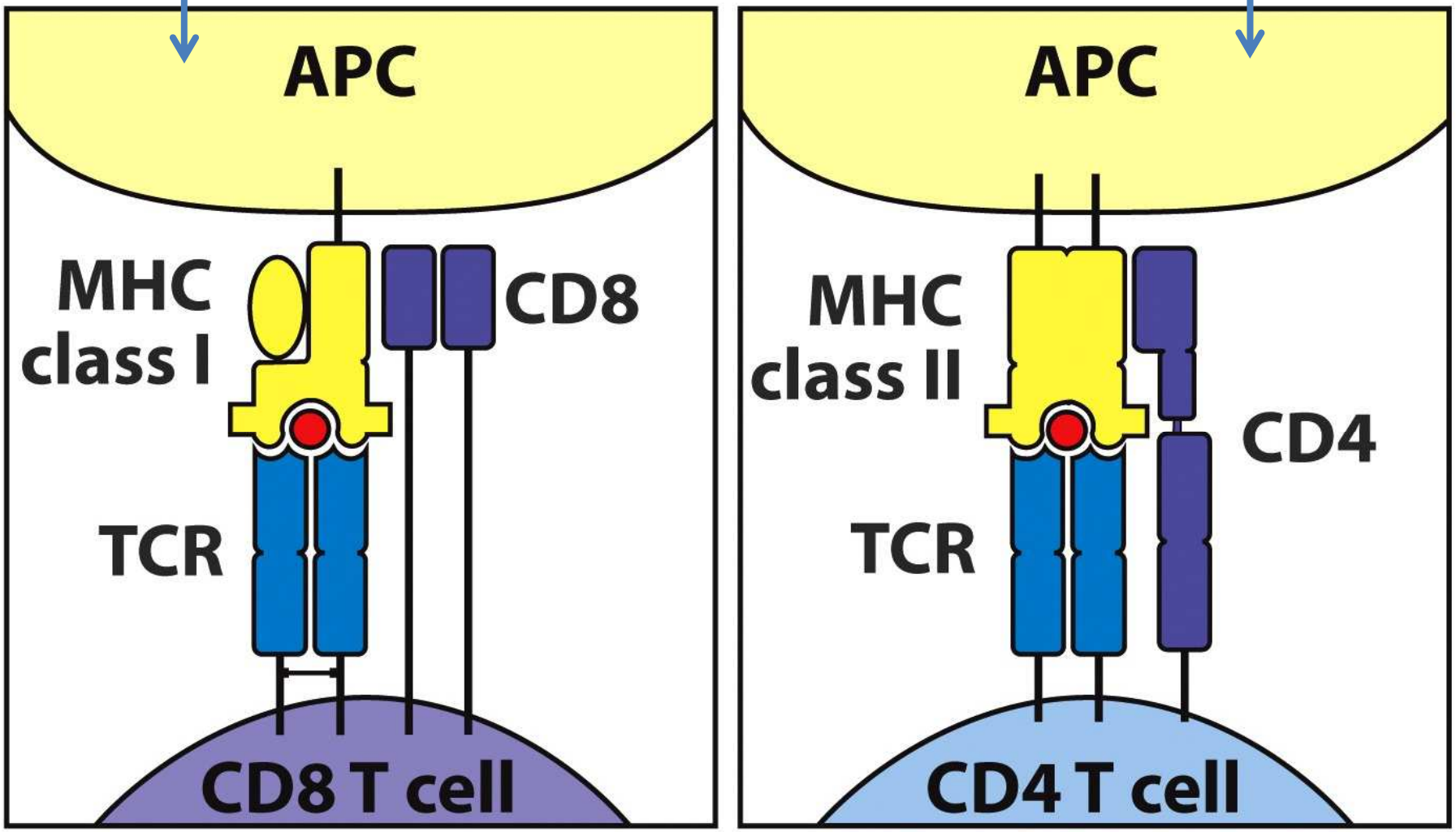


Figure 3.9 The Immune System, 3ed. (© Garland Science 2009)

Reminder: CD8+ T cell response to activation

1. Proliferation

2. **Differentiation into**
    1. **effector CTL (cytotoxic CD8+ T lymphocytes)**
    2. **Memory CD8+ T cells**

3. Produce cytokines

4. When the effector CTL synapse with an infected cell , **they release toxic proteins to lyse the infected cell (cytolysis) ; induce target cell death (apoptosis)**
   E.g. perforin, granzymes

