HSCT in Primary Immune Regulatory Disorders

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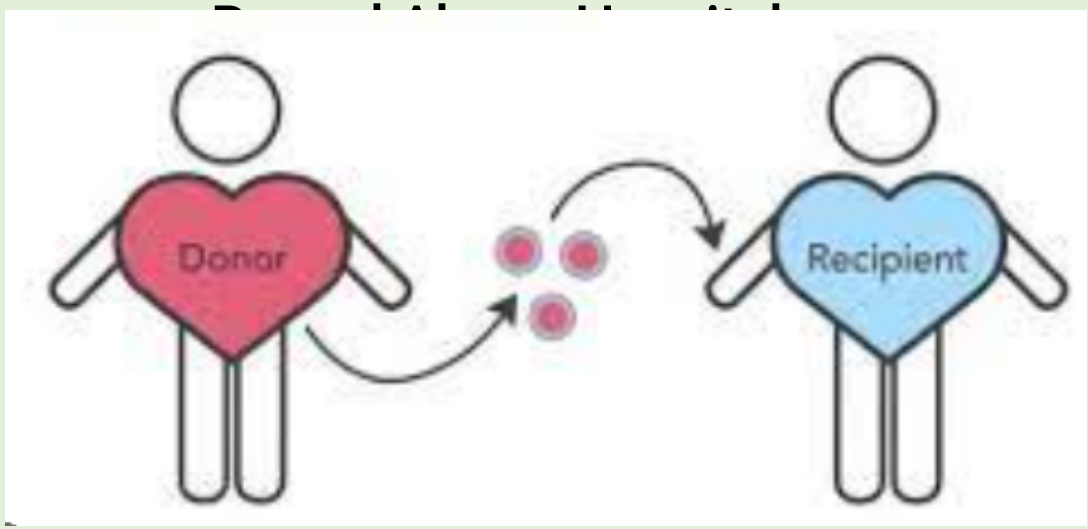


Towards Precision Medicine and a Personalized Approach to Hematopoietic Stem Cell Transplantation and Cellular Therapy for Inborn Errors of Immunity

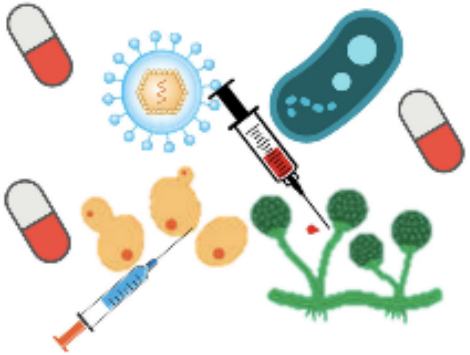
Early diagnosis

Precise molecular diagnosis

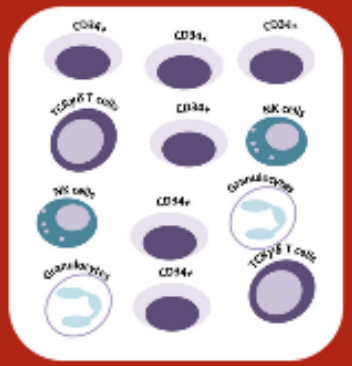
Optimizing of disease control

Targeted therapy
Monoclonal antibody

Surveillance, prophylaxis and treatment of infection prior to and during HSCT



Reduced toxicity conditioning
+
Individualized dosage optimization of conditioning (Pharmacokinetic study)



Precise graft prescription
Graft engineering

Post transplant care

Cellular therapy to boost immune recovery

New therapy to treat transplant-related complications

Vaccination

Survivorship program

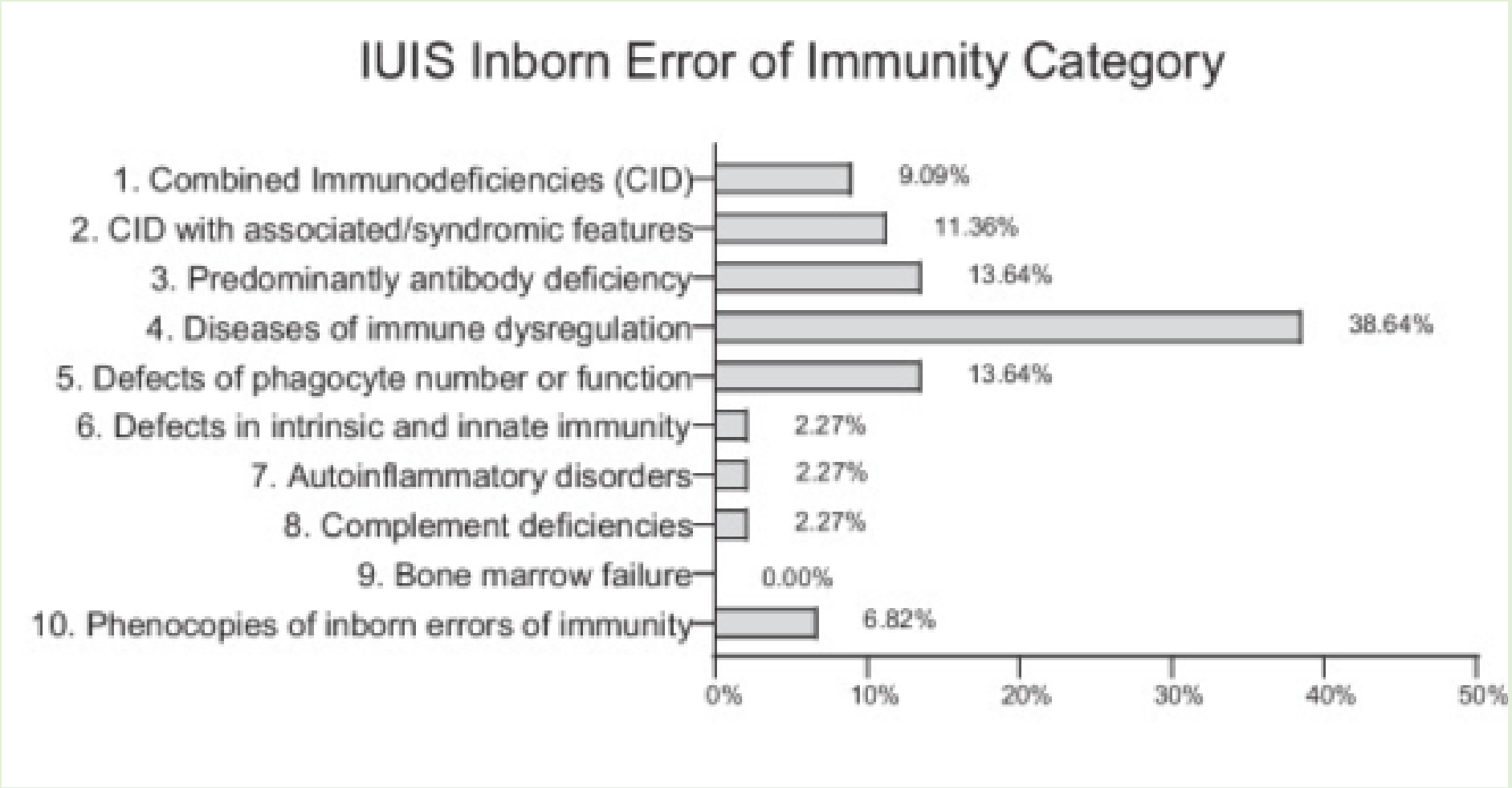
Screening for late effects

Primary immune dysregulation disorders (PIRDs)

