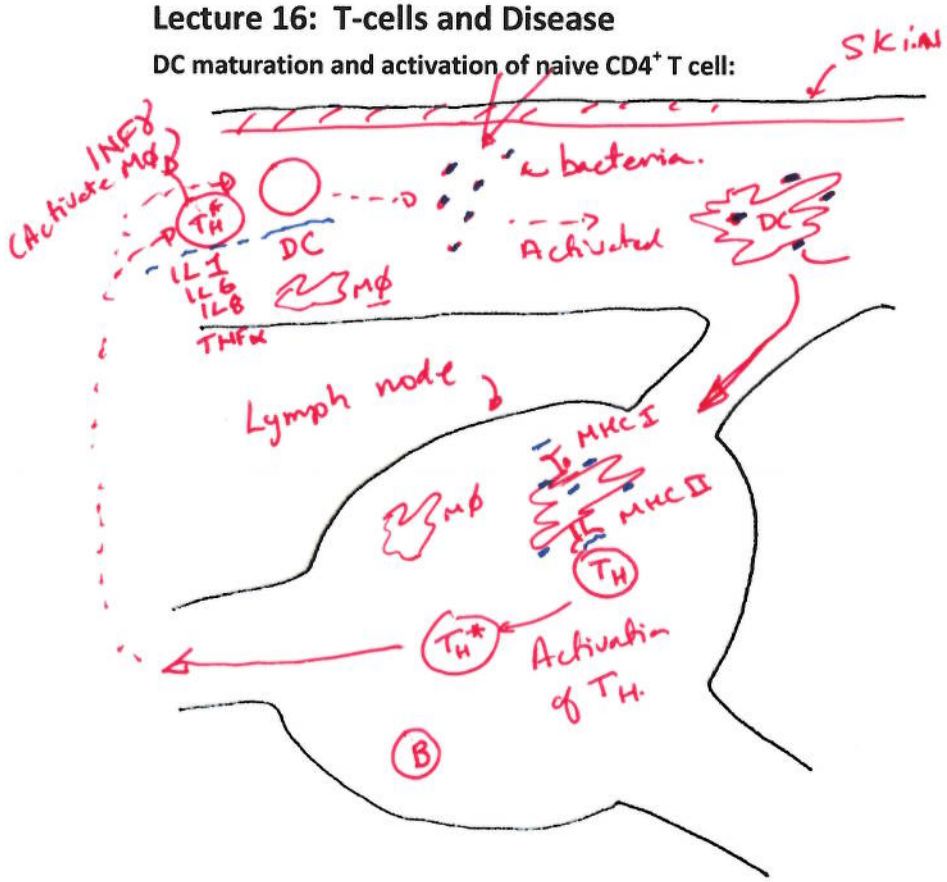
Lecture 16: T-cells and Disease

DC maturation and activation of naive CD4⁺ T cell:

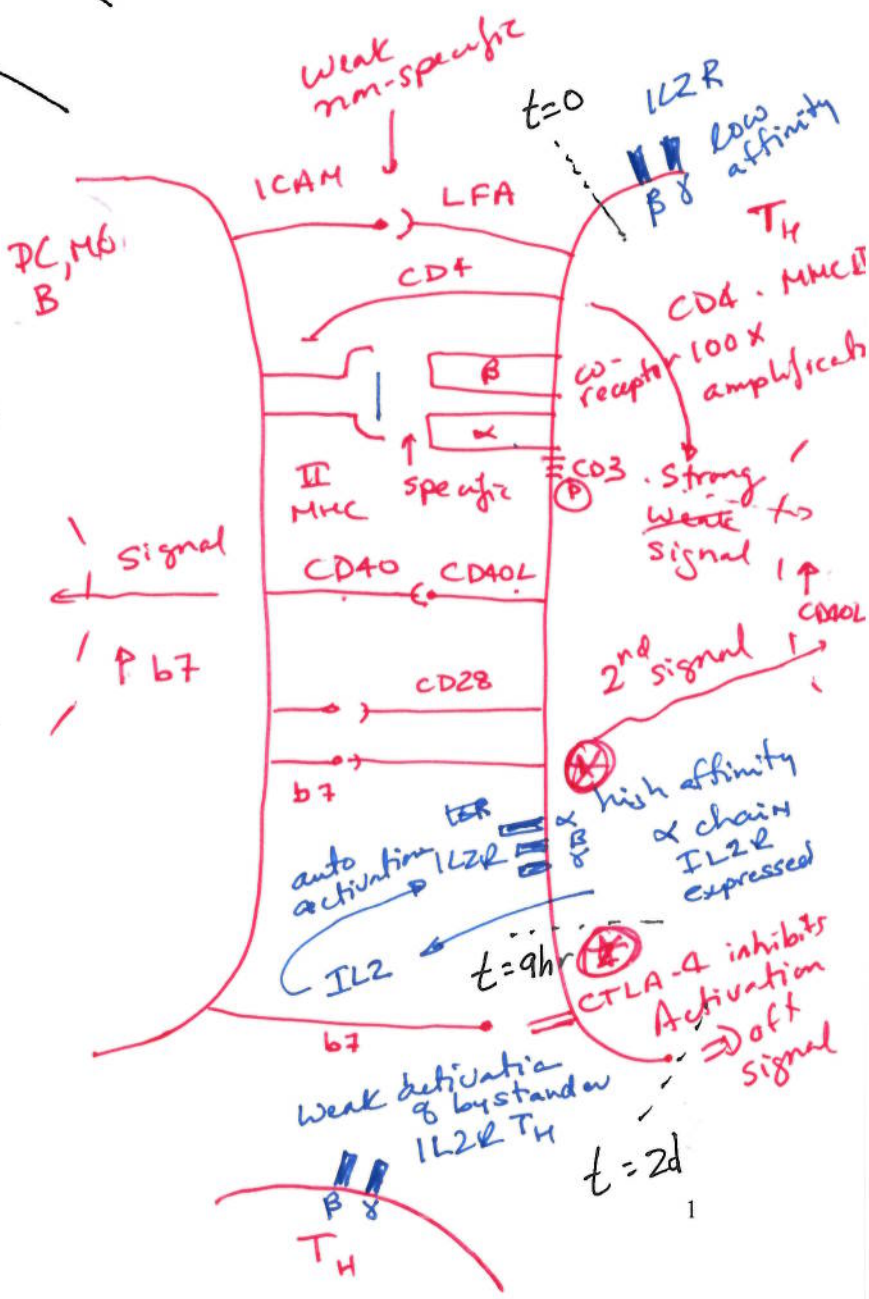


1) Recognition of novel pathogens via Toll like receptors (TLR), many are present on DCs.
2) Pathogen uptake and processing.
3) ↑↑ MHC Class II and B7.
4) Antigen presentation on MHC.
5) Cytokine secretion.
6) Change in DC morphology, loss of phagocytic capability.
7) Migration via afferent lymphatic vessel to draining lymph node.
8) Naïve T-cells enter from blood, interacts with antigen-laden DC - formation of **synapse**.
9) Increase in T cell's IL2 production, and subsequent proliferation.
10) Differentiation to effector (activated) T-cells.
11) Homing of T-cells to infection site.

Activation of CD4⁺ T cell by proAPCs

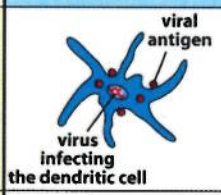
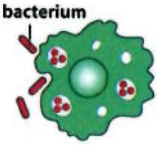
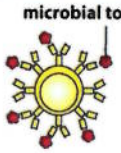
1. Initial binding: non-antigen specific adhesion molecules (ICAM & LFA)
2. First signal:
   - 2a. MHC Class II (or Class I) + peptide and TCR: necessary but insufficient
   - 2b. Co-receptor CD4 and MHC Class II (or CD8 and Class I): increases response to antigen ~100x; induces T cell signal transduction cascades
3. Second signal (costimulation)
   - 3a. CD40 and CD40L
   - 3b. B7 and CD28 (DC > B-cell > Mphage)

   Costimulation is required to activate T cells; non-activated T cells enter a state of anergy.
4. Consequences of T-cell activation:
   - 4a. Production of autocrine cytokine IL-2
   - 4b. IL-2 receptor affinity increases by binding of α chain to existing γβ chains. **Restricts IL-2 activation to the activated T-cells. Bystanders, with just the γβ chains, are not activated.**
   - 4c. Production of CTLA-4, an antagonist of CD28, reducing the activation signal (later response).

