Primary immune deficiencies:

defects in **acquired** immunity

Primary lymphocyte imunodeficiencies

- Caused by genetic defects that lead to:
  - blocks in the **maturation** of T and B lympho
  - impairment of lympho **activation** and **functions**

Primary lymphocyte immunodeficiencies

Features of congenital immunodeficiencies caused by defects in lymphocyte maturation

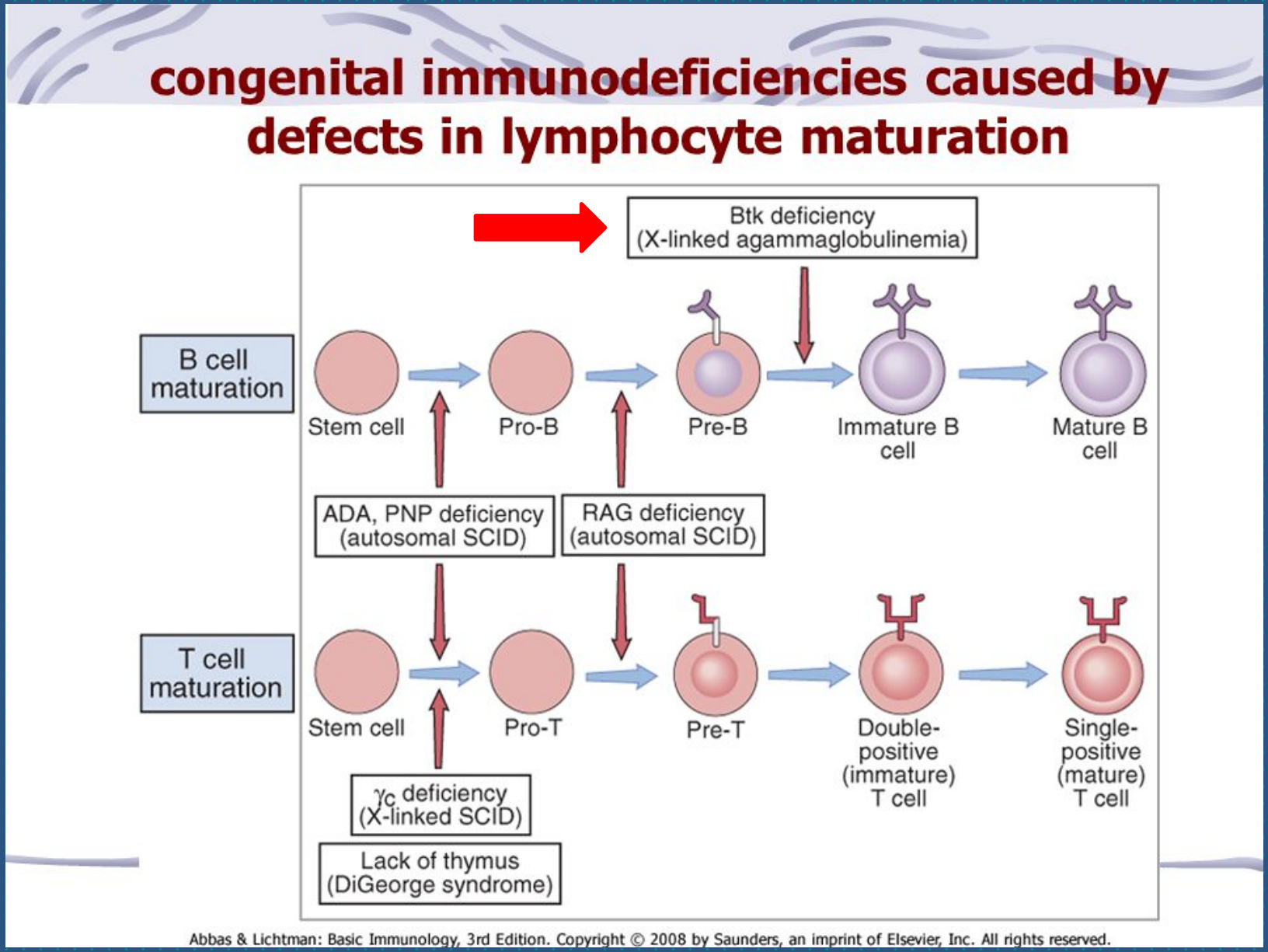
B cell immunodeficiencies Fig12-3

Disease	Functional deficiencies	Mechanism of defect
X-linked agammaglobulinemia	Decrease in all serum Ig isotypes; reduced B cell numbers	Block in maturation beyond pre-B cells, because of mutation in B cell tyrosine kinase
Ig heavy chain deletions	IgG1, IgG2, or IgG4 absent; sometimes associated with absent IgA or IgE	Chromosomal deletion at 14q32 (Ig heavy chain locus)

T cell immunodeficiencies

Disease	Functional deficiencies	Mechanism of defect
DiGeorge syndrome	Decreased T cells; normal B cells; normal or decreased serum Ig	Anomalous development of 3rd and 4th branchial pouches, leading to thymic hypoplasia

Primary lymphocyte imunodeficiencies

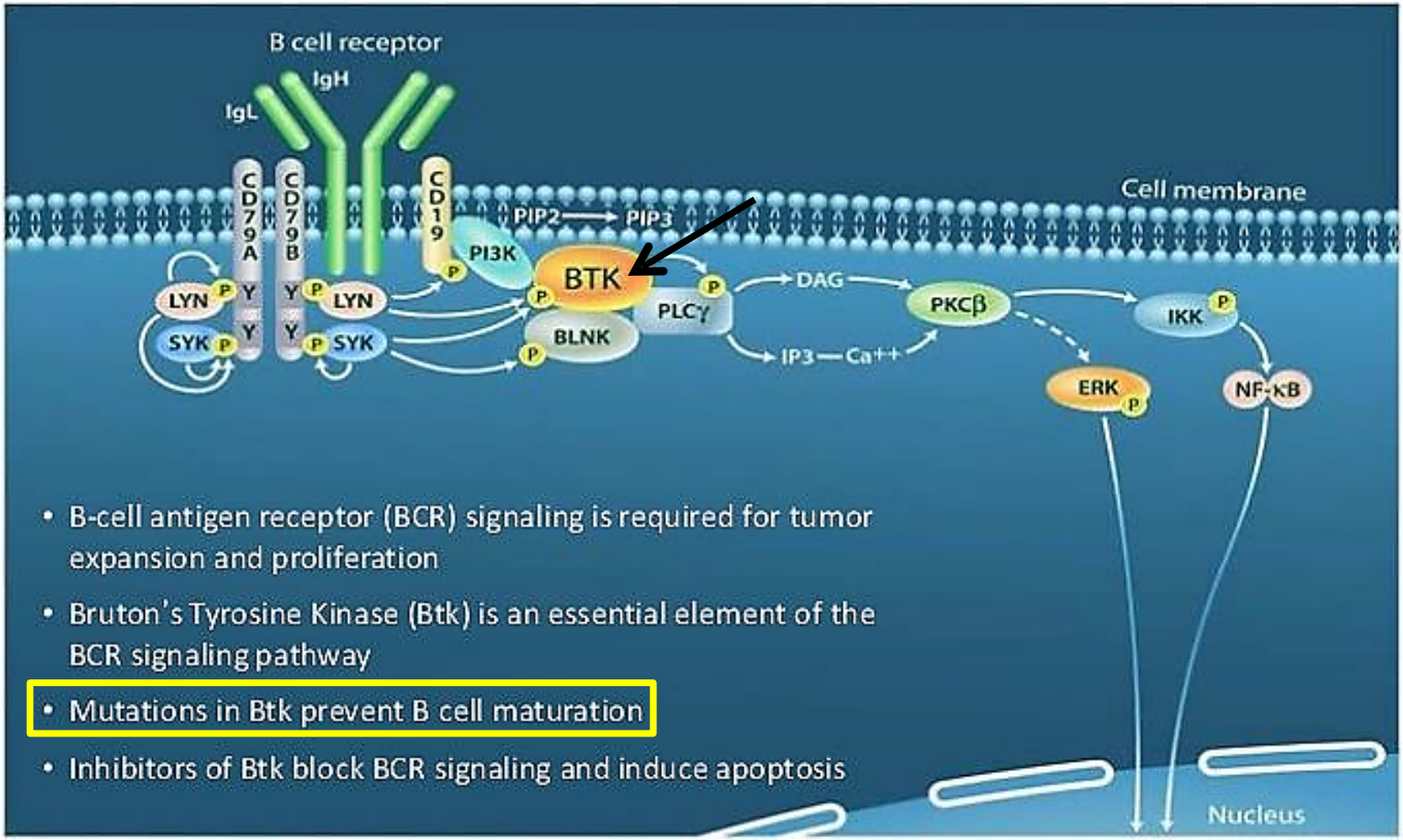


Primary B cell immunodeficiencies

X-linked agammaglobulinemia
Bruton's syndrome

- B cells in the bone marrow fail to mature beyond the preB cell stage
- Severe decrease or absence of mature B lympho and serum immunoglobulins
- Caused by mutations in the gene encoding the Bruton tyrosine kinase (Btk), that partecipates in delivering biochemical signals crucial for B cell maturation

