Genetics of Primary Immunodeficiencies

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Learning Objectives

- Define and classify primary immunodeficiency diseases
  → changing definition

- Review the role of clinical laboratory in the diagnosis of primary immunodeficiency diseases

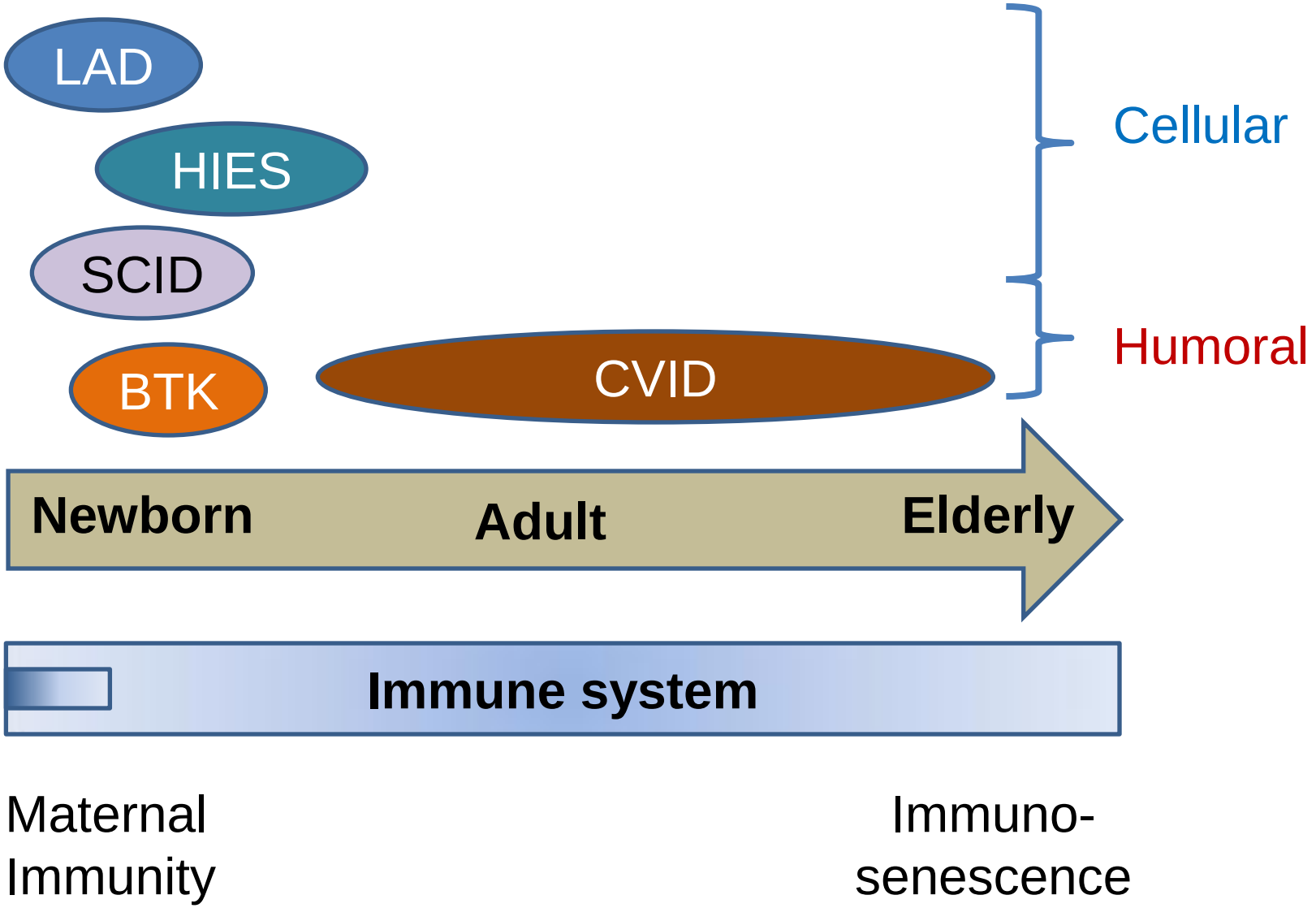
- Demonstrate the utility of molecular diagnosis in primary immunodeficiency diseases
  → changing methodology

- Review examples of genetic susceptibility to bacterial, fungal and viral infections:
  - Mendelian suscept. to chronic mucocutaneous candidiasis
  - Mendelian susceptibility to mycobacterial infections
  - Genetic susceptibility to herpes simplex encephalitis

Definitions

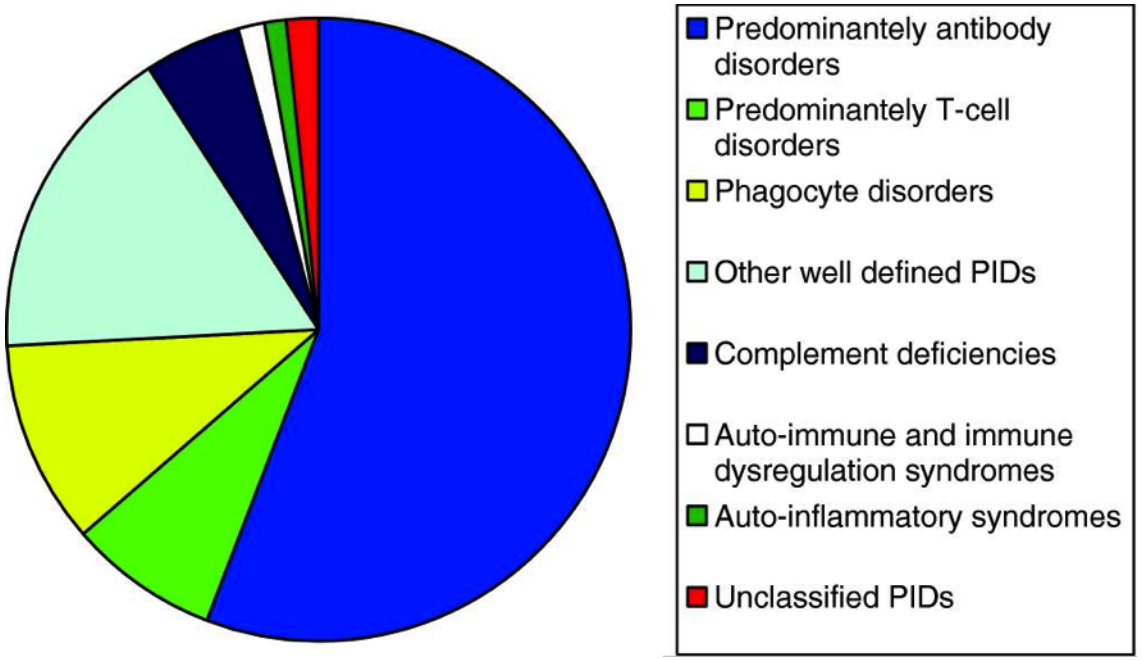
- Primary immunodeficiency (PID): genetic
- Secondary immunodeficiency: infection, malignancy, iatrogenic

Primary Immunodeficiencies



Primary antibody deficiencies are the most common PIDs

European ESID patient registry 2010



<u>Antibody deficiencies:</u>

Diagnosis ≥16yo = 86%

Diagnosis ≤15yo = 46%

Gathmann et al. Clin Exp Immunol 2009

http://www.esid.org/statistics

PID

- Prevalence: 86.2/100,000
- Incidence: 10.3/100,000

  (Joshi et al. 2009; Boyle and Buckley 2007)

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Leukemias

- Prevalence: 81.6/100,000
- Incidence: 12.5/100,000

(http://seer.cancer.gov/statfacts/html/leuks.html)

