Immune Deficiency Foundation

Lunch & Learn: Hemophagocytic Lymphohistiocytosis (HLH)

September 28th, 2022

IDF MISSION

Improving the diagnosis, treatment, and quality of life of people affected by primary immunodeficiency through fostering a community empowered by advocacy, education and research.

Immune Deficiency Foundation

HOUSEKEEPING

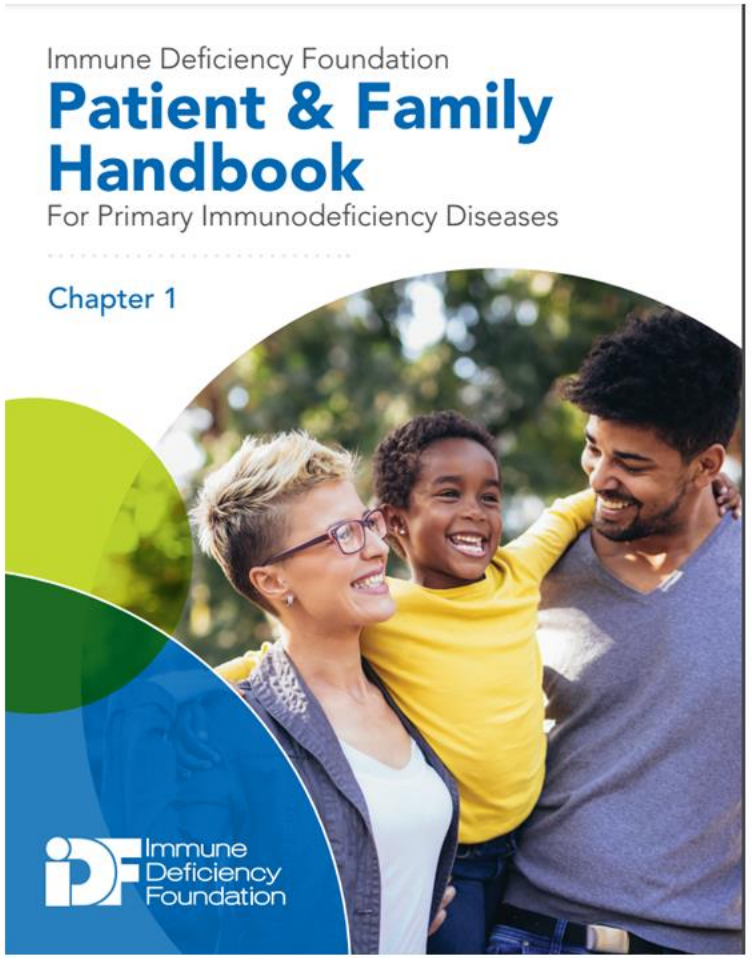
- Attendees will not have access to their microphone or webcam throughout the event.
- To see the full slides, you can adjust the settings on the speaker view panel on the top of the Zoom screen and select "side-by-side" in the dropdown option.
- Please submit all questions for the presenter via the Q&A box

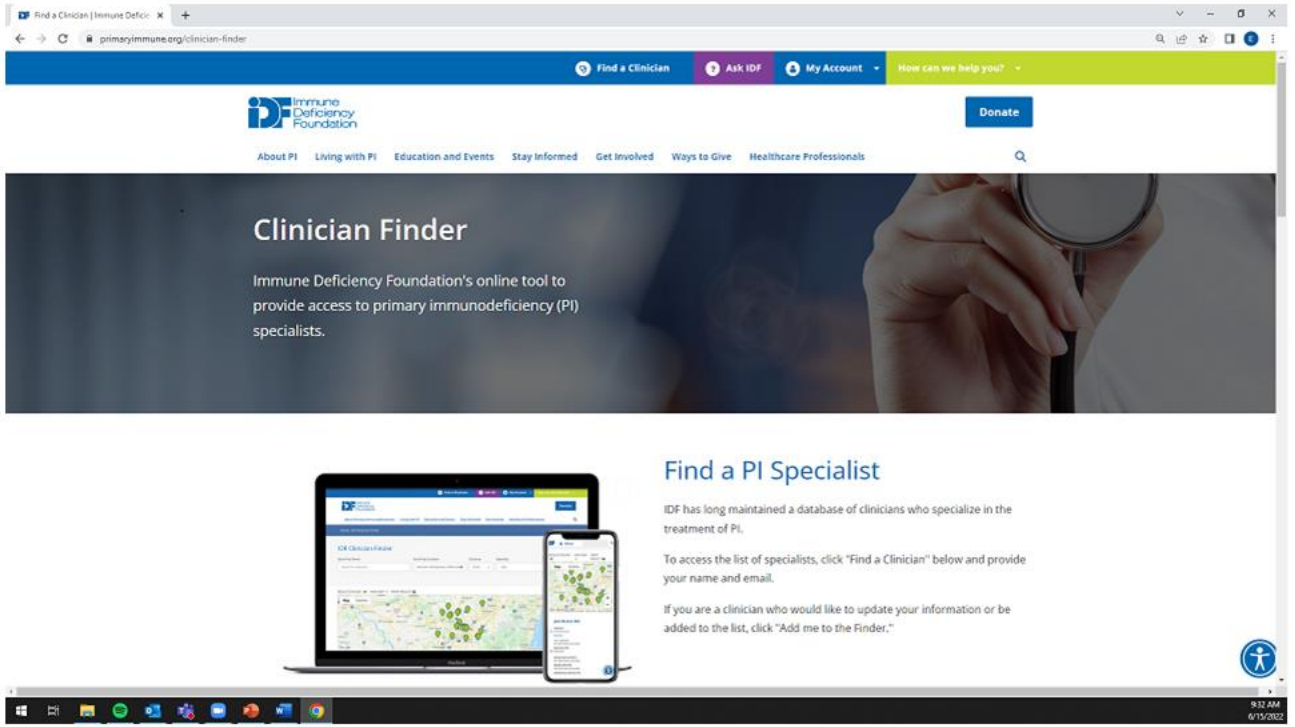
DISCLAIMER

Immune Deficiency (IDF) education events offer a wide array of educational presentations, including presentations developed by healthcare and life management professionals invited to serve as presenters. The views and opinions expressed by guest speakers do not necessarily reflect the views and opinions of IDF.

The information presented during this event is not medical advice, nor is it intended to be a substitute for medical advice, diagnosis or treatment. Always seek the advice of a physician or other qualified health provider with questions concerning a medical condition. Never disregard professional medical advice, or delay seeking it based on information presented during the event.

IDF Website: www.primaryimmune.org





Immune Deficiency Foundation

To view all HLH Resources and Materials, visit:

https://primaryimmune.org/disease/hemophagocytic-lymphohistiocytosis-hlh

PI COMMUNITY SERVICES

- Monthly Lunch & Learns- medical experts present on various diagnosis-specific topics
- Get Connected Groups: share experiences, receive information, and gain support
- IDF Forums
- Ask IDF
- Annual PI Conference

To view a list of all upcoming IDF events, visit: https://community.primaryimmune.org/s/events?language=en_US

WELCOME!

Rebecca Marsh, MD
Clinical Director, Primary Immune Deficiency Program and
HLH Center of Excellence
Cincinnati Children's Hospital

Immune Deficiency Foundation

HLH 101
Lunch & Learn

Rebecca Marsh, MD

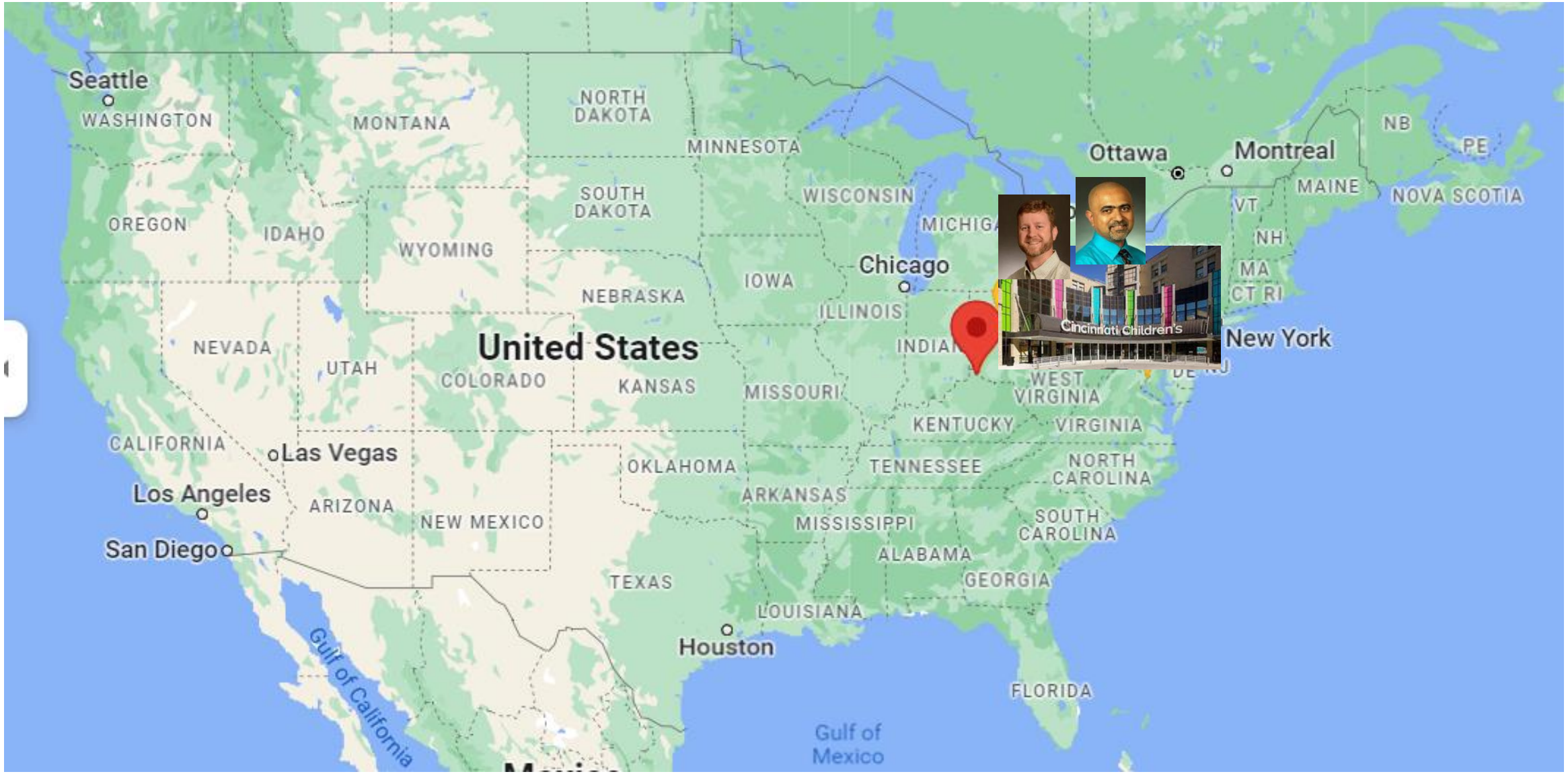
Outline for Today

- Brief introductory case
- Review HLH terminology
- Discuss why HLH happens and genetic disorders that cause HLH
- Talk about HLH testing
- Go over traditional and newer treatments

Disclosures

- I have no disclosures other than I will be discussing off-label use of several therapeutics

Introductory Case: Sunday Morning in Cincinnati, OH….

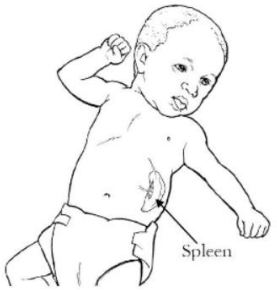


Introductory Case: Sunday Morning in Cincinnati, OH….

Brief Presentation

- 6 month old male comes to the Emergency Room with 5 days of fever, not eating well, less active
- No other symptoms, had a cold 2 weeks ago

- Exam: Has a fever, heart rate is fast, and doctors can feel an enlarged spleen



https://www.nationwidechildrens.org/family-resources-education/health-wellness-and-safety-resources/helping-hands/splenectomy

Brief Presentation

- Labs:
  - Several blood counts are low:
    - Platelets 47
    - White blood cell count 1.9, Neutrophil count 1137
  - Liver enzymes are elevated (liver seems a little sick)
    - AST 296, ALT 77
  - Fibrinogen is low 137
    - Fibrinogen is a protein made by the liver that helps stop bleeding by helping blood clots to form
  - Ferritin is high 2970
    - Ferritin is a blood protein that contains iron, and ferritin is elevated in inflammation

Course

- Baby was admitted to the hospital, given IV fluids and antibiotics.
- Several specialized doctors were consulted to help determine what was wrong: evaluate for infections or cancer or other problems
  - Bone marrow examination: no cancer
  - CT Scan did not show any concerns for cancer or infection
  - Lots of testing for infections: negative.
  - Specialized blood tests for inflammation were checked and were high:
    - Soluble IL-2Rα 13,234
    - CXCL9 5,783
    - IL-18 987

Does This Patient Have HLH?

Does This Patient Have HLH?

- Yes (We are at an HLH Education Session after all)

Does This Patient Have HLH?

- Yes (We are at an HLH Education Session after all)
- No (This seems like a trick question since we are at an HLH Education Session!)

HLH: What do we mean?

- HLH=Hemophagocytic Lymphohistiocytosis
  - Same # of syllables as: Supercalifragilisticexpialidocious!

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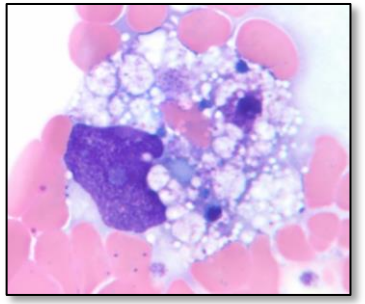
  - Hemophagocytic
    - hem = blood
    - phagocytic = of a cell that eats
  - Lymphocytosis = expansion of lymphocytes
  - Histiocytosis = expansion of tissue macrophages



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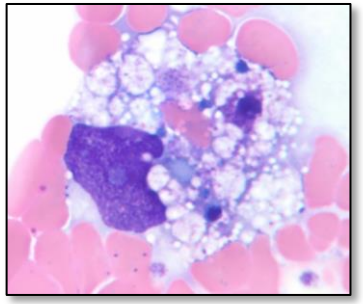

- HLH= a severe hyperinflammatory syndrome:
  - a recognizable pattern of clinical, laboratory, and microscopic findings caused by inflammation

What does this syndrome look like?

- Many doctors use the HLH-1994/2004 “criteria”
  - Developed for the Histiocyte Society treatment studies
  - Caveat 1: patients may lack 5/8
  - Caveat 2: patients with 5/8 may have something else
- Other manifestations can include:
  - Liver problems or liver failure
  - Brain/Spine Disease (sometimes isolated)
  - Other labs may be abnormal
    - LDH, D-Dimer

Table 1. Diagnostic criteria for HLH used in the HLH-2004 trial*

The diagnosis of HLH† may be established:
A. Molecular diagnosis consistent with HLH: pathologic mutations of *PRF1*, *UNC13D*, *Munc18-2*, *Rab27a*, *STX11*, *SH2D1A*, or *BIRC4*
or
B. Five of the 8 criteria listed below are fulfilled:
1. Fever ≥ 38.5°C
2. Splenomegaly
3. Cytopenias (affecting at least 2 of 3 lineages in the peripheral blood)
Hemoglobin < 9 g/dL (in infants < 4 weeks: hemoglobin < 10 g/dL)
Platelets < 100×10^3/mL
Neutrophils < 1×10^3/mL
4. Hypertriglyceridemia (fasting, > 265 mg/dL) and/or hypofibrinogenemia (< 150 mg/dL)
5. Hemophagocytosis in bone marrow, spleen, lymph nodes, or liver
6. Low or absent NK-cell activity
7. Ferritin > 500 ng/mL‡
8. Elevated sCD25 (α chain of sIL-2 receptor)§

*Adapted from Henter et al.[7]

Caution: Not very accurate

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Other Tools to Diagnose HLH or MAS

- The HScore (Fardet et al, 2014)
  - Developed in adults with primarily malignancy or infection-associated HLH

Questions

1.	Known underlying immunosuppression?	No
2.	Temperature?	38.4-39.4 °C
3.	Organomegaly?	Hepatomegaly or splenom...
4.	Number of cytopenias?	2 lineages
5.	Ferritin?	2,000-6,000 ng/mL
6.	Triglyceride level?	1.5-4 mmol/L
7.	Fibrinogen?	≤2.5 g/L
8.	AST?	≥30 U/L
9.	Hemophagocytosis features on bone marrow aspirate?	No

Results ☆ Save Copy Results

H Score
208

Probability of Hemophagocytic syndrome
88-93%

- The MAS-2016 criteria (Ravelli et al, 2016)
  - Developed to classify MAS in patients with systemic JIA

A febrile patient with known or suspected systemic juvenile idiopathic arthritis is classified as having macrophage activation syndrome if the following criteria are met:

Ferritin >684 ng/ml

and any 2 of the following:

Platelet count ≤181 x 10^9/liter

Aspartate aminotransferase >48 units/liter

Triglycerides >156 mg/dl

Fibrinogen ≤360 mg/dl

Who develops the syndrome of HLH?

- And what is primary versus secondary HLH?