- As our understanding and definition of immune deficiency broaden, so too do the indications for HSCT

- An increasing number of diseases of immune dysregulation are emerging which may be amenable to treatment with HSCT

- T regulatory defects such as:
- IPEX syndrome
- CTLA4 deficiency
- immune dysregulation with colitis


IUIS Inborn Error of Immunity Category
1. Combined Immunodeficiencies (CID)
2. CID with associated/syndromic features
3. Predominantly antibody deficiency
4. Diseases of immune dysregulation
5. Defects of phagocyte number or function
6. Defects in intrinsic and innate immunity
7. Autoinflammatory disorders
8. Complement deficiencies
9. Bone marrow failure
10. Phenocopies of inborn errors of immunity
9.09%
11.36%
13.64%
38.64%
13.64%
2.27%
2.27%
2.27%
0.00%
6.82%
0%
10%
20%
30%
40%
50%

IV. Diseases of immune dysregulation

Hemophagocytic Lymphohistiocytosis (HLH)

Hypopigmentation

Specific hair shaft anomaly
Neutropenia
Increased bleeding
Low degranulation (T, NK).
Hermansky Pudlak sd type 2 *(AP3B)*

Giant lysosomes in Leukocytes on blood smears
Specific hair shaft anomaly
Low degranulation (T,NK)
Primary neurological disease
Chediak Higashi sd *(LYST)*

Specific hair shaft anomaly
Low degranulation (T, NK).
Griscelli sd type 2 *(RAB27a)*

Specific hair shaft anomaly
Hermansky Pudlak sd type 9 *(PLDN)*

Severe inflammation, persistent fever

Normal CD107 Degranulation

Perforin deficiency (CMF)
FHL3 *(PRF1)*

Low CD107 Degranulation (T, NK)

Munc 13-4 deficiency
FHL3 *(UNC13-D)*

Munc 18-2/STXBP2 deficiency
Primary Bowel disease
Increased bleedings.
FHL5 *(STXBP2)*

Syntaxin 11 deficiency.
FHL4 *(STX11)*

EBV-associated lymphoproliferation

XL, Hypogammaglobulinemia, Lymphoma, Hepatitis, Frequent EBV induction of HLH. NKT cell deficiency. Reduced CTL activity to EBV. SAP deficiency (CMF).
XLP1 *(SH2D1A)*

XL, Splenomegaly, Colitis, XIAP deficiency (CMF) **XLP2** *(XIAP)*

Syndromes with Autoimmunity

ALPS Splenomegaly, adenopathy, defective lymphocyte apoptosis, CD3 double negative > 2,5 %?

No

Autoimmune polyendrocrinopathy with candidiasis and ectodermal dystrophy: Autoimmunity affecting parathyroid, adrenal, other endocrine organs; candidiasis; dental enamel hypoplasia **APECED** *(AIRE)*

Immune dysregulation, polyendocrinopathy, enteropathy XL : Autoimmune enteritis, early onset diabetes, thyroiditis, hemolytic anemia, thrombocytopenia, eczema. Lack of CD4+ CD25+ FOXP3+ Regulatory T cells. IgA, IgE↑. **IPEX** *(FOXP3)*

Lymphoproliferation, autoimmunity, impaired T-cell function. **CD25 deficiency** *(IL2RA)*

Multi-organ autoimmunity, chronic lung disease, failure to thrive, developmental delay, macrocephaly **ITCH def** *(ITCH)*

Lymphoproliferation, Solid organ autoimmunity, recurrent infections. **STAT3 GOF** *(STAT3)*

Variable lymphoproliferation, severe autoimmune cytopenias, hypergammaglobulinemia, recurrent infections. **Tripeptidyl-Peptidase II def** *(TPP2)*

Hypogammaglobulinemia, recurrent infections and multiple autoimmune clinical features, decreased circulating B cells
CTLA4 def (ALPS-V) *(CTLA4)*

Yes

AD, AR, autoimmune blood cytopenias
ALPS-FAS *(FAS)*

AD or AR, lupus, autoimmune blood cytopenias **ALPS-FASLG** *(FASLG)*

AD autoimmune disease
ALPS-CASP10 (CASP10)

AR, Recurrent bacterial and viral infections, Functional hypoplenism, liver dysfunction, defective IFNγ biology **FADD deficiency** *(FADD)*

AD, Recurrent bacterial and viral infections, defective lymphocyte activation
CASPASE 8 defect (CASP8)

AR, Recurrent infections; EBV chronic infection. Lymphoproliferation . SLE-like autoimmunity (Nephrotic and anti-phospholipid syndromes) HypoIgG **PRKCdelta def** *(PRKCD)*

Immune dysregulation with colitis

Inflammatory bowel disease (IBD) Folliculitis, Recurrent respiratory diseases, Arthritis
IL-10 def *(IL10)*

