HLH: NAVIGATING TO SAFE HARBOR THROUGH THE CYTOKINE STORM

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Disclosure Statement

- I have no industry relationships to disclose
- I will discuss off-label use of medications

- Case studies have no individually identifiable patient information; all names and pictures are for illustrative purposes only

Learning Outcomes

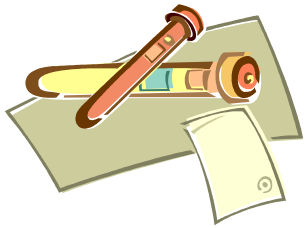
- Able to discuss diagnostic criteria for HLH
- Able to explain the rationale for use of conventional and new agents to treat HLH

Case Study: Rickon

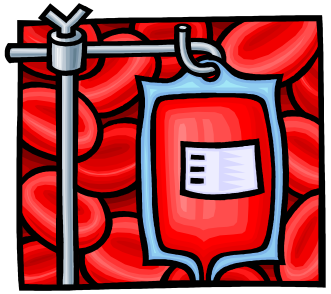
- 20 month old with 2 week history of high fever
- Diagnosed with ear infection and treated with oral antibiotic
- But persistent high fever to 40°C for 4 days

Initial Presentation

- Exam: Irritable, palpable spleen
- CBC: Hgb 6.5 g/dL, PLT 119K, ANC 180

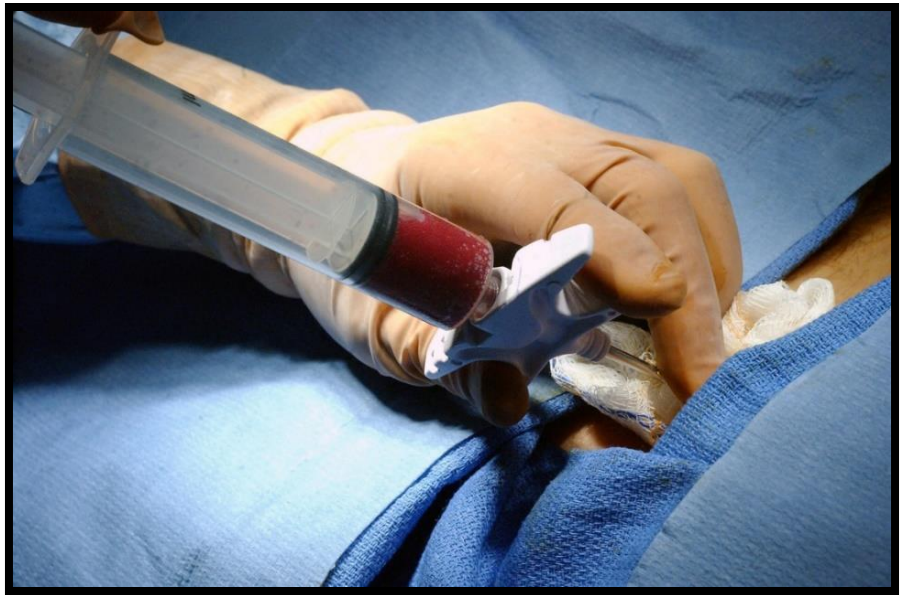


- Admitted for febrile neutropenia
- Transfused with red blood cells



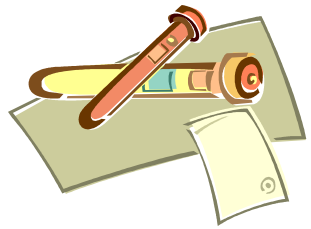
Workup

- Bone marrow aspirate to r/o leukemia: negative/unremarkable
- Infectious work-up: negative



Clinical Changes

- Day 5: New onset jaundice and hepatomegaly
- Labs: Hgb 6 g/dL, PLT 21K, ANC 400 (↓↓)
  Bilirubin 2.3 (↑), ALT 1507, LDH 5264 (↑↑)
  Ferritin 16,230 (↑↑)
  Fibrinogen 126 (↓)



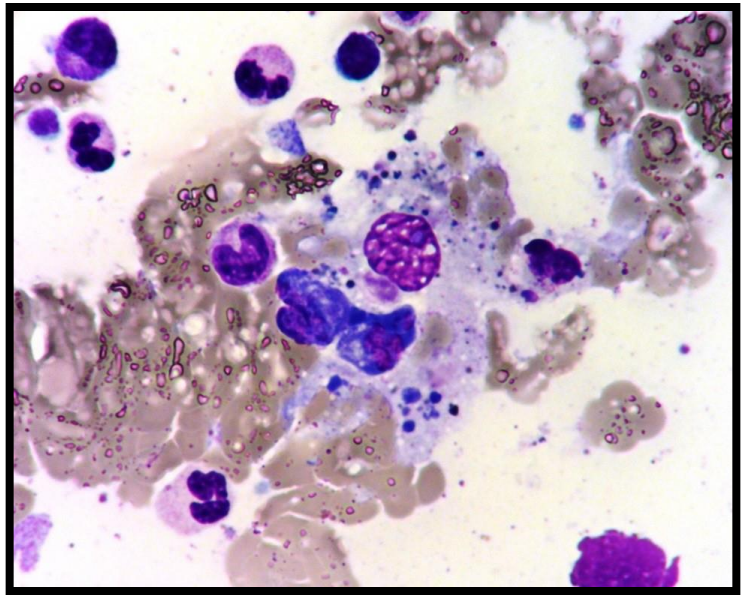
- Repeat bone marrow shows hemophagocytosis

Diagnosis and Treatment

- Hemophagocytic lymphohistiocytosis (HLH)
- HLH-directed treatment with aggressive supportive care

- Day 14: Death from multi-organ failure

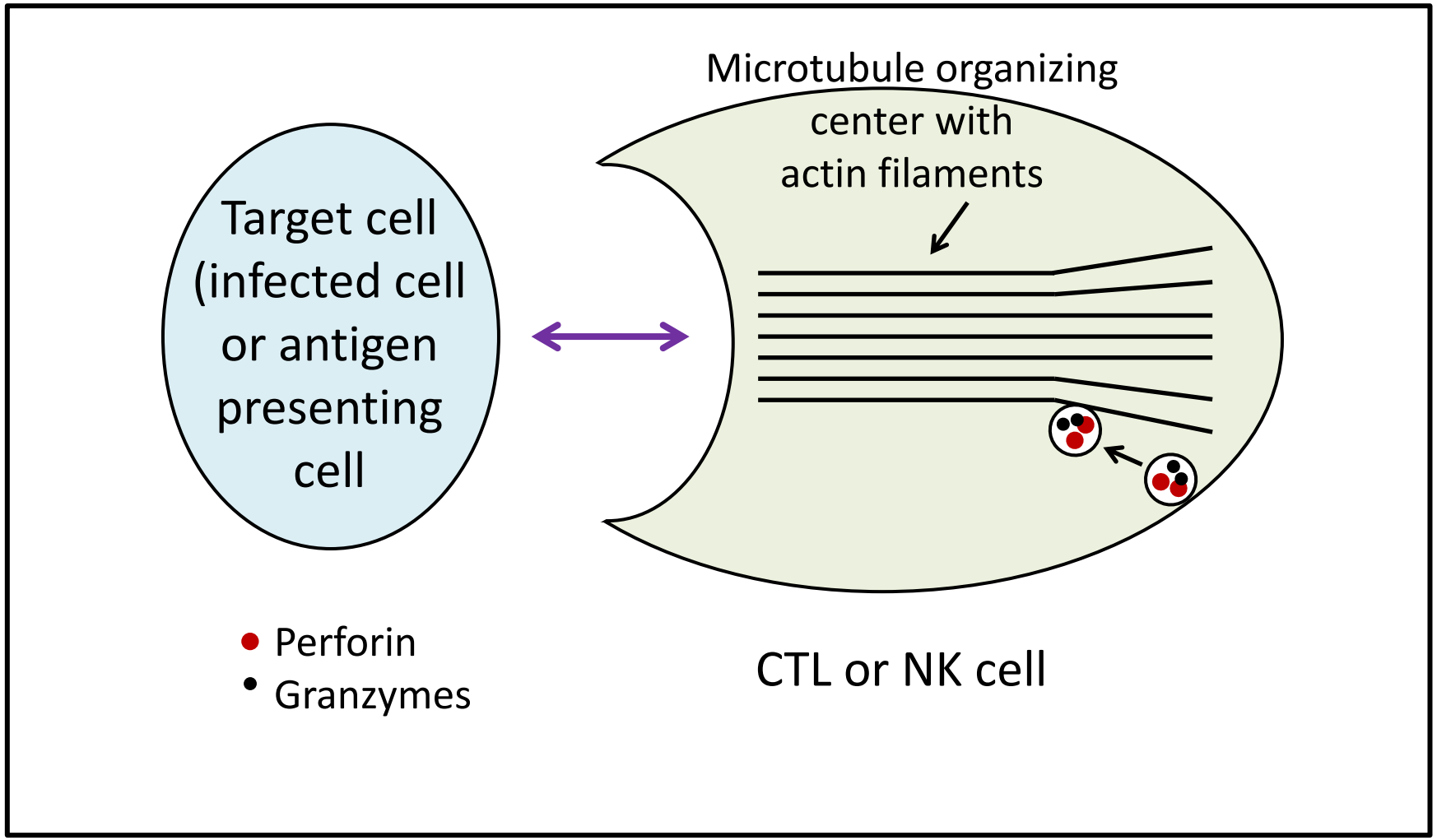
Pathophysiology



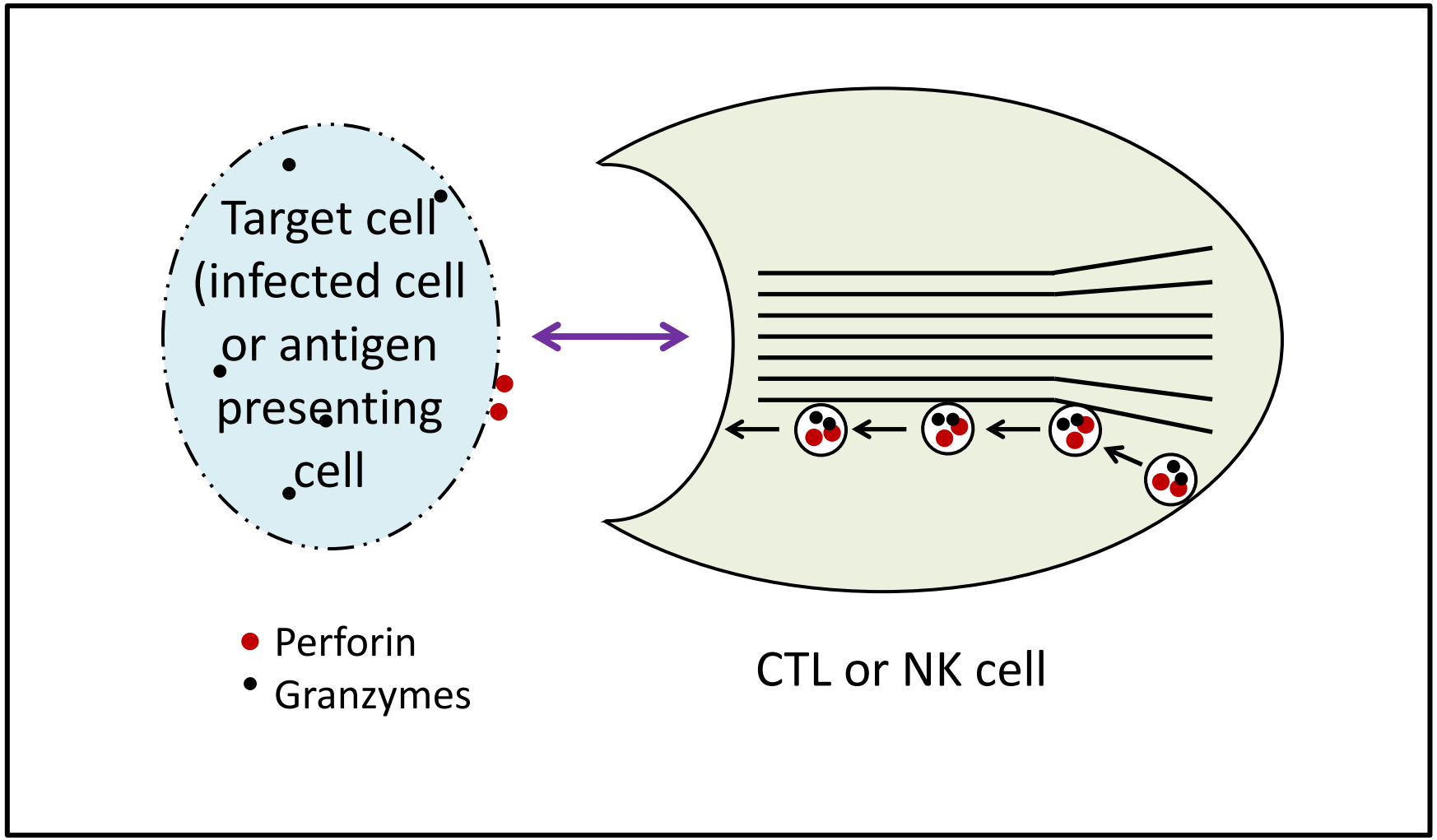
What is HLH?

