Hemophagocytic lymphohistiocytosis

– a differential diagnostic prangster

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Danish rep in ped. HLH

DIPS, Korsør October 2016

Scope of today

Recognize the HLH child when you see it, it needs your action

- Definition of classic HLH
- Diagnosis
- Disease classification
- Handling and initial treatment
- Future aspects

HLH?

- Clinically mimics most often severe uncontrolled sepsis like infection
- Lethal disease characterized by “cytokine storm” due to absent cytotoxicity in T and NK-cells
- Rare disease with very few scientific studies
- Spectrum of diseases overlapping from primary lethal HLH to secundary HLH-like disease
- Diagnosis difficult but manageable

Primary HLH - pathophysiology

- Normal response to infections by release of cytotoxic granules from NK-cells and activated CD8+ T-cells to infected cell is defect

- Due to ongoing tissue damage more cytokines are released attracting more ineffective immunoactive cells further producing pro-inflammatory cytokines and chemokines (IFNγ, IL1β, IL6, IL12, IL18 and TNF-α)

- Activated macrophages produce Ferritin and cytokine storm. The products are thought to explain cytopenia, fever, hypertriglyceridemia and low fibrinogen.

Ellen Brisse et al , Br J Haematology, 2016, 174

Case - 5 week old boy

- 2nd child of consanguinous arab parents
- Day 1: admitted after 2 days of high fever
- Septic, meningitis?, bioch DIC
- Platelets 50; Neutrophiles 0.6; CRP 50
- Day 2: Platelets 12, Bilirubin 77, ascites, Ferritin 8.800.
- Bone marrow biopsy shows hemophagocytosis
- Day 3 multi organ failure, kept on ventilator
- Dexamethason and CyA

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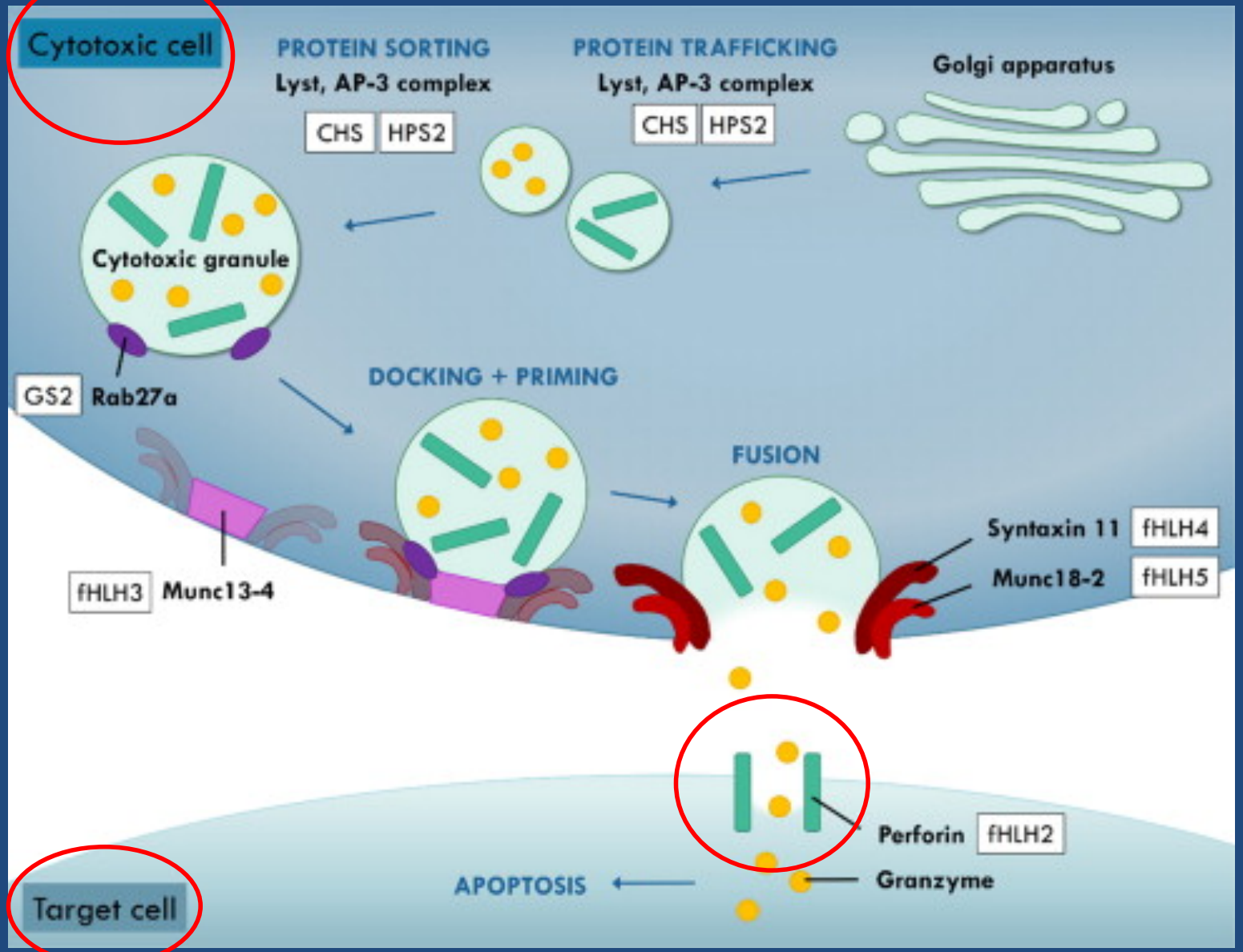
- Day 4-5 lactate 15-36
- Etopofos, HLH 2004
- Day 6 clinically stable
- Day 90 HSCT, Bu-Flud, UCB
- Today: 3 years from SCT, no GvHD, neurologic seq (epilepsia)
- Dysfunctional perforin
- Compound heterozygous mutation in PRF1-gene (FHL2)