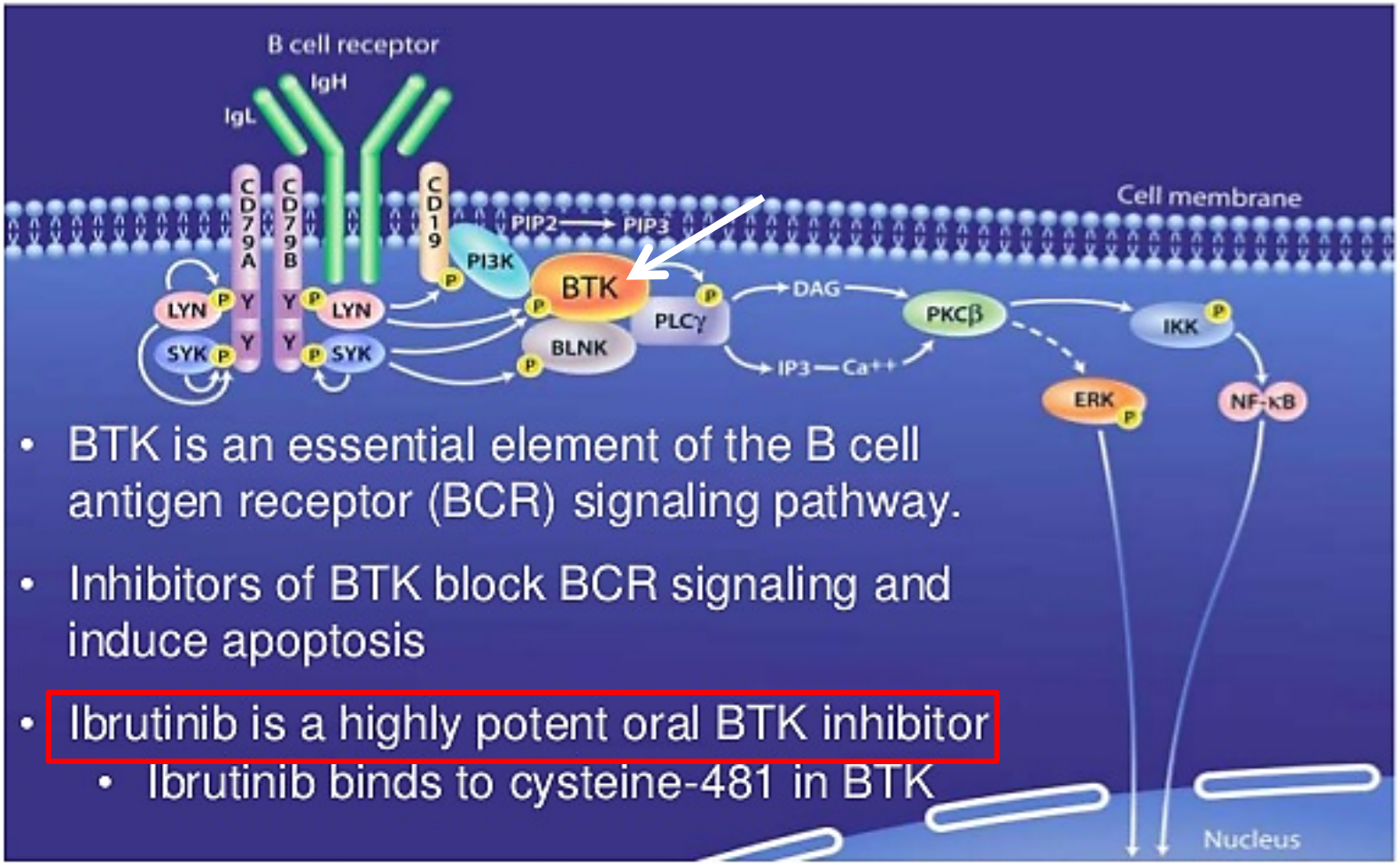
Bruton's Tyrosine Kinase (Btk)
A Critical B-Cell Signaling Kinase



- B-cell antigen receptor (BCR) signaling is required for tumor expansion and proliferation
- Bruton's Tyrosine Kinase (Btk) is an essential element of the BCR signaling pathway
- Mutations in Btk prevent B cell maturation
- Inhibitors of Btk block BCR signaling and induce apoptosis

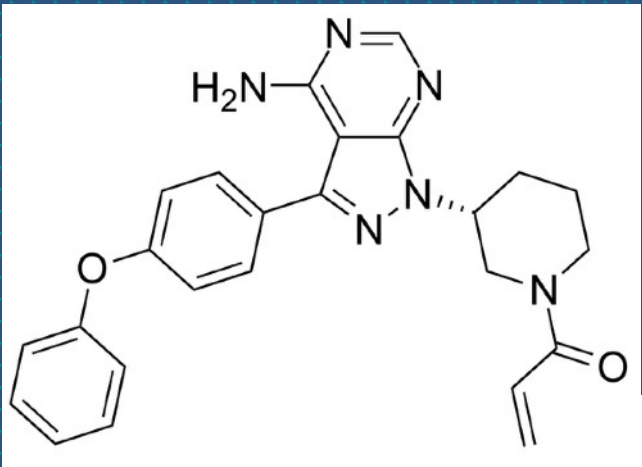
2015: Novel targeted therapies in B-cell lymphomas

Bruton's Tyrosine Kinase (BTK): Critical kinase for lymphoma cell survival and proliferation



- BTK is an essential element of the B cell antigen receptor (BCR) signaling pathway.
- Inhibitors of BTK block BCR signaling and induce apoptosis
- Ibrutinib is a highly potent oral BTK inhibitor
  - Ibrutinib binds to cysteine-481 in BTK

IBRUTINIB


N
H2N
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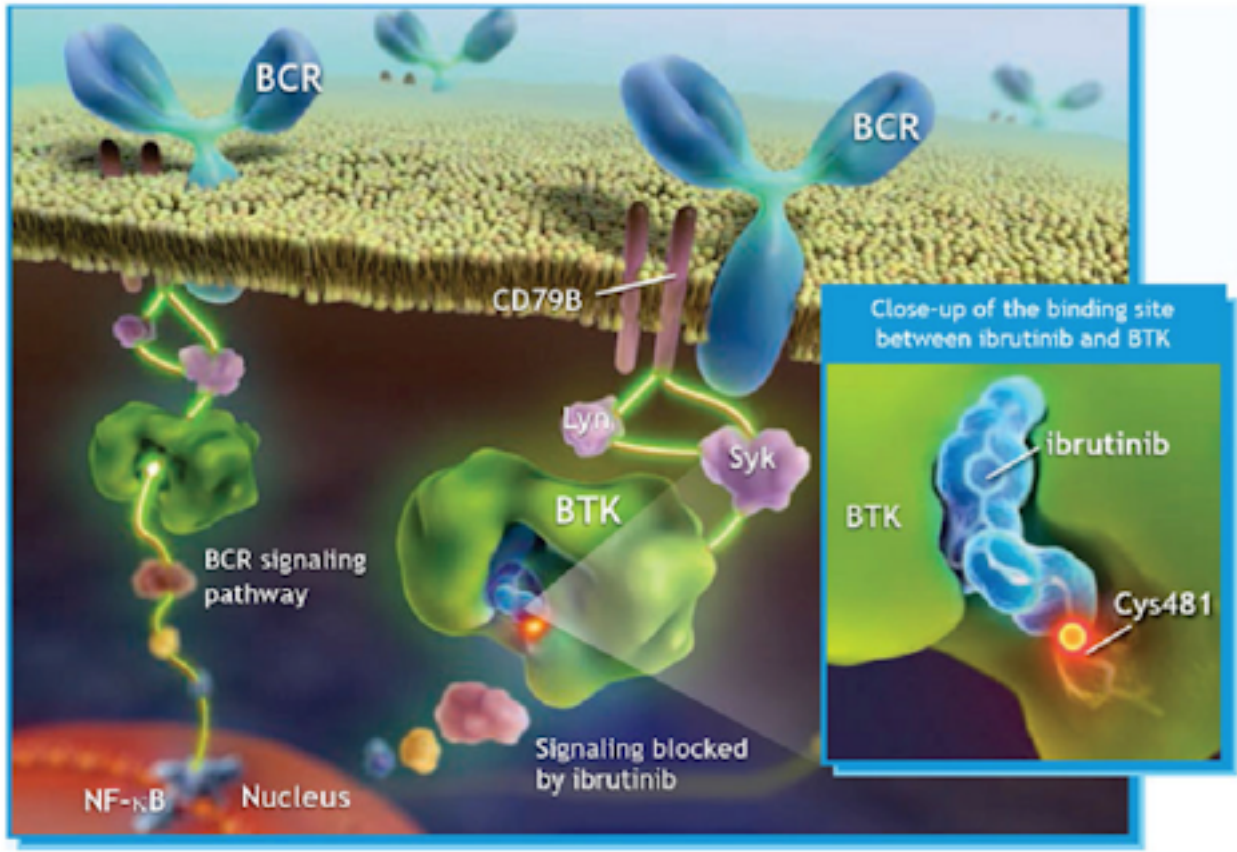