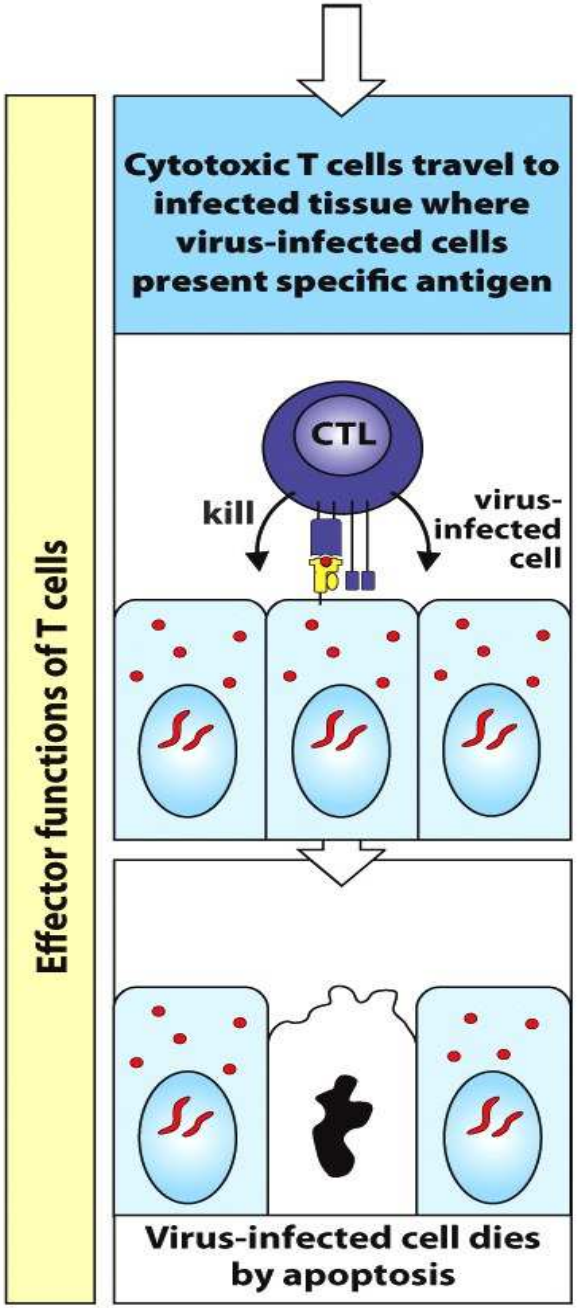


Figure 8.39 part 2 of 2 The Immune System,

CD4+ T cell response to activation

1. Proliferation

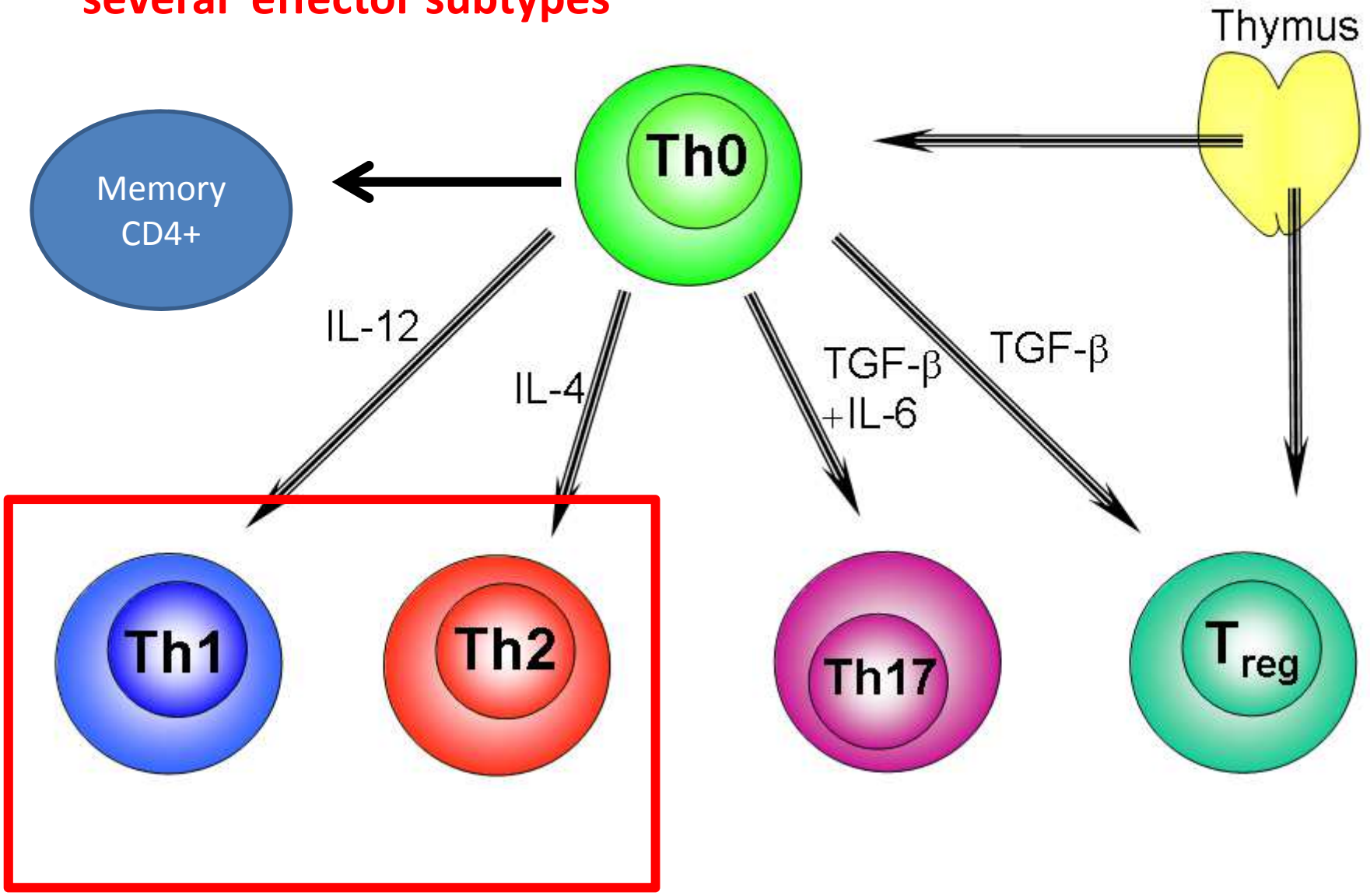
2. Differentiation into
    1. **CD4+ Th1 or Th2 effector cells (or other types)**
    2. **memory CD4+ T cells**

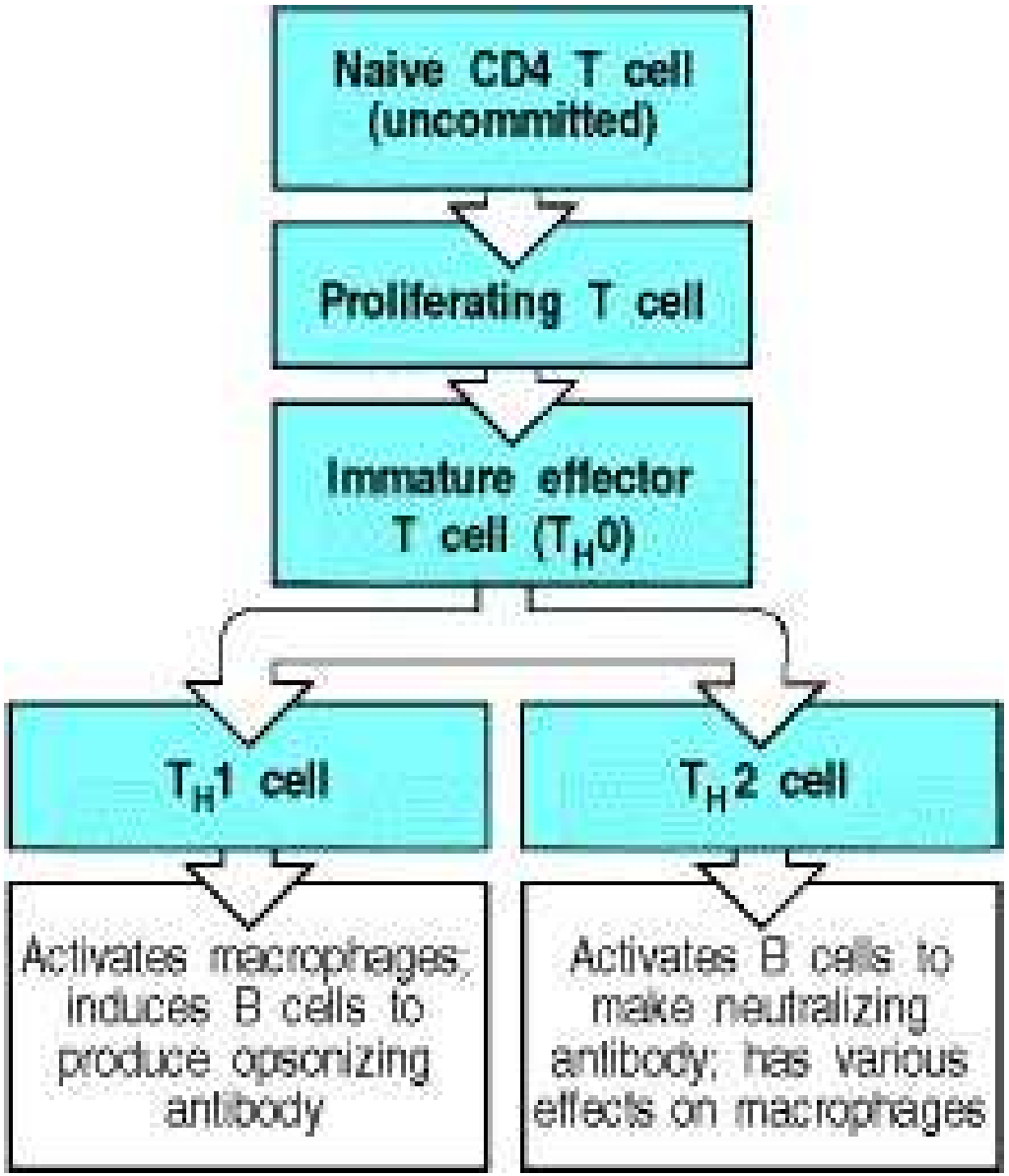
3. Produce cytokines

4. **Effector functions of Th1 or Th2 helper cells = activate macrophages or B cells respectively**

