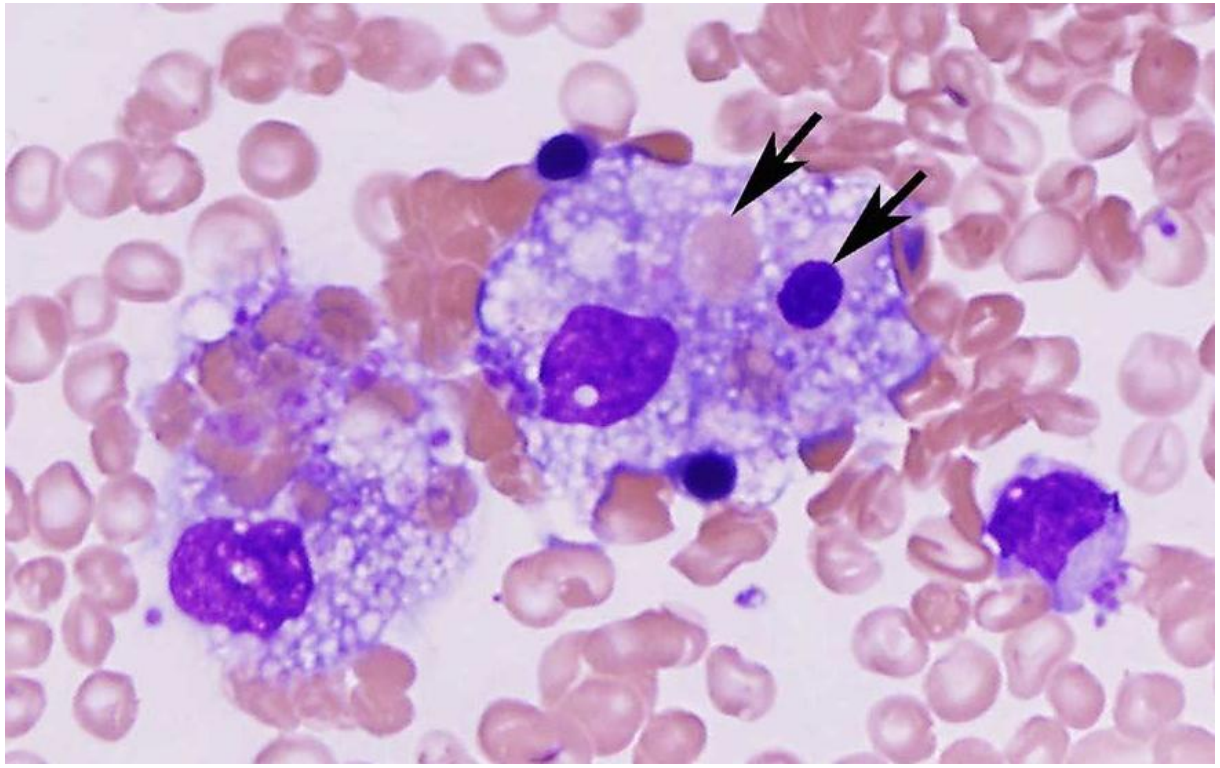
Hemophagocytic lymphohistiocytosis (HLH): Overview and current challenges



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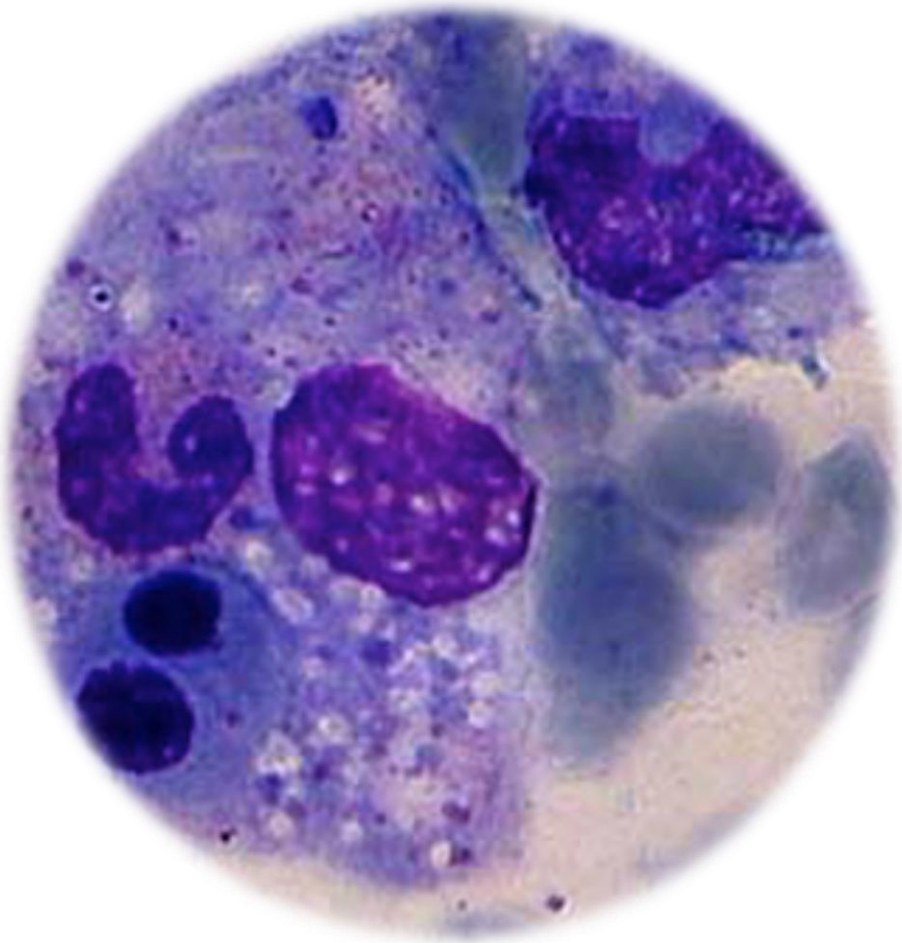
Disclosures

Consultant:
SOBI

Research support:
BMS
Sobi

Overview

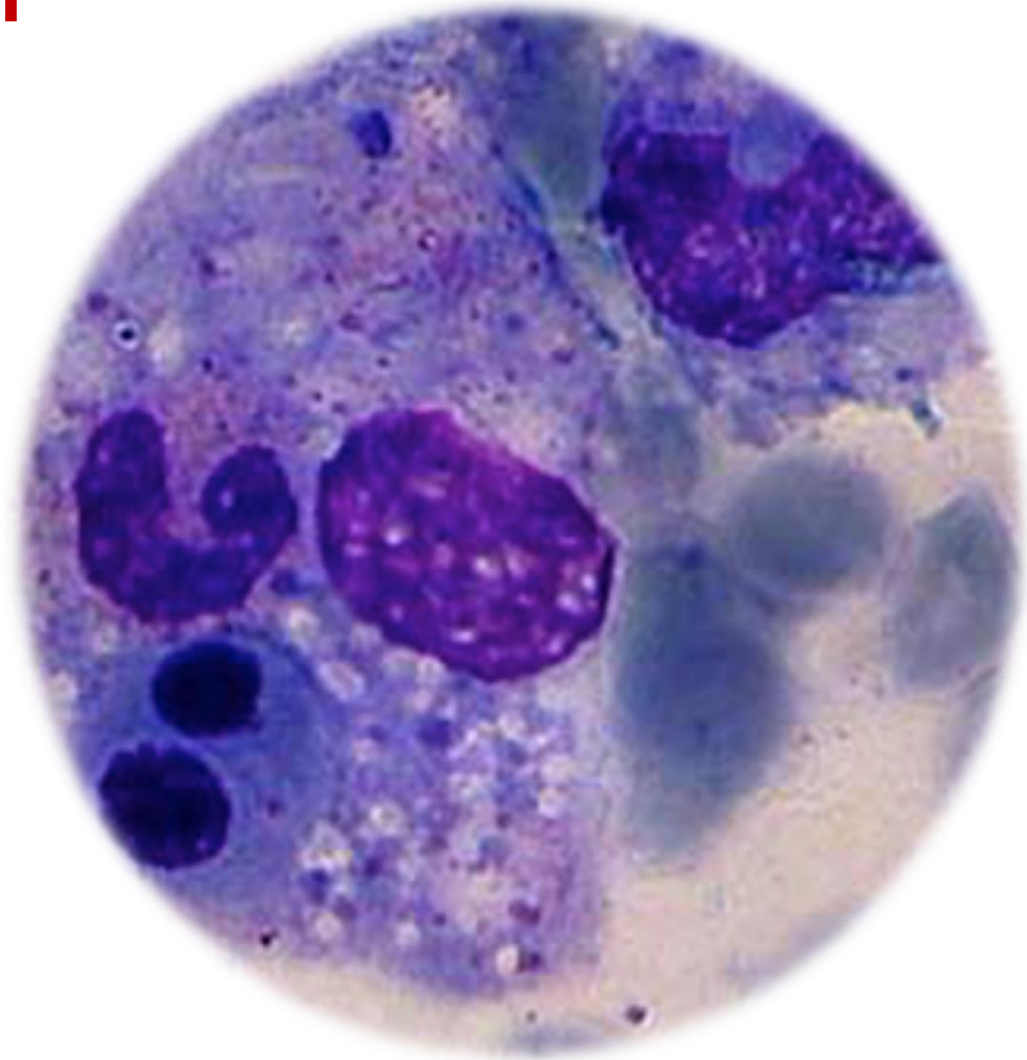
- What is HLH?
- Challenges in diagnosing HLH
- Challenges in treating HLH



(Simple) Definition of HLH

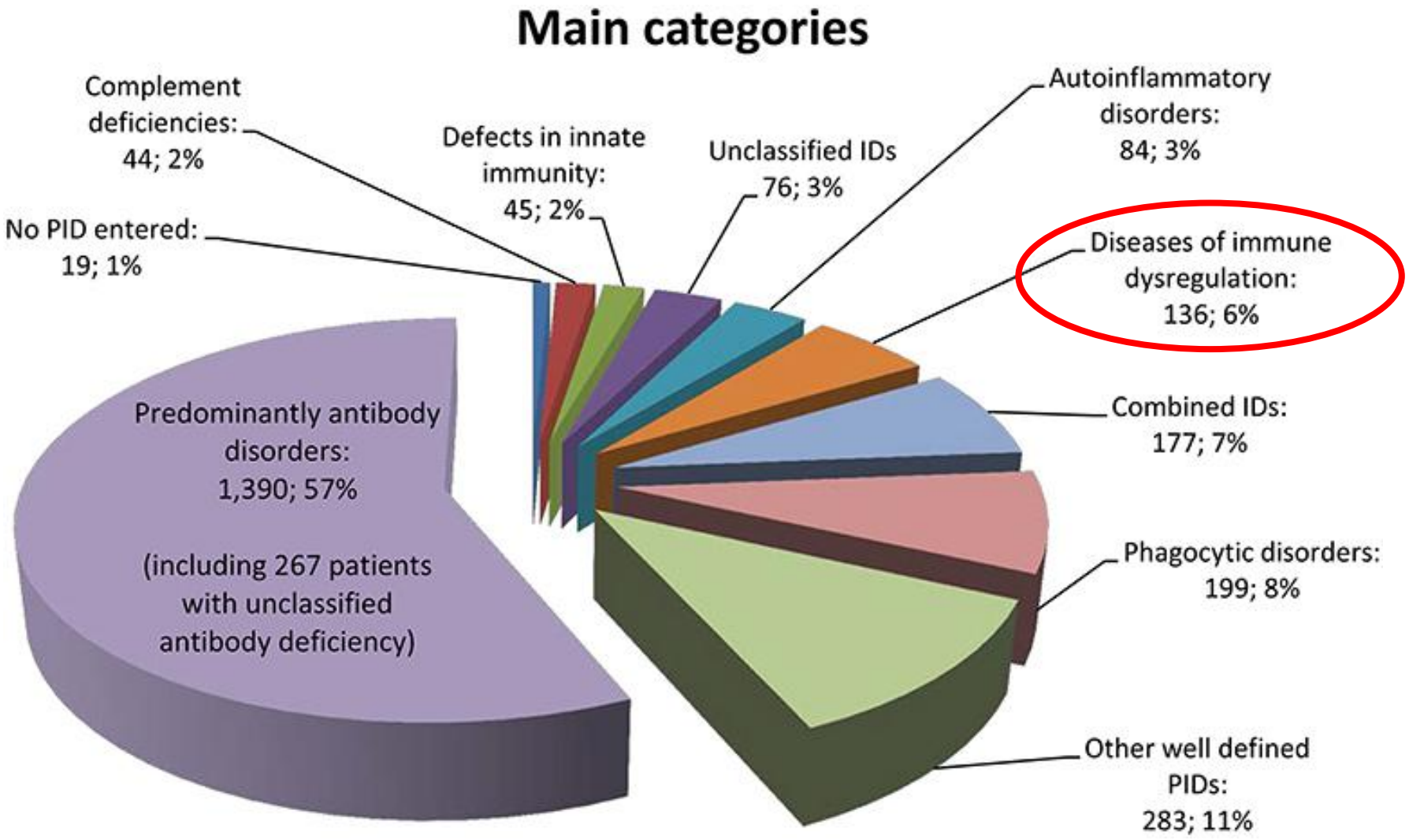
Hemophagocytic lymphohistiocytosis

A life-threatening *hyper*-inflammatory syndrome characterized by extreme T cell activation and toxic recruitment of macrophages.