Primary HLH: A number of conditions due to defects in perforin dependent cytotoxicity



Ellen Brisse et al , Cytokine & Growth Factor Reviews, 2014

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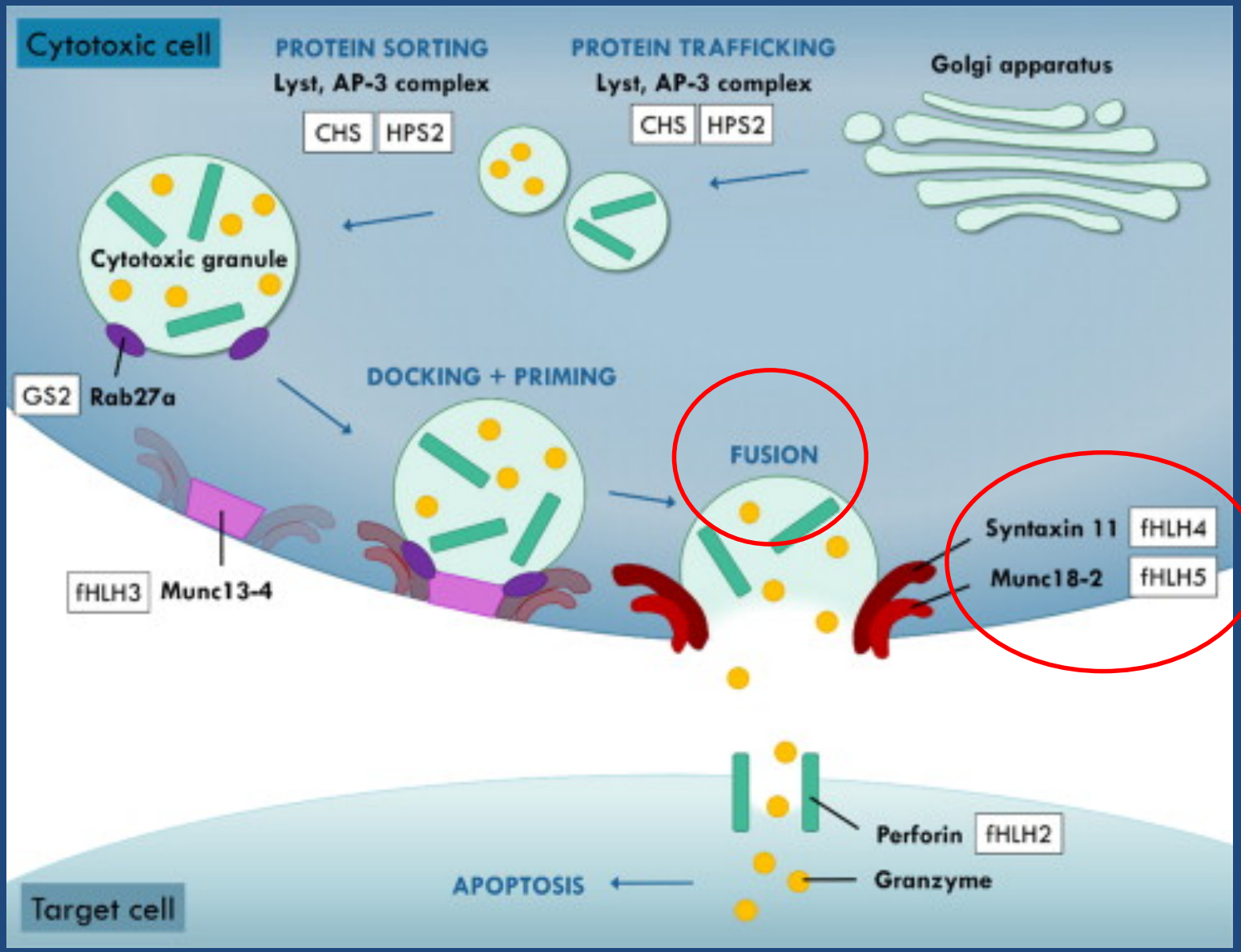