BCR
BCR
CD79B
Lyn
Syk
BTK
BCR signaling pathway
NF-κB
Nucleus
Signaling blocked by ibrutinib
Close-up of the binding site between ibrutinib and BTK
ibrutinib
BTK
Cys481

IBRUTINIB

Alteration in BTK

Patient	Protein Domain*	Exon	Nucleotide Change	Involved Codon	Effect on Coding Sequence
BTK 14	PH	2	AAA/TAA 187	K19	Lys→Stop
BTK 26	PH	2	CGC/CAC 215	R28	Arg→His
BTK 27	PH	2	CGC/CAC 215	R28	Arg→His
BTK 10	PH	2	TAC/TCC 248	Y39	Tyr→Ser
BTK 34	PH	6	534 C del	R 134	Frameshift
BTK 19	TH	7	654-655 T ins	L175	Frameshift
BTK 39	TH	7	688 A ins	K 185	Frameshift
BTK 40	TH	8	CGA/TGA 895	R255	Arg→Stop
BTK 18	SH2	11	CAA/TAA 1109	Q293	Gln→Stop
BTK 25	SH3	9	CAG/TAG 911	Q260	Gln→Stop
BTK 4	KIN	15	1599-1602 GCGC del	R490/H491	Frameshift
BTK 51	KIN	15	TGT/TAT 1649	C506Y	Cys→Tyr
BTK 61	KIN	15	TGT/TAT 1649	C506Y	Cys→Tyr
BTK 35	KIN	15	CTG/CCG 1667	L512	Leu→Pro
BTK 36	KIN	15	CTG/CCG 1667	L512	Leu→Pro
BTK 37	KIN	15	CTG/CAG 1667	L512	Leu→Gln
BTK 22	KIN	–	G/T	(522)	Splice-donor defect (+1)
BTK 28	KIN	16	CGA/CCA 1706	R525	Arg→Pro
BTK 52	KIN	16	1712-1713 TG del	C527	Frameshift
BTK 49	KIN	16	AGG/GGG1763	R544	Arg→Gly
BTK 50	KIN	16	AGG/GGG1763	R544	Arg→Gly
BTK 38	KIN	17	TGT/TAT 1866	S578	Ser→Tyr
BTK 29	KIN	18	GAA/AAA 1897	E589	Glu→Lys
BTK 5	KIN	18	GGG/CGG 1912	G594	Gly→Arg
BTK 12	KIN	18	GGG/GAG 1913	G594	Gly→Glu
BTK 13	KIN	18	GGG/GAG 1913	G594	Gly→Glu
BTK 33	KIN	18	GGG/GAG 1913	G594	Gly→Glu
BTK 7	KIN	18	2037-2038 TTTTAG ins	635FB636	In frame insertion
BTK 8	KIN	19	CGT/TGT 2053	R641	Arg→Cys

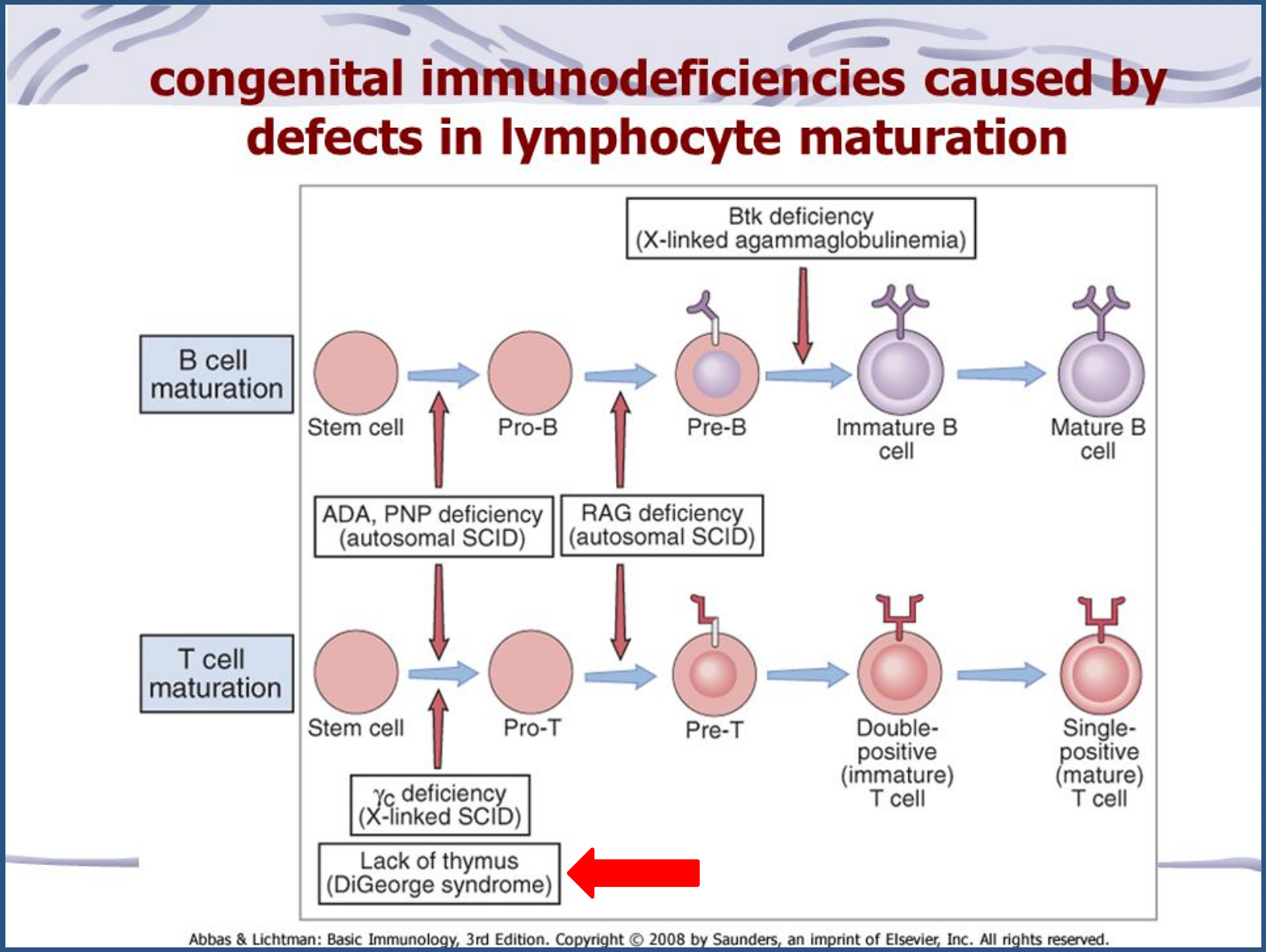
*KIN = kinase domain; PH = pleckstrin homology domain; SH = Src homology domain; TH = Tec homology domain

Table 1. Characteristics of Six Patients with Resistance to Ibrutinib.

Patient No.	Age	Prior Therapies	Baseline Cytogenetic Features*	Study Treatment and Daily Dose†	Duration of Ibrutinib Treatment
	yr	*no.*			*days*
1	59	5	del(17p13.1), trisomy 12	Ibrutinib, 560 mg	621
2	59	3	del(11q22.3)	Bendamustine–rituximab for 6 cycles; ibrutinib, 420 mg	388
3	51	2	complex karyotype	Ofatumumab for 24 wk; ibrutinib, 420 mg	674
4	69	9	del(17p13.1), complex karyotype	Ibrutinib, 840 mg	868
5	61	4	del(17p13.1), complex karyotype	Ofatumumab for 24 wk; ibrutinib, 420 mg	505
6	75	2	del(17p13.1), complex karyotype	Ibrutinib, 420 mg	673

* We used fluorescence in situ hybridization to detect del(17p13.1), del(11q22.3), centrome
stimulated G-banded cells to determine complexity.
† Doses are given for ibrutinib only.
‡ All functional mutations that were detected only at the time of relapse are listed in Table

Primary lymphocyte imunodeficiencies



Defects in T cell maturation: DiGeorge syndrome

- Selective T cell deficiency due to a congenital malformation that results in many developmental alterations, including **hypolasia** or **agenesis** of the **thymus** and consequent deficient T cell maturation

- Microdeletion on chromosome 22, approximately 40 genes
- Among them, the **TBX1** gene is suspected to play a major role in many of the typical features of this syndrome
- Tbx-1 (transcription factor) controls genes involved in the development of the parathyroid and thymus glands
- Other genes involved in DiGeorge syndrome?