Identification of patients with PID

- Diagnosis of PIDs requires integration of data from clinical findings with laboratory immunological analyses and genetic testing

→ Infections

- recurrent
- life-threatening
- unusual

→Autoimmune diseases

→Malignancies

Diagnosis of PIDs

Clinical and family history-based diagnostic approach

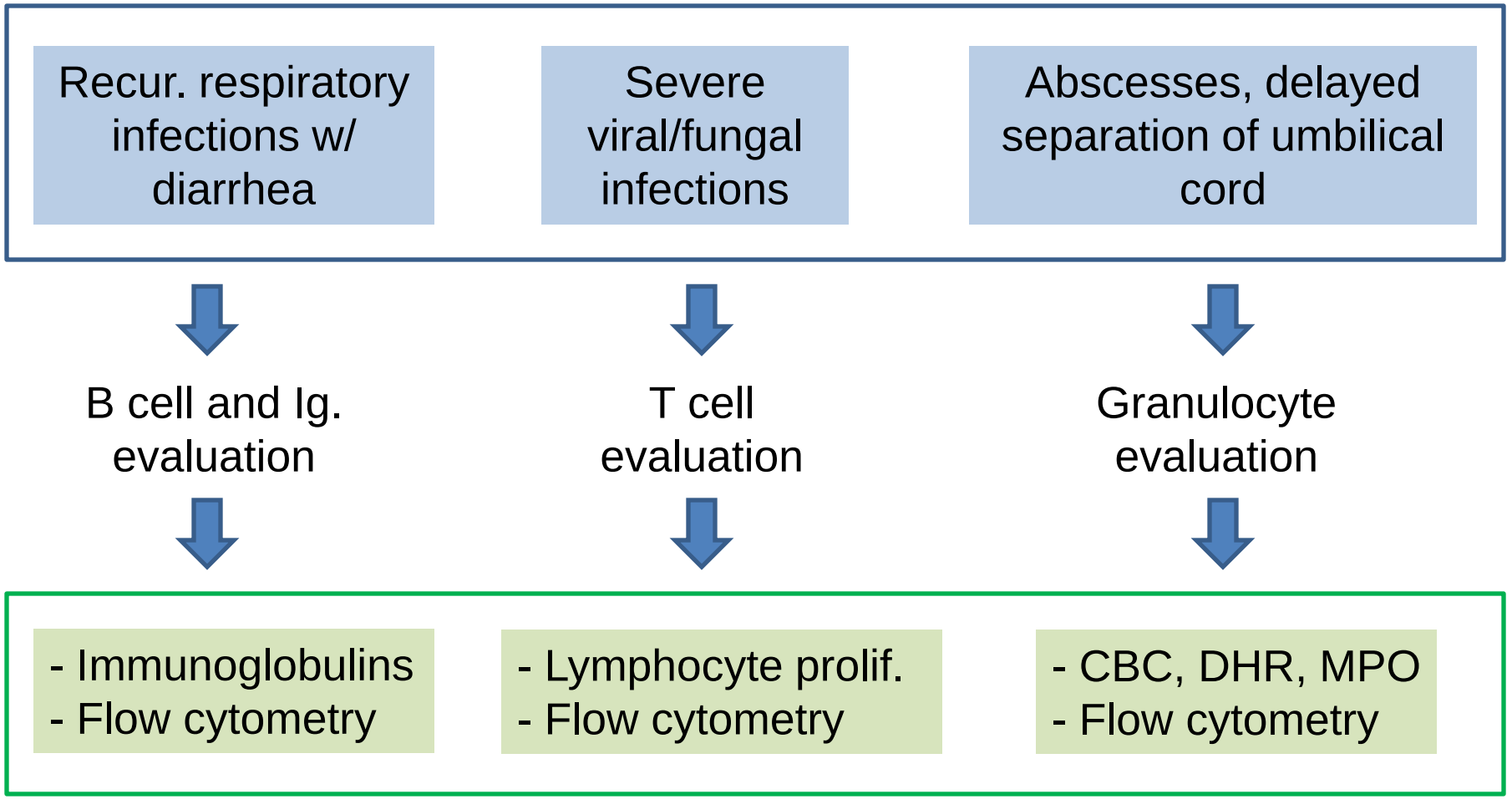
↓

Diagnostic immunology lab supports, refine phenotype

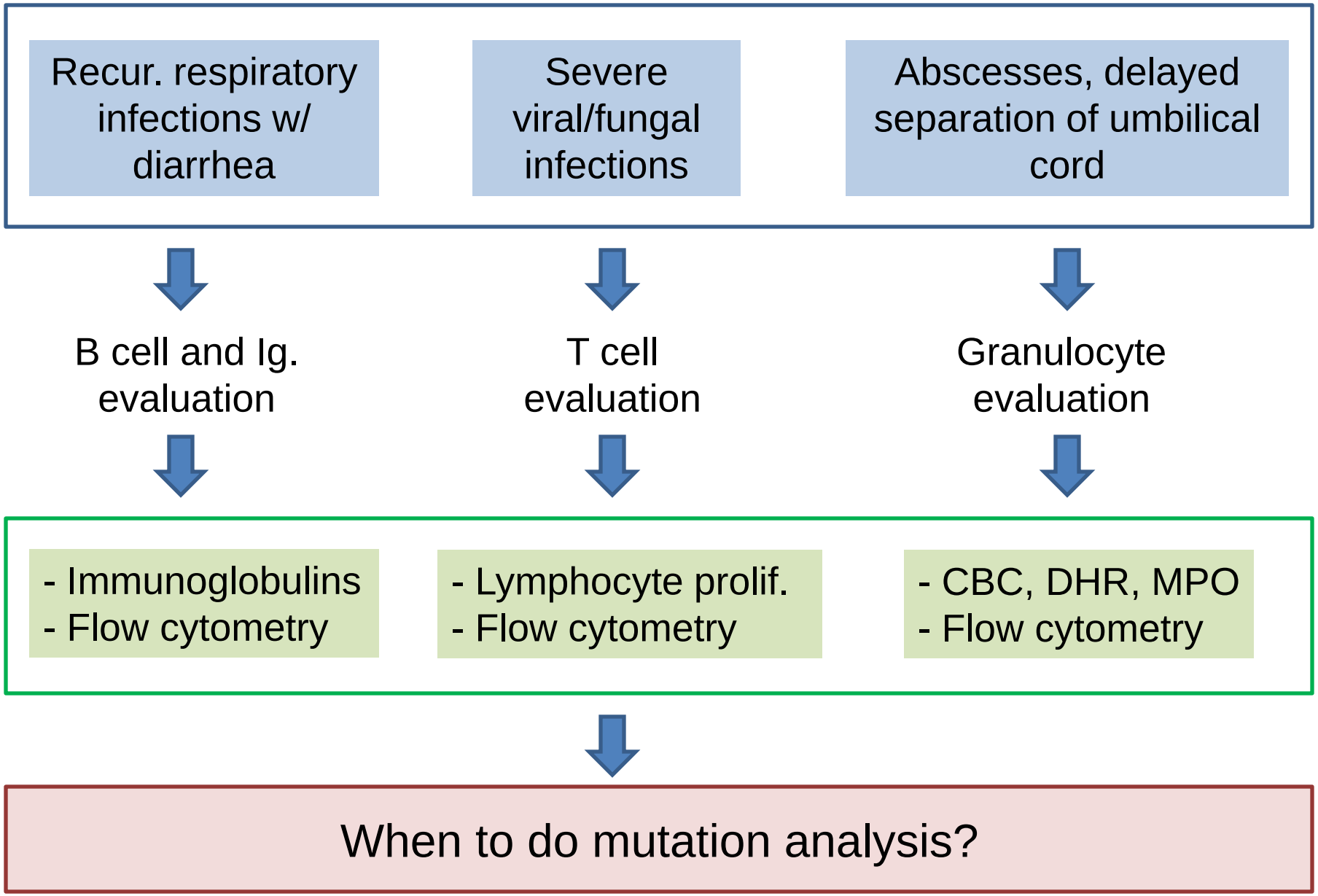
↓

Molecular lab: diagnosis, genotype-phenotype, etc

Clinical and family history-based approach



Clinical and family history-based approach



Mutation analysis in PIDs

- Definitive diagnosis (atypical presentations)
- Presymptomatic identification
- Carrier identification, genetic counseling, prenatal diagnosis
- Prognosis (strong genotype-phenotype correlation)
- Technical considerations (DNA stability vs. live cells)