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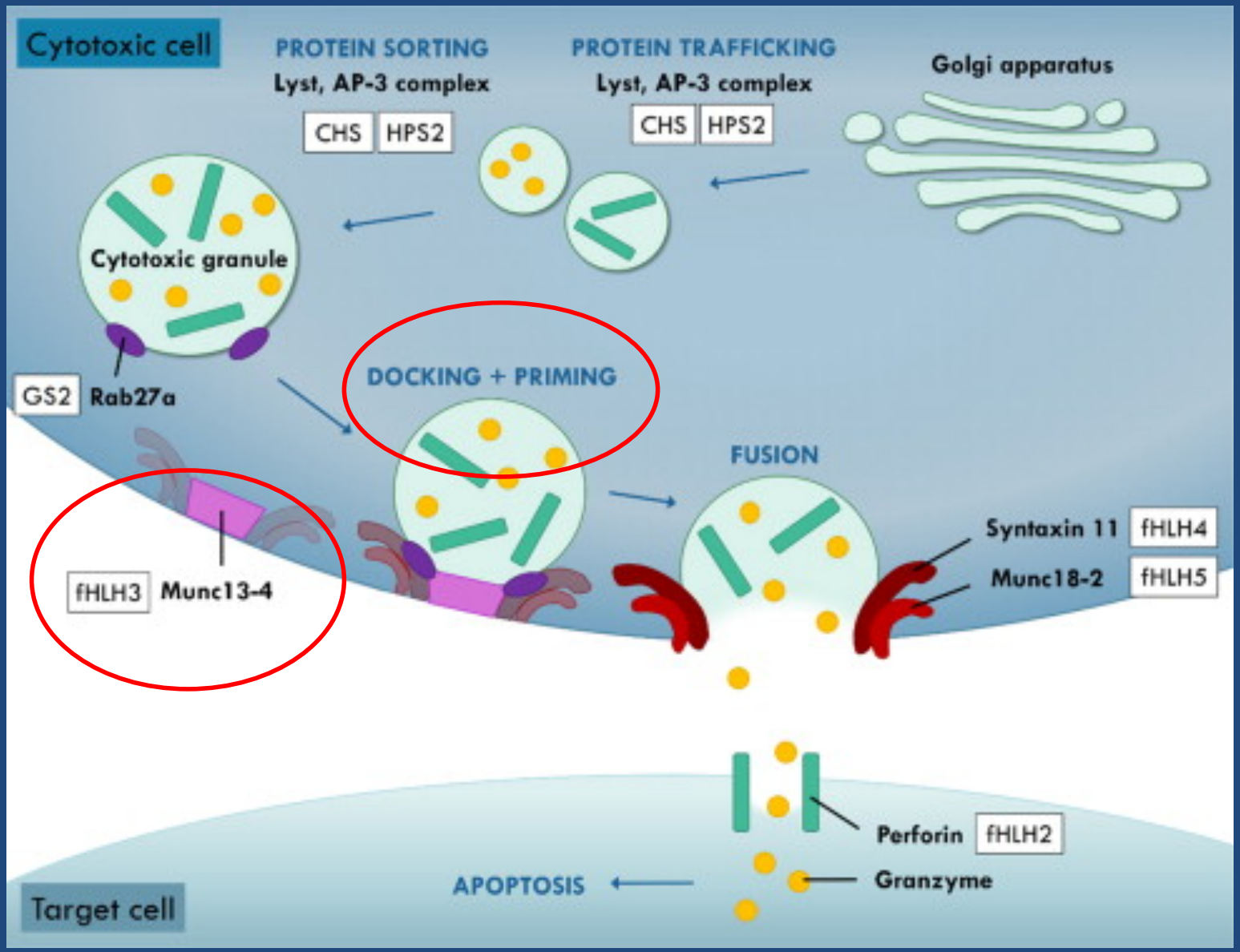

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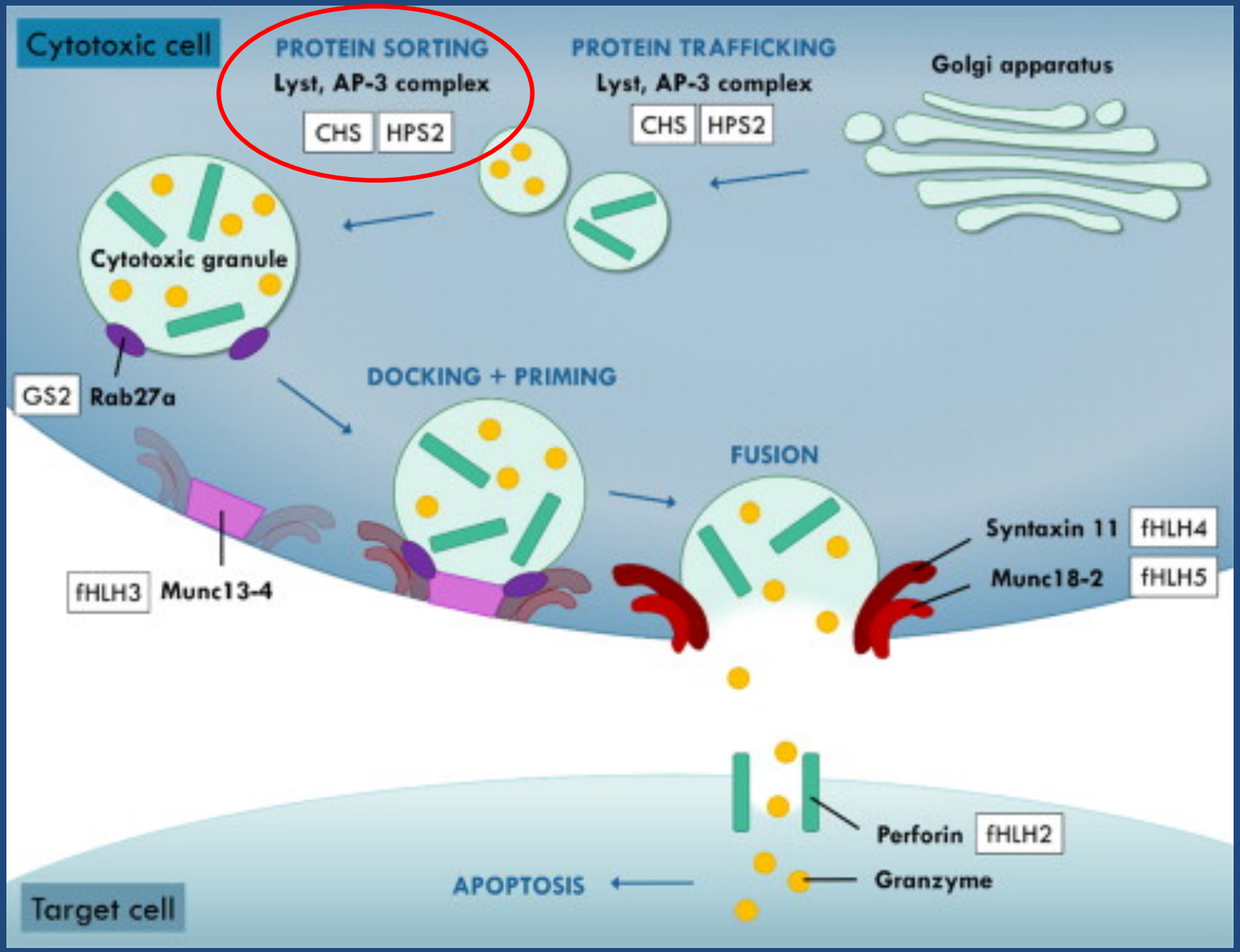


