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Gale and Ira Drukier Institute
for Children's Health

Old and Emergent Players in Human Autoimmunity:

Lessons from Patient Immune Profiling

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Disclosures

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- Consultant fees: Neovacs, Astra Zeneca, Sanofi

Two Ends of an Immune Spectrum

Inappropriate recognition of our own cells/tissues

CPI Induce Immune-related Adverse Events (IrAEs)

- **Common and typically mild, but can be severe/fatal**
  Vitiligo, colitis, endocrinopathies…
- ***Mainly "Organ-Specific" rather than "Systemic"***
- **More common with CTLA-4 than with PD1 blockade**
- **Tend to improve with treatment interruption**
  Corticosteroids, anti-TNF, anti-IL6, switch from CTLA-4 to PD1 blockade

Opportunities

- Improve out understanding of cancer immunology
- Improve our understanding of mechanisms leading to inflammation/autoimmunity
- New therapeutic strategies

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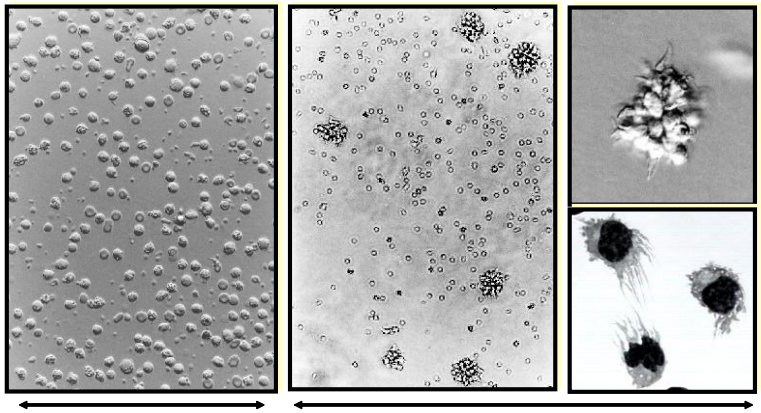
SLE

- *Breakdown of Tolerance to Nucleic Acids*
  - *Tremendous clinical heterogeneity*

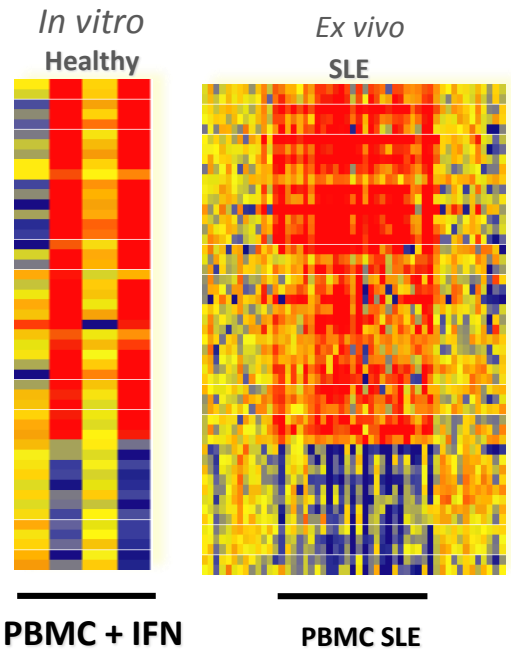
Monocytes differentiate into dendritic cells when exposed to SLE serum

This effect is Type I IFN-dependent



Blanco et al. *Science*. 2001;294(5546):1540-3

A Blood IFN Signature is detected in the majority of patients



Bennett et al. J Exp Med 2003

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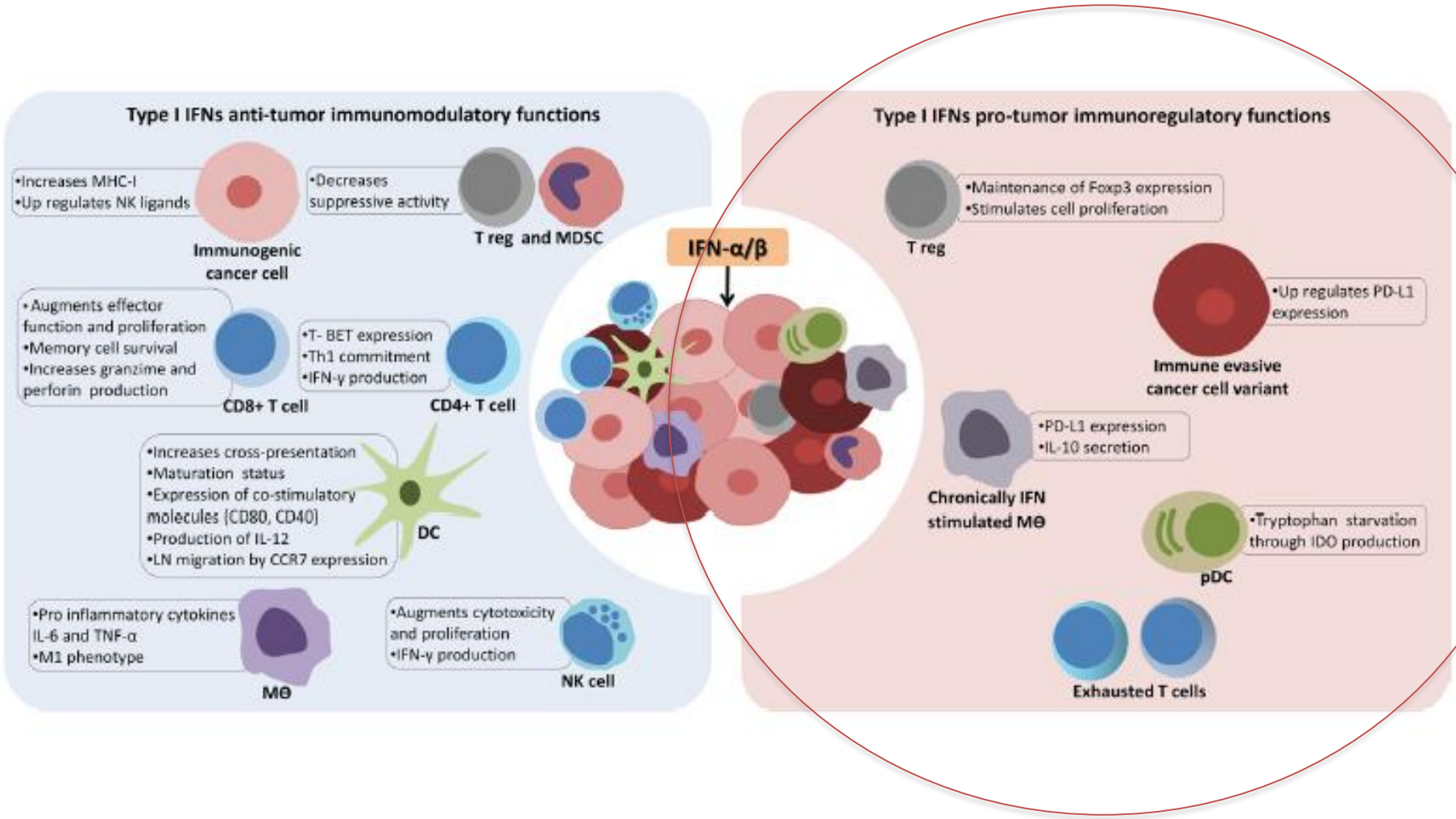
The complex and context-dependent role of Interferon in cancer immunity



