

Lecture 19 – Immunodeficiencies

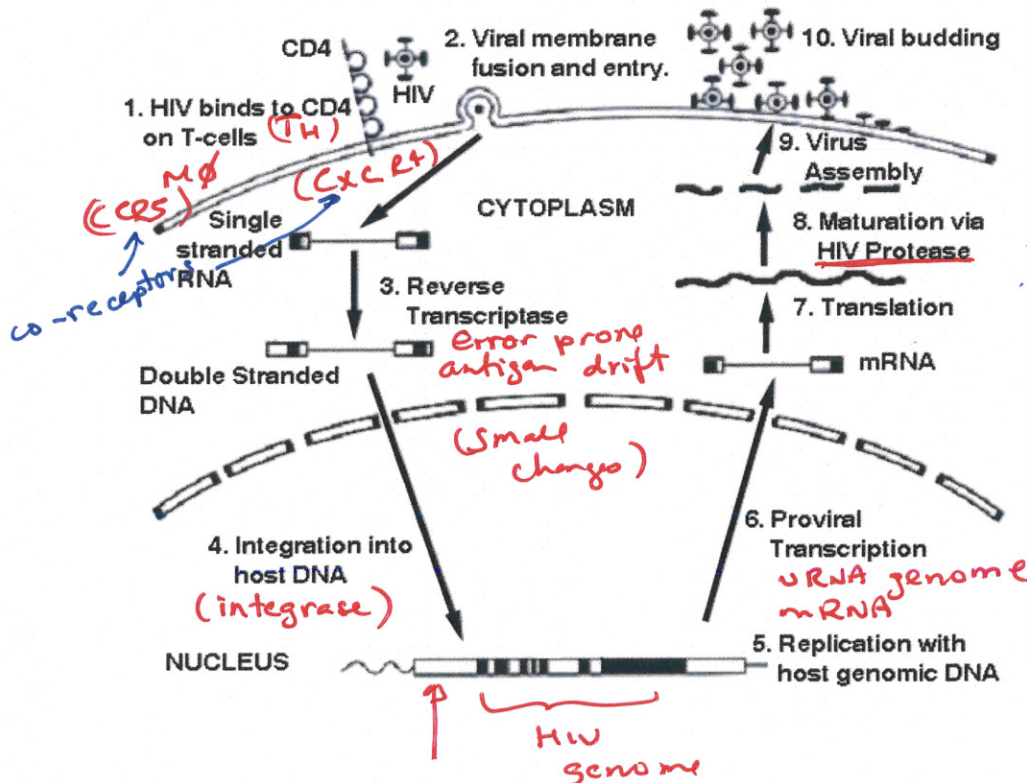
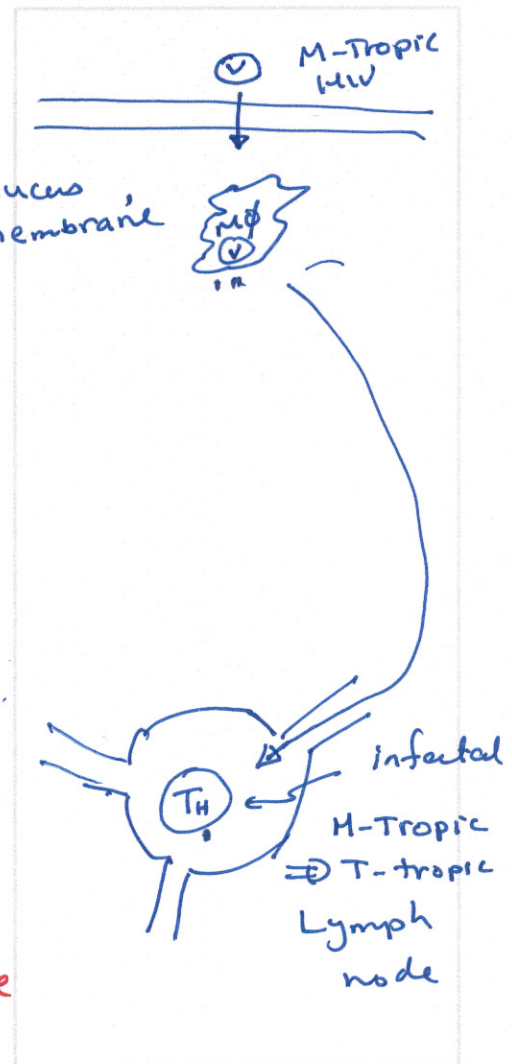
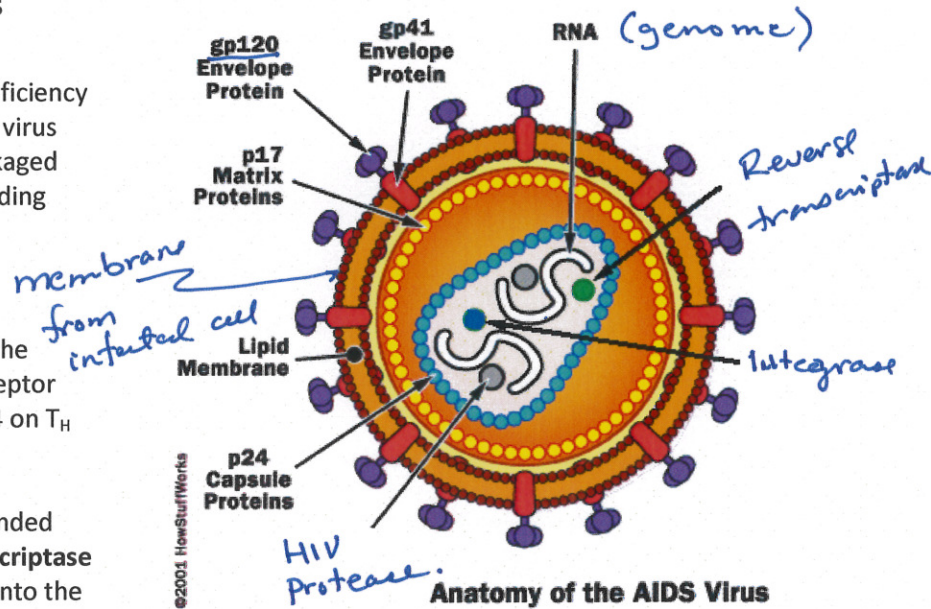
Acquired Immunodeficiency - HIV