+ Lymphoma
IL-10Rα def *(IL10RA)*
IL-10Rβ def *(IL10RB)*

IBD, recurrent sinopulmonary infections **NFAT5 haploinsufficiency** *(NFAT5)*

Type 1 Interferonopathies

+ Skin vascularitis, mouth ulcers, arthropathy
SAMHD1 def, AGS5 *(SAMHD1)*

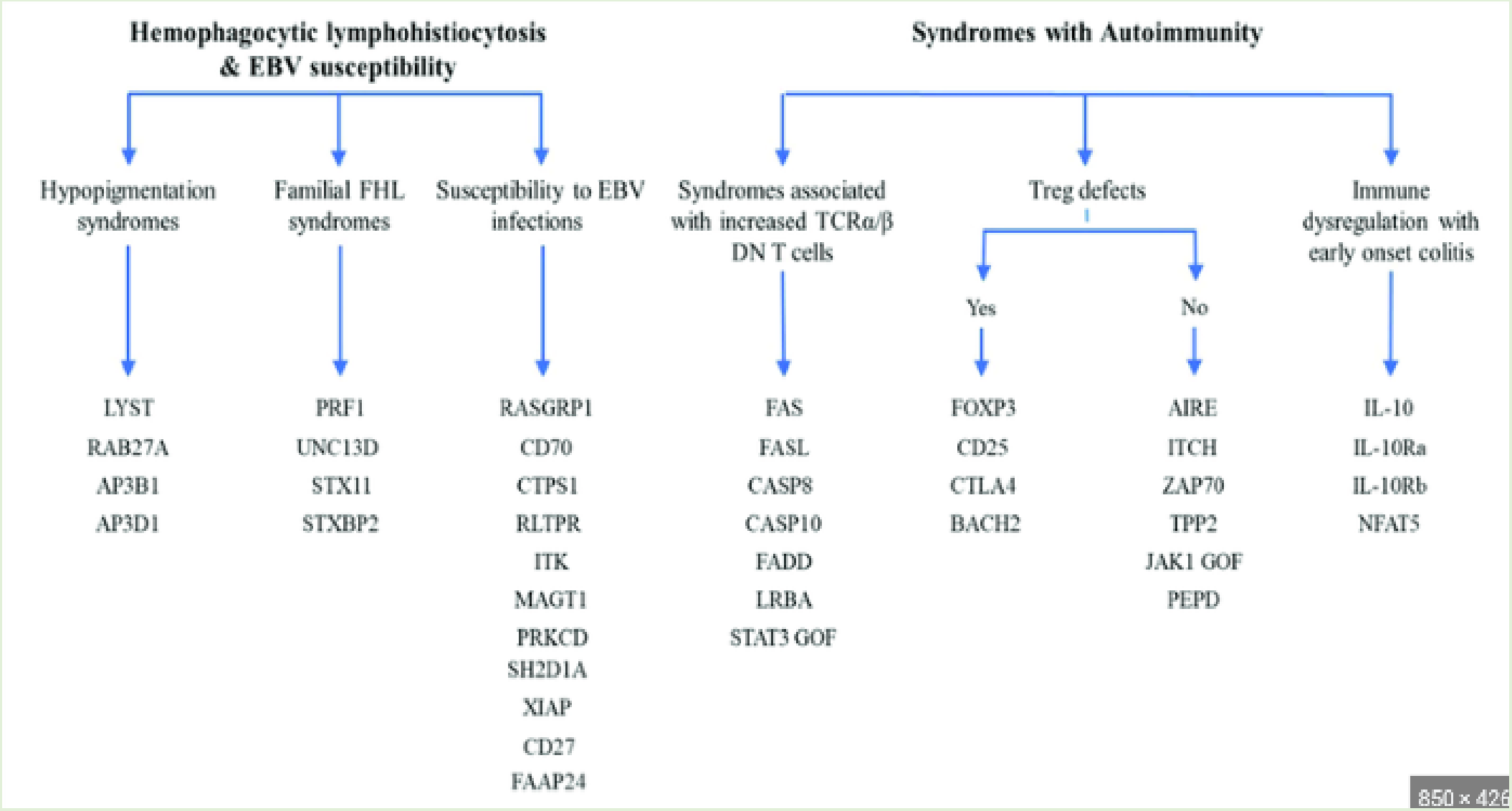
Progressive encephalopathy Intracranial calcifications, Cerebral atrophy, leukodystrophy HSMG, Thrombocytopenia, Elevated hepatic transaminases Chronic cerebrospinal fluid (CSF) lymphocytosis **Aicardi-Goutieres** *(TREX1, RNASEH2B, RNASEH2C, RNASEH2A)*,

Progressive encephalopathy Intracranial calcification, Severe developmental delay, leukodystrophy **ADAR1 def, AGS6** *(ADAR1)* . **AGS7** *(IFIH1)*.

Recurrent bacterial and viral infections, Intracranial calcification, SLE-like autoimmunity (Sjögren's syndrome, hypothyroidism, inflammatory myositis, Raynaud's disease and vitiligo), hemolytic anemia, thrombocytopenia, skeletal dysplasia, short stature **SPENCD** *(ACP5)*

Early-onset inflammatory disease, rash, tachypnea, systemic inflammation, vascular inflam, pulmonary inflammation **VACI** *(STING)*

Recurrent fever, Early-onset stroke, Livedo racemosa, low IgM, Hypogamma, Lymphopenia, Polyarteritis nodosa, childhood-onset **ADA2**


Hemophagocytic lymphohistiocytosis & EBV susceptibility
Hypopigmentation syndromes
Familial FHL syndromes
Susceptibility to EBV infections
LYST
RAB27A
AP3B1
AP3D1
PRF1
UNC13D
STX11
STXBP2
RASGRP1
CD70
CTPS1
RLTPR
ITK
MAGT1
PRKCD
SH2D1A
XIAP
CD27
FAAP24
Syndromes with Autoimmunity
Syndromes associated with increased TCRα/β DN T cells
Treg defects
Immune dysregulation with early onset colitis
Yes
No
FAS
FASL
CASP8
CASP10
FADD
LRBA
STAT3 GOF
FOXP3
CD25
CTLA4
BACH2
AIRE
ITCH
ZAP70
TPP2
JAK1 GOF
PEPD
IL-10
IL-10Ra
IL-10Rb
NFAT5

Hemophagocytic lymphohistiocytosis (HLH)

- Regardless of the underlying genetic cause of primary HLH
- disease remission at the time of HSCT remains a key factor in overall survival
- The challenge is often to balance achieving disease control and reaching HSCT in a timely manner

- Highly immuno- and myelosuppresive drugs are used to control HLH prior to HSCT
- associated with multi-organ toxicity and infective complications