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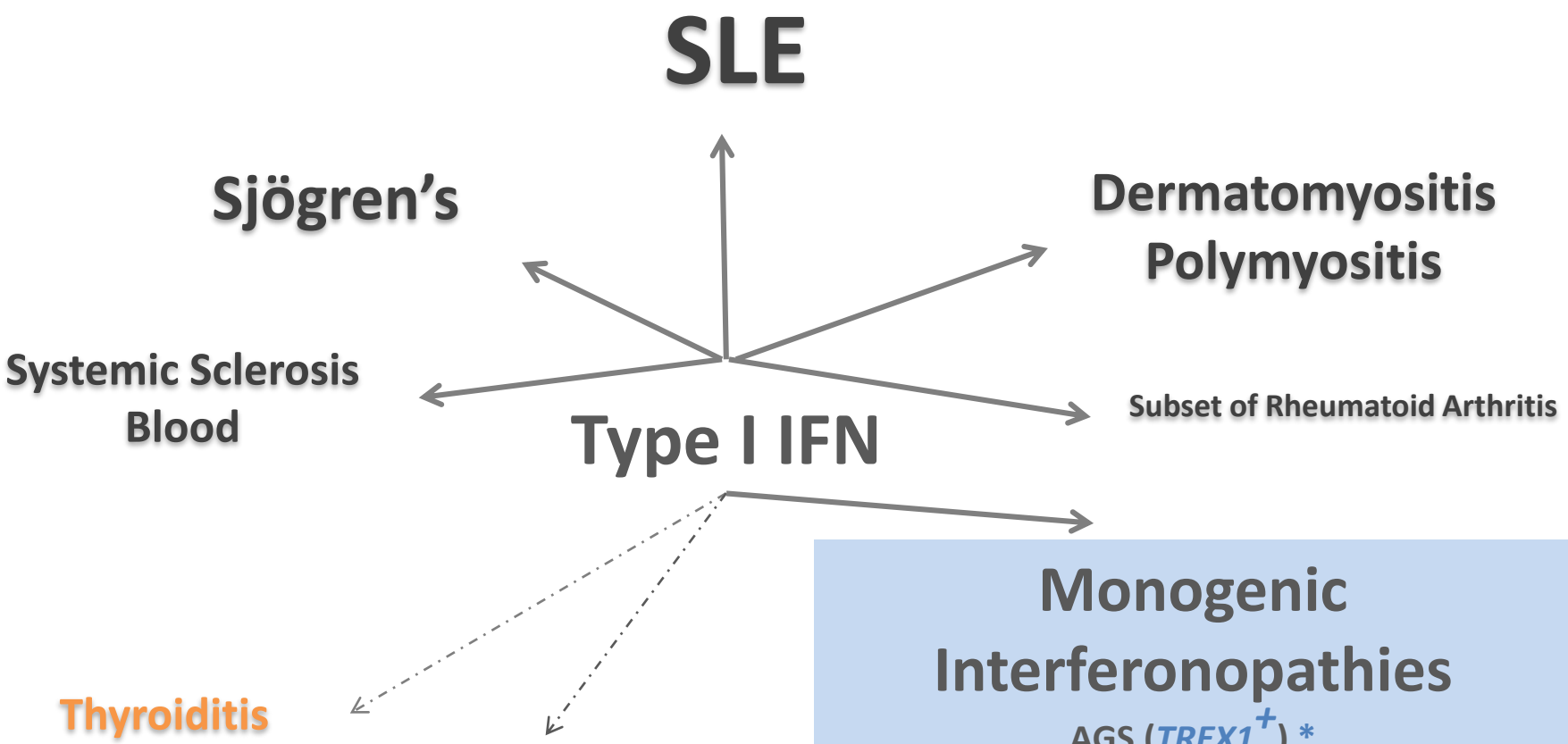
Medrano et al., Oncotarger 2017

The Growing Spectrum of Autoimmune "Interferonopathies"



Monogenic Interferonopathies

AGS (*TREX1*$^{+}$) *
SPENCD (*TRAP*) ***
ISG15 Deficiency
USP18 Deficiency
ADA2 Deficiency
CANDLE (*PSM8*)
SAVI (*TMEM173*/STING)