A. Virus Structure. HIV (human immunodeficiency virus) is an enveloped (membrane coated) virus that uses RNA as its genetic material. Packaged within the virus are several enzymes, including reverse transcriptase and HIV protease.

B. Life Cycle of HIV:

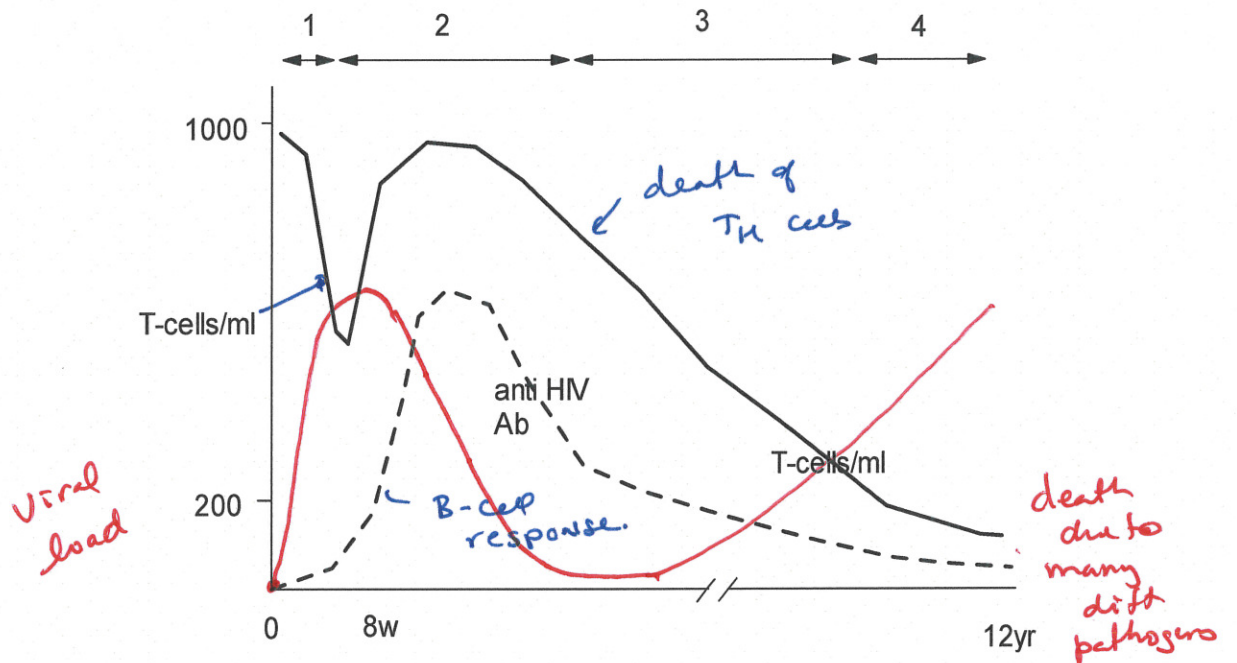
The steps in its lifecycle are as follows:

1. Binding to a specific protein (CD4) on the surface of T-cells/macrophages (co-receptor involved, CCR5 on macrophages, CXCR4 on T_H cells).
2. Fusion and entry into the cell.
3. Conversion of its RNA into double stranded DNA by an enzyme called reverse transcriptase (RT). This step introduces many errors into the genetic code of the virus because this polymerase lacks a proofreading activity, giving rise to a large number of mutant viruses. The mutant viruses can be resistant to HIV drugs.
4. The viral DNA is integrated into the host DNA by the enzyme integrase.
5. The viral DNA is replicated along with the host DNA.
6. High levels of transcription of the viral DNA sequences only occurs in activated T-cells. Viral RNA and viral messenger RNA are produced.
7. Translation of the viral mRNA generates immature viral proteins.
8. HIV protease converts the immature viral proteins to mature ones by cleavage.
9. New viral particles assemble on the surface of the cell.
10. Mature virus is released to infect other cells.



binding sites for transcription factors
 (Activation of T_H cells → production of HIV RNA)

C. Stages of HIV Infection:



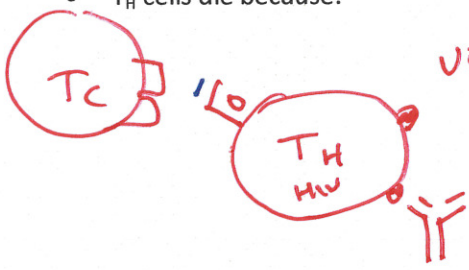
1. Pre-clinical (1-2 weeks)

- Infection of macrophages and dendritic cells by M-tropic HIV via CD4/CCR5 co-receptor at site of virus entry (mucosal membranes).
- Gradual transition to T-tropic virus, which infects T_H via CD4/CXCR4 co-receptor.

2. Acute infection

- Symptoms typical of viral infection occur – flu like symptoms.
- T_H cells die because:

i) No T_H
ii) No lymph nodes



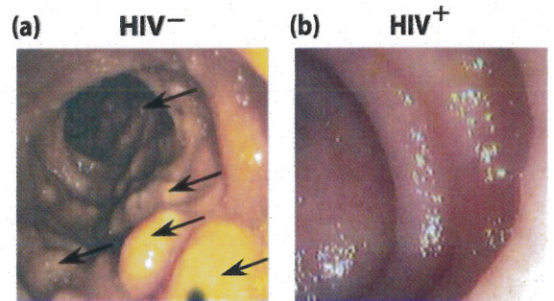
- i) death due to viral replication
- ii) complement ADCC
- iii) F_c → NK cells, Mφ
- iv) T_CCTL

3. Chronic Latent phase:

- T_H cell count continues to decrease, CD4⁺/CD8⁺ ratio drops from normal 2/1 level.
- Lymph node damage accumulates due to inflammatory activity in response to infected T-cells.

4. Crisis Phase. T_H count <200 cells/ul

- Rapid viral replication in remaining activated T-cells.
- Lymph nodes become ineffectual as sites for antigen presentation.
- Higher mutational rate in HIV genome, allows it to evade Ab.
- General failure of immune system, resulting in;
 1. unusual malignancies
 2. opportunistic infections
 3. neurological syndromes.