HLH

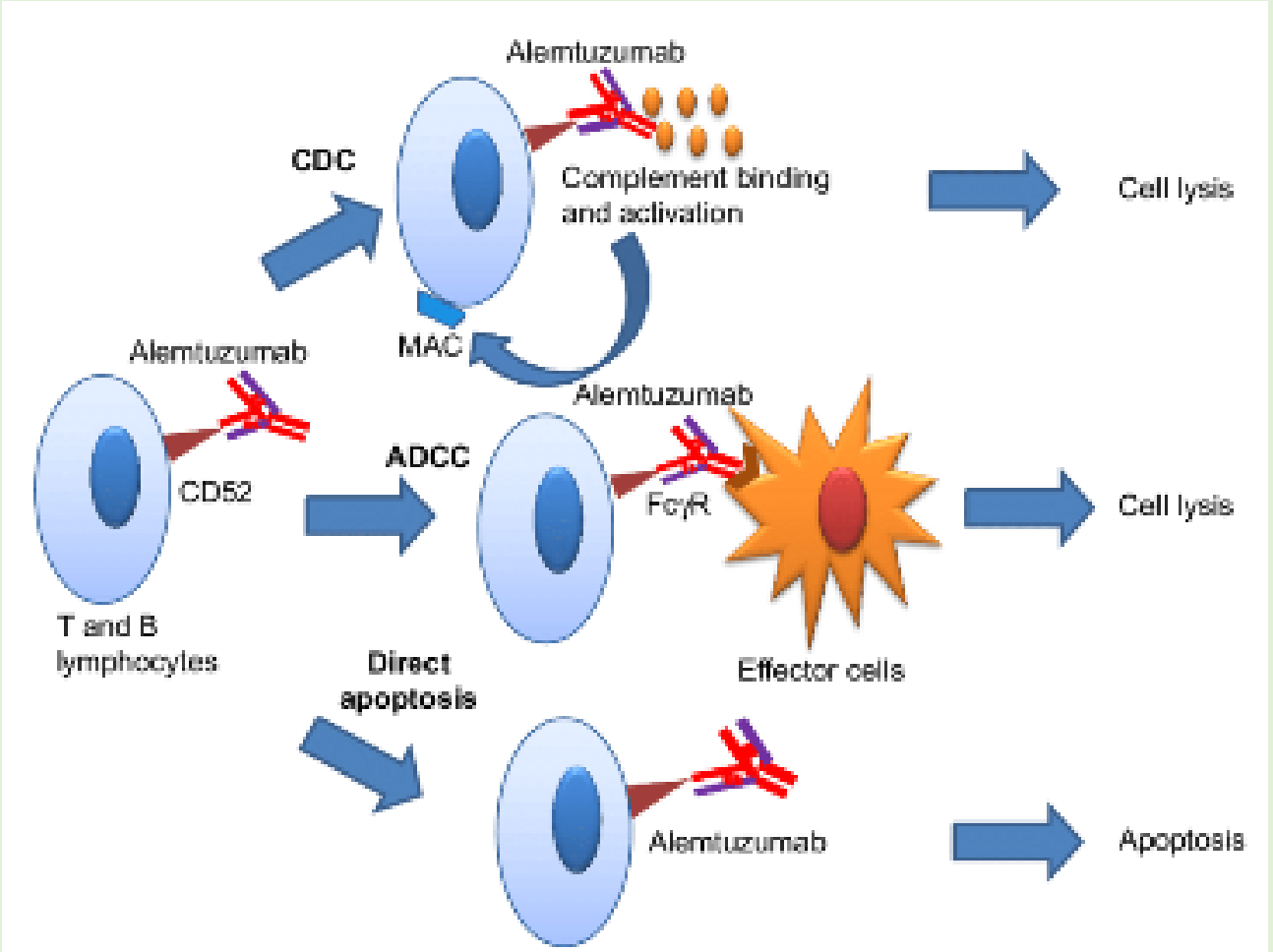
- More targeted novel therapies including Alemtuzumab (a humanized monoclonal anti-CD52 antibody) may reduce this toxicity and improve the patients' condition prior to HSCT

- The efficacy of anti IFN gamma antibodies and JAK-Inhibitors

need yet to be evaluated

- VOD is common in this group (treatment related toxicity and disease):

prophylactic defibrotide in infants under 18 months of age or those over 18 months with clear hepatic involvement



Alemtuzumab-induced cytolysis and apoptosis of T- and B-lymphocytes. Abbreviations: ADCC, antibody-dependent cell-mediated cytotoxicity; CDC, complement-dependent cytotoxicity; MAC, membrane attack complex; FcγR, Fc gamma receptor.

HLH

- outcomes post HSCT were poor using a fully myeloablative regimen
- improved with reduced toxicity conditioning protocols and better HLH control prior to conditioning

- Stable high-level donor chimerism is desired and mixed chimerism is seen more commonly after treosulfan and melphalan based regimens

- It is likely that >20–30% T-cell chimerism is sufficient to protect against disease relapse

- Several monogenic defects that primarily manifest with HLH
- primary HLH:
- *PRF1*, *UNC13D*, *STX11*, *STXBP2*, *RAB27A, LYST*, and *AP3B1*:
- need HSCT for complete disease cure

- Other genetic causes of HLH:
- susceptibility to EBV infection and EBV-related HLH:
- XIAP and SAP deficiencies or *MAGT1* and *ITK* mutations

- Secondary HLH might be caused by infections, malignancy, metabolic diseases, or other primary immunodeficiencies

HLH

- XIAP deficient patients

- outcome is significantly worse than for other forms of primary HLH
- even in the context of RIC regimes
- particularly sensitive to alkylating agents
- more severe GvHD which leads to higher mortality

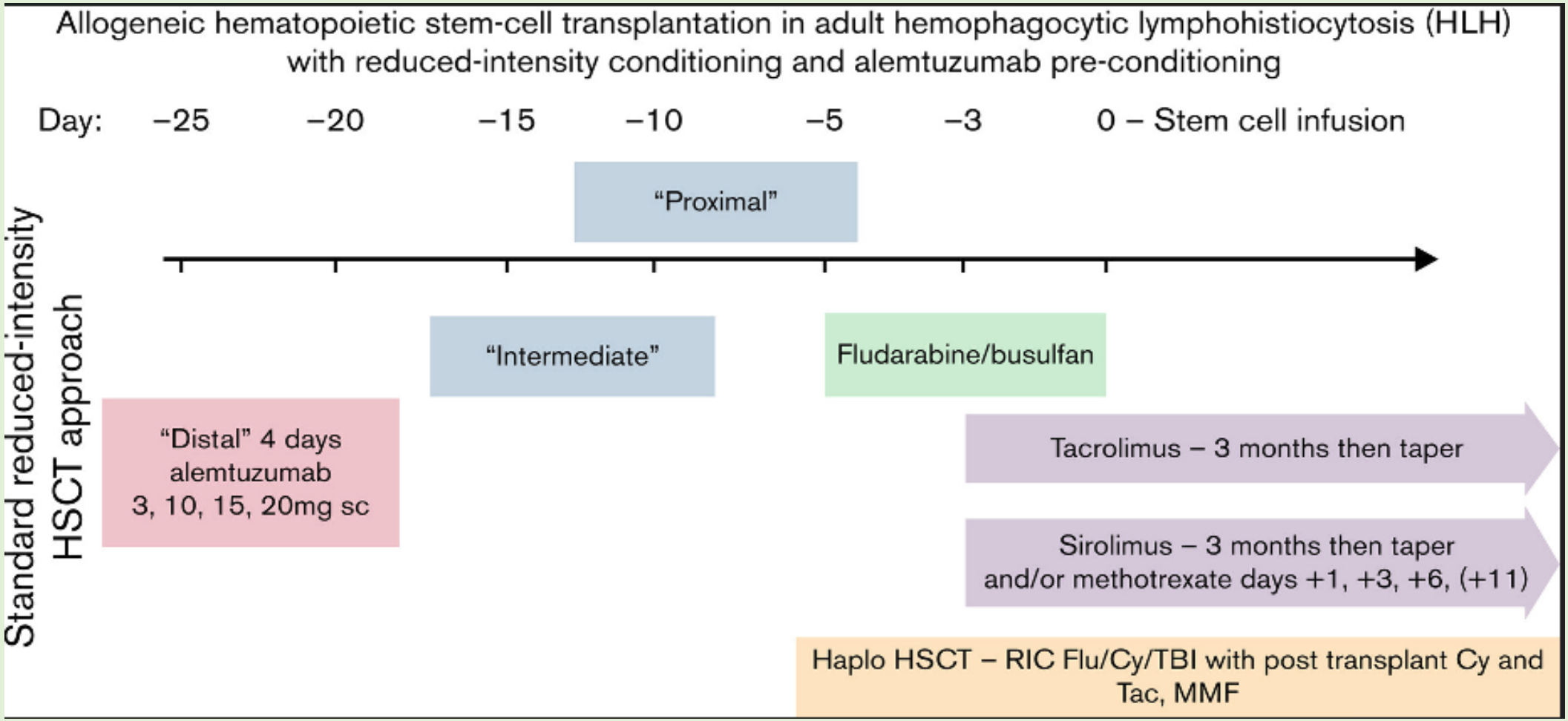
- if HLH is in remission and a reduced regimen is used (best results):

survival after HSCT is reported to be between 86 and 100%

- The associated colitis can take a long period post-HSCT
- HLH reactivation has been reported in up to 50% of patients

