# Primary Immunodeficiencies for USMLE Step One

Part I

Part II

Lymphocyte Disorders:
SCID
Bruton's X-Linked Agammaglobulinemia
CVID

Wiskott-Aldrich
Neutrophil Disorders
Chronic Granulomatous Disease
Chediak-Higashi
Leukocyte Adhesion Deficiency

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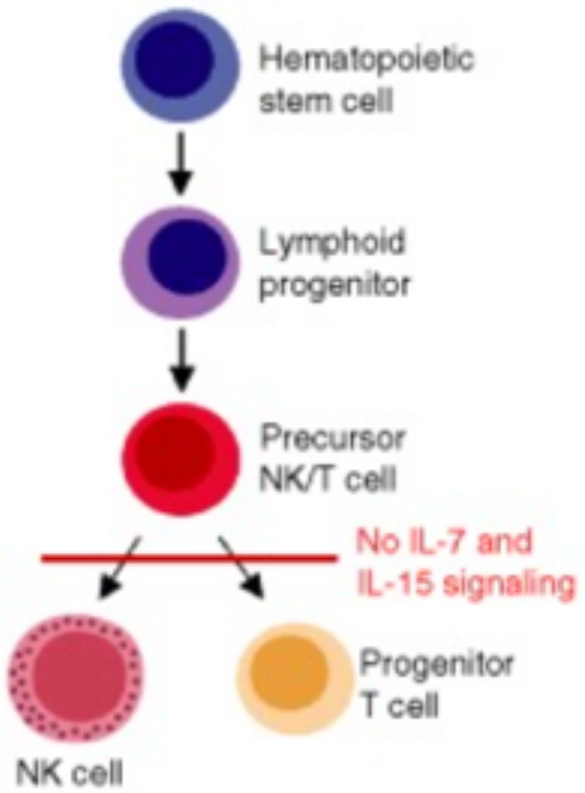
# the Primary Immunodeficiency Syndromes

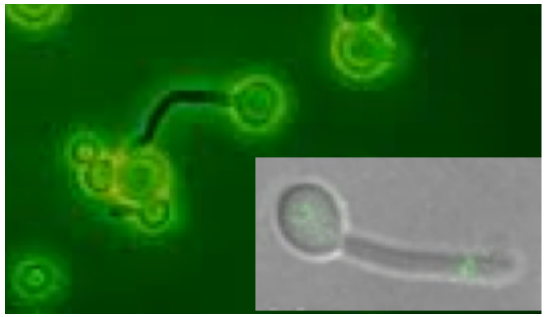
- Lymphocyte-predominant defect
  - SCID: Severe Combined Immunodeficiency (T → B)
  - Bruton's (X-linked) Agammaglobulinemia (BTK → B-maturation)
  - CVID: Common Variable Immunodeficiency (B-differentiation)
- Cytoskeleton defect
  - Wiskott-Aldrich (Φ actin polymerization → failure of 'immunologic synapse')
- Neutrophil-predominant defect
  - CGD: Chronic Granulomatous Defect (Enzyme deficiency, NADPH oxidase)
  - Chediak-Higashi (Lysosomal transport defect; LYST)
  - LAD: Leukocyte Adhesion Deficiency (Integrin failure; β chain - CD 11/18)

# Severe Combined Immunodeficiency (SCID)

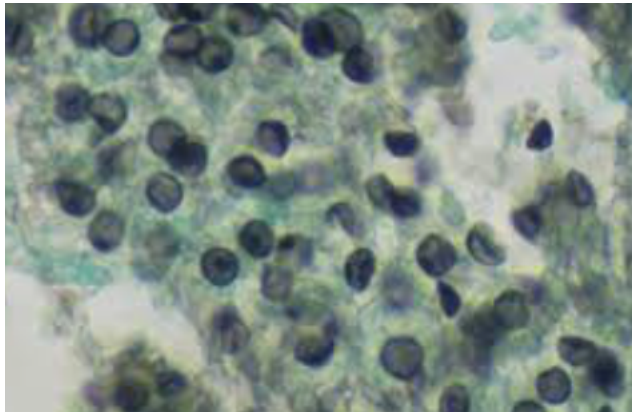
- Background:
  - Characteristic Feature: Failure of Lymphocyte Progenitor (Pro-T) Cell with profound susceptibility to infection
- Pathogenesis
  - Multiple mutations: failure to develop T and consequently B lymphocytes.
    - Subtype: Adenosine deaminase (ADA) deficiency leads to accumulation of adenosine, toxic to lymphocytes.
- Clinical Features of Profound Lymphocyte Failure
  - Failure to thrive/Chronic Diarrhea (2° to peristence of enteropathogens)
  - Infections: fungal (mucocutaneous candidiasis → thrush/diaper rash, Pneumocystis); bacteria/viral
- Distinguishing Features
  - Absence of T-cells and thymic shadow.
- Therapy:
  - Bone marrow transplant (hematopoietic stem cells) – no rejection
  - Gene/Replacement therapy: Adenosine deaminase