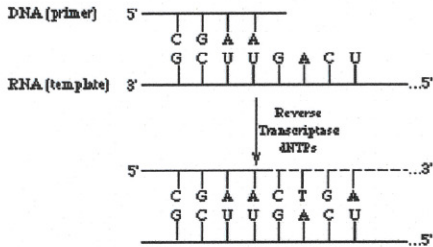


D. HIV Treatment:

- Current treatments can extend life such that under *ideal* conditions the patient is more likely to die of natural causes.
- Numerous issues are associated with HIV drug treatment.
 - Side effects
 - compliance

Current drugs:

1. Reverse transcriptase inhibitors (inhibit vRNA to DNA):



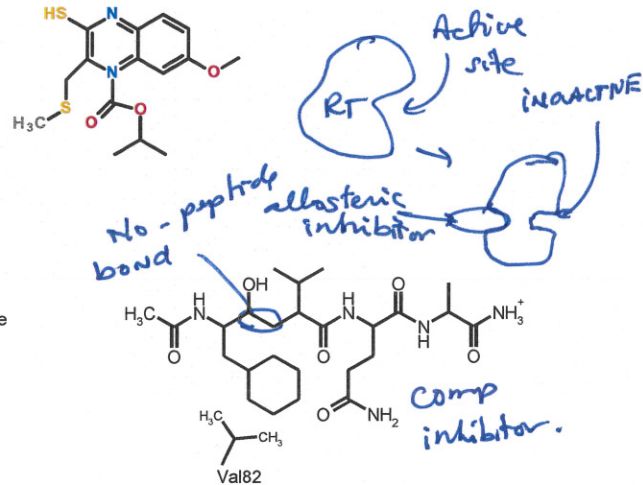
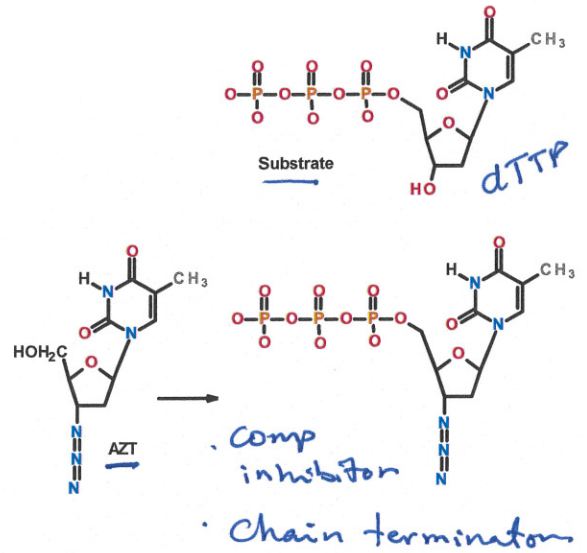
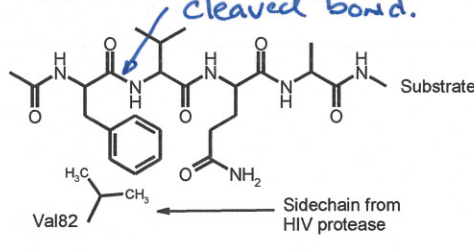
i. Nucleoside reverse transcriptase inhibitors.

- prodrugs have to be phosphorylated to triphosphate to become active.
- lack 3'OH group so after they are incorporated they terminate the growing DNA chain.

ii. Non-nucleoside reverse transcriptase inhibitors.

