(Auto) Inflammatory consequences of unopposed IL-18

Scott Canna, MD

Rheumatology & Immune Dysregulation | The Children's Hospital of Philadelphia

Assistant Professor of Pediatrics | Perelman SOM of University of Pennsylvania

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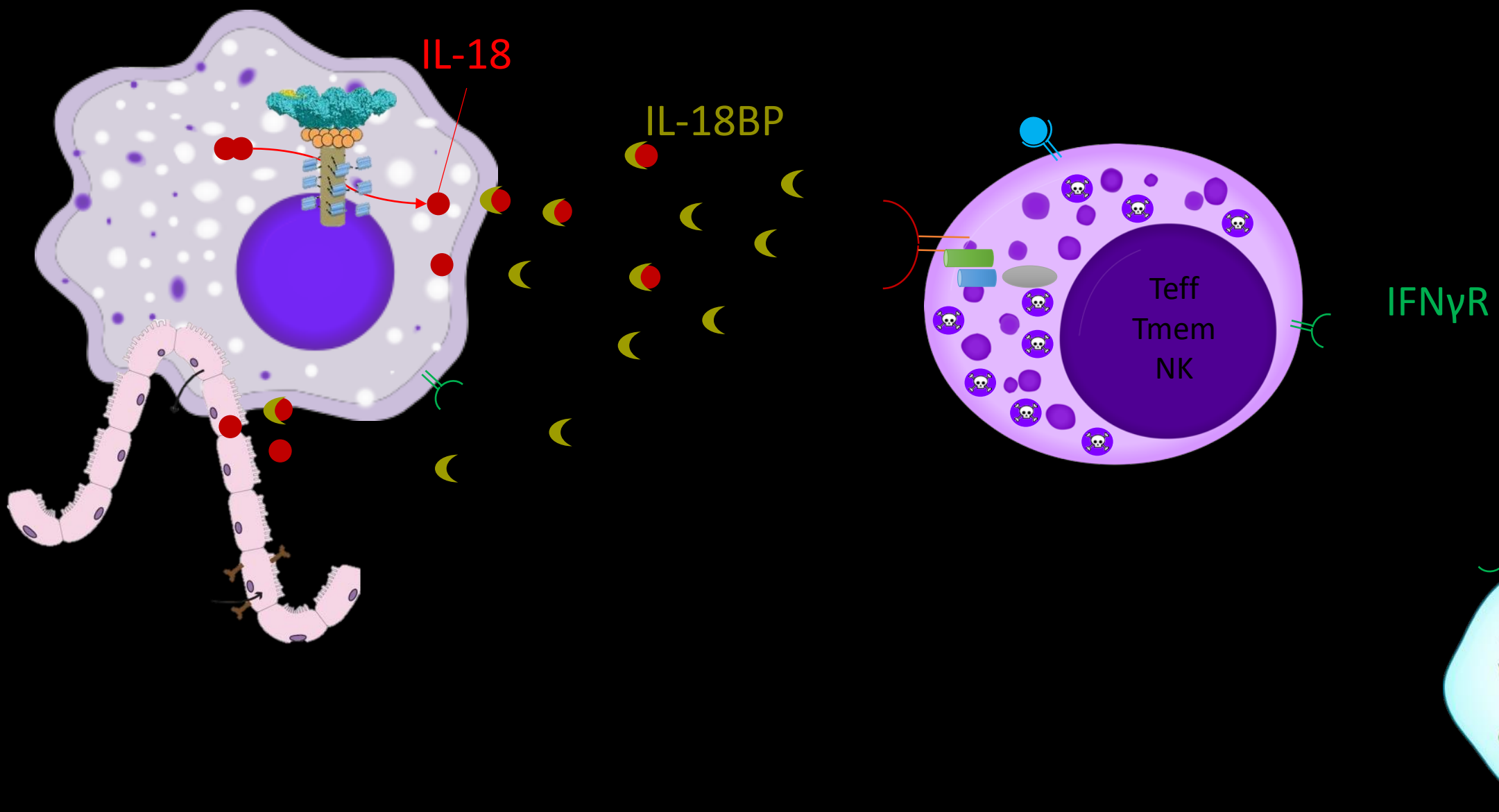
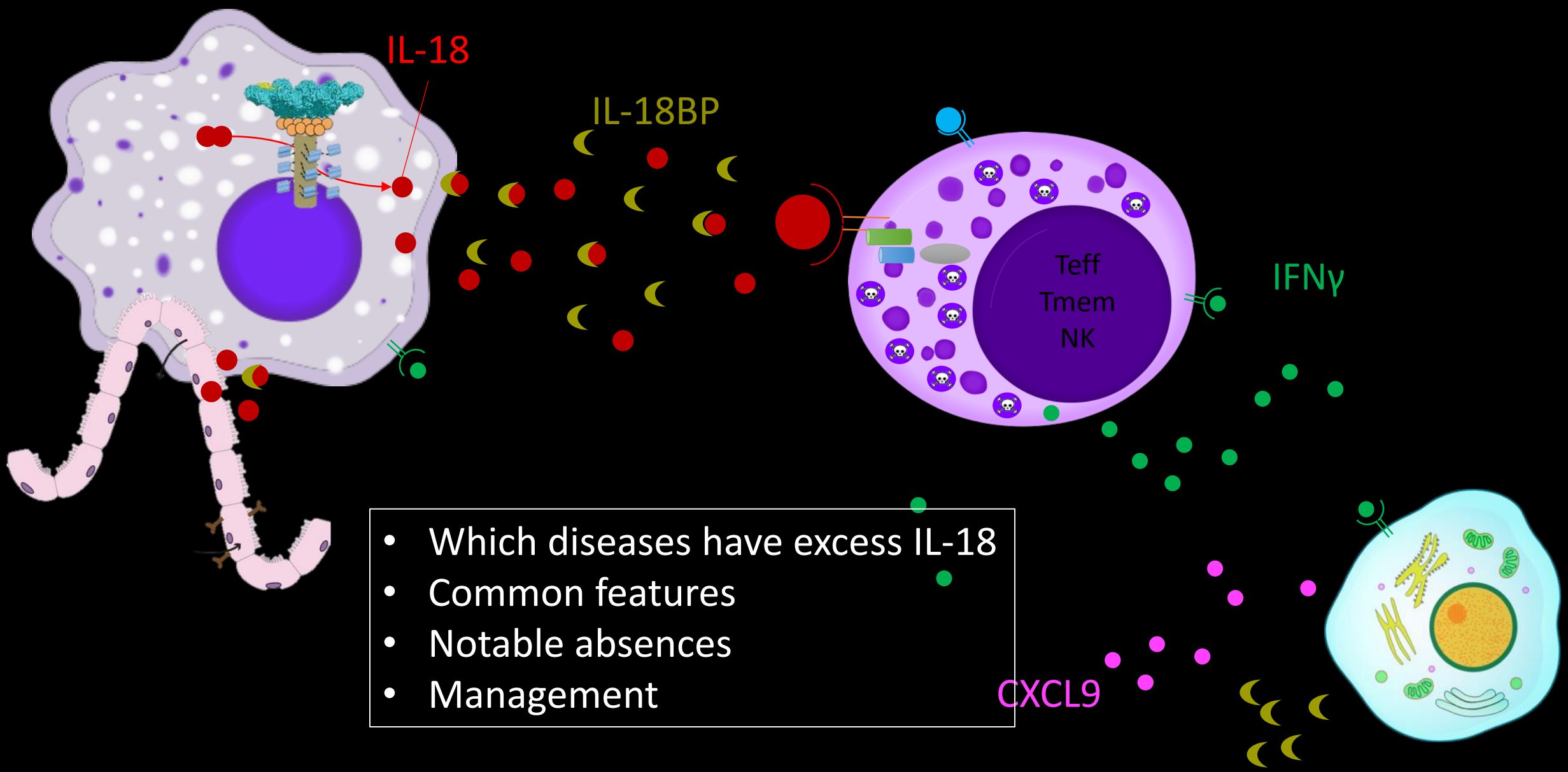
Competing Interests

- Consultant: Simcha Therapeutics, SOBI, AB2Bio
- Research support: IMMVention Therapeutix
- Clinical trial Site PI: AB2Bio (past), SOBI, Novartis

Typical lifecycle of systemic IL-18



Unopposed systemic IL-18



- Which diseases have excess IL-18
- Common features
- Notable absences
- Management