Primary immunodeficiencies

PIDs are like other genetic diseases, but

- secondary causes of ID are more common than primary (esp. in adults)

- manifestations (infections) can be the same in both primary and secondary ID as well in “healthy” individuals

Primary immunodeficiencies

- PID: changing definition

  from very severe Mendelian traits to varying degree of susceptibility to infections, including susceptibility to single infectious agents

  →not all-or-nothing (normal vs. immune deficient)
- ~150 recognized PIDS
- >200 genes (increasing fast)

  - candidate genes

  - mapping studies

  - novel technologies (genome/exome sequencing)

- Pathways not genes

Mendelian susceptibility to chronic mucocutaneous candidiasis

- *Candida albicans* is present in GI flora and and reproductive mucosa of **healthy** subjects
- **Immunocompromised** patients *C albicans* can cause systemic or mucosal disease
- Systemic candidiasis is an acute, disseminated, and invasive form mainly in patients with inherited or acquired neutrophil and T cell disorders

  - Candidemia is one of the most prevalent bloodstream infections in hospital settings and is associated with significant morbidity and mortality

- CMC is candidiasis localized to the skin, nails, and mucous membranes (no predisposition to invasive disease, such as sepsis or pneumonia)

Predisposition to systemic candidiasis

- invasive surgery
- total parenteral nutrition
- diabetes mellitus
- intensive care conditions
- central lines
- neoplasia
- long-term use of broad-spectrum antibiotics or immunosuppressive agents
- HIV
- any global T-cell deficiency or neutrophil disorders

Immunity to candida

- Impaired T cell immunity: HIV/AIDS, SCID, DiGeorge syn., DOCK8 deficiency, etc.

- Congenital neutropenias or secondary neutropenia (e.g. after chemotherapy)

- Recognition:

  - mannans (outer portion of the cell wall)

    →TLR4, Mannose Receptor, DC-SIGN, and Dectin2

  - β-glucans (inner portion of the fungal cell wall)