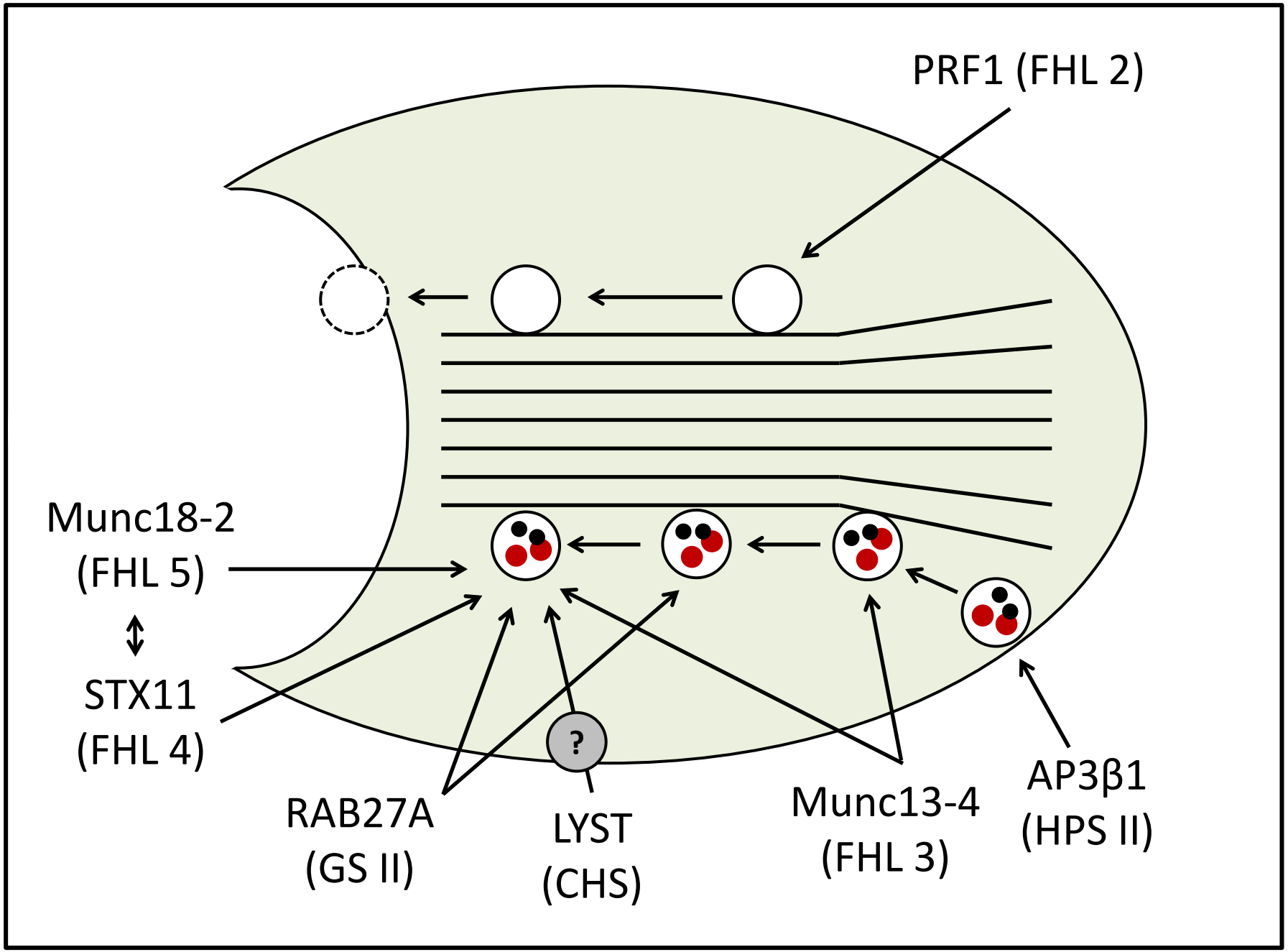
- Rare, life-threatening disorder of immune system
- Uncontrolled hyper-inflammatory response
- “Cytokine storm” syndrome

Contact Dependent Cytotoxicity

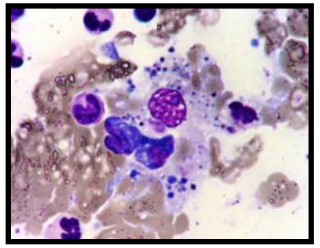


Contact Dependent Cytotoxicity

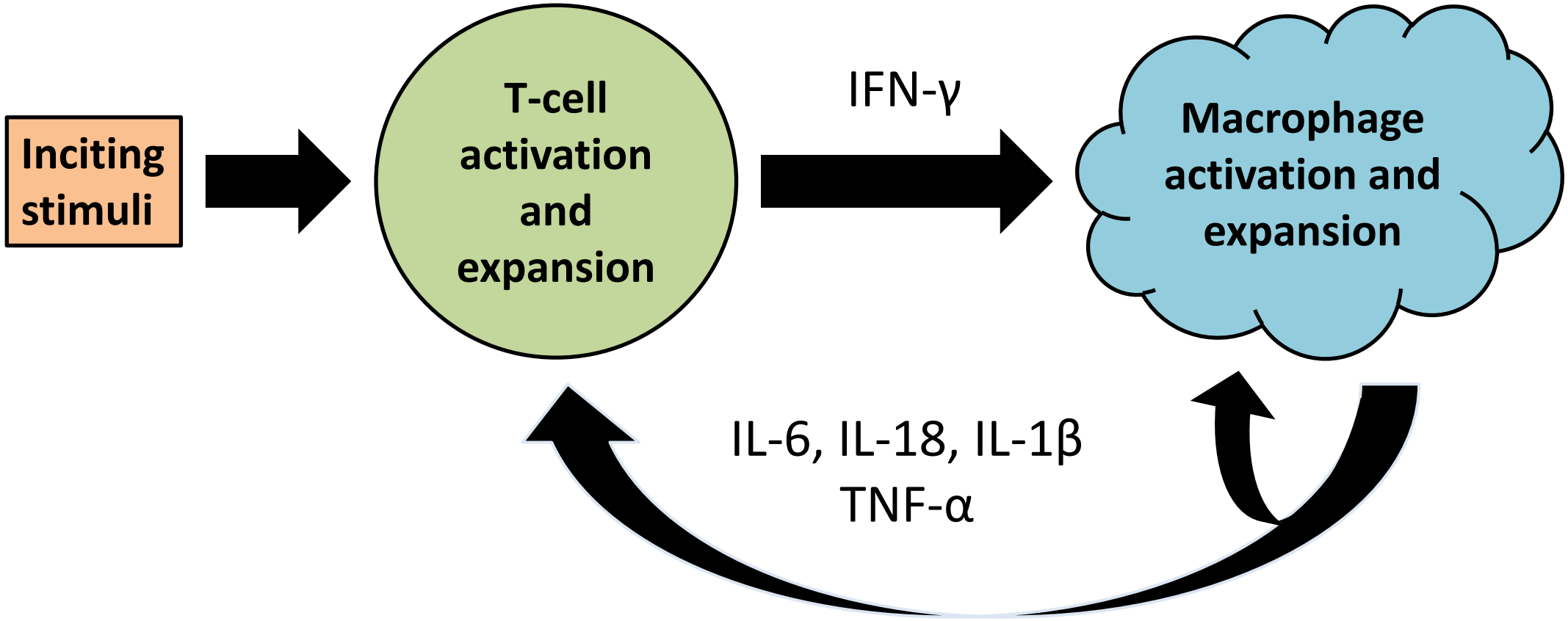


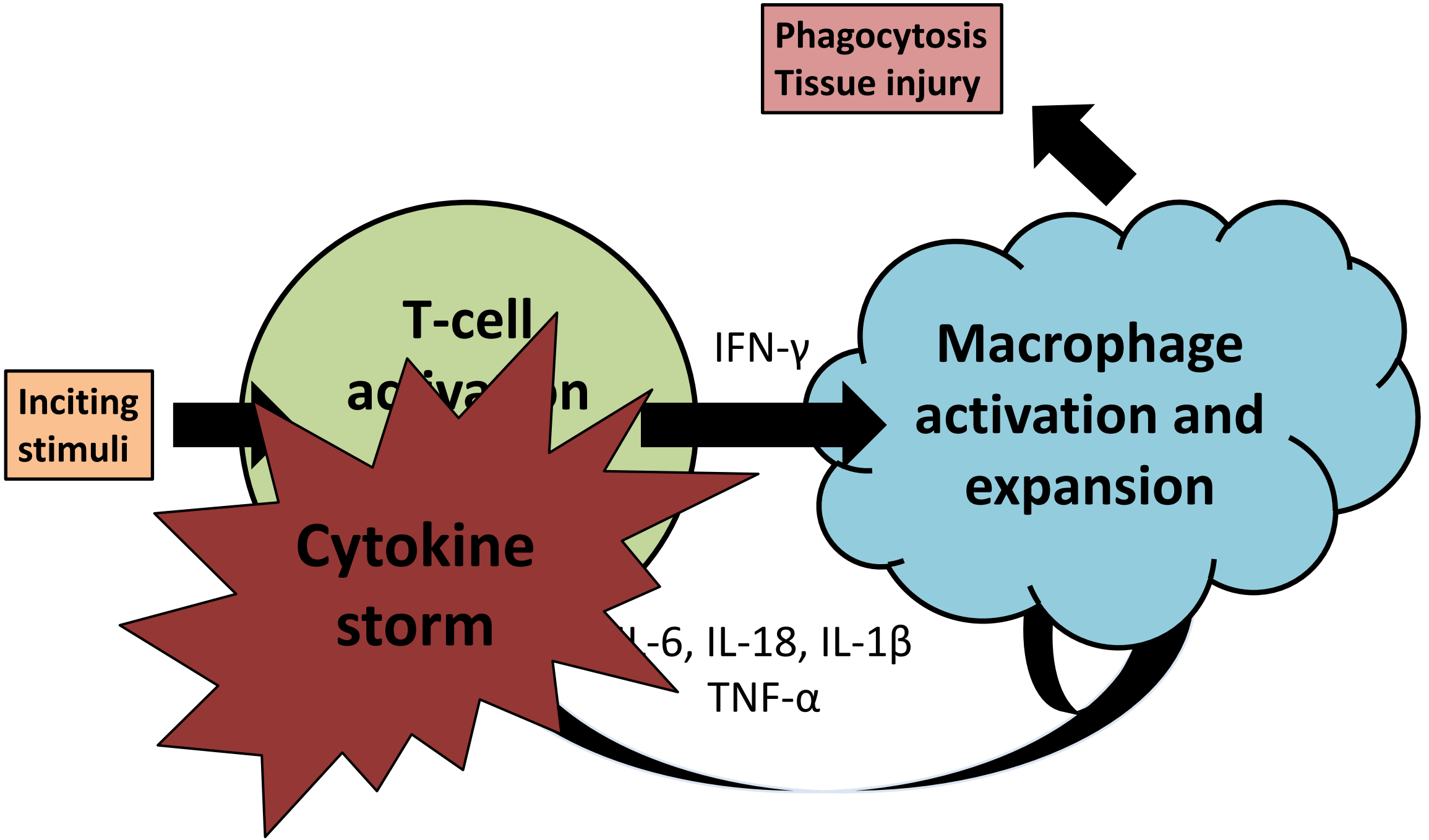

PRF1 (FHL 2)
Munc18-2
(FHL 5)
STX11
(FHL 4)
?
RAB27A
(GS II)
LYST
(CHS)
Munc13-4
(FHL 3)
AP3β1
(HPS II)