IL-18 is elevated in inflammatory diseases

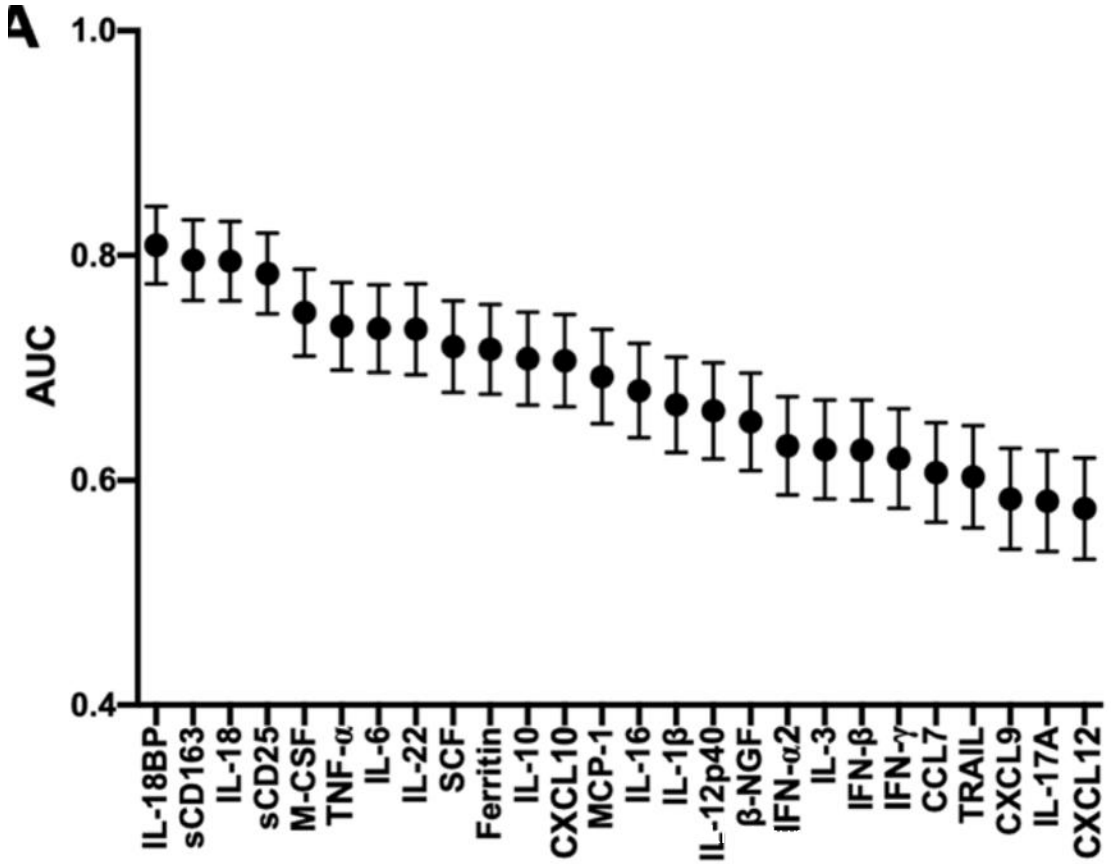
Disease	Range in Disease	Range in HC	Reference
Kawasaki Dis.	< 1000 pg/mL	<800	Takahara et al., Rheum Int, 2015
ALPS*	>500	~300	Oliveira et al., Blood, 2010
HIV/AIDS	< 2000 in AIDS	50-400	Donato et al., AIDS, 2000
T-cell Leukemia	< 3100	0-900	Chen et al., Blood, 2012
Acute Asthma	< 600	< 300	Tanaka et al., JACI, 2001
Sarcoidosis	< 800		
COPD	< 350	< 175	Imaoka et al., Eur Resp J, 2008
SLE	< 1500	Na	Park et al., Clin Rheum, 2004
PFAPA	< 1100	< 600	Stojanov et al., PNAS, 2011
Type II Diabetes	189	159	Thorand et al., 2003
Coronary Artery Disease	68	59	Blankenberg et al., 2007

*part of secondary criteria

IL-18 as prognostic marker

+ correlation with mortality in sepsis

Eidt, Clinical Chimica Act, 2016
Anderko, Int Care Medicine Experimental, 2022



Anderko, Int Care Medicine Experimental, 2022

IL-18 as prognostic marker

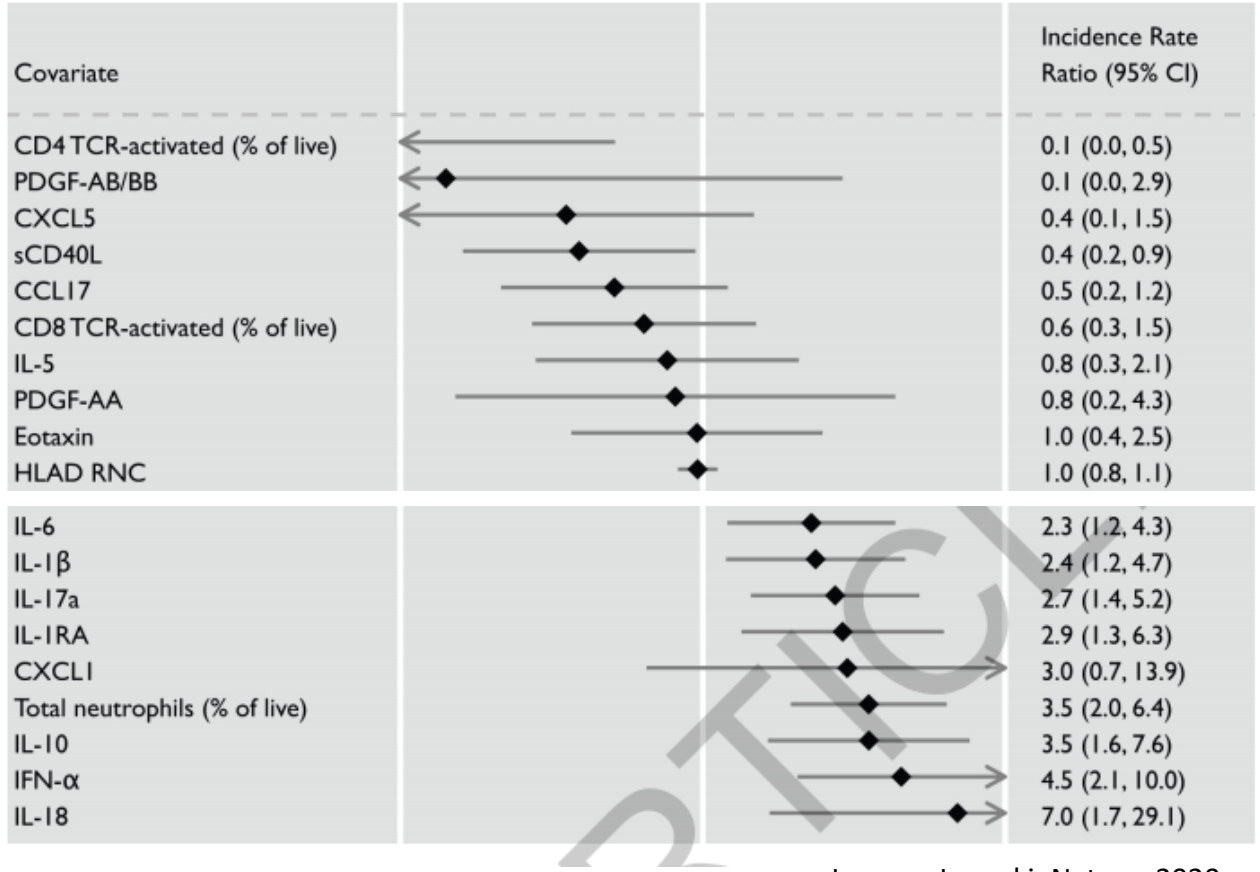
+ correlation with mortality in sepsis

Eidt, Clinical Chimica Act, 2016
Anderko, Int Care Medicine Experimental, 2022

+ correlation with severity in COVID-19

Predictor of TB-IRIS

Tan, AIDs, 2015. Tan JI Immunol 2022



Lucas … Iwasaki, Nature, 2020

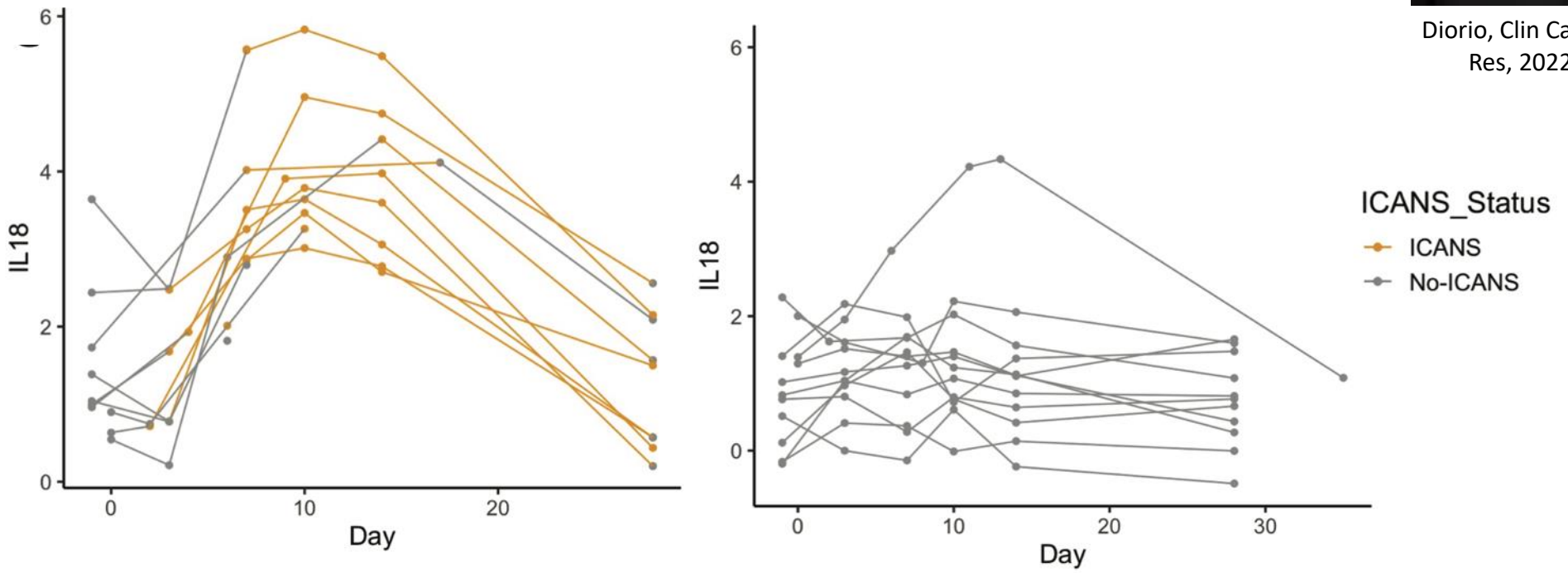
IL-18 as prognostic marker

Cytokine release syndrome (CRS)

Immune effector cell therapy-Associated Neurotoxicity Syndrome (ICANS)