Primary Versus Secondary HLH

- **Primary (or Genetic) HLH**: Inherited genetic immune deficiencies/immune dysregulation disorders that cause HLH
  - **Genetic problems lead to immune systems that are broken in 1 of 2 ways:**
    - 1: Immune system cells can’t kill infected or cancerous cells
    - 2: Immune system is making too many inflammation proteins

Primary Versus Secondary HLH

- **Secondary HLH:** HLH that occurs in “normal” people because of a *strong immune stimulus*: Cancer, Infection, Metabolic or Rheumatologic Disease

NACHO Conceptualization

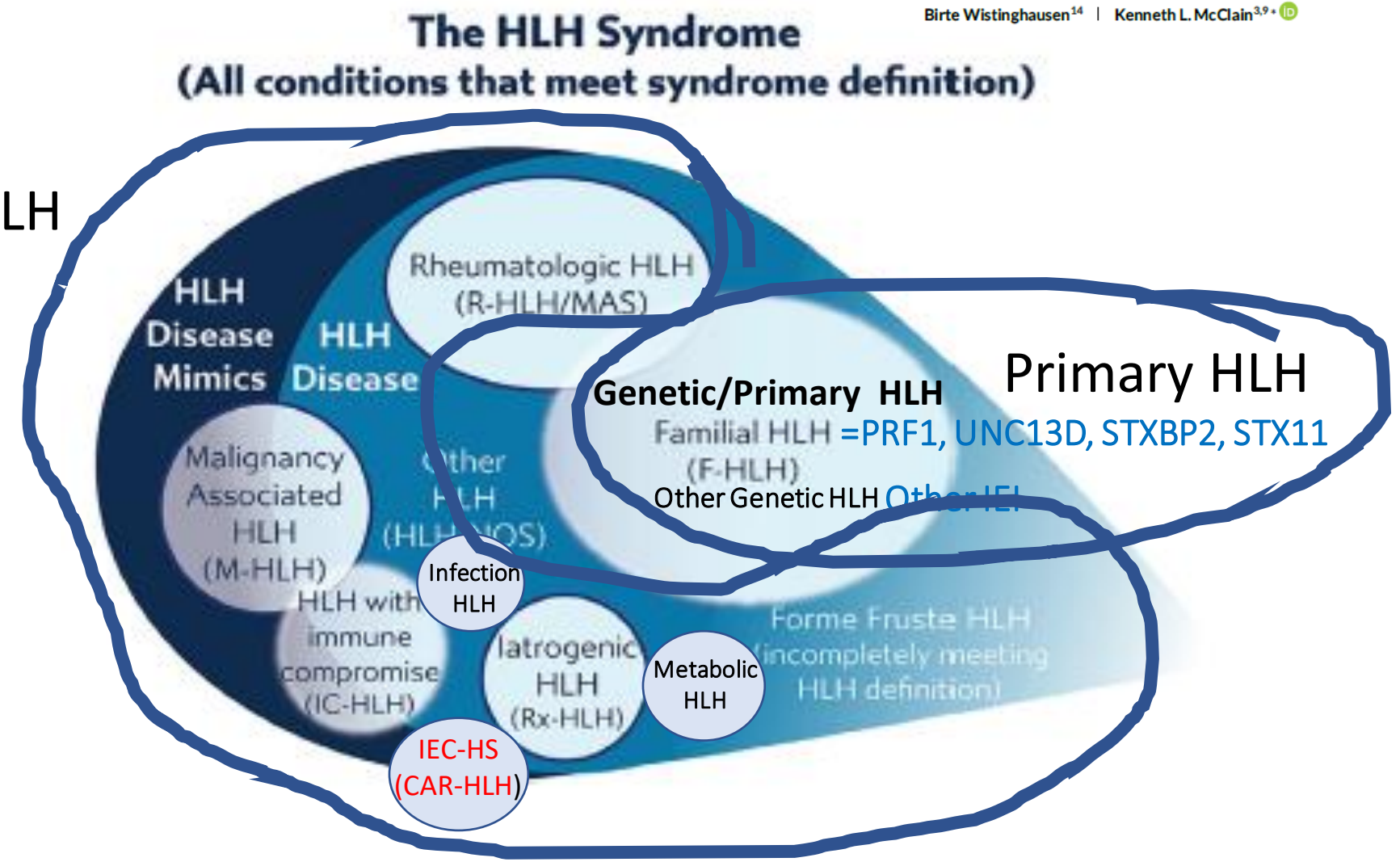
REVIEW

Cancer WILEY

Challenges in the diagnosis of hemophagocytic lymphohistiocytosis: Recommendations from the North American Consortium for Histiocytosis (NACHO)

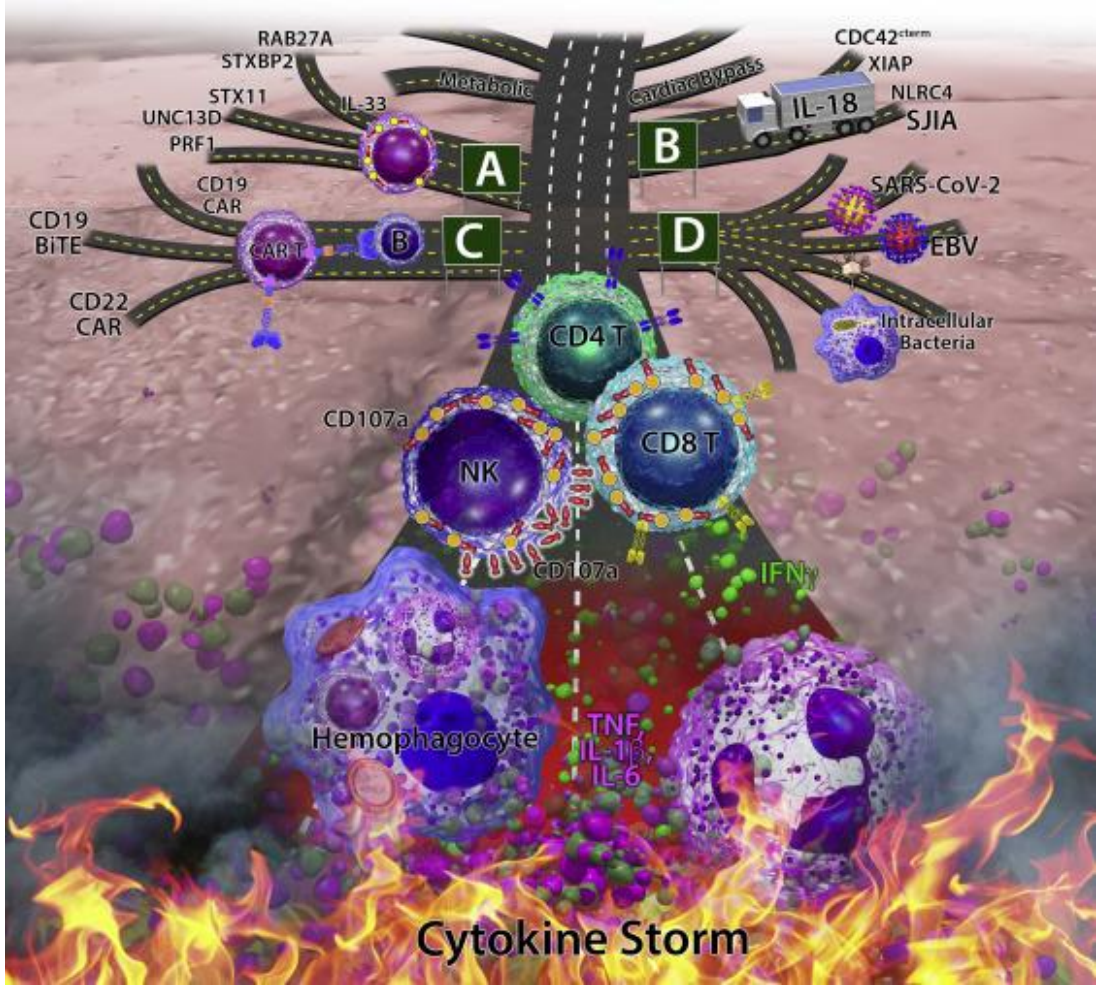
Michael B. Jordan[1,2] | Carl E. Allen[3] | Jay Greenberg[4] | Michael Henry[5] | Michelle L. Hermiston[6] | Ashish Kumar[7] | Melissa Hines[8] | Olive Eckstein[9] | Stephan Ladisch[10] | Kim E. Nichols[11] | Carlos Rodriguez-Galindo[12,13] | Birte Wistinghausen[14] | Kenneth L. McClain[3,9]*

Secondary HLH



Why does the HLH happen?

- Let’s start with the syndrome of HLH in the genetic HLH disorder setting



Scott Canna & Randy Cron

Genetic HLH Disorders

- Inborn errors of immunity which have a high risk of developing HLH and HLH is a main problem of the disorder.

- **Familial HLH:** Defective lymphocyte granule mediated cytotoxicity
  - *PRF1*, *UNC13D, STXBP2, STX11 RHOG*
- **Pigmentary Disorders Associated with HLH*:*** Defective lymphocyte granule mediated cytotoxicity
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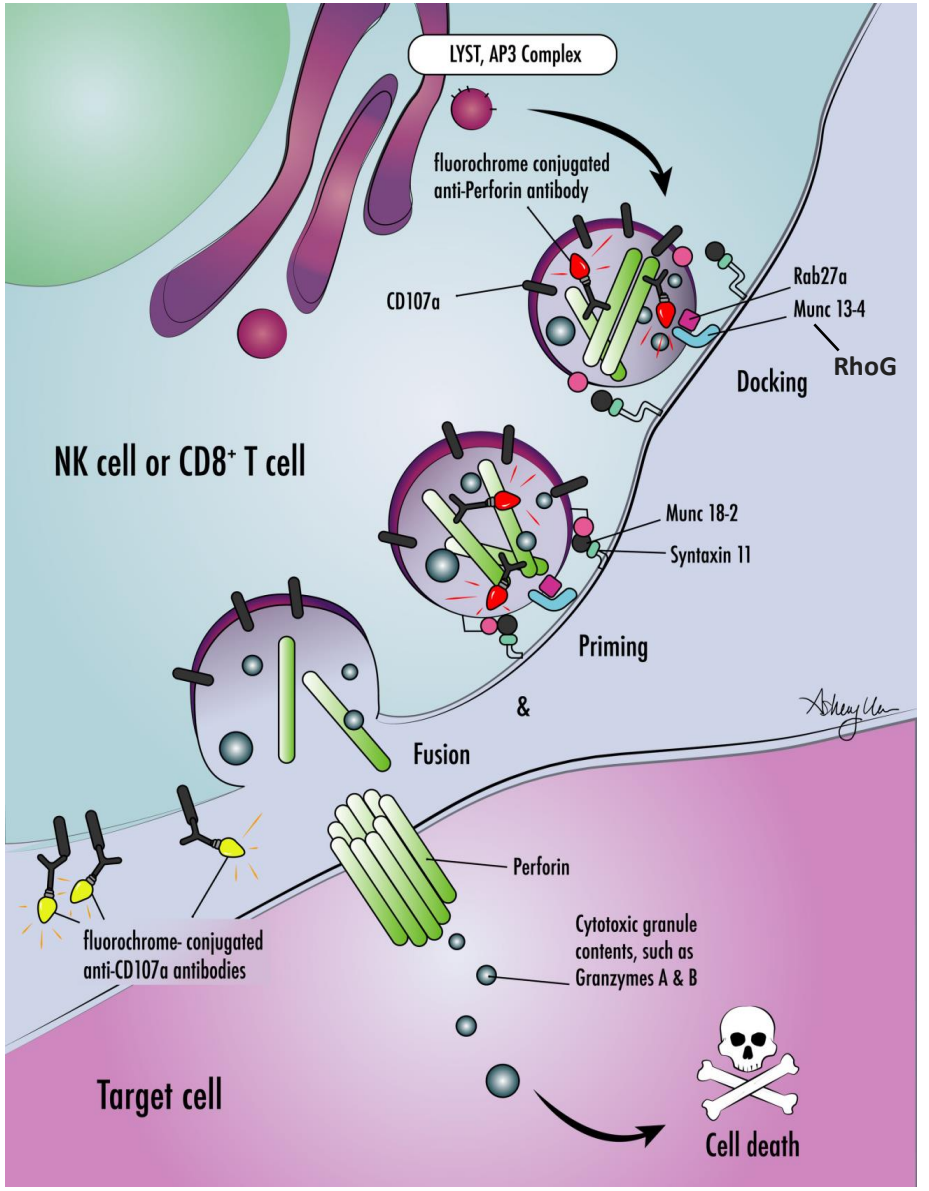

Marsh RA and Haddad E. *Br J Haematol*, Volume. 2018, DOI: (10.1111/bjh.15274)

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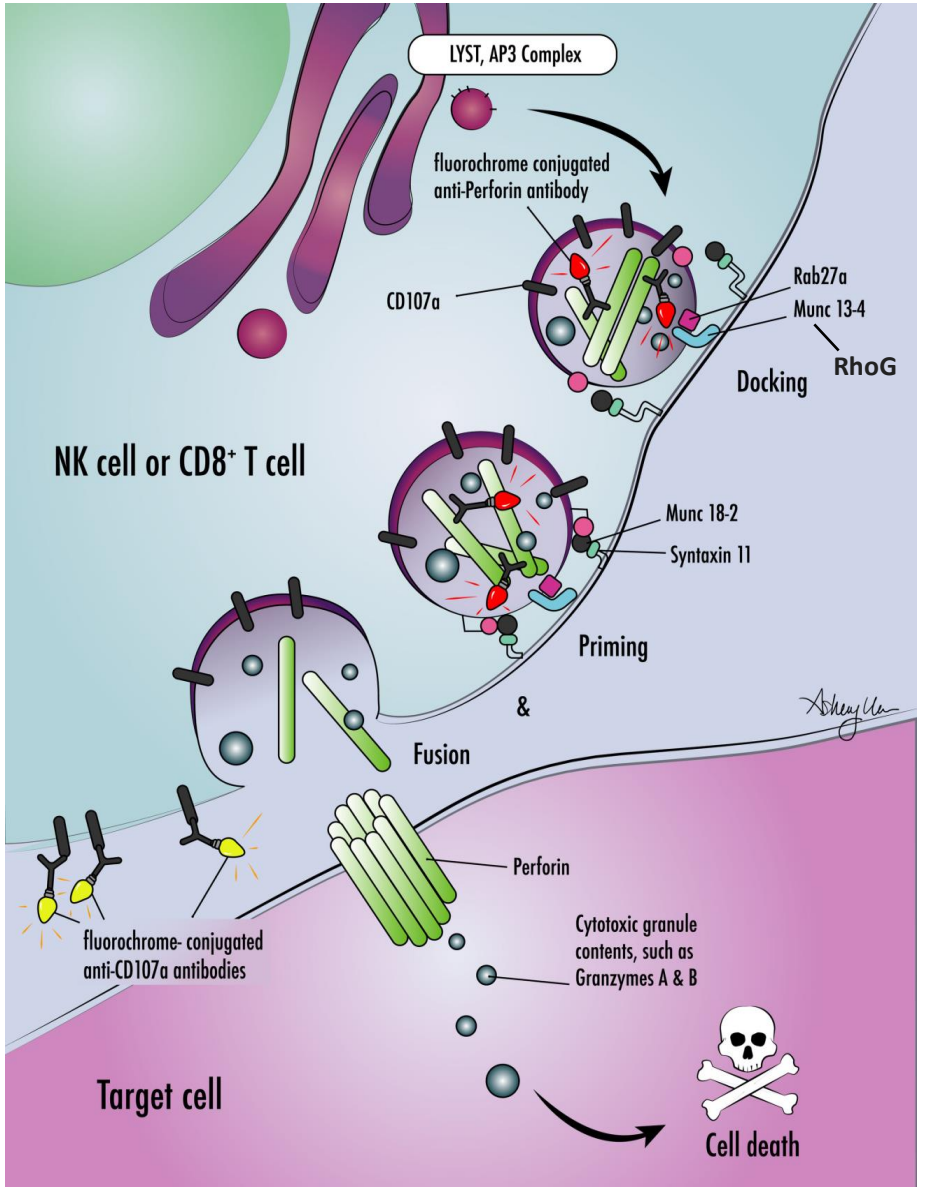
These broken genes mean the immune system can't kill infected or cancerous cells

That makes the immune system angry and it gets all fired up!