Macrophages (Histiocytes)

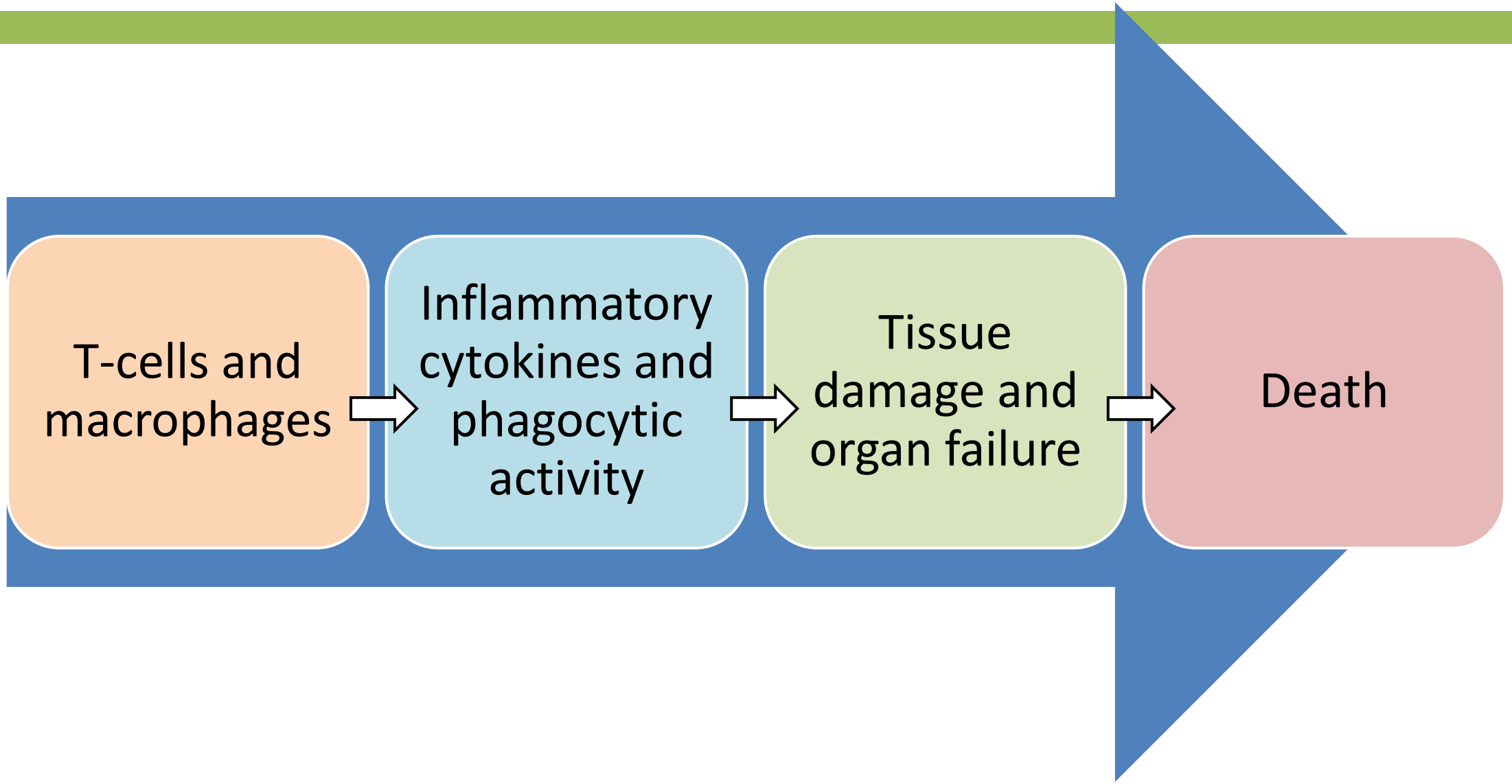


- Antigen presentation
  - Initiate immune response by presenting antigens of digested cells to helper T-cells
- Secretory
  - Cytokines; regulate immune response
- Phagocytosis
  - Remove dead cells/cellular debris
  - Hemophagocytosis: remove blood cells in peripheral blood, bone marrow and tissue


Inciting stimuli
T-cell activation and expansion
IFN-γ
Macrophage activation and expansion
IL-6, IL-18, IL-1β
TNF-α


Phagocytosis
Tissue injury
Inciting stimuli
T-cell
IFN-γ
Macrophage activation and expansion
Cytokine storm
-6, IL-18, IL-1β
TNF-α

What is HLH?


T-cells and macrophages
Inflammatory cytokines and phagocytic activity
Tissue damage and organ failure
Death

Primary / Familial HLH

- Autosomal recessive
- 5 types (FHL 1-5)
- 4 known mutations (FHL 2-5)
- 70% present in infancy
- Often triggered by infection

HLH Predisposition

- Immune deficiency syndromes

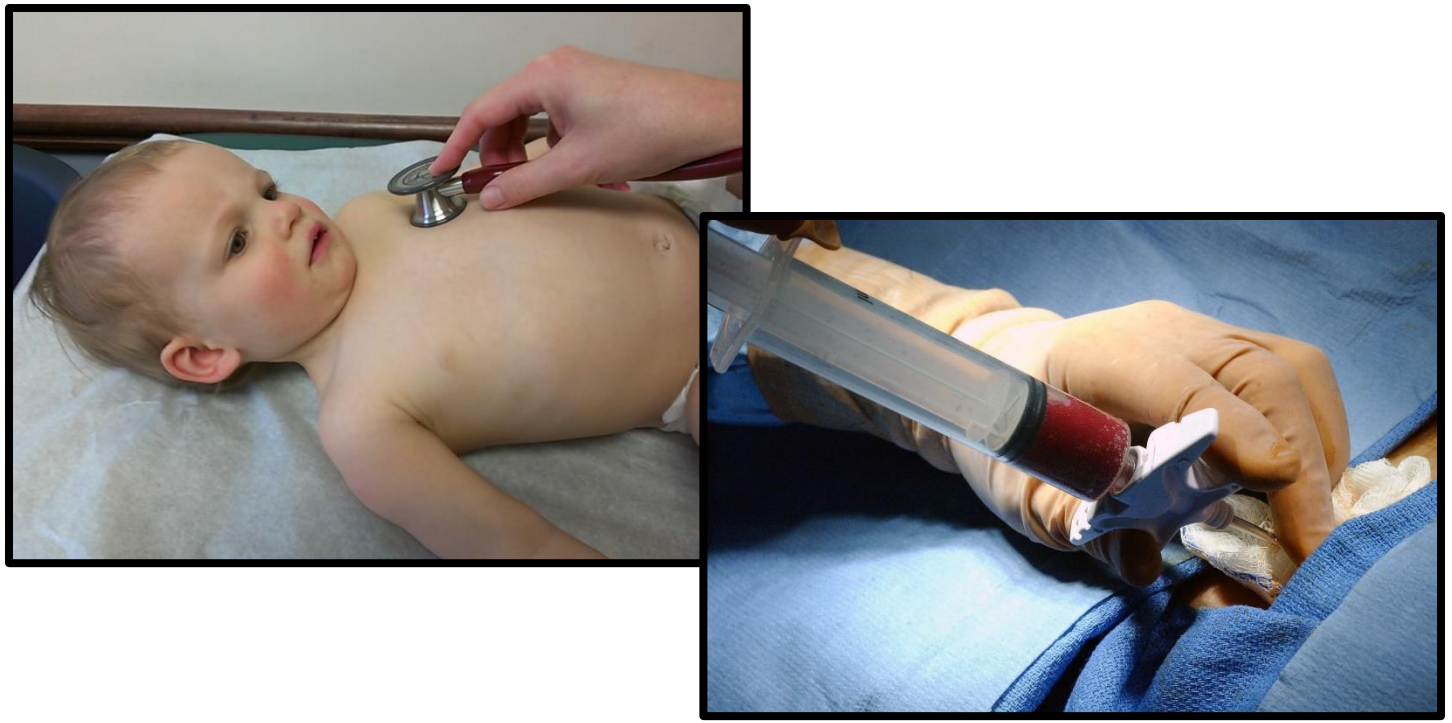
- Chédiak Higashi syndrome
- Griscelli syndrome type II
- X-linked lymphoproliferative disorders

Secondary / Acquired HLH

- No known or suspected genetic mutation

- Infection
- Autoimmune disorders
- Lymphoid malignancies
- Immune suppression

Presentation and Diagnosis



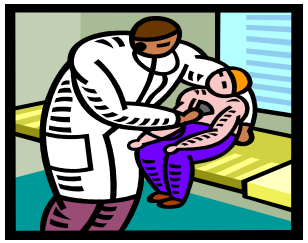
General Clinical Symptoms

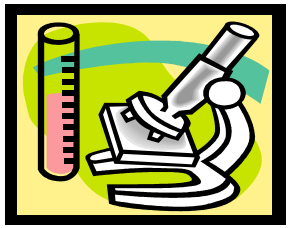
- Initial presentation often non-specific
- Common: **prolonged fever, hepatosplenomegaly, cytopenias**
- CNS abnormalities (~40% cases)

- Less common: lymphadenopathy, jaundice, edema, rash, diarrhea

Signs of Immune Activation

- Fever: induced by IL-1, IL-6, and TNF-α
- Hepatosplenomegaly





- **↑ Ferritin:** secreted by activated macrophages; often >10,000
- **↑ Soluble interleukin-2 receptor** [sIL-2R, sCD25]: activated lymphocytes