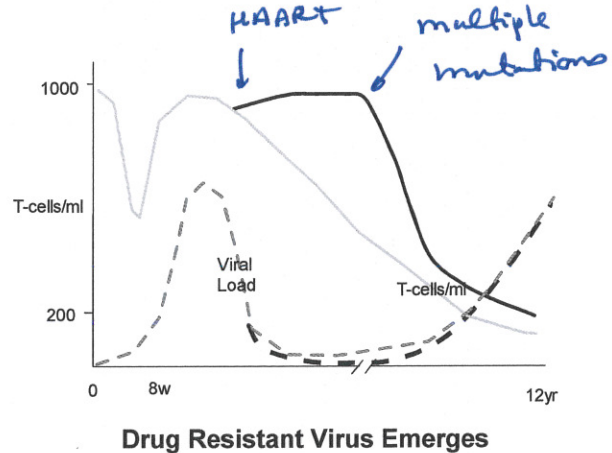
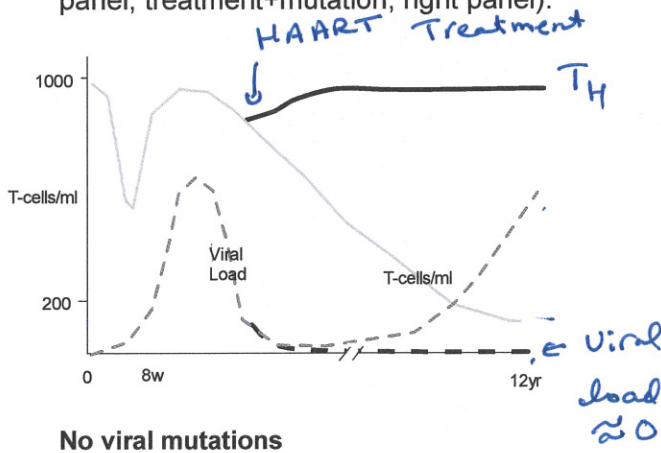
- Bind outside the active site, causing an allosteric change that inhibits reverse transcriptase.

2. HIV Protease Inhibitors (competitive inhibitors)



Viral resistance to any one of these drugs occurs rapidly due to lack of proofreading in RT. Error rate in reverse transcriptase is $\sim 1/10^5$, typical viral production is 10^9 /day.

HAART treatment (highly active antiretroviral therapy) employs all three of these drug classes, greatly reducing the risk of obtaining viral particles that can replicate (dark lines = with treatment (left panel, treatment+mutation, right panel).



Primary (Genetic) Immunodeficiencies are the result of failure of one or more components of the immune system leading to inadequate protection of host. Typified by inability to combat infections, consequently recurrent infections are observed in individuals. In severe cases there can be a significant reduction in the lifespan of the affected individual.

Immunodeficiencies arise due to abnormalities in

- Development and differentiation of cells of the immune system
- production of molecules
- cell-cell interaction and communication.

In summary - almost anything that can go wrong has. Deficiencies have been observed in:

1. Innate Immunity
2. Complement
3. T-cell Development
4. B-cell Development
5. B-cell activation and differentiation
6. T-cell activation and differentiation

Genetic deficiencies, causing primary immunodeficiencies, occur in all of the above.

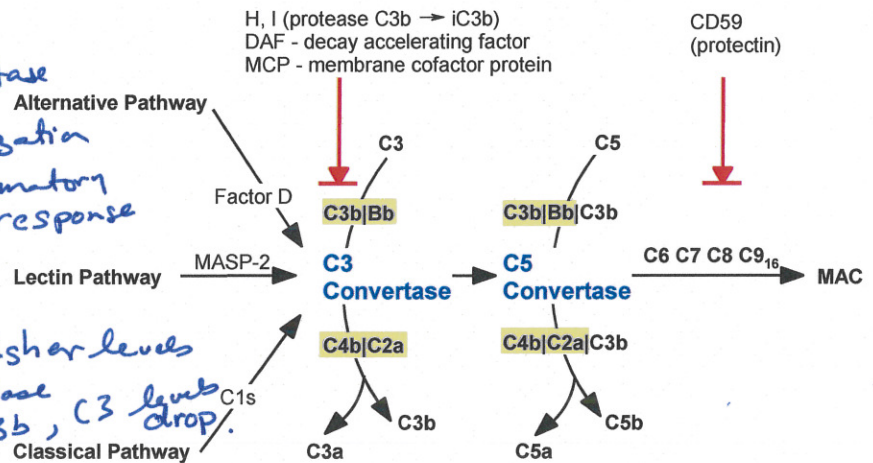
A. Complement system defects.

- C3 defects are the most severe:

- No C3 convertase
- poor opsonization
- poor inflammatory response

- Individuals lacking C9 have no clinical symptoms!