Excess is the essence of the problem

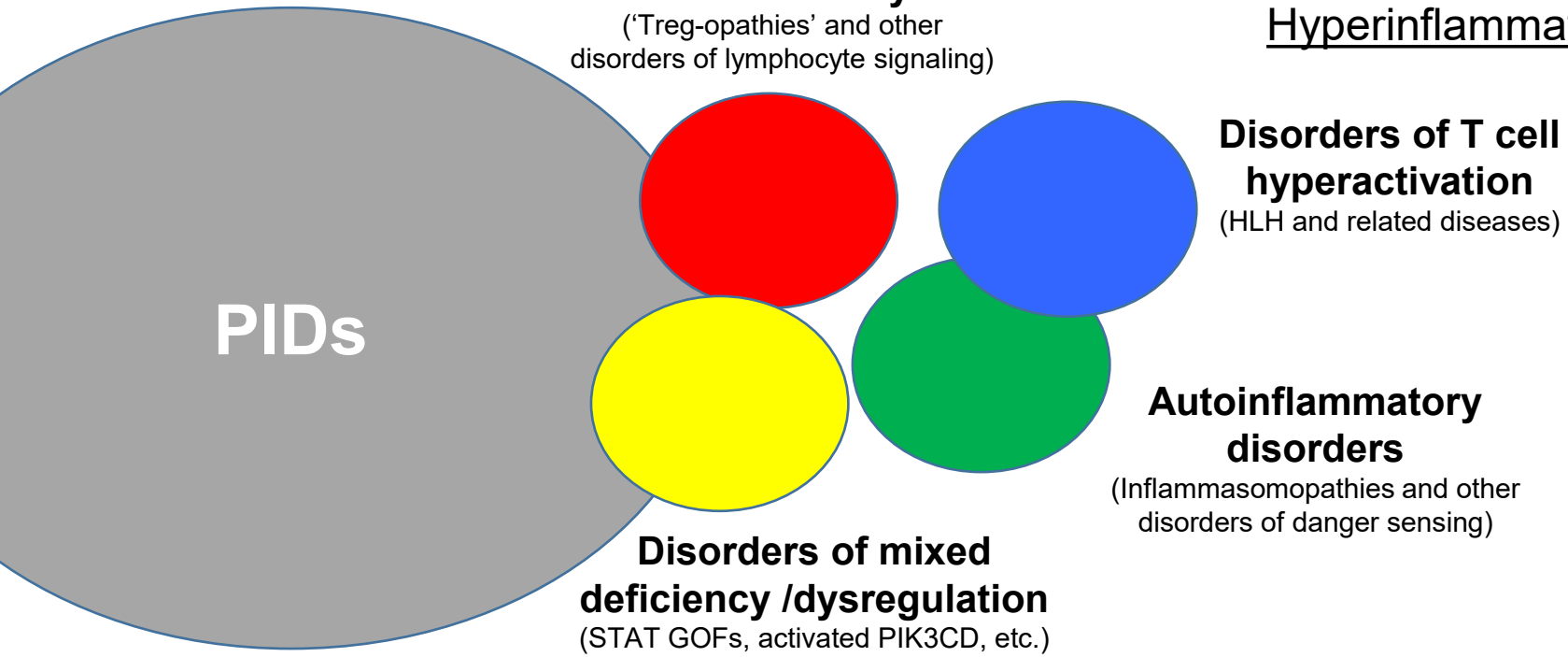
PIDD or PIRD?



El Halou et al, 2019

Categorizing genetic disorders of immune regulation
(primary immune regulatory disorders, 'PIRDs')

Immune 'Sins':
Immunodeficiency: Inadequate function
Autoimmunity: Directed at self
Autoinflammation: Turned on without reason
Hyperinflammation: Too intense and can't turn off



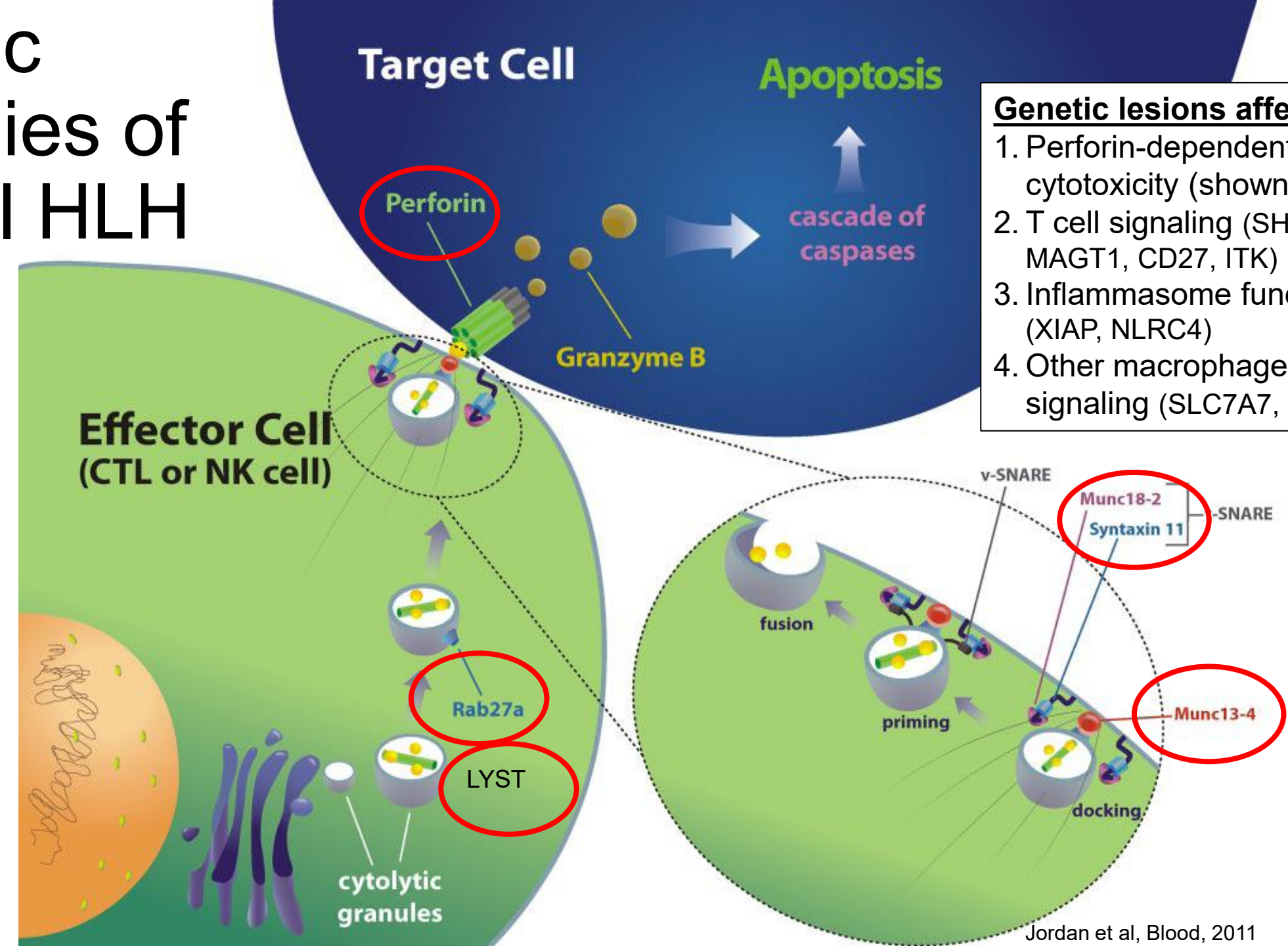
Mendelian disorders of autoimmunity
('Treg-opathies' and other disorders of lymphocyte signaling)

Disorders of T cell hyperactivation
(HLH and related diseases)

Autoinflammatory disorders
(Inflammasomopathies and other disorders of danger sensing)

Disorders of mixed deficiency /dysregulation
(STAT GOFs, activated PIK3CD, etc.)

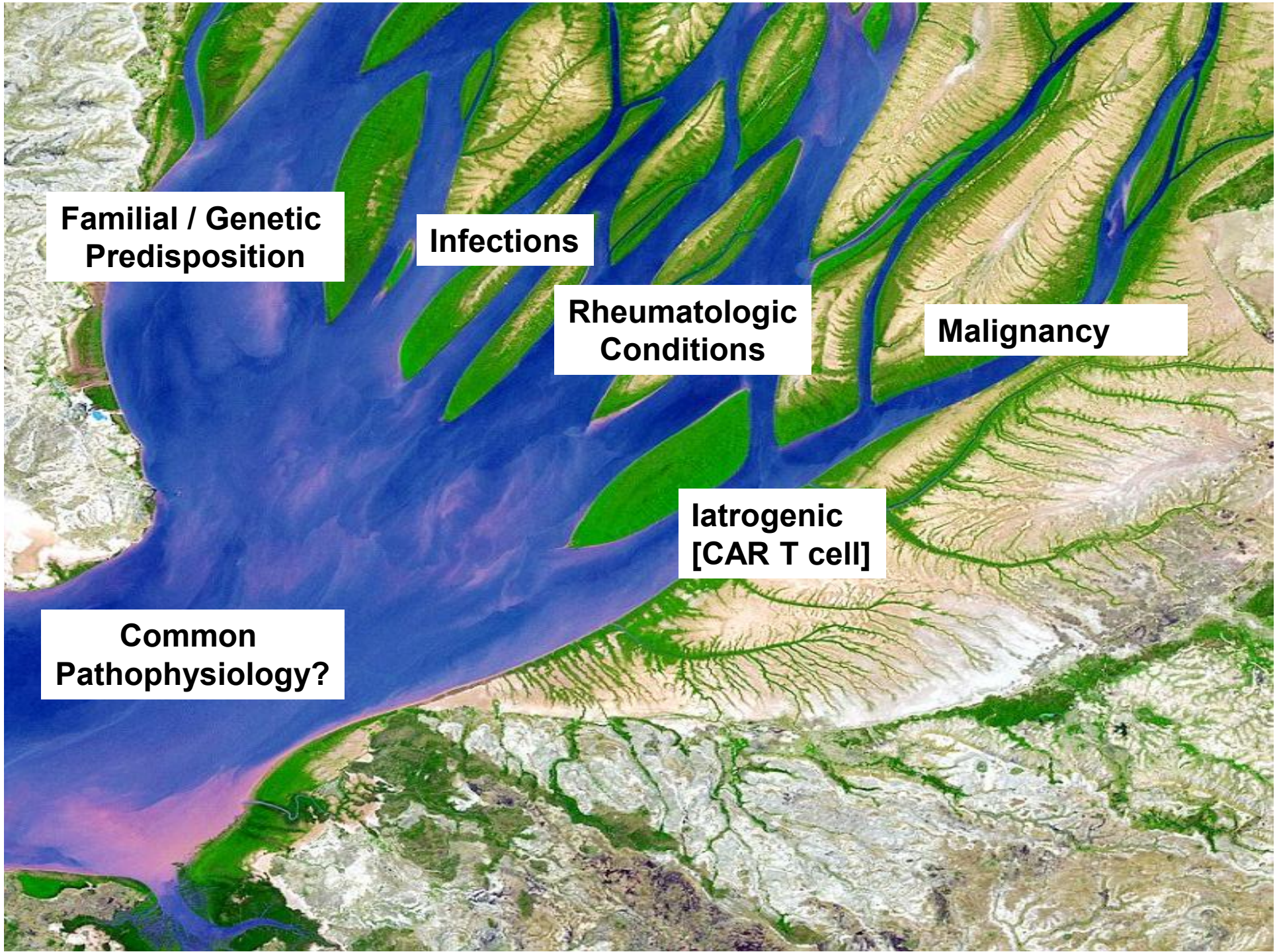
Genetic etiologies of familial HLH



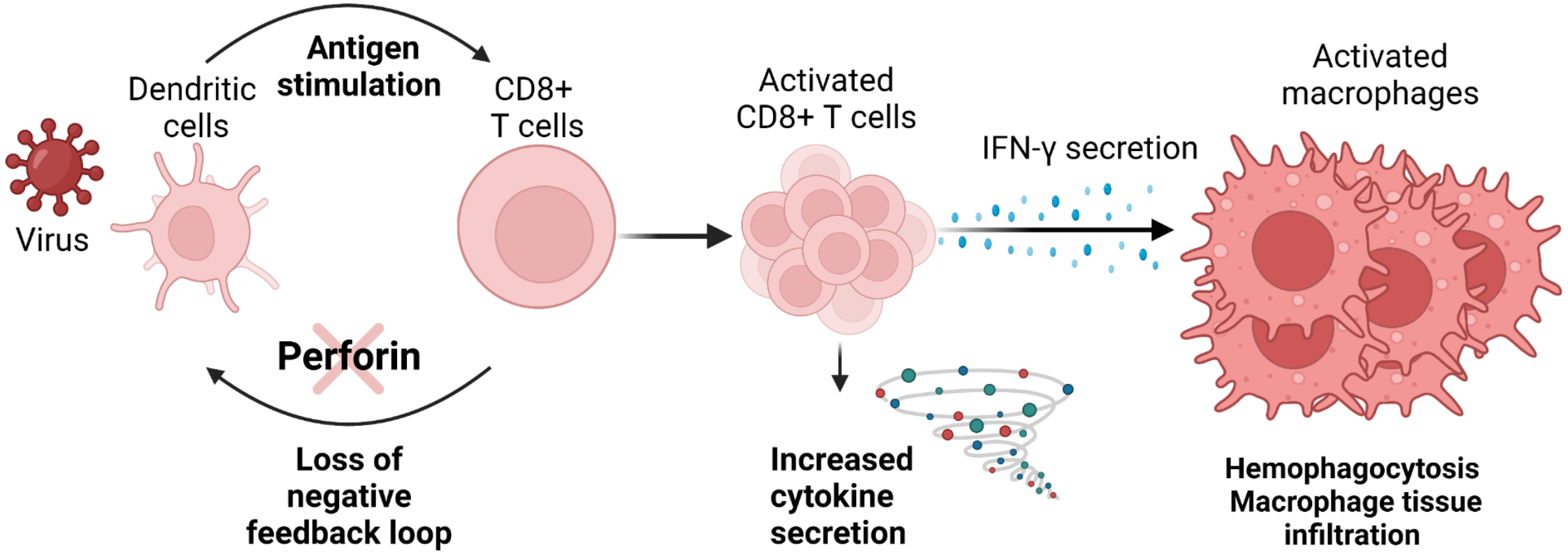
Genetic lesions affecting:

1. Perforin-dependent cytotoxicity (shown)
2. T cell signaling (SH2D1A, MAGT1, CD27, ITK)
3. Inflammasome function (XIAP, NLRC4)
4. Other macrophage signaling (SLC7A7, HMOX1)

Jordan et al, Blood, 2011

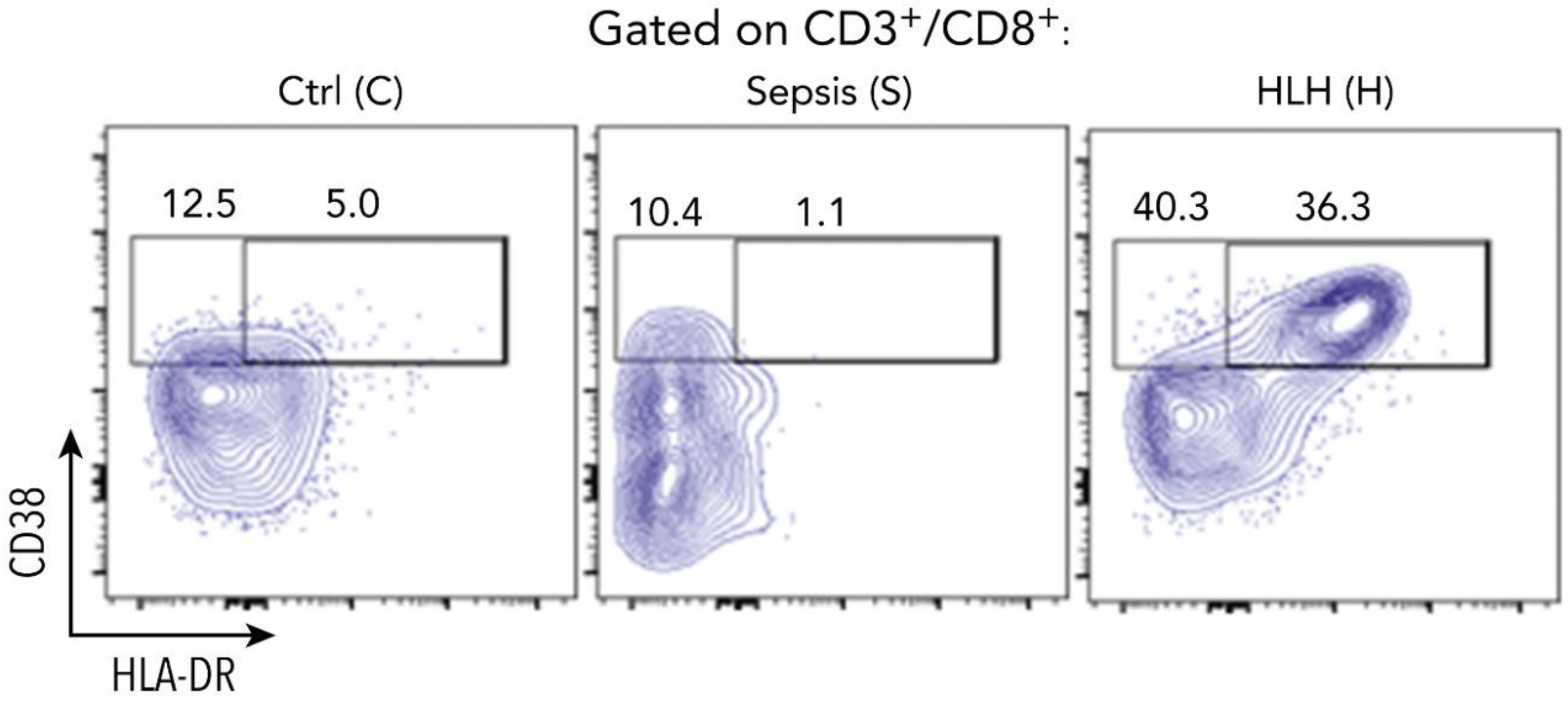

Familial / Genetic Predisposition
Infections
Rheumatologic Conditions
Malignancy
Iatrogenic [CAR T cell]
Common Pathophysiology?

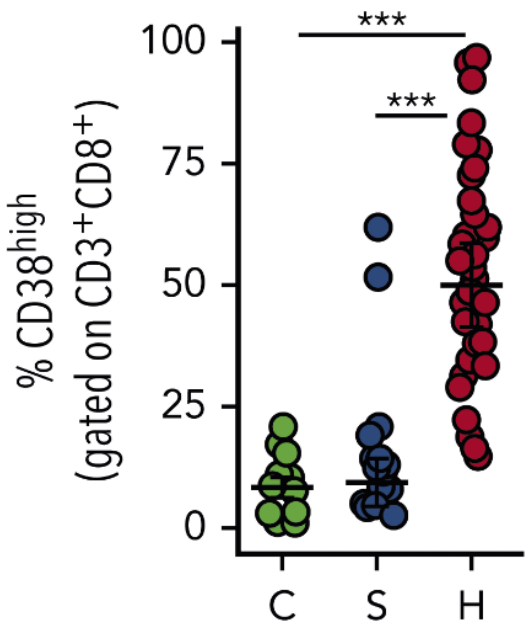
The pathogenesis of familial HLH



Zoref-Lorenz A, Ellis M, Jordan MB. Inpatient recognition and management of HLH. Hematology Am Soc Hematol Educ Program. 2023 Dec

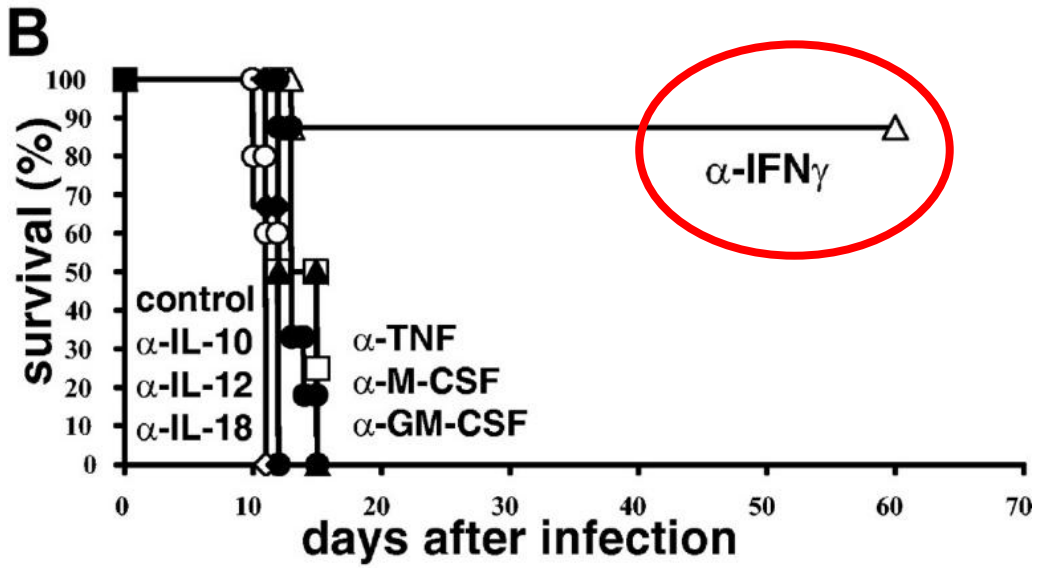
Recently activated (HLADR+/CD38^{bright}) CD8+ T cells are characteristic of HLH





Chaturvedi V, Marsh R, Zoref-Lorenz et. Al. Blood 2021

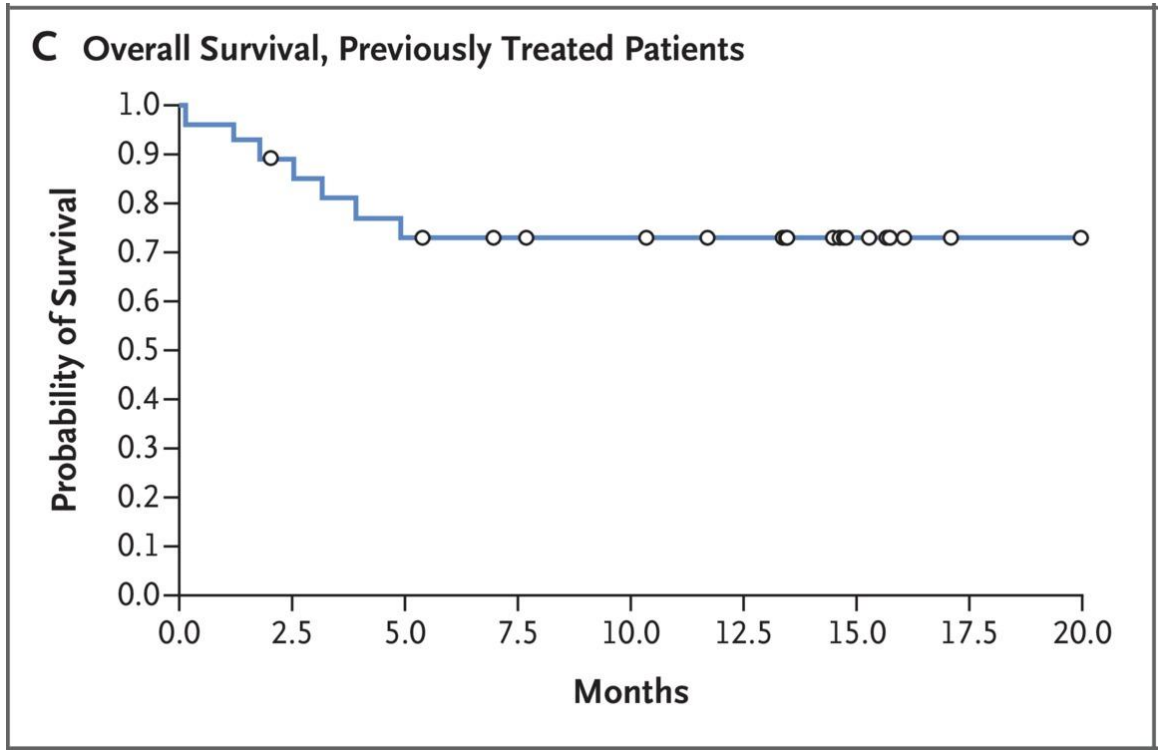
IFN-γ is an essential driver of familial HLH



Jordan et al. Blood 2004;104:735-743

Also:

Pachlopnik, 2009
Sepulveda, 2013
Kogl, 2013
Jessen, 2013



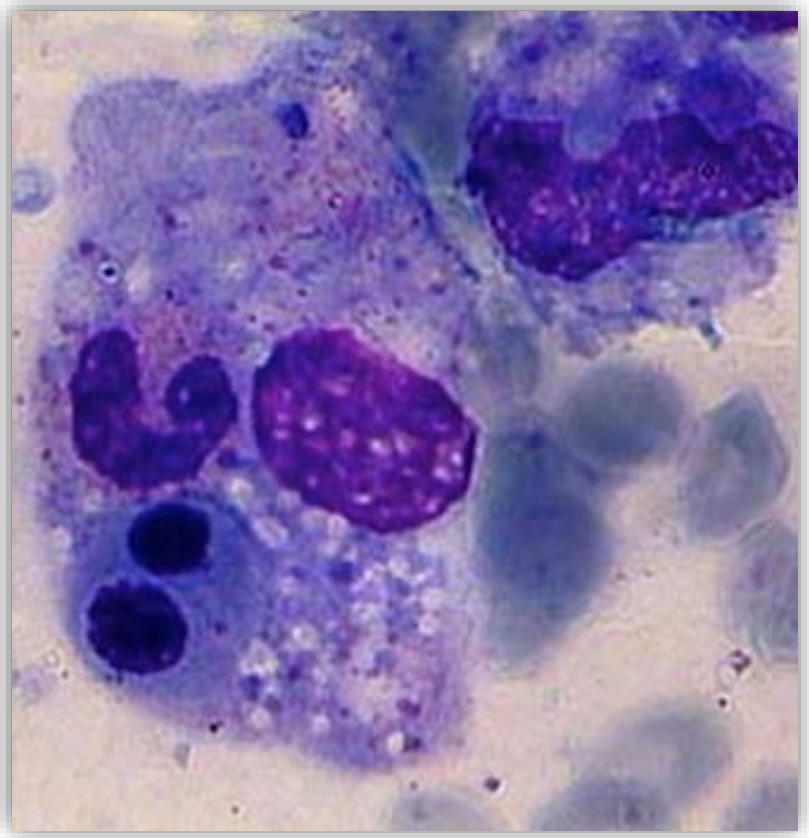
Treatment with emapalumab (anti-IFN-γ)

Locatelli, Jordan et al. N Engl J Med 2020;382:1811-1822

Challenges in understanding HLH
(and how to meet them)

1. How does HLH develop in patients without ‘classic’ familial HLH genetics?
    - Stills disease (sJIA)?
    - Cancer?
    - (only) infection?
2. What are the main disease mediators in each context?