Correlated with time of onset

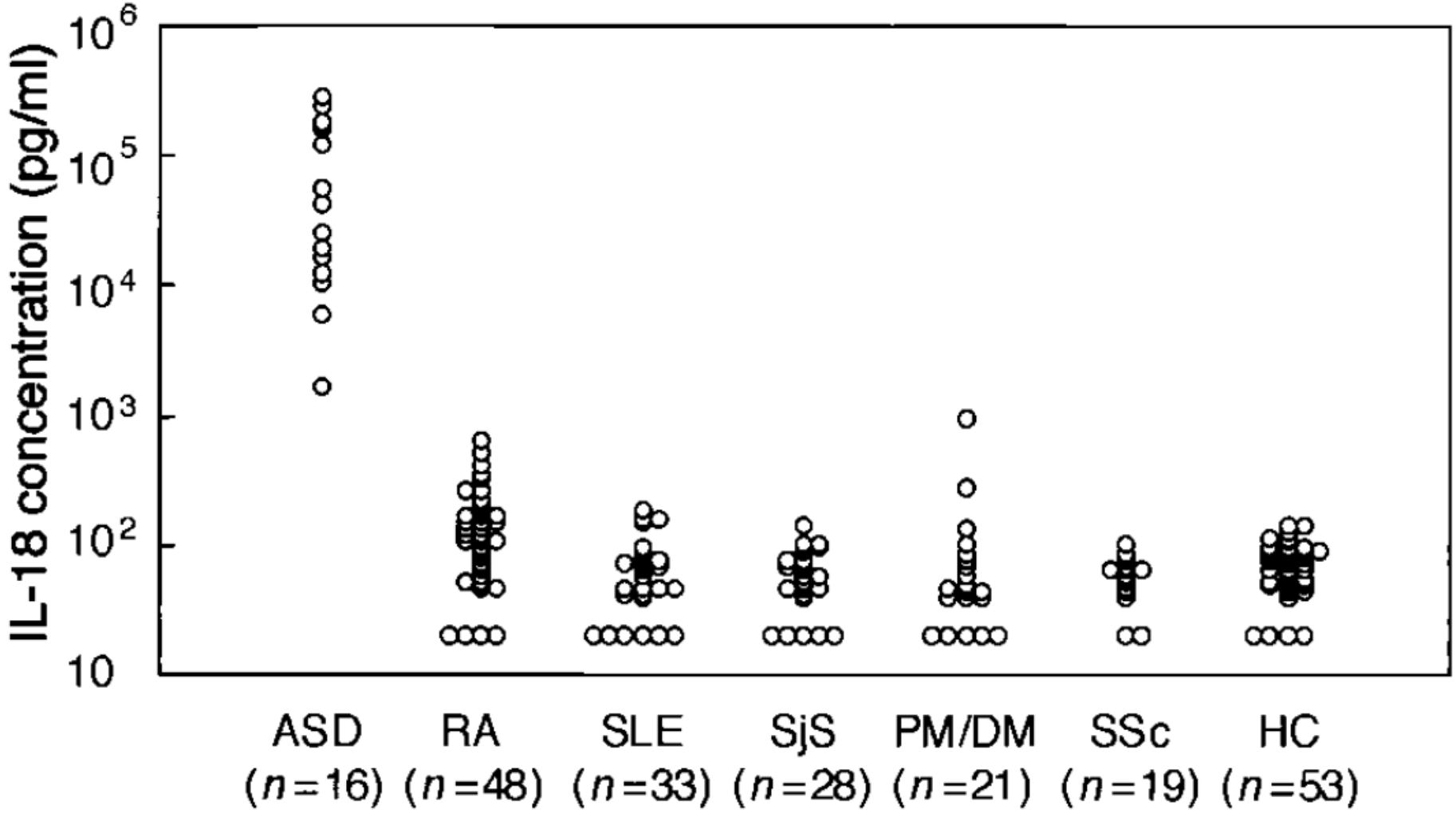
Diorio, Clin Cancer Res, 2022



Society for Immunotherapy of Cancer

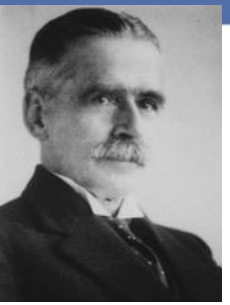
Where is IL-18 > IL-18BP?

IL-18 in Still's Disease / SJIA / MAS



Kawashima A&R 2001

IL-18 in Still's Disease / SJIA



Systemic Juvenile Idiopathic Arthritis

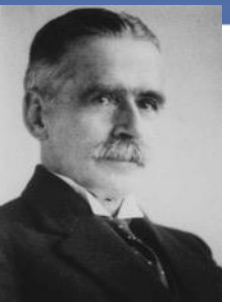
Arthritis
>2 fever

AND ≥1 of the following:

- Rash
- Generalized lymphadenopathy
- Hepatomegaly and/or splenomegaly
- Serositis

ILAR 2001 Criteria

IL-18 in Still's Disease / SJIA



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- Serositis

ILAR 2001 Criteria

=

Adult-onset Still's Disease

4+ major OR 3+2

Major criteria

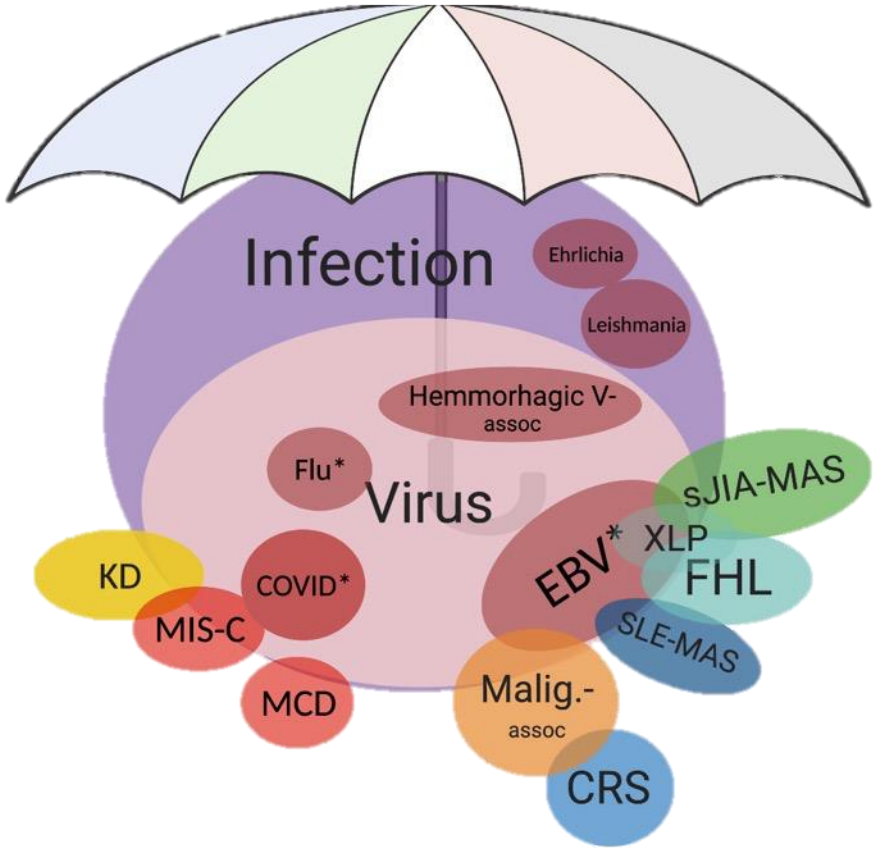
- Spiking fever ≥39 °C
- Arthralgia
- Transient erythema
- Pharyngitis
- Polymorphonuclear cells ≥80%
- Glycosylated ferritin ≤20%