(activated CD4+ T cells do not actively kill pathogen themselves but HELP other cell types to do so)

Naïve T helper cells (CD4+ Th0) can differentiate into several effector subtypes





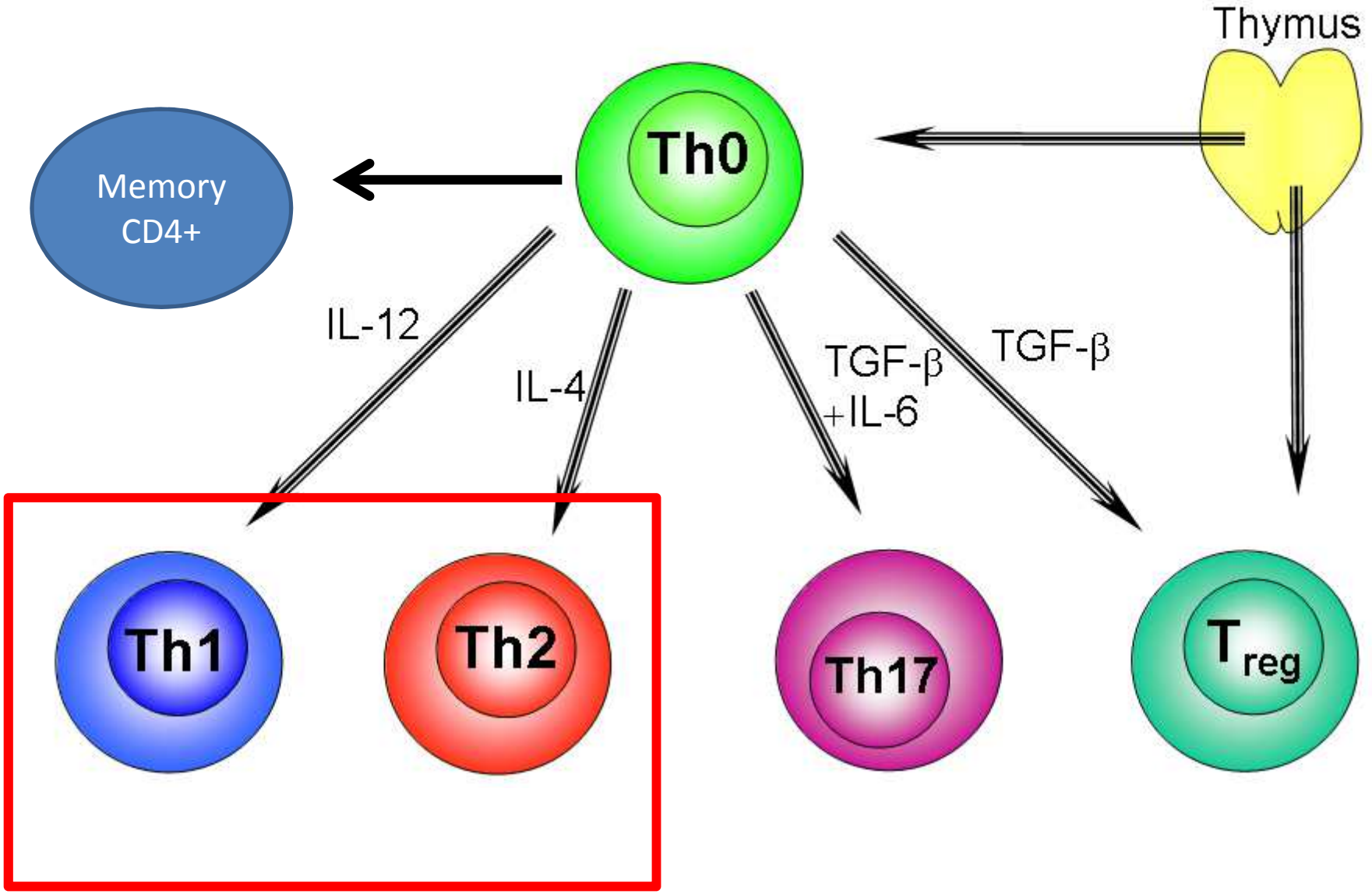
Janeway 2001
Figure 8.24 The stages of activation of CD4 T cells

Naive CD4 T cells first respond to their specific peptide:MHC class II complexes by making IL-2 and proliferating.

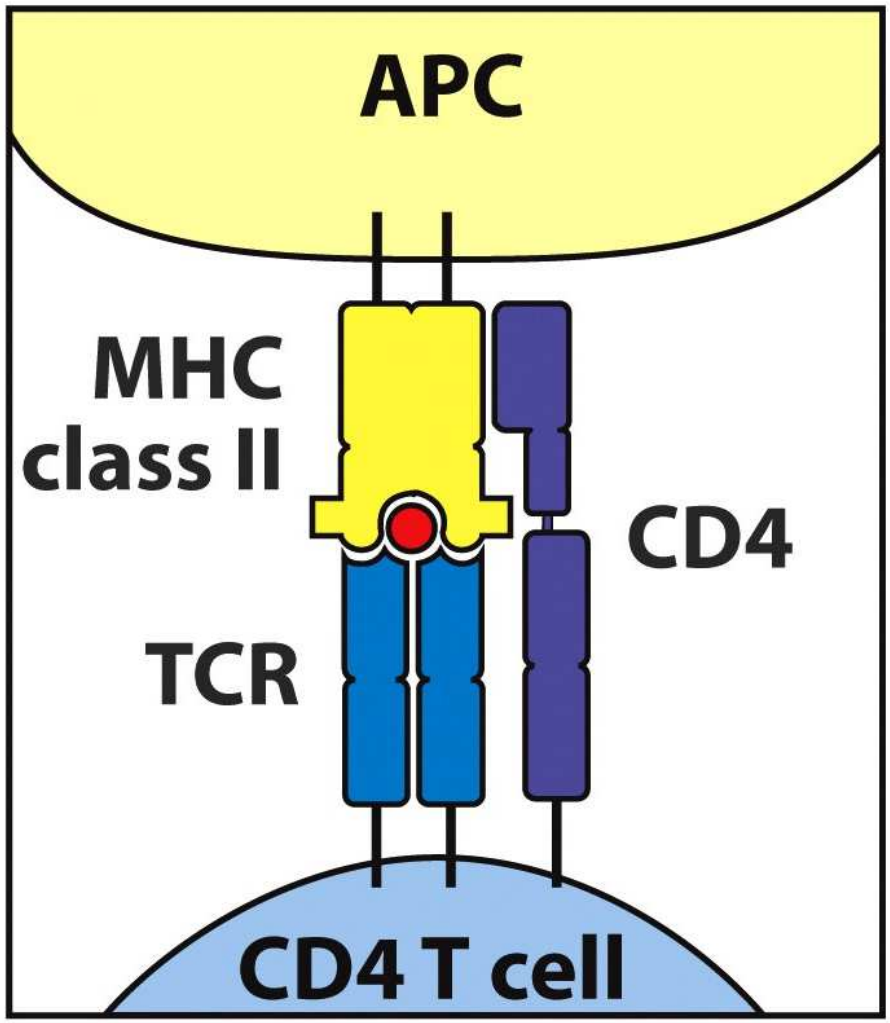
These cells then differentiate …

The T_H0 cell has the potential to become either a T_H1 cell or a T_H2 cell.