- Antibody-based conditioning regimens may improve the

- Serotherapy may be adapted
- Distal serotherapy: decreased mixed chimerism, increased GVHD



- rituximab:
- usually used to control EBV-related HLH

- A human IgG1 monoclonal antibody against IFN-γ, emapalumab:
- received approval for primary HLH in both pediatric and adult patients in 2018

- Patients receiving transplants for HLH secondary to Griscelli syndrome type 2 or Chediak-Higashi syndrome:
- can be success-fully cured of the immunological disorder

- neurological disease may develop or progress, even when full donor chimerism is present

Primary immune dysregulation disorders (PIRDs)

- An increasing number of diseases of immune dysregulation are emerging which may be amenable to treatment with HSCT

- These include T regulatory cell defects such as IPEX syndrome and CTLA4 deficiency and immune dysregulation with colitis

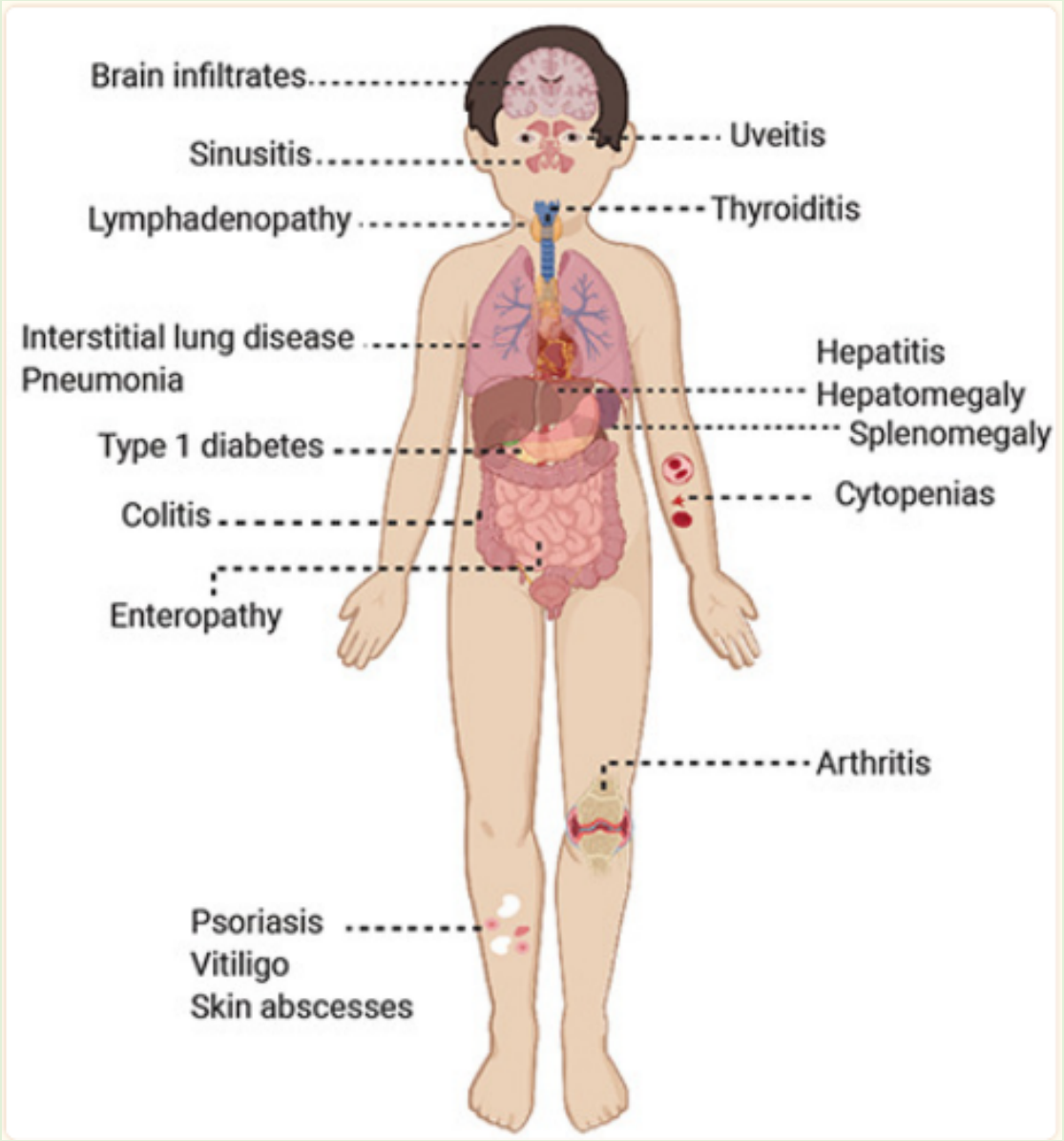

Brain infiltrates
Sinusitis
Lymphadenopathy
Interstitial lung disease
Pneumonia
Type 1 diabetes
Colitis
Enteropathy
Psoriasis
Vitiligo
Skin abscesses
Uveitis
Thyroiditis
Hepatitis
Hepatomegaly
Splenomegaly
Cytopenias
Arthritis

TABLE 2 | Indications for HSCT in PID.

HSCT curative	HSCT partially curative	HSCT controversial
SCID	Cartilage Hair Hypoplasia	CVID
CID^	PGM3 deficiency	Agammaglobulinemia
CGD	STAT1-GOF	Complement deficiencies (other than C1q deficiency)
DOCK8 deficiency	STAT3- GOF	DGS
DOCK2 deficiency	Severe congenital neutropenia	IKBA deficiency
IPEX	ADA2 deficiency	NEMO deficiency
WAS	CIQ deficiency	
WIP deficiency	CD25 deficiency	
ARPC1B deficiency	IL-10 deficiency	
CD40 ligand deficiency	IL-10 Receptor deficiency	
CD40 deficiency	DNA double-strand break repair disorders	
XLP1, XLP2		
APDS		
MHC Class II deficiency		
AD Hyper IgE syndrome		
CTLA4 haploinsufficiency		
LRBA deficiency		
Familial HLH types 1–5		
GATA2 deficiency		
RAB27A deficiency		
LAD I		
Reticular Dysgenesis		

PIRDs

- A large multicenter study of IPEX syndrome:
- a clear advantage in overall survival and quality of life in transplanted patients compared to those treated with immunosuppression

- all patients with this disease should be considered for transplant

- Mixed chimerism is sufficient for cure
- donor chimerism in T regulatory cells has been shown to be higher than in other cell lines