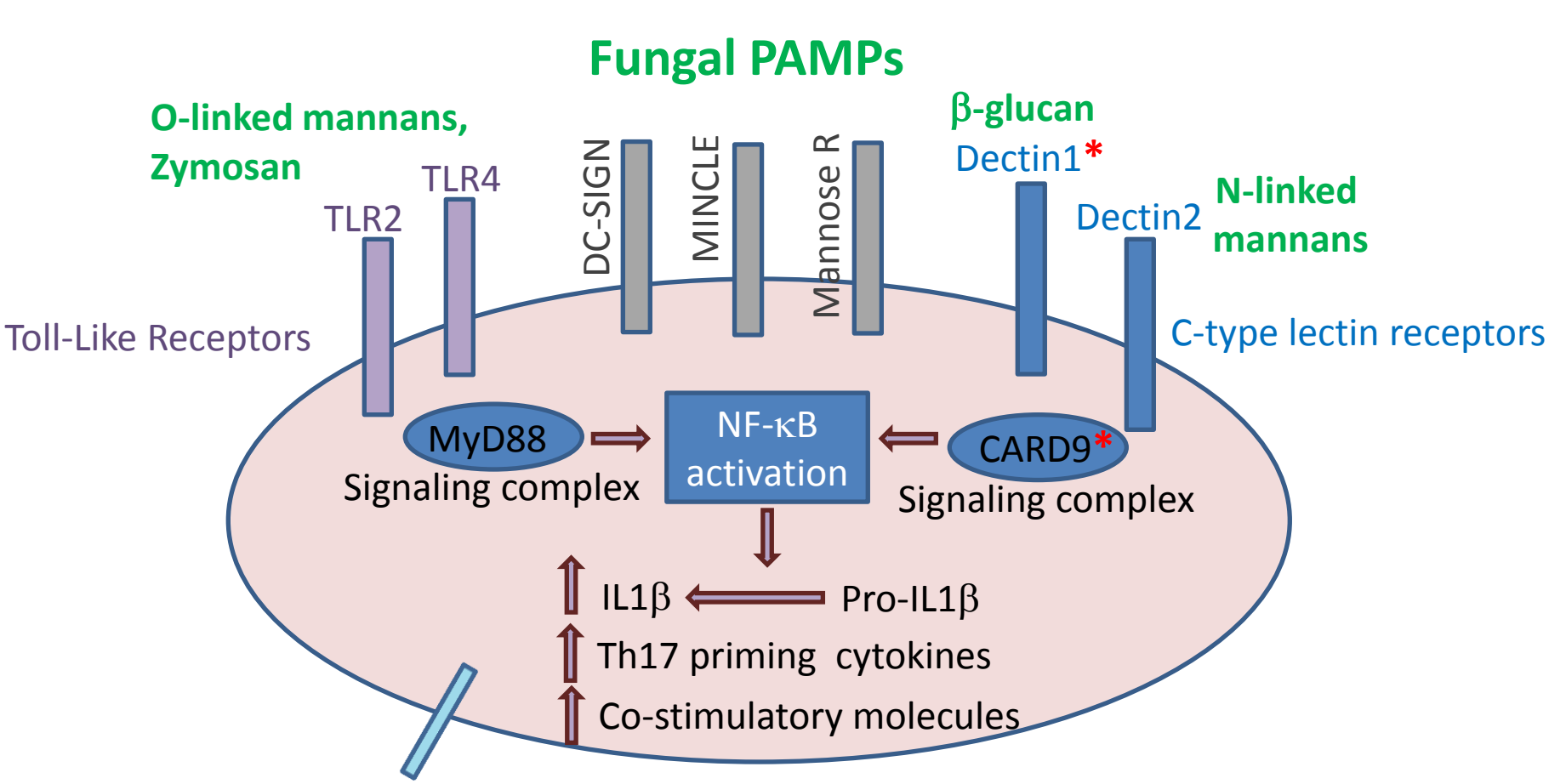
    → Dectin1, and MINCLE

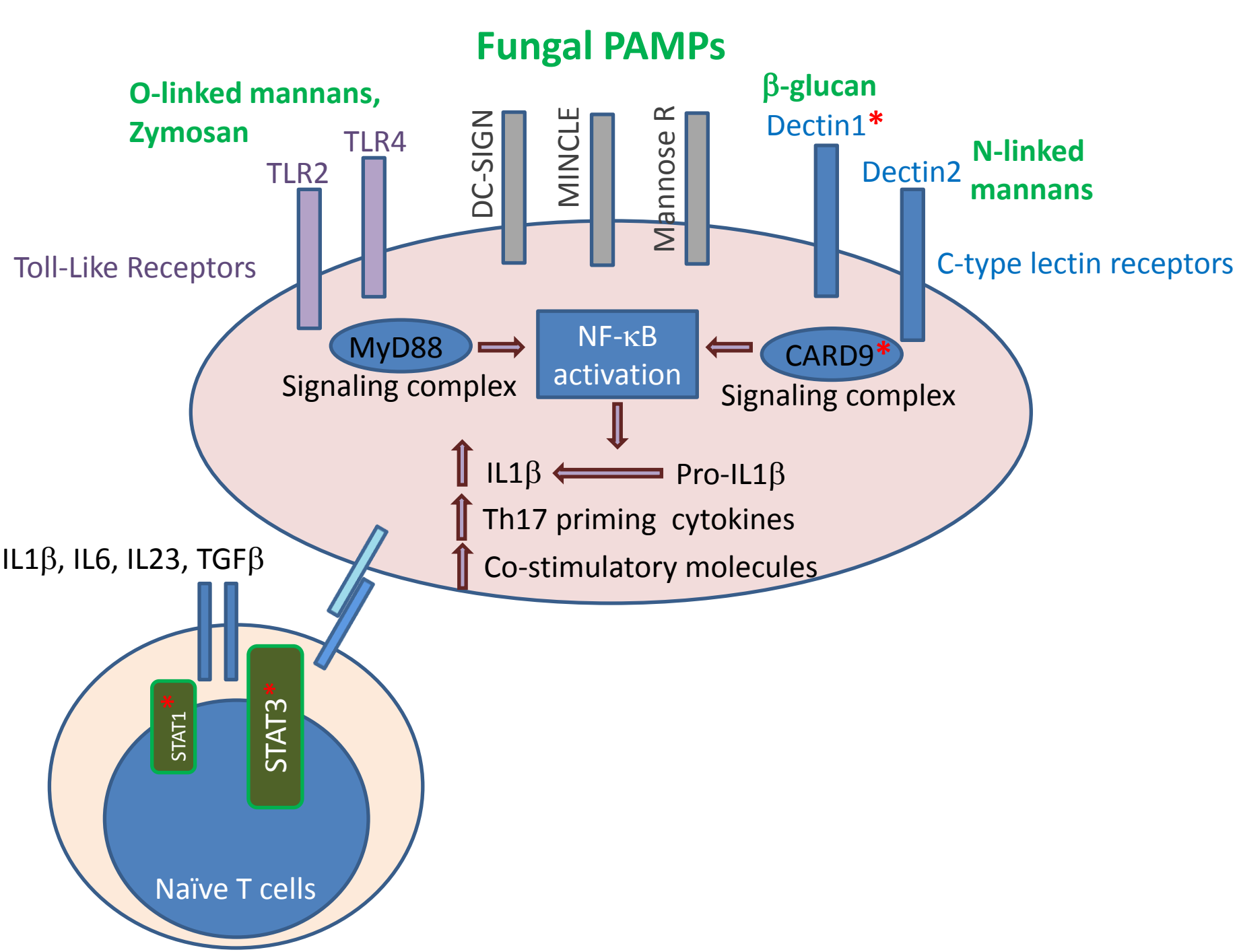
Genetics of CMC

- Dectin-1 deficiency (AR)
- CARD-9 deficiency (AR)
- AD Hyper IgE syndrome or Job syndrome: STAT3 deficiency
- AR Hyper IgE syndrome: DOCK8 deficiency
- STAT1 mutations (AD)
- IL-17F deficiency (AR)
- IL-17RA deficiency (AR)
- APECED (or APS type I): AIRE deficiency (AR)