Ellen Brisse et al , Cytokine & Growth Factor Reviews, 2014

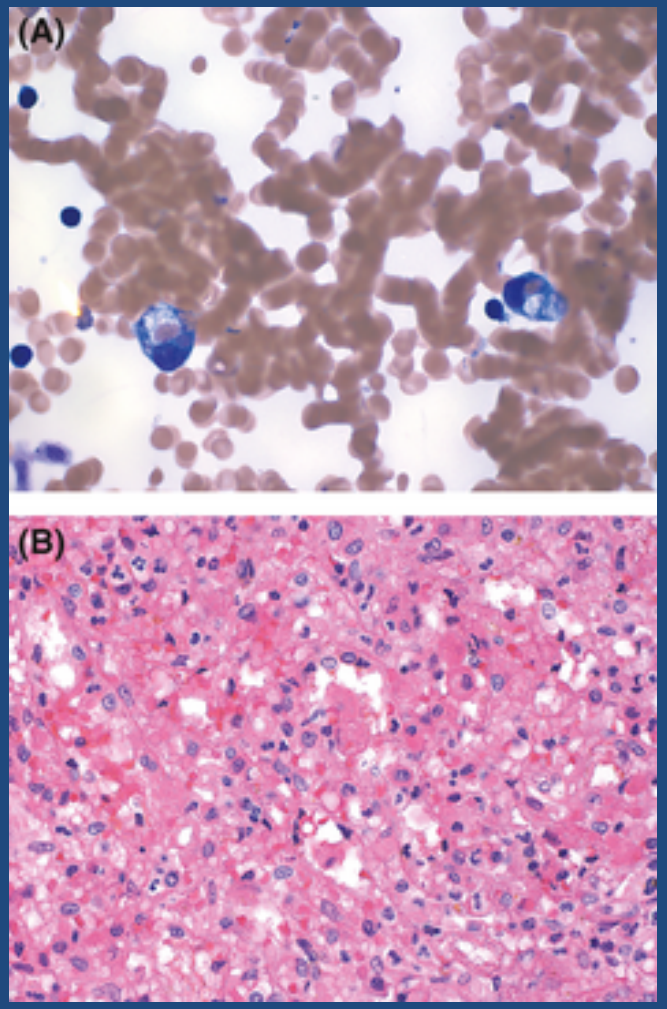
Known mutations in primary HLH

Gene	Location	Disease	Defect
PRF1	10q21-22	FHL2	Perforin
UNC13D	17q25	FHL3	Munc13-4
STX11	6q24	FHL4	Syntaxin-11
STXBP2	19p13	FHL5	Munc 18-2
Unknown	9q21.3-22	FHL1	?
LYST	1q42.1-42.2	Chediak-Higashi syndrome	LYST
RAB27A	15q21	Griscelli syndrome type 2	Rab27a
AP3B1	5q14.1	Hermansky-Pudlak type 2	β3A of AP3
SH2D1A	Xq24-26	XLP1	SAP
XIAP/BIRC4	Xq25	XLP2/X-linked HLH	XIAP

Defect granulation involved in albinism in Pakistani girl who later developed EBV-related HLH (Griscelli)

HLH, diagnostic criteria

- Known familial genetic defect or
- 5/8 clinical or biochemical criteria:
  - Fever
  - Splenomegaly
  - Cytopenia > 1 cell line
  - Raised triglycerids/ low fibrinogen
  - Ferritin > 500 microg/l
  - sCD25 > 2400 U/ml
  - Reduced or absent cytotoxicity
  - Hemophagocytosis



Classification

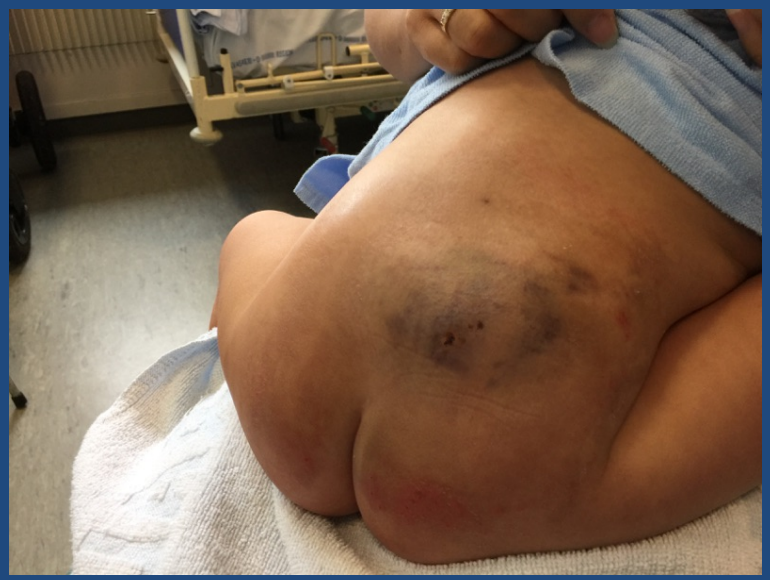
- **Primary**
  - Familial (FHL1-5)
  - X-linked lymphoproliferative disease (boys)
  - Other inherited diseases with albinism (ie Griscelli)
- **Secundary HLH**
  - Malignancies (ie NHL, AML)
  - Infections (ie EBV, Infl A+B, mycoplasma, Leishmania)
  - Macrophage activating syndrome (MAS)
    - Rheumatological diseases (ie JIA, Kawasaki)