Diagnosing HLH



Hemo- phago- cyt-ic Lympho- histiocyt- osis
Blood eating cell lymphocyte macrophage condition

Disorder with unusual engulfment of blood cells and expansion of lymphocytes and macrophages

HLH syndrome

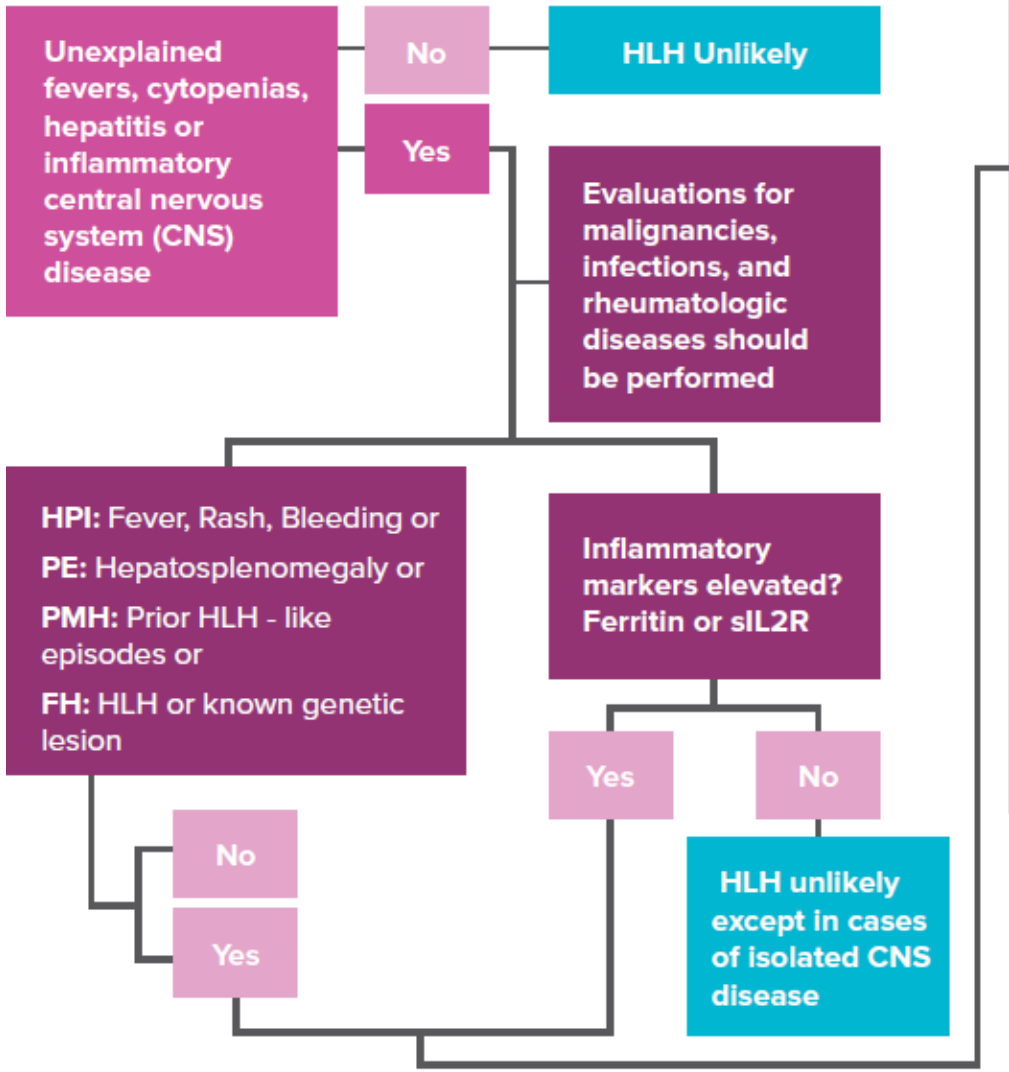
HLH-2004 diagnostic criteria

Defined* in the context of FHL as a patient fulfilling 5/8 criteria:

1. fever >38
2. splenomegaly
3. cytopenias in 2 or more lineages
4. Ferritin >500 ng/mL
5. sCD25 >2,400 U/mL
6. low NK cell function
7. hemophagocytosis on biopsy
8. Fibrinogen <150 ng/mL or Triglycerides > 265 ng/mL

Henter JI, Horne A, Aricó M…Janka G. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2007

HLH Diagnostic Strategy



Diagnostic Work-up

1. Diagnose active HLH

- CBC
- Fibrinogen, Coags
- Triglycerides (fasting)
- ALT, bilirubin
- Ferritin
- sIL2r, CXCL9, IL-18
- Marrow (or other) biopsy

2. Screening studies for genetic causes of HLH

- Perforin/granzyme B
- Degranulation (CD107a) or T cell degranulation
- SAP protein (for males)
- XIAP protein (for males)

3. Ancillary Studies**

- CT of Chest/Abd/Neck
- MRI of brain
- Consider testing for tick or mosquito-born diseases in your area
- Viral PCRs: EBV, CMV, Adenovirus, etc.
- Consider PET-CT to evaluate for lymphoma

Yes, HLH

Cincinnati Children's HLH Genetic Panel (NGS)

See genetic algorithm on the next page

CNS Work-up

LP and Brain MRI

Follow-up Studies

To assess response to therapy

Daily (initially):

- CBC
- ALT
- Fibrinogen

Weekly:

- sIL2R
- Ferritin

*These studies are helpful because they may rapidly confirm a clinical diagnosis by defining a potential immune/genetic etiology for HLH.

**These studies may help eliminate other conditions in the differential diagnosis and/or define treatable underlying triggers for HLH.

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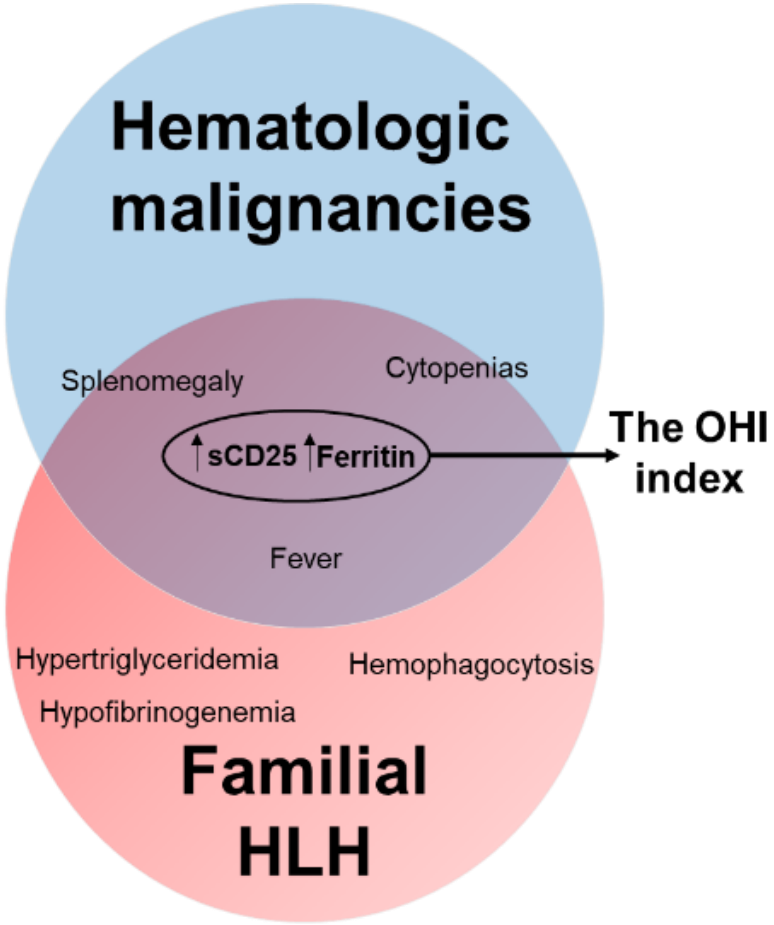
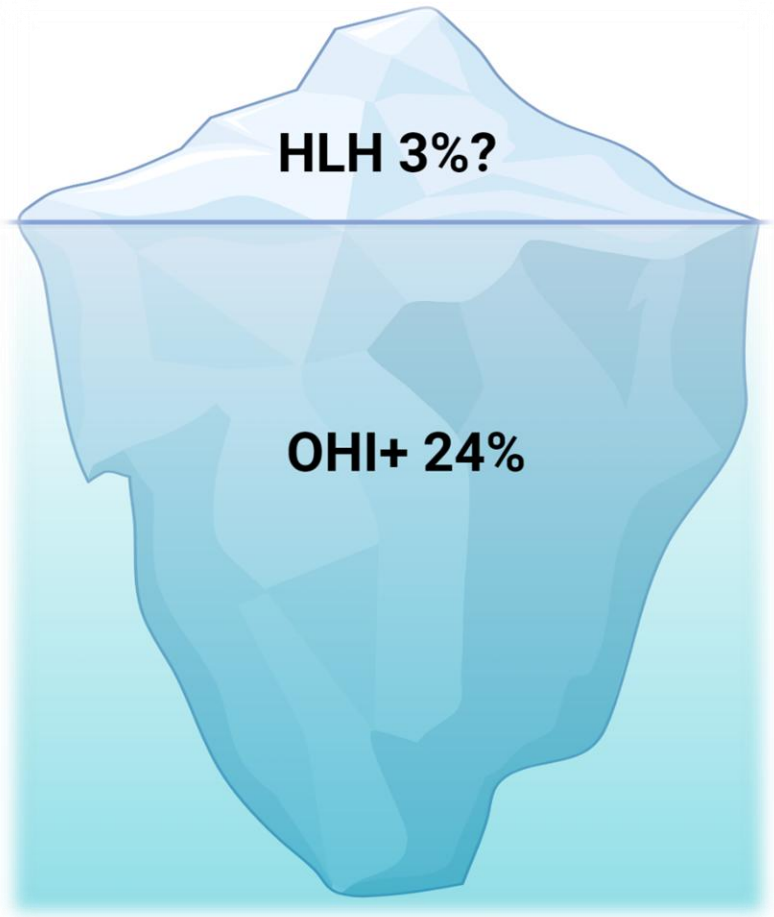
Optimizing HLH diagnosis for patients with hematologic malignancies



- Simpler (more focused)
- Better (more sensitive and accurate)
- Faster (less to test; no irrelevant delays)

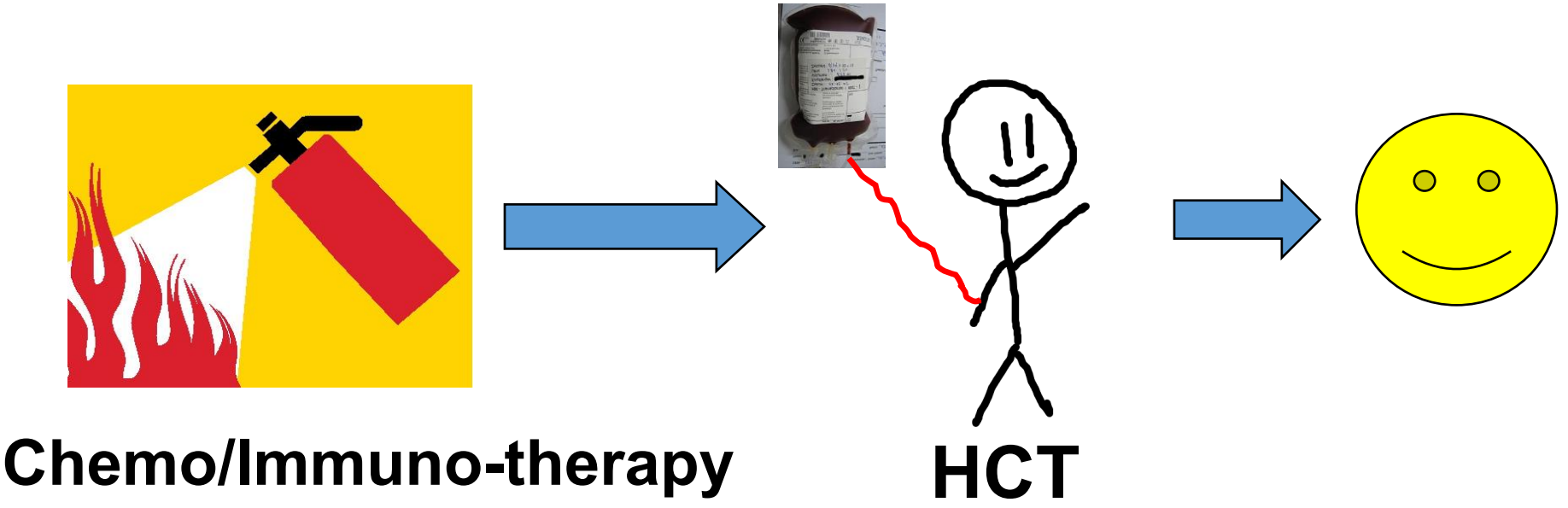


Zoref-Lorenz A, Murakami J, Hofstetter L, Iyer SP, Alotaibi AS, Mohamed SF, Miller PG, Guber E, Weinstein S, Yacobovich J, Nikiforow S, Ebert BL, Lane A, Pasvolsky O, Raanani P, Nagler A, Berliner N, Daver NG, Ellis M, Jordan MB. An improved index for diagnosis and mortality prediction in malignancy associated hemophagocytic lymphohistiocytosis. Blood. 2021 Nov 15:blood.