Molecular testing → diagnosis, prognosis, inheritance

Immune response: receptors → signaling → effector functions


Fungal PAMPs
O-linked mannans,
Zymosan
TLR2
TLR4
DC-SIGN
MINCLE
Mannose R
β-glucan
Dectin1*
Dectin2
N-linked
mannans
Toll-Like Receptors
C-type lectin receptors
MyD88
Signaling complex
NF-κB
activation
CARD9*
Signaling complex
IL1β
Pro-IL1β
Th17 priming cytokines
Co-stimulatory molecules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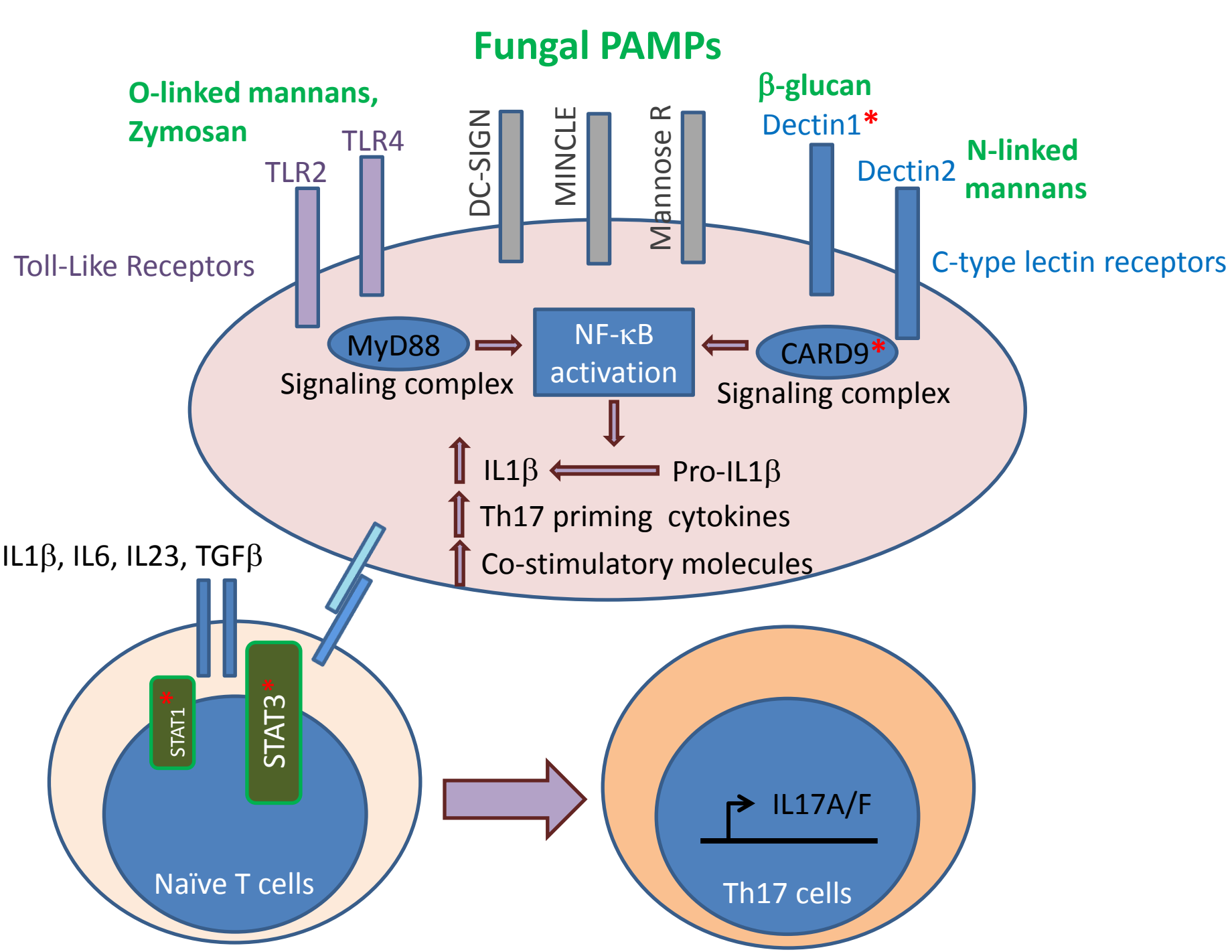
IL1β, IL6, IL23, TGFβ
STAT1*
STAT3*
Naïve T cells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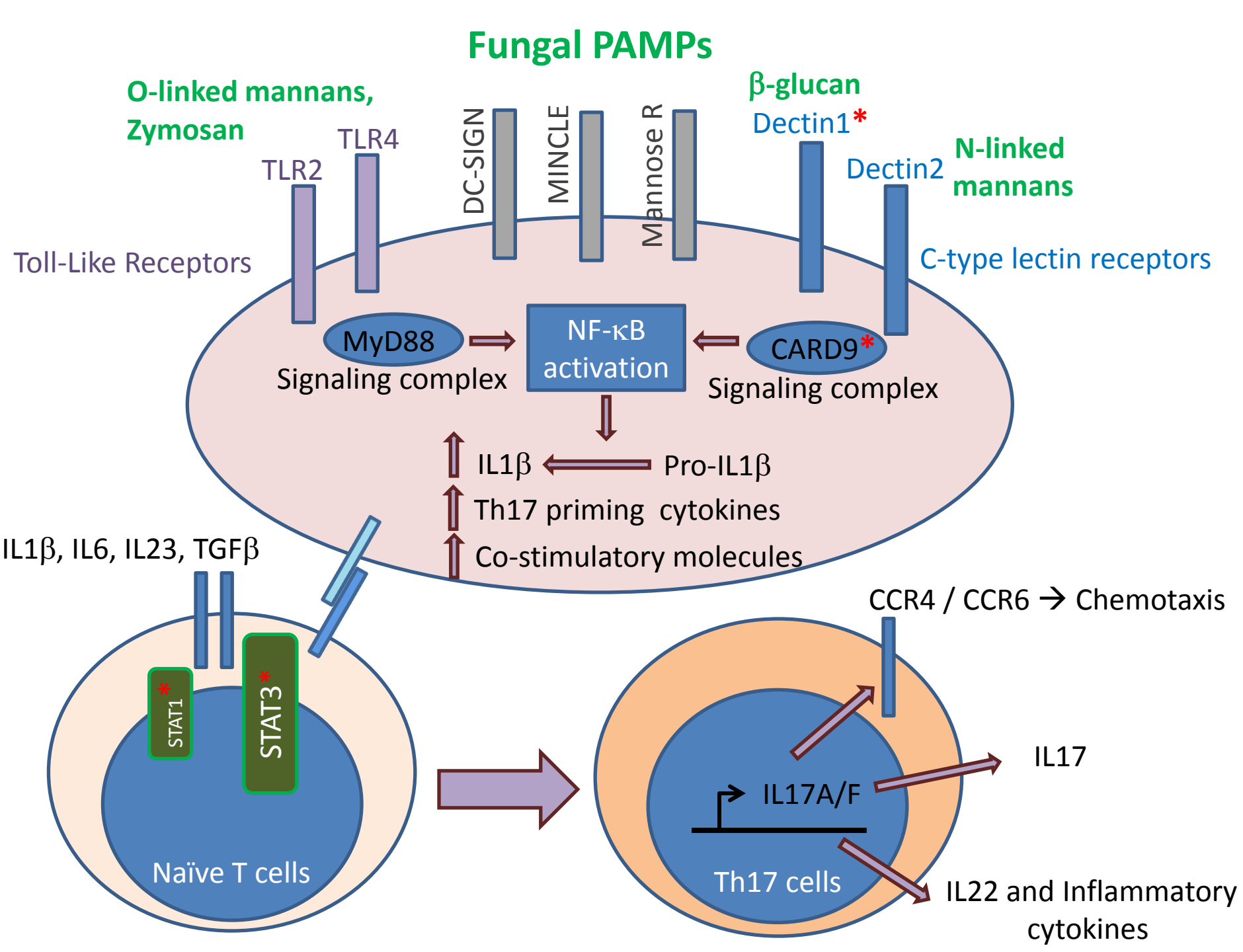