Clinical approach I

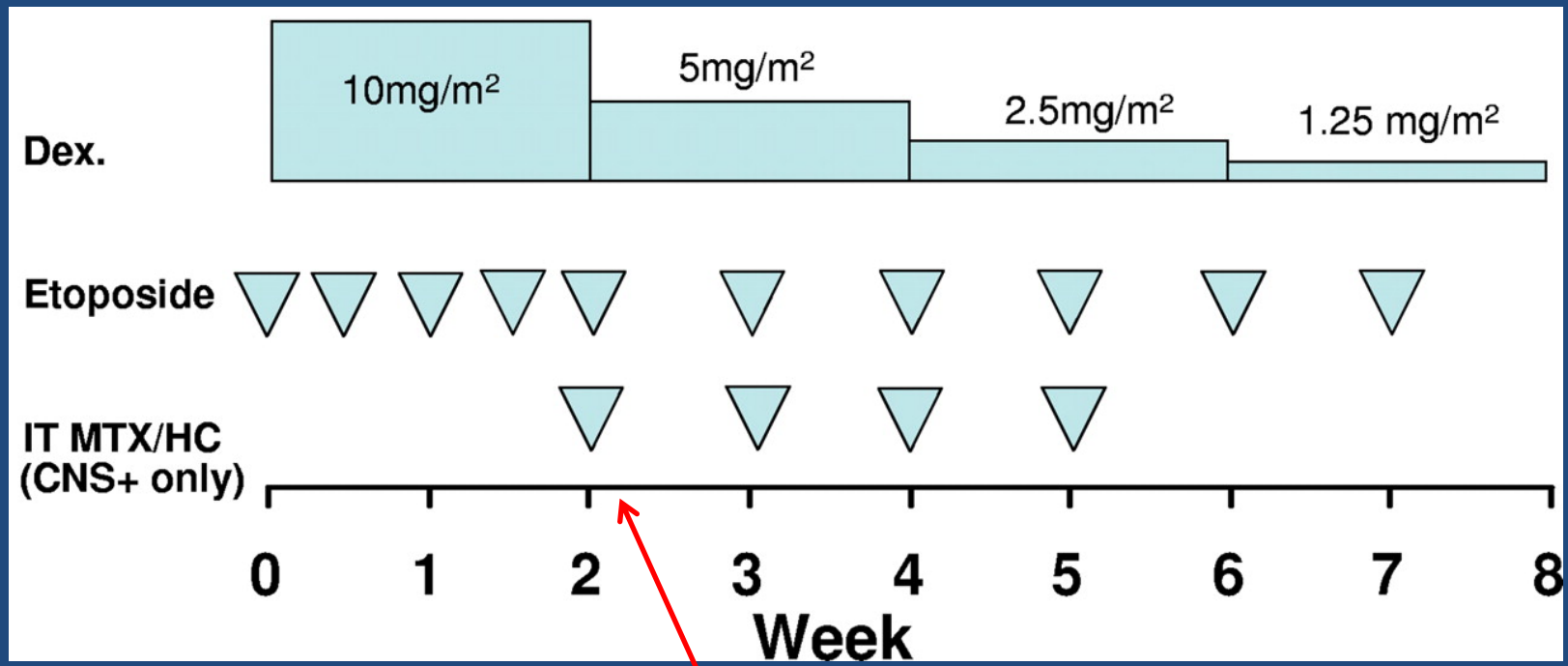
- Suspect the diasease!!!
- Timing is everything
- Any age, not only < 1 year
- Family history
- Sepsis like, EBV-like, flu-like, severe
  - Fever, unresponsive to treatment
  - Thrombocytopenia
  - Ferritin!
  - CNS
- Follow the biochemistry daily
  - Hb, platelets, WBC, ferritin, D-Dimer, Triglycerids, Fibrinogen, CRP
- Extensive microbiology incl EBV-PCR

Clinical approach II

- Very challenging supportive care
- Timing is everything
- Broad spectrum ABs
- Refer to tertiar centre
  - Bone marrow evaluation, LBP, MRI
  - Perforin/Granzyme/sIL2r
  - Functional and genetic analyses
- Start treatment (HLH 2004)
- SCT in CR or PR