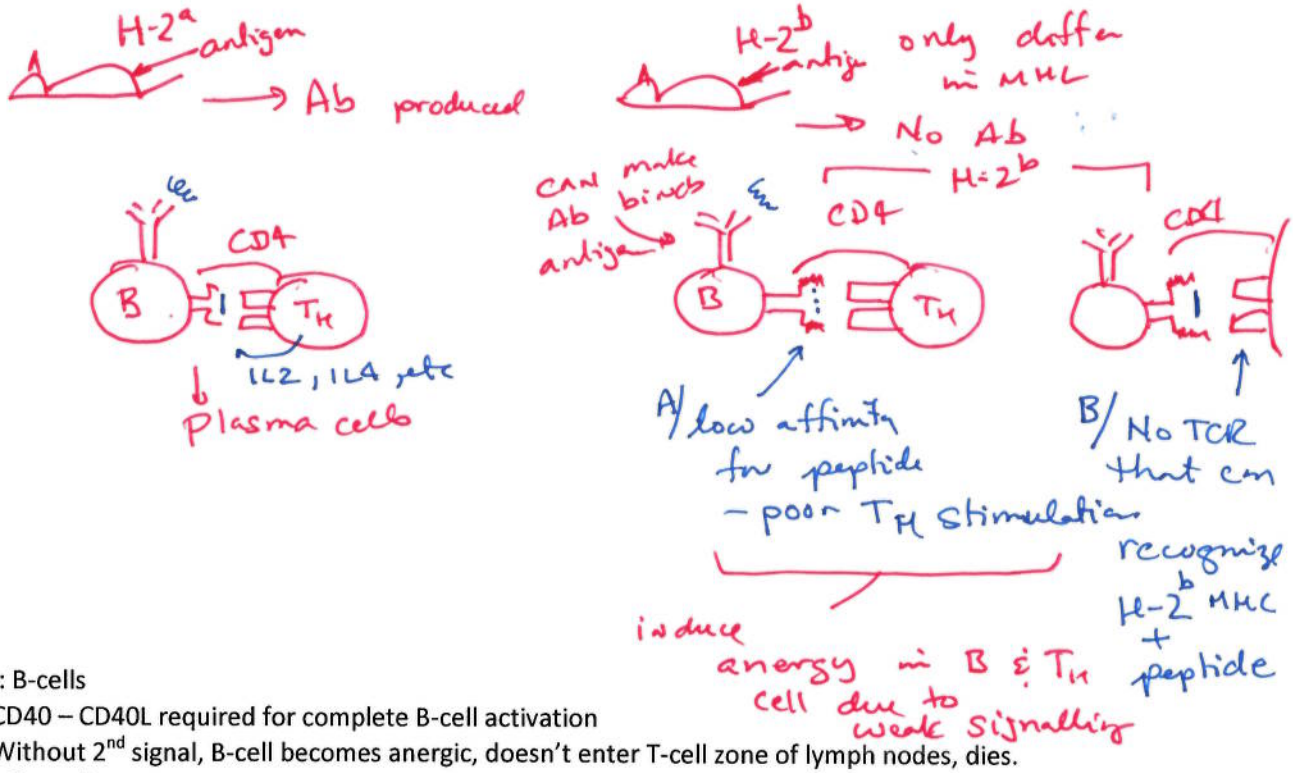


Relative Potential of Professional antigen presenting cells to activate T-cells:

TH Act → BEST WORST IN MIDDLE

	Dendritic cell	Macrophage	B cell
Cell type			
Location in lymph node			
b7 before	+	+	+
b7 after Act	+ + + ++	+ +	+ + +
Location	Ubiquitous throughout the body	Lymphoid tissue Connective tissue Body cavities	Lymphoid tissue Peripheral blood

T-cells and Immunological Holes in the Immune Response & Induction of Anergy (non-responsive).



Anergy: B-cells

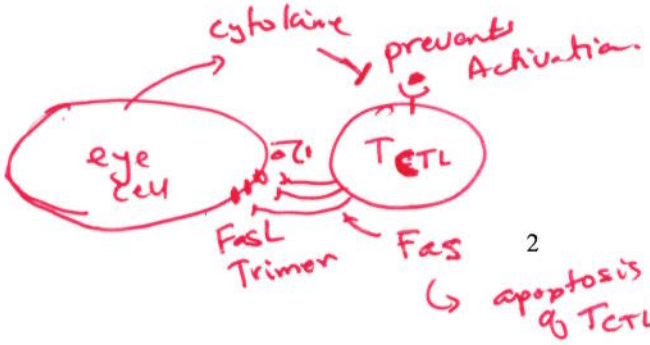
- CD40 – CD40L required for complete B-cell activation
- Without 2nd signal, B-cell becomes anergic, doesn't enter T-cell zone of lymph nodes, dies.

Anergy: T – cells

- B7- CD28 required for complete T-cell activation – only provided by **activated** DCs, macrophages, B-cells.
- APCs only express high levels of B7 during activation (e.g. complement receptor on B-cell).
- Without 2nd signal, T-cell becomes anergic

Immune privileged site (eye, testes, brain, ovary, placenta)

- These tissues produce immunosuppressive cytokines.
- Expression of FasL, inducing apoptosis of immune cells.



T-cell Subsets & T-cell Based Response to Pathogens:

T_{reg} – Regulatory T-cells (reduce auto-immunity)

- Possess the α chain of IL2R, binding IL-2 and preventing it from activating other T-cells.
- Secrete TGFβ, which inhibits T-cell activation.