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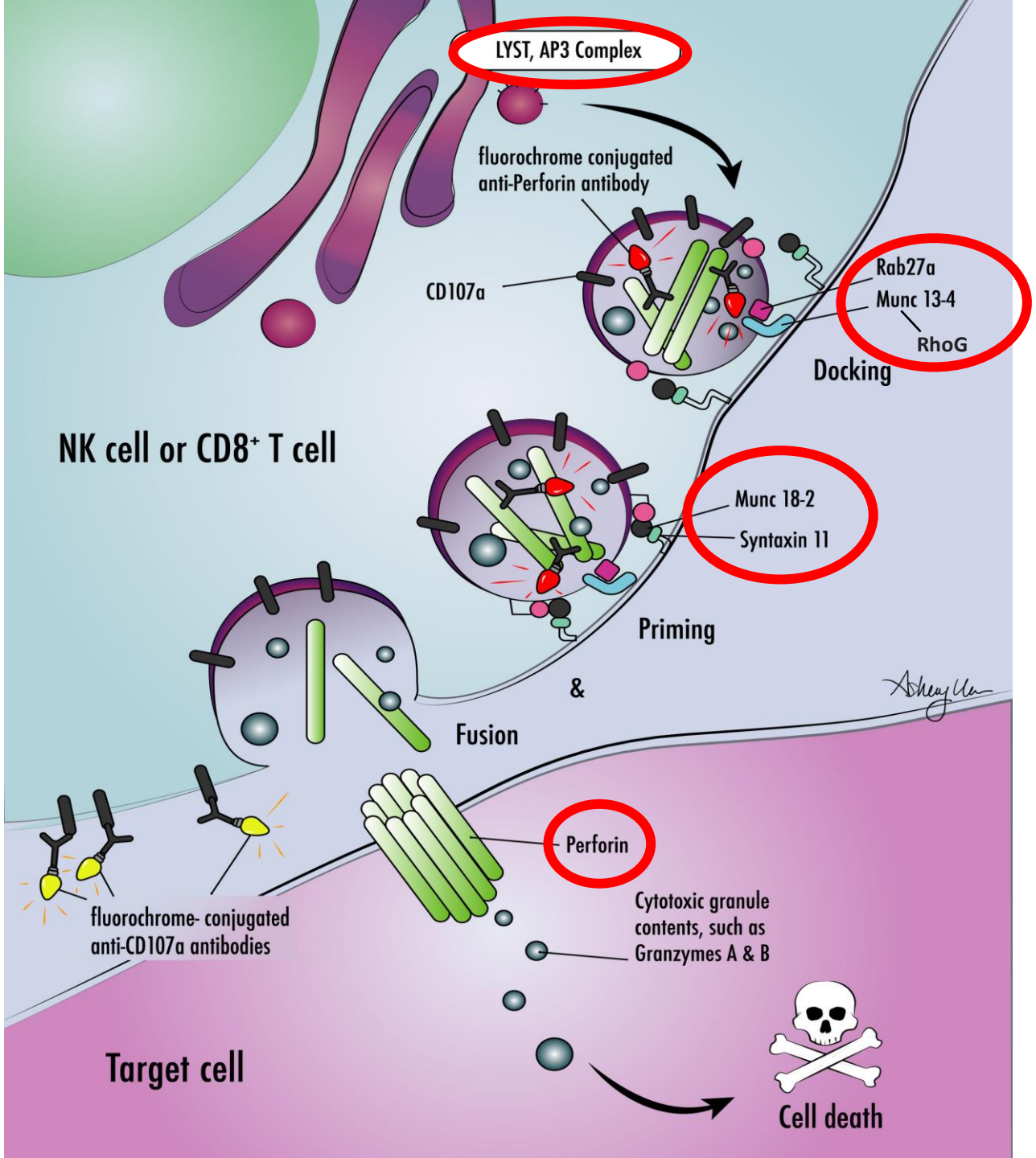
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fluorochrome conjugated
anti-Perforin antibody
CD107a
Rab27a
Munc 13-4
RhoG
Docking
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contents, such as
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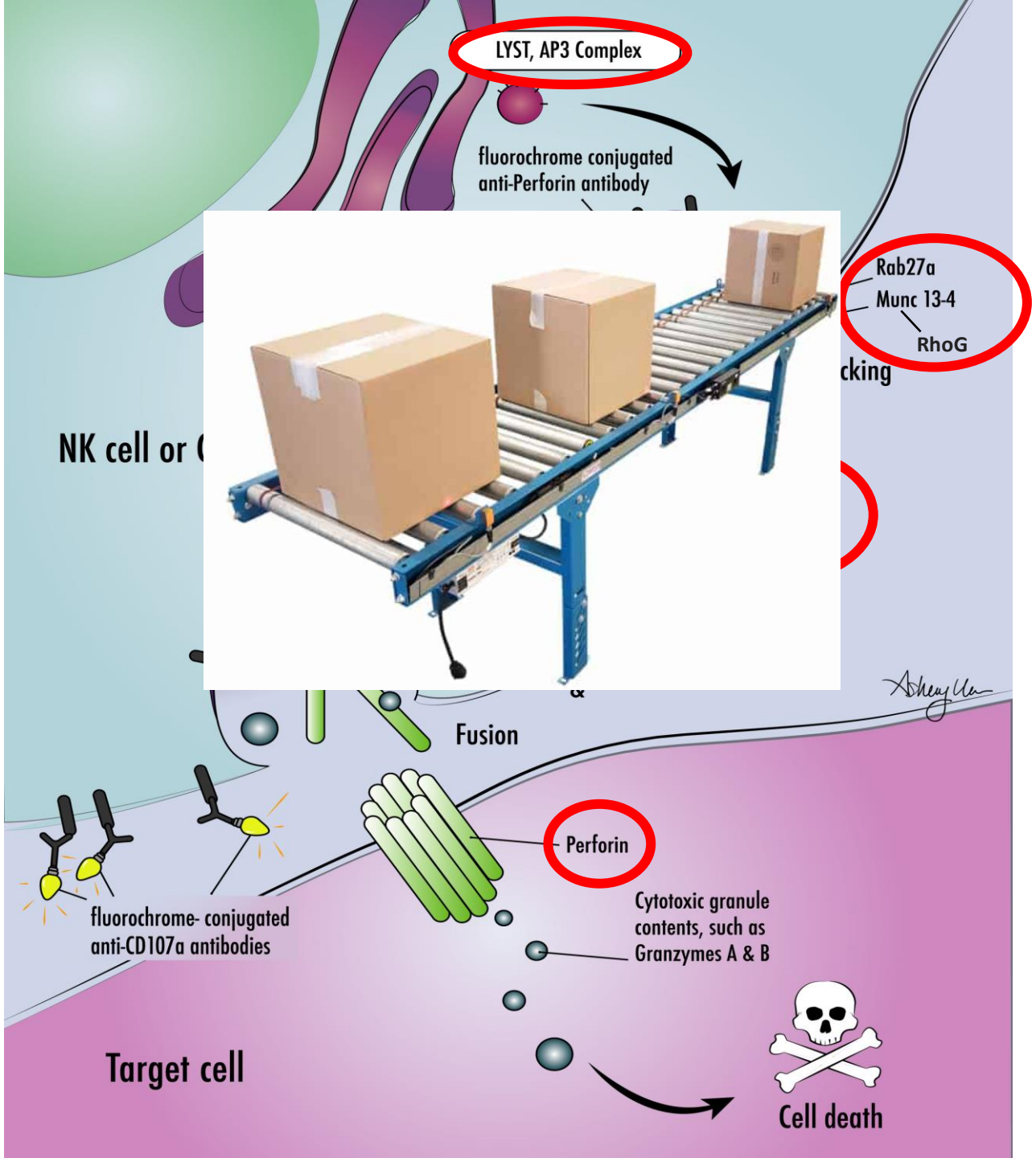
Target cell
Cell death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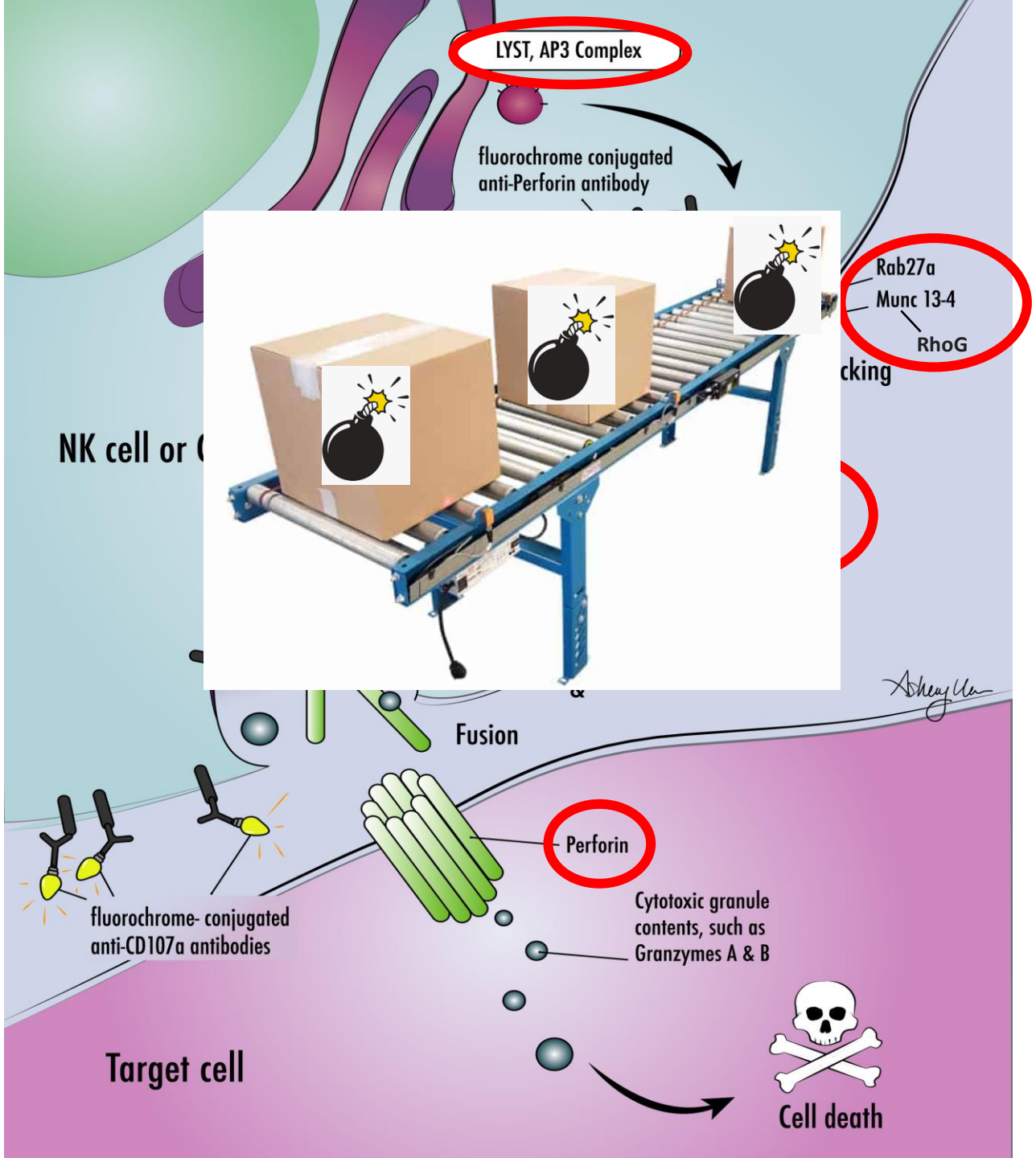
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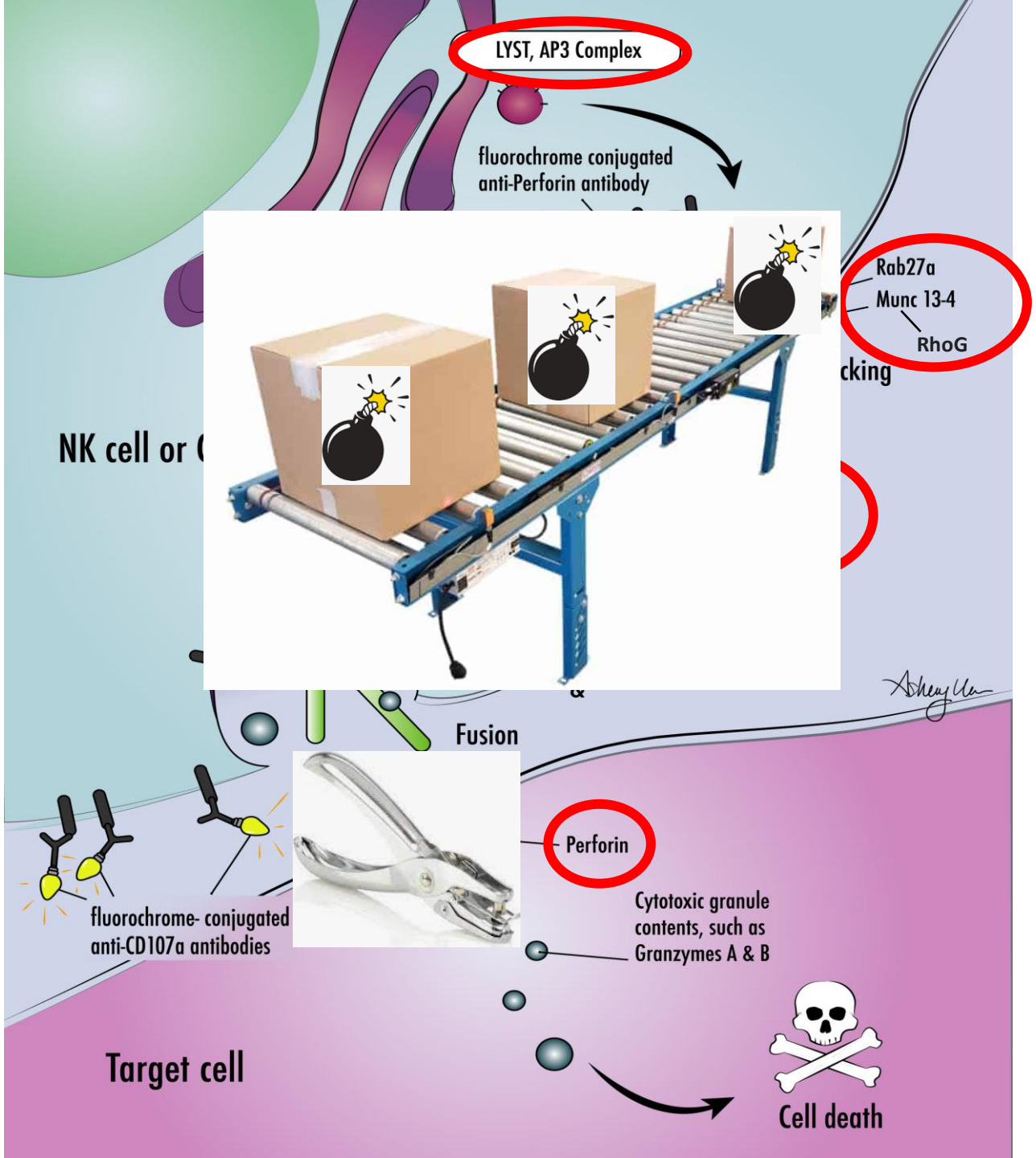
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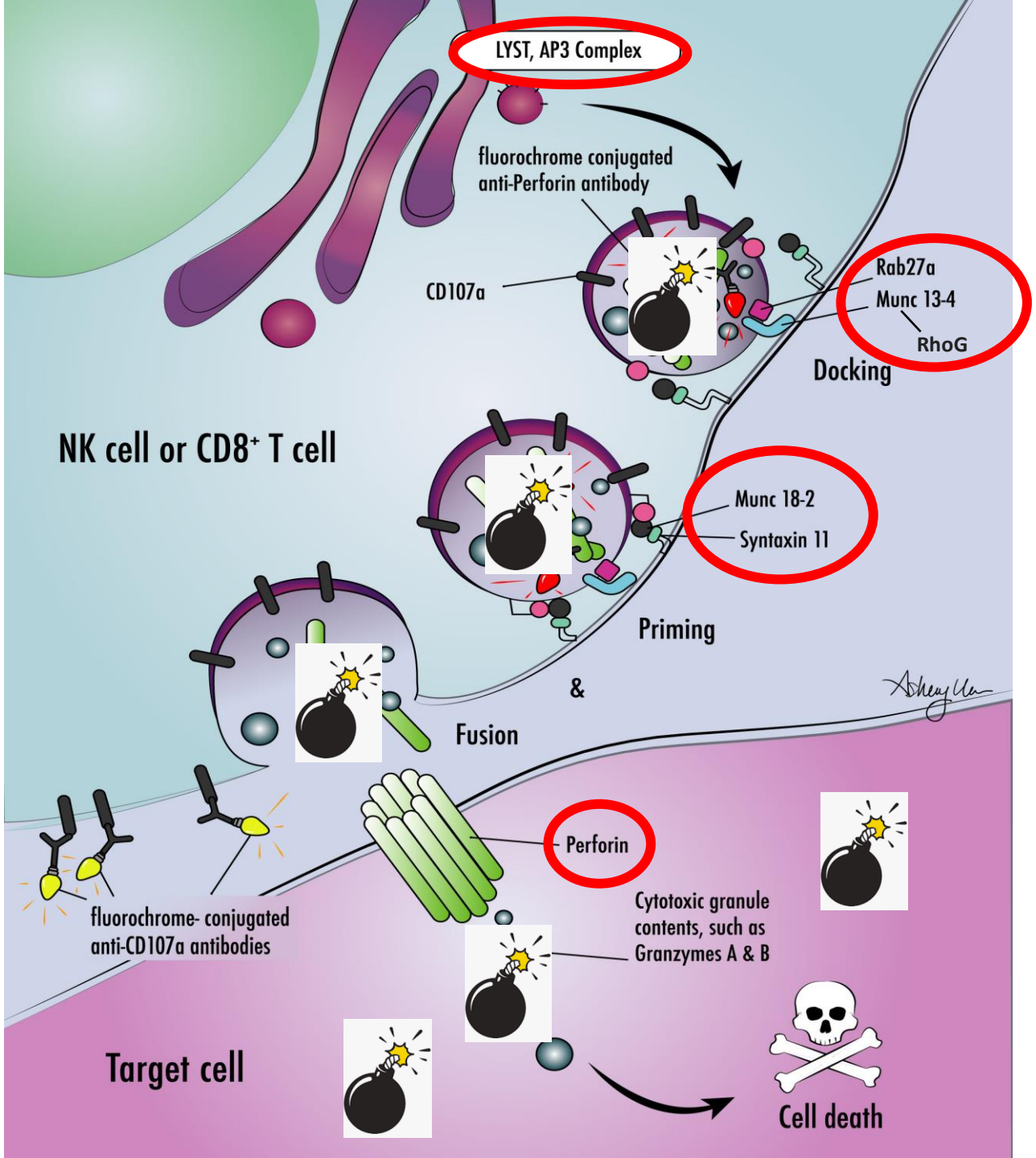
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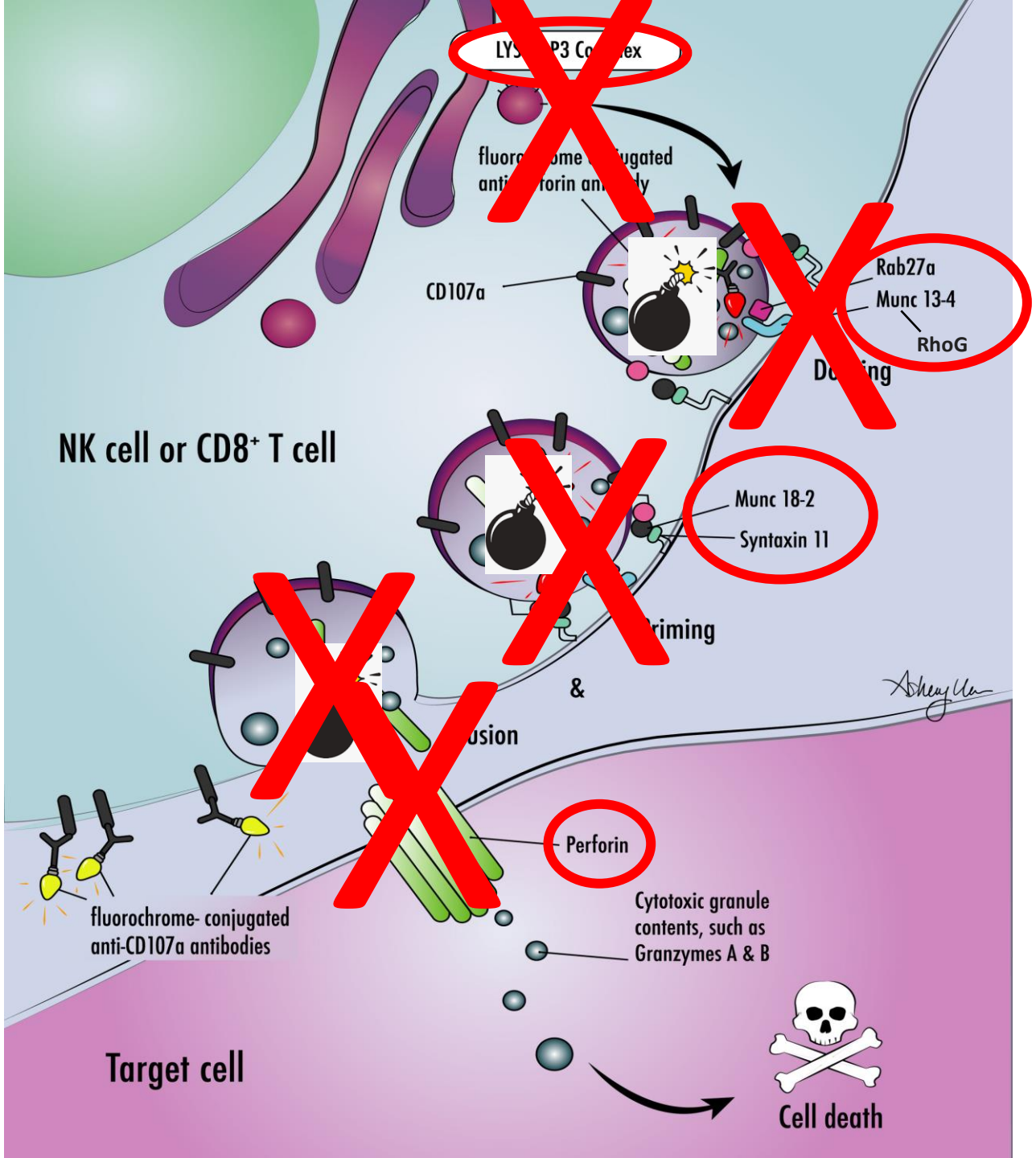
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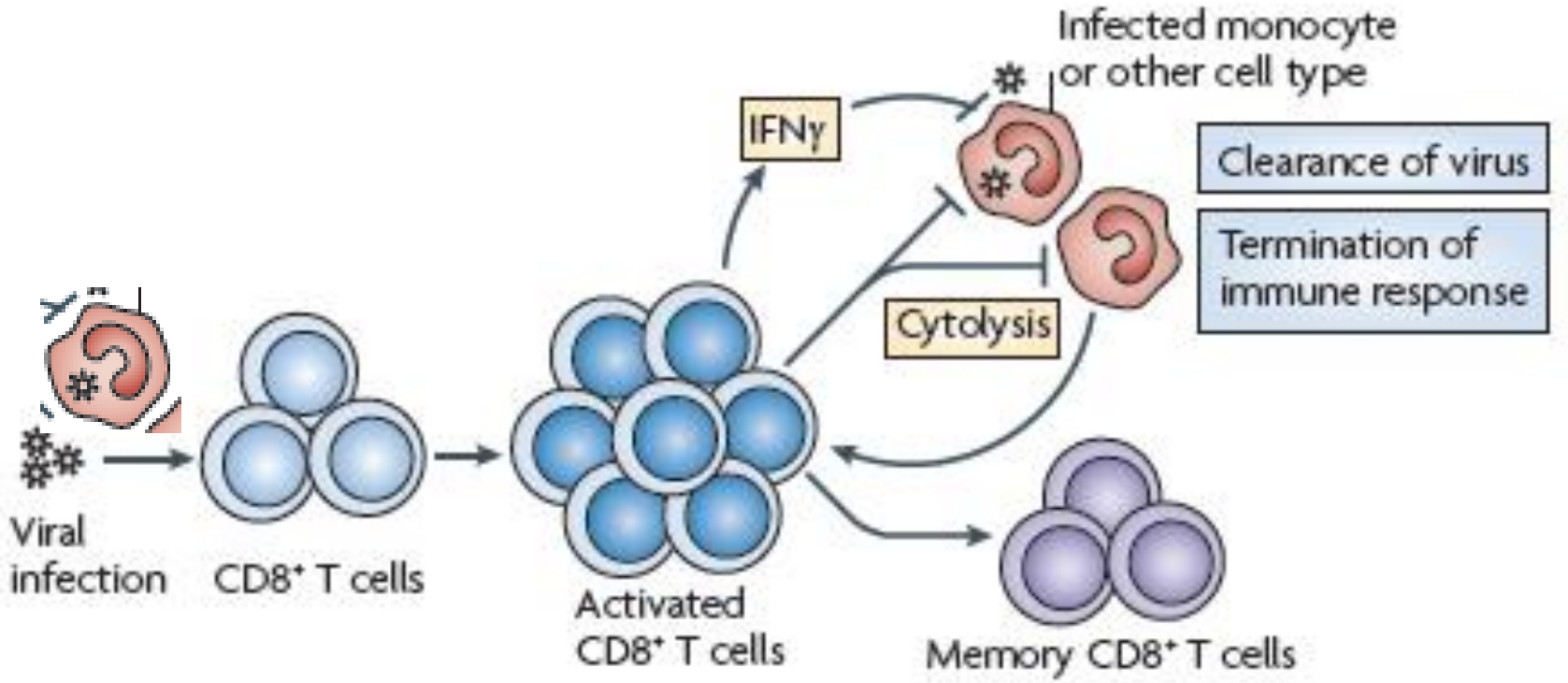
Normal Cytotoxic Response