Th17 cells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CCR4 / CCR6 → Chemotaxis
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IL22 and Inflammatory
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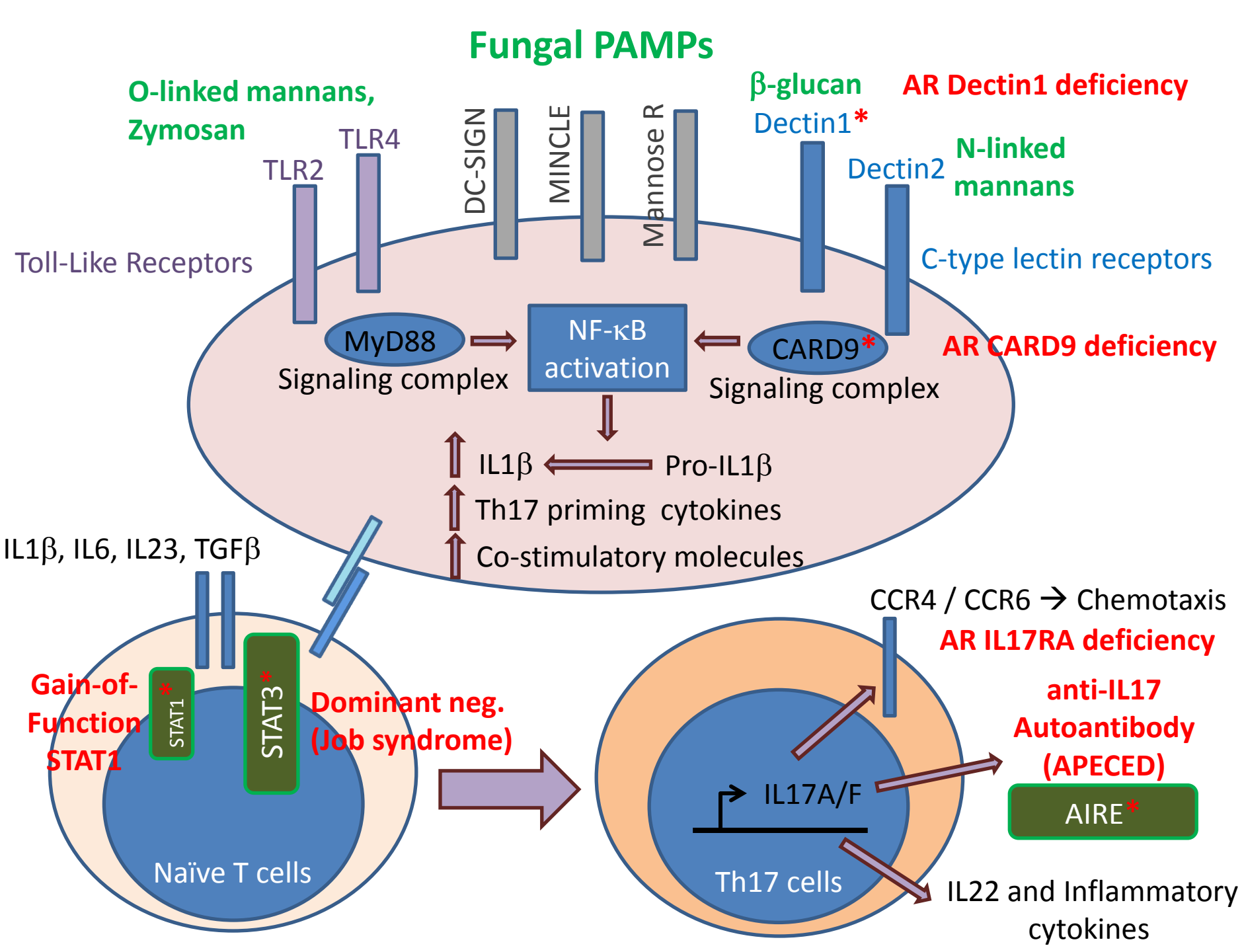
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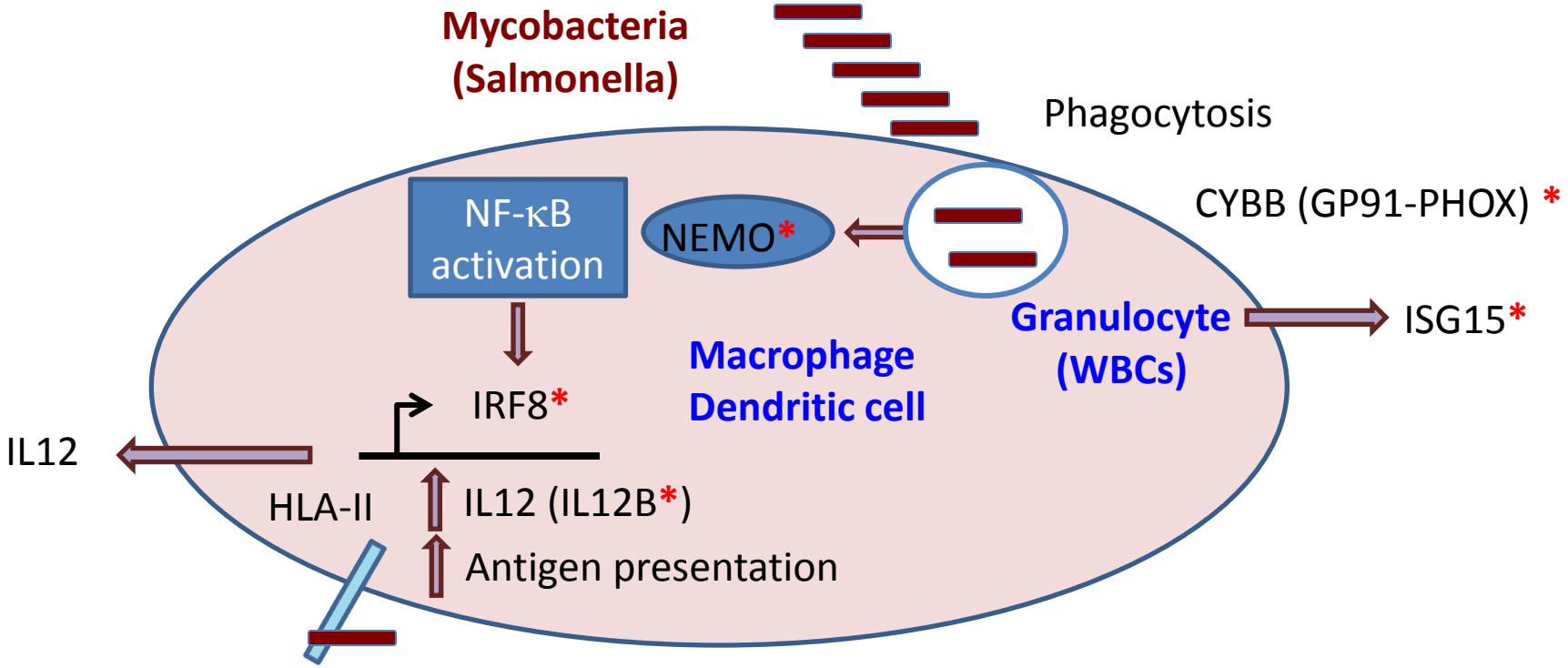
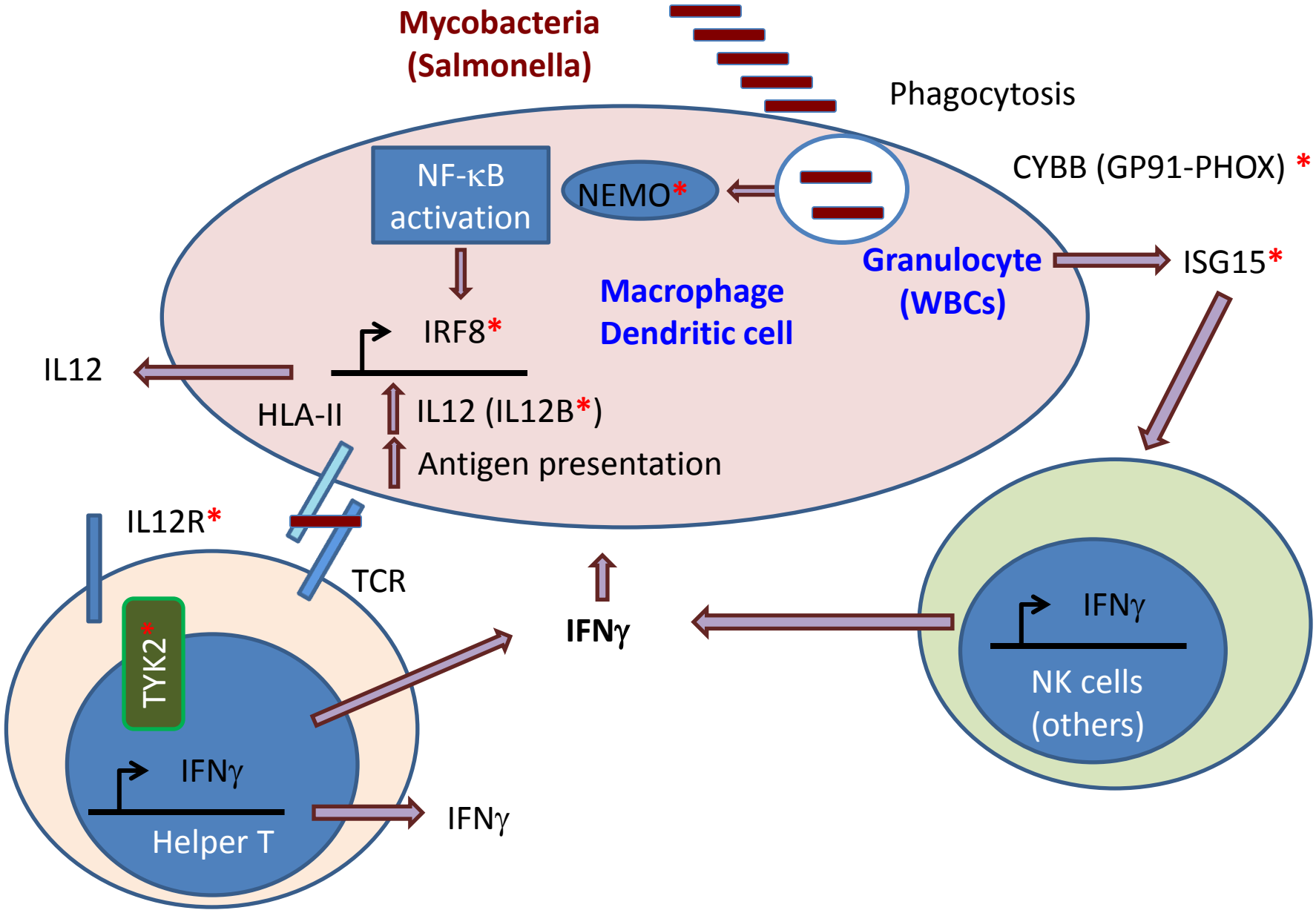
CCR4 / CCR6 → Chemotaxis
AR IL17RA deficiency
Gain-of-
Function
STAT1
STAT1*
STAT3*
Dominant neg.
(Job syndrome)
anti-IL17
Autoantibody
(APECED)
IL17A/F
AIRE*
Naïve T cells
Th17 cells
IL22 and Inflammatory
cytokines