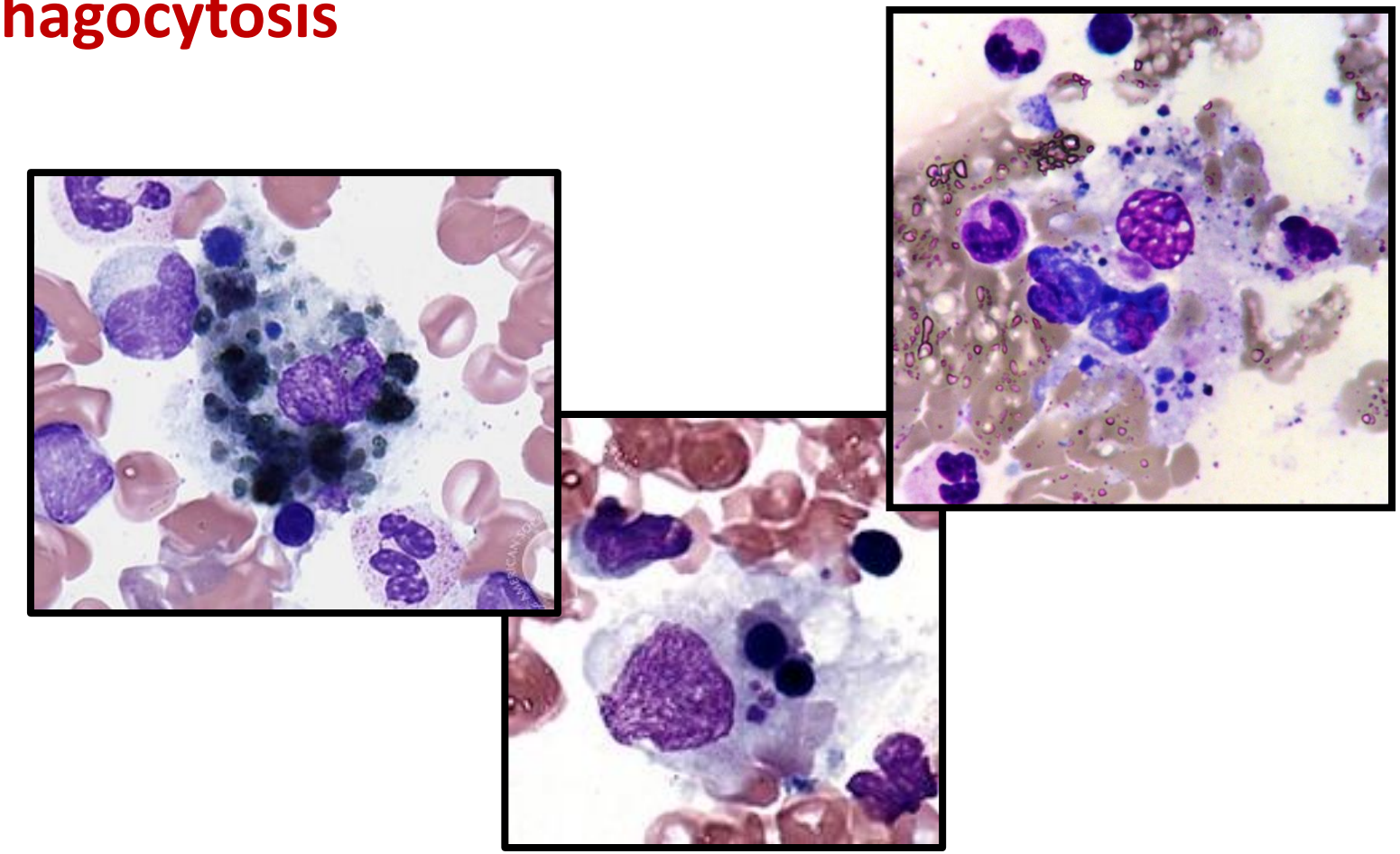
Immune Mediated Pathology

- **Cytopenias:** ↑ TNF-α and IFN-γ toxic to stem cells
- **↑ Triglycerides:** ↑ TNF-α
- **↓ Fibrinogen:** ↑ Tissue plasminogen activator

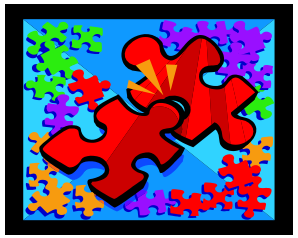
- **Hepatitis / CNS involvement** / pulmonary disease: organ infiltration by activated CTLs/histiocytes

Immune Mediated Pathology

- **Hemophagocytosis**



HLH Diagnostic Challenge

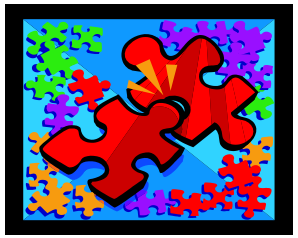


- Rare syndrome
- Long turnaround time for genetic testing
- No single clinical feature is diagnostic
- Complex diagnostic criteria

Diagnosis

- Molecular diagnosis (genetic testing)
- May take 3-8 weeks
- Test all patients
  - <2 years old at diagnosis
  - Prior to transplant
  - Concerning family history
- Clinical diagnosis (5 of 8 criteria)

Diagnostic Criteria (5 of 8)



- Fever ≥ 38.5°C
- Splenomegaly
- Cytopenias (≥ 2: Hgb <9, PLT <100K, ANC <1000)
- Triglycerides (fasting) ≥ 265 or fibrinogen ≤150
- Ferritin ≥ 500
- Low or absent NK-cell activity
- Elevated sIL-2 receptor (soluble CD25) ≥ 2400
- Hemophagocytosis

Treatment

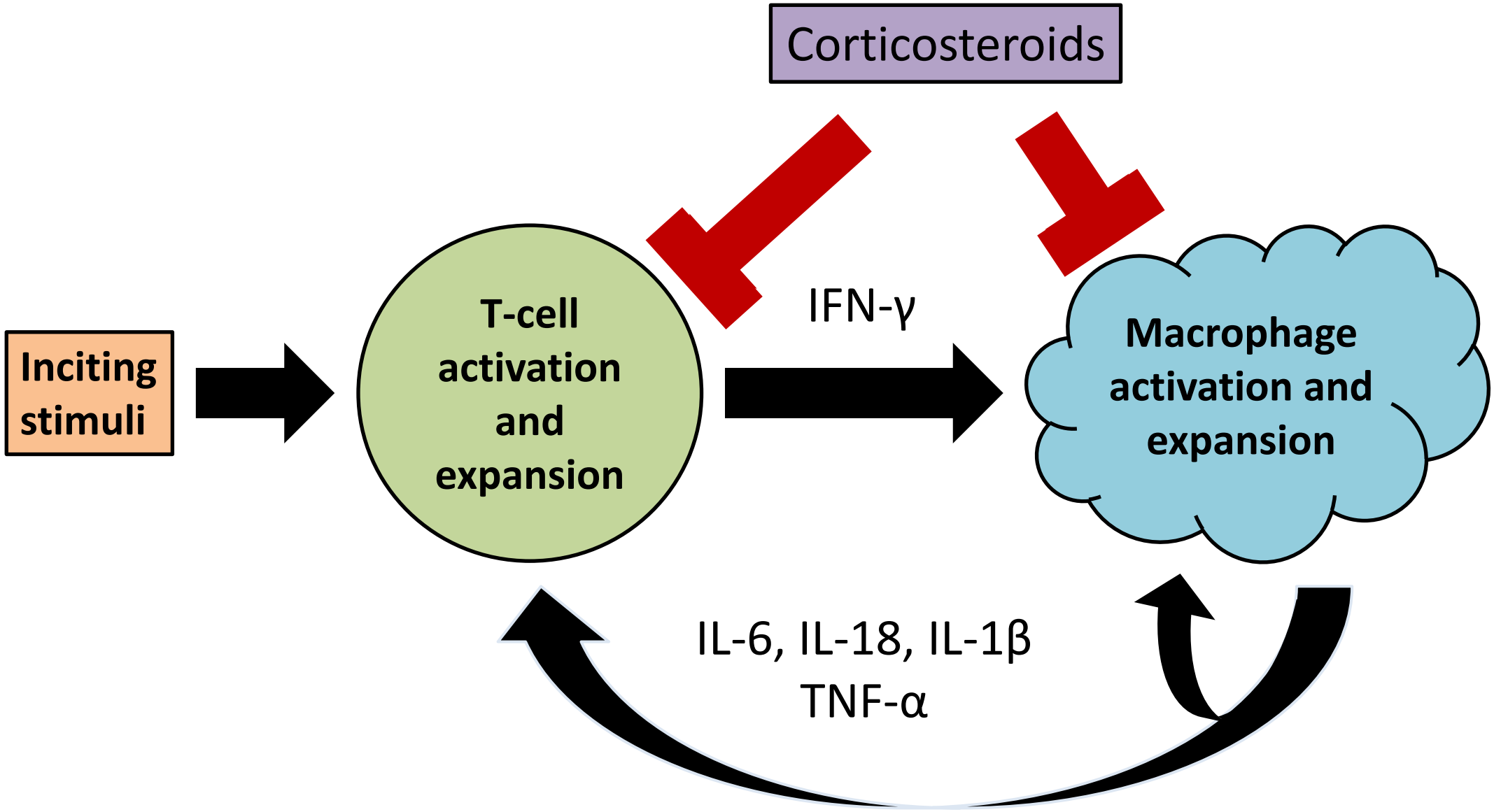
HLH-94

- First therapeutic trial
- 1994-1998, 113 patients, 21 countries
- Non randomized trial
- Chemotherapy + immunotherapy
- HSCT was used for familial or persistent disease

- Overall survival 55%
- Survival post transplant 62%

Treatment Principles

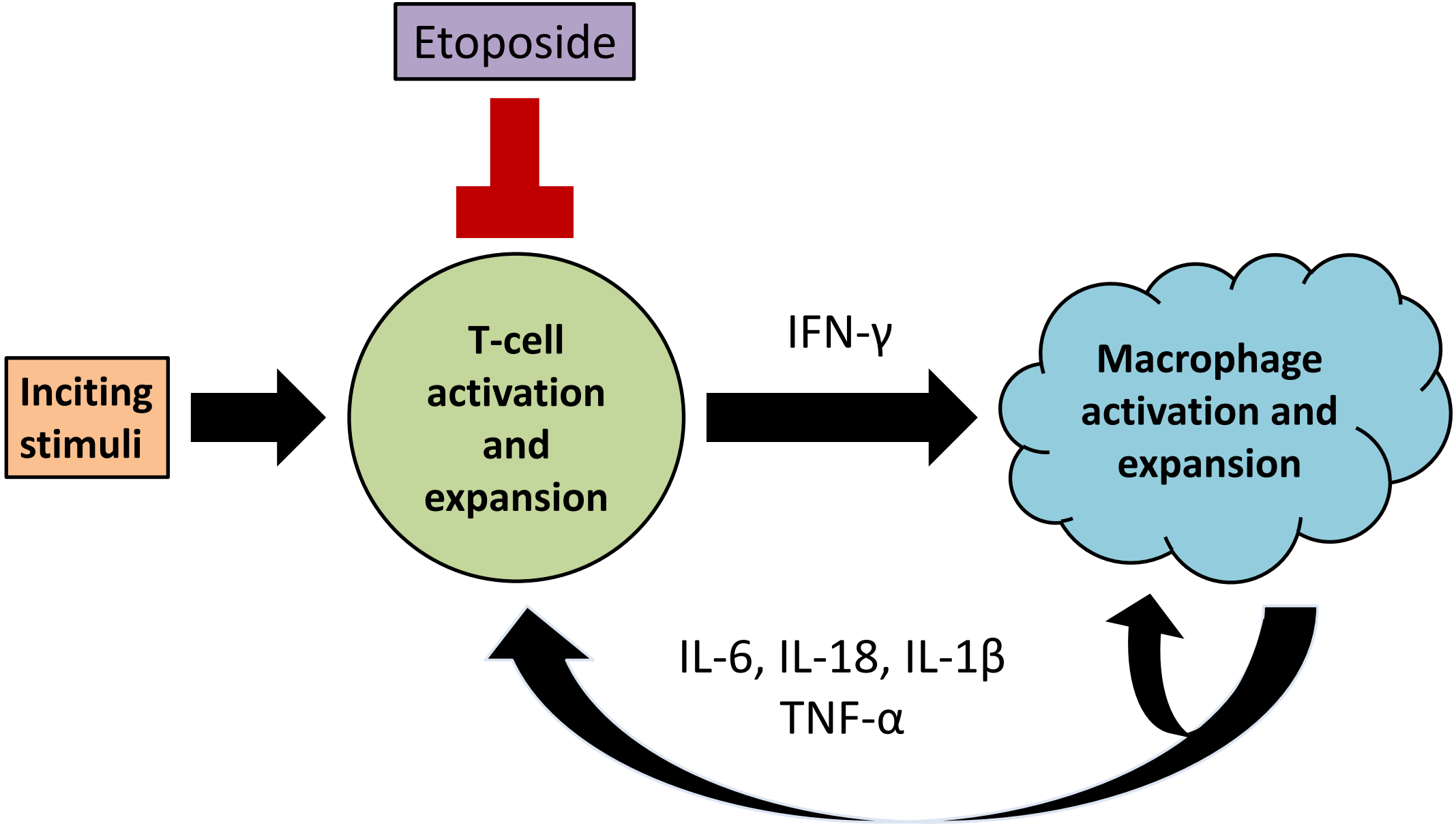
- Treat HLH
  - Quickly and adequately; DO NOT WAIT for results of genetic or specialized immunologic tests
  - Suppress hyper-inflammation
  - Eliminate activated lymphocytes/macrophages
- Treat underlying disease or infection
- Replace defective immune system (transplant)