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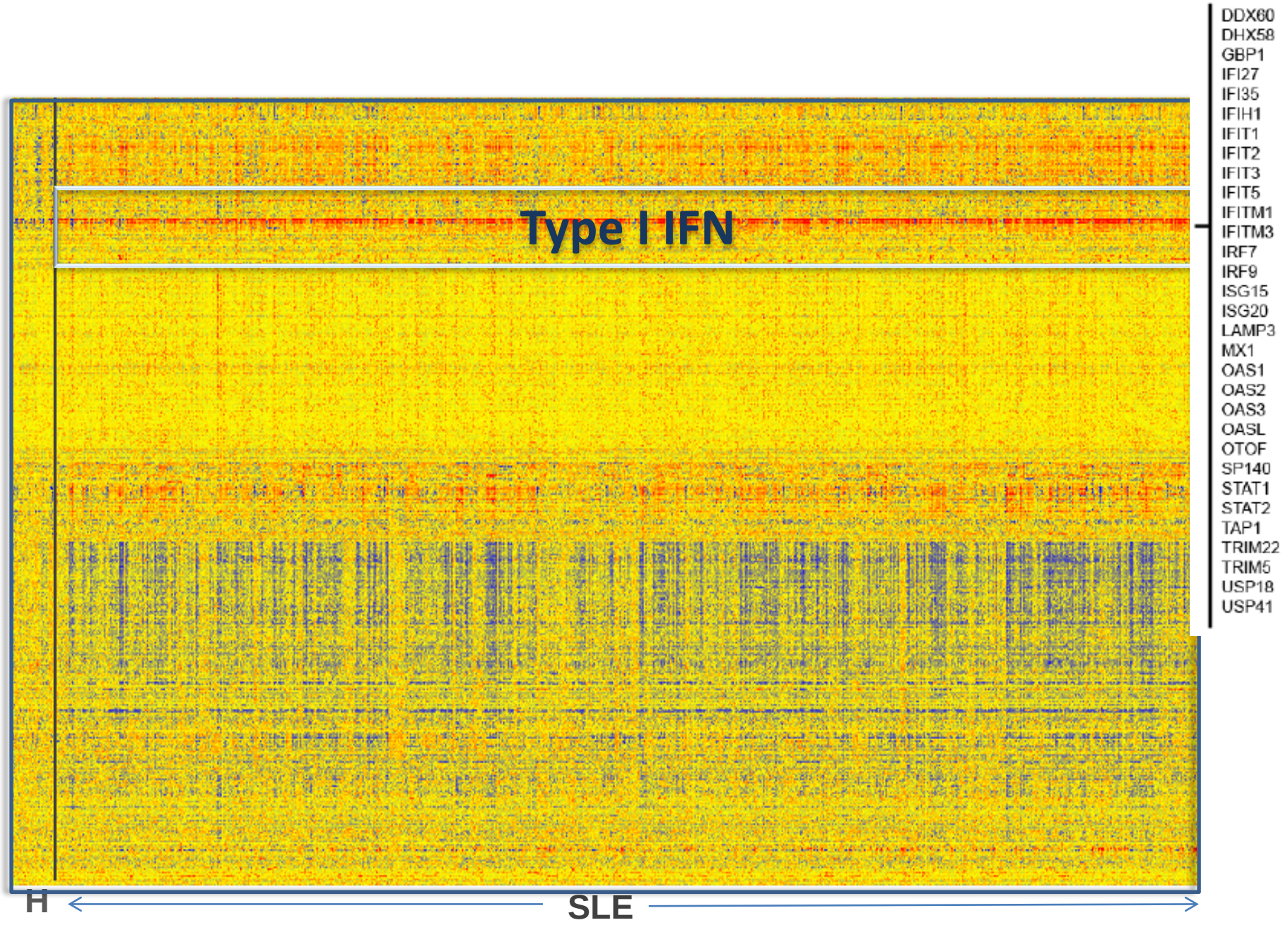
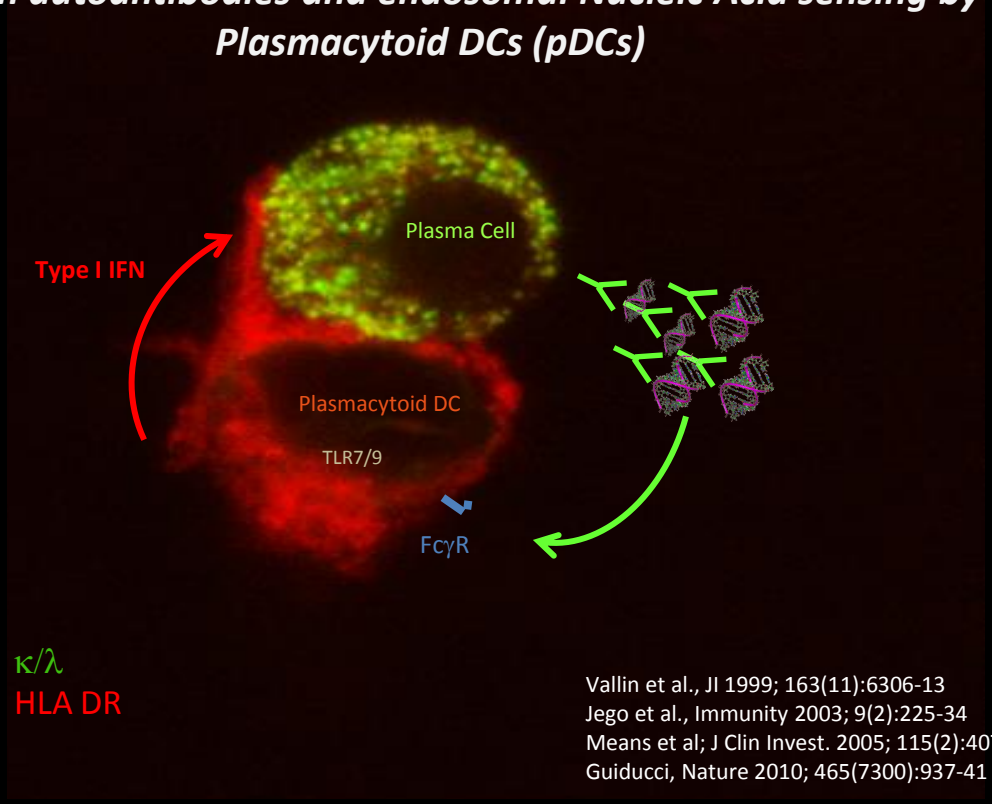
Scanning 960 pediatric SLE blood samples highlights the IFN signature prevalence

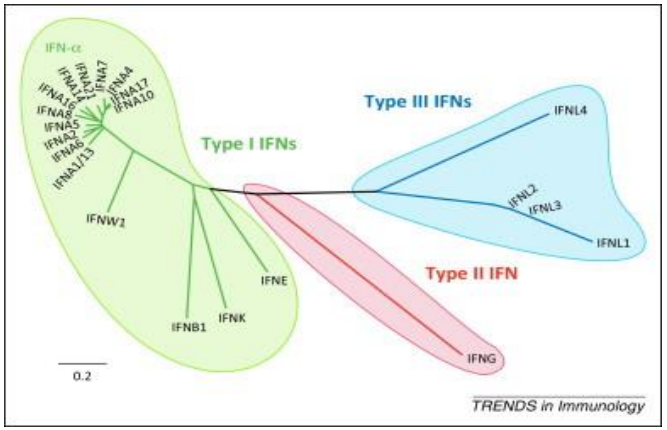


Banchereau et al; Cell, 2016

A self amplifying SLE pathogenic loop through autoantibodies and endosomal Nucleic Acid sensing by Plasmacytoid DCs (pDCs)



Vallin et al., JI 1999; 163(11):6306-13
Jego et al., Immunity 2003; 9(2):225-34
Means et al; J Clin Invest. 2005; 115(2):407-17
Guiducci, Nature 2010; 465(7300):937-41

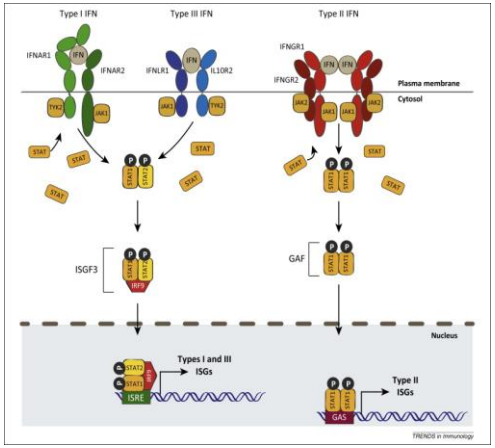


There are 21 IFN proteins belonging to 3 IFN families

Professional/Non Professional IFN-producing Cells

The origin of the Interferon signature and the role of IFN in non-familial SLE is NOT resolved yet