Challenges in diagnosing HLH
(and how to meet them)

1. **Recognizing a rare disorder:** Awareness, awareness, awareness….
2. **Distinguishing it from 'mimics':** HLH is a process, not just a pattern.
3. **Identifying HLH variants in specific contexts:** F-HLH vs MAS vs M-HLH
4. **Identifying HLH in adults**
5. **Better tests vs better utilization of old ones**
   ERs/ ICUs
   in specific populations (OHI)

HLH therapy 101



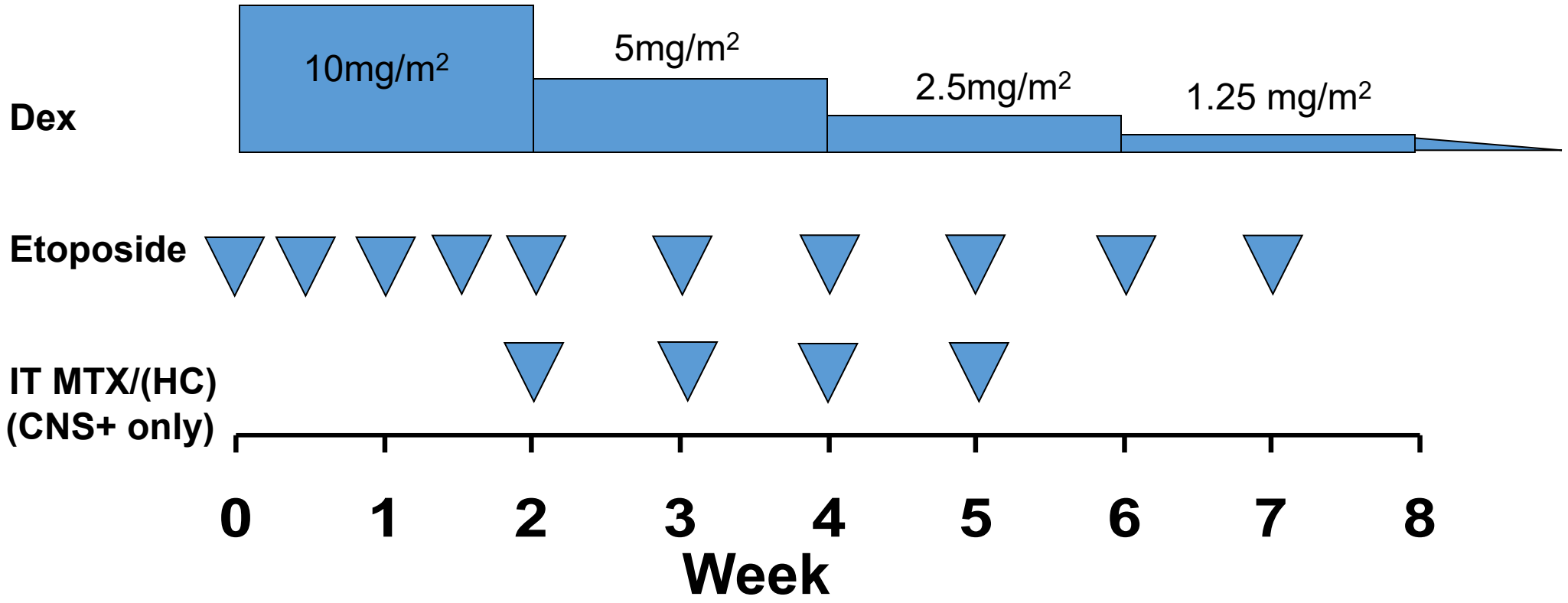
Chemo/Immuno-therapy

HCT

1970's- Uniformly fatal
1980- Etoposide
1993- ATG
1994- First HS trial
2004- Second HS trial
2019- emapalumab trial

1986- long term success of HCT
2006- improved outcomes with reduced intensity conditioning

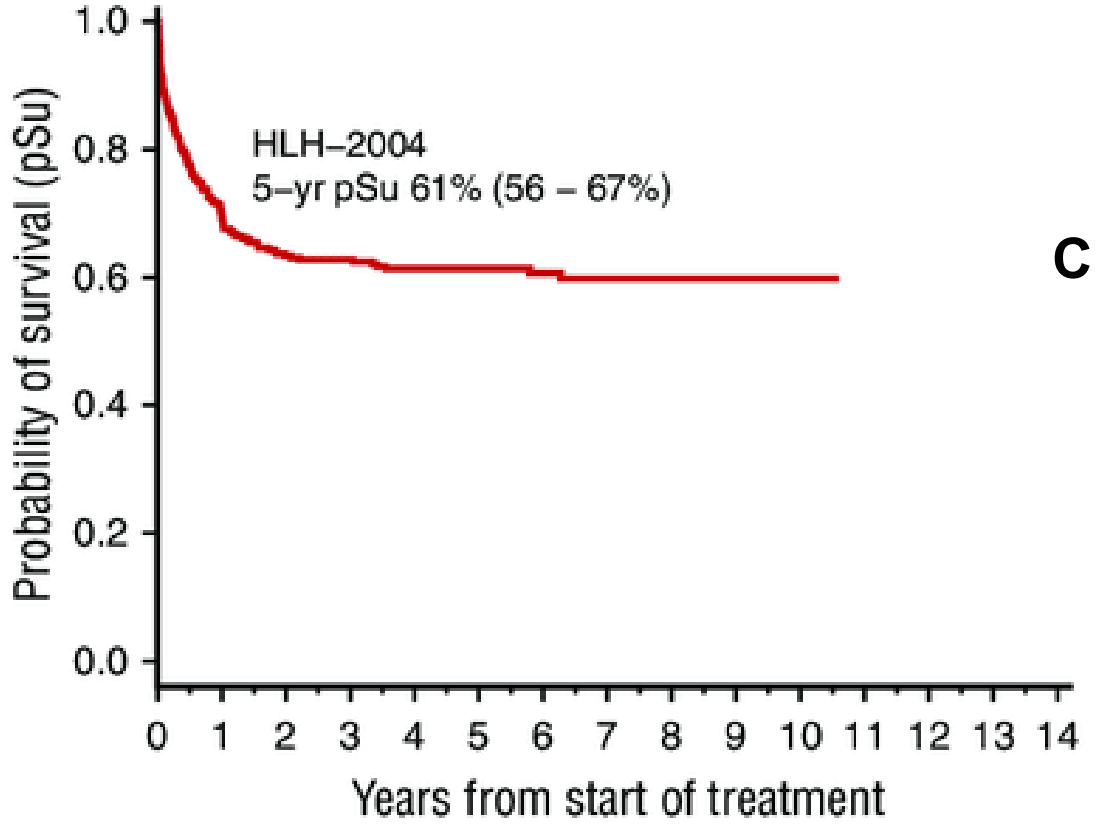
HLH-94:



Etoposide: 150mg/m^2

Survival after standard of care treatment for HLH

mortality
- Pre-BMT
- Post-BMT

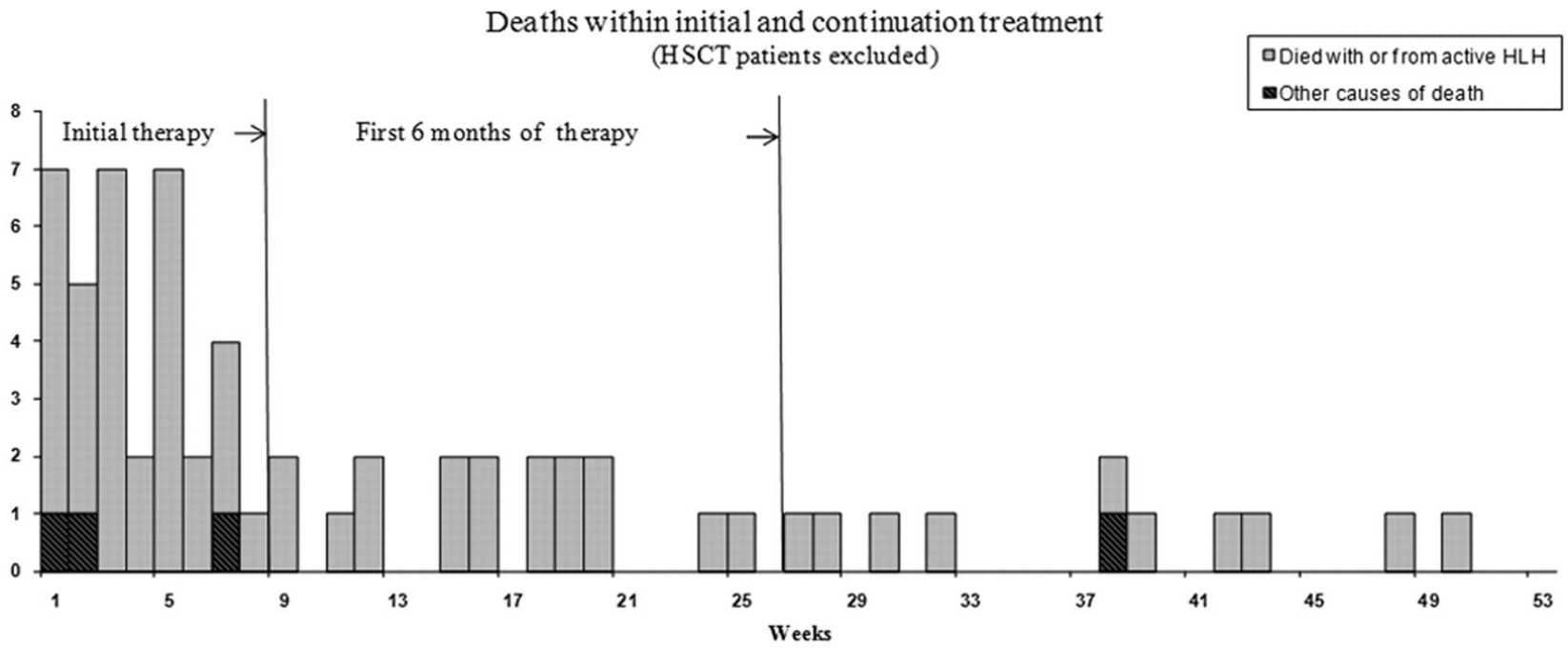


Chemo/Immunotherapy, then BMT

Bergsten et al, 2017

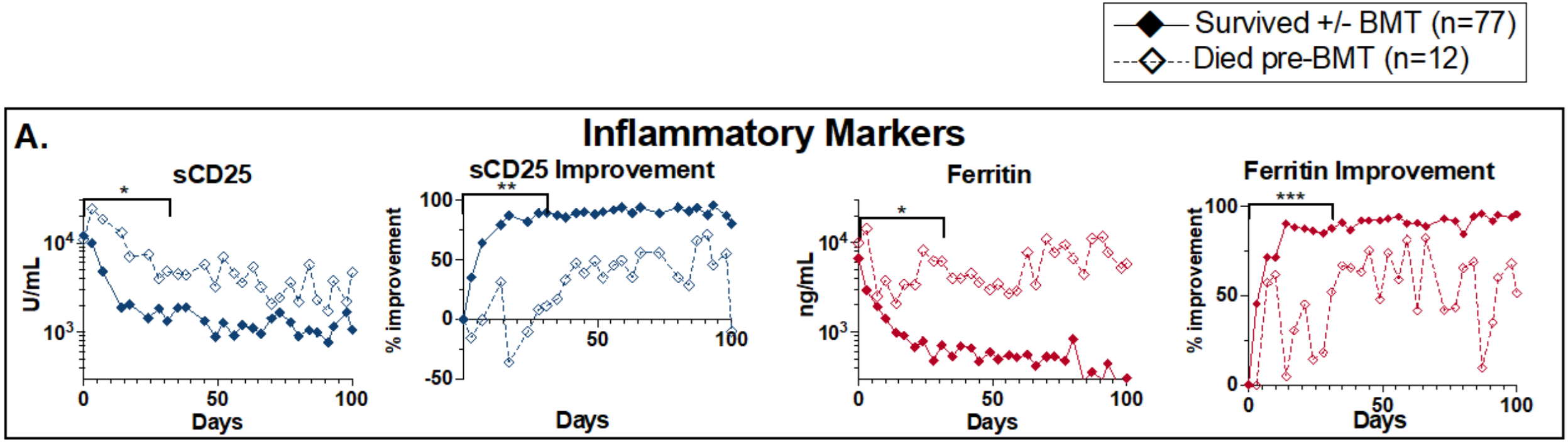
Cause and time of deaths for patients in HLH-94