De Saint Basile, Nature Rev Imm, 2010

Crippled Cytotoxic Response

#1 Can't Kill Target

#2 Expanded Lymphocytes Won't Die

De Saint Basile, Nature Rev Imm, 2010

Genetic HLH Disorders

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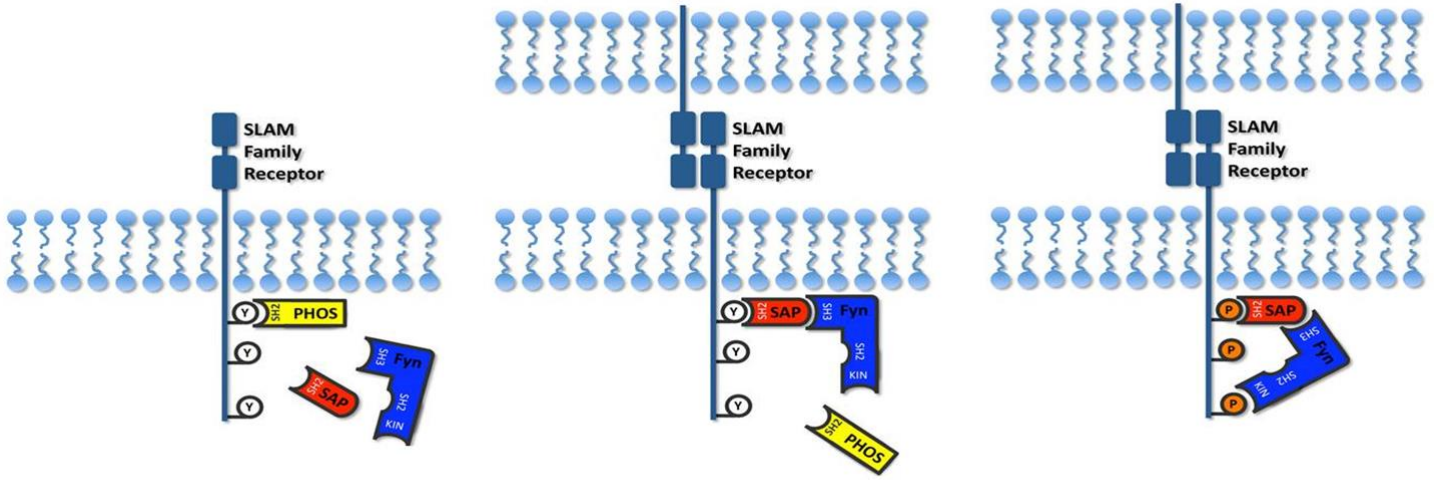
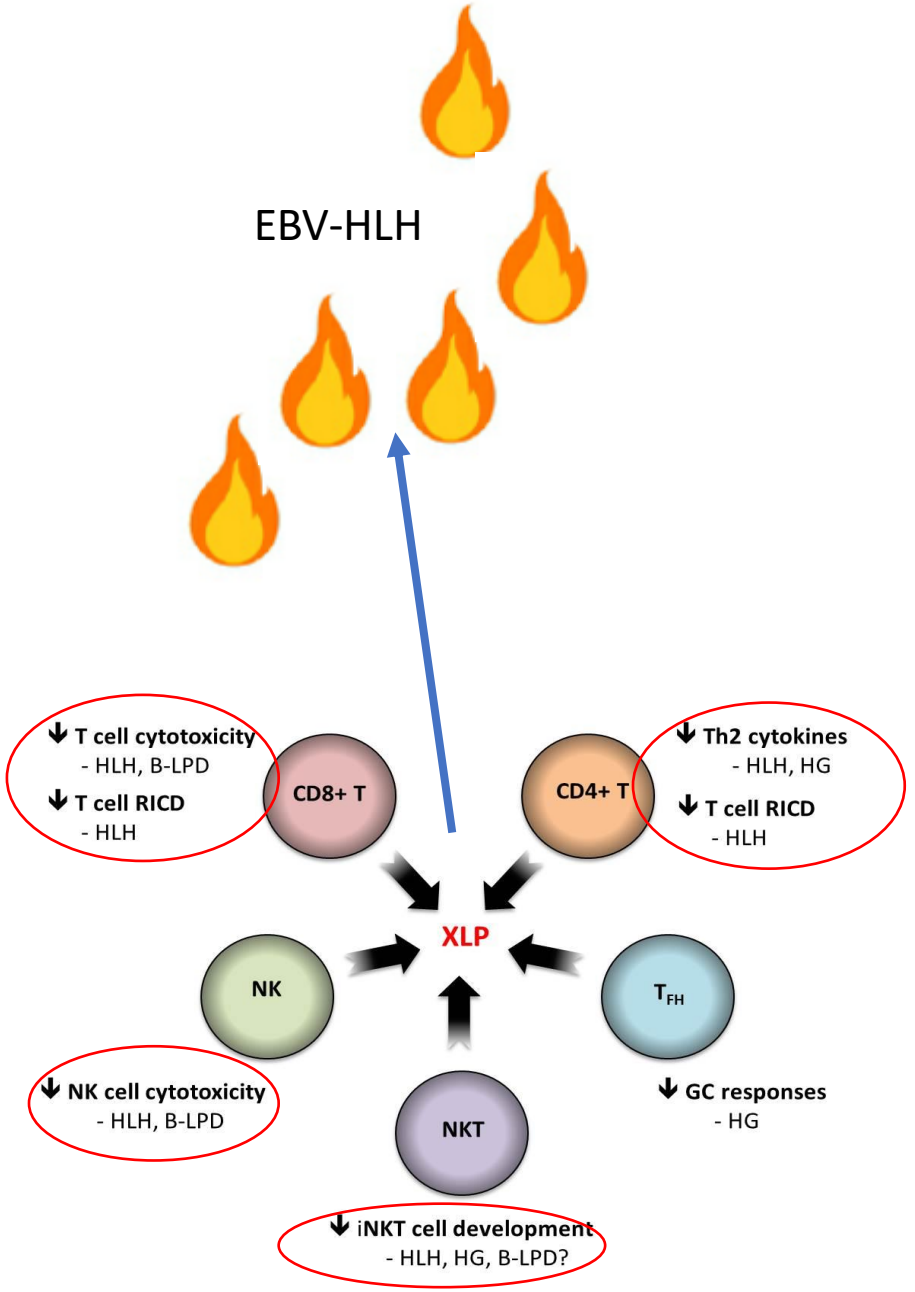
- **XLP-1: Defective** SLAM-receptor mediated **cytotoxicity** & other
  - *SH2D1A*





Nichols and Marsh

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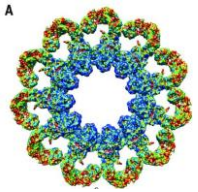
  - *SHD2D1A*
- **XLP-2:** Dysregulated TNF-R and NLRP3 **Inflammasome** function & other
  - *XIAP*
- ***NLCR4:*** *GOF/Constitutively Active NLRC4* ***Inflammasome*** *Function*
- ***CDC42:*** *GOF variants in the C-terminal region of CDC42 lead to increased Pyrin* ***Inflammasome*** *Function (Nishitani-Isa et al)*



NLRC4 Inflammasome

Zhang et al, 2015

Constitutively Active
Due to Pathogenic GOF Variants

IL-1B
IL-18

IL-1B
IL-18

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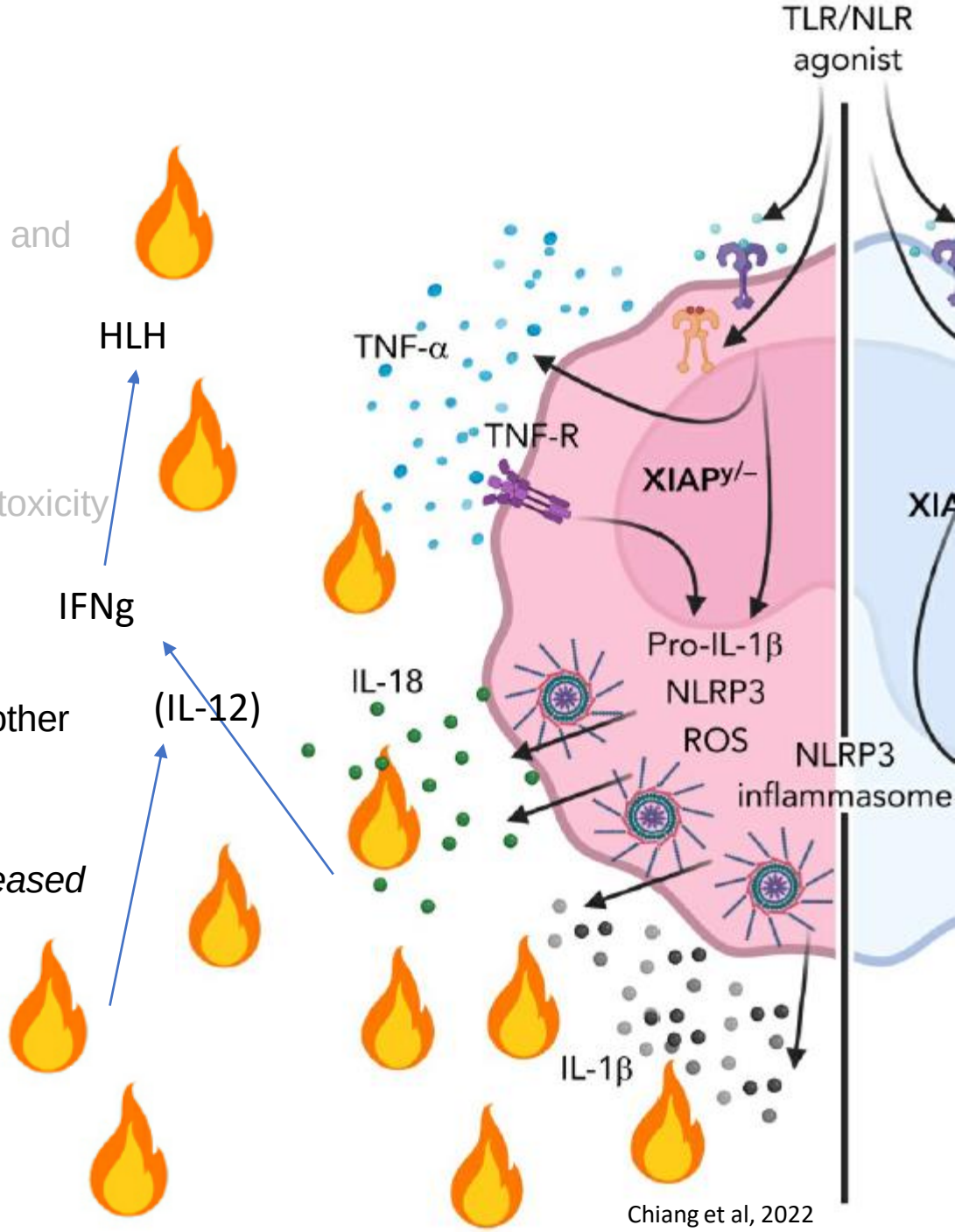

Chiang et al, 2022

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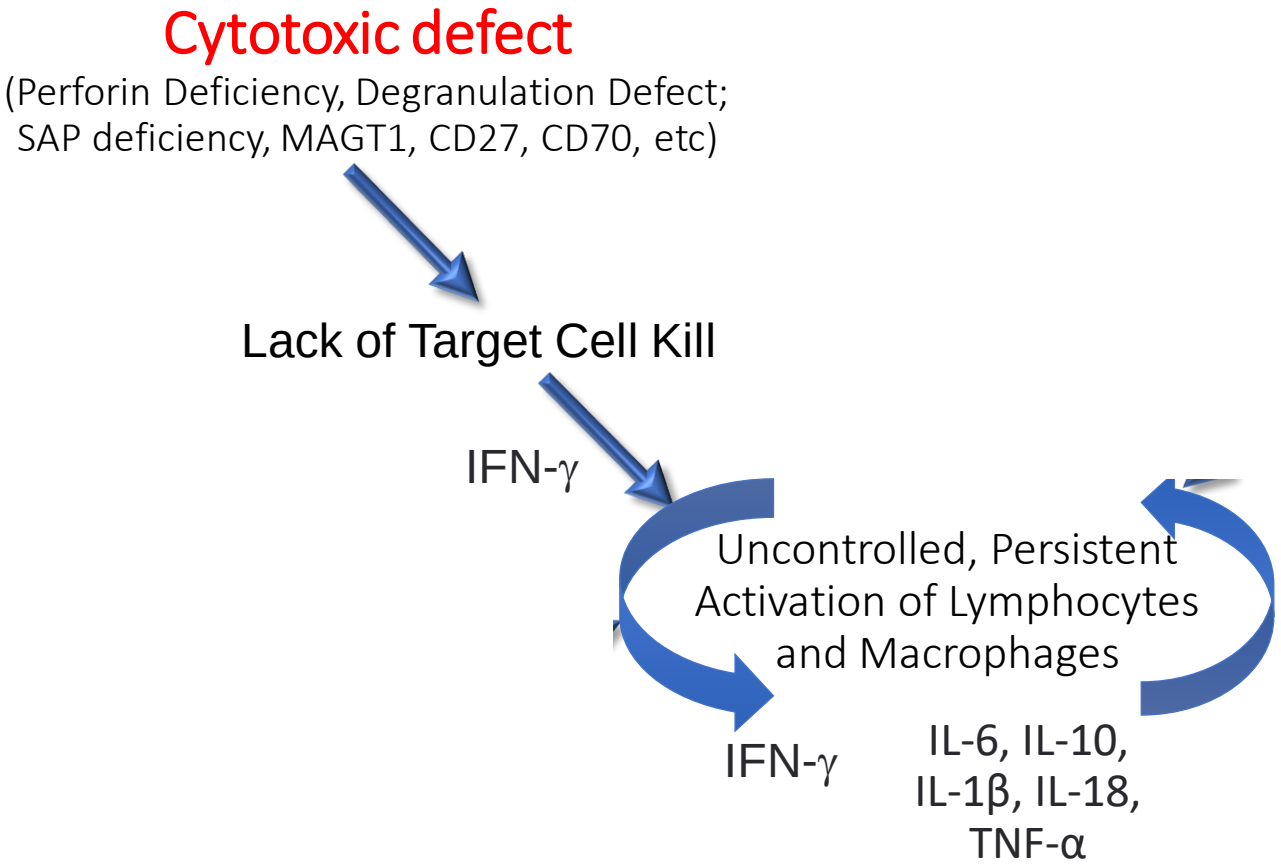
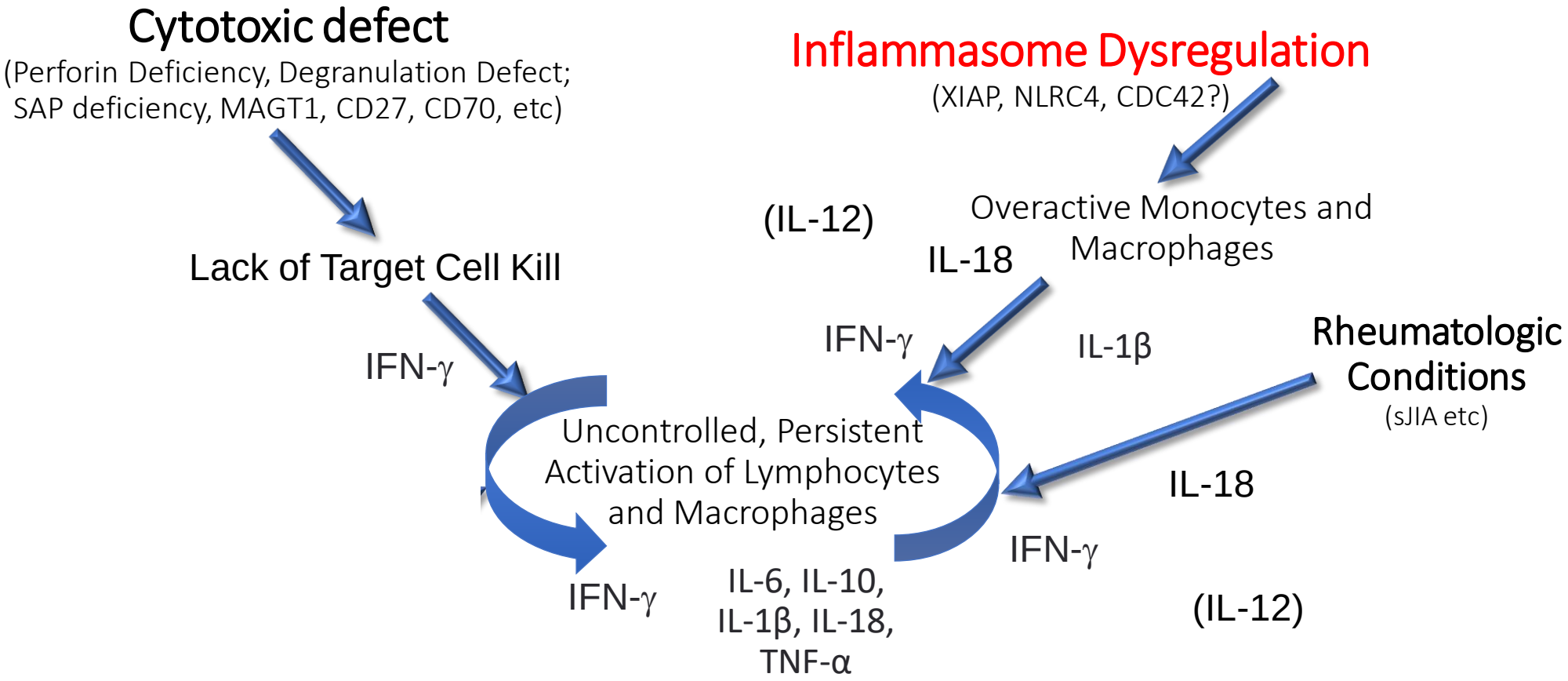
- ***CDC42:*** *Defective Formation of Actin-Based Structures; Defective Proliferation, Migration, and Cytotoxicity; Increased Inflammasome FunctionIL-1beta and Il-18 Production*
- **EBV Susceptibility Disorders:** *MAGT1, ITK, CD27, CD70, CTPS1, RASGRP1: Complex but many have specific* ***cytotoxicity defect***