# Severe Combined Immunodeficiency (SCID)

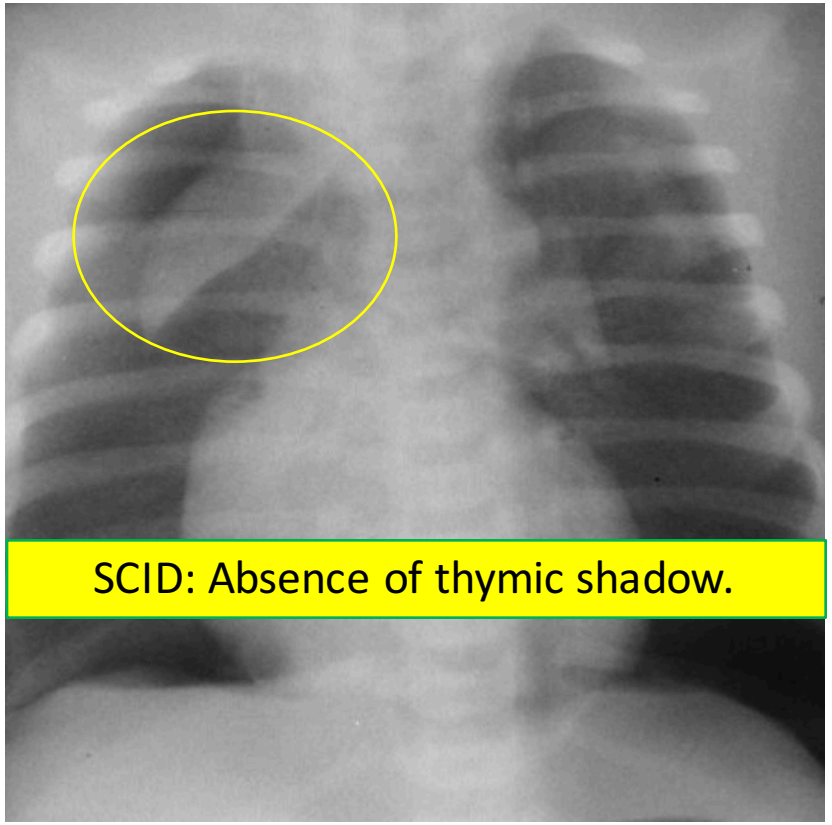


Candida: Germ Tubes (37°)



Pneumocystis jiroveci



SCID: Absence of thymic shadow.

# Bruton's (X-linked) Agammaglobulinemia

- Background
  - Failure of B-cell precursors to develop into mature B-cells (no plasma cells, no globulins).
- Pathogenesis
  - Tyrosine kinase deficiency (Btk)
    - Nonreceptor (protein) TK: involved in signal transduction required in all stages of B-cell development. Maturation ceases in the absence of TK signalling.