Corticosteroids
Inciting stimuli
T-cell activation and expansion
IFN-γ
Macrophage activation and expansion
IL-6, IL-18, IL-1β
TNF-α

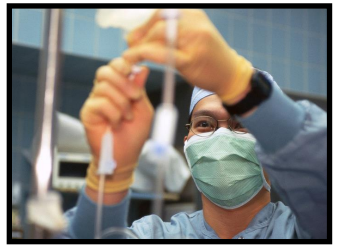
Dexamethasone

- Inhibits inflammation
- Inhibits macrophage differentiation
- Cytotoxic effect on lymphocytes

- Monotherapy sometimes used for rheumatologic or malignancy-associated HLH
- Better CNS penetration than prednisone
- Multiple acute and chronic toxicities


Etoposide
Inciting stimuli
T-cell activation and expansion
IFN-γ
Macrophage activation and expansion
IL-6, IL-18, IL-1β
TNF-α

Etoposide



- Induces apoptosis CTL and macrophages
- Intracellularly activates apoptosis cascades (bypasses perforin / granzyme B)

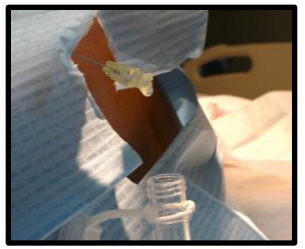
- Dose reduce for renal or hepatic dysfunction
- Low counts however are often due to disease, not therapy
- Risk of secondary cancers, especially AML; dose dependent

Cyclosporine A (CSA)

- Immunomodulatory
- Directly affects CTL activation and macrophage function

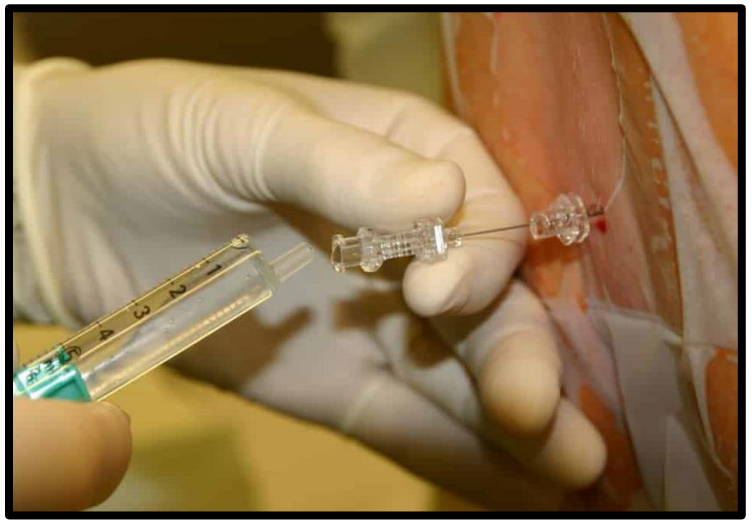
- Need to monitor blood levels
- Nephrotoxic

IT Methotrexate



- CNS disease is associated with poor prognosis

- IT chemotherapy if
  - Progressive neurological symptoms or persistent CSF abnormalities after 2 weeks of therapy
  - CNS reactivation
- Age dependent dosing
- Maximum 4 doses



Supportive Care

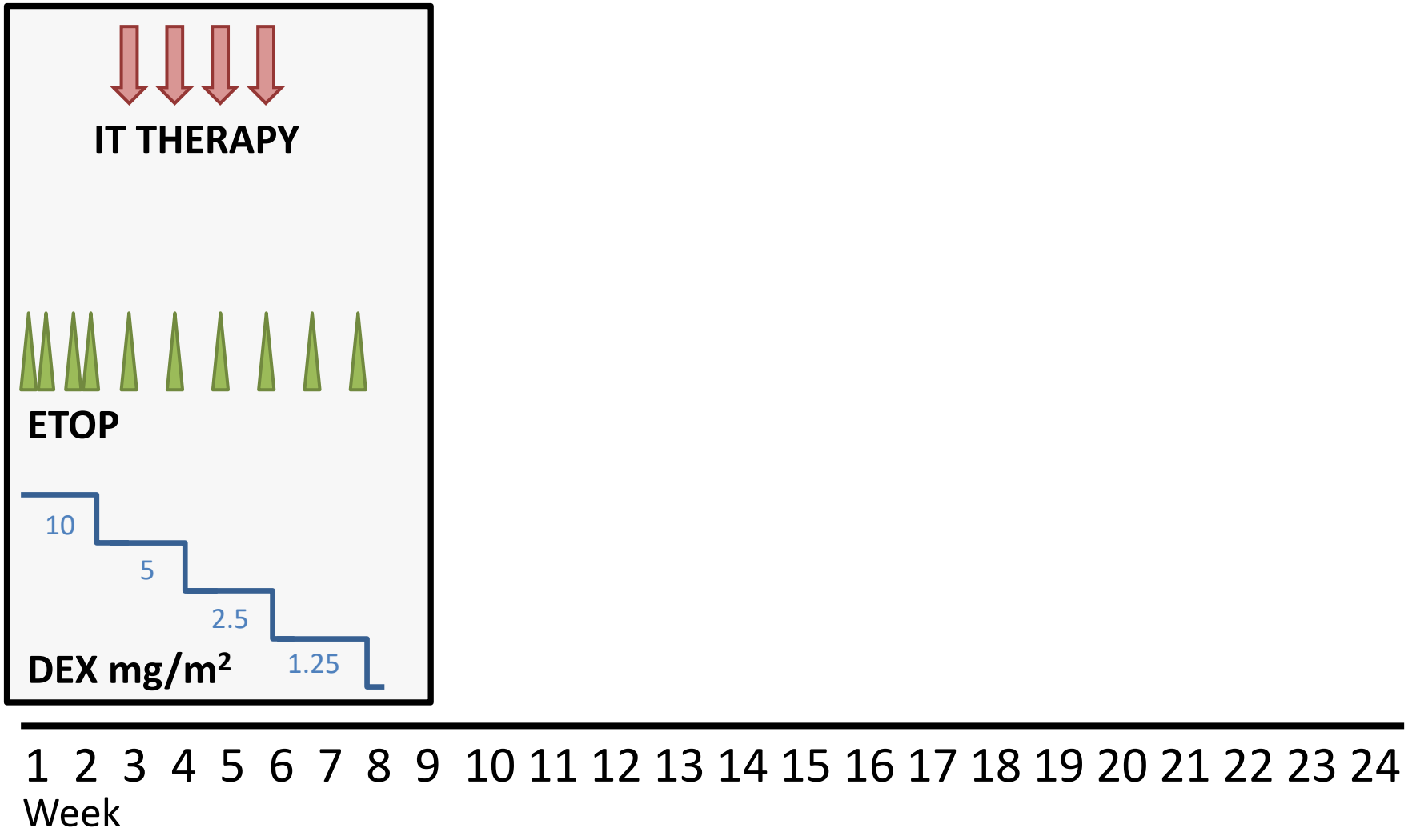
- Often require ICU level support
- Transfusions
- Prevent and treat bleeding
- Fluid and electrolyte balance
- Prevent and treat opportunistic infections
- Blood pressure control (high risk of PRES)

Induction Therapy

- 8 week therapy

- Dexamethasone PO
- Etoposide IV
- Methotrexate IT if CNS disease

Induction Therapy



Close Monitoring

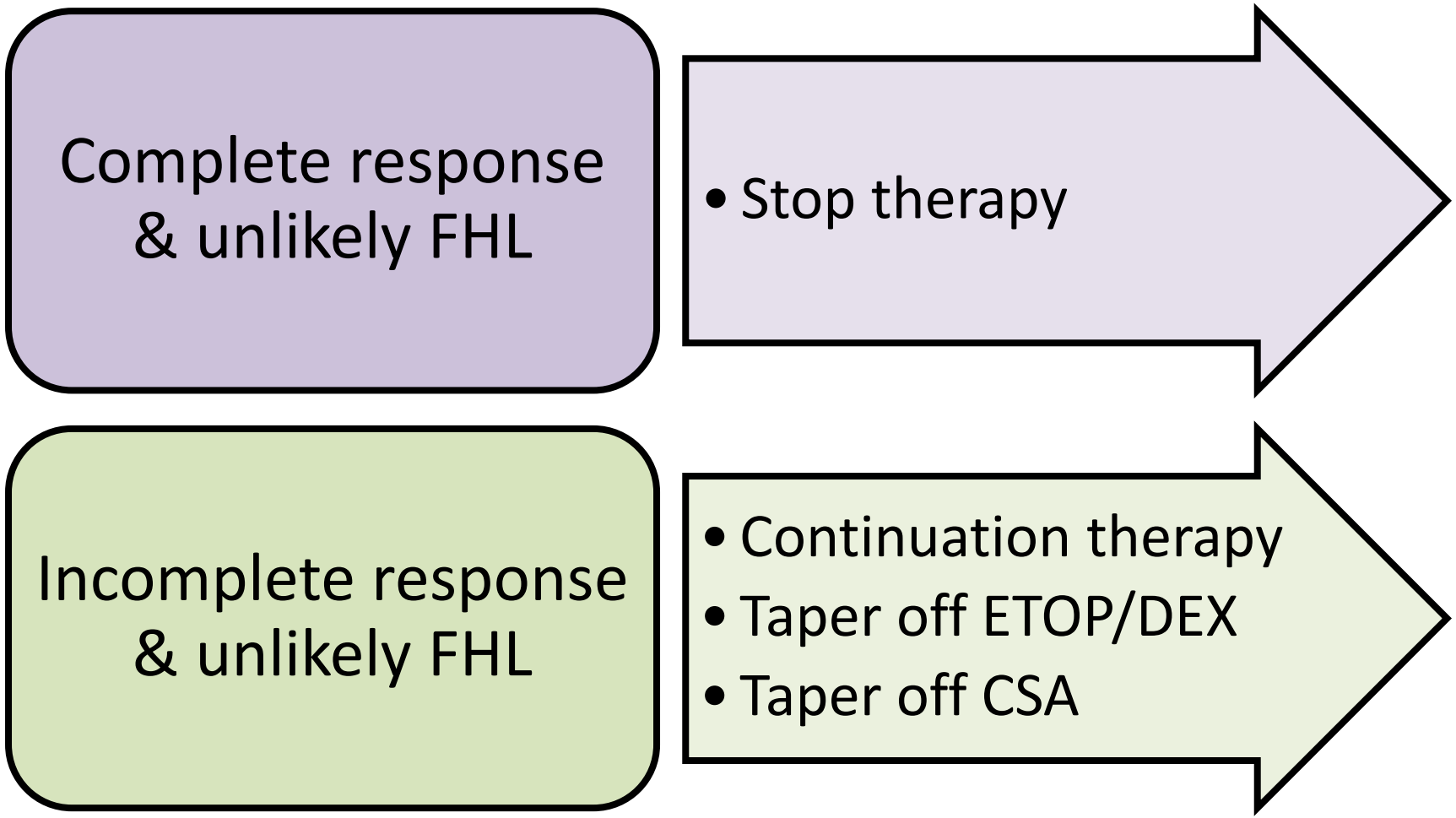
- Clinical status
- Labs
  - CBC
  - Ferritin
  - Triglycerides
  - Fibrinogen
  - sCD25 (sIL-2R)