- Patients with autoimmune enteropathy
- IPEX and enteropathy due to defects in IL-10 signaling pathways
- have successfully received transplants and been cured

PIRDs

- fully myeloablative conditioning may not be required in all PIRDs possibly with the exception of gain-of-function diseases

- An increasing number of reports are published for other disorders including but not restricted to

CTLA4

LRBA

ZAP70

APDS

STAT1 AND 3 GOF

- Primary genetic defects in immune function may lead to immune dysregulation and autoimmunity:
- which are also are treatable by HSCT

- Autoimmunity is a feature of Wiskott-Aldrich syndrome
- Omenn syndrome and other “conventional” immunodeficiencies

- Symptoms can be ameliorated by immunosuppression
- transplantation offers cure and can prevent progression of autoimmunity

- Data on the relevance of donor chimerism for cure are still limited
- in case of gain-of-function diseases and when aiming for complete donor chimerism, protocol A or B is probably preferred

- Severity of disease at transplant:

the most important predictor of success

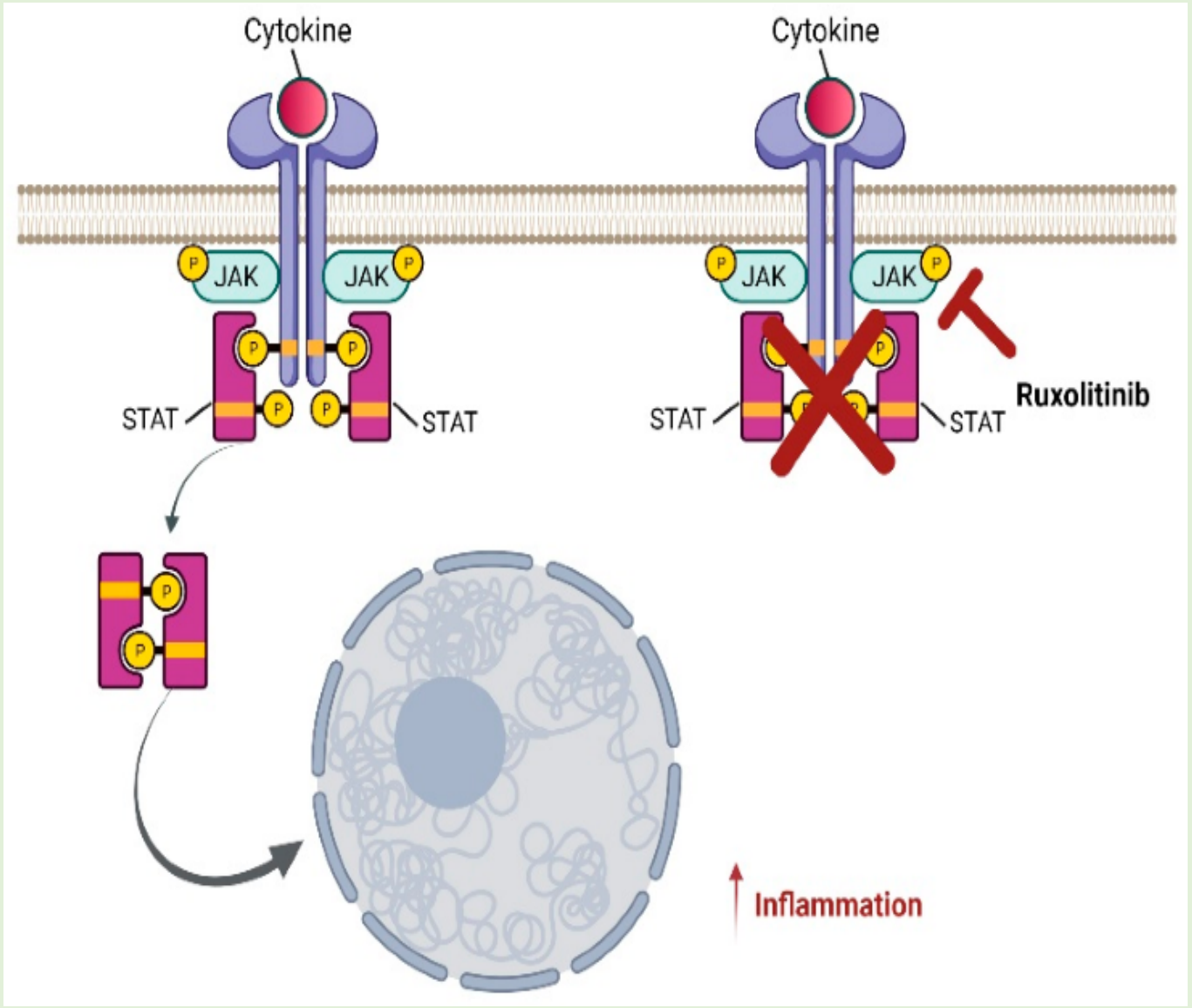
- immunosuppression prior to transplant to control the inflammatory features is of paramount importance

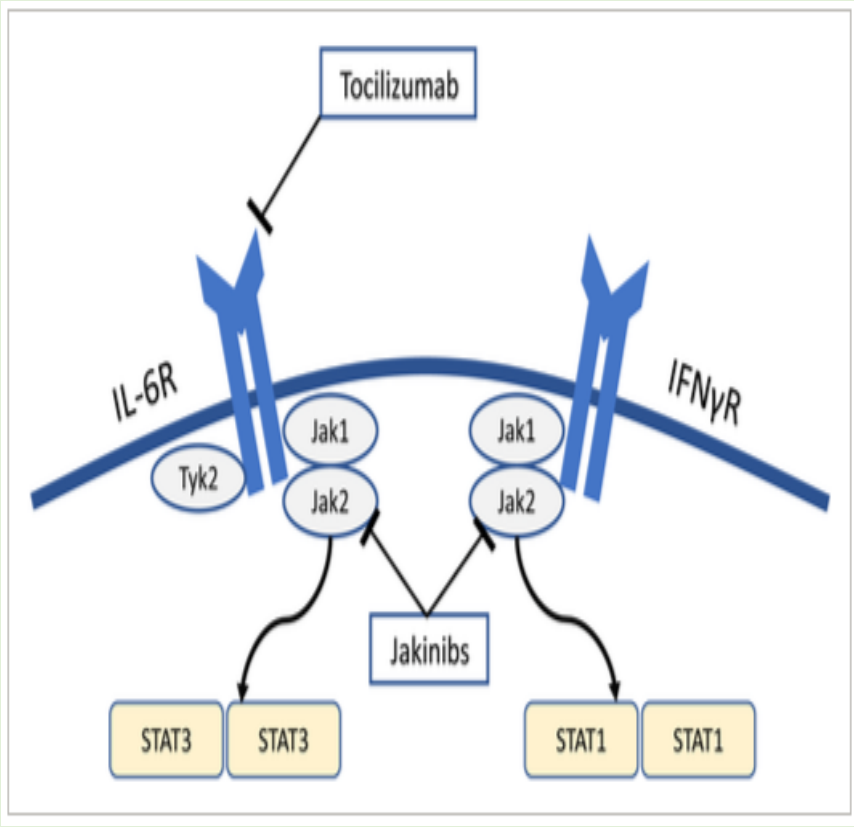
- It can be especially challenging to decide if and when to transplant in these patients