Mendelian susceptibility to mycobacterial disease

- Predisposition of otherwise apparently healthy individuals to infections caused by weakly virulent mycobacteria (BCG) and atypical (or nontuberculous) mycobacteria, *M. tuberculosis* and Salmonella
- Genes:
  - IFNGR1 (AR/AD)
  - IFNGR2 (AR)
  - STAT1 (AD)
  - IL12B (AR)
  - IL12RB1 (AR)*
  - NEMO (IKBKG) (XL)
  - CYBB (XL)
  - IRF8 (AR/AD)
  - ISG15 (AR)
  - (TYK2 – AR)

→ Impaired IFN-γ-mediated immunity (~50 % have unknown genetics)


Mycobacteria
(Salmonella)
Phagocytosis
CYBB (GP91-PHOX) *
NF-κB
activation
NEMO*
Granulocyte
(WBCs)
ISG15*
Macrophage
Dendritic cell
IRF8*
IL12
HLA-II
IL12 (IL12B*)
Antigen presentation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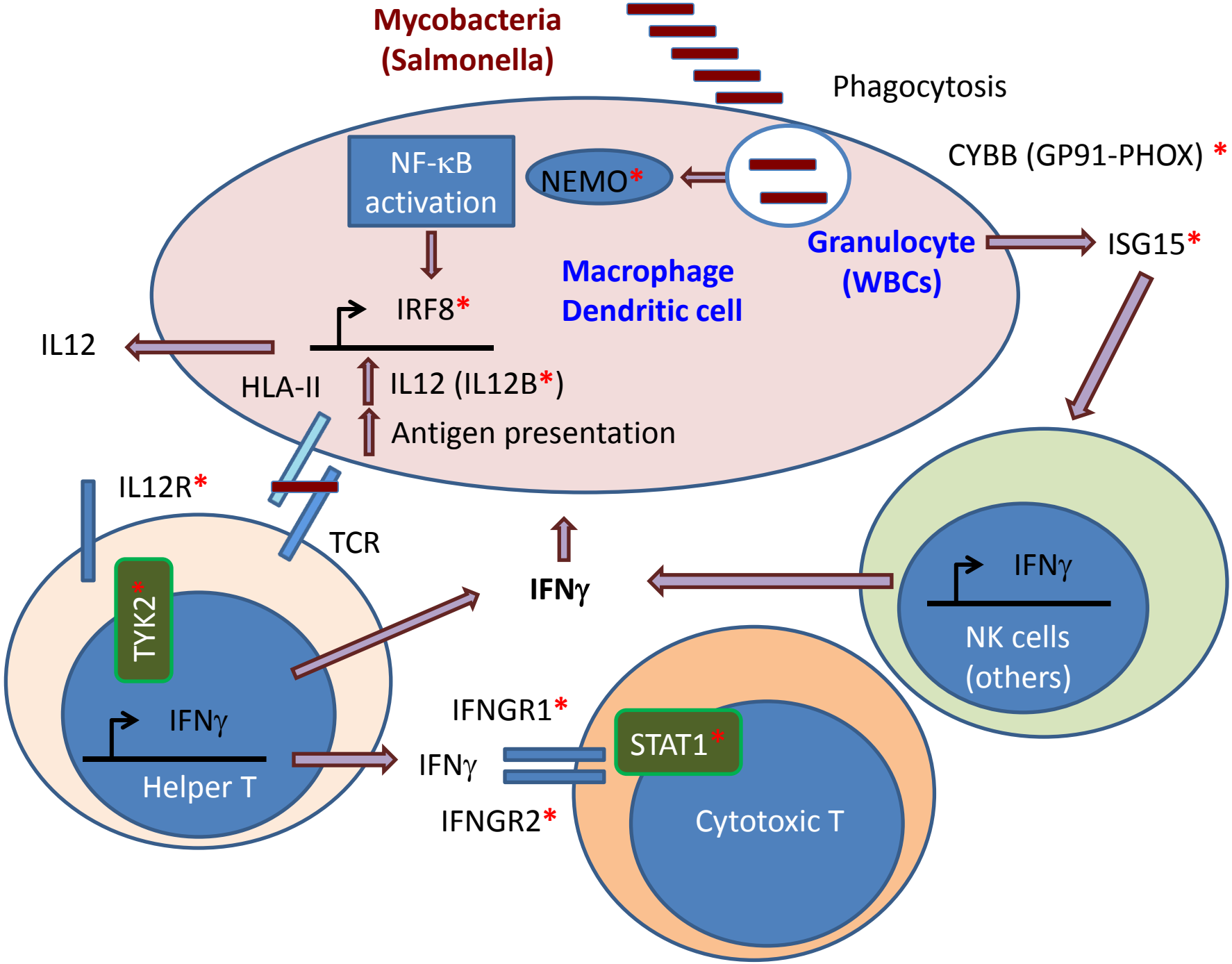
IL12
HLA-II
IL12 (IL12B*)
Antigen presentation
IL12R*
TCR
IFNγ
TYK2*
IFNγ
Helper T
IFNγ
IFNγ
NK cells
(others)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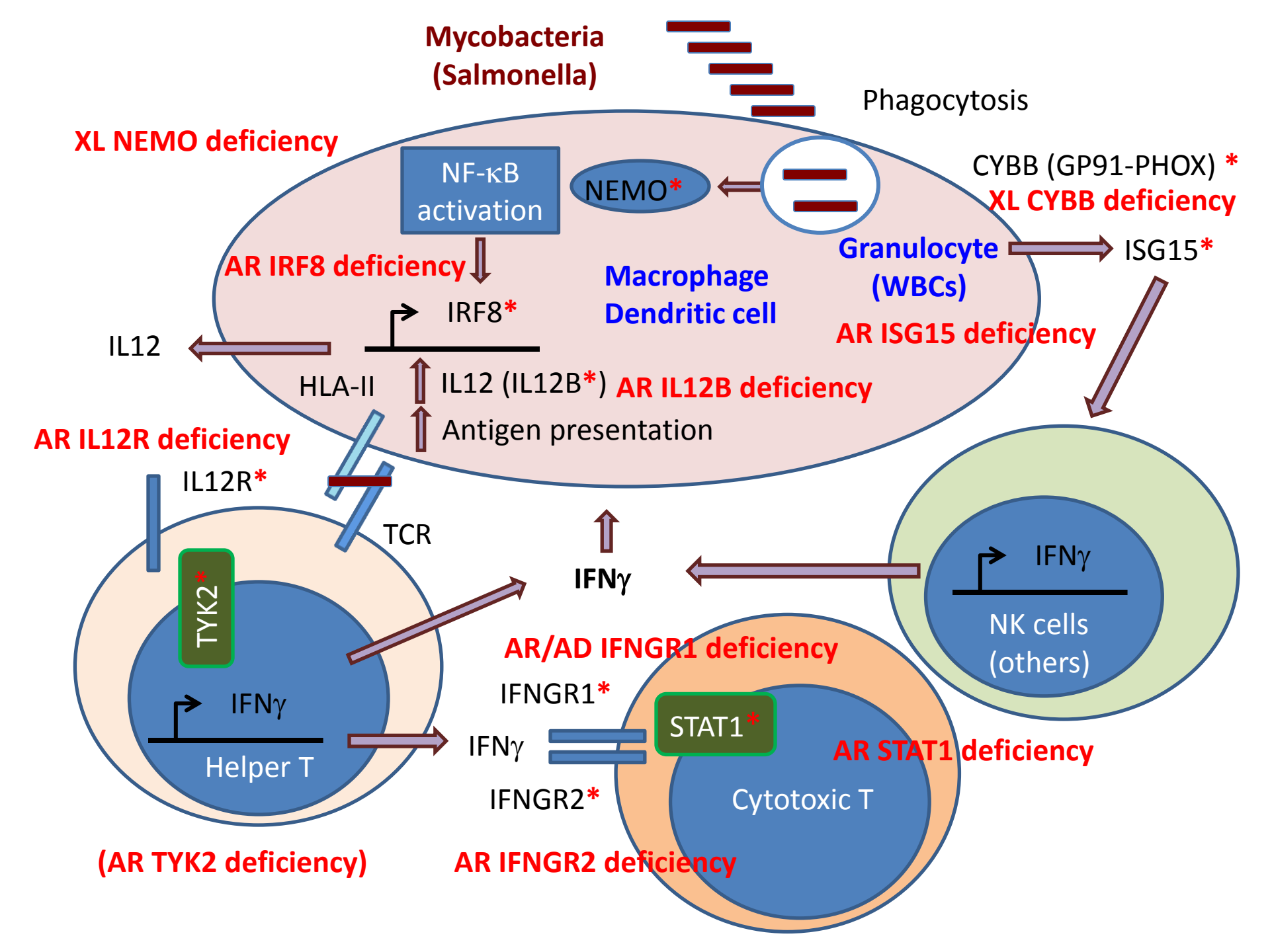
TYK2*
IFNγ
Helper T
NK cells
(others)
IFNGR1*
IFNγ
IFNGR2*
STAT1*
Cytotoxic T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AR ISG15 deficiency
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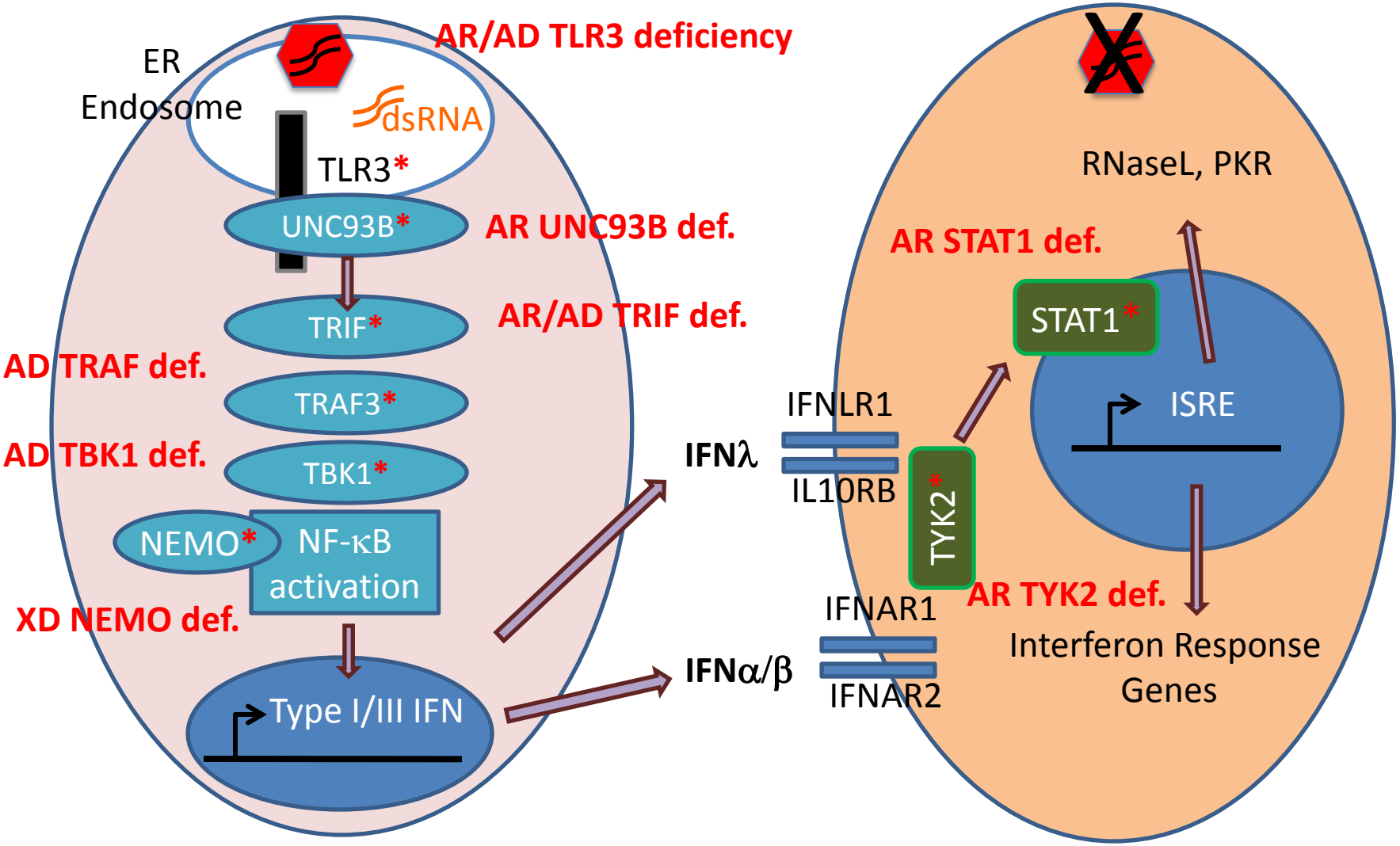
IL12 (IL12B*)
AR IL12B deficiency
Antigen presentation
AR IL12R deficiency
IL12R*
TCR
IFNγ
TYK2*
IFNγ
Helper T
NK cells
(others)
AR/AD IFNGR1 deficiency
IFNGR1*
STAT1*
IFNγ
AR STAT1 deficiency
IFNGR2*
Cytotoxic T
(AR TYK2 deficiency)
AR IFNGR2 deficiency