Endosomal/Cytosolic NA Sensors

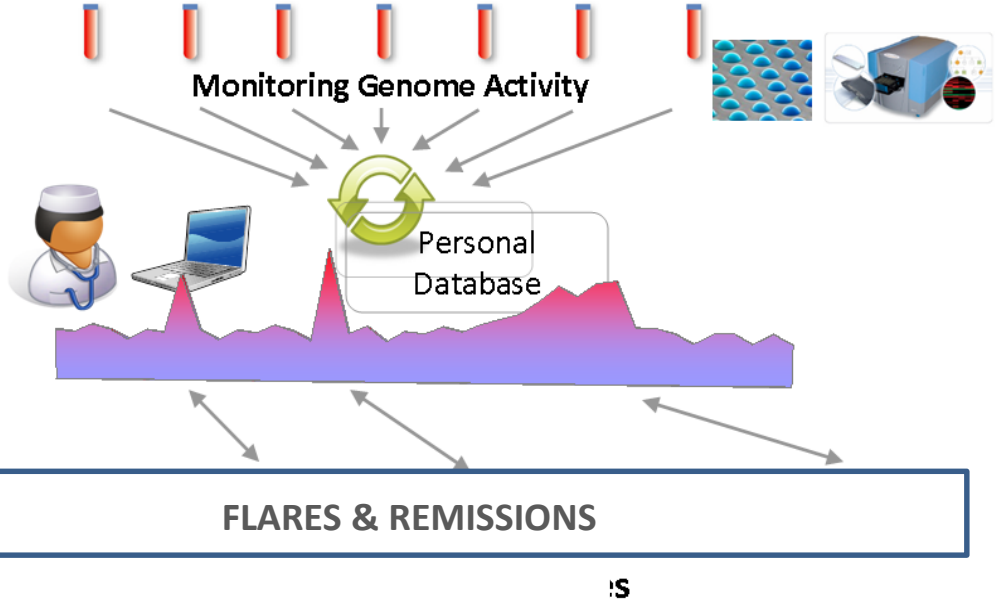


Hans-Heinrich Hoffmann , William M. Schneider , Charles M. Rice,

- *IFN is not alone in SLE*

LONGITUDINAL STUDIES TO UNDERSTAND PATHOGENESIS OF ACTIVE SLE and IDENTIFY BIOMARKERS

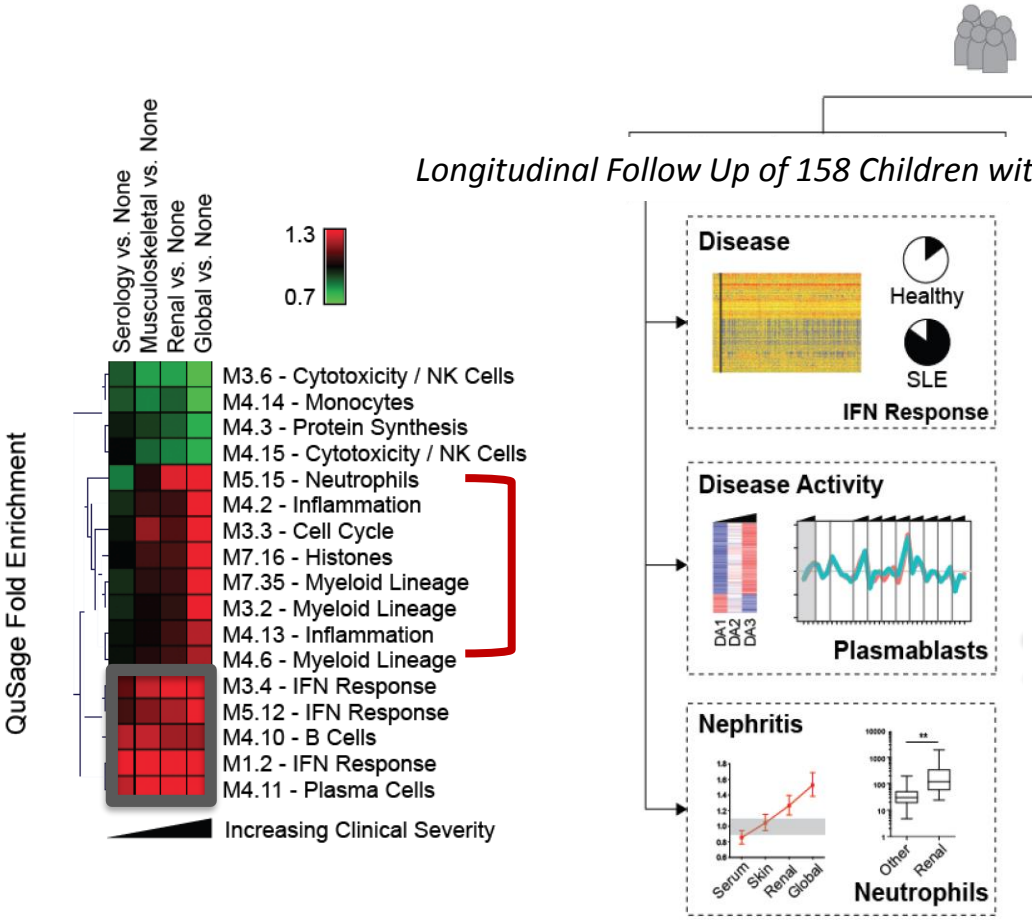
~500 children with SLE followed from 1-15 years every 2-3 months



BIIR

Banchereau et al., Cell, 2016

LESSONS FROM LONGITUDINAL MONITORING OF PEDIATRIC SLE PATIENTS



*An **IFN response** is detected in 85% of patients*

*A **plasmablast signature** correlates with disease activity, especially in African American patients*

*A **neutrophil signature** appears with nephritis*

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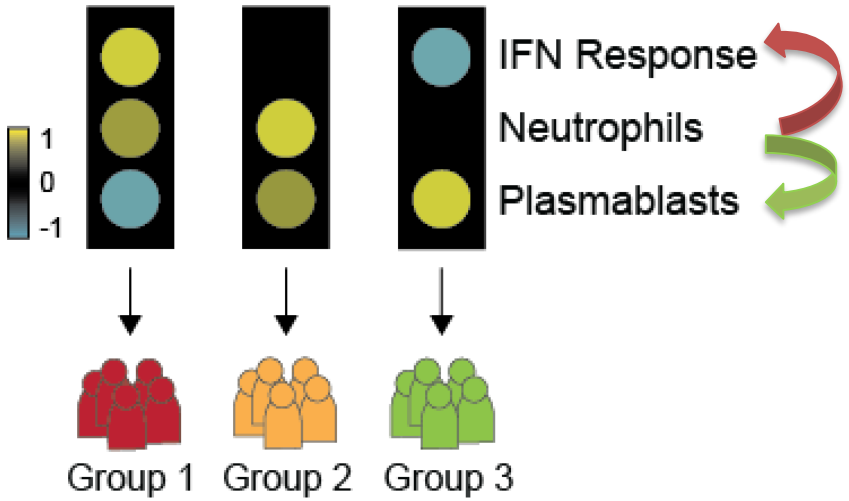
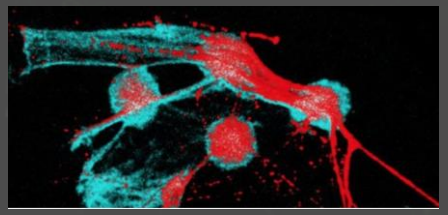
Banchereau et al., Cell, 2016

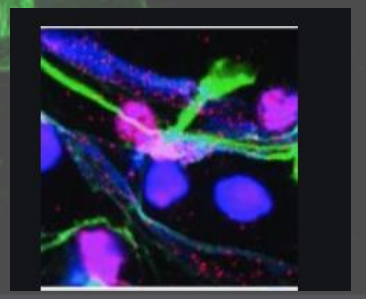
Longitudinal profiling of INDIVIDUAL SLE PATIENTS reveals molecular heterogeneity in signatures that correlate with DISEASE ACTIVITY



Banchereau et al., Cell 2016

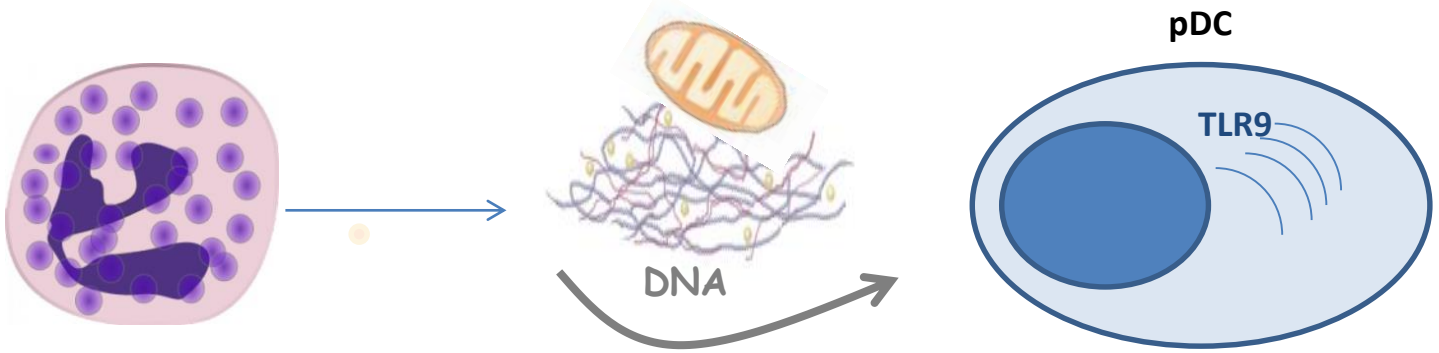


Neutrophils are a spectacular source of extra-cellular nucleic acids



× 800

Live Human Neutrophils Release Inert Mitochondrial DNA-Protein Complexes in the Steady State