Primary lymphocyte immunodeficiencies

Features of congenital immunodeficiencies caused by defects in lymphocyte maturation

Severe combined immunodeficiency (SCID) Fig12-3

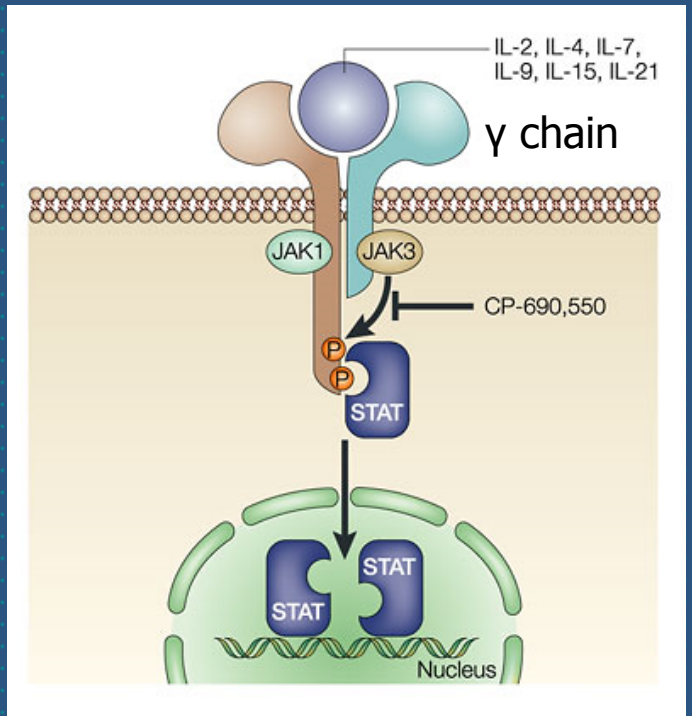
Disease	Functional deficiencies	Mechanism of defect
X-linked SCID	Markedly decreased T cells; normal or increased B cells; reduced serum Ig	Cytokine receptor common γ chain gene mutations, defective T cell maturation due to lack of IL-7 signals
Autosomal recessive SCID due to ADA, PNP deficiency	Progressive decrease in T and B cells (mostly T); reduced serum Ig in ADA deficiency, normal B cells and serum Ig in PNP deficiency	ADA or PNP deficiency leads to accumulation of toxic metabolites in lymphocytes
Autosomal recessive SCID due to other causes	Decreased T and B cells; reduced serum Ig	Defective maturation of T and B cells; genetic basis unknown in most cases; may be mutations in *RAG* genes

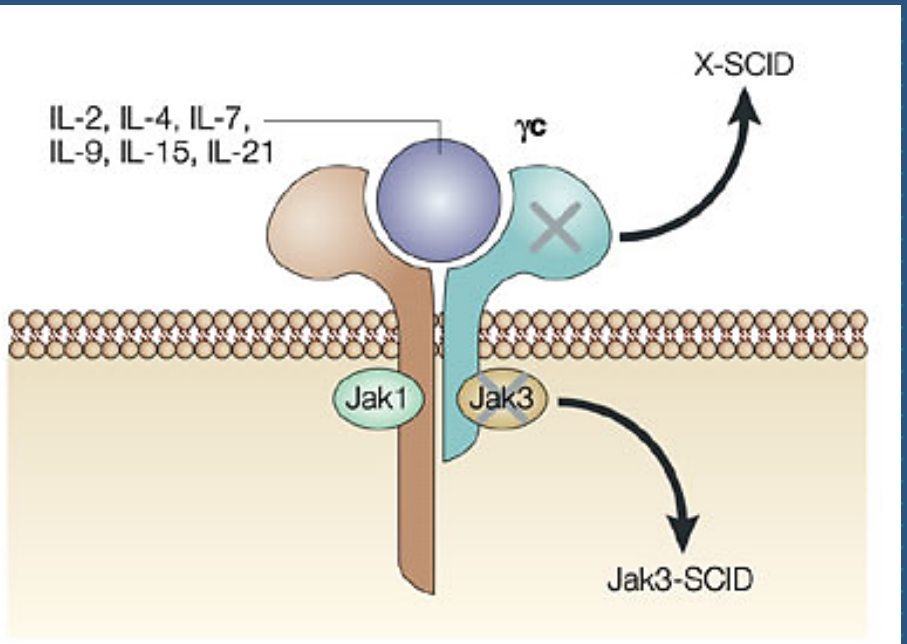
Severe Combined Immunodeficiencies (SCIDs)

- Disorders that affect both humoral (antibodies) and cell-mediated immunity
- Caused by deficiencies of **both** B and T cells, or **only** T cell
- In **some types of SCID** the **defect in humoral immunity** is due to **absence of helper T** cells
- Life-threatening infections during the **first year** of life

X-linked SCID

- Nearly **50%** of SCID cases
- Mutations in the gene encoding the common γ chain shared by the **receptors for IL-2, IL-4, IL-7, IL-9** and **IL-15**
- Impaired maturation of T and NK cells, reduced serum Ig
- **Failure of IL-7 receptor** causes **T cell deficiency** due to the inability of this cytokine to stimulate the growth of immature thymocytes
- **NK cell deficiency** is due to failure of the **receptor for IL-15**, a strong proliferative stimulus for NK cells





- A number of cytokines use the **common gamma-chain** in conjunction with a **ligand-specific chain** to form their receptors
- These receptor subunits bind the Janus kinases JAK3 and JAK1, respectively. On ligand binding, these kinases phosphorylate signal transducers and activators of transcription (STATs)
- Phosphorylated STATs translocate and accumulate in the nucleus where they regulate gene expression (proliferation, maturation)
- Mutations disrupting cytokine signalling lead to **severe combined immunodeficiency (SCID)**

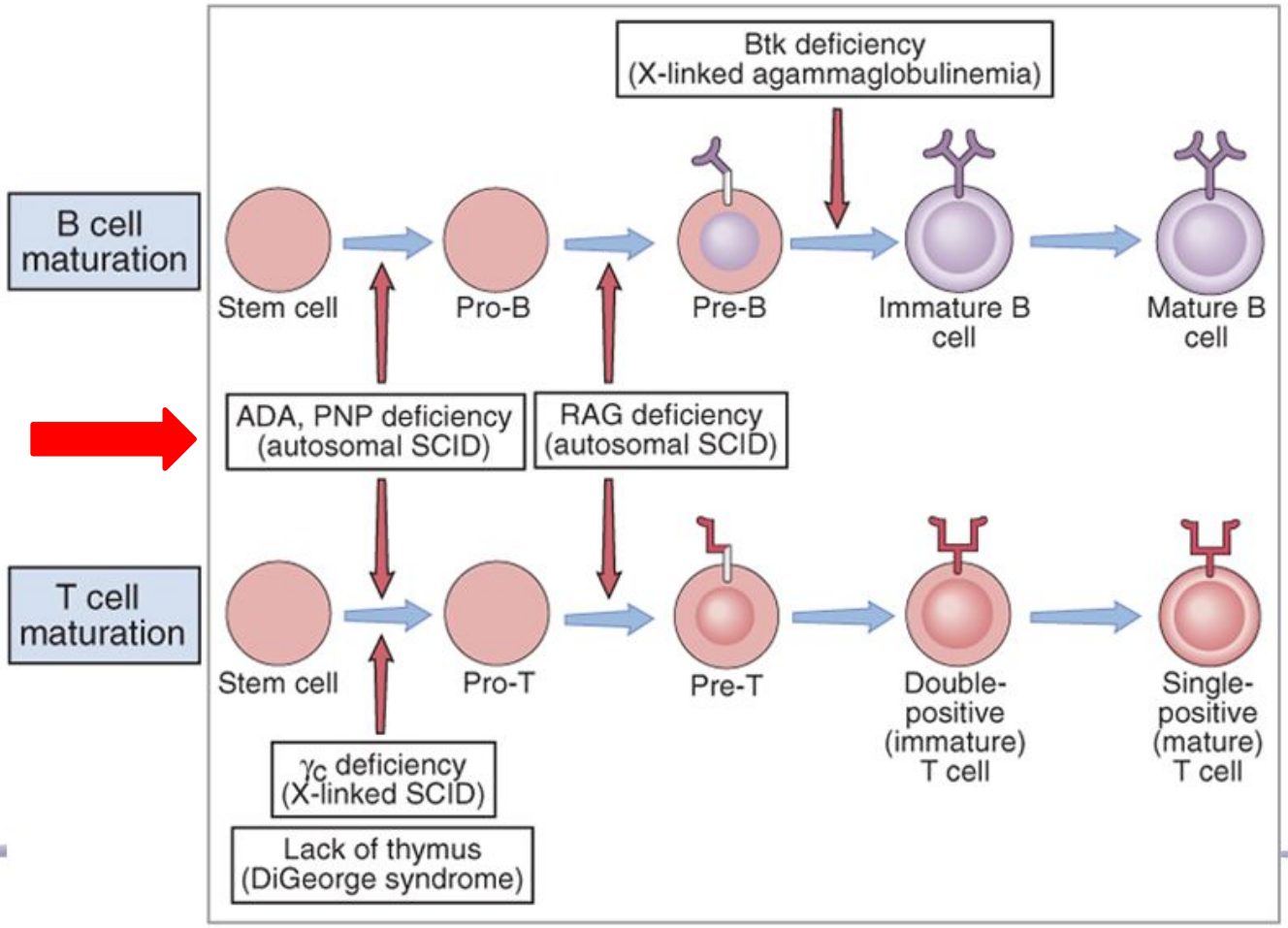
SCID: the case of the «Bubble Boy»

What's it like to live in a bubble?