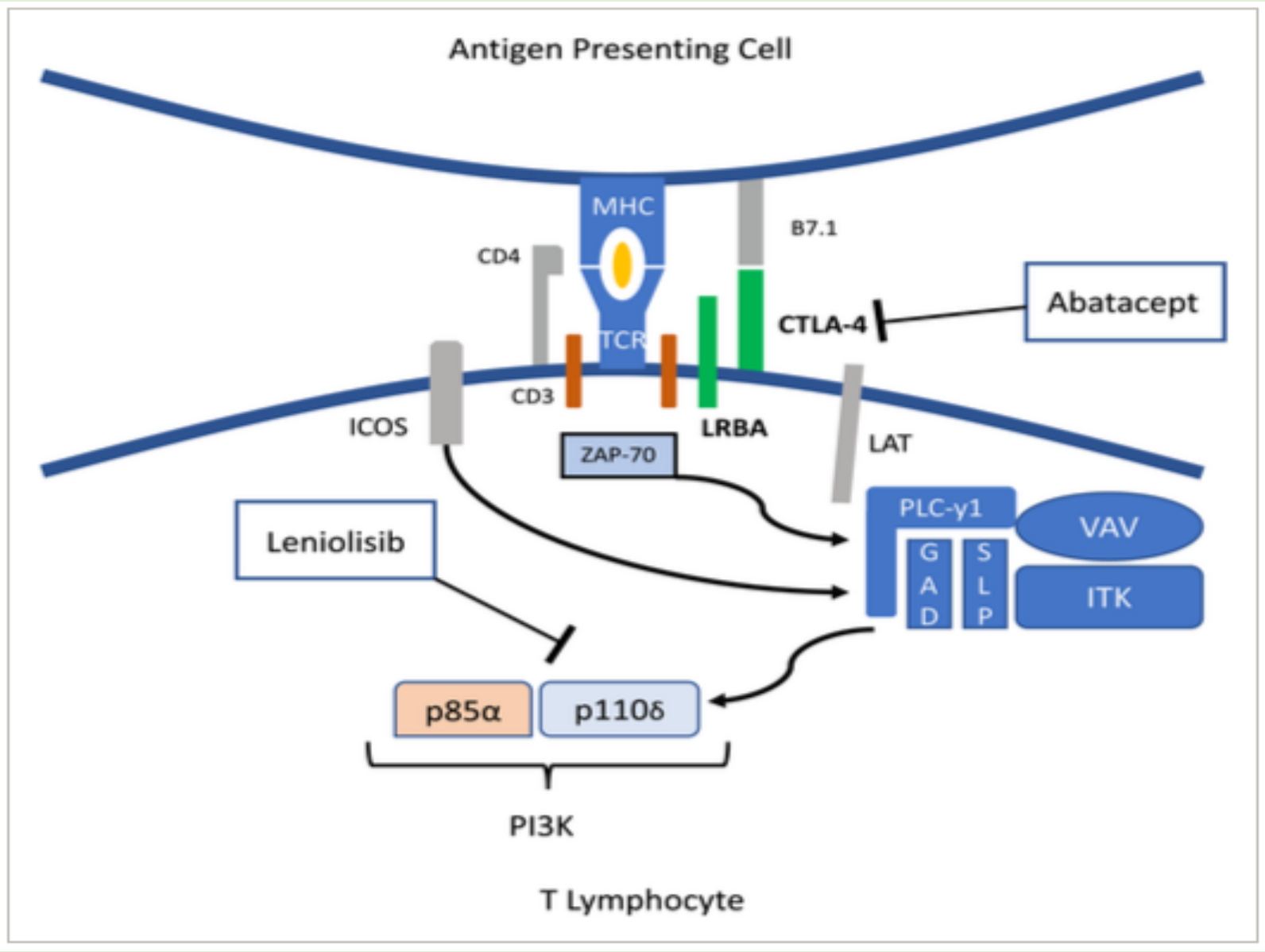
- Transplant outcome is better before organ damage and in the absence of ongoing severe inflammation

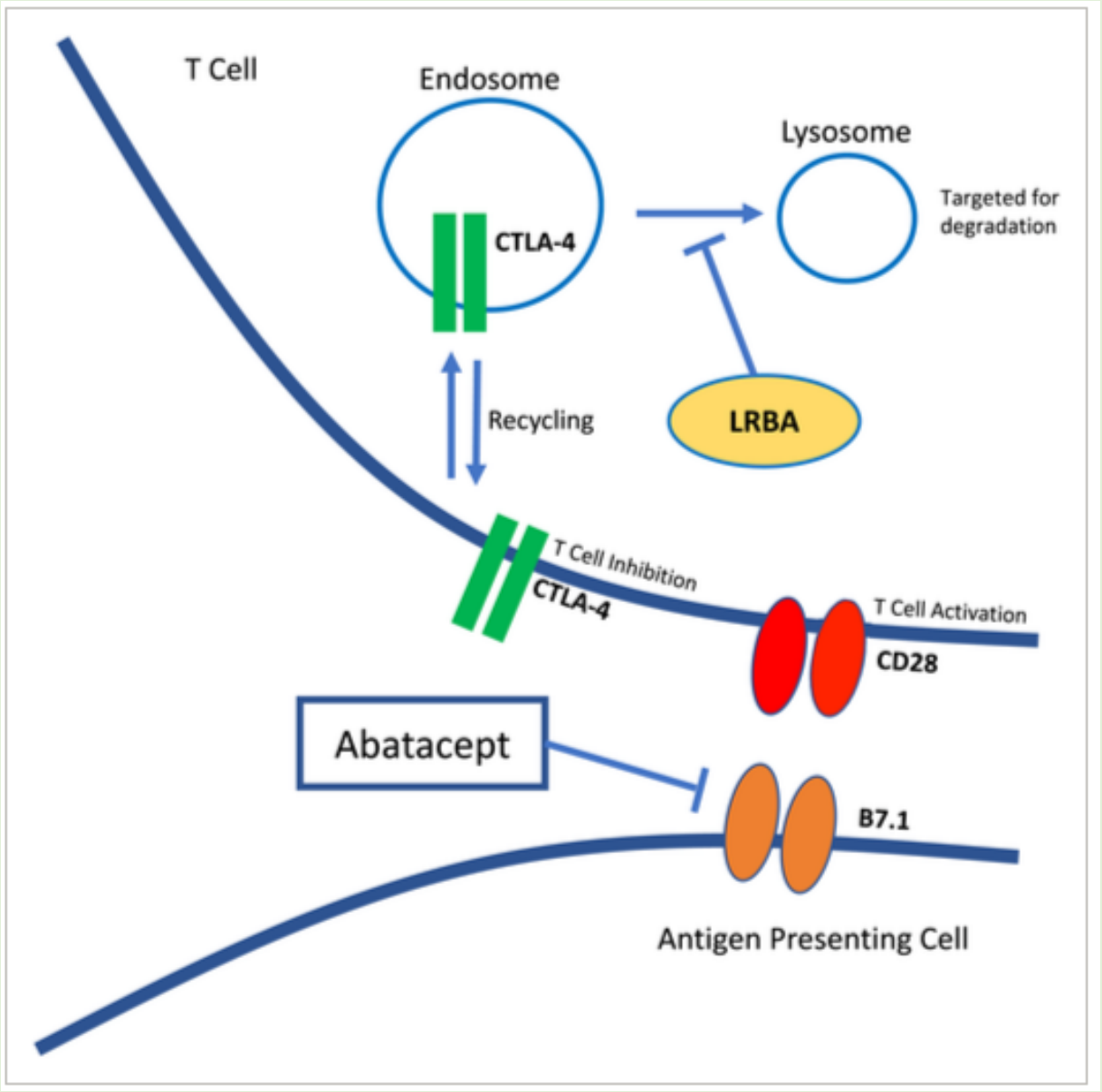
- Targeted biological agents such as abatacept or ruxolitinib
- significant reduction in disease activity
- complications of long-term use of these agents could be significant