Pathways to HLH/MAS



Pathways to HLH/MAS



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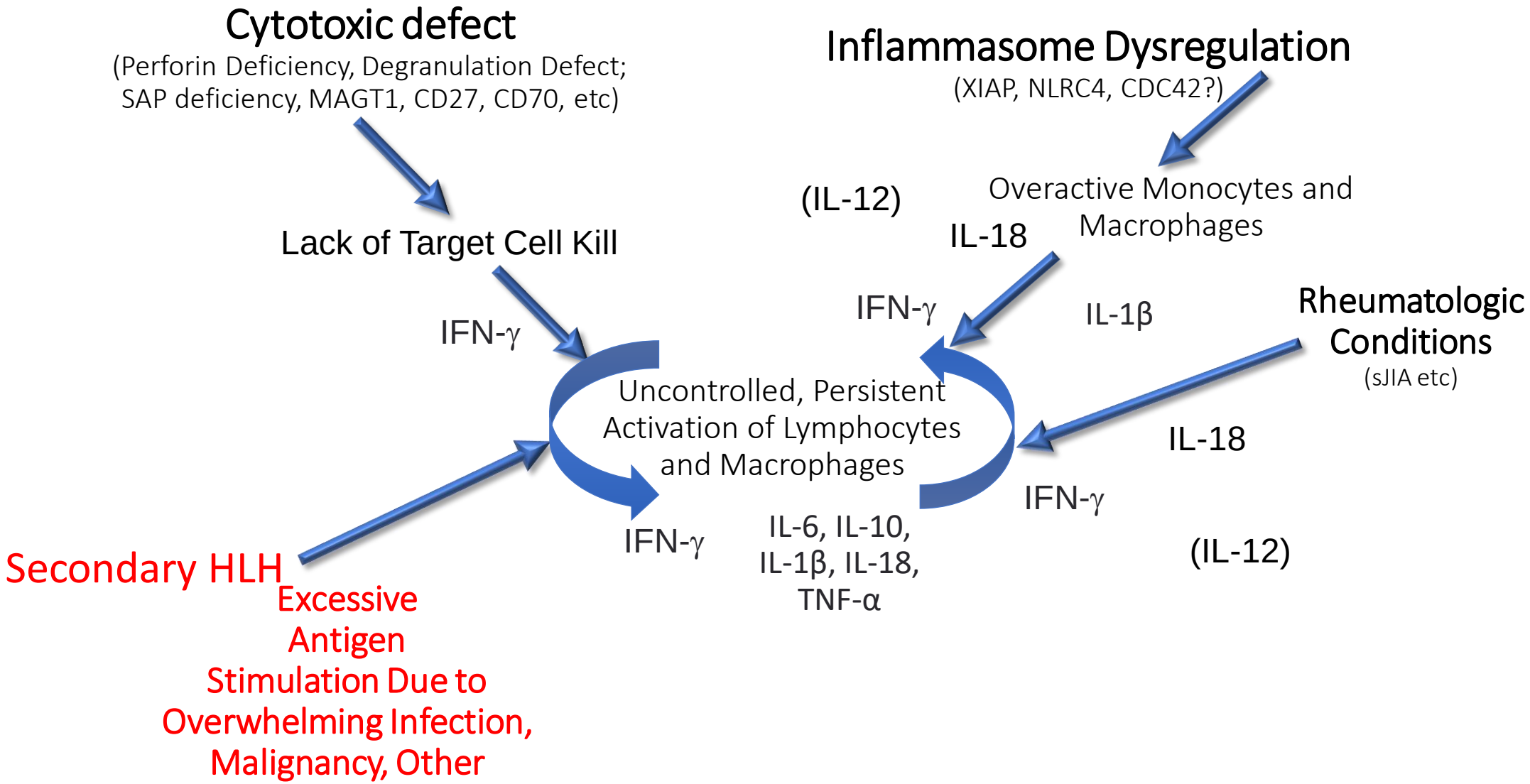
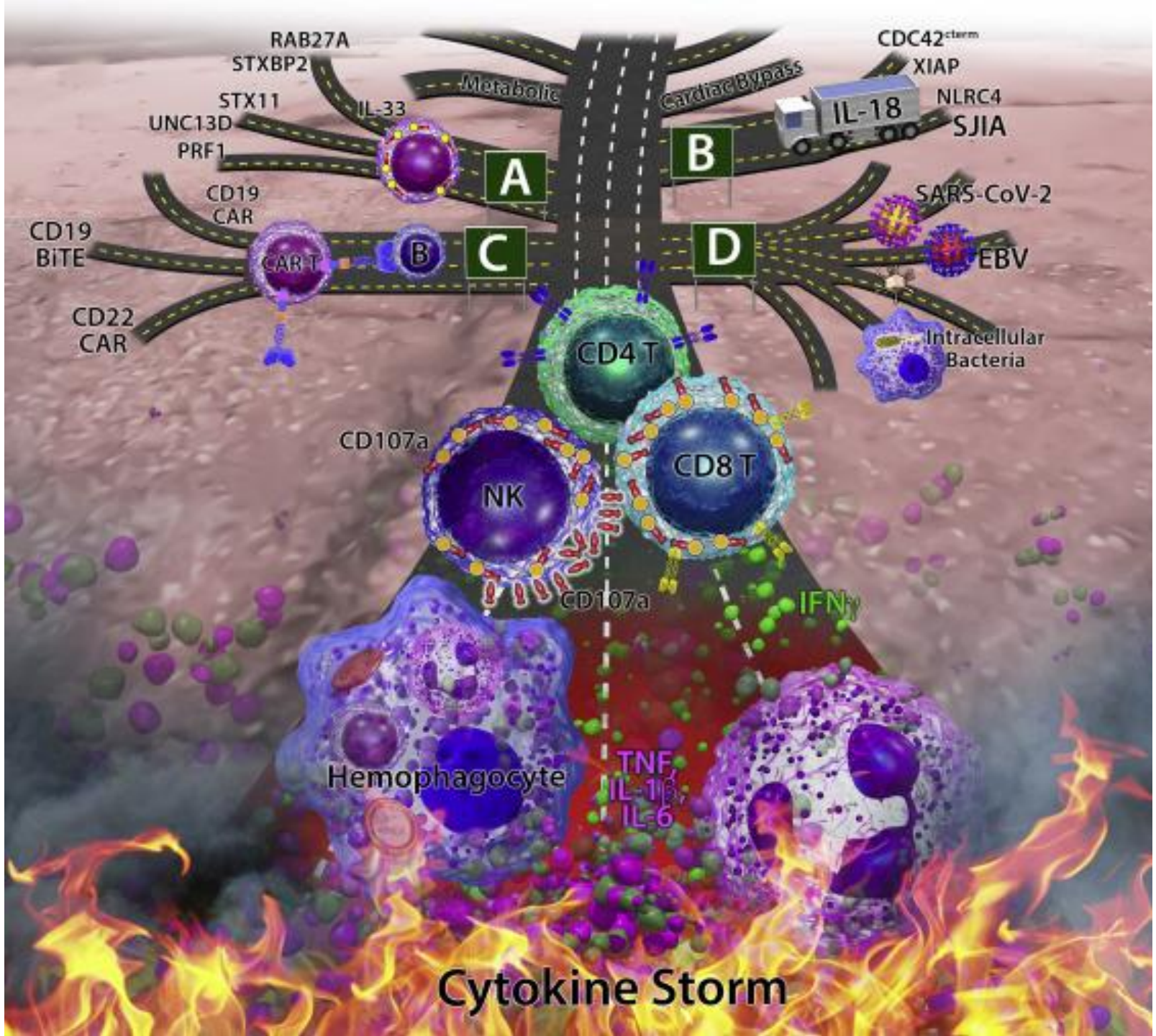




Scott Canna & Randy Cron

Blood tests that help diagnosis a syndrome of HLH and monitor activity: Biomarkers

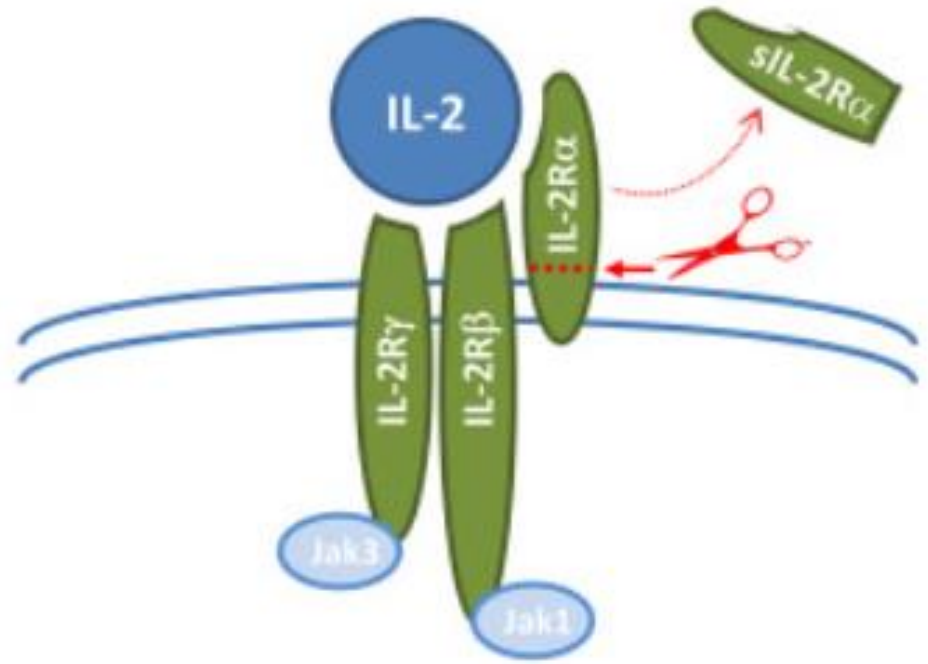
- Ferritin
- Soluble IL-2 Receptor
- HLA-DR
- CXCL9
- IL-18
- Others

Ferritin

- Ferritin stores iron
- Ferritin increases during inflammation
- Easy to check at most hospitals
- Some degree of ferritin elevation is essentially required for the diagnosis of HLH.
  - A level greater than 500 µg/L is very sensitive
  - A level greater than 2000 µg/L can better differentiate HLH

Soluble IL-2R

- Activated T cells (immune system cells) upregulate the IL-2 receptor, which is cleaved by proteases released by activated mononuclear phagocytes
- High levels indicate high levels of T cell activation- it's a good barometer of T cell activation

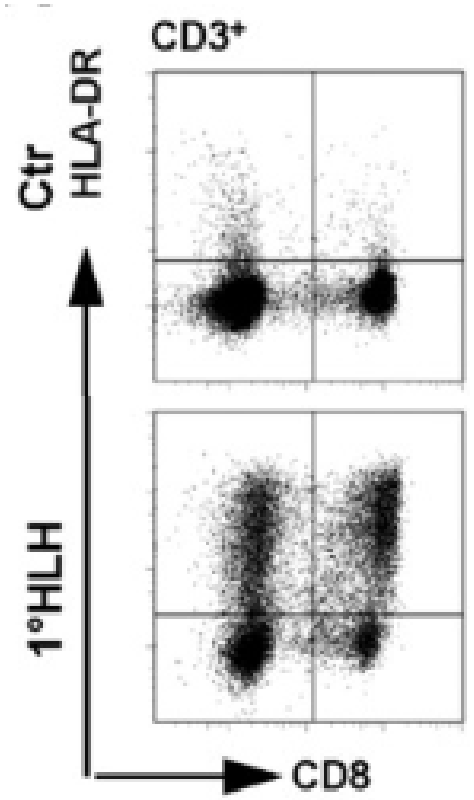


The IL-2 – IL-2 receptor pathway in health and disease: The role of the soluble IL-2 receptor

Jan Damoiseaux

HLA-DR

- Some centers use T cell HLA-DR expression (a marker of T cell activation) in place of or in addition to measurements of sIL-2R



Amman et al

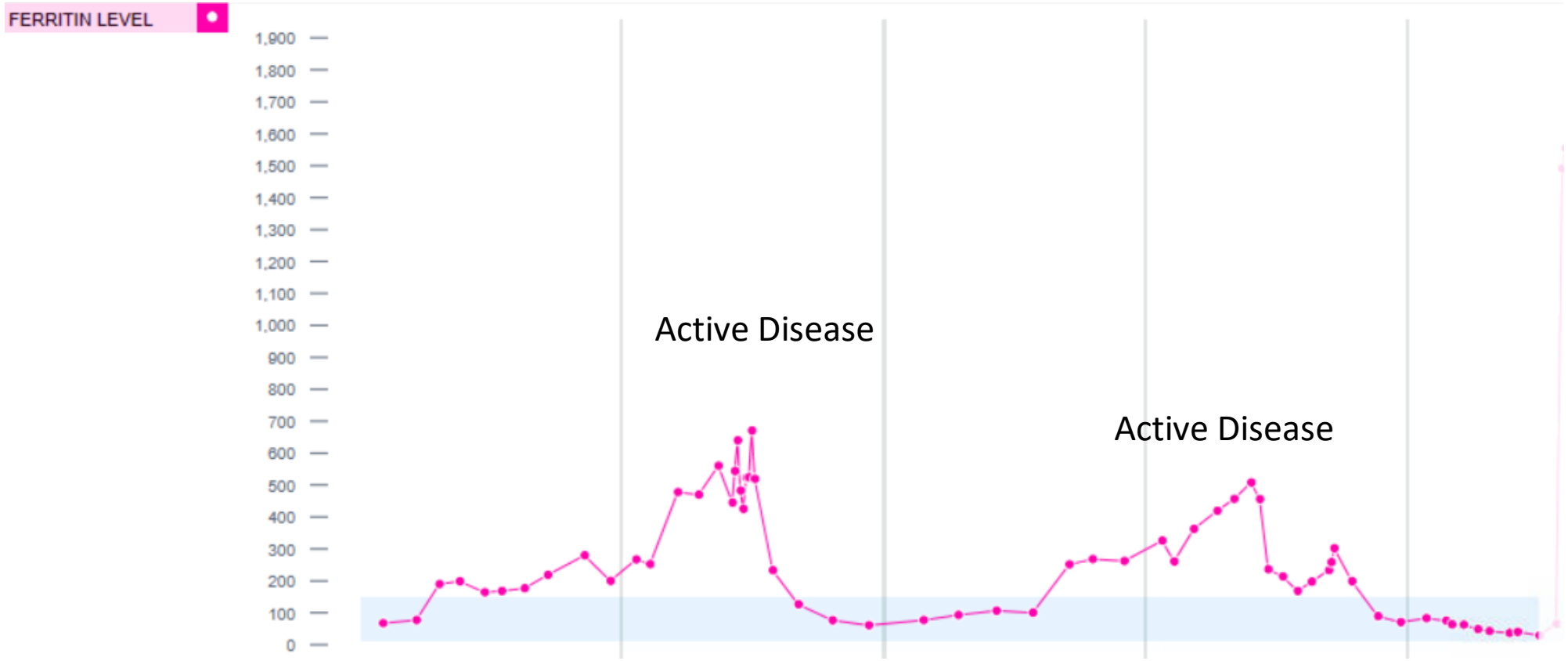
Newer Tests: CXCL9 and IL-18

- CXCL9: Good marker of IFNg pathway activity
  - CXCL9 is secreted by monocytes, endothelial cells, fibroblasts in response to IFN-γ which is a critical inflammatory cytokine in HLH
- IL-18: Good marker of Inflammasome Activity
  - The immature forms of IL-18 and IL-1beta are activated by inflammasomes, and high levels indicate that inflammasomes are abnormally active

How do we use these tests?

- Elevations in any or all of these tests help make a diagnosis of the syndrome of HLH
- We can also watch the levels rise and fall as HLH is more or less active

Example: Ferritin



How Do You Diagnose Genetic HLH Disorders?

GENETIC TESTING

SCREENING TESTS

Do All HLH Patients Need Genetic Testing?

- All “young” patients need testing
- Some “old” patients need testing

- It is important to know if there is a genetic disease that caused the HLH
  - Genetic= risk of recurrent HLH
  - Genetic= many (not all) will need a bone marrow transplant

Types of Genetic Tests

- HLH or Immune Deficiency Panels
  - Panels look at many HLH and/or Immune Deficiency genes all at once
- Whole Exome/Whole Genome Sequencing
  - This testing looks at HLH and Immune Deficiency genes along with genes outside of the immune system
- Single Gene Sequencing
  - This is used when the family is already known to have a genetic disease.
    - If one child has HLH due to pathogenic variants in *PRF1*, then the other siblings can just be tested for variants in *PRF1*

Screening Tests

Screening tests come back quicker than most genetic tests

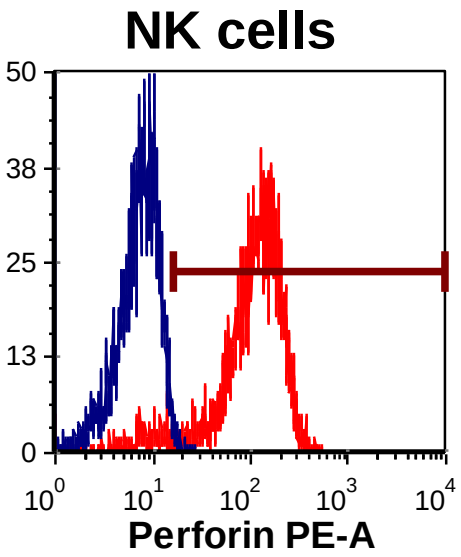
These are blood tests that look for protein deficiencies or abnormal immune system cell function

Selected Screening Tests

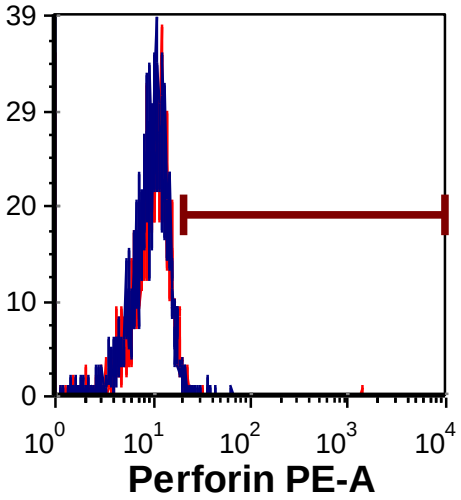
- Familial HLH
  - PRF1
    - Perforin Expression
  - UNC13D, STXBP2, STX11, RAB27A
    - CD107a
- XLP1
  - SAP Expression
- XLP2
  - XIAP Expression
  - Functional Assay
- Griscelli Syndrome
  - CD107a
- Chediak Higashi
  - CD107a