IL-4 causes Th2 to develop, whereas IL-12 causes Th1 to develop.

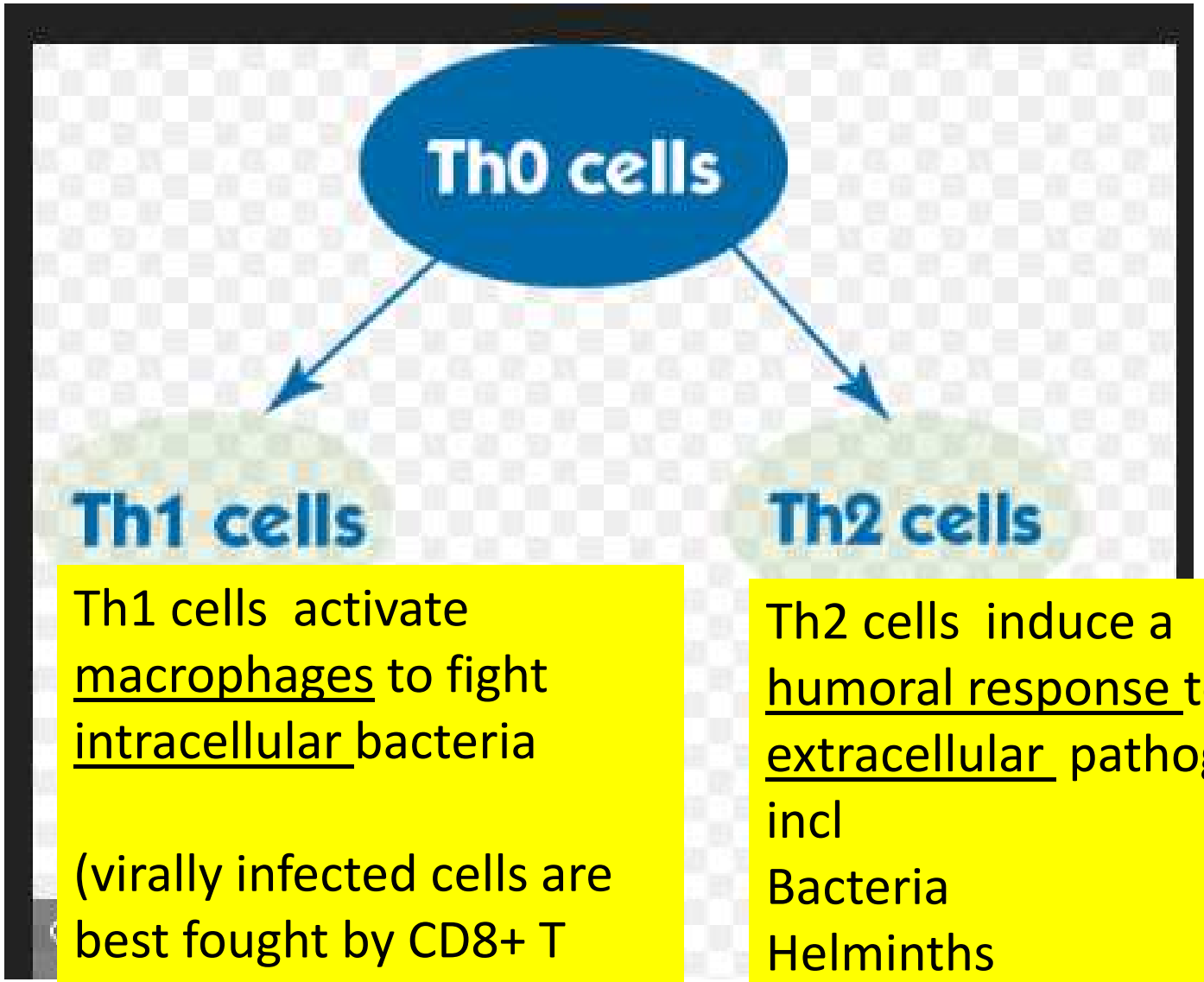


Th1 and Th2 cell activation



- Both Th1 and Th2 cells start as CD4+ helper T naïve cells
- They are activated via MHC class II and TCR
- The T cell then differentiates either into Th1 or Th2 (or other subtypes)

Th1 and Th2 cells eliminate different types of pathogens



Th1 cells activate <u>macrophages</u> to fight <u>intracellular</u> bacteria

(virally infected cells are best fought by CD8+ T cells)

Th2 cells induce a <u>humoral response</u> to fight <u>extracellular</u> pathogens , incl
Bacteria
Helminths
free virus outside cells

Th1 vs Th2 differentiation

- Usually the immune response swings in one direction over the other
- **EITHER Th1 OR Th2**
- Th1 response inhibits Th2 response and vice verse
- Favours elimination of intracellular or extracellular pathogens (not both simultaneously)