Minor criteria

- Maculopapular rash
- Leukocytosis ≥10K

Fautrel B. et al., . Medicine (Baltimore) 2002

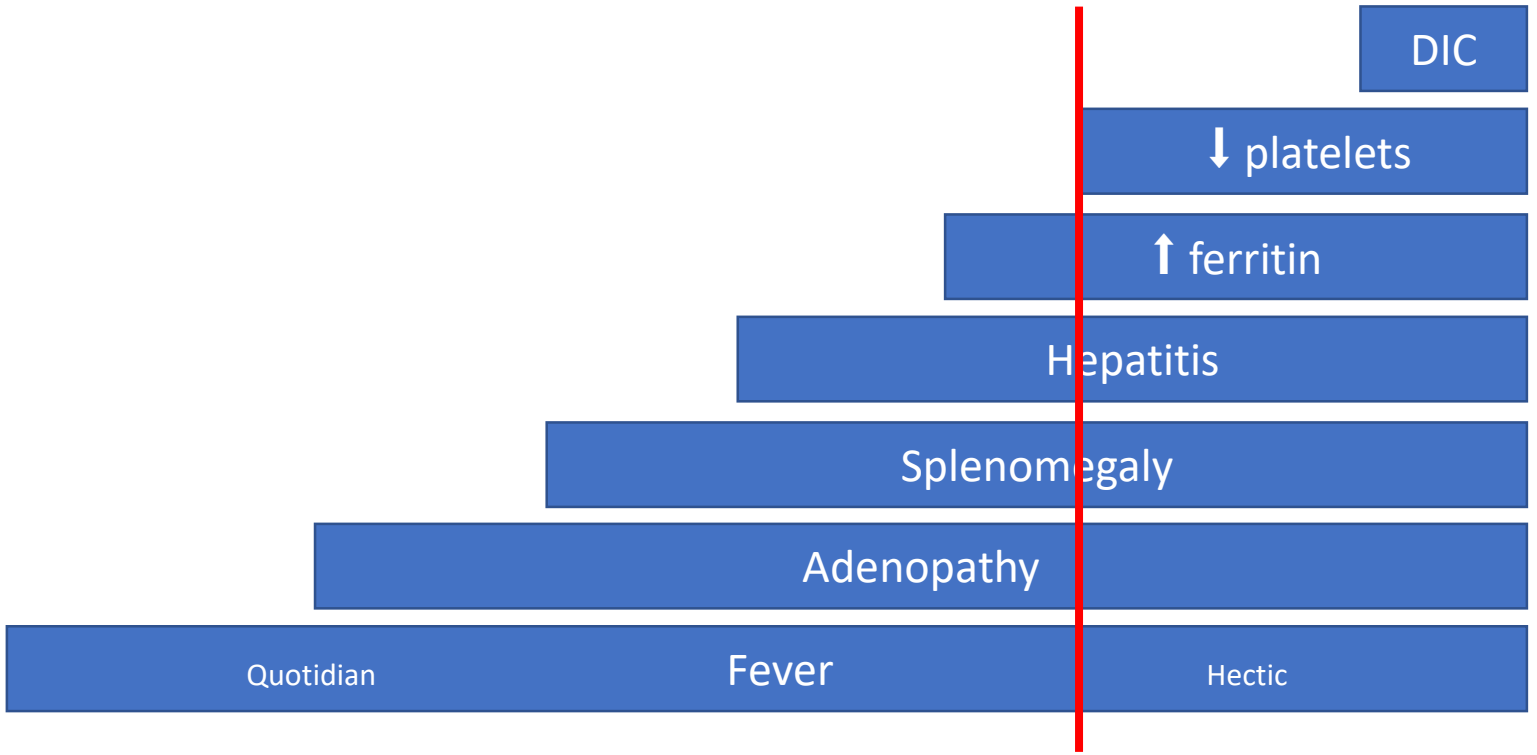
Macrophage Activation Syndrome



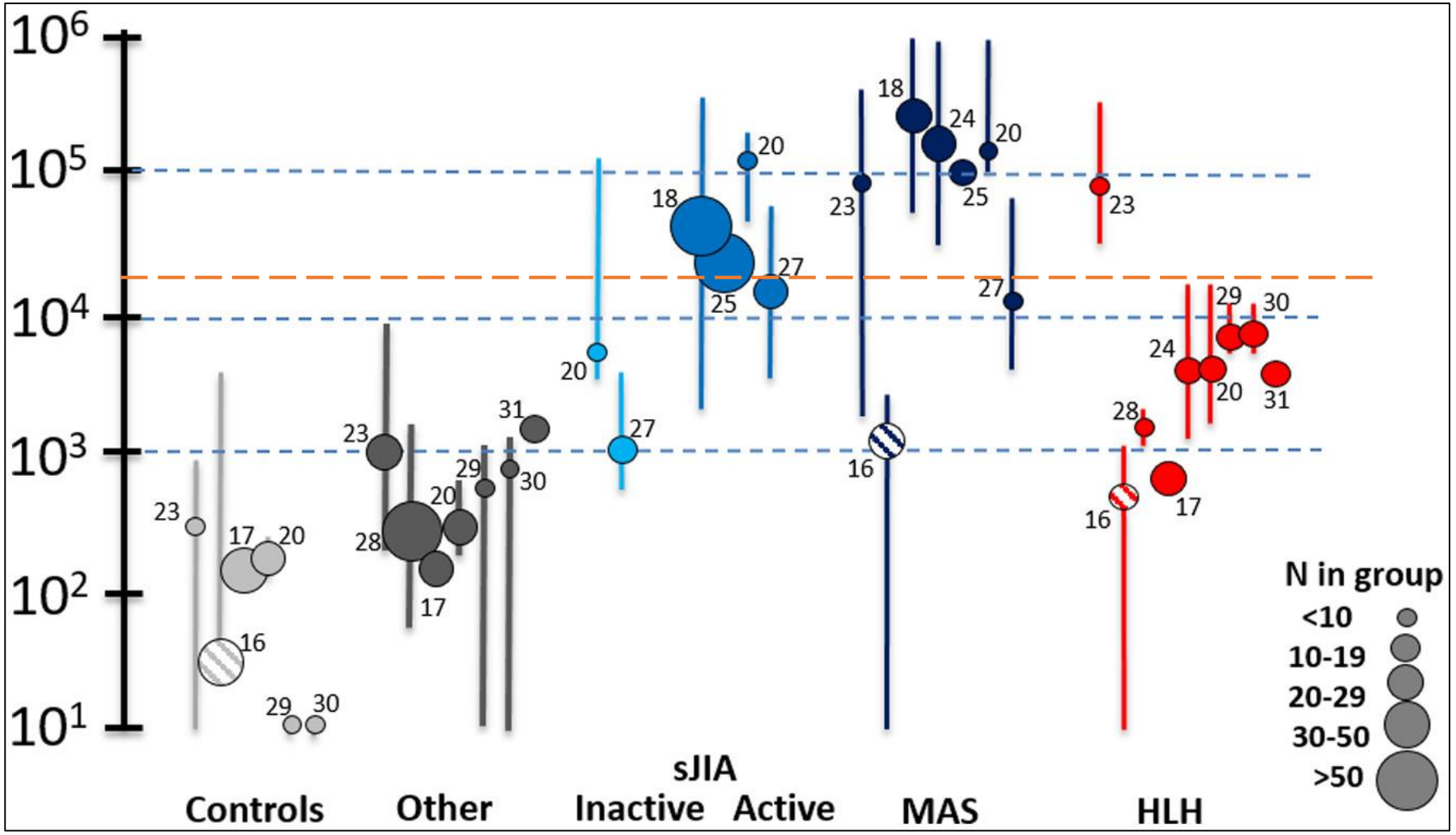
Adapated/updated from Henderson, Canna et al., A&R, 2020