Herpes Simplex Encephalitis

- HSE is the most common cause of sporadic fatal encephalitis worldwide (70% mortality if untreated)
- Acyclovir
- Lifelong neurological sequelae of varying severity in survivors is common (>30%)
- Genes:
  - TLR3 (AR/AD)
  - UNC-93B (AR)
  - TRIF (AR/AD)
  - TRAF3 (AD)
  - TBK1 (AD)
  - NEMO (XR)
  - STAT1 (AR)
  - TYK2 (AR)

Herpes Simplex Encephalitis



Different genes – same/similar clinical phenotype

- **CMC:**

  - IL-17RA, IL-17F, STAT1, DECTIN1, CARD9, STAT3, DOCK8, AIRE

- **MSMD:**

  - IFNGR1, IFNGR2, STAT1, IL12B**,** IL12RB1, NEMO, CYBB, IRF8, ISG15, TYK2

- **HSE:**

  -TLR3, UNC-93B, TRIF, TRAF3, TBK1, NEMO, STAT1

→ Molecular networks/pathways, not genes

→ Single gene testing vs. gene panels

One gene – multiple phenotypes

- AD STAT1 deficiency: dominant negative mutations
  → susceptibility to mycobacterial and salmonella infections

- AD STAT1 deficiency: gain-of-function mutations
  → chronic mucocutaneous candidiasis

- AR STAT1 deficiency: loss-of-function mutations
  → susceptibility to severe viral and mycobacterial disease

Definition of PIDs

- defined based on clinical/immunological phenotype
- defined based on the molecular defect

→ none of these definitions are perfect

Genetics of PIDs

- Manifestations (infections) can be the same in both primary and secondary ID as well in “healthy” individuals
  - Genetics + Environment
- ~150 PIDs, >200 genes (both growing)
  - increasing role for mutation testing (PIDs defined by genes)
  - novel technologies (whole genome/exome)
- One disease multiple genes (overlapping phenotypes)
  - CMC, MSMD, HSE
- One gene, multiple diseases
  - STAT1, NEMO
- Inheritance: AR, AD, XL
  - AR/AD IFNGR1
- Molecular networks/pathways, not genes
  - recognition → signaling → effector function

References

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