Th1 effector functions

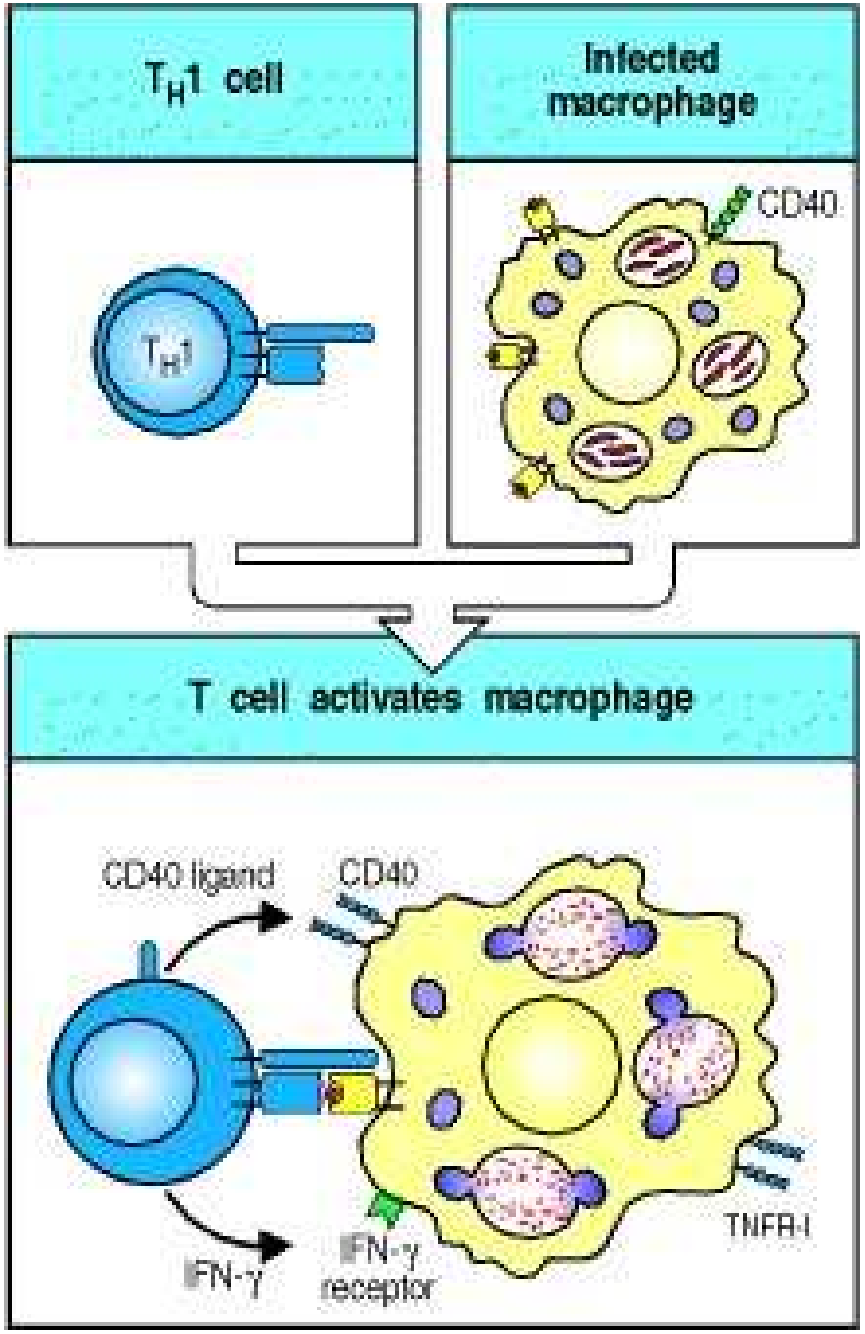
Th1 effector cells:

1. Produce **Th1 cytokines** (chemical messengers) such as **IFN-g**

2. **Synapse with macrophages** to increase macrophage function i.e. kill phagocytosed microbes or bacteria that like to live inside macrophages such as TB or leprosy

(3. May also interact with CD8+ T cells ?)

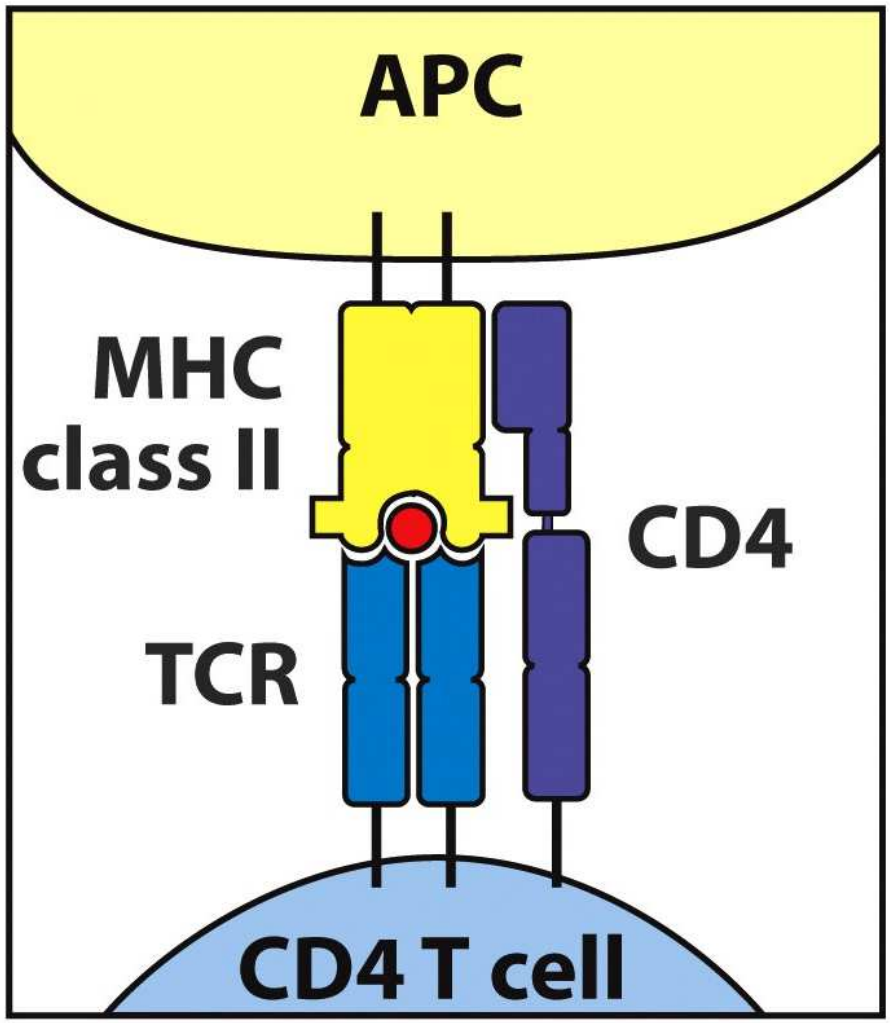
4. Increase **cell-mediated immunity**

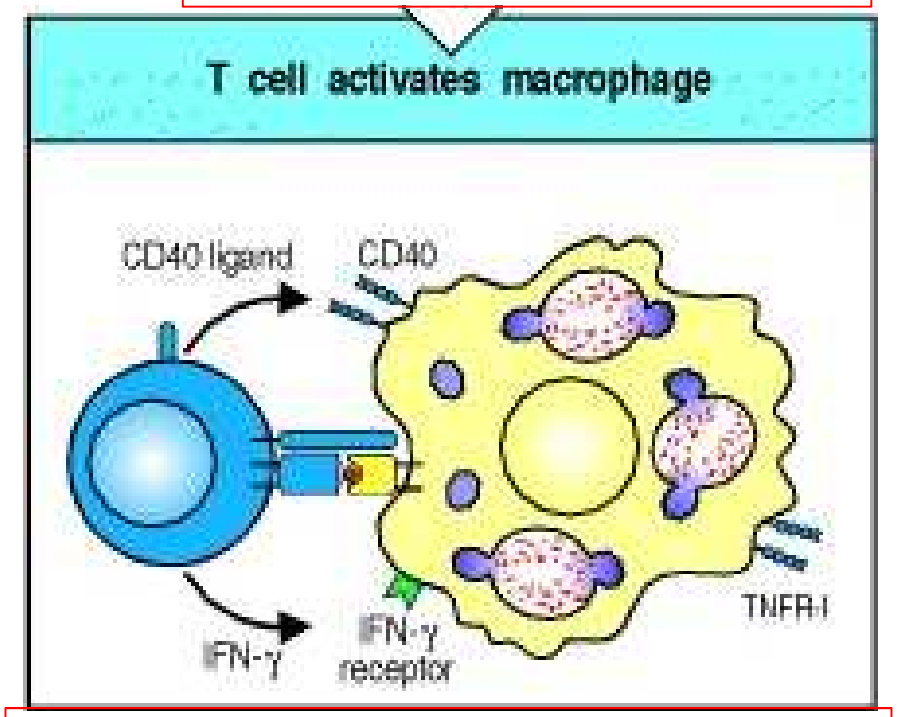

T_H1 cell
Infected macrophage
CD40
T_H1
T cell activates macrophage
CD40 ligand
CD40
IFN-γ
IFN-γ receptor
TNFR-I