No IFN production

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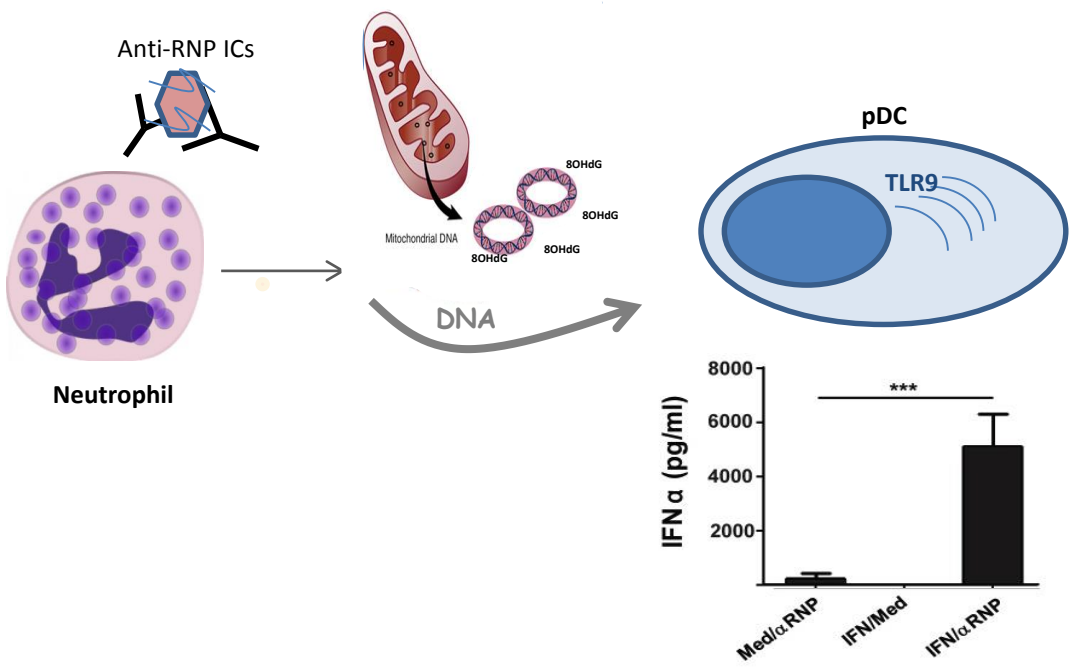
Yousefi et al., Cell Death Diff 2009
Caielli et al; J Exp Med, 2016

Lupus Neutrophils Exposed to SLE Anti-RNP Immune Complexes Release *Interferogenic DNA*



Caielli et al; J Exp Med, 2016; 213(5):697-713

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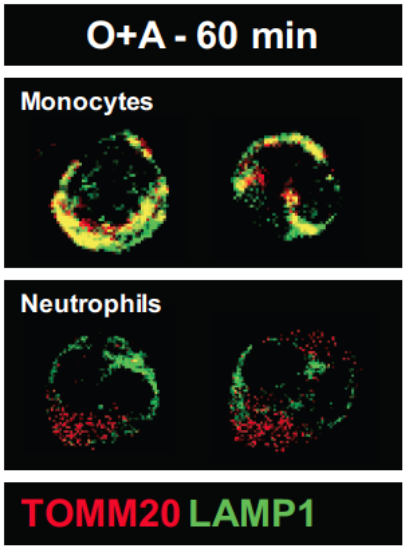
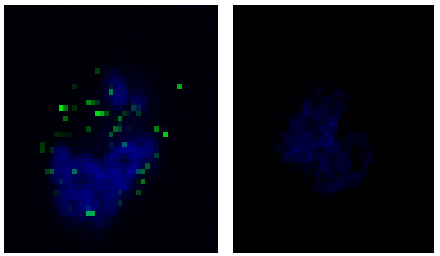
1. Healthy human neutrophils do not complete Mitophagy

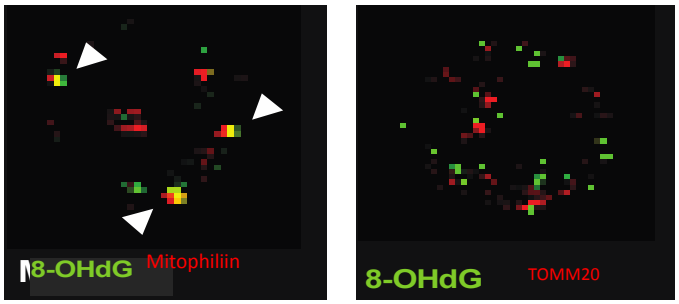


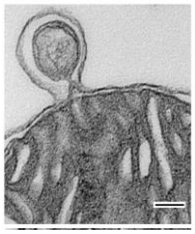
2. The cytosol of healthy neutrophils is loaded with Oxidized Mitochondrial DNA routed for lysosomal degradation