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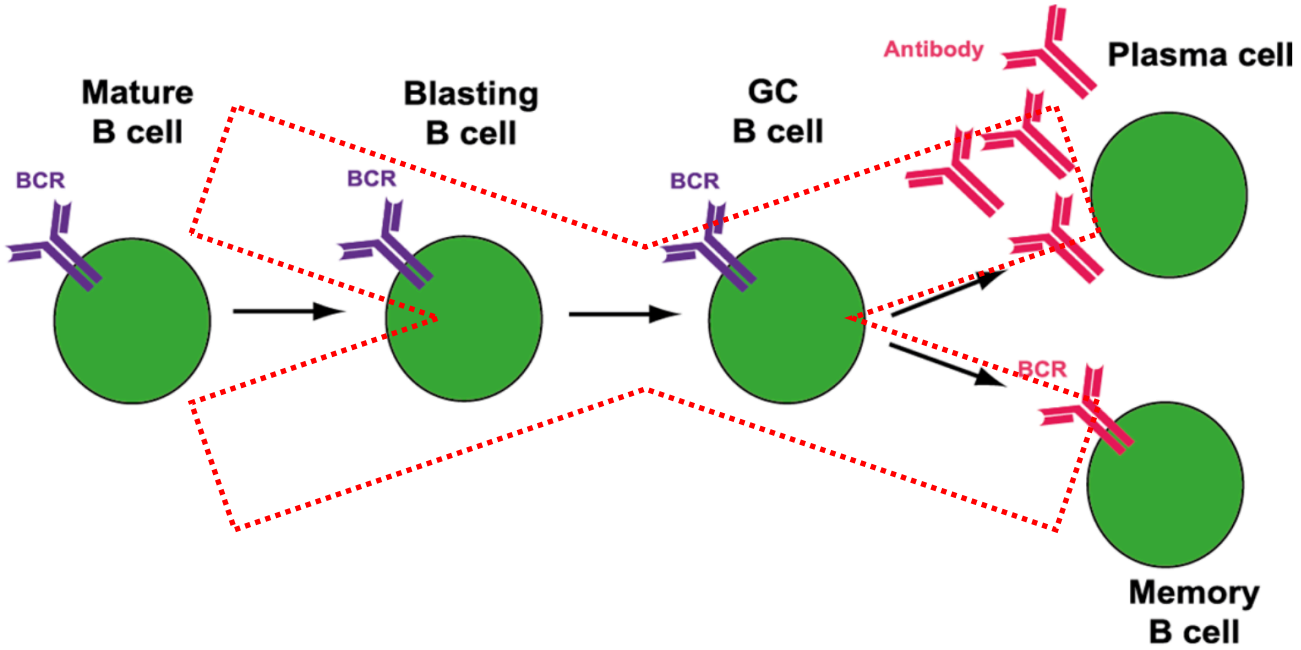


Agammaglobulinemia

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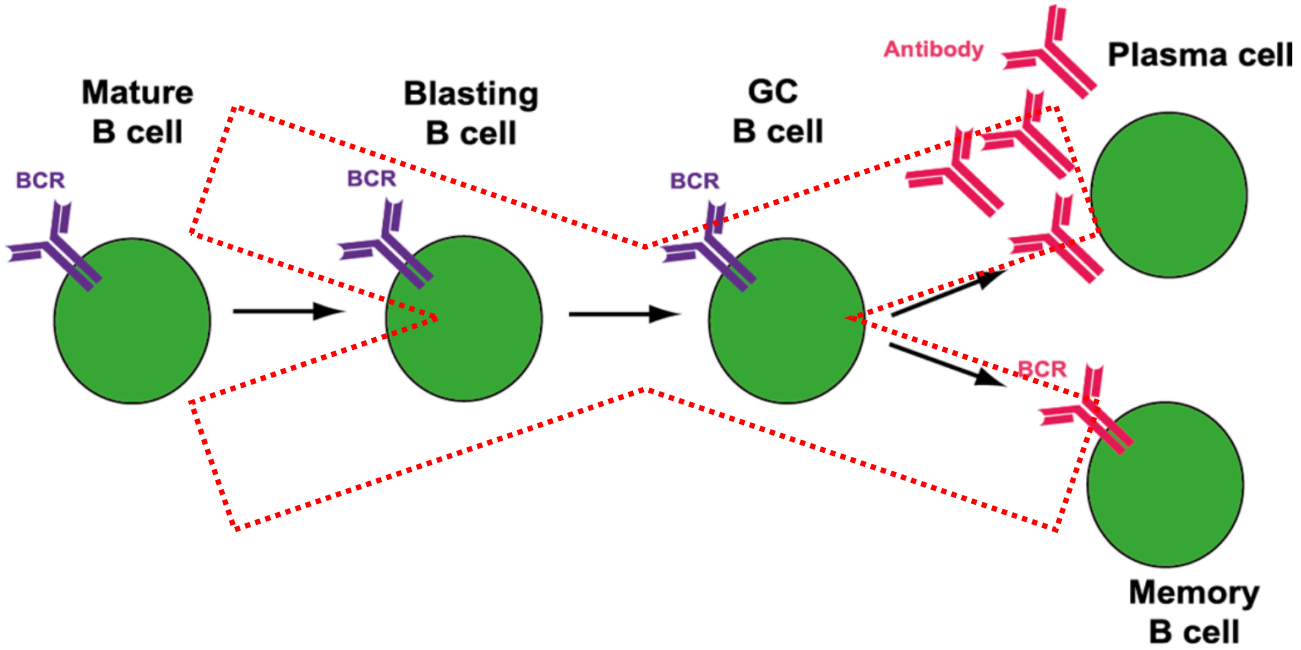