(those who did not receive transplantation within the first year of treatment, n=64)



Helena Trottestam et al. Blood 2011;118:4577-4584

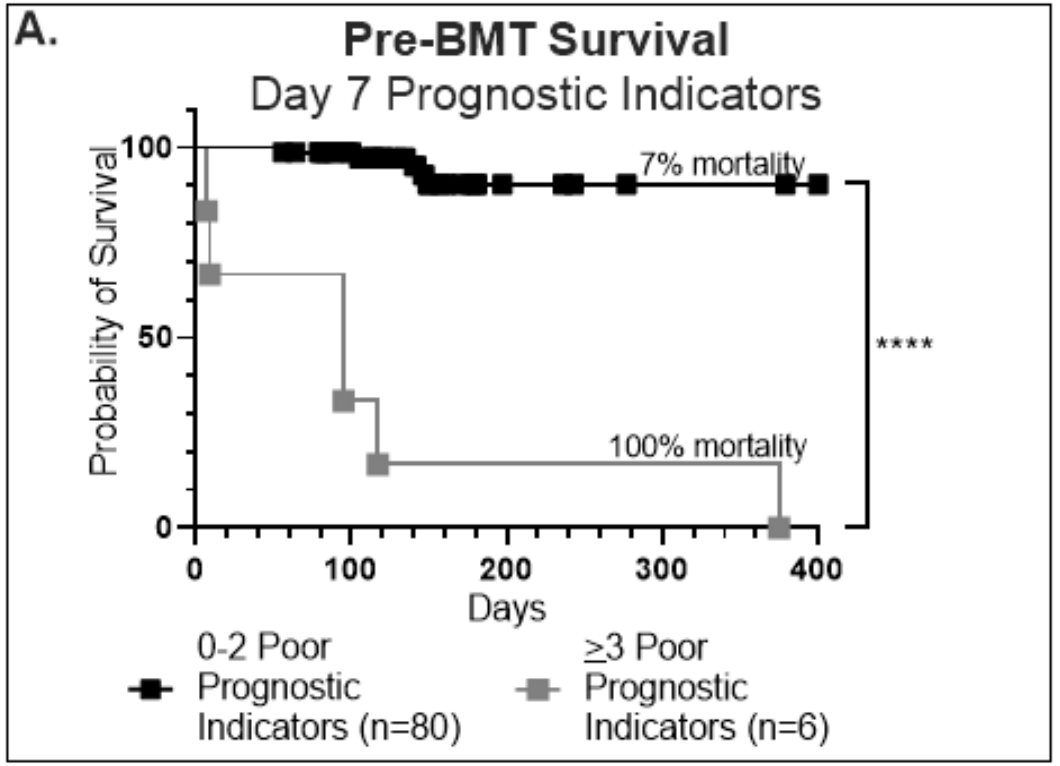
Inflammatory marker response and mortality

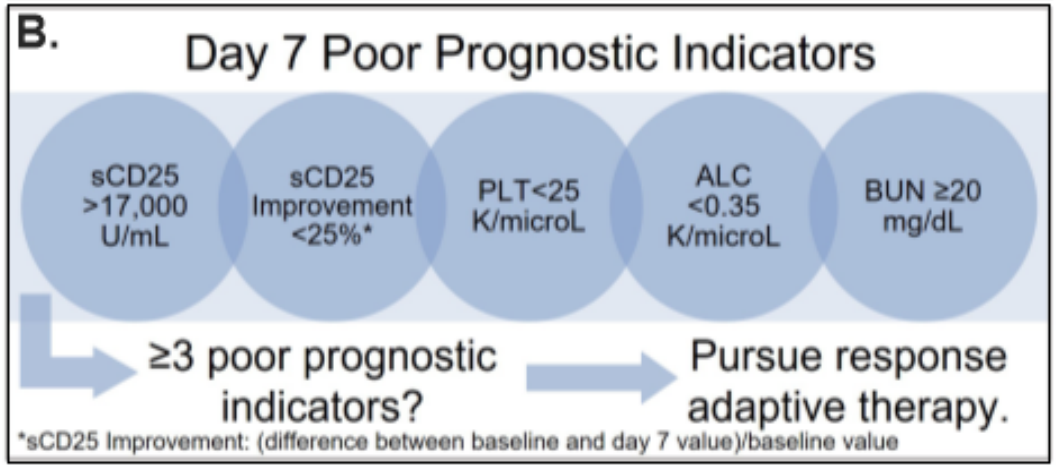


- Improvement from baseline: (difference between baseline and day X)/baseline value
- Fibrinogen, TG, ANC, AMC, bilirubin, and LDH kinetics were not significantly different between groups
- *ns* – not significant; **** p-value <0.0001; *** p-value <0.001; ** p-value <0.01; * p-value <0.05

Verkamp et al, 2023

Predicting (and responding to) poor prognosis





<u>Lesson</u>: serial assessment of inflammatory features is critical for optimizing outcomes

- Improvement from baseline: (difference between baseline and day X)/baseline value
- **** p-value <0.0001

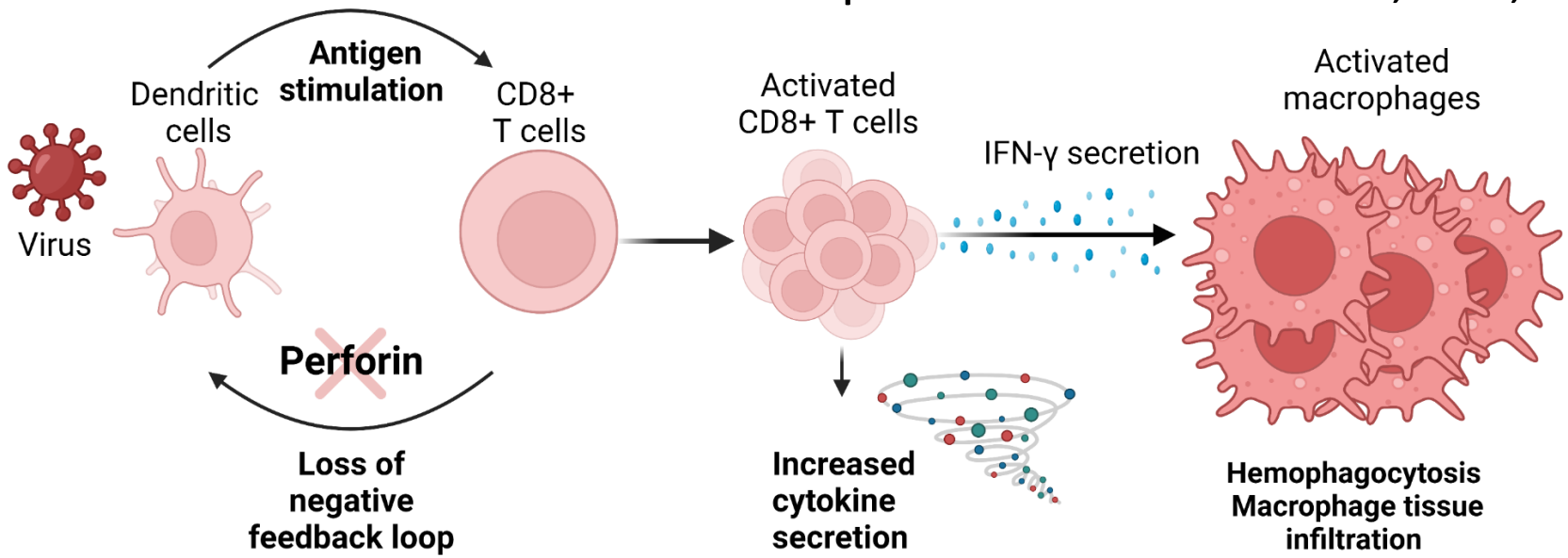
Verkamp et al, 2023

Multiple treatment modalities for familial HLH

--Corticosteroids----------

etoposide
alemtuzumab
abatacept

emapalumab
Jak inhibitors
anti-IL-6, IL-1, etc

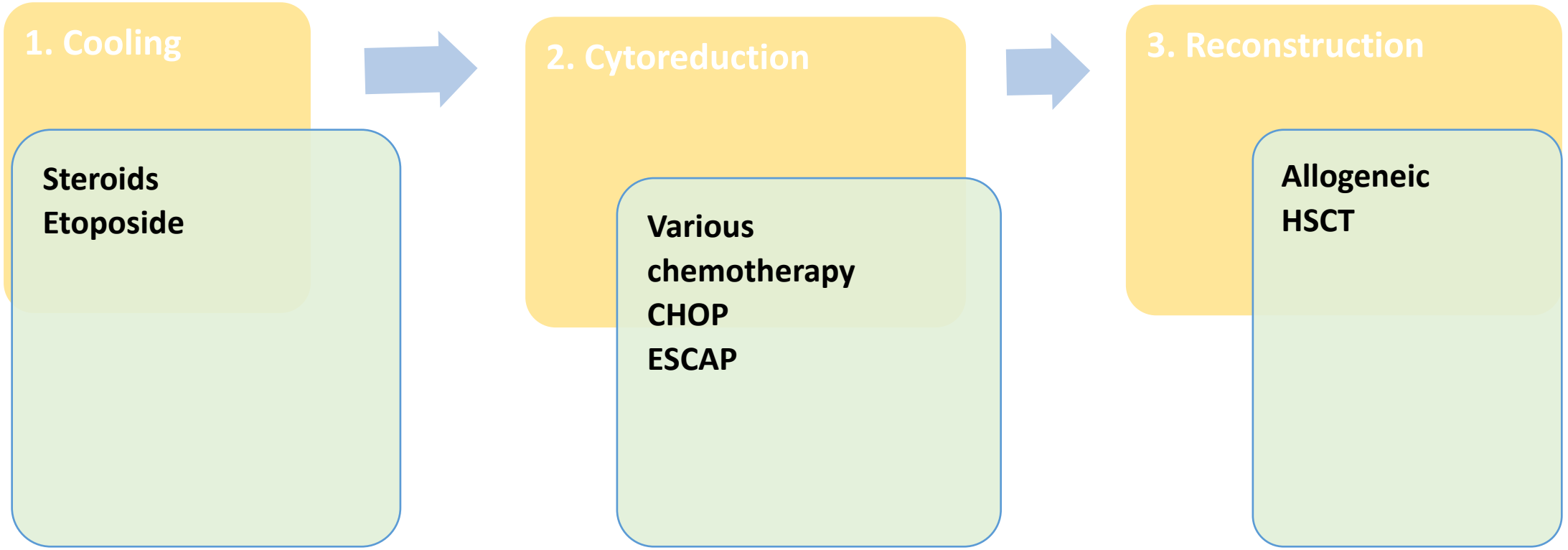


Zoref-Lorenz A, Ellis M, Jordan MB. Inpatient recognition and management of HLH. Hematology Am Soc Hematol Educ Program. 2023 Dec

HLH treatment: special situations

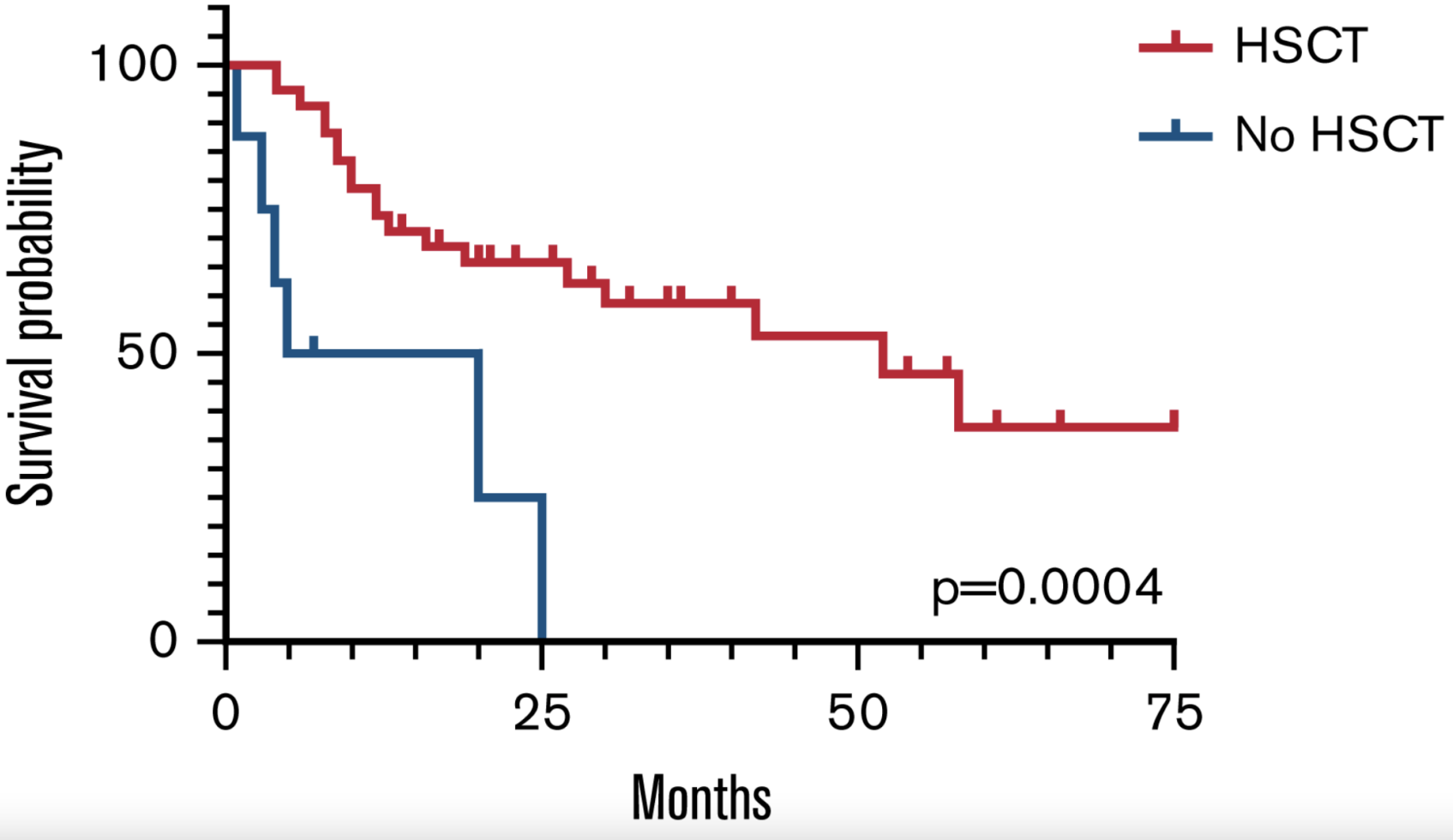
- **MAS: macrophage activation syndrome** – seen mostly in patients with Still's disease (sJIA), children and adults.
  - primarily treated with very high dose corticosteroids ('pulse')
  - Emapalumab now also approved in the USA
- **HLH in cancer:** optimal treatment unknown (prognosis is very poor), though cancer treatment is essential
- **EBV HLH:** most common driver of HLH in East Asia, common in Western countries too
  - A growing series of genetic disorders are known to predispose to HLH, but most patients don't have any genetic lesion (east Asian)
  - EBV usually found in B cells, but non-genetic cases (East Asian, ethnic?) usually have EBV in other immune cells (T or NK cells)
  - Often responsive to therapy, but often relapsing, leading to poor outcomes