Neutrophil | Monocyte

Neutrophil cytoplasmic vesicles display cargo selectivity

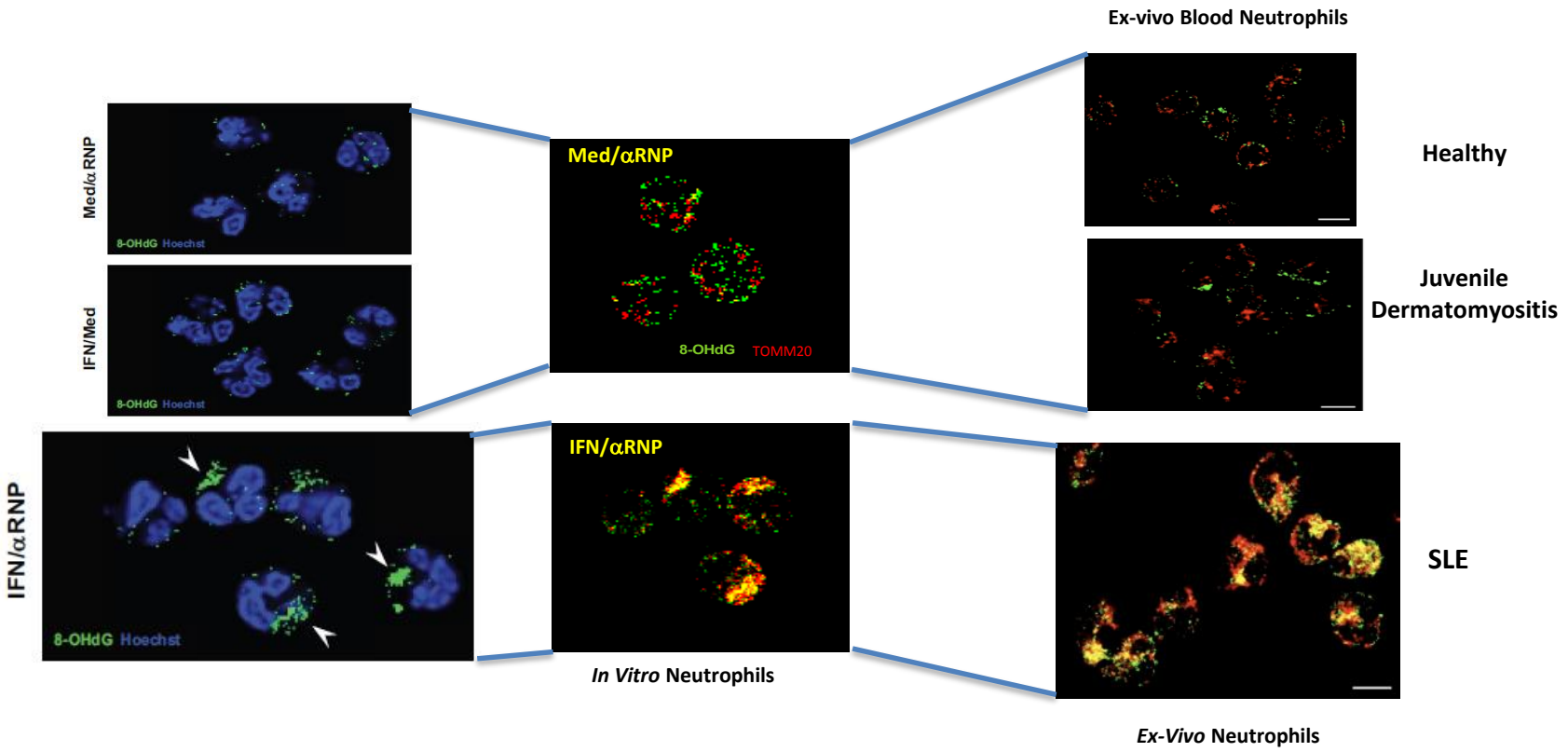




Curr Biol. 2012
A vesicular transport pathway shuttles cargo from mitochondria to lysosomes.
Soubannier et al.

Caielli et al; J Exp Med, 2016; 213(5):697-713

"Lupus-like" activation (IFN and TLR7/8-agonistic autoantibodies) increases the load and mitochondrial retention of oxidized mtDNA



Caielli et al; J Exp Med, 2016; 213(5):697-713

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SLE autoantibodies + INTERFERON

Simone Caielli

INTERFEROGENIC DNA

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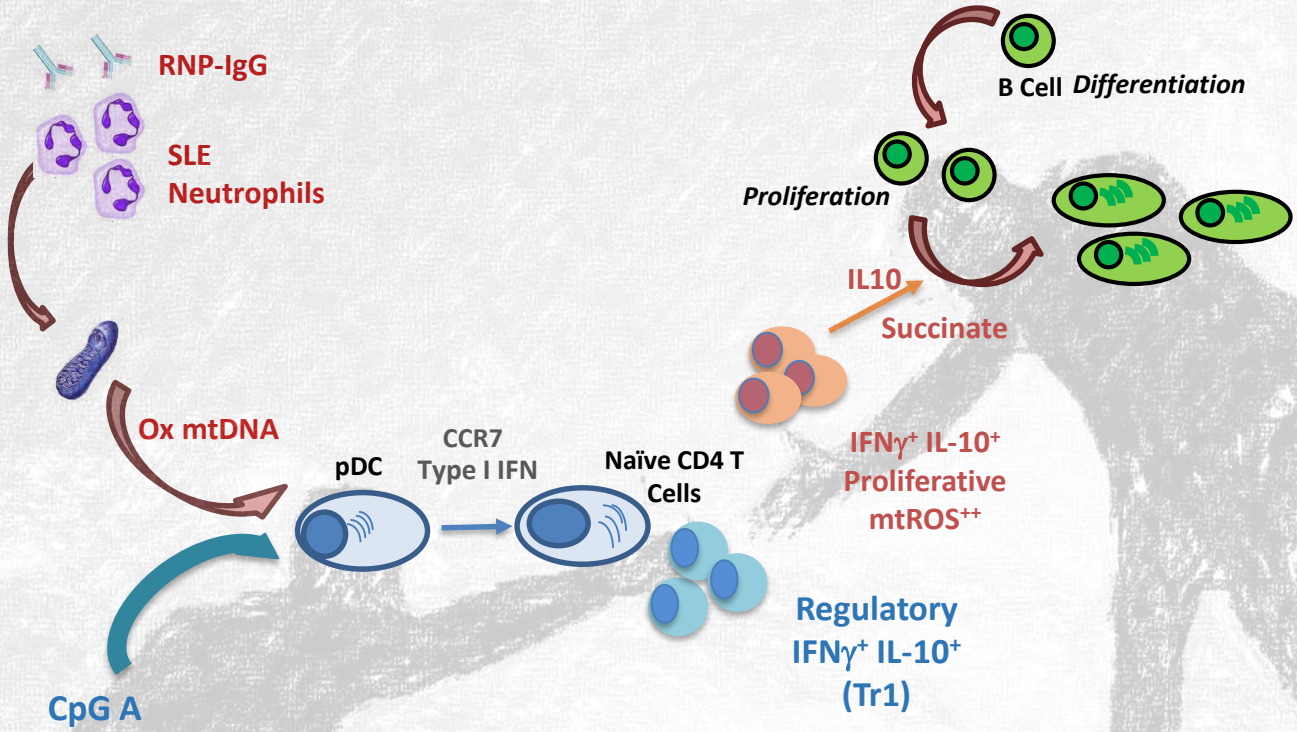
The identification of a neutrophil signature led to the elucidation of novel human neutrophil biology and the discovery of <u>novel adaptive immunity pathways in human SLE</u>



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Caielli et al., J. Exp. Med., 2016