David Vetter, a young boy from Texas, lived out in the real world in a plastic bubble. Nicknamed "Bubble Boy," David was born in 1971 with severe combined immunodeficiency (SCID), and was forced to live in a specially constructed sterile plastic bubble after 20 seconds of exposure to the world. At the age of 12, four months after receiving the bone marrow transfusion from his sister, David died from lymphoma, a cancer introduced into his system by the Epstein-Barr virus

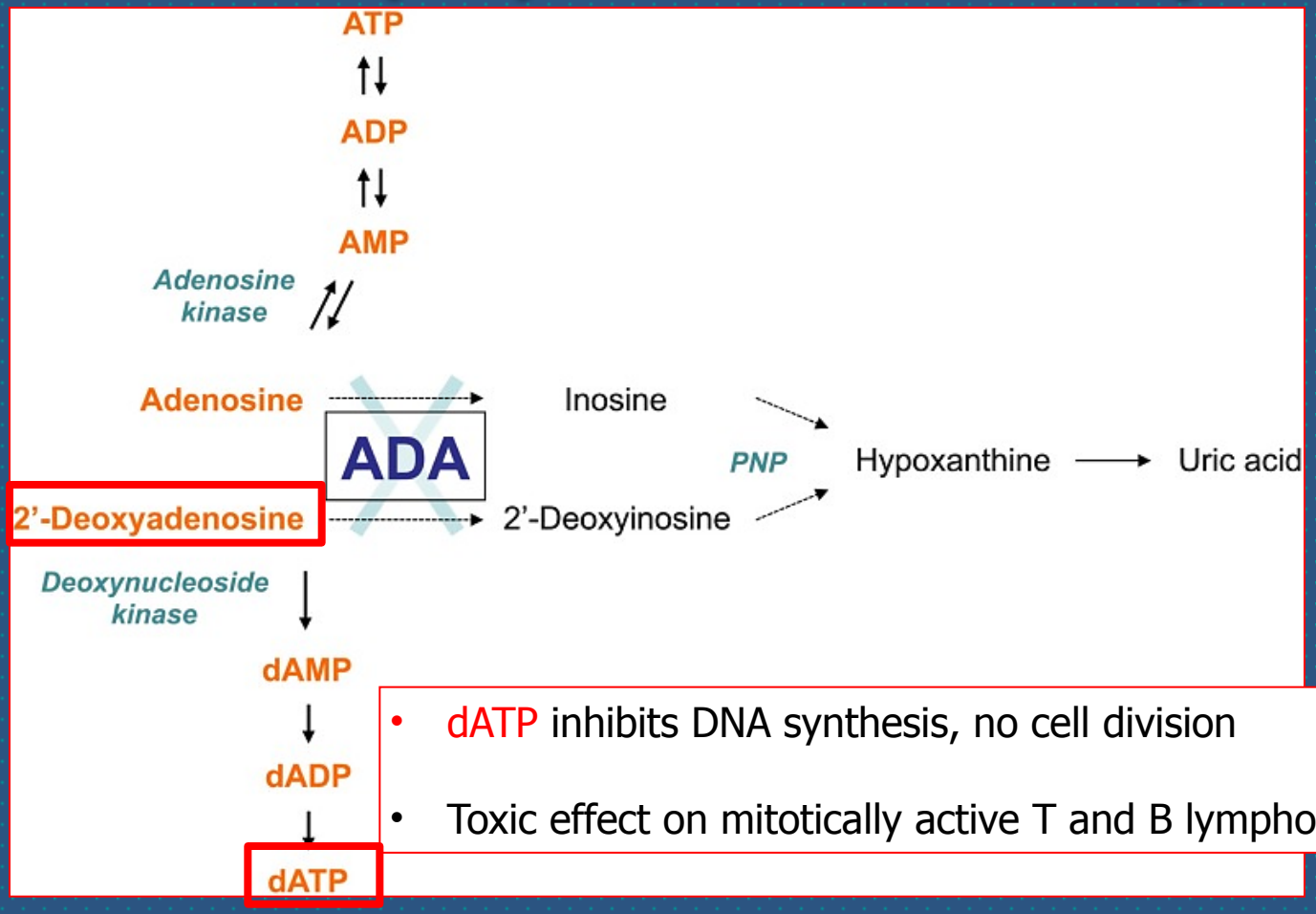
Primary lymphocyte imunodeficiencies

congenital immunodeficiencies caused by defects in lymphocyte maturation



SCID caused by adenosine deaminase (ADA) deficiency

- 50% of SCID patients show an autosomal recessive pattern of inheritance, nearly half of these cases are due to **deficiency** of **adenosine deaminase** (ADA) that is involved in **purine catabolism**



- dATP inhibits DNA synthesis, no cell division
- Toxic effect on mitotically active T and B lymphos

ADA-SCID

- Occurs in fewer than one in 100,000 live births
- ADA deficiency leads to reduced numbers of T and B cells
- profound lymphopenia and very low immunoglobulin levels of all isotypes resulting in severe and recurrent opportunistic infections
- **Treatments**:
  - allogenic hematopoietic stem cell transplantation (HSCT)
  - enzyme replacement therapy with adenosine deaminase enzyme
  - gene therapy by infusion of marrow cells that have been transduced with an ADA-containing vector (18 kids treated, 100% success)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 29, 2009 VOL. 360 NO. 5

Gene Therapy for Immunodeficiency Due to Adenosine Deaminase Deficiency

Alessandro Aiuti, M.D., Ph.D., Federica Cattaneo, M.D., Stefania Galimberti, Ph.D., Ulrike Benninghoff, M.D., Barbara Cassani, Ph.D., Luciano Callegaro, R.N., Samantha Scaramuzza, Ph.D., Grazia Andolfi, Massimiliano Mirolo, B.Sc., Immacolata Brigida, B.Sc., Antonella Tabucchi, Ph.D., Filippo Carlucci, Ph.D., Martha Eibl, M.D., Memet Aker, M.D., Shimon Slavin, M.D., Hamoud Al-Mousa, M.D., Abdulaziz Al Ghonaium, M.D., Alina Ferster, M.D., Andrea Duppenthaler, M.D., Luigi Notarangelo, M.D., Uwe Wintergerst, M.D., Rebecca H. Buckley, M.D., Marco Bregni, M.D., Sarah Marktel, M.D., Maria Grazia Valsecchi, Ph.D., Paolo Rossi, M.D., Fabio Ciceri, M.D., Roberto Miniero, M.D., Claudio Bordignon, M.D., and Maria-Grazia Roncarolo, M.D.

Autologous CD34+ bone marrow stem cells transduced with a retroviral vector containing the ADA gene into 10 children with SCID due to ADA deficiency who lacked an HLA-identical sibling donor

Primary lymphocyte imunodeficiencies

- Caused by genetic defects that lead to:
  - blocks in the maturation of T and B lympho
  - impairment of lympho activation and functions