EBV HLH Current treatment paradigm



- Adapted from Sawada et al. (2017, 2023):

Outcomes for chronic active EBV



Dávila Saldaña et al, Blood Advances, 2020

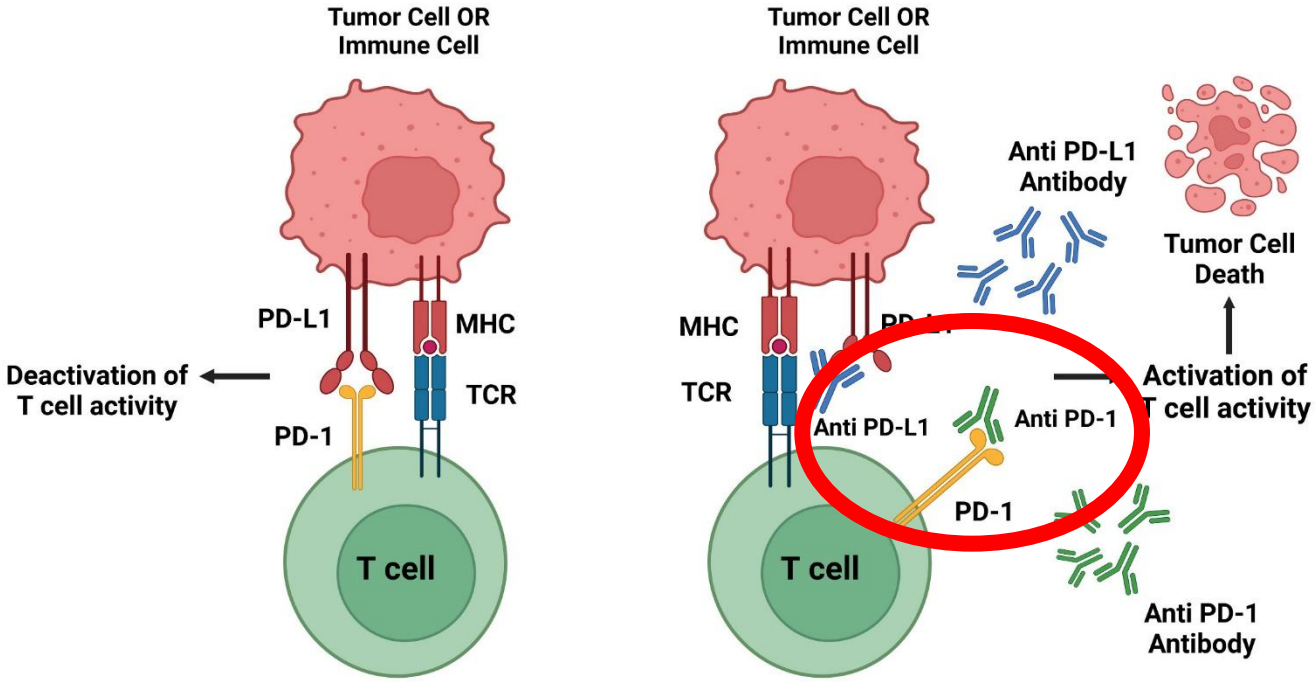
blood
Regular Article

IMMUNOBIOLOGY AND IMMUNOTHERAPY

Nivolumab treatment of relapsed/refractory Epstein-Barr virus–associated hemophagocytic lymphohistiocytosis in adults

Pengpeng Liu,* Xiangyu Pan,* Chong Chen, Ting Niu, Xiao Shuai, Jian Wang, Xuelan Chen, Jiazhuo Liu, Yong Guo, Liping Xie, Yu Wu, Yu Liu, and Ting Liu

Department of Hematology, Hematology Research Laboratory, State Key Laboratory of Biotherapy and Cancer Center, West China Hospital, Sichuan University, Chengdu, Sichuan, China



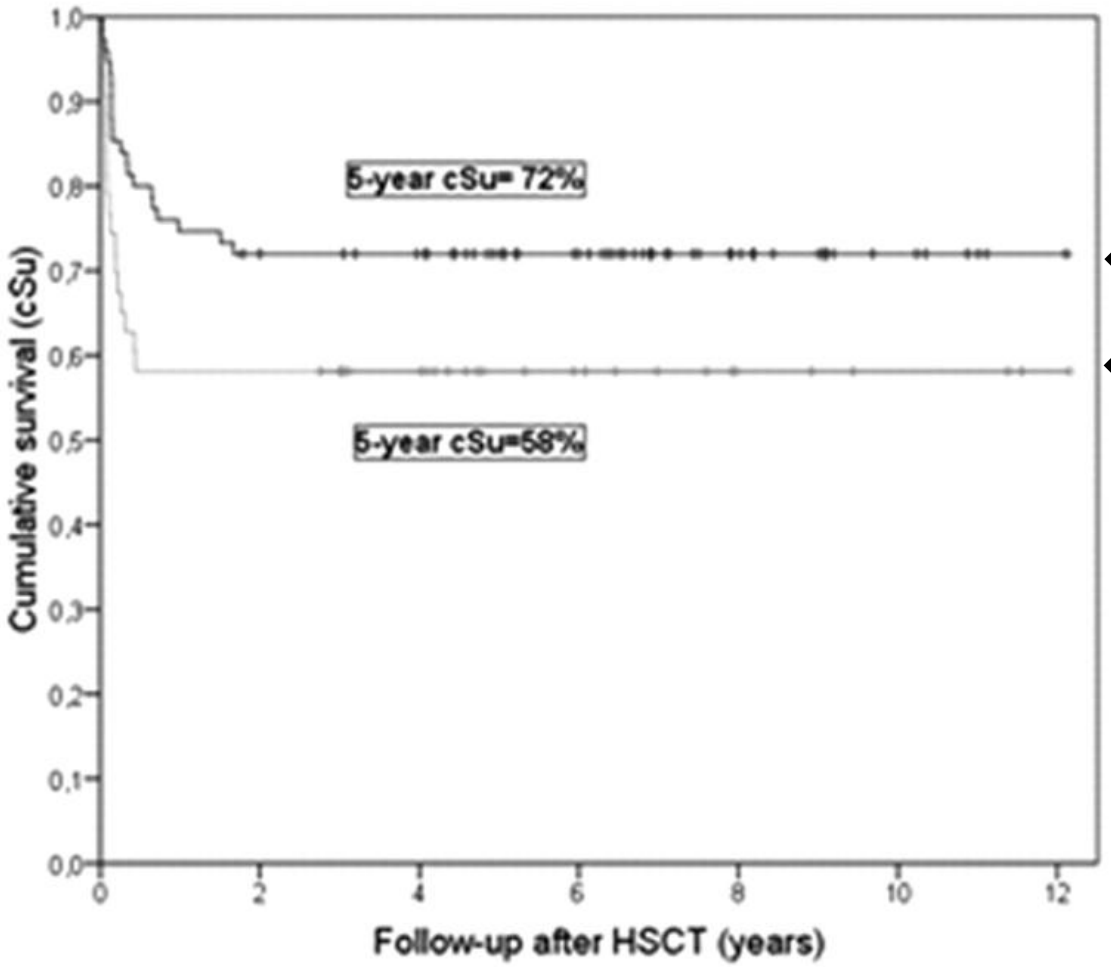
Ongoing CCHMC experience:

- 8 patients with EBV HLH, with EBV in T or NK cells, all treated with nivolumab
- 1 successfully proceeded to BMT
- 7 with sustained complete clinical responses (6 with full control of EBV)- not needing BMT
- 3 with known adverse effects of Nivolumab (myocarditis, pneumonitis) - treatable
- All 8 surviving

BMT for HLH

- After initial treatment/ control of HLH
- Essential for long-term cure of familial HLH and important for control of refractory HLH

Active HLH is associated with poor outcomes after HSCT



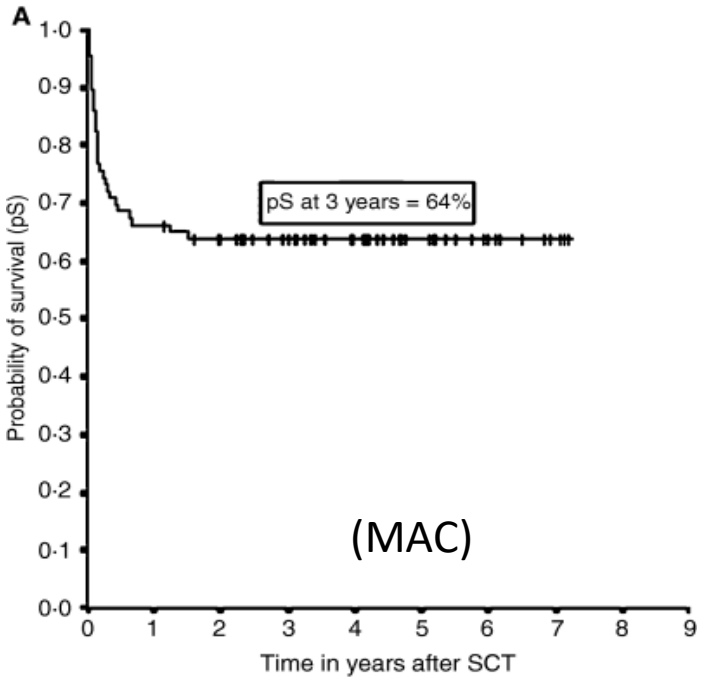
Non-active HLH

Active HLH

Helena Trottestam et al. Blood 2011;118:4577-4584

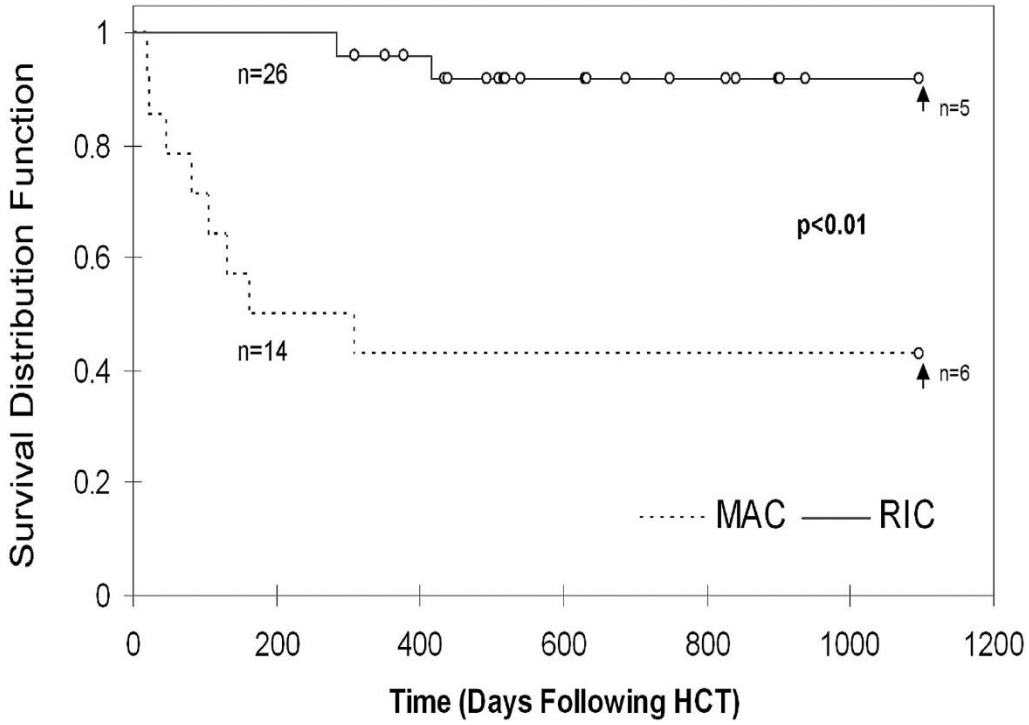
blood

Myeloablative prep regimens (MAC) are associated with excess mortality, compared to reduced intensity regimens (RIC) in patients with HLH