Caielli et al., Nature Medicine, 2019

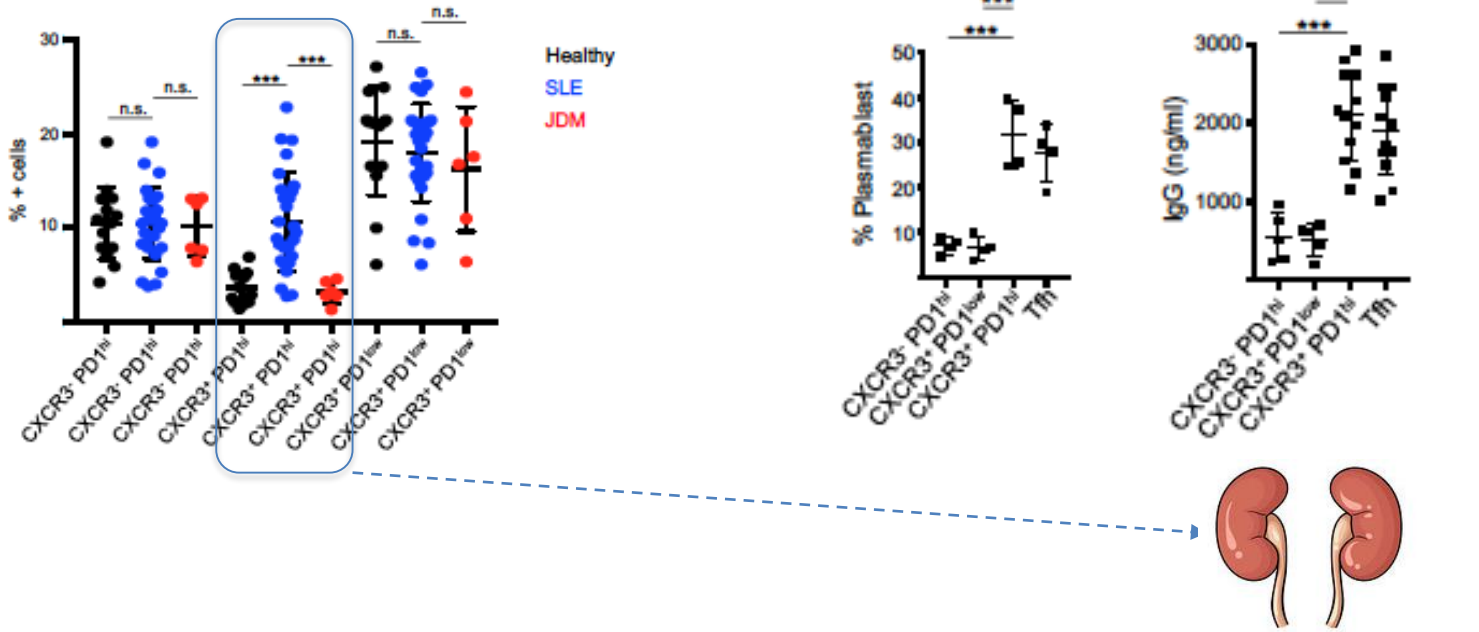
As opposed to Tr1 cells, CD4+ T cells exposed to Ox mtDNA-activated pDCs:

- Are not anergic
- Acquire a Th1-like phenotype characterized by high expression of IFNγ and IL10
- Express high levels of PD1
- Accumulate Succinate and undergo RET; RET generates high amounts of ROS
- *Help B cells independently of IL21 through IL10 + Succinate*

Are these cells relevant to Patients?

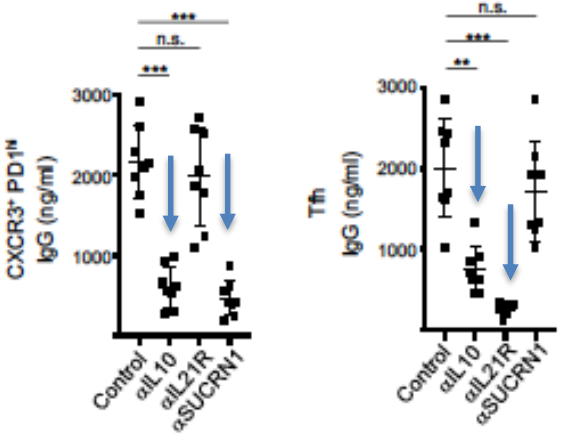
Caielli et al., Nature Medicine, 2019

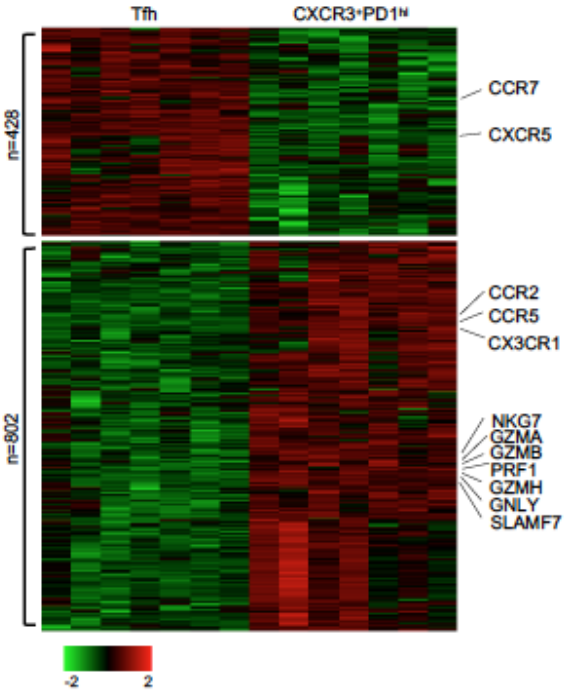
A distinct CXCR5^{-} CXCR3^{+} PD1^{+} CD4^{+} T helper cell subset sharing the features of Ox mtDNA CD4^{+} T cells is expanded in SLE blood



Caielli et al., Nat Med 2019

SLE blood CXCR3+ PD1+CD4+ T cells help as efficiently as Tfh but through a distinct mechanism





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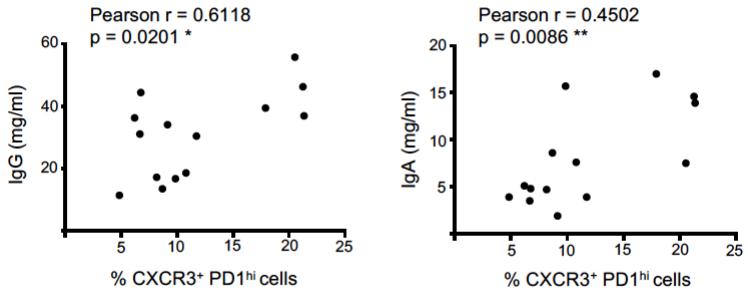


Role in other immune/autoimmune responses?

The Expanding Spectrum of Disease-Associated T helper Cells

T_{PH} HELP IN RHEUMATOID ARTHRITIS

”Like PD-1^{hi}CXCR5^{+} T follicular helper cells, **T_{PH}** (CXCR5^{-} PD1^{hi} CD4^{+} T cells) induce plasma cell differentiation in vitro through **IL-21** secretion and SLAMF5 interaction”