SJIA/Still's

Macrophage
Activation
Syndrome



IL-18 is a specific sJIA/MAS biomarker



Krei, Clin Exp Immuno, 2020

Shimizu Cytokine 2010

…

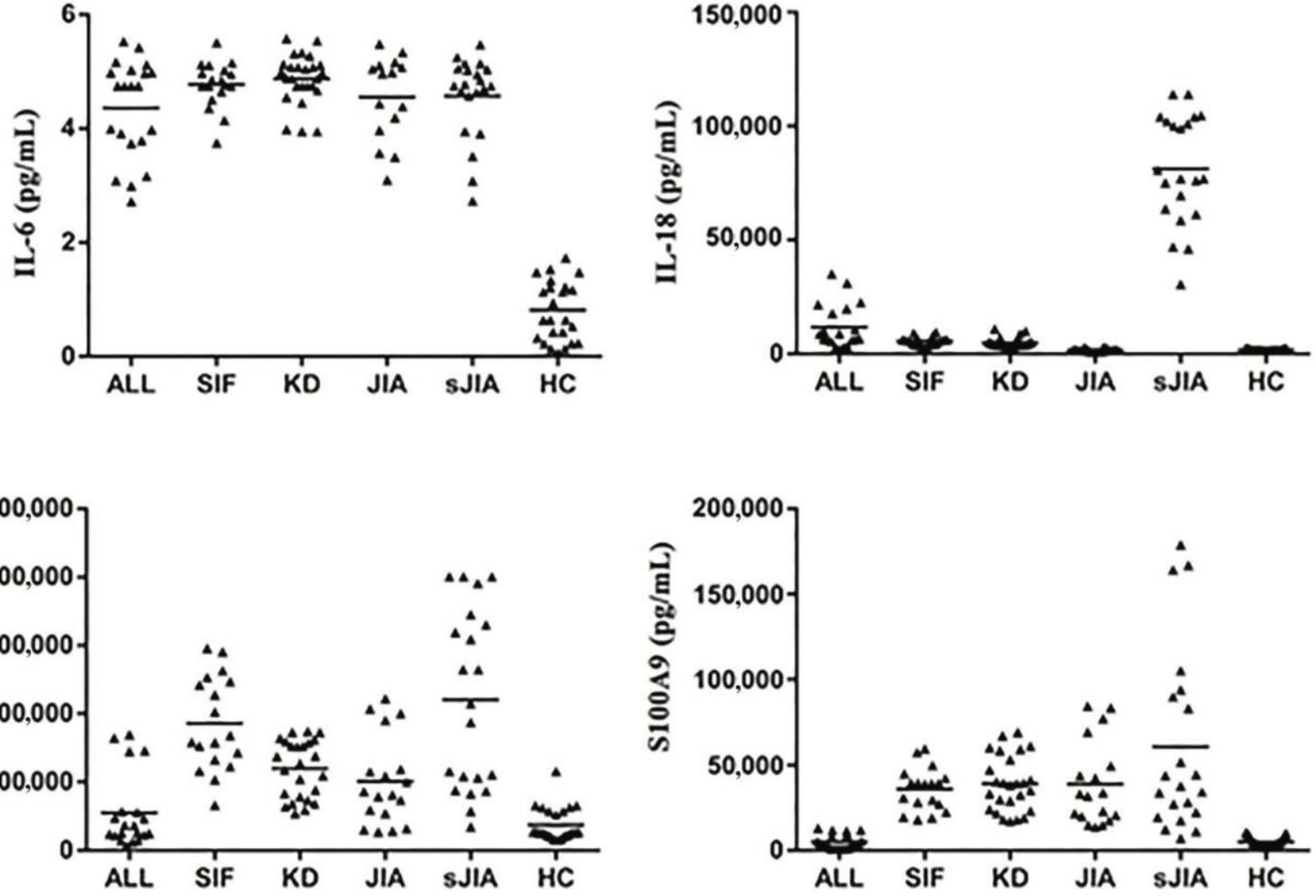
Xia, Braz J Med Biol Res, 2017

Weiss…Canna, Blood, 2018

Yasin…Schulert, Rheum, 2020

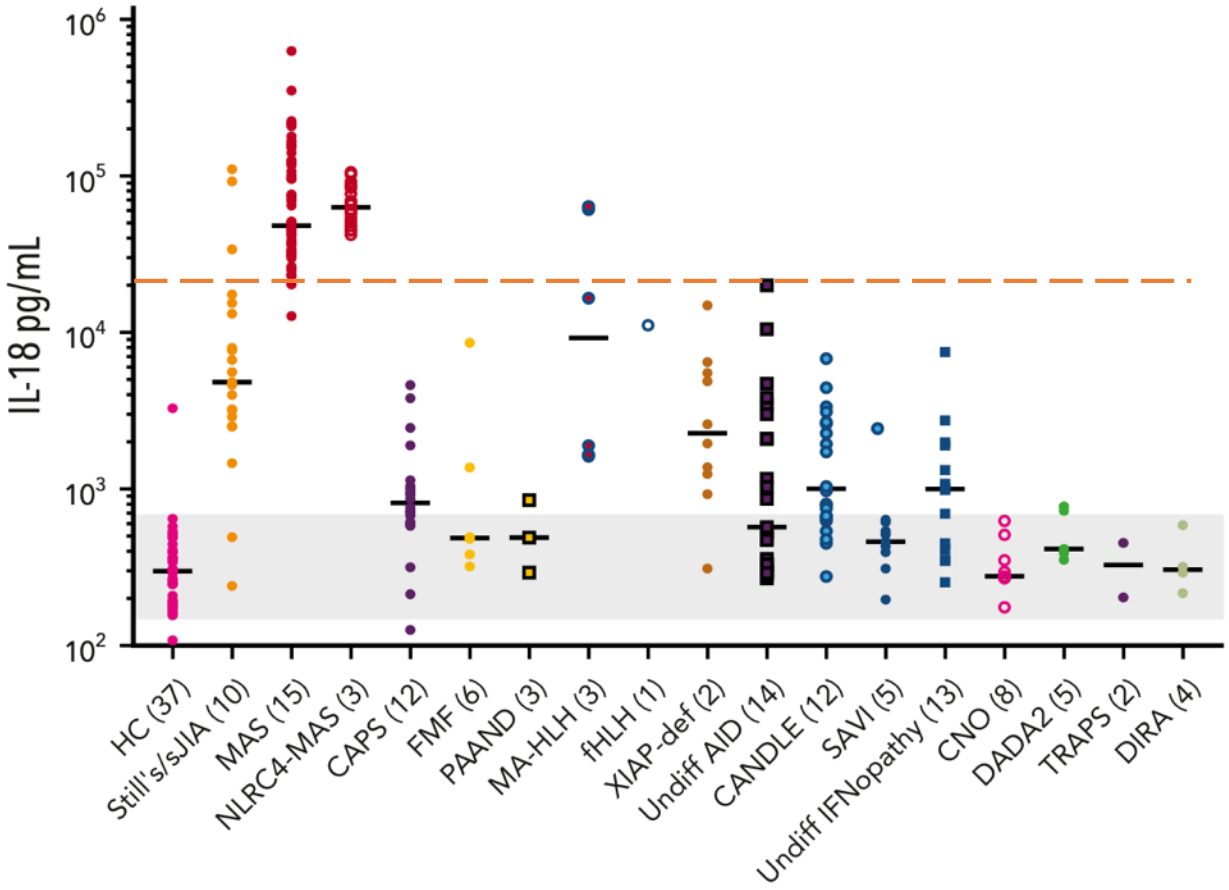
Rodriguez-Smith…Schulert, Lancet Rheum, 2021

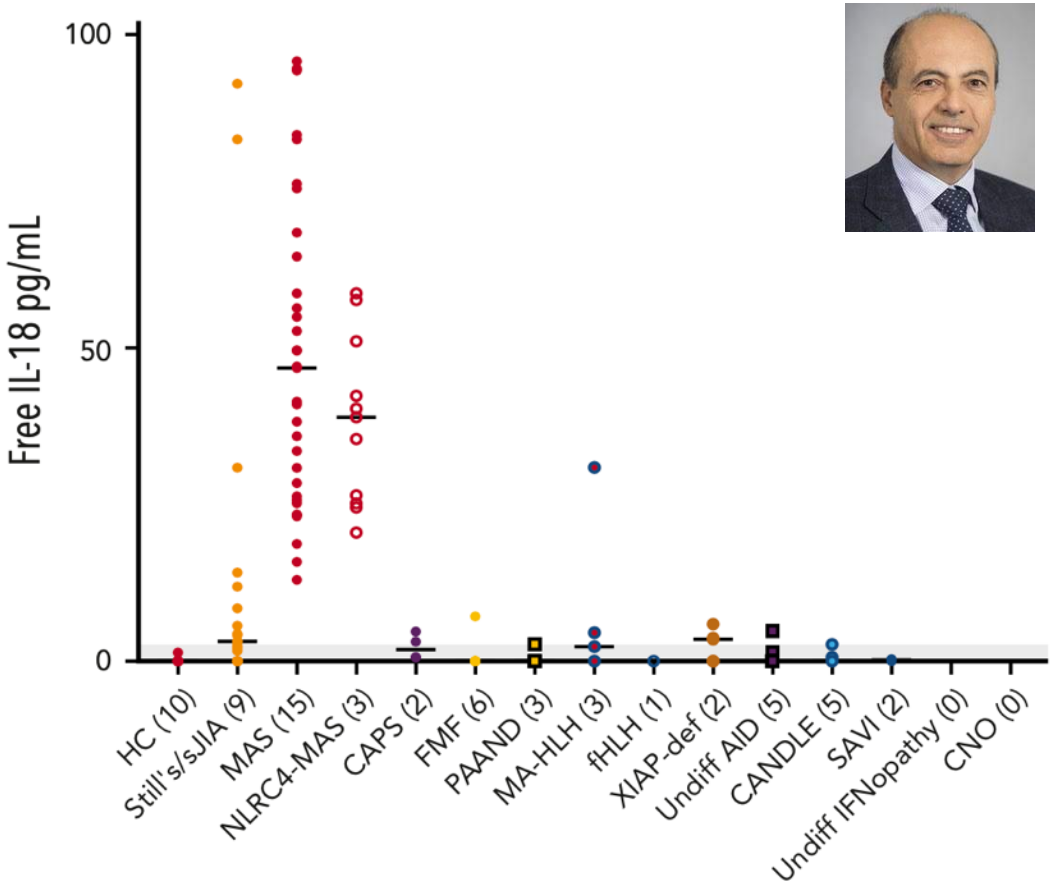
IL-18 is a specific sJIA/MAS biomarker



Xia, Braz J Med Biol Res, 2017

Quantitating “free” IL-18





Girard…Gabay, Rheum, 2016
Weiss…Canna Blood 2018

IL-18 just an enticing correlate … until

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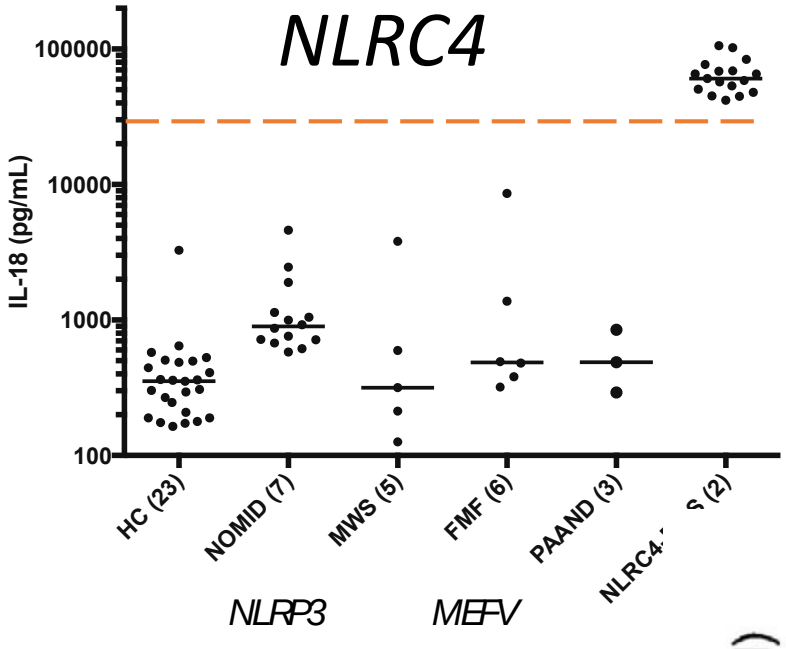
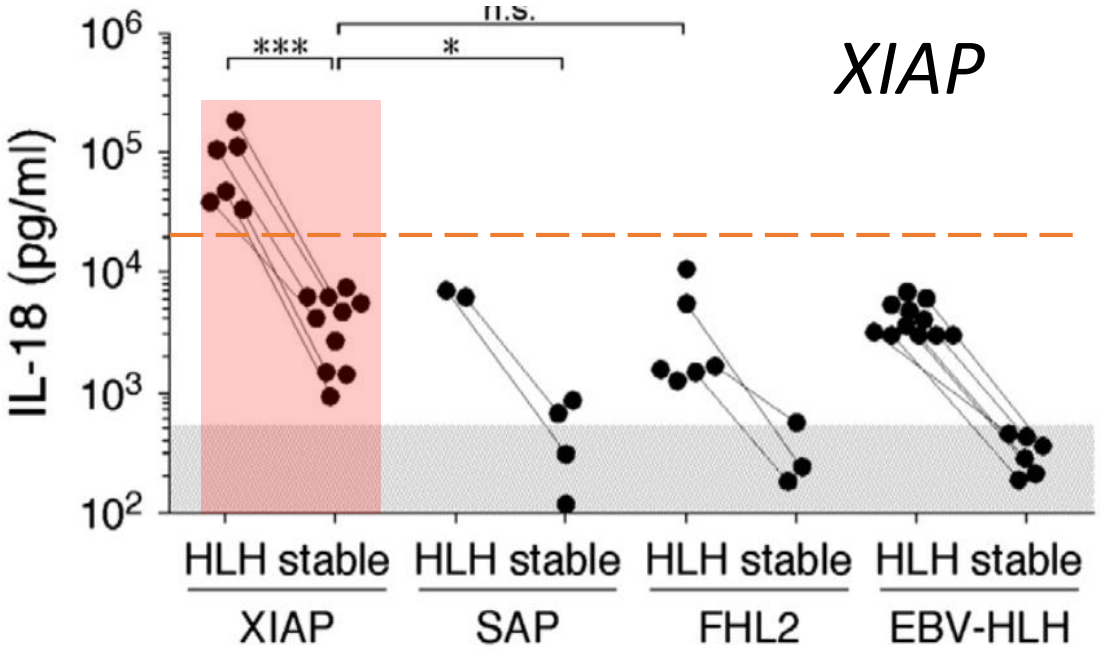
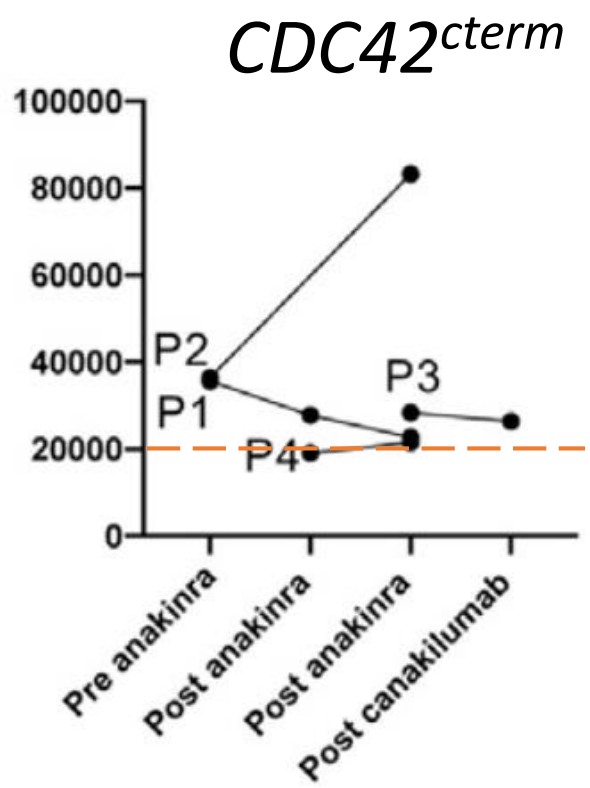
Monogenic IL-18opathies