(MAC)

- Horne et al, 2005

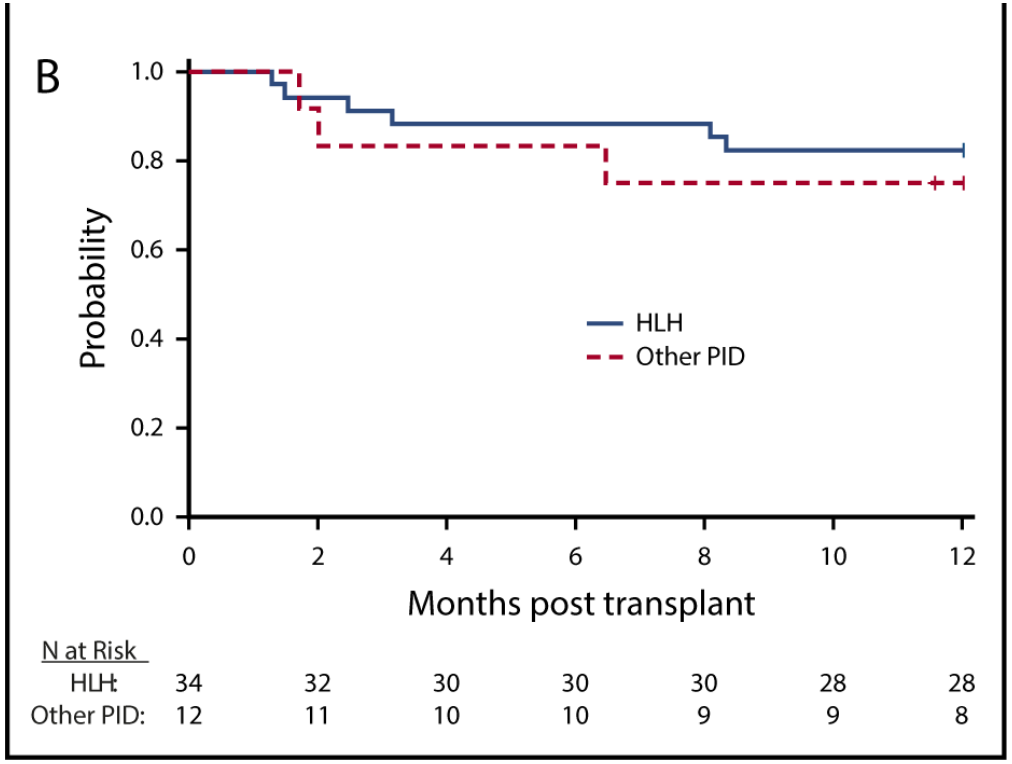


- Marsh 2010

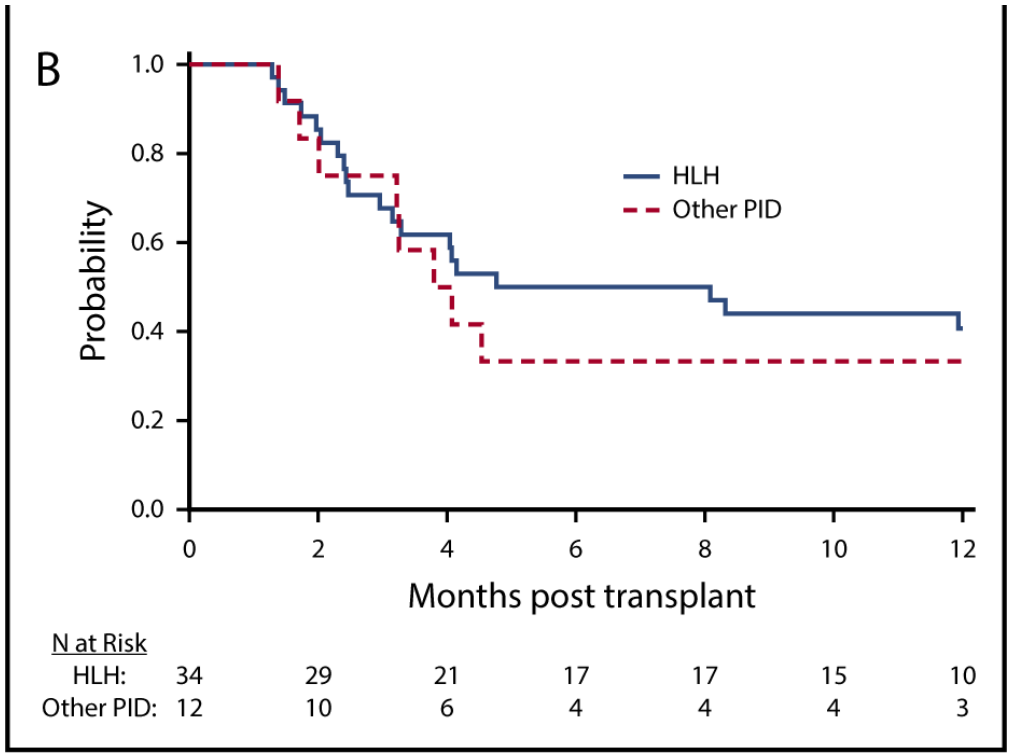
Excess:
VOD
IPS
All cause early mortality

RICHE study (RIC BMT): OS vs IFS

Overall survival (OS)



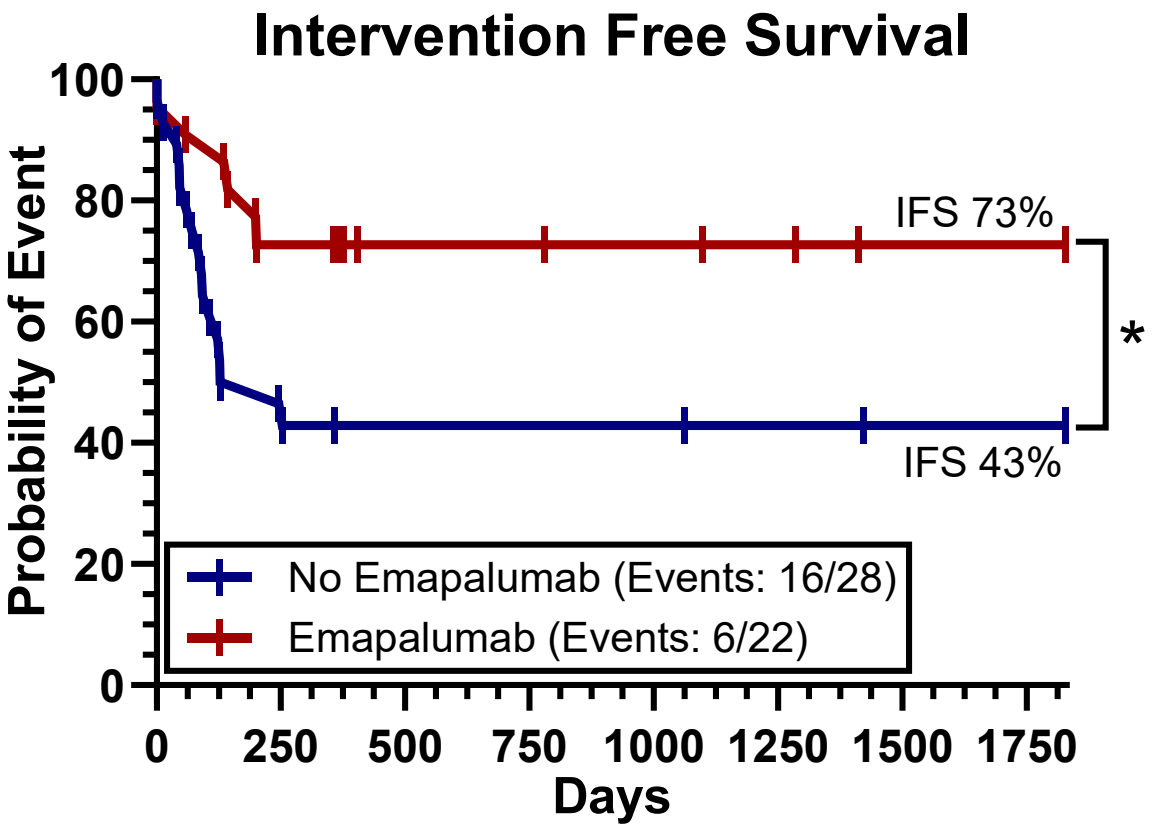
Intervention free survival (IFS)



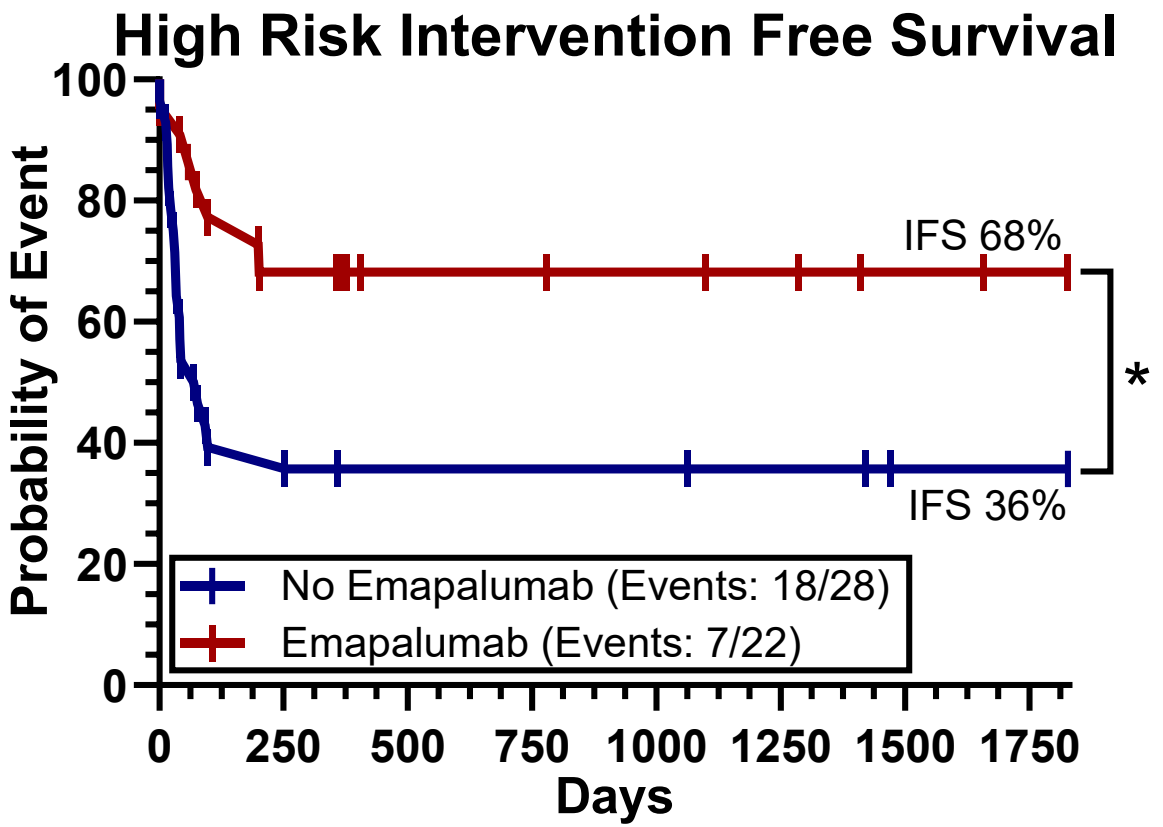
Intervention free survival= survival without second cellular product

Allen et al, 2018

Pre-BMT emapalumab treatment is associated with improved intervention free survival.



IFS: No DLI, CD34 boost, 2nd HSCT, or death



High risk IFS: no rapid taper of immunosuppression, DLI, 2nd HSCT, or death

* p-value <0.05

Verkamp et al, 2024

Challenges in treating HLH

1. **How to optimally utilize emapalumab**: dosing, monitoring, etc.
2. **Weighing the risks/ benefits of newer /emerging therapies:** depends on context?
3. **How to best combine treatments?** Multi-modal regimes to be developed
4. **EBV: Immune suppression vs. chemo VS immune potentiation:** TBD
5. **BMT:** how to optimize survival and graft function

The INTO-HLH Registry

Insight into the **N**atural History and **T**reatment **O**utcomes of **H**emophagocytic **L**ymphohistiocytosis (**HLH**)

www.hlhregistry.org

INTO HLH

Conclusions

- HLH is a multifaceted clinical syndrome: familial inborn error of immune regulation; hyperinflammatory syndrome complicating infection, cancer, rheumatologic diagnoses, etc.
- Diagnoses has improved, but remains challenging
- Therapy for HLH is evolving; strategies to emerge for OHI+ malignancies