- a bridging therapy to optimize condition of the patient prior to transplant


Cytokine
JAK
JAK
STAT
STAT
Cytokine
JAK
JAK
STAT
STAT
Ruxolitinib
Inflammation


Tocilizumab
IL-6R
IFNγR
Jak1
Jak1
Tyk2
Jak2
Jak2
Jakinibs
STAT3
STAT3
STAT1
STAT1


Antigen Presenting Cell
MHC
B7.1
CD4
Abatacept
CTLA-4
TCR
CD3
ICOS
LRBA
LAT
ZAP-70
PLC-γ1
VAV
Leniolisib
G
A
D
S
L
P
ITK
p85α
p110δ
PI3K
T Lymphocyte


T Cell
Endosome
Lysosome
Targeted for degradation
CTLA-4
Recycling
LRBA
T Cell Inhibition
CTLA-4
T Cell Activation
CD28
Abatacept
B7.1
Antigen Presenting Cell

- Alemtuzumab, a humanized monoclonal anti-CD52 antibody:
- first-line therapy with 91% survival

- The interferon-gamma targeted monoclonal antibody Emapulumab showed promising results in achieving remission

- targeting key cytokines such as IL1, IL6 and inhibition of the JAK1/2-STAT1 pathway are also being increasingly used

- Molecular diagnosis is important particulary in Very-early-onset Inflammatory Bowel Disease
- as HSCT is not indicated for an enteropathy due to an epithelial defect

- Given the highly variable genotype–phenotype correlation in most of these diseases

- family donors should be screened to avoid using an affected donor who may have a mild phenotype or late onset disease

- Alternative options:

- Gene therapy trials for a number of these disorders are in preclinical status

- PIRDs are newly emerging indications for HSCT:
- alternative medical or biological treatments are available

- For younger patients, these emerging therapies may best be used as a bridge to HSCT,
- to reduce inflammation and autoimmunity pre-transplant

- The issue of degree of donor chimerism required to achieve control of disease is unknown

- Adolescent and adult patients (>15 years) with IEI are increasingly being referred for consideration of HSCT

- For many IEI patients, complications accumulate with age,
- end organ damage, reduced quality of life and early death

- identifying which patients and when may benefit from HSCT:

remains challenging

due to phenotypic heterogeneity

- advances in genetic diagnostics
- improved survival into adulthood with conservative treatment

good outcomes following HSCT in these older patients have led to this change in clinical practice

- worse outcome :
- a degree of preexisting organ damage
- infectious burden
- malignancy at the time of HSCT

Adolescents and adults

- In older patients

reduced intensity conditioning regimens are preferred to limit excess toxicity (C, D, or E)

- higher risk of GVHD compared to children
- As with other IEI, the best possible control of autoimmunity and autoinflammation (i.e., colitis, lung disease) is recommended pre HSCT,
- even though complete remissions may not be achievable

Adolescents and adults

- Alternative options:

- For some specific forms of IEI, targeted therapies may offer a bridge to HSCT or be offered as an alternative therapy

- Autologous stem cell gene therapy in older patients is currently being evaluated in clinical trials

- in most IEIs and in particular in PIRDs
- the indication for HSCT can be influenced by many factors:

- specific genotype–phenotype
- comorbidities (previous infections, organ damage, donor availability, alternative immunomodulation strategies)

- Overall, the most important factor for improved survival rate:

- introduction of the haploidentical TCRab/CD19-depleted platform

- A precise genetic diagnosis:

- targeted therapy
- patients transplanted with a genetic diagnosis rather than having a retrospective genetic finding, will have better outcomes

- These data show the importance of gene sequencing as standard of care

- Features in STAT3 GOF :
- lymphoproliferation, autoimmune cytopenias, enteropathy, ILD, growth failure
- shared by many PIRDs FOXP3, CTLA-4, LRBA, PIK3CD
- demonstrating the importance of genetic testing

- targeted therapy led to improved patient outcomes

- fundamental challenges:

- whether to plan an early HSCT with a better outcome before organ impairment, recurrent infection and malignancy occur
- treat with targeted therapy for which the longterm effects are unknown
- wait for HSCT when further disease manifestations occur

- requires careful patient counselling with rigorous collection of long-term outcome data for the different therapeutic options

- improved outcome of HSCT:
- Knowledge of an underlying genetic diagnosis
- HSCT at a younger age before organ impairment improves outcomes

- Determining which patients to offer HSCT to is challenging

- Long-term outcome studies are required to compare conservative management, targeted therapy and HSCT outcomes

- CTLA-4:
- binds to the CD80 and CD86 ligands on APCs outcompeting CD28 mediated activating signals
- downregulates the immune response by inhibiting T cell activation

- Absence of LRBA leads to decreased CTLA-4 expression:
- impaired Treg cell function
- Sirolimus:
- inhibits the CD28 signalling pathway which decreases T cell hyperactivity
- enhances T regulatory cells
- The CTLA-4 fusion proteins Abatacept and Belatacept show promising results

- Gain of Function mutations in PIK3CD or loss of function mutations in PIK3RI lead to Activated PI3K delta Syndrome (APDS):

- Sirolimus:
- inhibits downstream enhanced mTORC1 activity

- Leniolisib:
- oral small molecule inhibitor of the p100 delta subunit of PI3K
- inhibit PI3K activation directly

- GOF mutations in STAT1 and STAT3 cause hyperactivation in STAT1 and STAT3 respectively

- Jakinibs are direct inhibitors of the JAK/STAT pathway

- Ruxolitinib or tofacitinib :
- used successfully to target the STAT hyperresponsiveness in patients with STAT1 and STAT3 GOF

- Key concepts in bridging therapies:

- Biologic modifiers are available to treat specific diseases

- Outcome of long-term therapy needs to be studied

- Optimising patient status prior to HSCT with such agents is useful to improve outcome