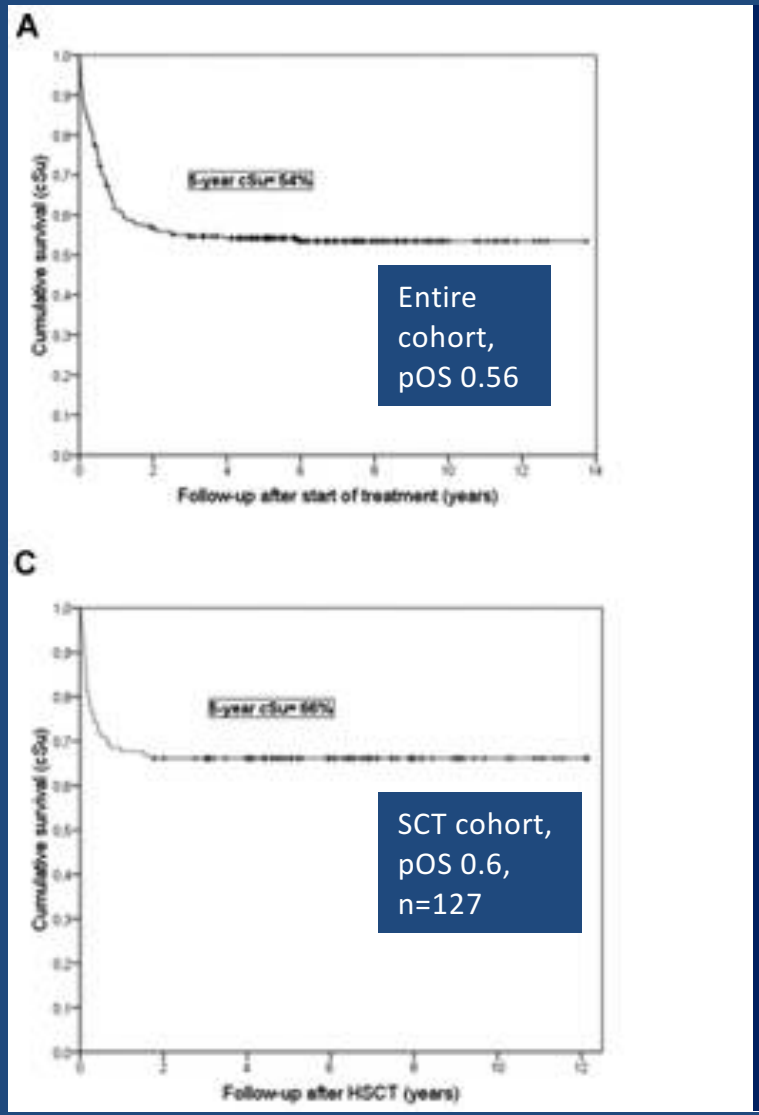


HLH 2004 protocol, induction



After 2 weeks: Initiate Cyclosporin A

HLH 94-protocol, outcome

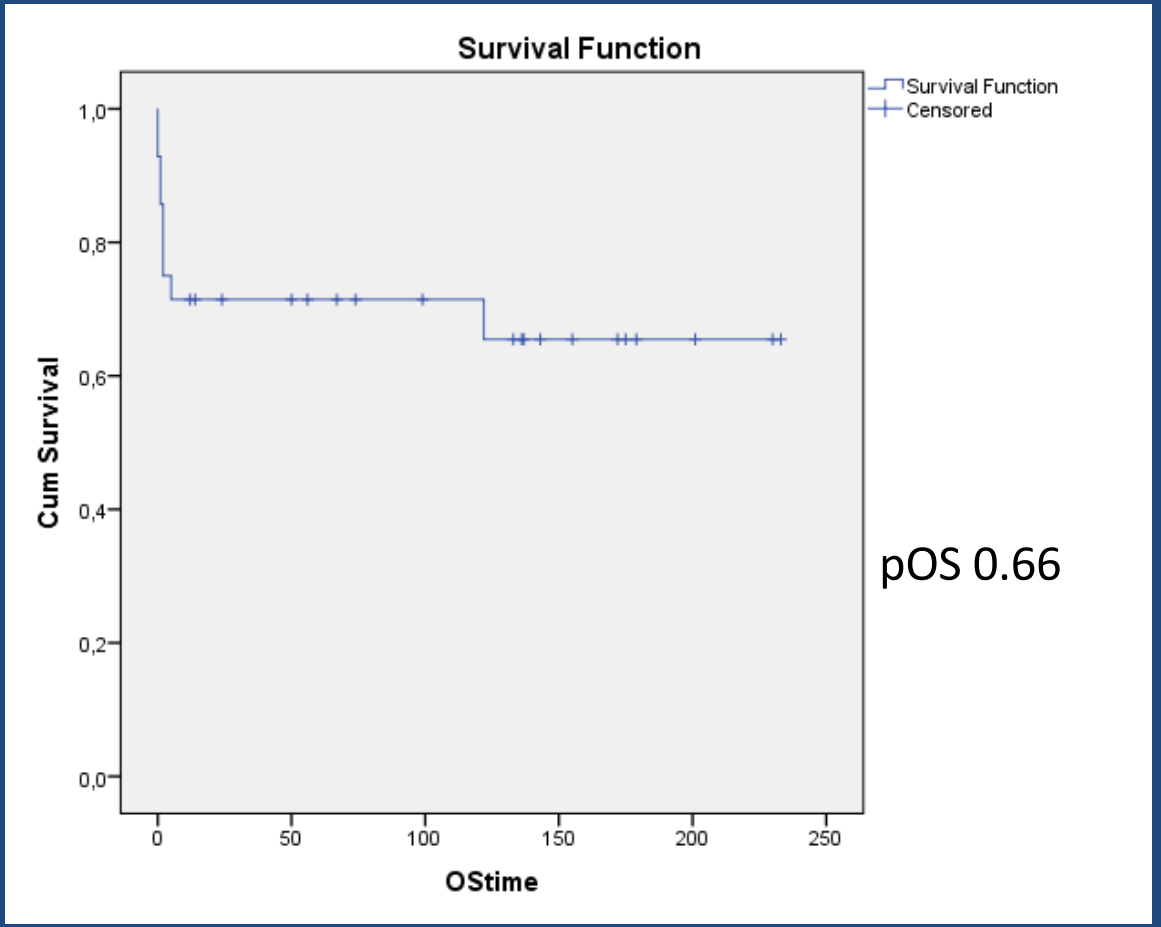


- N= 249 included
- 29% died before SCT
- 5-y pOS 0.56

Trottestam et al, Blood 2011

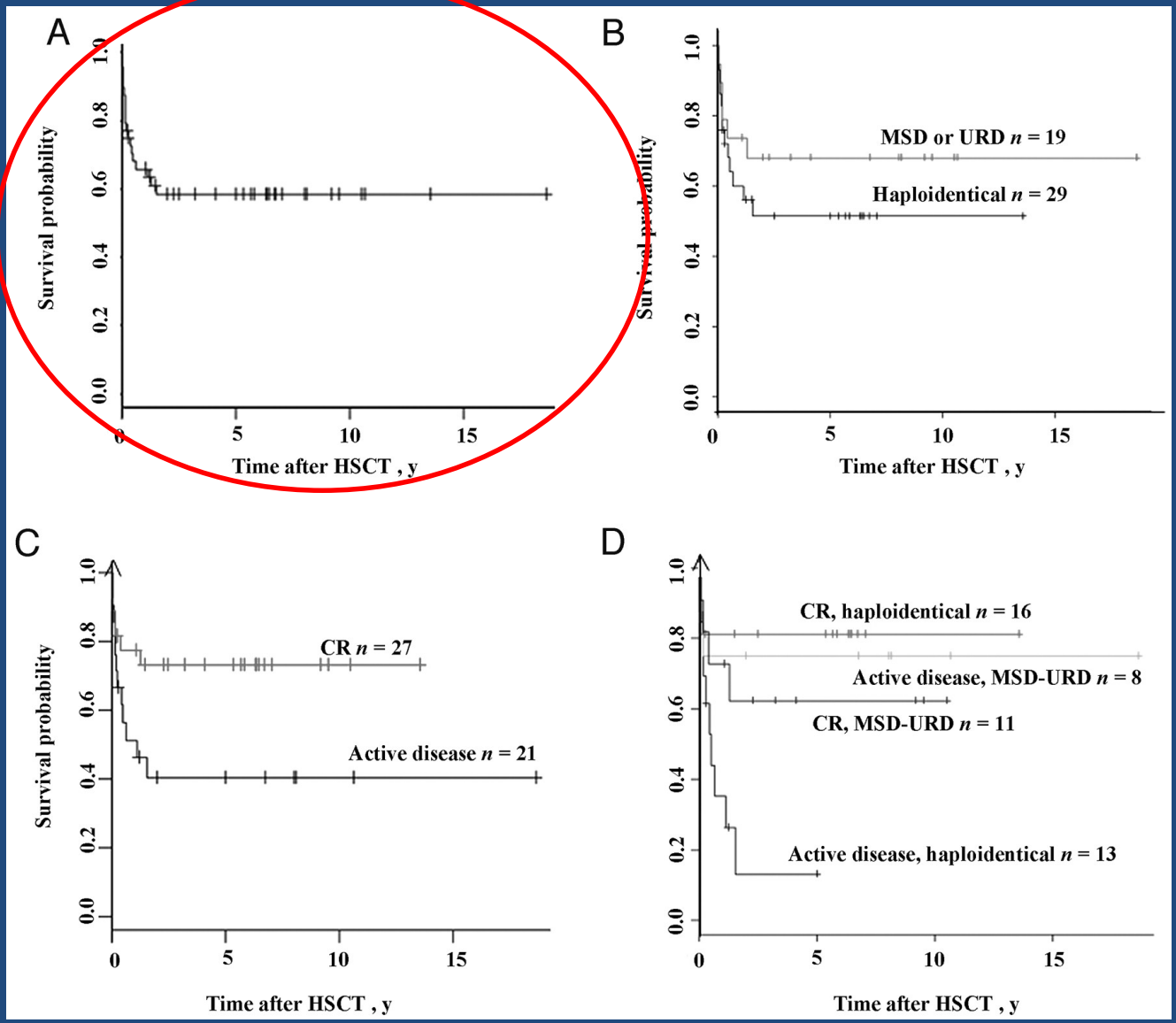
Survival post SCT – DK per 06/2016

- 28 patients
- 68% boys
- 5 dead (TRM)
- 16 HLH
- 3 Chediak-Higashi
- 8 XLP
- 1 Griscelli



pOS 0.66

HLH survival post SCT



Marie Ouachée-Chardin et al. Pediatrics 2006

Case II: 15 months old boy

- Consanguinous parents
- Recurrent fever now 40. Pneumonia? Sepsis?
- Hb 4.5, Neutrophiles 2.6; Platelets 90
- Ferritin 14.200; Triglycerids 2.54, Fibrinogen 16.4, LDH 6450, D-dimer 6.9
- CRP 50
- FHL ?????

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- Bone marrow biopsy: hemophagocytosis
- Lymphocyte subsets: CD3 1.5 (ratio 3.2) , CD19 0.63, NK 0.048
- Perforin/Granzyme normal
- Dexametason 10 mg/m2, immediate improvement
- Normal degranulation assays
- Tapered dexa, normalized all biochemistry in 2 weeks

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HLH – future aspects

- National S.O.P Oct 2016
- Danish adult-pediatric network
  - Primary vs secondary HLH?
- International HLH registry
- Targeted anti-inflammatory treatment (anti-IFNγ), Jordan M et al, ASH 2015
- RIC-SCTs
- Neonatal screening
- Individualized treatment
- Gene therapy

HLH – collaborative studies needed

Patientinformation vedrørende international registrering af patientdata samt funktionelle og genetiske studier af immunsystemet i familier med mistænkt hæmofagocyterende lymfohistiocytose (HLH).