- Recurrence of fever/inflammatory markers

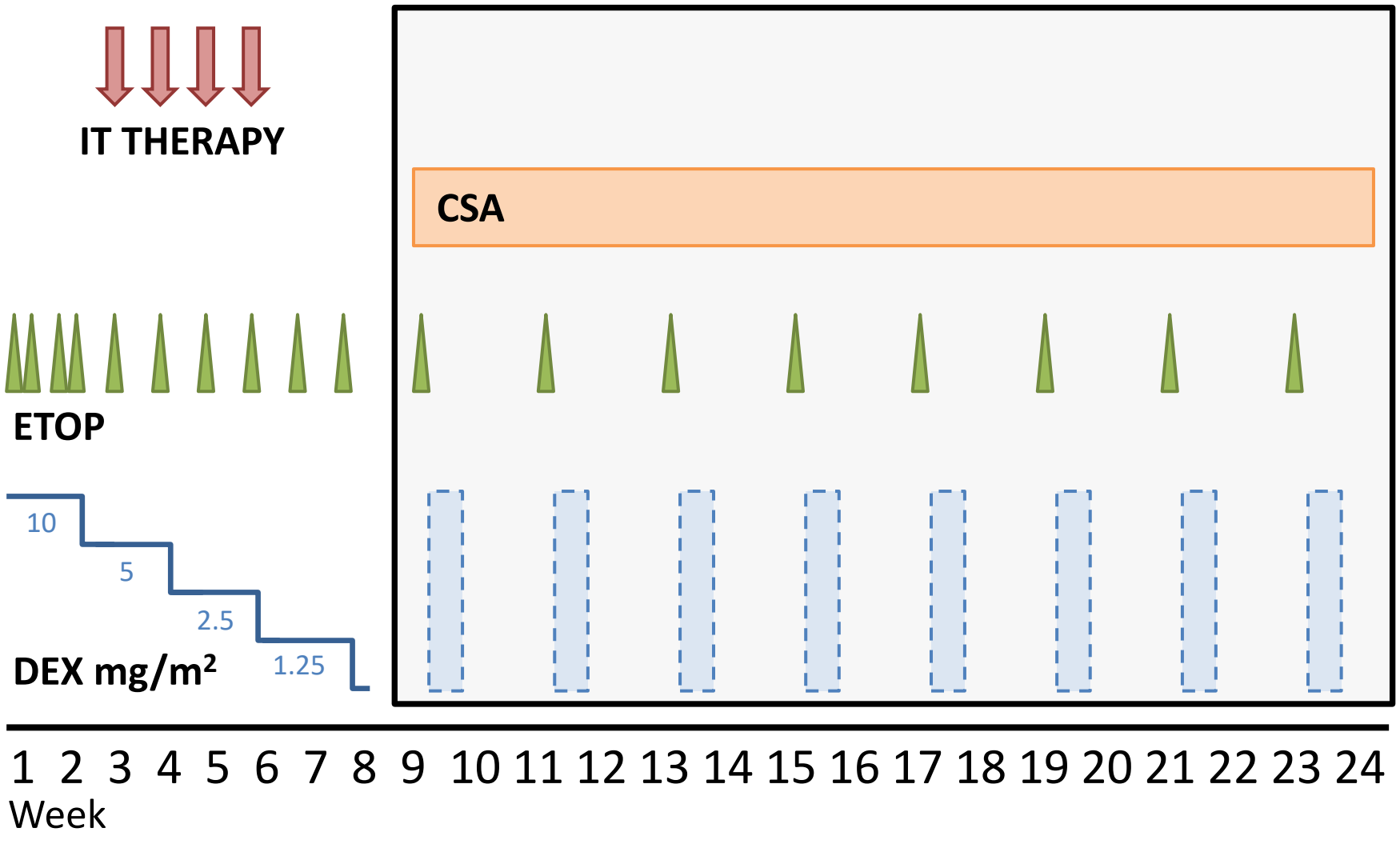
HLH Response Criteria

- No fever
- No splenomegaly
- No cytopenias
- Normal ferritin
- Normal triglycerides
- Normal CSF
- ↓ sCD25 (sIL-2R)

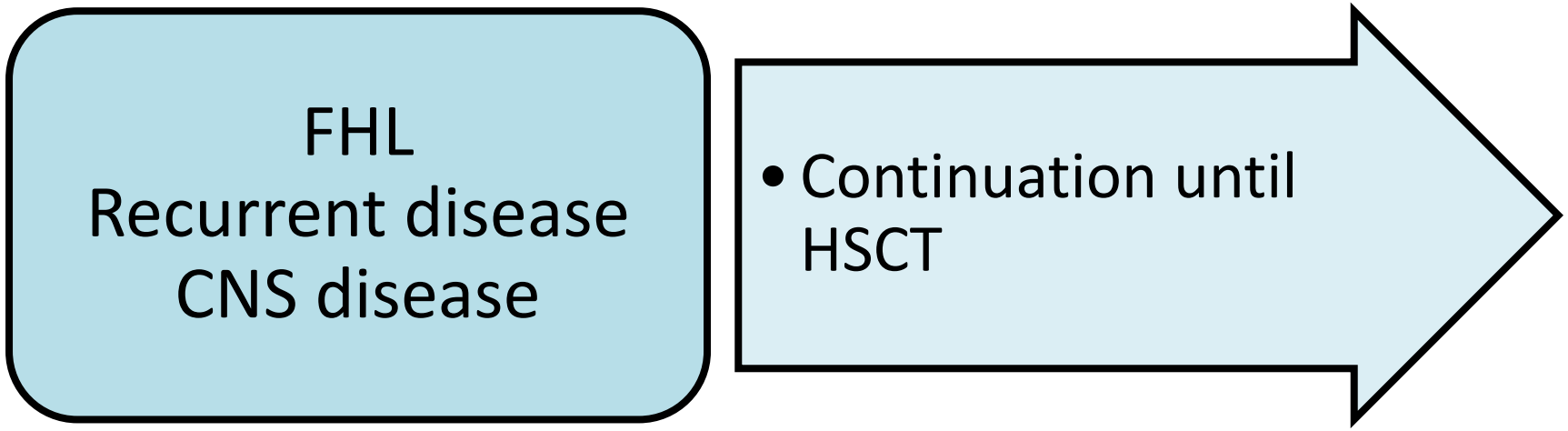
Post Induction Therapy



Continuation Therapy

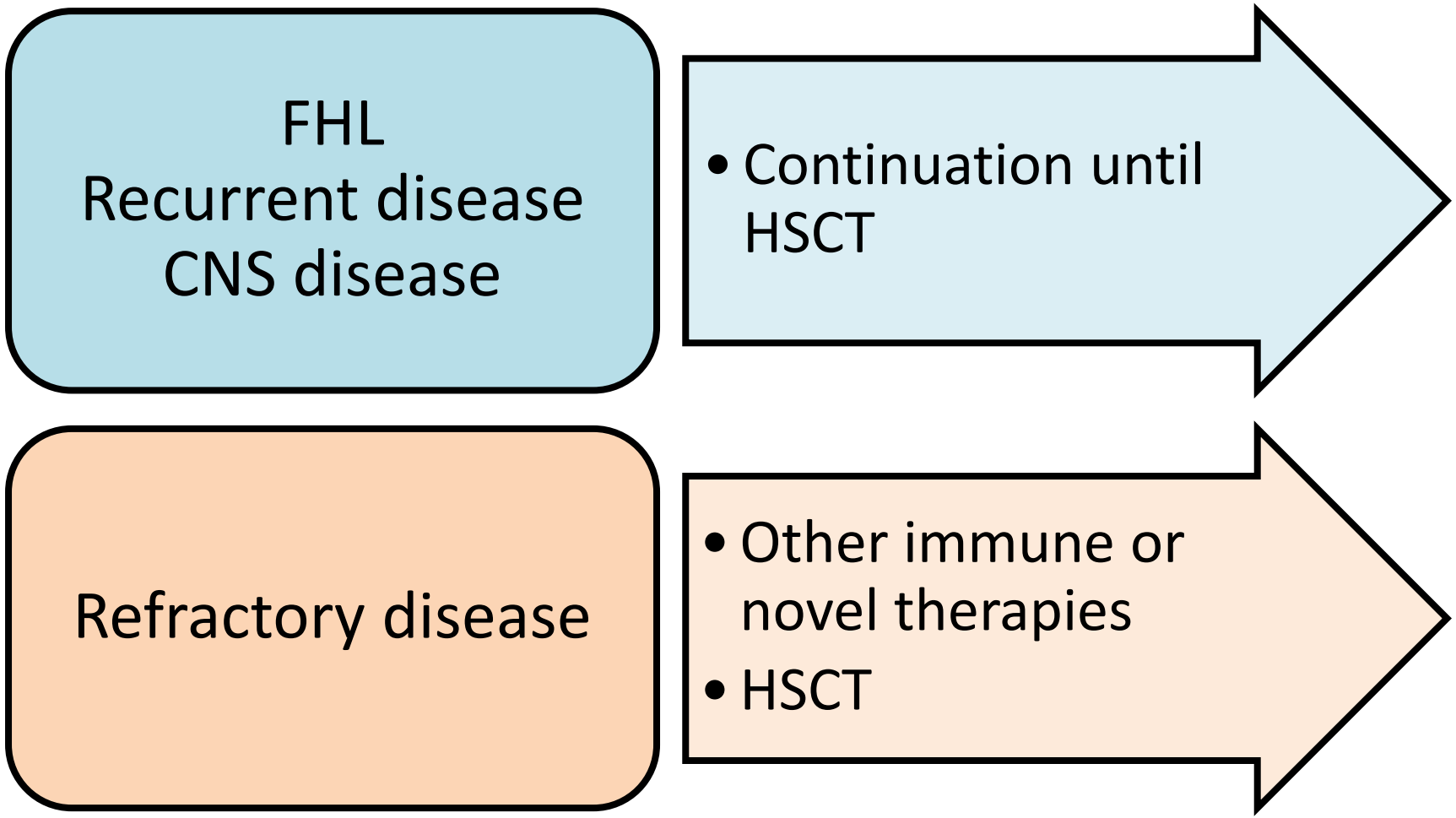


Post Induction Therapy



Transplant regimens: Myeloablative conditioning (MAC) vs Reduced intensity conditioning (RIC)