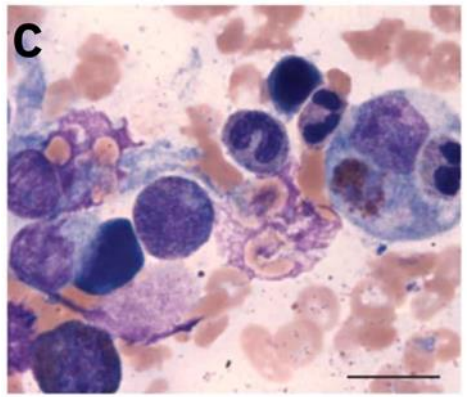


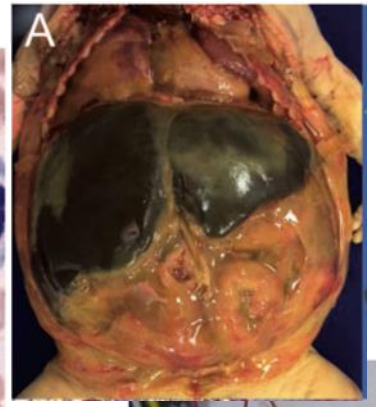


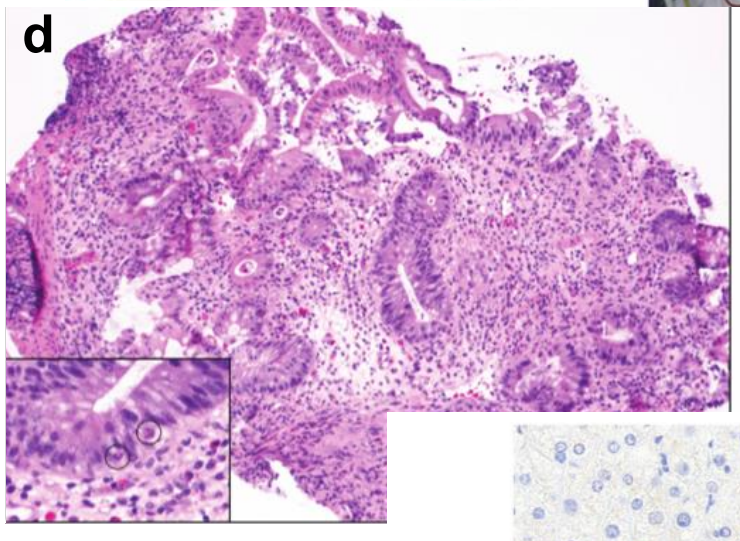
Canna, Nat Gen 2014
Romberg, Al Mousawi, Nat Gen 2014
Wada, Cytokine, 2014
Gernez…Weinacht, JACI, 2019
Lam…Tartagliea, J Exp Med 2019

Autoinflammation, MAS, & entercolitis

NLRC4



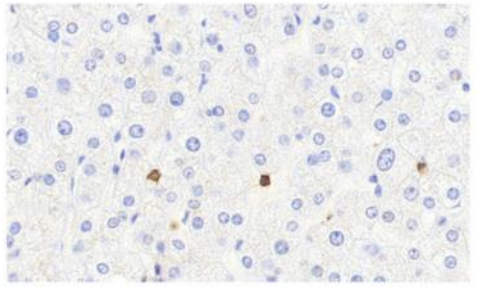


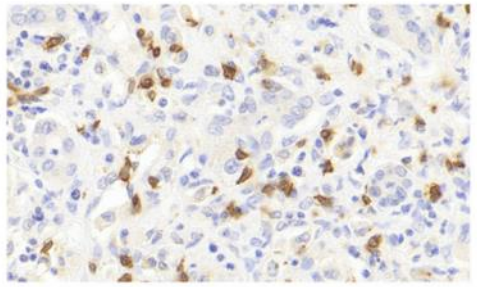


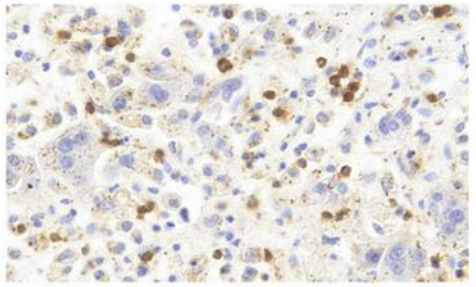
CDC42^{cterm}

IL18BP

CD8

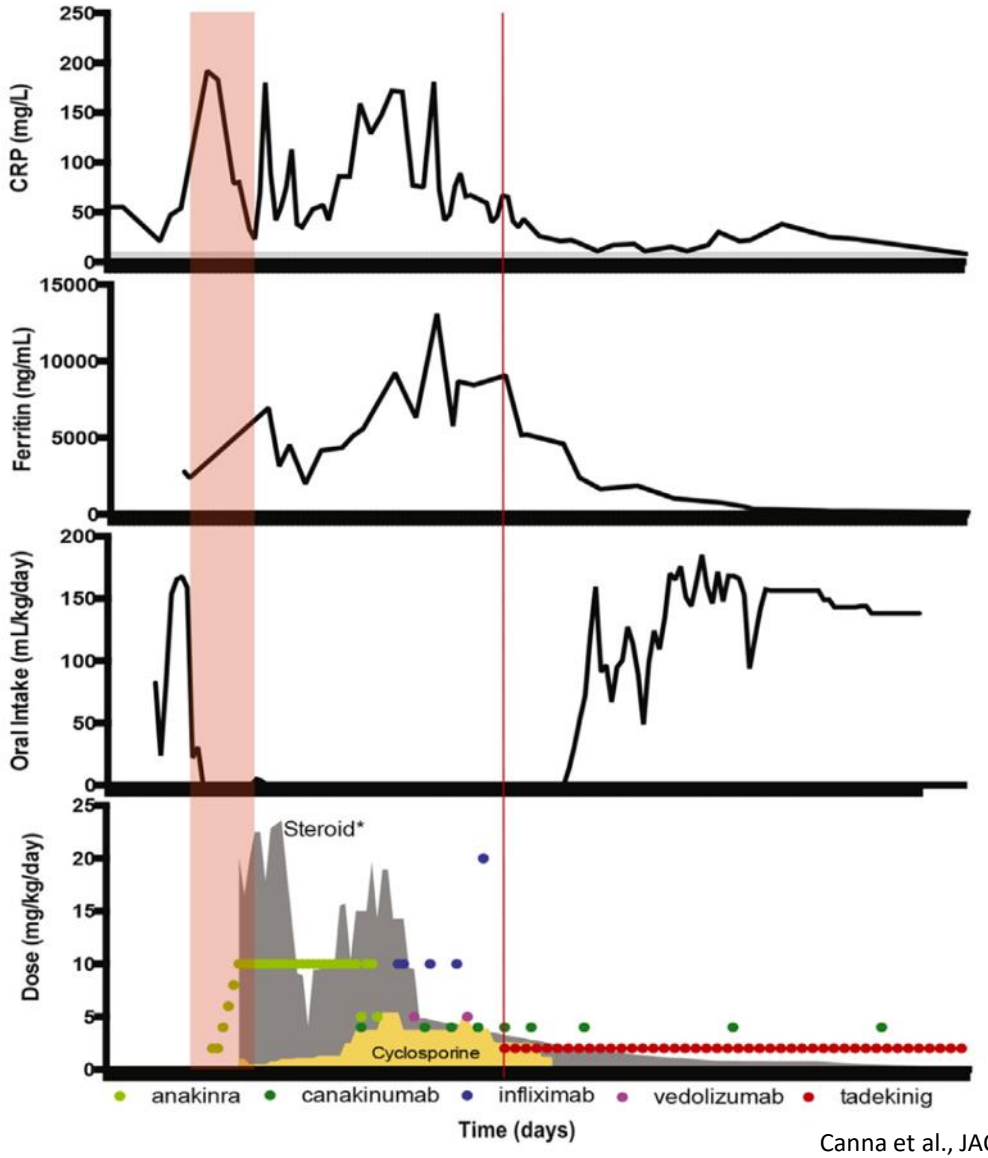






Weiss, Blood, 2018
Canna, Nat Gen, 2014
Romberg, Al Moussawi, Nat Gen, 2014
Liang, Ped Dev Path, 2017
Lam, J Exp Med, 2019
Belkaya, JEM, 2019

Therapeutic Proof of principle



Canna et al., JACI, 2016

Recombinant IL-18BP
NCT03512314

Bispecific IL-1β/IL-18
NCT04641442

MAS in IL-18 cancer immunotherapy trials?