Example: Perforin Deficiency

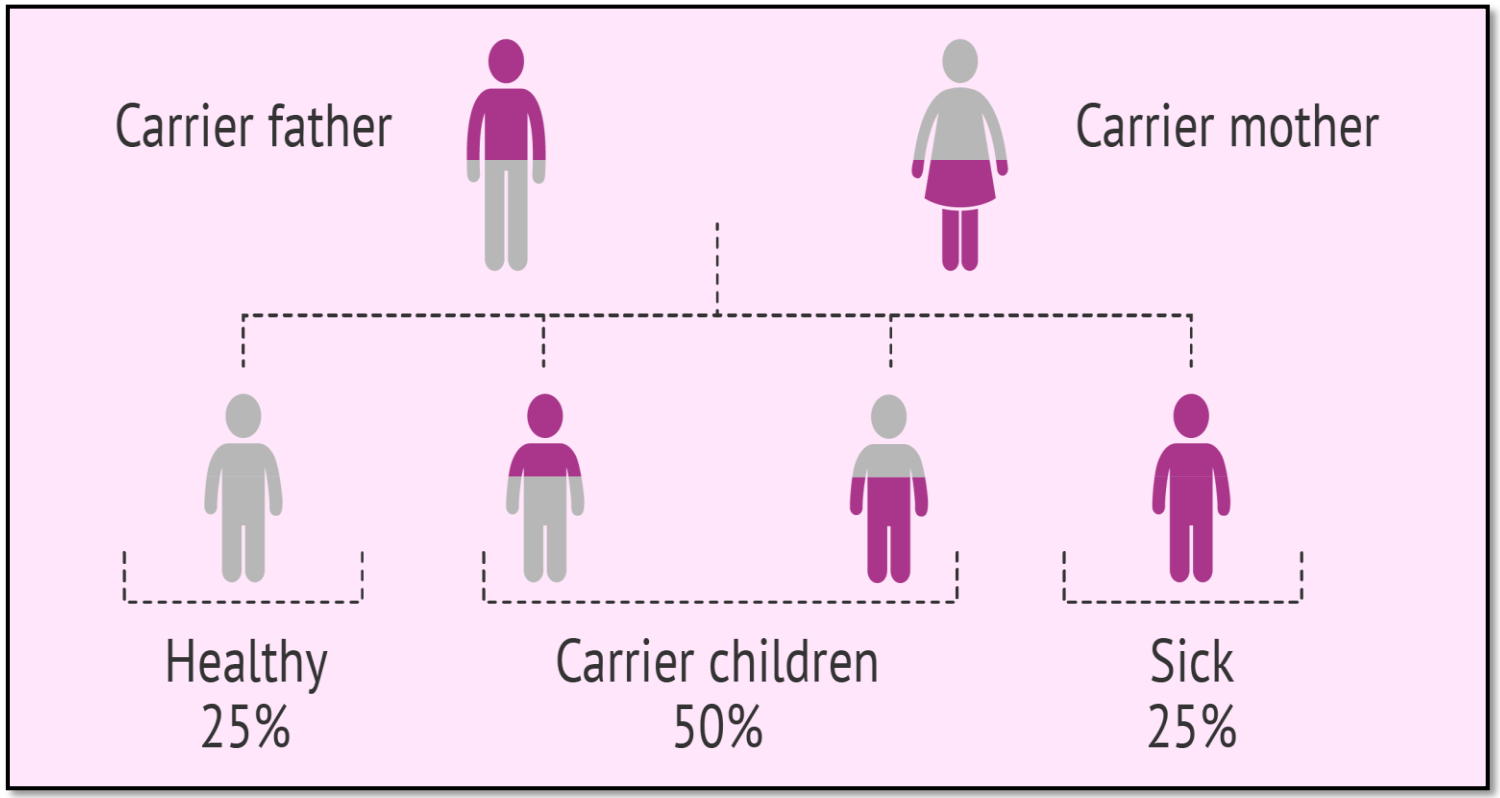
Normal Adult



Patient



Inheritance of Genetic HLH Disorders

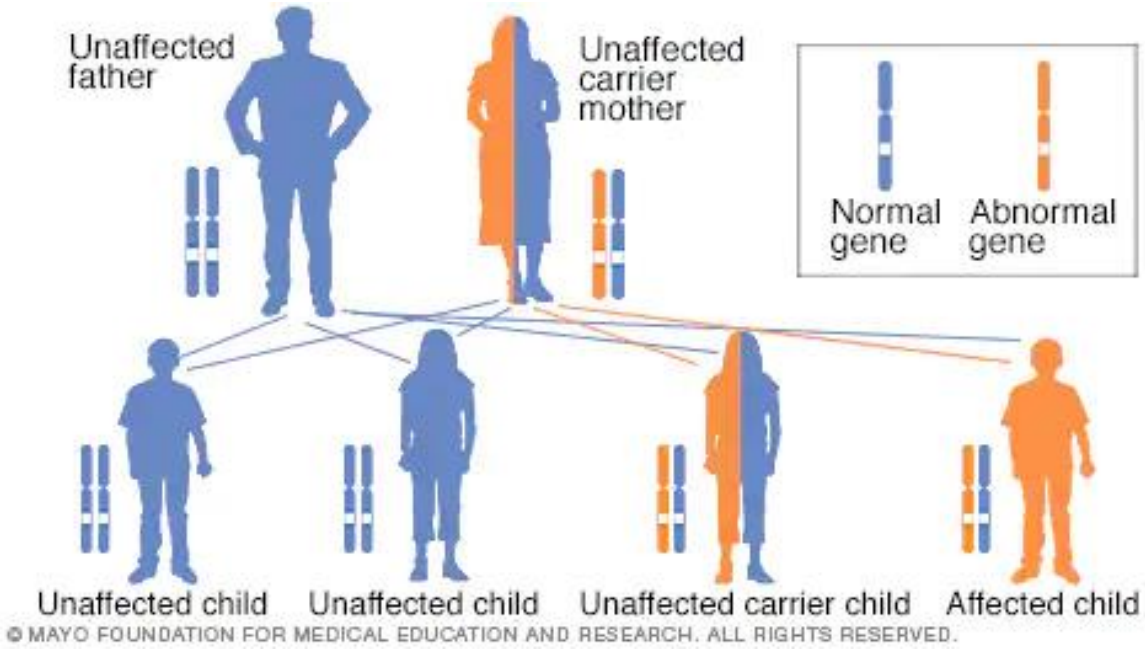


Autosomal Recessive

PRF1, UNC13D, STXBP2, STX11

25% of children are sick

(male or female)

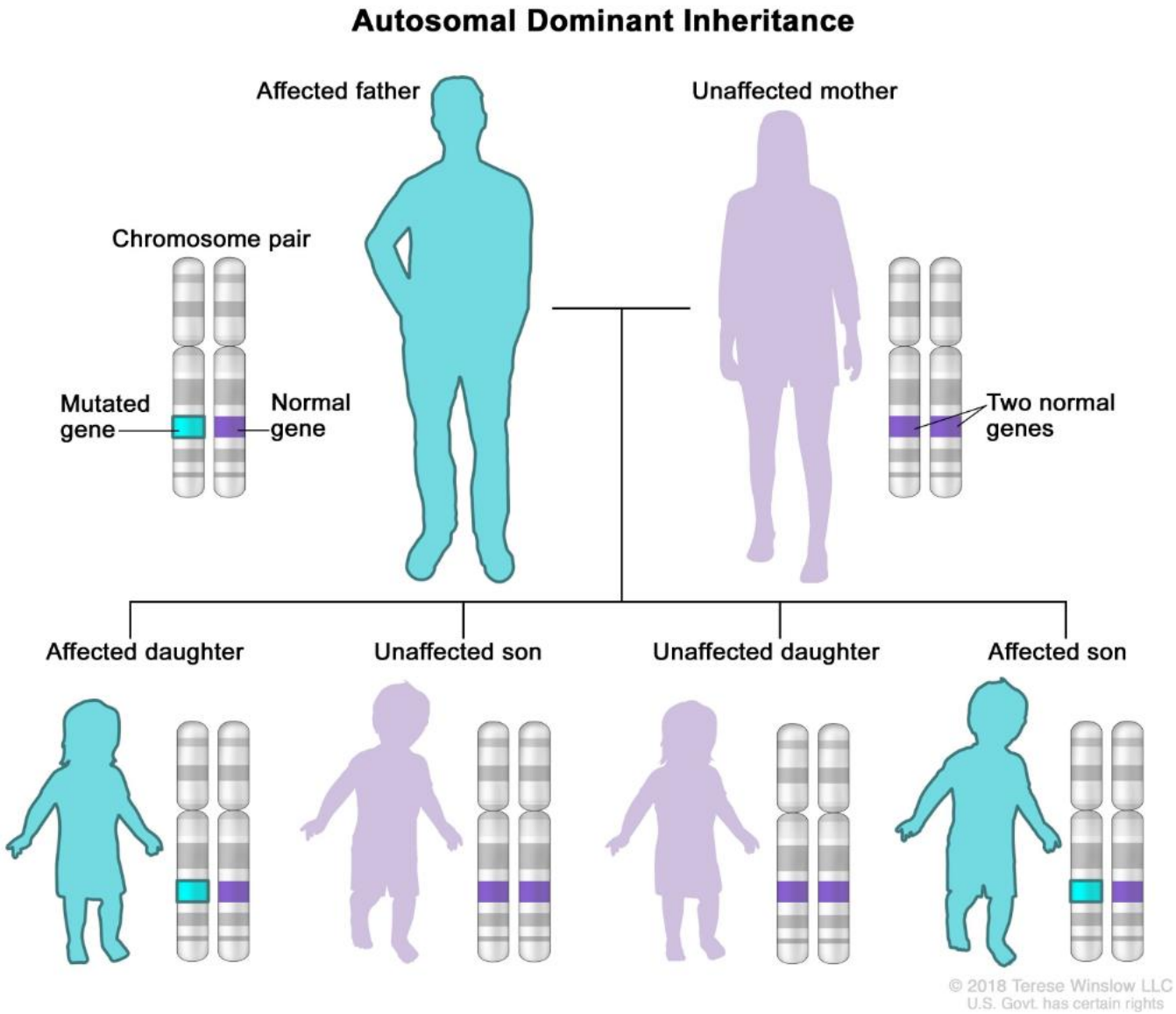


X-linked

XIAP, SH2D1A

50% of males are sick

50% of females are carriers



Autosomal Dominant

NLRC4

50% of children are sick

(male or female)

How Do We Treat HLH/MAS?

How Do We Treat HLH/MAS?

Treat HLH/MAS with Chemo/Immuno-Therapy

Secondary HLH

Many (not all) Primary HLH

HCT

Figure Out What Is Causing HLH

Treat Underlying Predisposition/Trigger

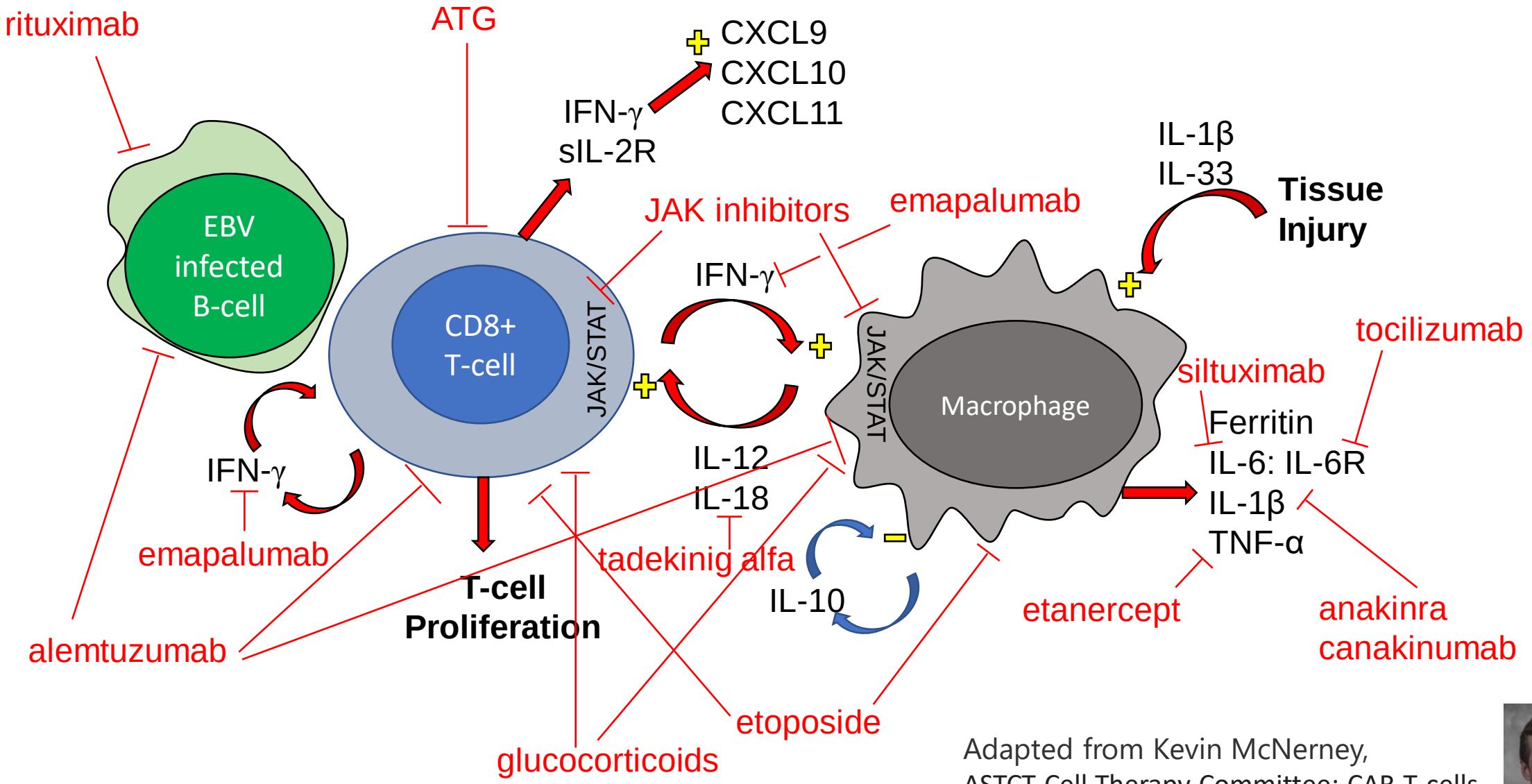
Adapted from Mike Jordan

How do we treat HLH? No single answer.

- Treatment modeled on HLH-1994 (steroids, etoposide/VP-16, with or without cyclosporine) is still widely used and recommended, but more treatment approaches are now available, and care is evolving.

- Disclaimer: Individual treatment decisions should be made with the clinical context of the patient in mind, with consideration of local center practices, and in consultation with physicians experienced in the treatment of HLH.

What can we use to treat HLH?



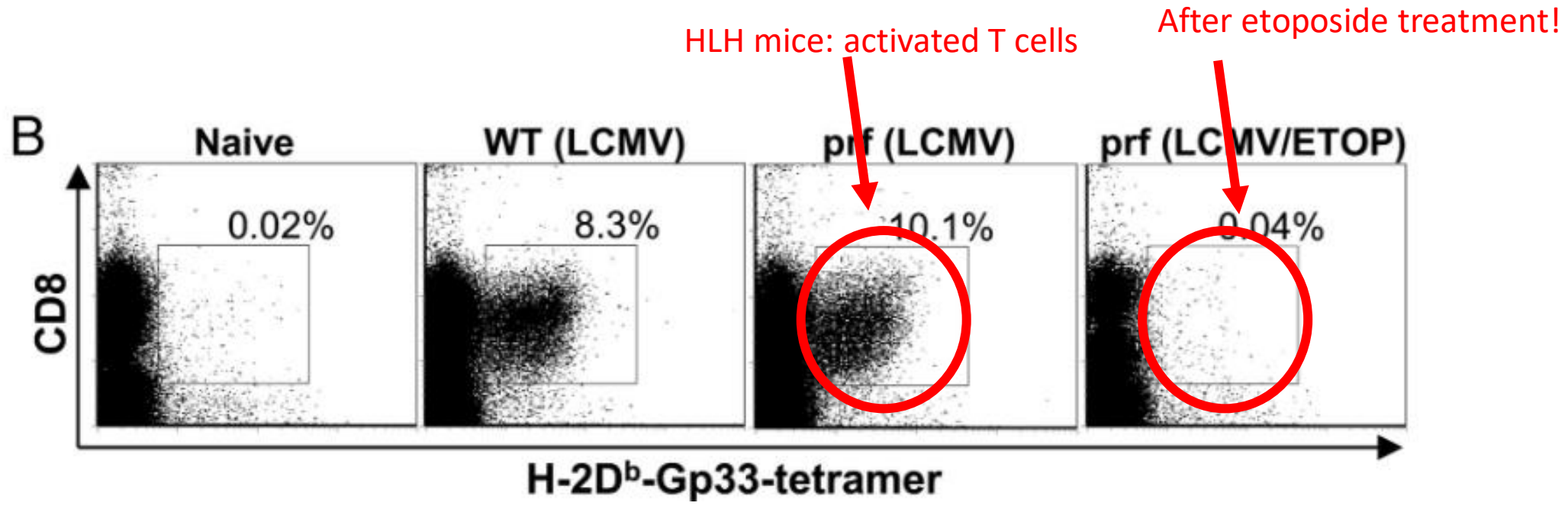
Adapted from Kevin McNerney, ASTCT Cell Therapy Committee: CAR T-cells and HLH Working Group

Dexamethasone & Etoposide +/- Cyclosporine

- Dexamethasone and etoposide usually “modeled” on the HLH 1994 protocol.

Etoposide kills activated immune system cells and reduces inflammation

- Etoposide is a chemotherapy used in various cancer treatments



Johnson et al, 2014

Histiocyte Society Recommendations

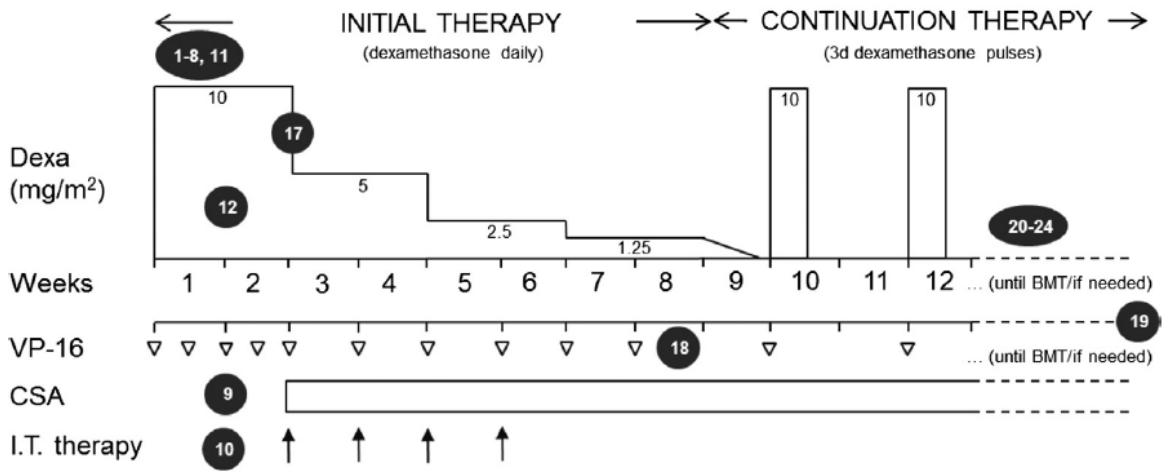
Review > J Allergy Clin Immunol Pract. 2018 Sep-Oct;6(5):1508-1517.
doi: 10.1016/j.jaip.2018.05.031. Epub 2018 Jul 4.