PHASES OF T CELL RESPONSE

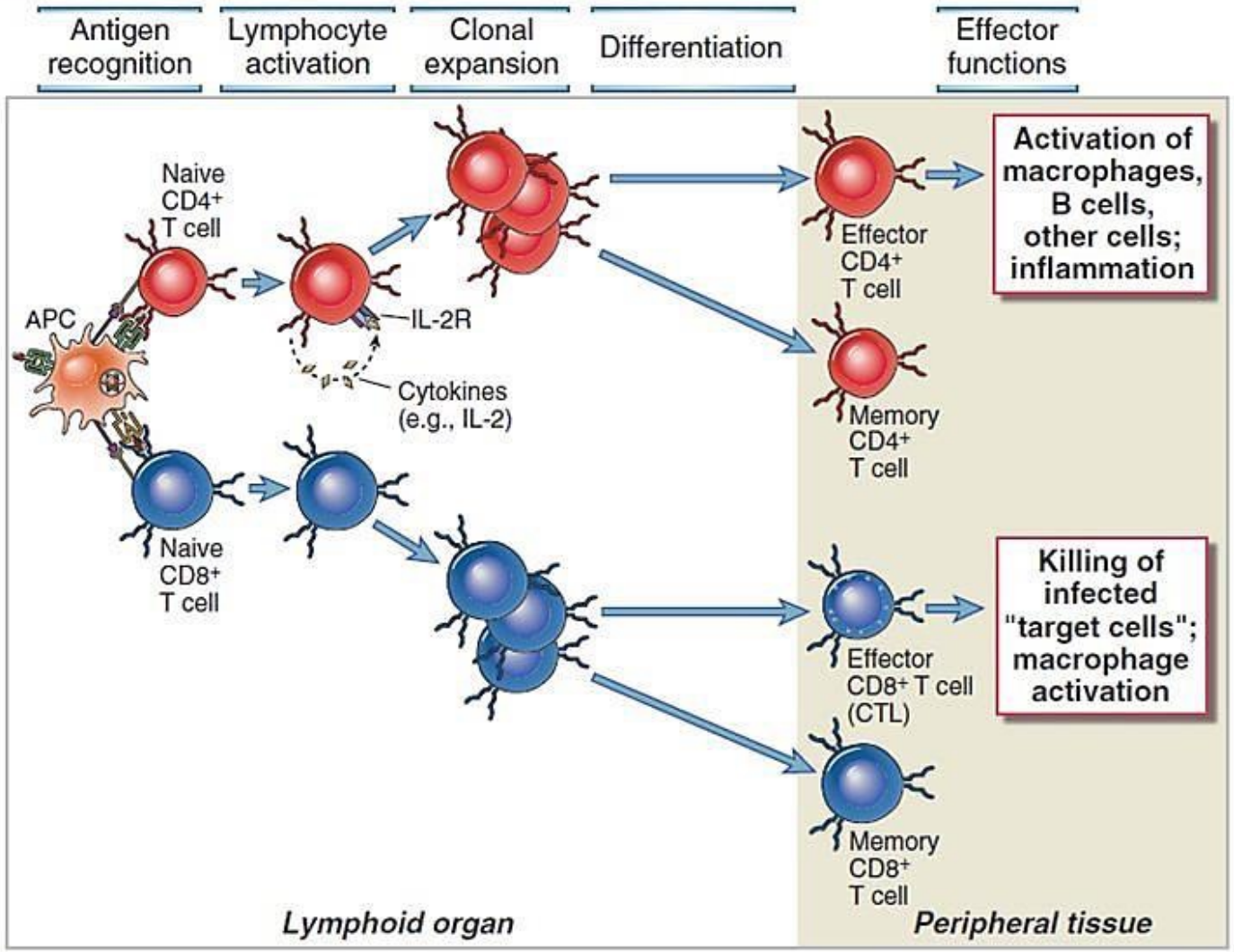


FIGURE 9–2 Phases of T cell responses. Antigen recognition by T cells induces cytokine (e.g., IL-2) secretion, particularly in $CD4^+$ T cells, clonal expansion as a result of cell proliferation, and differentiation of the T cells into effector cells or memory cells. In the effector phase of the response, the effector $CD4^+$ T cells respond to antigen by producing cytokines that have several actions, such as the recruitment and activation of leukocytes and activation of B lymphocytes, and $CD8^+$ CTLs respond by killing other cells.

PHASES OF THE HUMORAL IMMUNE RESPONSE

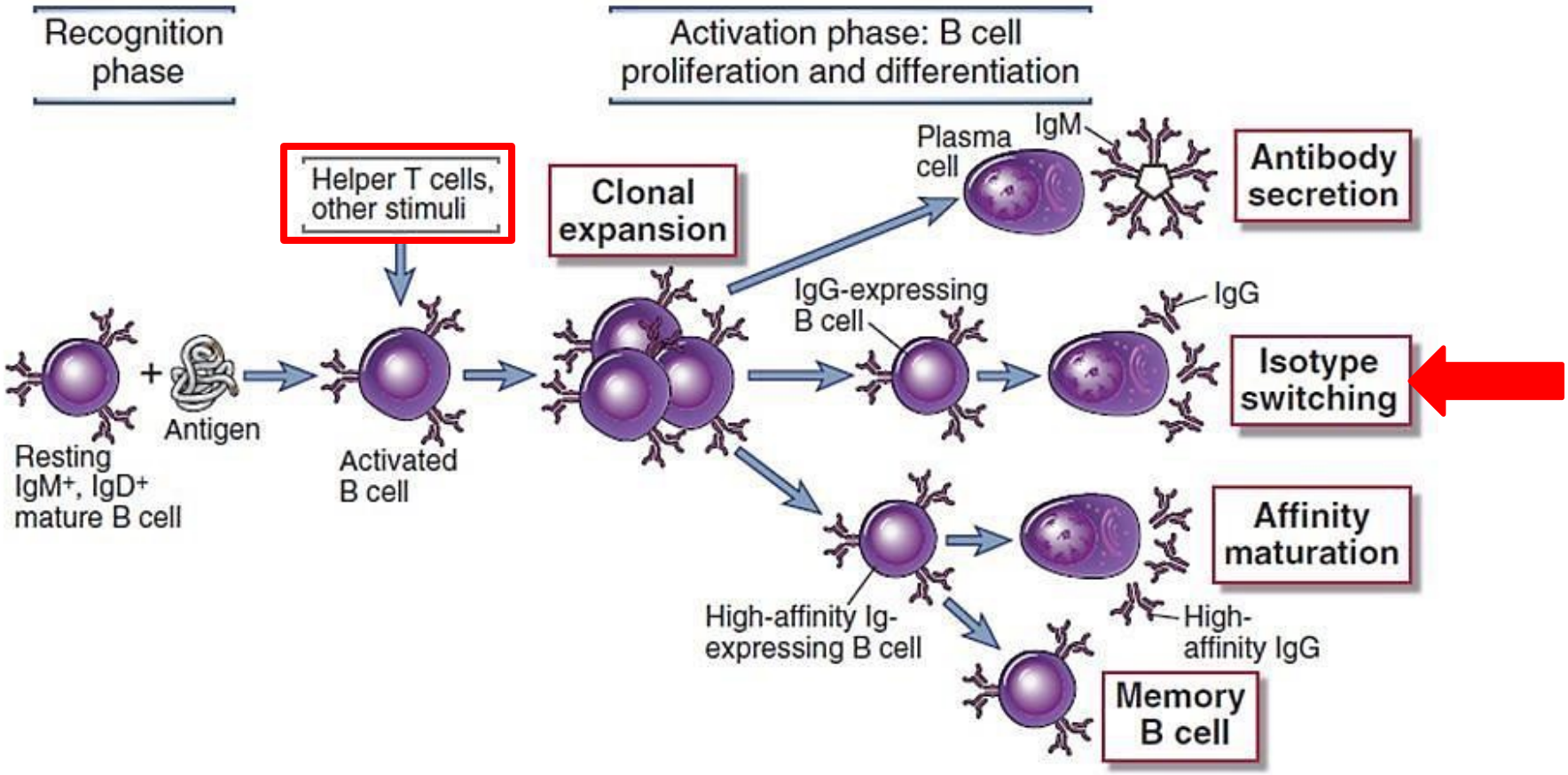
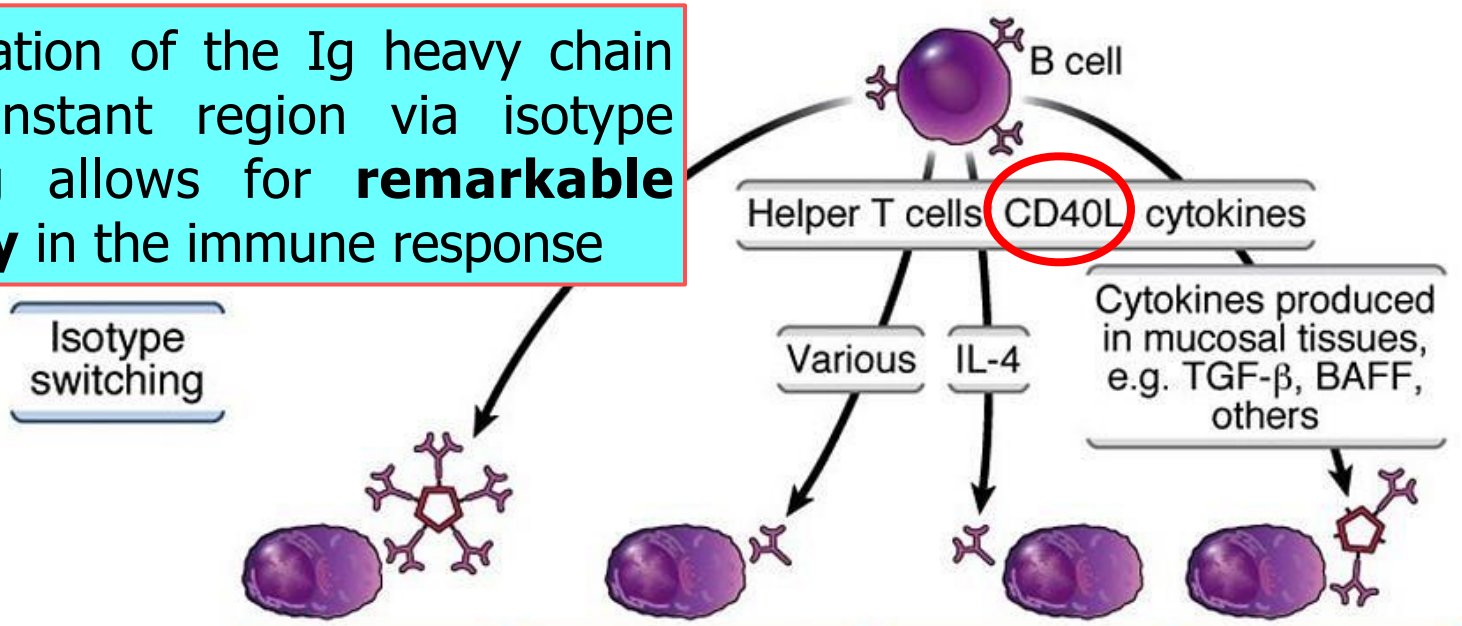