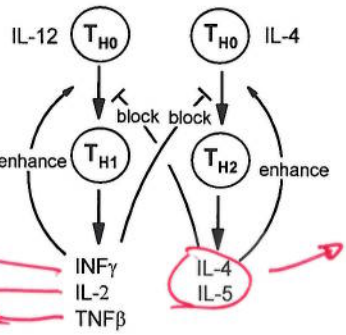
T_{H1} – cellular immune response:

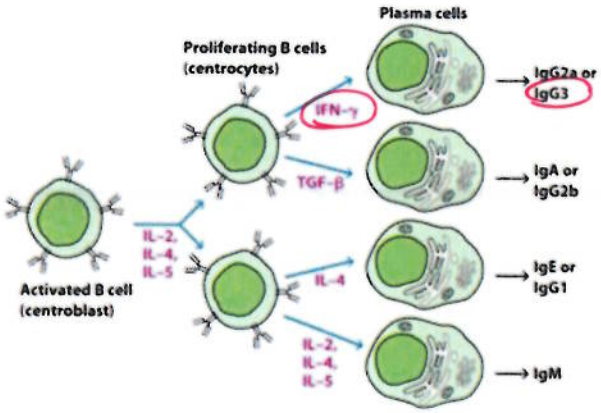
- IL-2: Activation of $T_C \rightarrow T_{CTL}$
- INFγ:
  - Activation of macrophages
  - Production of IgG3 Ab
- TNFβ (=TNFα) - aids in recruitment of macrophages to site (inflammation)

T_{H2} – antibody based immune response:

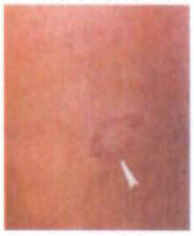
- IL-5 & IL-4: Activation of B-cells
- IL-4: Class switch to IgE or IgG1

Cross-regulation by cytokines:

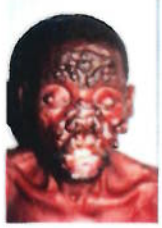




A. Intracellular Pathogens - Leprosy: *Mycobacterium leprae*

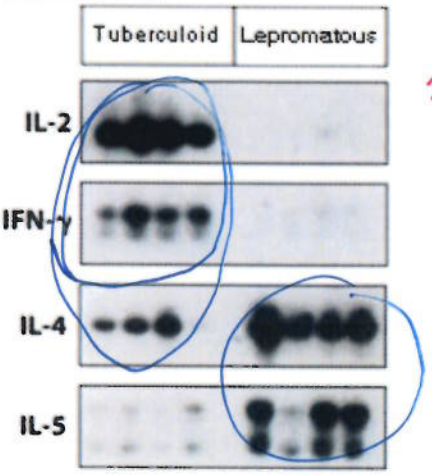


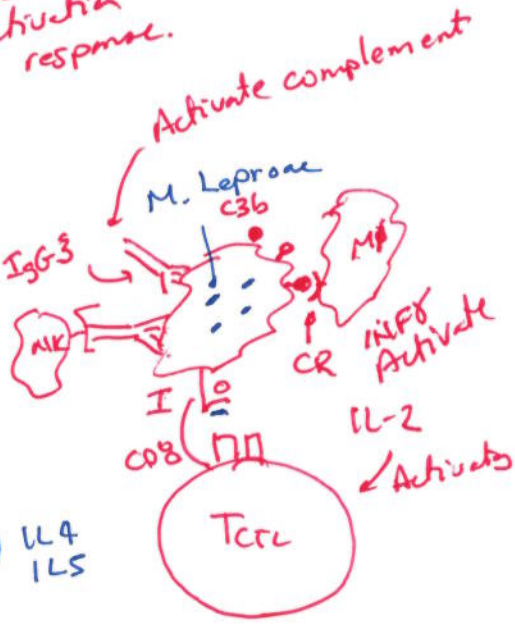
Tuberculoid



Lepromatous

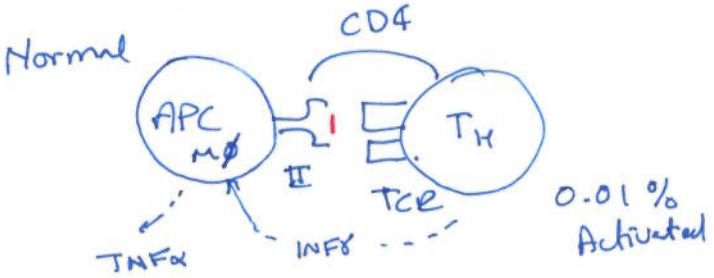
Which T-cell response is more effective against leprosy? *Why?*





B. Disease caused by over-reaction of T-cell Immune Response to Bacterial components (exotoxins). Staphylococcal Food poisoning & Toxic Shock Syndrome:

Exotoxins produced by bacteria act as "superantigens" that non-specifically activate large numbers of T cells. Toxic shock syndrome occurs with contaminated surgical dressing and long-term use of certain types of feminine hygiene products (tampons).



C. T_{H1} cells are largely responsible for transplant rejection.