Recommendations for the Use of Etoposide-Based Therapy and Bone Marrow Transplantation for the Treatment of HLH: Consensus Statements by the HLH Steering Committee of the Histiocyte Society

Stephan Ehl [1], Itziar Astigarraga [2], Tatiana von Bahr Greenwood [3], Melissa Hines [4], AnnaCarin Horne [3], Eiichi Ishii [5], Gritta Janka [6], Michael B Jordan [7], Paul La Rosée [8], Kai Lehmberg [9], Rafal Machowicz [10], Kim E Nichols [11], Elena Sieni [12], Zhao Wang [13], Jan-Inge Henter [14]

Histiocyte Society Consensus Recommendations

HLH-94: 2018 consensus recommendations



Dexa = Dexamethasone daily with 10 mg/m2 for 2 weeks, 5 mg/m2 for 2 weeks, 2,5 mg/m2 for 2 weeks, 1,25 mg/m2 for 1 week and taper and discontinue during 1 week. Then pulses starting every second week with 10 mg/m2 for 3 days

VP-16 (13-16) = Etoposide 150 mg/m2 i.v.

CSA = Cyclosporine A aiming at blood levels of around 200 microgram/L (monoclonal, trough value). Start after 2 weeks with 6 mg/kg daily perorally (divided in 2 daily doses)

I.T. therapy = Methotrexate doses: < 1 year 6 mg, 1-2 years 8 mg, 2-3 years 10 mg, > 3 years 12 mg each dose. Maximum 4 doses prior to re-evaluation, but start only if progressive neurological symptoms or if an abnormal CSF has not improved.

Notes Regarding Etoposide Use

- Bone marrow suppression is common. CBC should be monitored.
- Reactions can occur.
- Requires dose adjustment with renal insufficiency.
- Low blood pressure can happen if given too quickly in 1% to 2% of patients. Usually given over 1 hour.
- Other side effects: Generally well tolerated in HLH. Side effects can include hair loss, nausea, vomiting, and inflamed and sore mouth. Small increase in secondary cancer risk, particularly with cumulative dosing of 2.0 g/m2 (Pedersen-Bjergaard et al 1991).
- **Lower moderate dosing of 50-100mg/M2 once weekly recently reported by Horne et al 2021
- DO NOT USE FOR MONTHS ON END
- Patients should be on medicines to prevent infections

Notes Regarding Dexamethasone and Other Corticosteroid Use: The List is Long

- Muscle weakness
- High blood sugar
- Difficulty in regulating emotion
- Difficulty in maintaining linear thinking
- Weight gain due to increased appetite
- Corticosteroid-induced lipodystrophy (moon face, central obesity)
- Immune suppression
- Depression, mania, psychosis
- Unusual fatigue or weakness
- Abdominal pain
- Peptic ulcer (Patients should receive prophylaxis)
- Bone thinning/weakness
- Other bone problems
- Stretch marks
- Trouble sleeping
- Severe joint pain
- Cataracts or glaucoma
- Anxiety
- Severe swelling
- Mouth sores or dry mouth

Cyclosporine

9. CSA is not recommended in the first weeks of HLH-94 therapy as this may induce toxicity. In patients with primary HLH who have achieved remission, CSA may be used to potentially prevent disease reactivation. [Strong Consensus]

Review > J Allergy Clin Immunol Pract. 2018 Sep-Oct;6(5):1508-1517.
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- Side Effects: unusual hair growth/hirsutism, high blood pressure, abnormal kidney blood tests, kidney toxicity, seizures/posterior reversible encephalopathy syndrome, tremor, gum tissue growth
- Monitor Levels
- Some experts use, some experts don't.

General Care

- Patients should be on medicines to prevent infections per each institution’s standard of care
- Patients may need varying levels of supportive care and blood transfusion and other support
- May need brain/central nervous system treatment

How Well Do Dexamethasone and Etoposide Work?

- Dexamethasone, Etoposide, -/+ Cyclosporine
  - 25% Remission Rate
  - 50% Remission Rate
  - 75% Remission Rate
  - 100% Remission Rate

How Well Do Dexamethasone and Etoposide Work?

- Dexamethasone, Etoposide, -/+ Cyclosporine
  - 25% Remission Rate
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  - 75% Remission Rate
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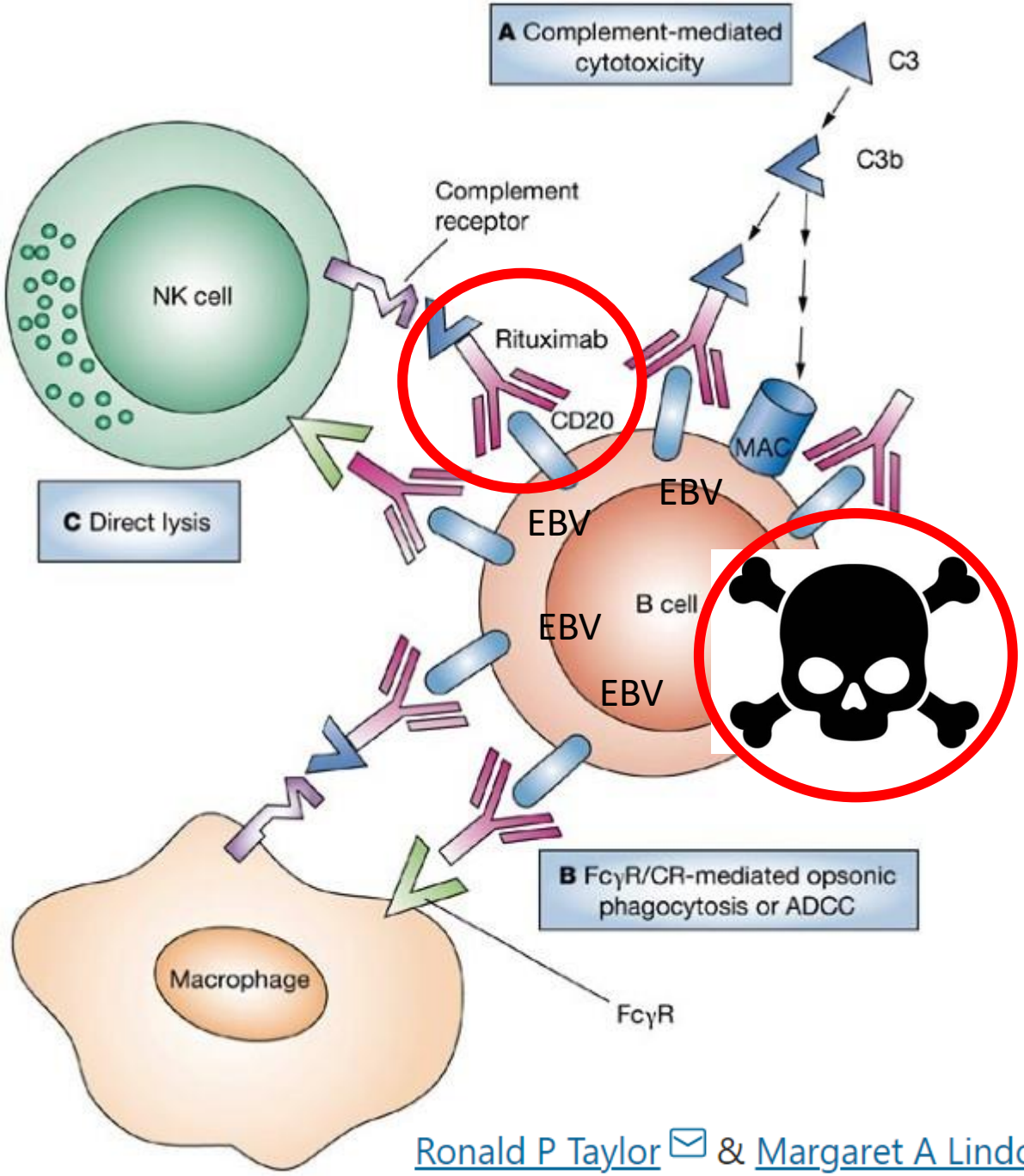
What are some other treatments can we use?

- Rituximab (for EBV-HLH)
- Anakinra
- Emapalumab
- Liposomal Doxorubicin Regimen
- PD-1 Inhibitors? (for EBV-HLH)
- ATG
- Alemtuzumab
- Jak Inhibitors

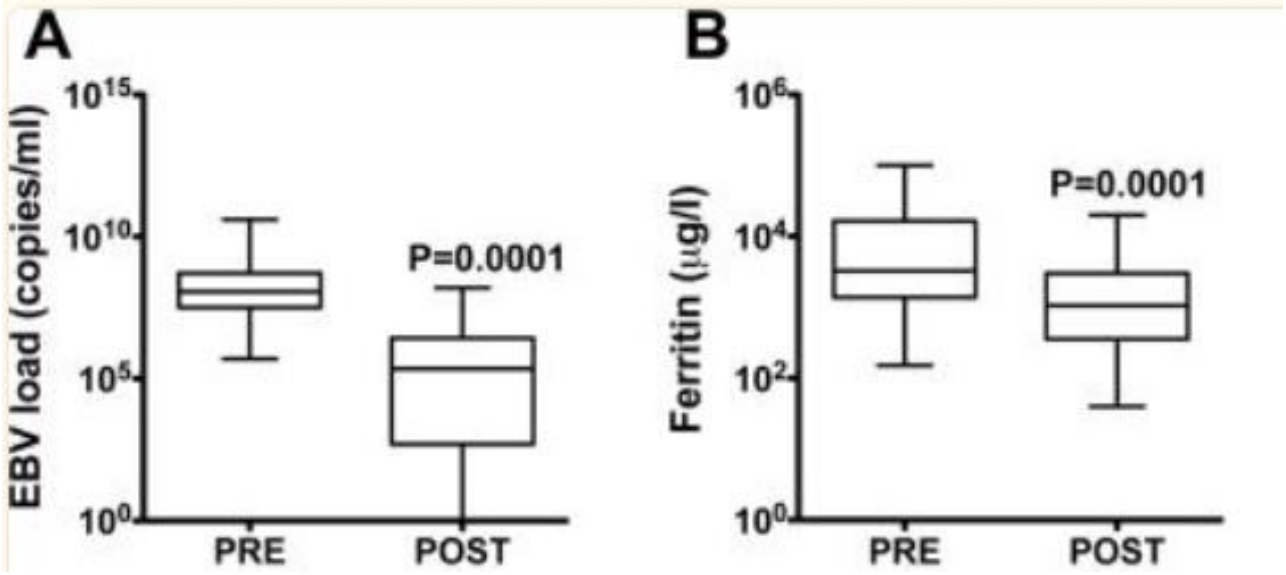
Rituximab

- Antibody that binds CD20 on B cells
- B cells typically infected with EBV
  - If no more EBV+ B cells, then hopefully no more trigger of HLH
- *Will not get rid of other EBV infected cells*



Ronald P Taylor ✉ & Margaret A Lindorfer

Rituximab: Effects in EBV-HLH



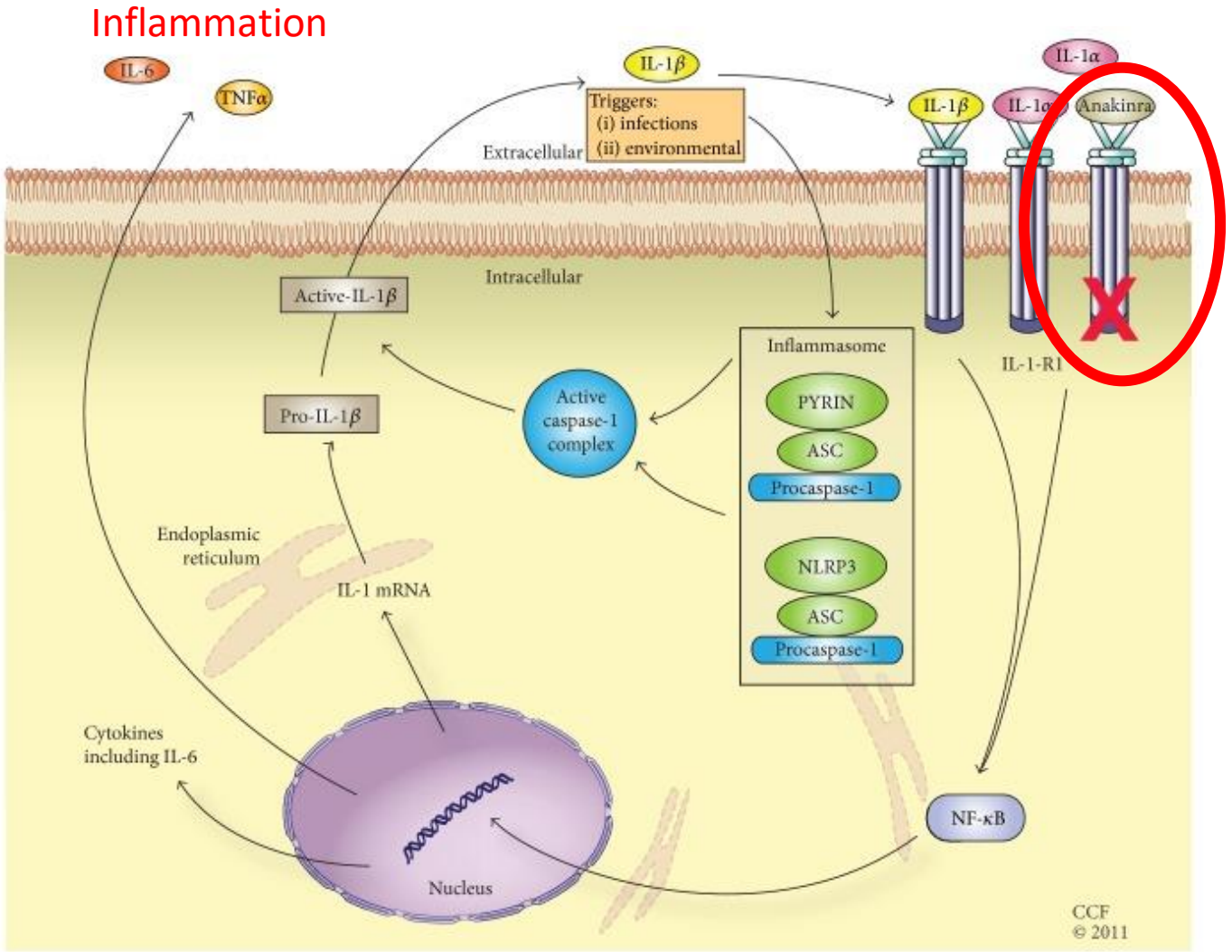
Chellapandian et al

Rituximab Notes

- **Severe allergic reactions**/Infusion Reactions
- Prolonged or permanent destruction of B cells. B cells make antibodies. If B cells are not working, patients need antibody replacement infusions (IVIG).
- Progressive multifocal leukoencephalopathy (PML)
- Hepatitis B reactivation

Anakinra

- Interleukin-1 (IL-1) receptor antagonist: prevents the action of IL-1 which is an inflammatory cytokine
- *Mostly useful in the Rheumatologic setting
- *Data is limited- and most patients also receive other therapies
- However: the rheumatologists can tell you that it works nicely for some patients with rheumatologic HLH/macrophage activation syndrome



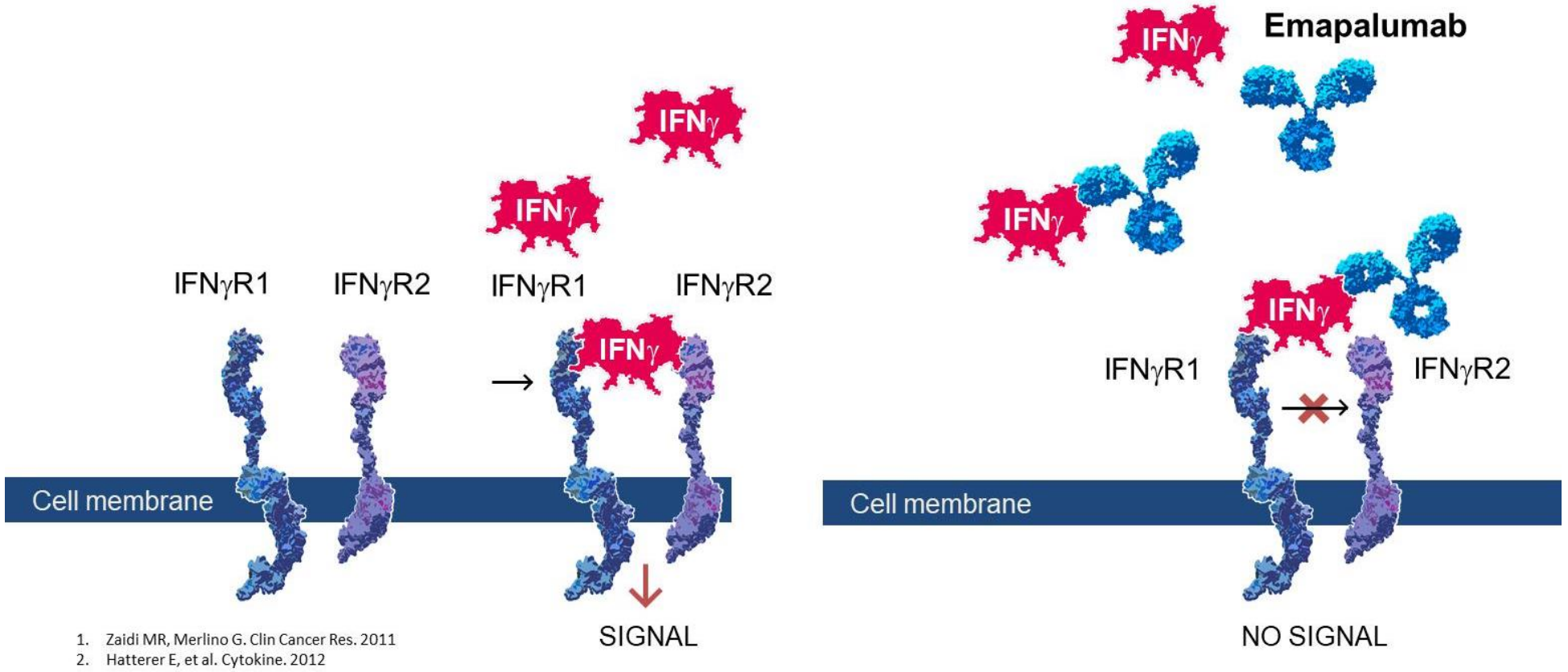
Baskar et al, 2016

Anakinra Notes

- In general, it is safe compared to other agents
  - Increased incidence of serious infections only 2% vs. Placebo < 1% in RA trials
  - Be careful about using it in combination with TNF targeting agents (or other agents) due to increased infection risk
- You may need to increase the dose.
- Give every other day in patients with end-stage renal disease
- Reactions are possible
- Can cause low neutrophil counts- reduce dose
- In general- not enough for true HLH.