Society for Immunotherapy of Cancer

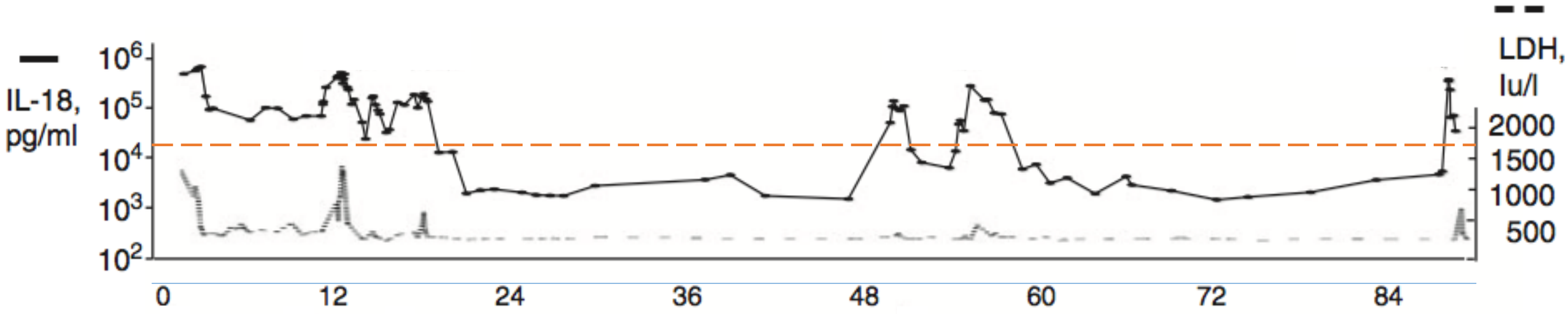
	Robertson et al. Clin Cancer Res 2006	Robertson et al. Clin Cancer Res 2008	Tarhini et al. Cancer 2009
	Ph1 Daily x 5 days	Ph1: Daily x 5 days q 28 Weekly x 6mos	Ph2: melanoma Daily x 5 days q 28
Symptoms	Chills, fever, nausea, HA, hypotension	"	Chills/fever Fatigue, pleural effusion
Clinical labs	↓ANC, Hgb, Plt, Alb, Na ↑LFTs	"	↓ALC, ↑Glc, ↑AST
Clinical Summary	Nothing dose dependent	"	Dose-dependent
Cytokines	↑IFNg, GM-CSF, IL-18BP, sFasL	Attenuated responses Lesser effect on "Th2"	
Cellular phenotype	↓ NK cells	", but ↑ in CD69+	
Research Summary	? Dose-response		

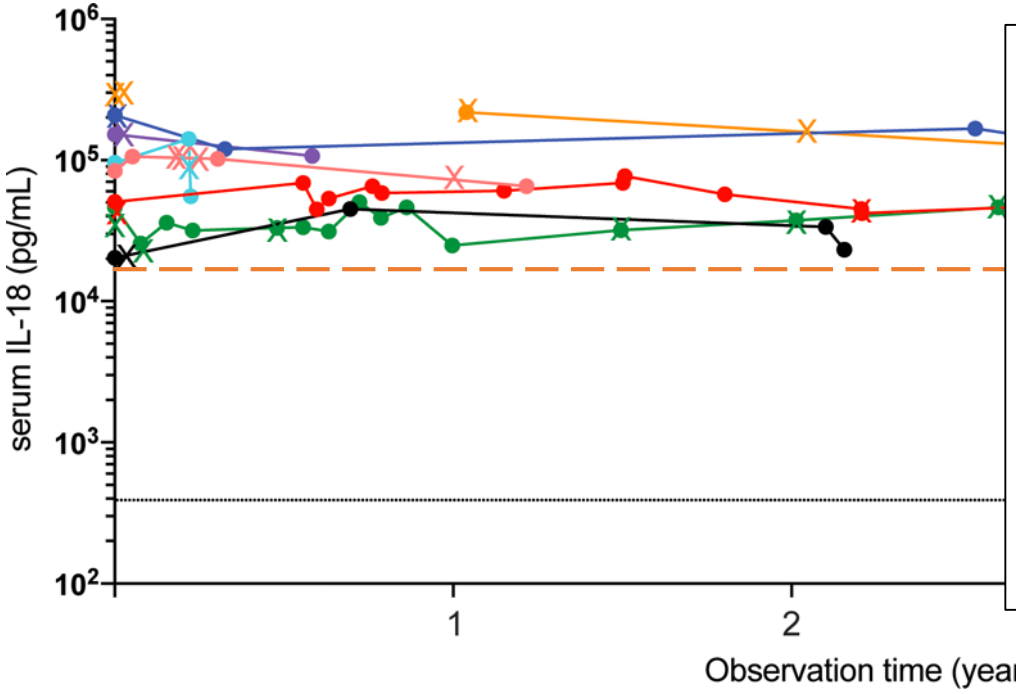
TABLE I. Comparison of CSS

	Test
✓	Fever
?	Ferritin (ng/mL)
	Splenomegaly
	Hepatomegaly
✓	Neutrophils (cells/μL)
✓	Hemoglobin (g/dL)
✓	Platelet count (10^9/L)
✓	Aspartate aminotransferase (U/L)
	Triglycerides (mg/dL)
	Fibrinogen (mg/dL)
	Hemophagocytosis
	Low/absent NK-cell activity
	Soluble IL-2Ra (CD25) (U/L)
	Known immunosuppression

Canna, JACI, 2020

IL-18 is a persistent sJIA/MAS biomarker





<u>Despite Free IL-18 Every Day</u>

NO:

- compensatory IL-18BP elevation
- antigen-specific autoimmunity
- early degenerative/inflammatory dis.
- developmental defects
- Severe allergy/atopy

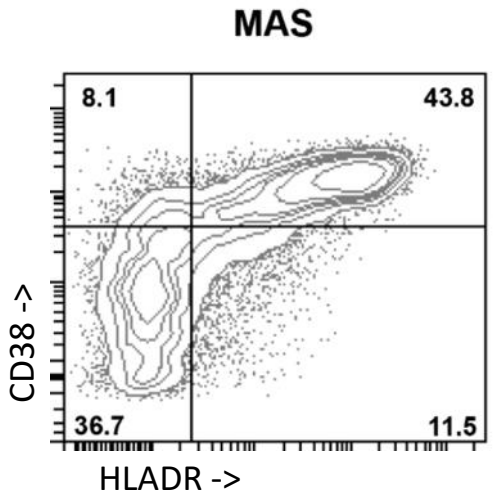
Shimizu, Cytokine, 2010
Canna, IOVS, 2018

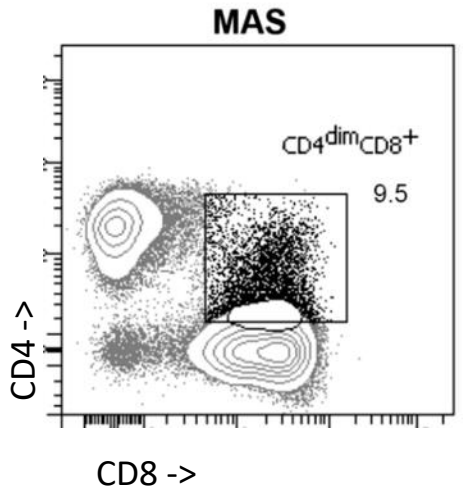
Heirarchy of IL-18 response: CD8>CD4>>NK