- Factor I deficiencies deplete C3. Why?
higher levels of C3 convertase
∴ C3 → C3a, C3b, C3 drop



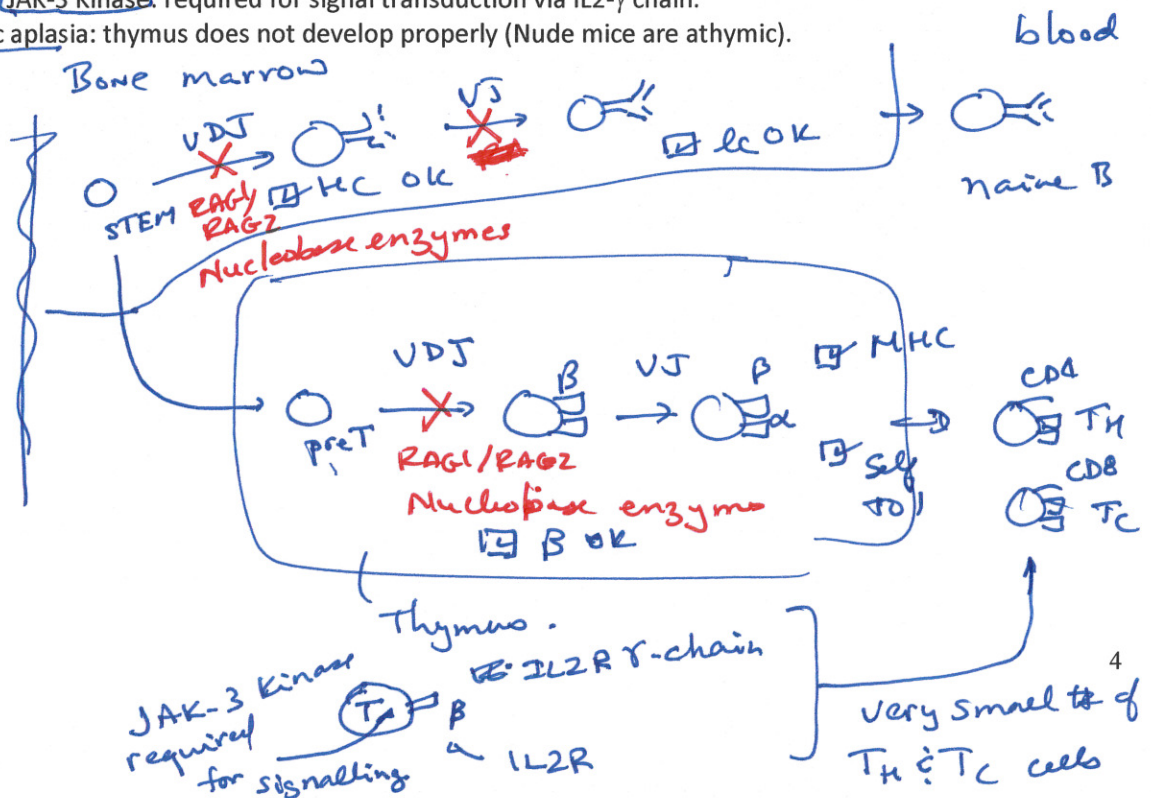
B. SCID - Severe Combined Immunodeficiency (Acquired)

TB⁻: No functional B- or T-Cells:

1. Adenine deaminase (ADA)/ Purine nucleoside phosphorylase (PNP)
3. RAG1/RAG2 deficiencies.

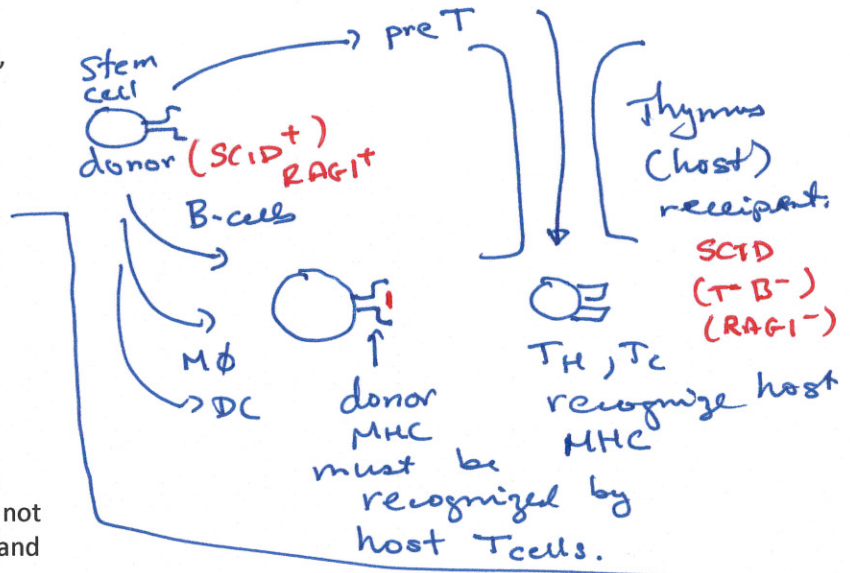
TB⁺: No functional T-cells develop:

1. Loss of IL-2 receptor γ -chain. This chain is found in the IL-2 cytokine receptor.
2. Loss of JAK-3 Kinase required for signal transduction via IL2- γ chain.
3. Thymic aplasia: thymus does not develop properly (Nude mice are athymic).



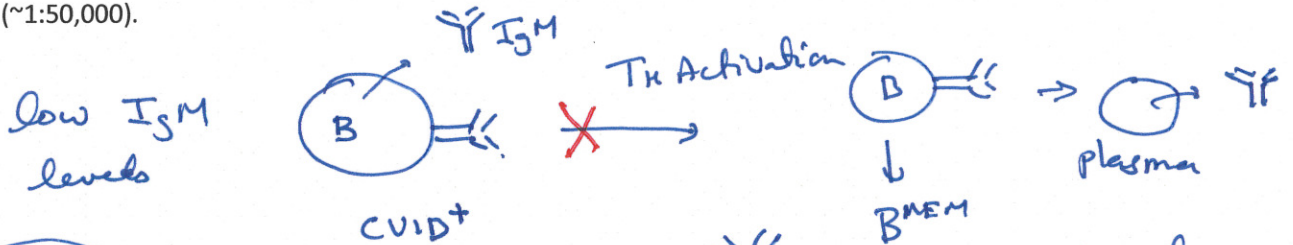
SCID Treatment – Simple genetic deficiency, e.g. RAG1/RAG2, nucleotide metabolism

- A. Replacement of immune system.
 i) destroy person's immune system (drugs, irradiation)
 ii) inject bone marrow cells from donor → repopulate stem cells.
 Best outcome from **close MHC match**.
- B. Selective replacement by Gene Therapy:
 i) remove stem cells from SCID patient.
 ii) Introduce genetic material to produce functional protein.
 iii) Inject modified cells back into patient.
RAG1/RAG2/ADA



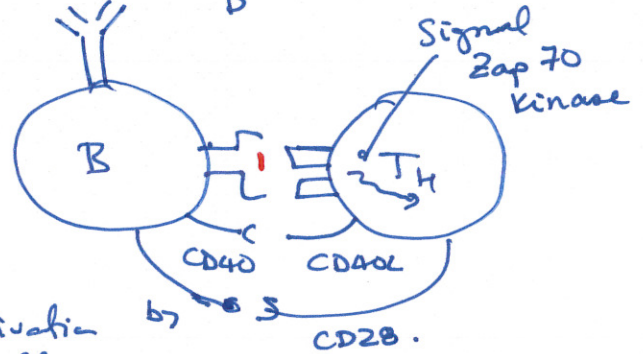
C. Antibody Production Disorders:

1. Common Variable immunodeficiency Disease (CVID). Mature naive B-cells do not undergo differentiation to plasma cells and do not class switch to IgG or IgA. (~1:50,000).



2. Hyper IgM Syndrome: Disorder in B-cell TH-cell communication (~1:10,000)

- No MHC II on B-cells.
- No CD40 on B-cells.
- No CD40L gene expressed in T-cells
- Defective Zap70 kinase in T-cells.



- weak activation of B-cell

∴ IgM produced at high level
 No class switching, (no affinity maturation)

3. IgA deficiency (1:800)

- Recurrent ear, respiratory, and genital-urinary track infection.
- Only effects secreted IgA, surface IgA molecules can be found on B-cells.

Cannot be treated by injected IgA.

because deficiency is in the transport

Cannot secrete IgA