FIGURE 11–1 Phases of the humoral immune response. The activation of B cells is initiated by specific recognition of antigens by the surface Ig receptors of the cells. Antigen and other stimuli, including helper T cells, stimulate the proliferation and differentiation of the specific B cell clone. Progeny of the clone may produce IgM or other Ig isotypes (e.g., IgG), may undergo affinity maturation, or may persist as memory cells.

Immunoglobulin (Ig) heavy chain isotype (class) switching

Diversification of the Ig heavy chain (IgH) constant region via isotype switching allows for **remarkable plasticity** in the immune response



	IgM	IgG subclasses (IgG1, IgG3)	IgE	IgA
Principal effector functions	Complement activation	Fc receptor-dependent phagocyte responses; complement activation; neonatal immunity (placental transfer)	Immunity against helminths Mast cell degranulation (immediate hypersensitivity)	Mucosal immunity (transport of IgA through epithelia)

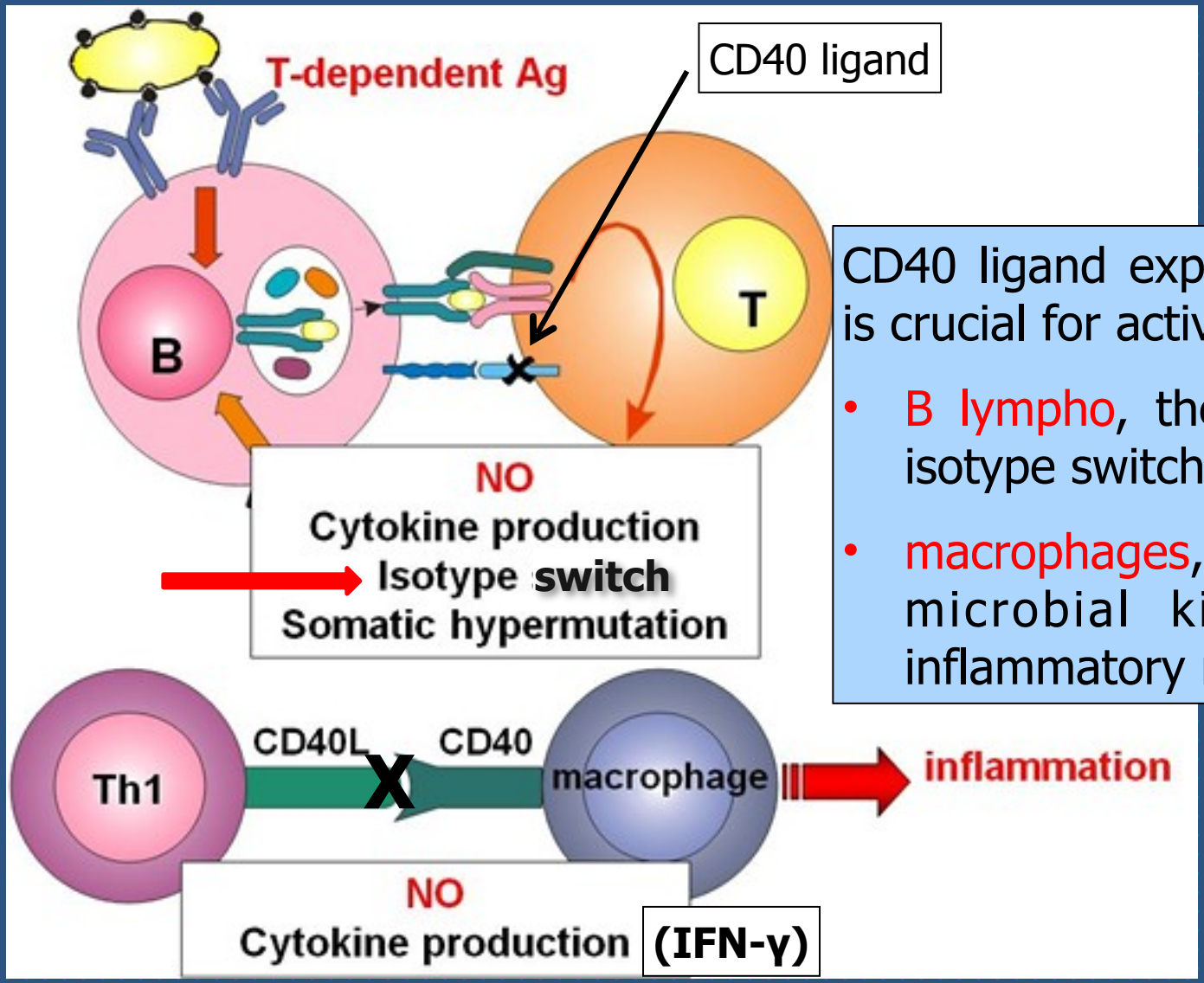
Primary lymphocyte immunodeficiencies

Congenital immunodeficiencies associated with defects in lymphocyte activation and effector functions

Fig12-4: Features of some of resulting deficiency disorders

Ⓑ Disease	Functional Deficiencies	Mechanisms of Defect
X-linked hyper-IgM syndrome	Defects in helper T cell–dependent B cell and macrophage activation	Mutations in CD40 ligand
Selective immunoglobulin isotype deficiencies	Reduced or no production of selective isotypes or subtypes of immunoglobulins; susceptibility to bacterial infections or no clinical problems	Unknown; may be defect in B cell differentiation or T cell help
Defective class II MHC expression: The bare lymphocyte syndrome	Lack of class II MHC expression and impaired $CD4^+$ T cell activation; defective cell-mediated immunity and T cell–dependent humoral immunity	Mutations in genes encoding transcription factors required for class II MHC gene expression
Defects in T cell receptor complex expression or signaling	Decreased T cells or abnormal ratios of $CD4^+$ and $CD8^+$ subsets; decreased cell-mediated immunity	Rare cases due to mutations or deletions in genes encoding CD3 proteins, ZAP-70

X-linked hyper-IgM syndrome



CD40 ligand exposed by Th lympho is crucial for activating:

- B lympho, thereby promoting Ig isotype switch
- macrophages, thereby enhancing microbial killing during the inflammatory response

Primary lymphocyte immunodeficiencies

Congenital immunodeficiencies associated with defects in lymphocyte activation and effector functions