Agammaglobulinemia

No Germinal Centers

Failure of Humoral Immunity

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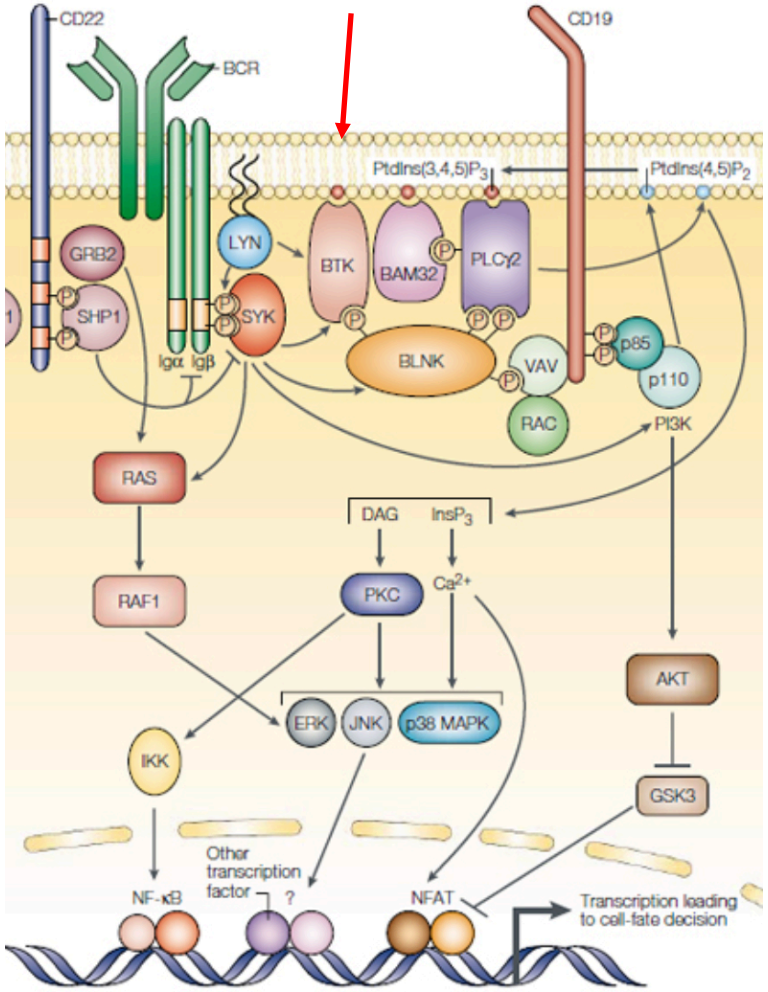
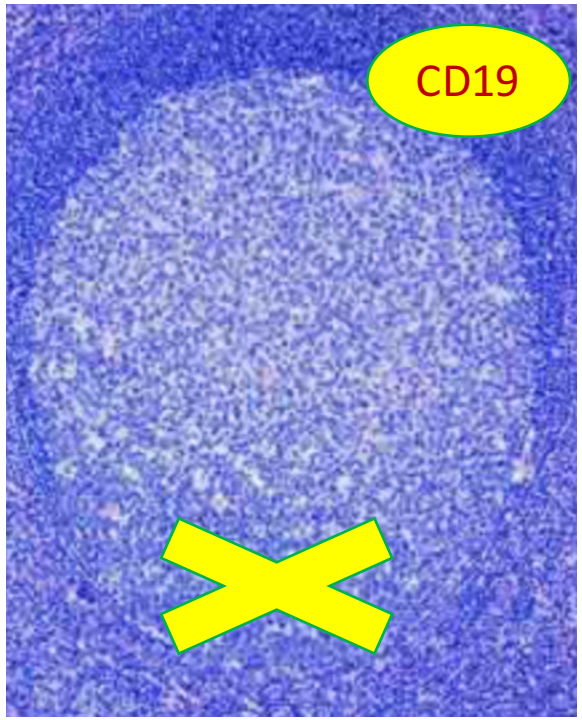
- Distinguishing Features of B-lymphocyte Failure (i.e. agammaglobulinemia)
  - No B-cells: no CD19, underdeveloped Germinal Center, no plasma cells or humoral immunity
  - Respiratory: pyogenic infections (encapsulated organisms; loss of opsonizing aby)
  - GI: especially enterovirus and Giardia (low IgA)
- Rx: IVIG
- Notes:
  - Initial protection from maternal IgG.
  - Association with heme and GI malignancies
  - Normal T-cells: Type IV hypersensitivity intact, fungal infection uncommon