Med denne patientinformation vil vi gerne anmode om din/dit barns deltagelse i

- registrering af patientdata i internationalt HLH-register i Hannover
- en videnskabelig undersøgelse af immunsystemets funktion og eventuelle nedarvede sygdomsfremkaldende forandringer i arvematerialet (DNA).


IN CASE OF FIRE -
BREAK GLASS
Dexa
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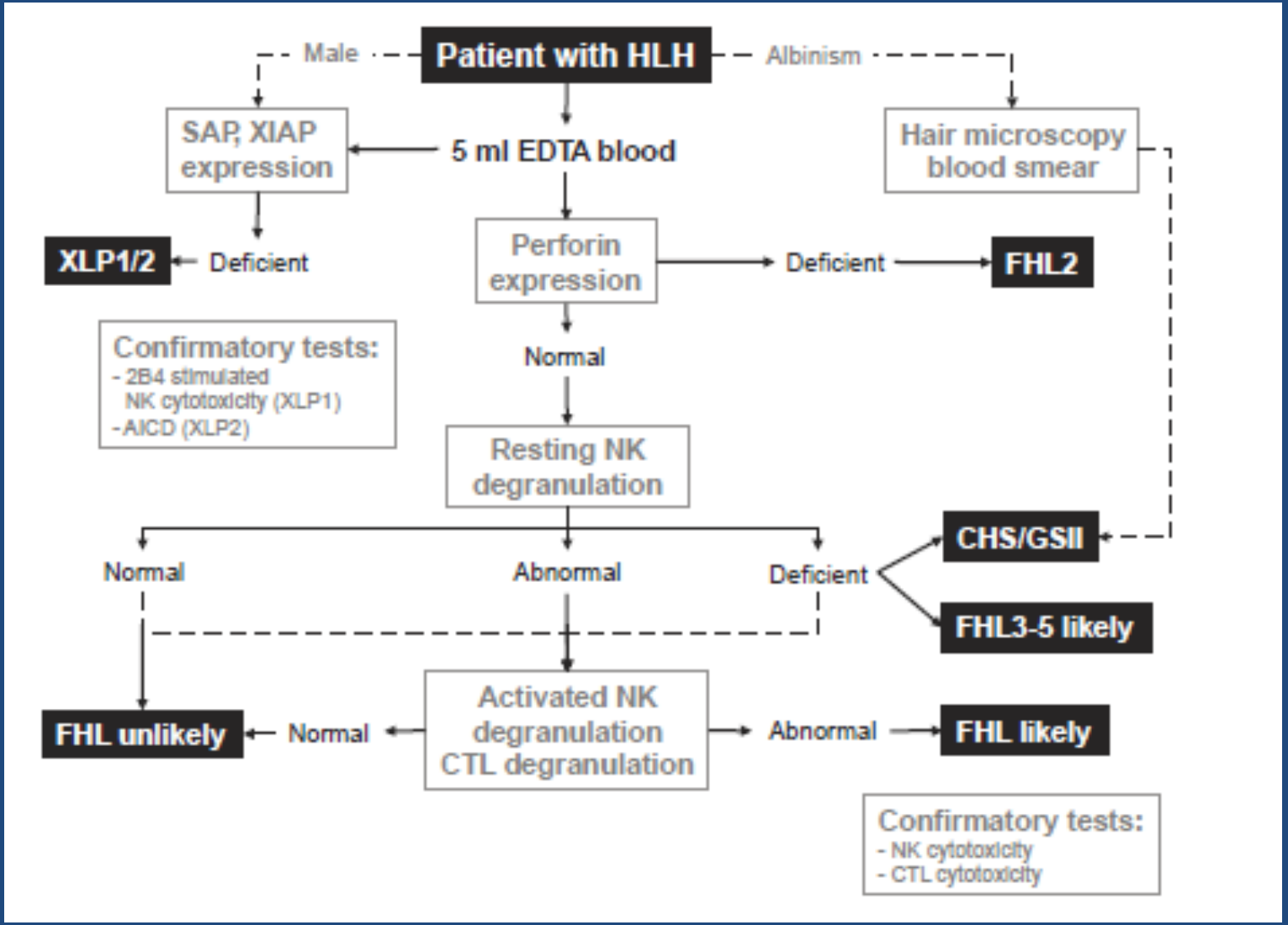
ESID registry for HLH

Inclusion criteria	• **Patients with primary immunodeficiencies predisposing to HLH (all ages)** • **Patients with active HLH that is not secondary to underlying conditions such as rheumatological disease, malignancy, metabolic disease or Leishmania infection (patients under 18 years of age) (mostly "infection-only" HLH)** • **Patients (or their legal representatives) having provided informed consent**
exclusion criteria	• Patients with malignancy • Patients with rheumatological/autoinflammatory/autoimmune disease • Patients with metabolic diseases • Patients with Leishmania infection • No written consent available
Data Collected	Initial registration: • Demographic characteristics • Form of HLH (preliminary classification) • Trigger of HLH • HLH clinical criteria • Diagnostic assays performed • CNS disease • HLH directed treatment Follow-up registration (1 year later) • HSCT and time to HSCT • Chimerism • Outcome • Form of HLH (final classification) • Disease-causing mutation • Patient qualification for treatment study

Suggested algorithm



K Lehmberg, S.Ehl, Br J Haem 2013

Cytokin storm leading to clinical HLH