Society for Immunotherapy of Cancer

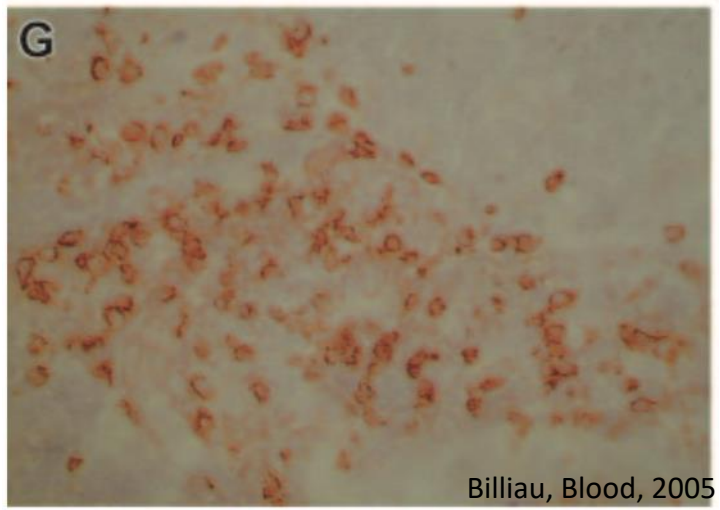
NK cytopenia and IL-18 resistance

Grom J Peds 2003
de Jager, A&R, 2009
Put, A&R, 2017
Ohya, ACR Open Rheum, 2022

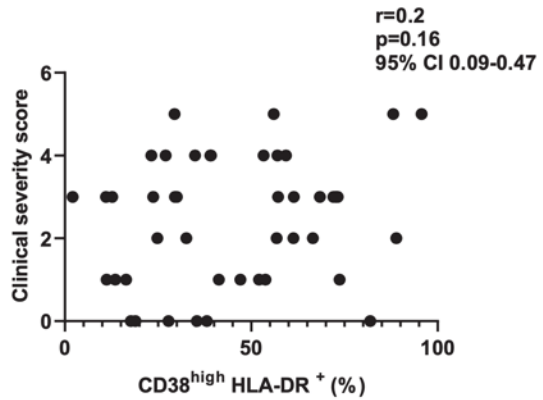


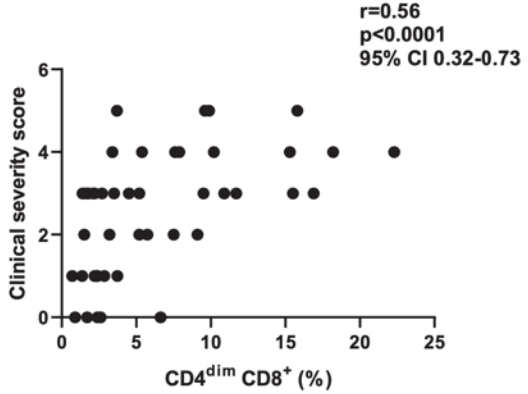


Liver CD8 IHC in MAS



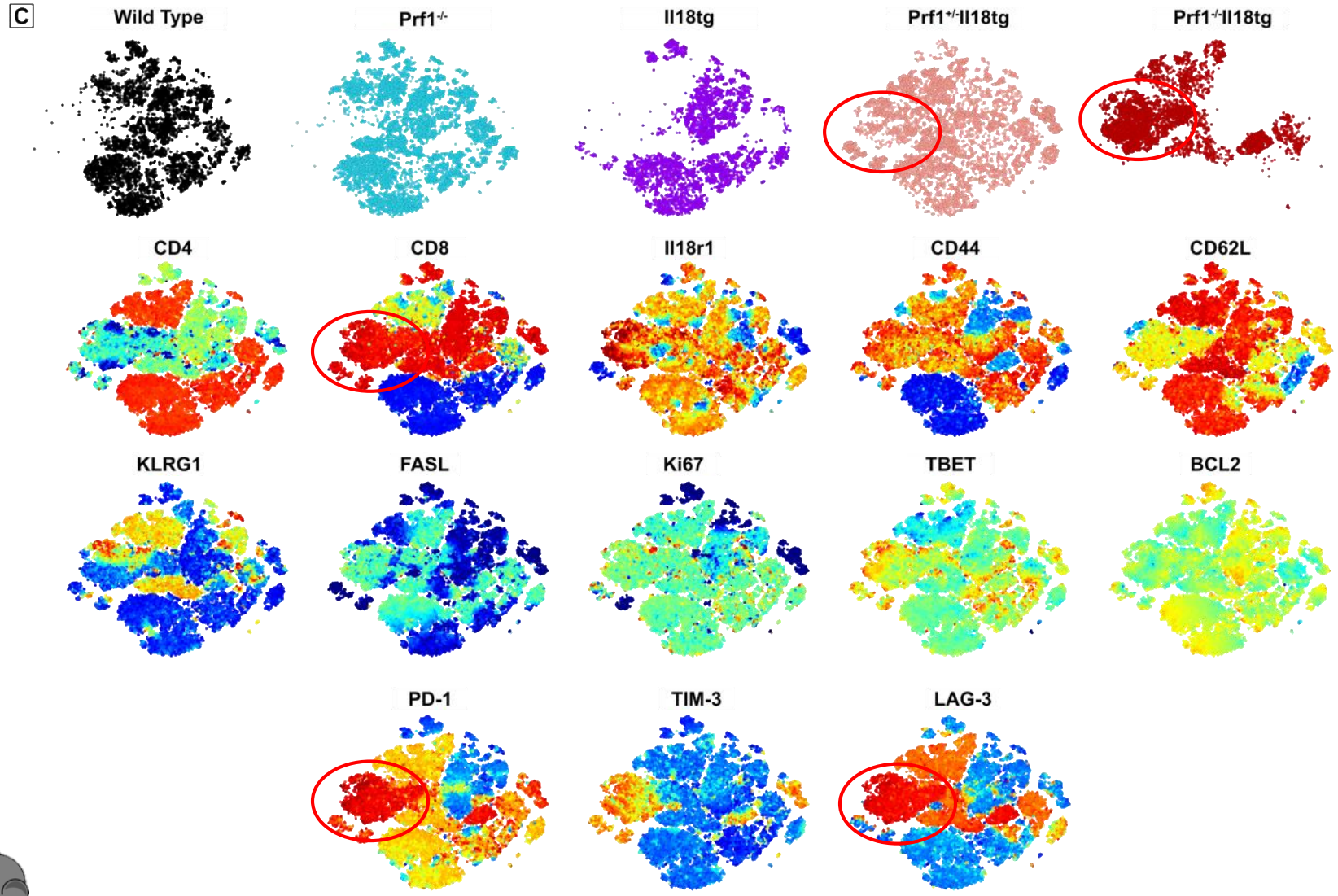
Billiau, Blood, 2005





Matteis / Prencipe, Blood, 2022

Heirarchy of IL-18 response: CD8>CD4>>NK

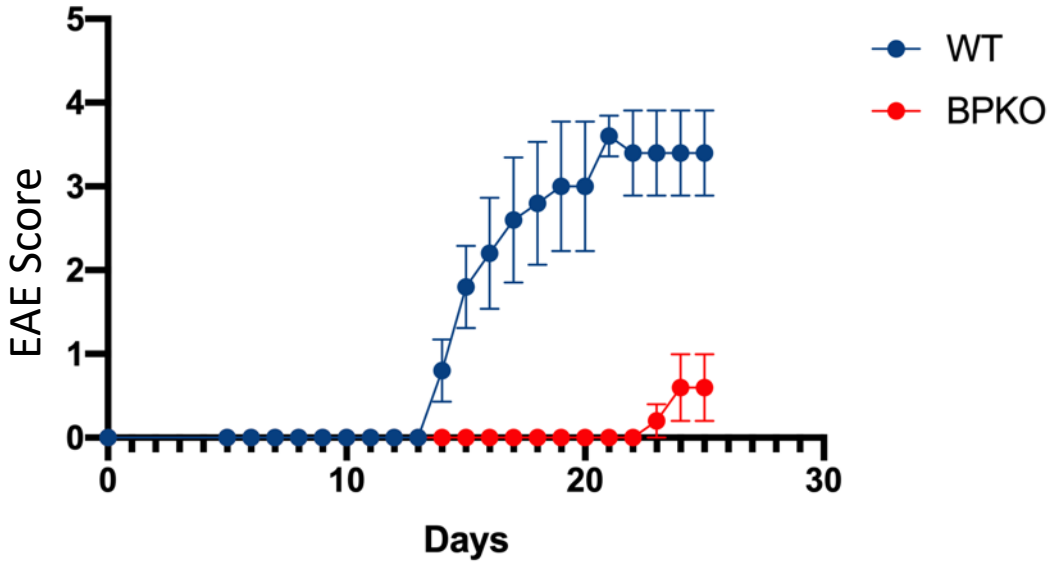


- Same in Il18tg + LCMV
- Oligoclonal
- IFNg & TNF – producing
- Transcriptionally Teff

Tsoukas / Canna, Blood, 2020
Landy / Canna, unpublished

Is unopposed IL-18 protective from autoimmunity?

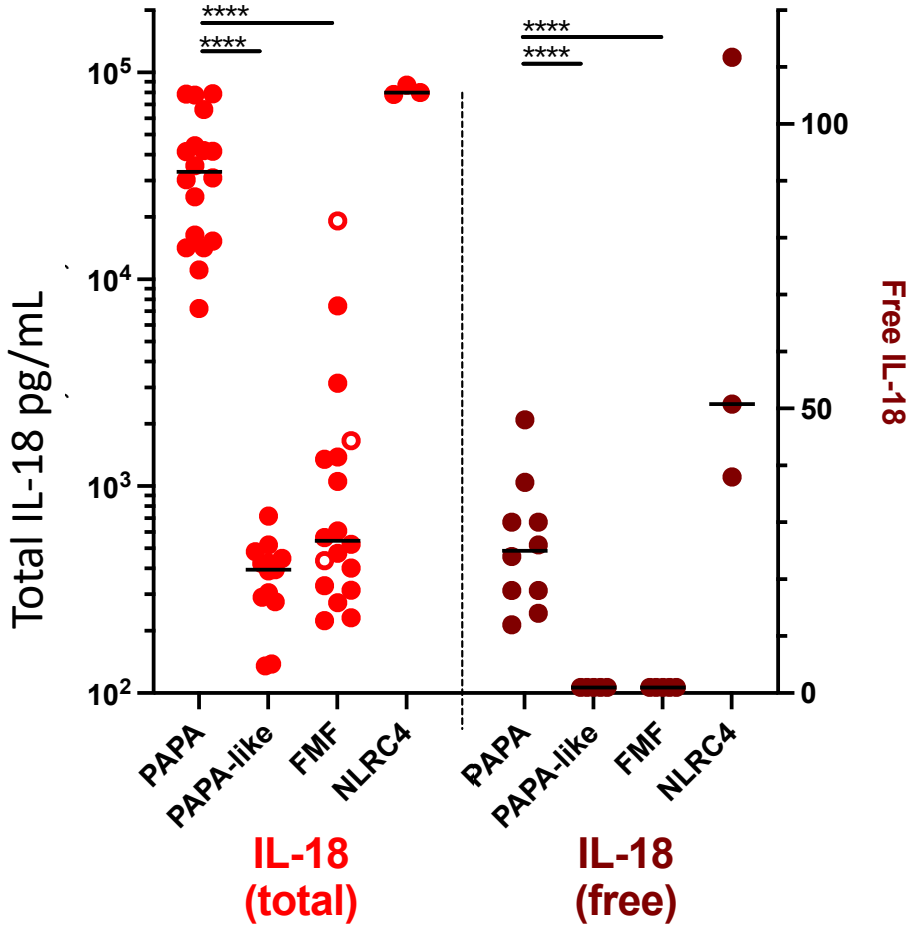
Unopposed IL-18 protects from EAE



Substantial increase in CD8 T-cells in CNS of *Il18bp*$^{-/-}$ mice

Dang…Canna, unpublished

Skin, PSTPIP1 & the MAS paradigm



Stone…Canna, A&R, 2021

Hong, JAAD, 2009

Pyogenic
Arthritis
Pyoderma gangrenosum
Acne

No MAS

What we don’t know

Effects on memory

Why no signal for autoimmunity?

Effects on homeostatic function

Problems with Type2 / Type 17 suppression

Organ specificity

Conclusions

- Modest total IL-18 elevation is common
- Free “IL-18opathies”
  - Macrophage Activation Syndrome
  - Epithelial phenotypes: GI, rash, PAPA
- Free IL-18emia is remarkably well-tolerated
  - Amplifier > primary mover
- Type 1 responses, CD8 > CD4 T-cells >> NK cells
- Outcomes in MAS (even without targeted treatment) >> other forms of HLH

Group Members

- Emily Landy
- Vinh Dang
- Jemy Varghese
- Anastasia Frank-Kamenetskii, PhD
- Leonardo Huang
- Junior Nguyen
- Jessica Lee
- Lauren Van Der Kraak*
- Paul Tsoukas*
- Eric Weiss*

*past lab member

@Canna_lab

www.labcanna.org

Collaborators

- Ed Behrens
- Caroline Diorio / David Teachey
- Raphaela Goldbach-Mansky
- Debbie Stone / Dan Kastner
- Cem Gabay
- Grant Schulert / Alexei Grom
- Dirk Holzinger / Christoph Kessel
- Pui Lee / Peter Nigrovic
- Aaron Ring

Children's Hospital of Philadelphia
Immune Dysregulation Program

Program in Microbiology & Immunology

Penn University of Pennsylvania

IFI Institute for Immunology

Rheumatology Research Foundation
Malley Family Foundation

NIH

NIAMS Intramural
NIAID K22 AI123366
NICHD R01 HD098428