Emapalumab

Anti-Interferon gamma monoclonal antibody therapy
Prevents the action of interferon-gamma, an inflammatory cytokine



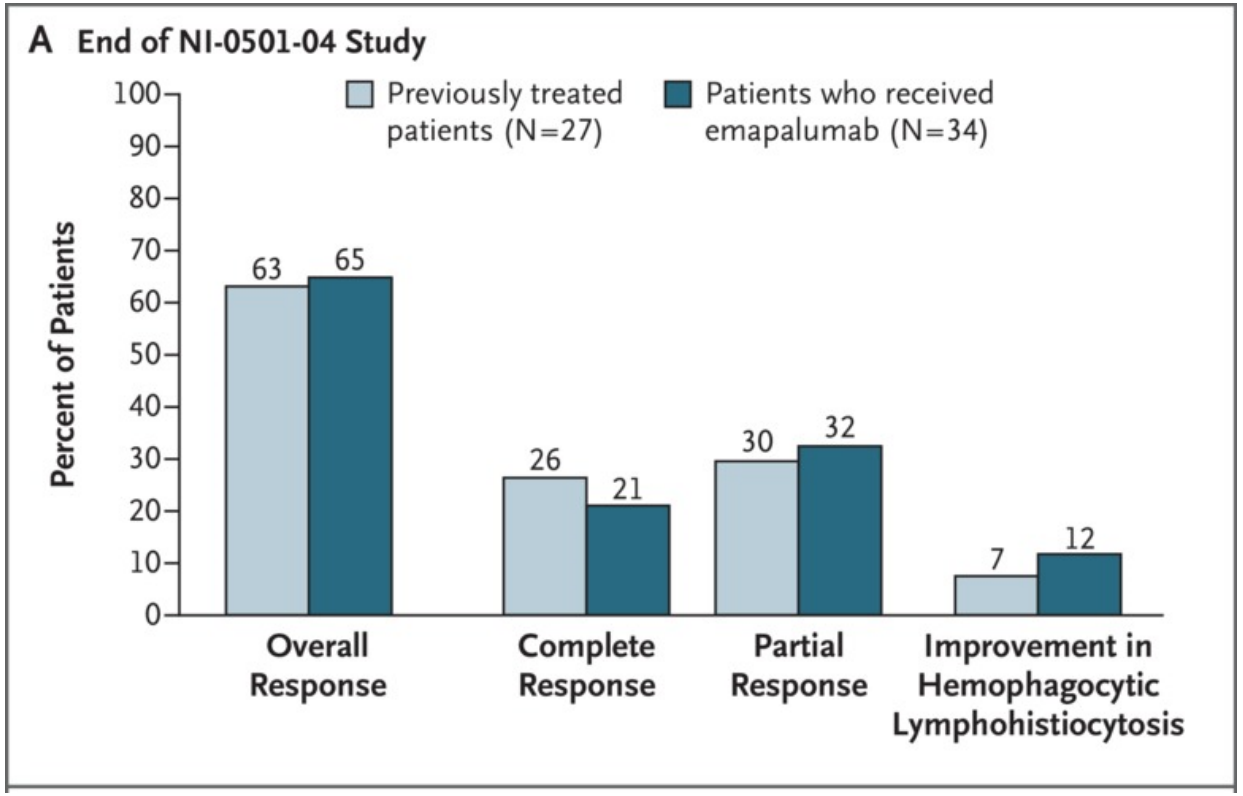
1. Zaidi MR, Merlino G. Clin Cancer Res. 2011
2. Hatterer E, et al. Cytokine. 2012

Courtesy Dr. Michael Jordan

Response to Emapalumab

- Complete Response: 21-26%
- Partial Response: 30-32%
- Improvement: 7-12%

- FDA approved for second line therapy of patients with HLH 2018



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

Emapalumab Notes

- The package insert says to start dosing at 1mg/kg: patients usually need more
- CXCL9 monitoring is very useful
  - Are they responding/are we giving enough?
  - Useful to monitor other treatments too
- Patients should be on medicines to prevent infections

Alemtuzumab

- Alemtuzumab is a monoclonal antibody that destroys most immune system cells
- It is very powerful

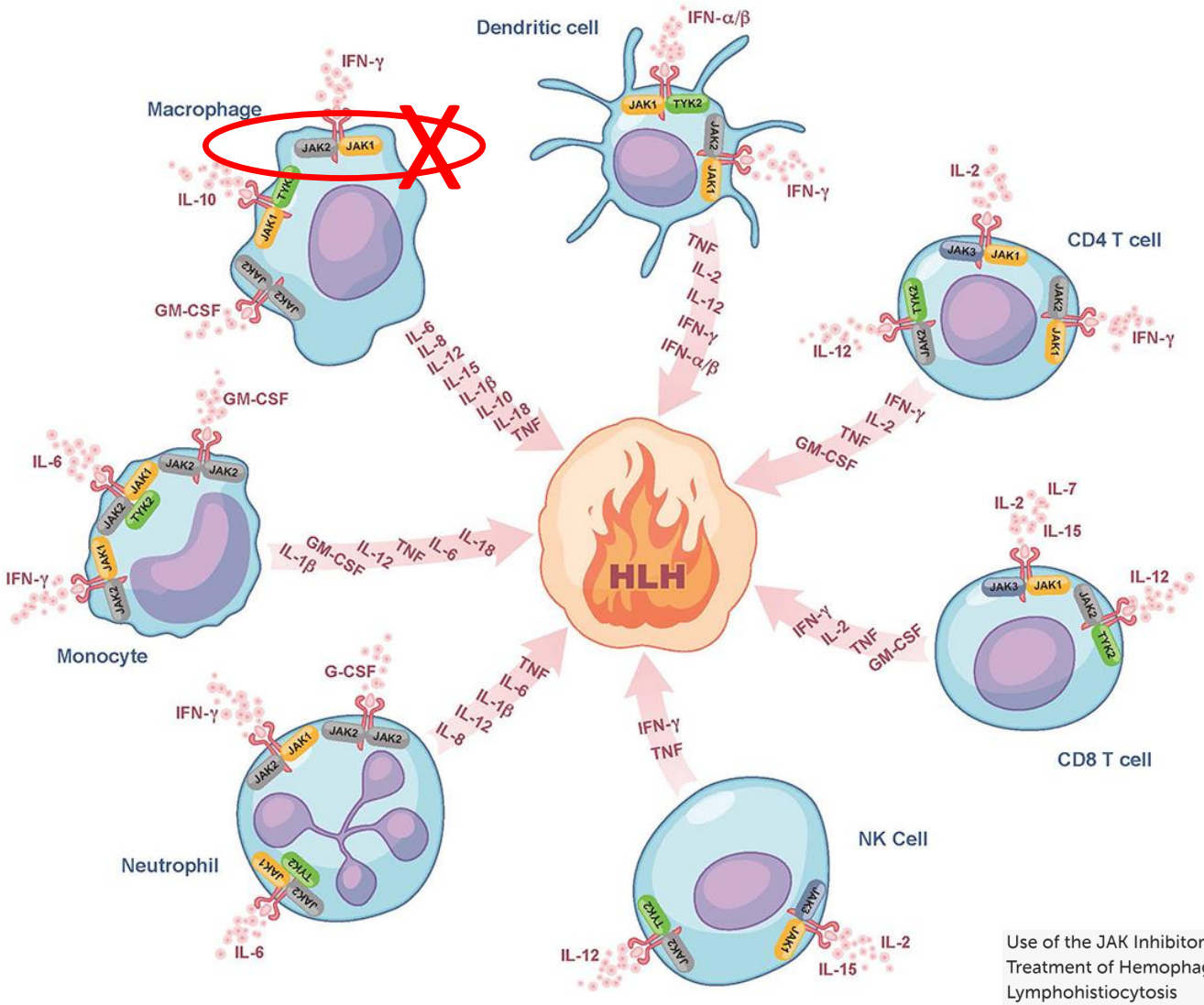
Alemtuzumab Notes

- Severe allergic reactions can occur
  - Pre-medications should be given (steroids, diphenhydramine)
- Fever, chills, flushing, dizziness, shortness of breath, nausea, vomiting, or rash/itching
- Patients have a high chance of viral and other infections
  - Patients need to be on medications to prevent infections
  - Patients need to be monitored for EBV, CMV, adenovirus and other viral reactivations which commonly occur
- Usually used in refractory cases or as a bridge to transplant
  - Sometimes used up front, especially if you live in France

JAK Inhibitors: Ruxolitinib

- Several case reports/series
- Blocks signaling of inflammatory cytokines

- Open multi-center trial (Melissa Hines and Kim Nichols: St Jude Research Hospital)



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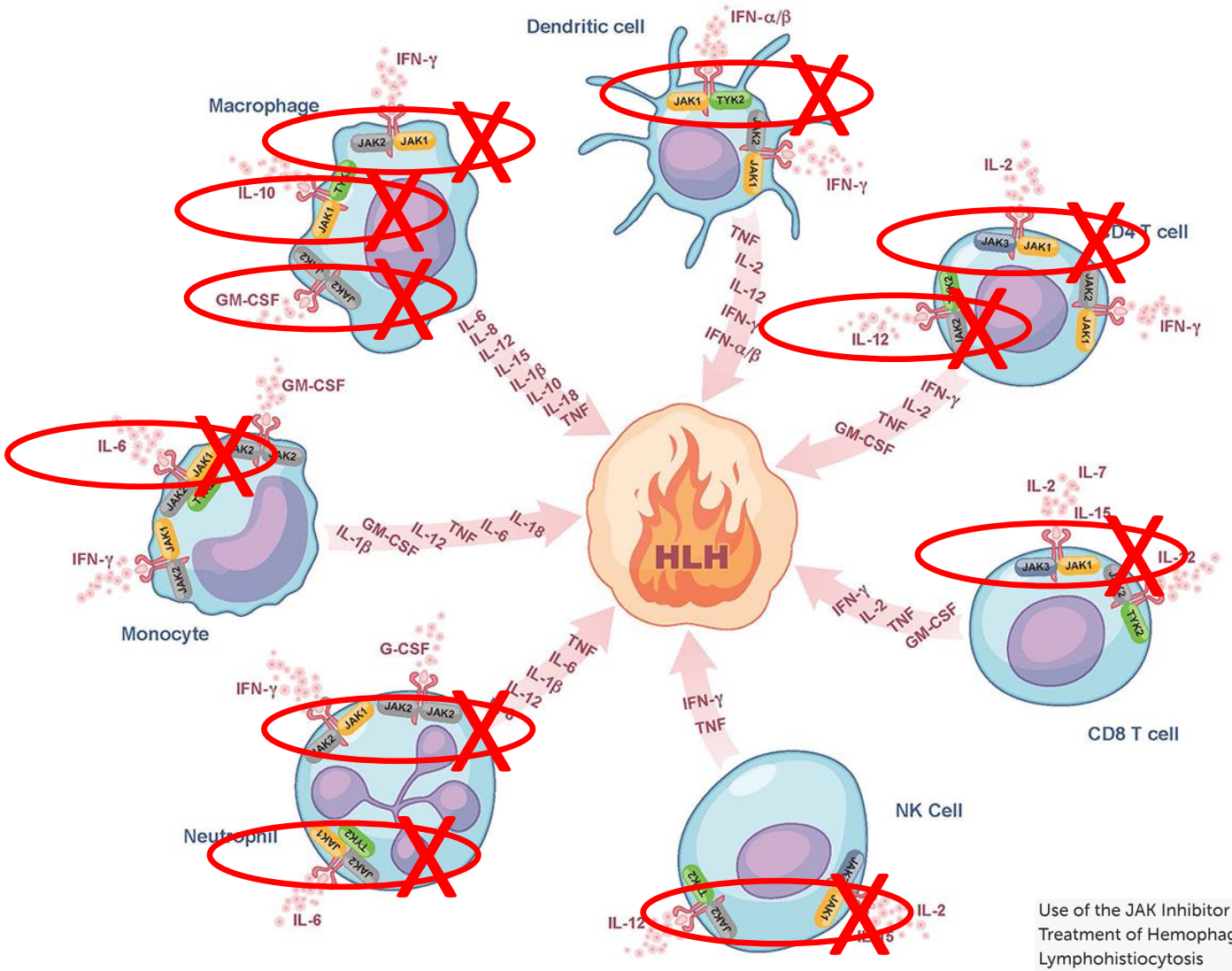


Use of the JAK Inhibitor Ruxolitinib in the Treatment of Hemophagocytic Lymphohistiocytosis

Camille Keenan, Kim E. Nichols and Sabrin Albeituni

Ruxolitinib Notes

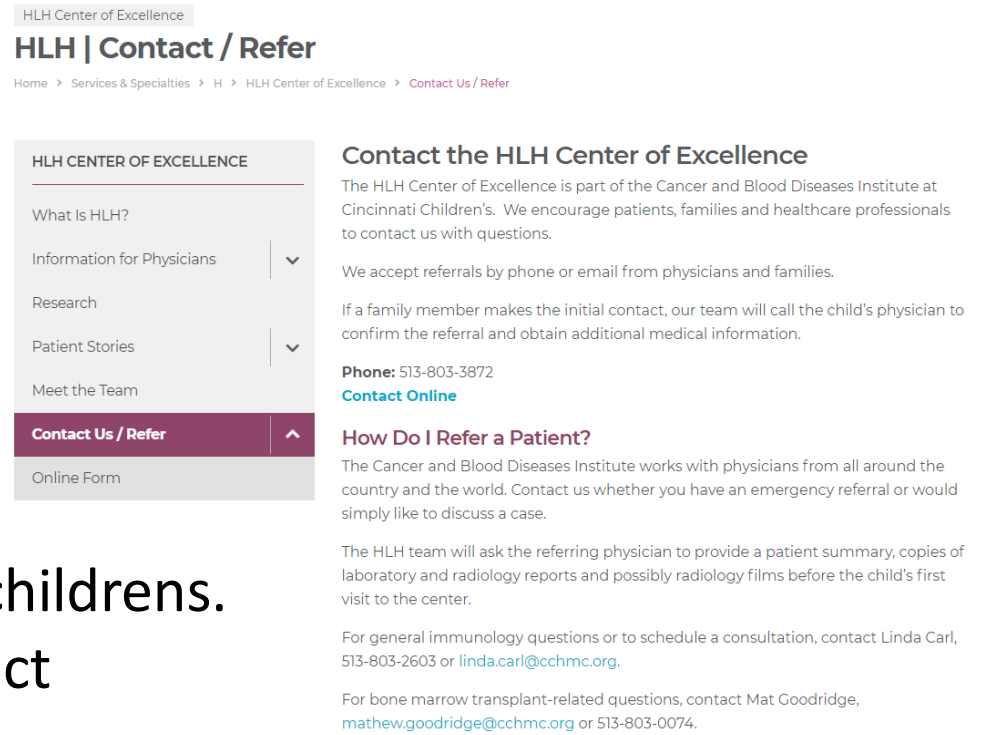
- Need to be able to take by mouth
- Increased risk of infections
- Can cause anemia, low platelets, and low neutrophil counts- monitor CBC
- Reduce dose if on strong CYP3A4 Inhibitors (azoles)
- Dose adjustment for renal impairment
- Dose adjustment for hepatic impairment

Conclusions

- HLH is a severe life-threatening syndrome of extreme inflammation
- The syndrome can be recognized based on clinical manifestations and laboratory tests
- Some patients with the syndrome of HLH have underlying genetic immune deficiencies
  - A portion of these patients will need a bone marrow transplant
- First line treatments for HLH will not be effective in all patients but treatments are expanding

Resources

- HLH Center of Excellence at CCHMC



https://www.cincinnatichildrens.org/service/h/hlh/contact

Other Resources:

https://primaryimmune.org/disease/hemophagocytic-lymphohistiocytosis-hlh

https://www.matthewandandrew.org/

https://www.liamslighthousefoundation.org/

https://histio.org/

Several other major academic centers also have good resources- Google your favorite:
https://www.chop.edu/conditions-diseases/hemophagocytic-lymphohistiocytosis-hlh

Q&A SESSION:
YOUR QUESTIONS ANSWERED

Additional Resources

- **Cincinnati Children's HLH Center for Excellence:** https://www.cincinnatichildrens.org/service/h/hlh
- **IDF's HSCT Resources:** https://primaryimmune.org/hematopoietic-stem-cell-transplantation-hsct
- **IDF Resource Center:** https://primaryimmune.org/resource-center
- **IDF Support Services:** https://primaryimmune.org/support-services

Learn more about hematopoietic stem cell transplantation at scidcompass.org

Primary immunodeficiency diseases (PI) cause a wide spectrum of symptoms with varying severity. Some forms of PI are mild and don't cause significant harm, or may be effectively treated with agents like immunoglobulin (Ig) replacement therapy. Other forms of PI are so severe that individuals have a very poor quality of life or can die as a result of their disease. When PI is likely to cause significant harm or death to someone, allogeneic hematopoietic stem cell transplantation (HSCT) may be the best treatment option. Some common indications for allogeneic HSCT include Severe Combined Immunodeficiency (SCID), Wiskott-Aldrich Syndrome (WAS), Chronic Granulomatous Disease (CGD), Leukocyte Adhesion Deficiency (LAD), Immune dysregulation, Polyendocrinopathy, Enteropathy, X-linked (IPEX)

Have more Questions?

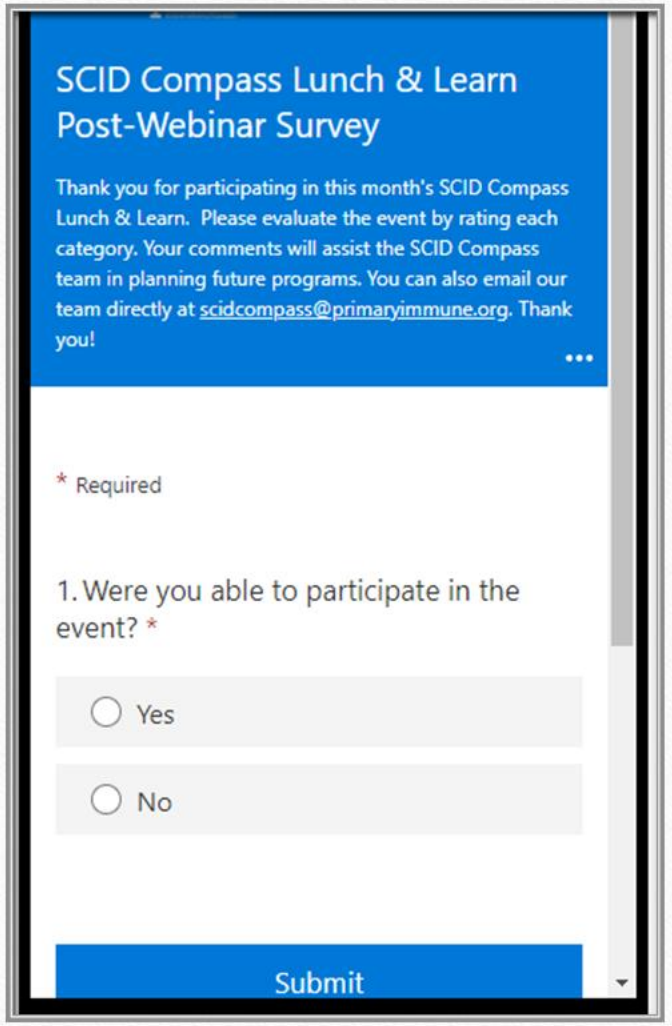
www.Primaryimmune.org/ask-idf

800-296-4433

Immune Deficiency Foundation

WE VALUE YOUR FEEDBACK…

Please take a moment to complete our Evaluation Survey after the Program!



Upcoming Events

2022 PI Conference

Thursday October 6-
Saturday, October 8th

IDF Lunch & Learn:
Hyper IgE/ JOB Syndrome

Wednesday, 10/19/22

Alexandra Freeman, MD

2:30 PM ET

For a list of all upcoming IDF Events, visit:

https://community.primaryimmune.org/s/events?language=en_US

THANK YOU!

Rebecca Marsh, MD
Clinical Director, Primary Immune Deficiency Program and
HLH Center of Excellence
Cincinnati Children's Hospital