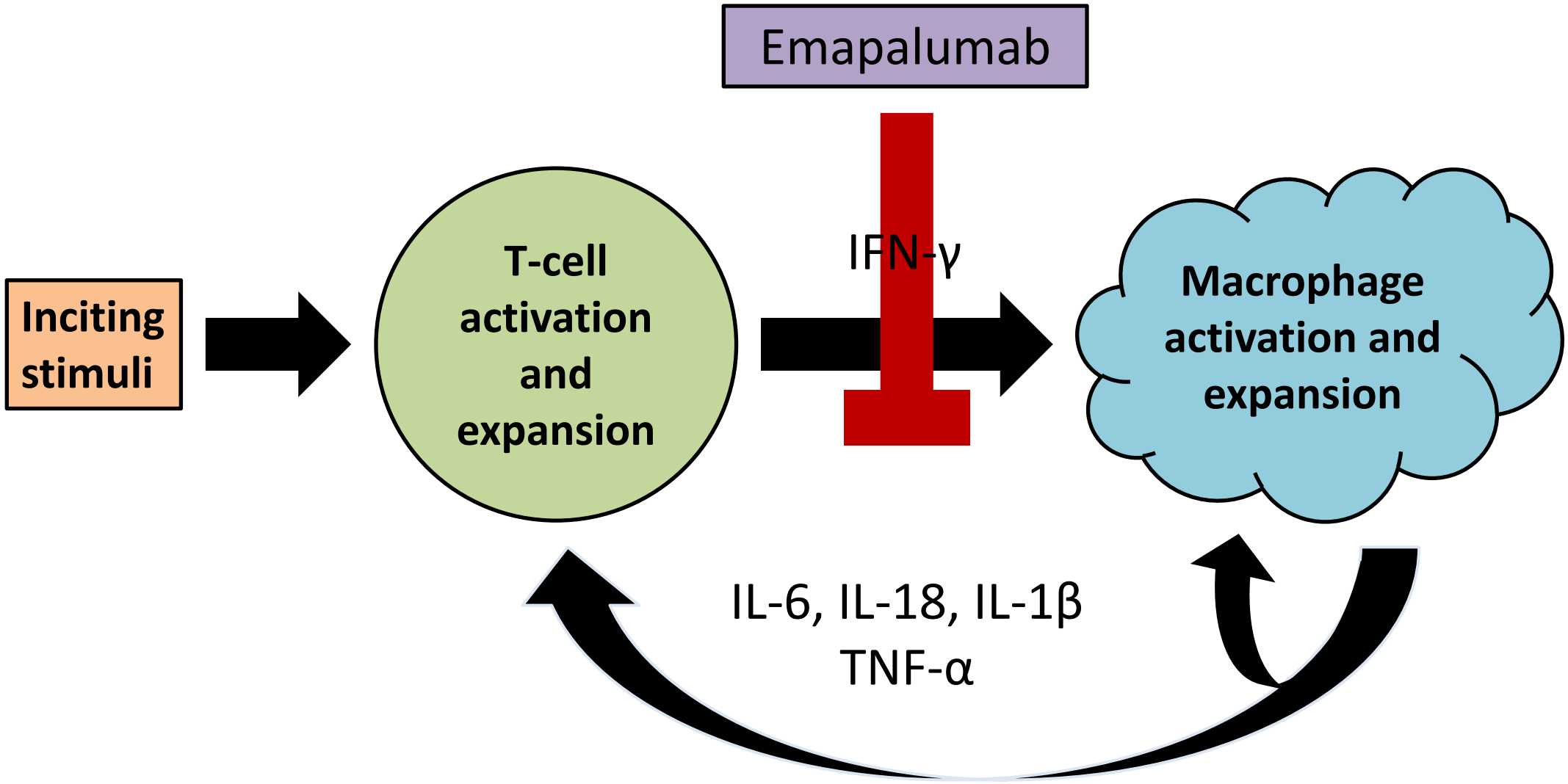
Post Induction Therapy



Novel Therapies

Hybrid Immune Therapy (HIT-HLH)

- ATG/PRED regimen used in France
  - ATG is horse-derived antibodies against human T-cells
  - Similar response to conventional ETOP/DEX
- Hybrid ImmunoTherapy (HIT-HLH)
  - ATG + ETOP/DEX
  - Phase 2, single-arm, multicenter trial
  - 2010-2016
  - Results?

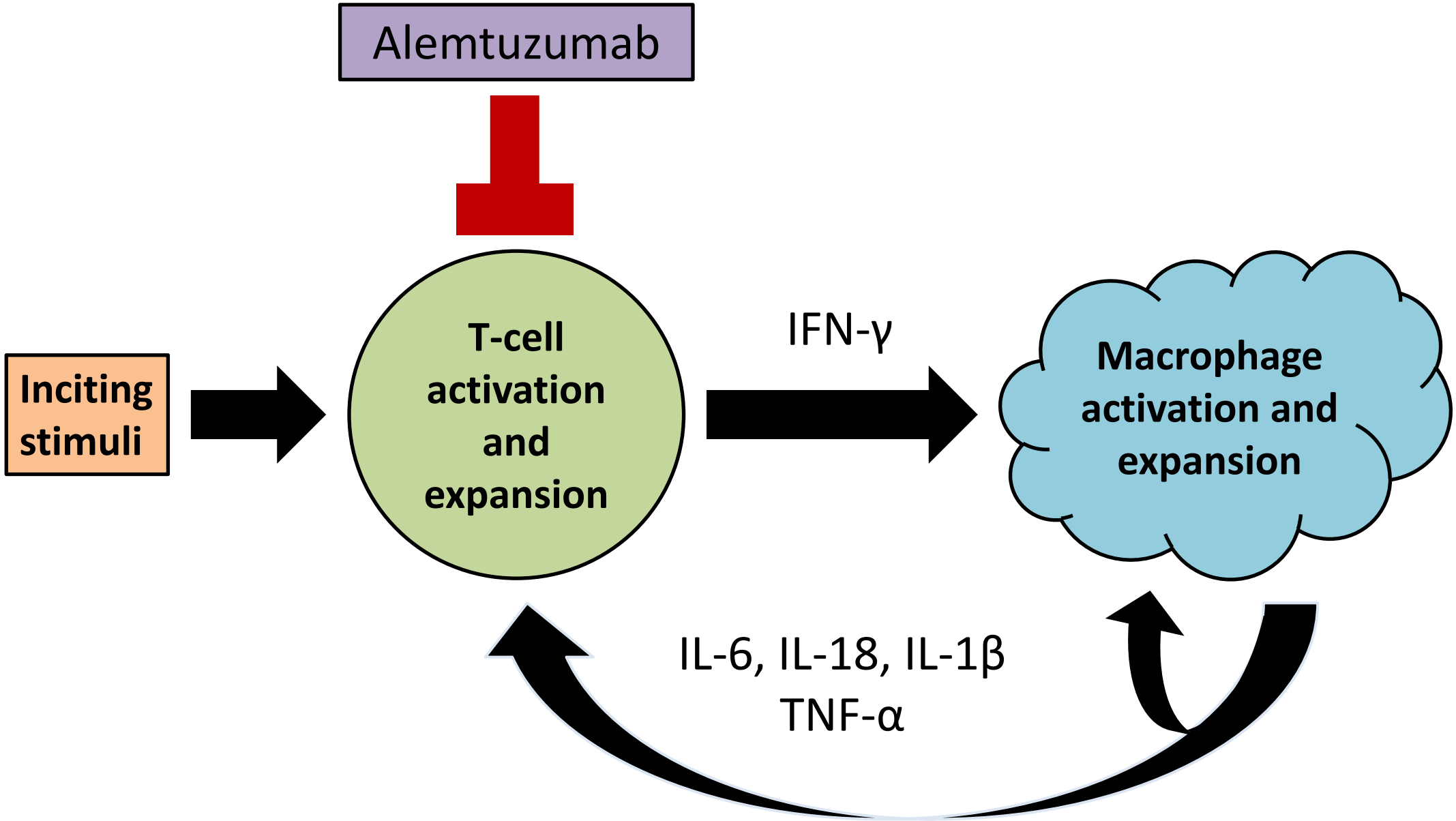

Emapalumab
Inciting stimuli
T-cell activation and expansion
IFN-γ
Macrophage activation and expansion
IL-6, IL-18, IL-1β
TNF-α

Emapalumab (NI-0501; Gamifant®)

- Fully human monoclonal antibody against IFN-γ
- Goal: Induce disease control without immuno-suppressive chemotherapy
- Phase II/III, single-arm, multicenter trial (Locatelli, 2020)
  - 2013-2019
  - Given in combination with DEX
  - 1 mg/kg IV infusion over 1 hour Q3 days; adjusted based on PK or clinical lab response; treatment duration 4-8 weeks

Results

- 34 patients: 27 previously treated, 7 treatment naïve; 26 completed the study
- 65% response
- 65-70% of patients proceeded to HSCT
- Emapalumab was not associated with any organ toxicity
- Severe infections developed in 10 patients
- First FDA-approved therapy for primary HLH

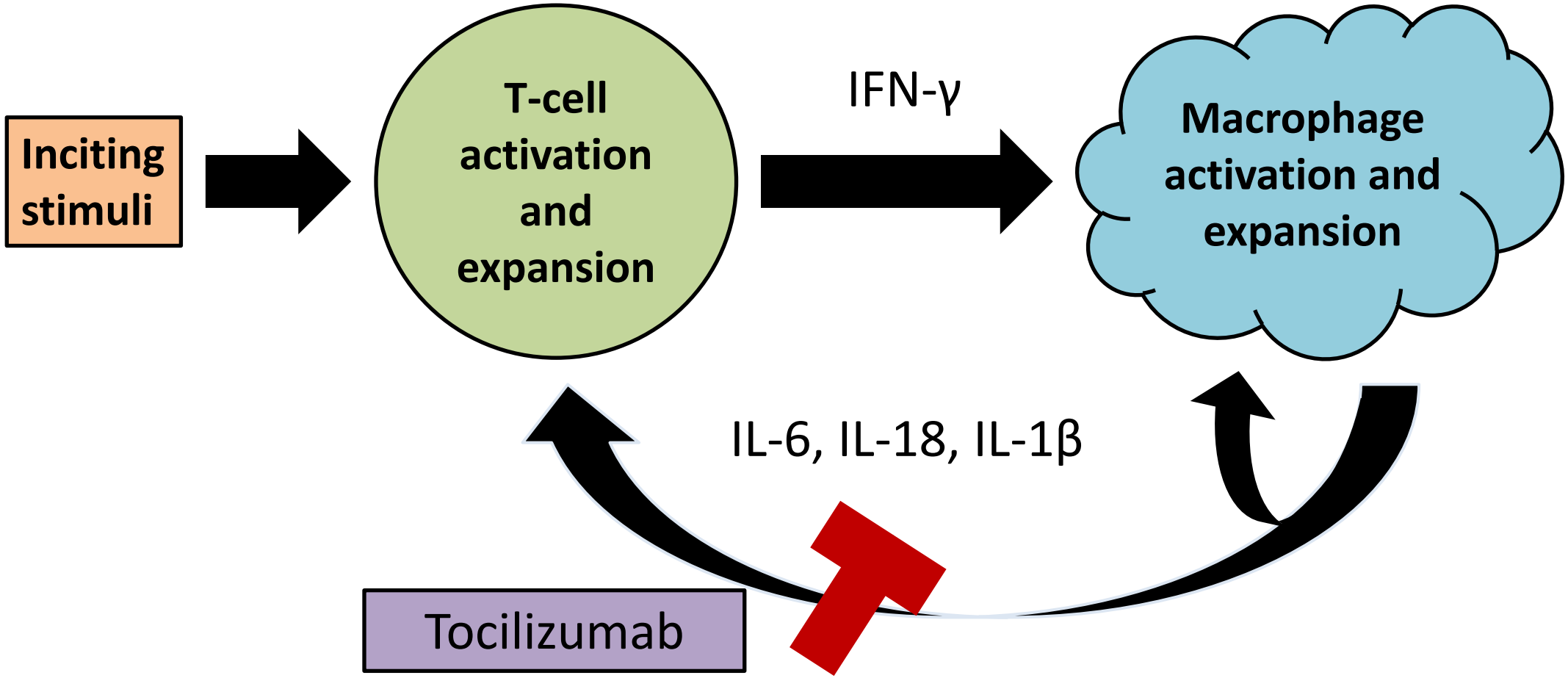

Alemtuzumab
Inciting stimuli
T-cell activation and expansion
IFN-γ
Macrophage activation and expansion
IL-6, IL-18, IL-1β
TNF-α

Alemtuzumab (Campath®)

- Humanized (from rat) monoclonal antibody against CD52, a common antigen found on B and T cells
- In contrast to ATG, alemtuzumab does not activate T lymphocytes while killing them
- Goal: Better tolerance and efficacy
- Phase I/II, single arm, multicenter trial (Moshous, 2019)
  - Retrospective 1/2009-6/2015; prospective 6/2015-6/2019
  - Given in combination with methylprednisolone and cyclosporine

Results

- 54 patients, treat naïve except for steroids/CSA
- In prospective study, the majority of patients received 1-2 courses, though a few received 3-4 courses
- 92% of patients survived to HSCT
- Favorable safety and tolerability profile in a very fragile population


Inciting stimuli
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Tocilizumab