Step1. Macrophage or other APC activates CD4+ T cell

Step 2. CD4+ T cell differentiates into Th1 cell

Step 3. CD4+ Th1 cell activates macrophage





Step 4. macrophage increases cell-mediated immunity and lysis of phagocytosed / intracellular bacteria

Th2 effector functions

Th2 effector cells:

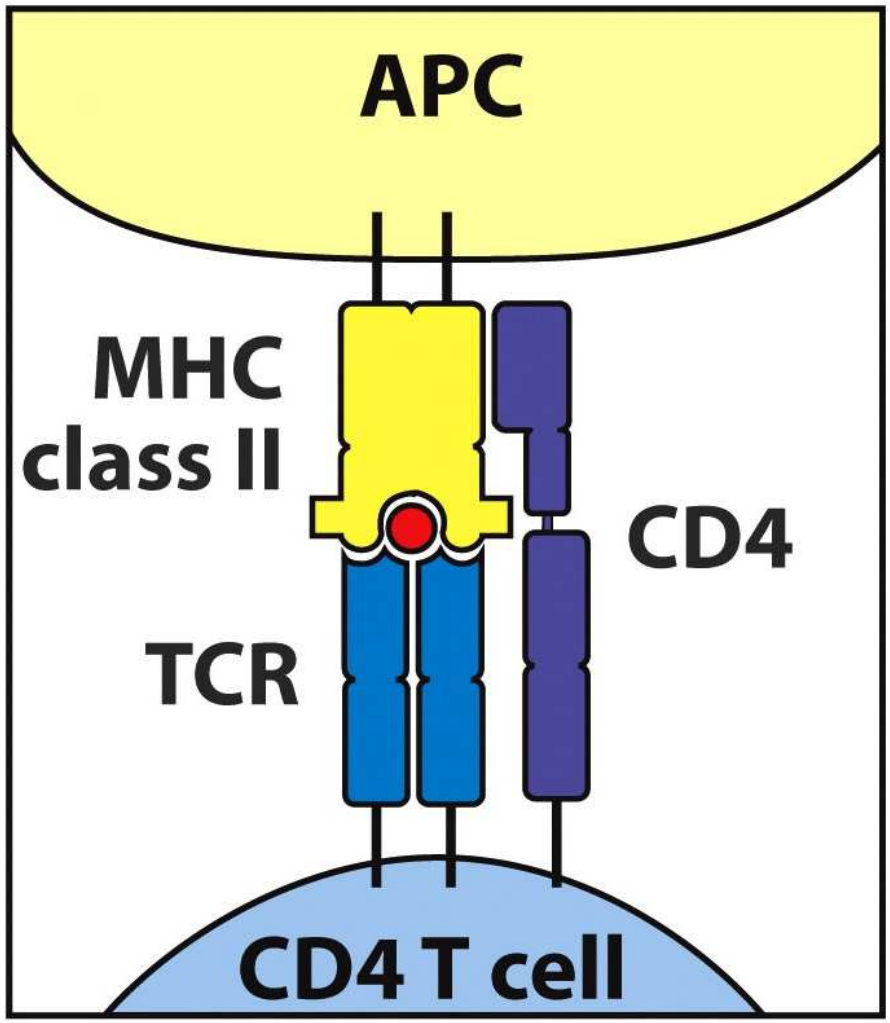
1. Produce **Th2 cytokines** (chemical messengers) such as **IL-4**

2. Activate eosinophils (defense against parasites)

3. **Synapse with B cells** to activate them (antibody production)

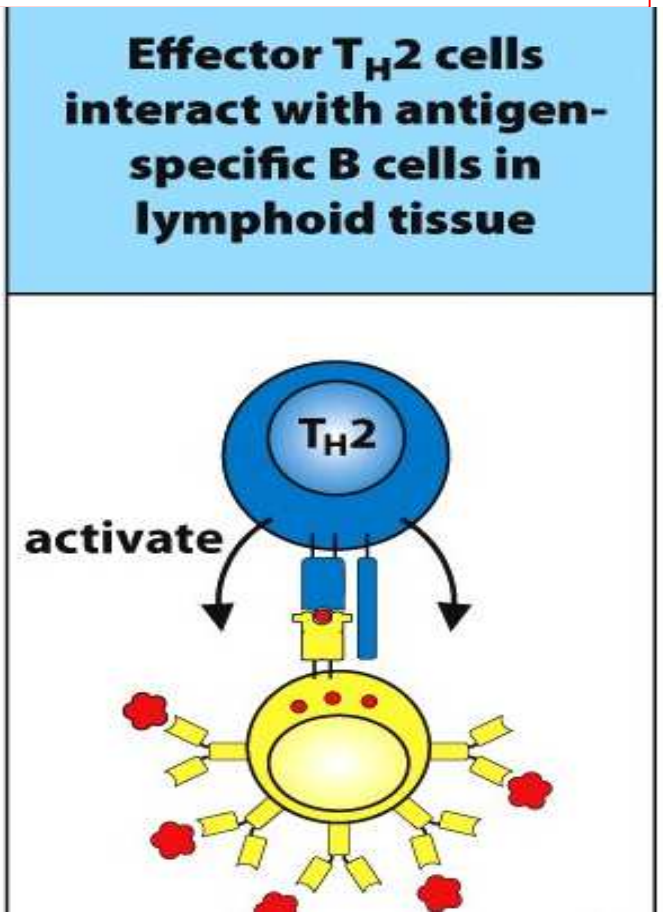
4. Increase **humoral immunity** (antibody –based)

Step1. APC activates CD4+ T cell



Step 2. CD4+ T cell differentiates into Th2 cell

Step 3. CD4+ Th2 cell activates B cell



Th2 effector functions

Th2 effector cells:

1. Produce **Th2 cytokines** (chemical messengers) such as IL-4
2. Activate eosinophils
3. **Synapse with B cells** to activate them
4. Increase **humoral immunity**

Note: T cells are not antigen presenting cells.
The Th2 cell cannot present antigen to help the B cell…
Th2 can only produce cytokines…

Comparison between Th1 and Th2 cell function

Th1 effector cells:	Th2 effector cells:
1. Produce **Th1 cytokines** (chemical messengers) such as IFN-g	1. Produce **Th2 cytokines** (chemical messengers) such as IL-4
2. **Synapse with macrophages** to increase macrophage function	2. **Synapse with B cells** to activate them 3. Also activate **eosinophils**
3. Increase **cell-mediated immunity**	4. Increase **humoral immunity**