Fig12-4: Features of some of resulting deficiency disorders

Ⓑ Disease	Functional Deficiencies	Mechanisms of Defect
X-linked hyper-IgM syndrome	Defects in helper T cell–dependent B cell and macrophage activation	Mutations in CD40 ligand
Selective immunoglobulin isotype deficiencies	Reduced or no production of selective isotypes or subtypes of immunoglobulins; susceptibility to bacterial infections or no clinical problems	Unknown; may be defect in B cell differentiation or T cell help
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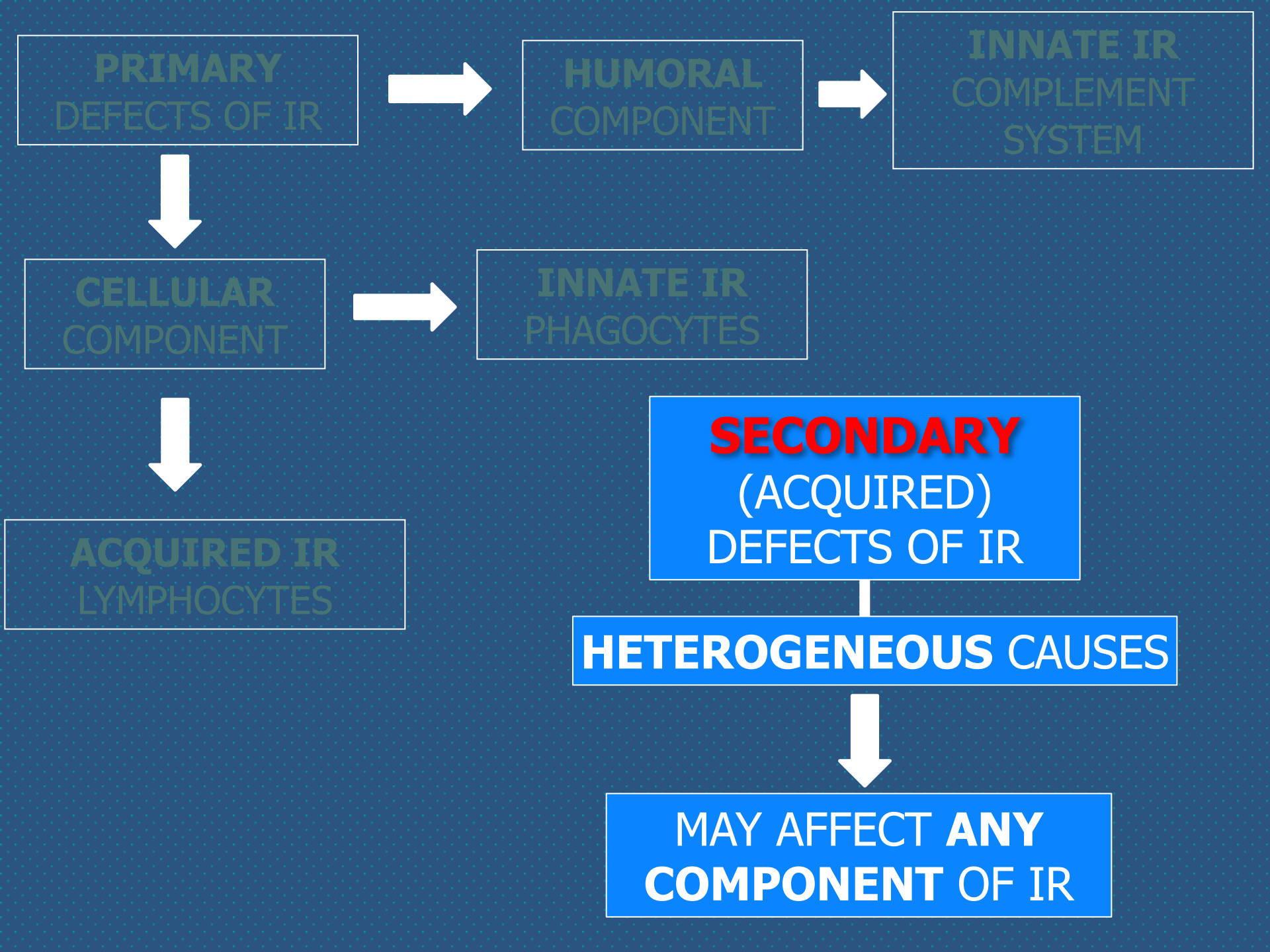
Defects in T cell receptor complex expression or signaling	Decreased T cells or abnormal ratios of $CD4^+$ and $CD8^+$ subsets; decreased cell-mediated immunity	Rare cases due to mutations or deletions in genes encoding CD3 proteins, ZAP-70


PRIMARY
DEFECTS OF IR
HUMORAL
COMPONENT
INNATE IR
COMPLEMENT
SYSTEM
CELLULAR
COMPONENT
INNATE IR
PHAGOCYTES
ACQUIRED IR
LYMPHOCYTES
SECONDARY
(ACQUIRED)
DEFECTS OF IR
HETEROGENEOUS CAUSES
MAY AFFECT ANY
COMPONENT OF IR

Secondary immunodeficiencies (1)

- Also known as acquired immunodeficiencies, can result from various immunosuppressive agents

Secondary or acquired immunodeficiency diseases

Cause	Mechanism
Human immunodeficiency virus infection	Depletion of $CD4^+$ helper T cells
Irradiation and chemotherapy treatments for cancer	Decreased bone marrow precursors for all leukocytes
Involvement of bone marrow by cancers (metastases, leukemias)	Reduced site of leukocyte development
Protein-calorie malnutrition	Metabolic derangements inhibit lymphocyte maturation and function
Removal of spleen	Decreased phagocytosis of microbes

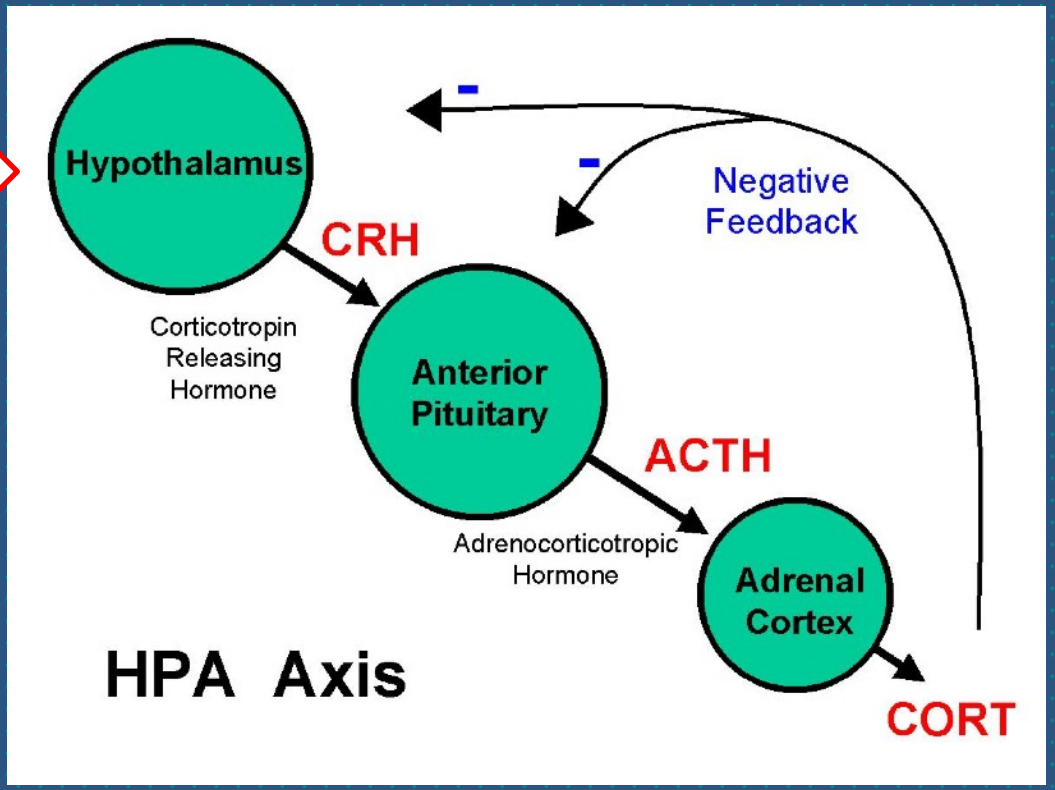
Secondary immunodeficiencies (2)

Aging	Defective T lymphocyte functions Defective phagocytic activity Chronic diseases common among the elderly (diabetes, nephropathy)
Drugs	antirheumatic drugs, glucocorticoids immunosuppressive drugs before and after bone marrow and organ transplants
Stress	Effects of cortisol

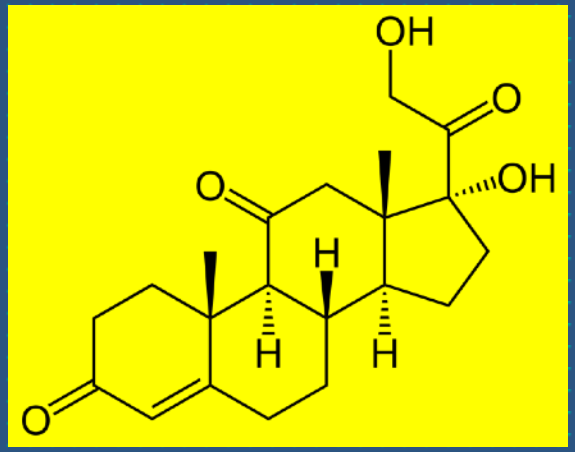
Stress-induced activation of the hypothalamus-pituitary-adrenal axis

STRESS

- **physical**
- **psychological**
- **enviromental**



Cortisol



Chronic elevated cortisol levels can:

- increase blood pressure
- increase glycemia
- downregulate the immune system
- decrease libido
- produce acne
- contribute to obesity

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How stress influences the immune response

David A. Padgett[1] and Ronald Glaser[2]

Psychological stress alters cytokine production.

In **medical students taking exams**, psychological stress produced a shift in the **cytokine balance**. The data showed **decreased synthesis of Th1 cytokines**, including IFN-γ, and **increased production of Th2 cytokines**, including IL-10. This stress-induced decrease of Th1 cytokines results in **dysregulation of cell-mediated immune responses**

Examples:

- Low response to **infections**
- Delayed cutaneous **wound healing**