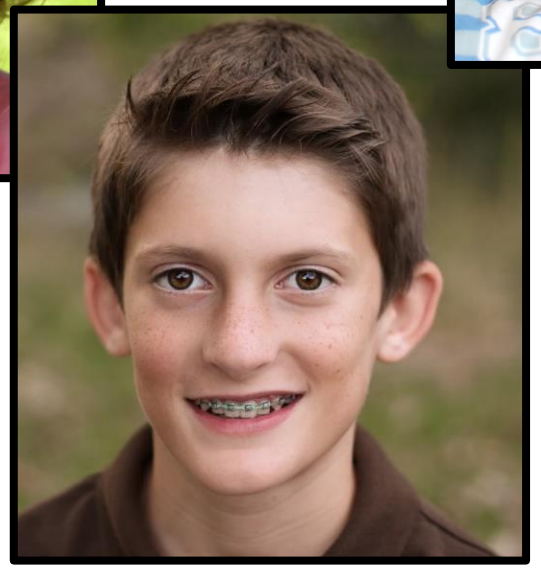
Tocilizumab (Actemra®)

- Humanized (from mouse) monoclonal antibody against interleukin-6 receptor (IL-6R); binds soluble as well as membrane bound IL-6R, hindering IL-6 from exerting pro-inflammatory effects;
- Alternative treatment targeting major cytokine precipitating CSS
- Goal: Avoid long-lasting etoposide-induced neutropenia
- Non-randomized, single center report (Dufranc, 2020)
  - Single IV dose 8 mg/kg
  - Given in combination with DEX (4), cyclophosphamide (2), or IVIG (1)

Results

- 9 critically ill, treat naïve adult patients
- 8/9 patients achieved remission (89%)
- No patient developed severe neutropenia (ANC<500)
- Four patients died during hospitalization (sepsis-related multi-organ, relapse/refractory disease)
- IL-6R blockade with tocilizumab may be an alternative in critically ill patients with moderate forms of HLH

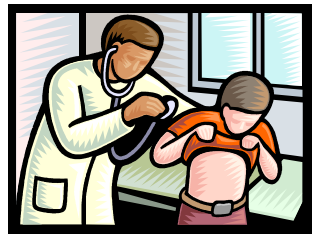
Case Studies



Sansa

- 16-month-old female
- 2 week history of high fever, rash, and gum bleeding

Workup



- Exam: Fever, no splenomegaly
- Labs: ↓ Hgb/PLT, ↑ ferritin (>10K), ↑ AST (1136), ↓ fibrinogen / ↑ triglycerides, ↑ sIL-2R (11,650)
- BMA: Histiocytic infiltrate/hemophagocytosis
- CSF/MRI brain: Negative
- Infectious disease work-up: EBV PCR+

- Diagnosis: HLH (primary EBV infection)

Treatment

- HLH induction (ETOP/DEX)
- Response: Excellent; all labs/exam findings improved by week 2 including clearance of EBV, and were normal by week 4
- Genetic work-up: Negative
- Discontinued treatment after induction

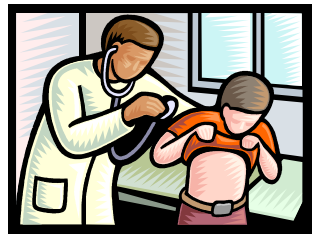
Outcome

- 2 days after completing steroid taper: Fever✓, ↓Hgb/PLT/ANC,✓↑ ferritin (5100),✓EBV PCR+
- Diagnosis: HLH reactivation
- Re-Induction with rapid disease control
- Continuation therapy until unrelated donor HCST
- Doing well at 3 years post-transplant

Robb

- 13-year-old male
- 2 week history of high fever
- PCP treated with 6 days of steroids
- Symptoms improved, but then recurred

Workup



- Exam: Splenomegaly✓, edema/ascites, fever✓
- Labs: ↓ Hgb/PLT;✓ ↑ ferritin (5610),✓ ↑ sIL-2R (13,000),✓ ↑ triglycerides✓
- BMA: Histiocytic infiltrate/hemophagocytosis✓
- CSF/MRI brain: Negative
- Infectious disease work-up: Negative

- Diagnosis: HLH

Treatment

- HLH induction (ETOP/DEX)
- Response: Persistent lab abnormalities at end of induction (↑ferritin, ↑ triglycerides) and persistent marrow hemophagocytosis
- Genetic work-up: Negative

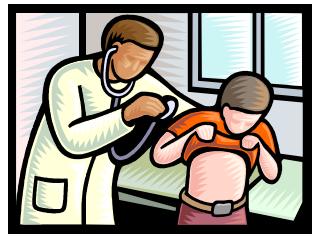
Outcome

- Continuation therapy
  - Labs improved/normalized
  - ETOP/DEX tapered to Q3 weeks, then Q4, then d/c
  - Tapered off CSA
- Doing well at 1 year off therapy

Jon

- 2-month-old male
- 1 week fever and bilateral ear infection
- Treated with Amoxicillin

Workup



- Persistent fever; found to have splenomegaly ✓
- Labs: ↓ Hgb/PLT/ANC, ↑ ferritin (>10K), ↑ sIL-2R, ↓ fibrinogen / ↑ triglycerides ✓
- BMA: Minimal hemophagocytosis in marrow ✓
- CSF/MRI brain: Positive
- Infectious disease work-up: Negative

- Diagnosis: HLH

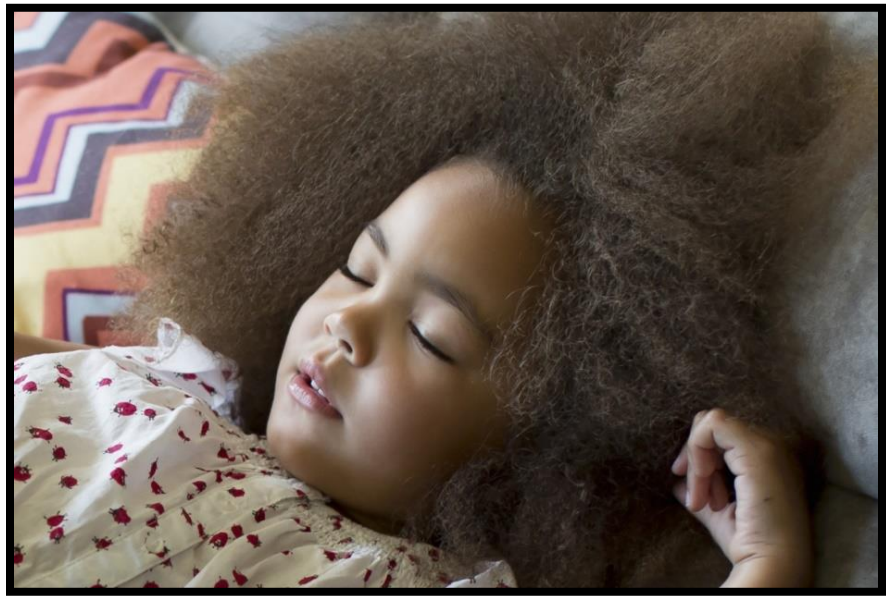
Treatment

- HLH induction (ETOP/DEX)
- Response
  - Initial improvement
  - Flare week 6 with fever, ↑ ferritin(>10K), ↑ sIL-2R
  - Improved with increased DEX, but then flared again
  - Disease controlled with increased frequency of ETOP
- Genetic testing: PRF1 mutation (FHL 2)

Outcome

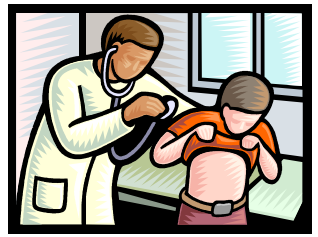
- Continuation therapy until unrelated donor HCST
- Doing well at 2 years post-transplant

Dany



- 5-year-old female direct admit to PICU from outside hospital with fever, shock, and capillary leak syndrome

Workup

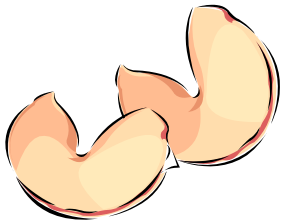


- Exam: Fever✓, splenomegaly✓, pleural effusions
- Labs: ↓ Hgb/PLT✓, ↑ ferritin (>10K)✓, ↑ sIL-2R✓, ↓ fibrinogen / ↑ triglycerides✓
- BMA: Histiocytic infiltrate/hemophagocytosis✓
- CSF/MRI brain: Negative
- Infectious disease work-up: Negative
- Diagnosis: HLH

Treatment

- Treatment: Emapalumab and DEX
- Response: Excellent; all labs/exam findings improved by week 2 and normal by week 4
- Genetic work-up: Negative
- Discontinued treatment after induction
- Doing well at 14 months off therapy

Take Home Messages



- HLH is a rapidly progressive, life-threatening syndrome of excessive immune activation
- Current treatments suppress hyper-inflammation and eliminate activated lymphocytes/macrophages
- Primary (genetic) disease requires HSC transplant
- Overall survival is still <80% due to death from organ damage or infection
- Novel therapeutic approaches are being explored to improve response and decrease toxicity

References

- Al-Samkari, H., & Berliner, N. (2018). Hemophagocytic lymphohistiocytosis. *Annual Review of Pathology: Mechanisms of Disease, 13*, 27-49.
- Benson, L. A., et al. (2019). Pediatric CNS-isolated hemophagocytic lymphohistiocytosis. *Neurology-Neuroimmunology Neuroinflammation, 6*(3), e560.
- Bergsten, E., et al. (2017). Confirmed efficacy of etoposide and dexamethasone in HLH treatment: long-term results of the cooperative HLH-2004 study. *Blood, The Journal of the American Society of Hematology, 130*(25), 2728-2738.
- Degar, B. (2015). Familial hemophagocytic lymphohistiocytosis. *Hematology/Oncology Clinics, 29*(5), 903-913.
- Dufranc, E., et al. (2020). IL6-R blocking with tocilizumab in critically ill patients with hemophagocytic syndrome. *Critical Care*, *24*(1), 1-3.

References

- Esteban, Y. M., de Jong, J. L., & Tesher, M. S. (2017). An overview of hemophagocytic lymphohistiocytosis. *Pediatric Annals, 46*(8), e309-e313.
- Filipovich, A. H., & Chandrakasan, S. (2015). Pathogenesis of hemophagocytic lymphohistiocytosis. *Hematology/Oncology Clinics, 29*(5), 895-902.
- Halyabar, O., et al. (2019). Calm in the midst of cytokine storm: a collaborative approach to the diagnosis and treatment of hemophagocytic lymphohistiocytosis and macrophage activation syndrome. *Pediatric Rheumatology, 17*(1),
- Janka, G. E., & Lehmberg, K. (2014). Hemophagocytic syndromes - an update. *Blood Reviews, 28*(4), 135-142.
- Jordan, M. B. (2018). Emergence of targeted therapy for hemophagocytic lymphohistiocytosis. *The Hematologist, 15*(2), 6-7.

References

- Locatelli, F., et al. (2020). Emapalumab in children with primary Hemophagocytic Lymphohistiocytosis. *New England Journal of Medicine*, *382*(19), 1811-1822.
- Marsh, R. A., & Haddad, E. (2018). How I treat primary haemophagocytic lymphohistiocytosis. *British Journal of Haematology*, *182*(2), 185-199.
- Morimoto, A., Nakazawa, Y., & Ishii, E. (2016). Hemophagocytic lymphohistiocytosis: pathogenesis, diagnosis, and management. *Pediatrics International, 58*(9), 817-825.
- Moshous, D., et al. (2019). Alemtuzumab as first line treatment in children with familial lymphohistiocytosis. *Blood, 134* (Supplement 1): 80.
- Ramachandran, S., et al. (2017). Recent advances in diagnostic and therapeutic guidelines for primary and secondary hemophagocytic lymphohistiocytosis. *Blood Cells, Molecules, and Diseases, 64*, 53-57.

References

- Skinner, J., Yankey, B., & Shelton, B. K. (2019). Hemophagocytic lymphohistiocytosis. *AACN Advanced Critical Care, 30*(2), 151-164.
- Wang, Y., & Wang, Z. (2017). Treatment of hemophagocytic lymphohistiocytosis. *Current Opinion in Hematology, 24*(1), 54-58.