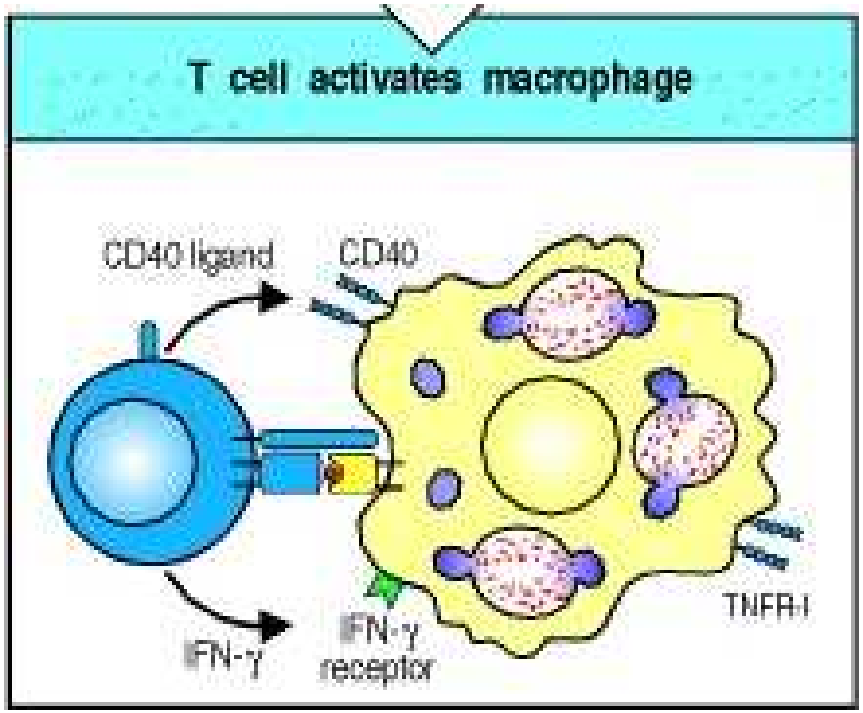
Comparison between Th1 and Th2 cell function

Th1 effector cells:	Th2 effector cells:
1. Produce **Th1 cytokines** (chemical messengers) such as IFN-g	1. Produce **Th2 cytokines** (chemical messengers) such as IL-4
2. **Synapse with macrophages** to increase macrophage function	2. **Synapse with B cells** to activate them
3. Increase **cell-media immunity**	

T helper cells cannot do much by themselves except for produce cytokines.

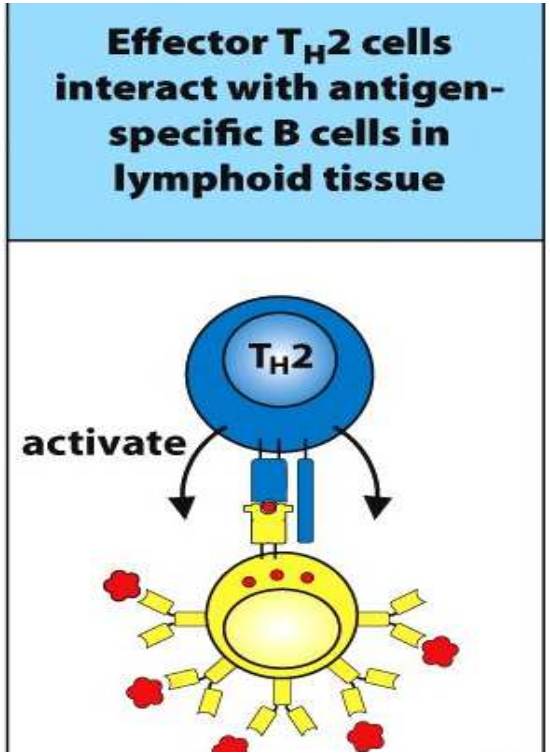
Their main effector function is to "help" other cells become more effective

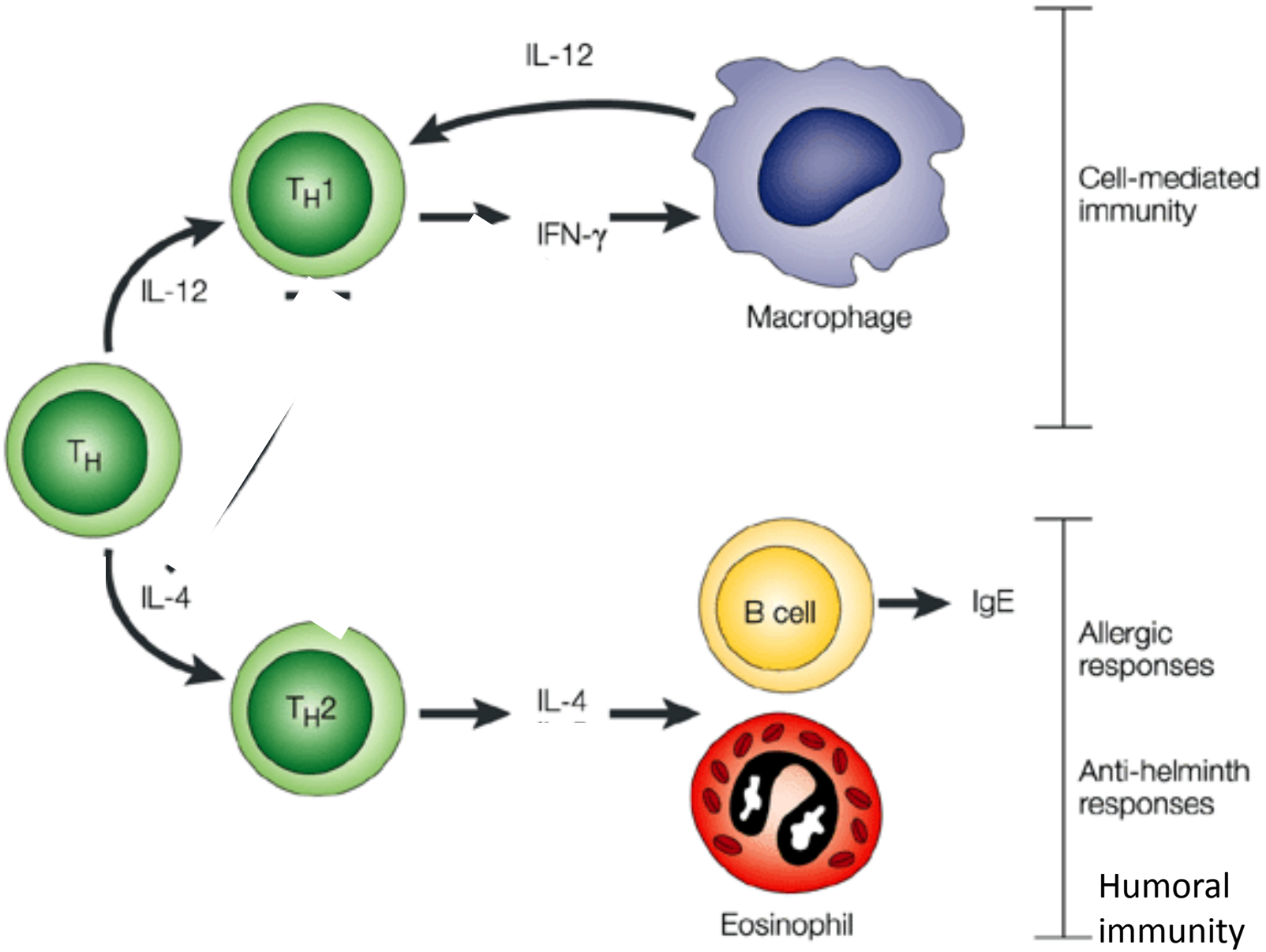
Comparison between CD4+ Th1 and Th2 cell function