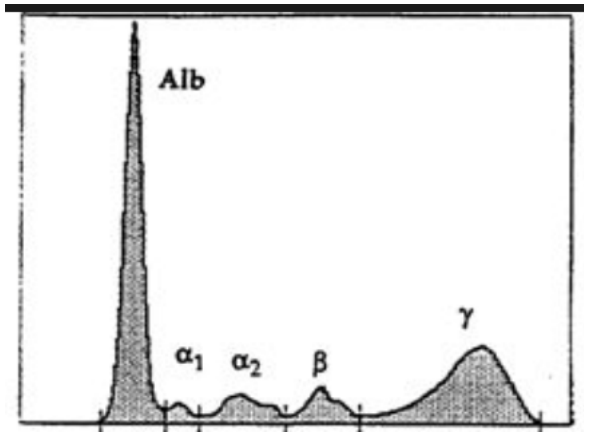
BTK ‘complex’ involved in signaling and B-cell development



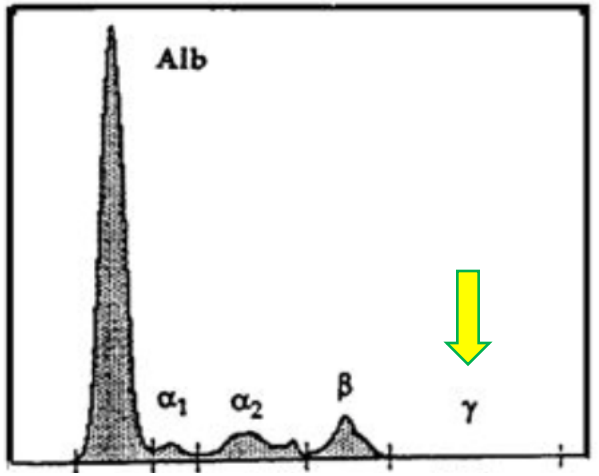

No signal transduction for B-cell development

No Germinal Center




No Immunoglobulins



# Common Variable Immunodeficiency

- Background
  - Defect: impaired B-cell differentiation into plasma cells with impaired Ig secretion/production → hypogammaglobulinemia
- Variable
  - Variable phenotypic expression
  - Variable genetic defects (i.e. group of disorders sharing low globulins in common)
  - Variable = Lousy board derivatives
- Presentation: 20-45 yrs old
  - Pulmonary: PNA, sinusitis/otitis, bronchietasis
  - GI: viral, parasite, bacteria
- Dx: Ig levels and IgG response to vaccines (tetanus, diptheria, PVX)
  - B-cell number is normal but decrease in isotype-switched memory B cells.
- Rx: IVIG
- Notes:
  - Immune dysregulation → autoimmunity (AIHA, ITP; RA)
  - Malignancy (lymphoma)

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