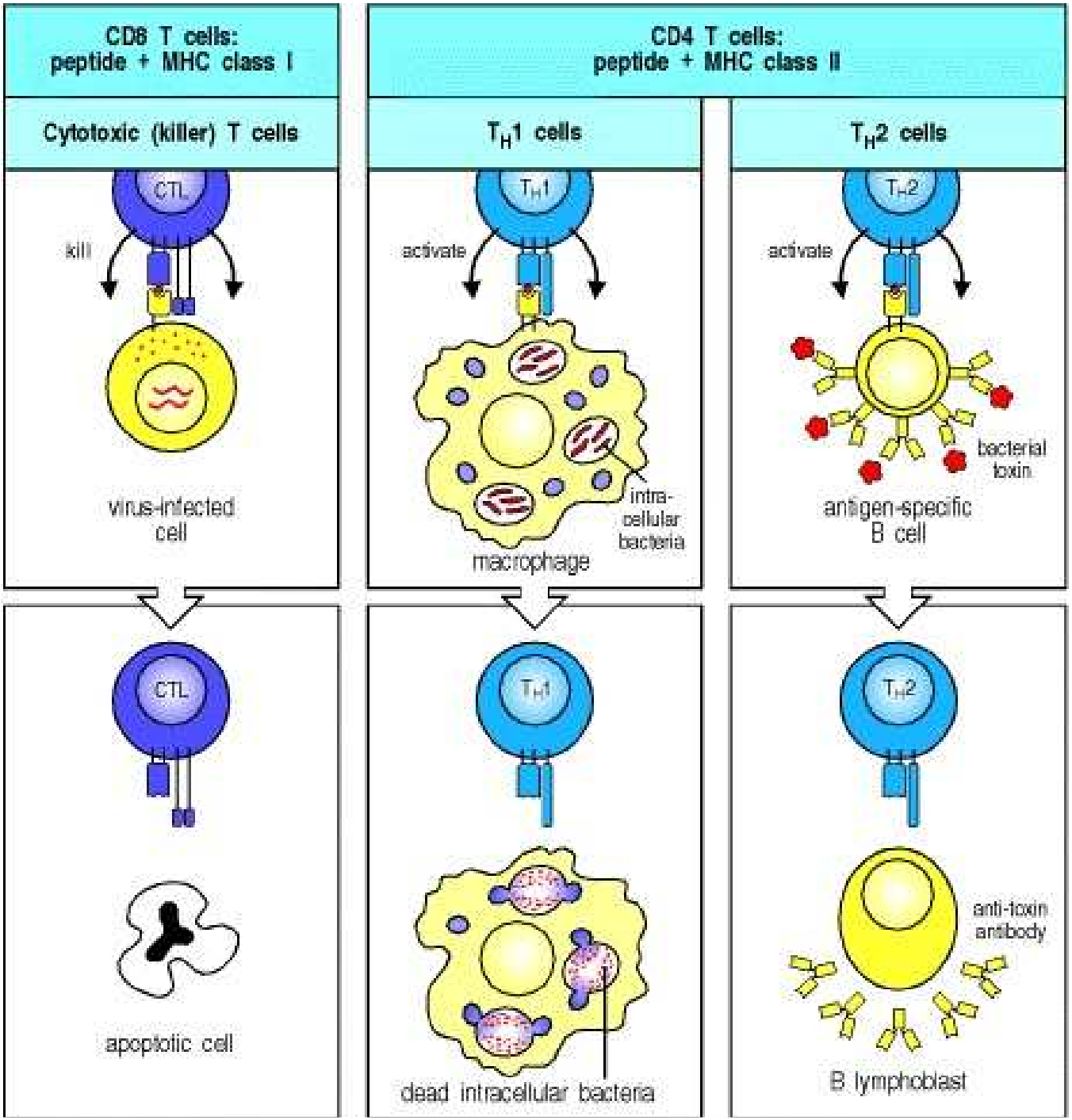
Th1 cells synapse with **macrophages** to increase **cell mediated** immunity

Th2 cells synapse with **B cells** to increase **humoral** immunity




IL-12
T_H1
IFN-γ
Macrophage
IL-12
T_H
IL-4
T_H2
IL-4
B cell
IgE
Eosinophil
Cell-mediated immunity
Allergic responses
Anti-helminth responses
Humoral immunity

Steps in Immune response	CD8+ T cell	CD4+ T cells
Activation	TCR binds antigen on HLA class I	TCR binds antigen on HLA class II
proliferation	yes	yes
Differentiation	Memory CTL	Memory Th1 Th2
Cytokine production	IL-2, IFNg	Th1: IL-12, IFNg Th2: IL-4
Cytotoxic	yes	no
Other functions	no	Helper immune synapse Th1: macrophage Th2: B cells


CD8 T cells:
peptide + MHC class I
CD4 T cells:
peptide + MHC class II
Cytotoxic (killer) T cells
TH1 cells
TH2 cells
CTL
kill
virus-infected cell
TH1
activate
intra-cellular bacteria
macrophage
TH2
activate
bacterial toxin
antigen-specific B cell
CTL
apoptotic cell
TH1
dead intracellular bacteria
TH2
anti-toxin antibody
B lymphoblast

The Hygiene hypothesis

- Children usually exposed to a wide variety microbes
- this exposure to many viruses / intracellular bacteria leads to Th1 immune responses
- Th1 usually suppresses Th2 response

- in modern times, children experience decreased exposure to microbes (raw food types, antibiotics, pasteurised milk, increased hygiene - running water, washing etc)
- Children who are not exposed to enough microbes have insufficient Th1 stimulation
- They develop an overactive Th2 state
- Th2 activates eosinophils, which leads to a high rate of allergies e.g. asthma , eczema
- ? Role in diabetes, MS, other immune disorders?

Folkerts, Gert; Walzl, Gerhard; Openshaw, Peter J.M. (2000). "Do common childhood infections 'teach' the immune system not to be allergic?". Immunology Today. **21** (3): 118–20. PMID 10777250. doi:10.1016/S0167-5699(00)01582-6.

Check your understanding

1. How many different types of T cells can you name?

2. Which type of T cell recognises antigen on HLA class I?
3. Which type of T cell recognisees antigen on HLA class II?

4. Which cell types synapse with Th1 cells?
5. Which cell types synapse with Th2 cells?

6. What is the major function of Th1 cells?
7. What is the major function of Th2 cells?

8. HIV infection causes decreased CD4+ T cells and a Th2 type immune response . What opportunistic infections are most likely to occur?

Check your understanding

What is the main difference between
NK cell response to HLA
And
T cell response to HLA?

Same question as previously but now can answer in more detail!

Check your understanding

Q: How many different types of innate and adaptive immune synapses have you learnt about so far and what are their major functions?