nature medicine

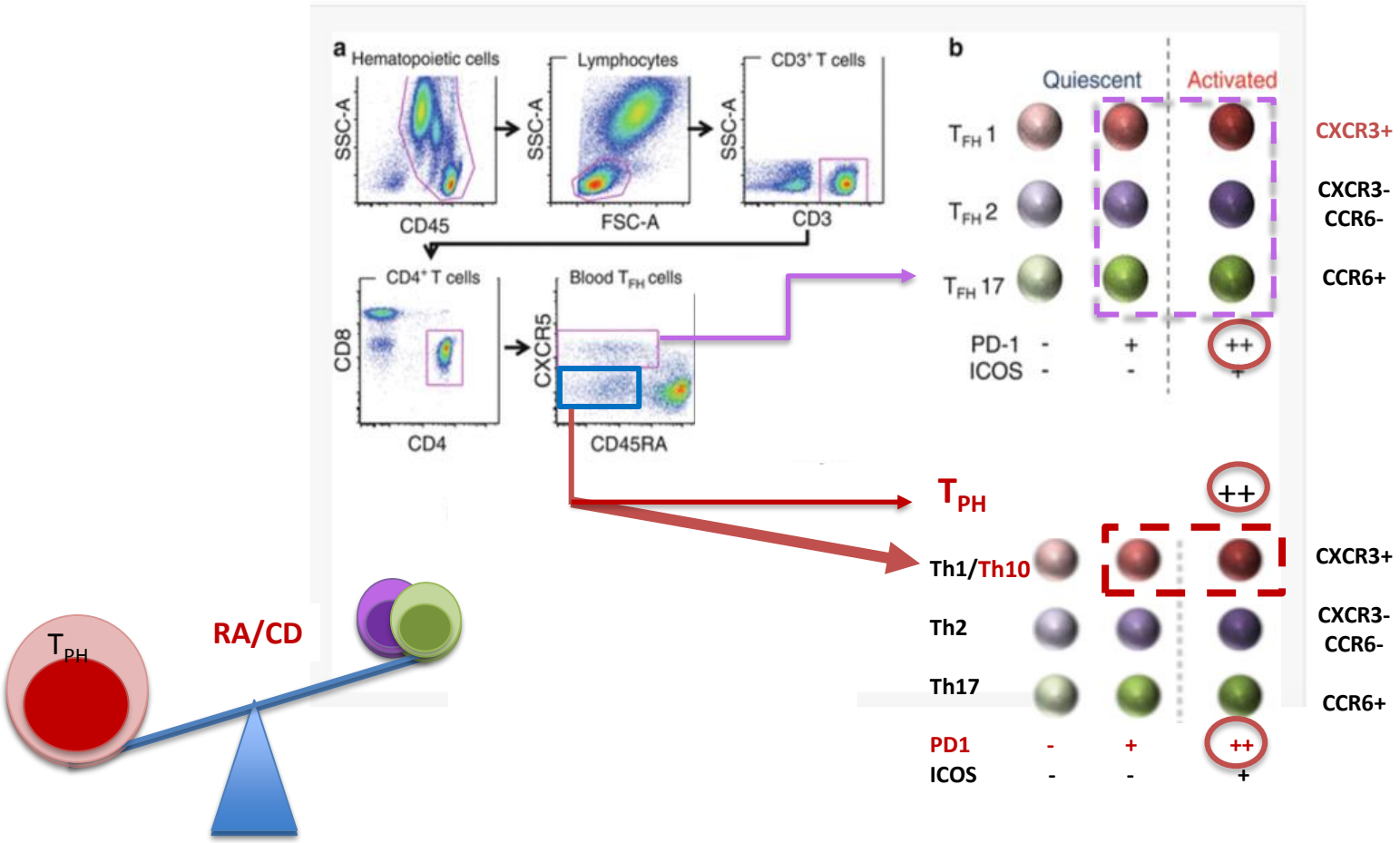
BRIEF COMMUNICATION

https://doi.org/10.1038/s41591-019-0403-9

Distinct phenotype of CD4^{+} T cells driving celiac disease identified in multiple autoimmune conditions

Asbjørn Christophersen[1,2,3,4], Eivind G. Lund[1,2,3,14], Omri Snir[1,2,3,14], Elsa Solà[4,5], Chakravarthi Kanduri[1,6], Shiva Dahal-Koirala[1,2,3], Stephanie Zühlke[1,2,3], Øyvind Molberg[2,7], Paul J. Utz[4], Mina Rohani-Pichavant[4], Julia F. Simard[8], Cornelia L. Dekker[9], Knut E. A. Lundin[1,2,10], Ludvig M. Sollid[1,2,3,11,15*] and Mark M. Davis[4,12,13,15*]

The expanding SLE CD4⁺ T cell helper landscape in human autoimmunity



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- **Seunghee Hong**
- Tracey Wright
- Genomics Core

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NIAMS Center for Lupus Research

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- **Sharleen So**
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Baylor Scott & White System

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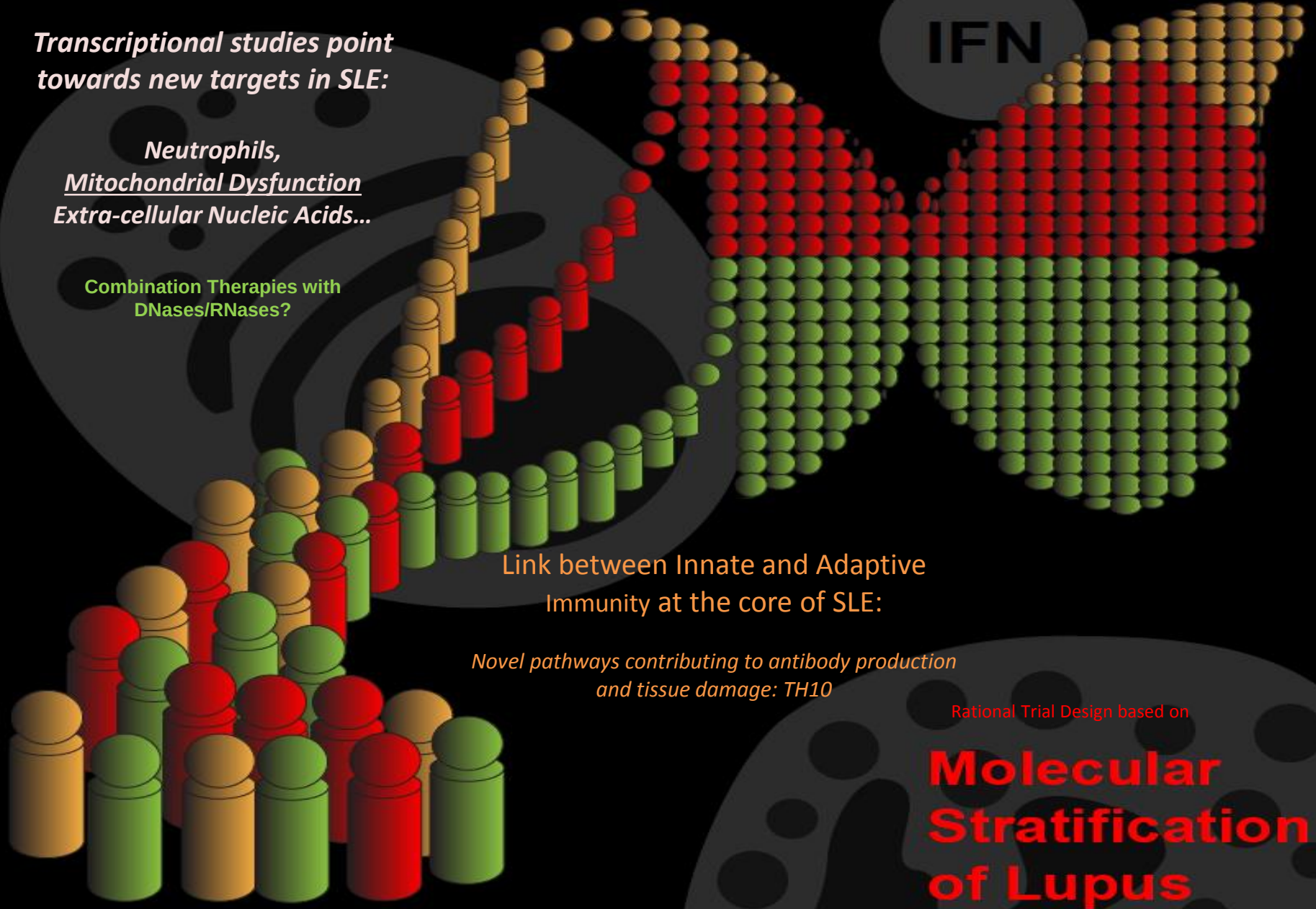
Lessons Learned

Transcriptional studies point towards new targets in SLE:

Neutrophils,
Mitochondrial Dysfunction
Extra-cellular Nucleic Acids…

Combination Therapies with DNases/RNases?



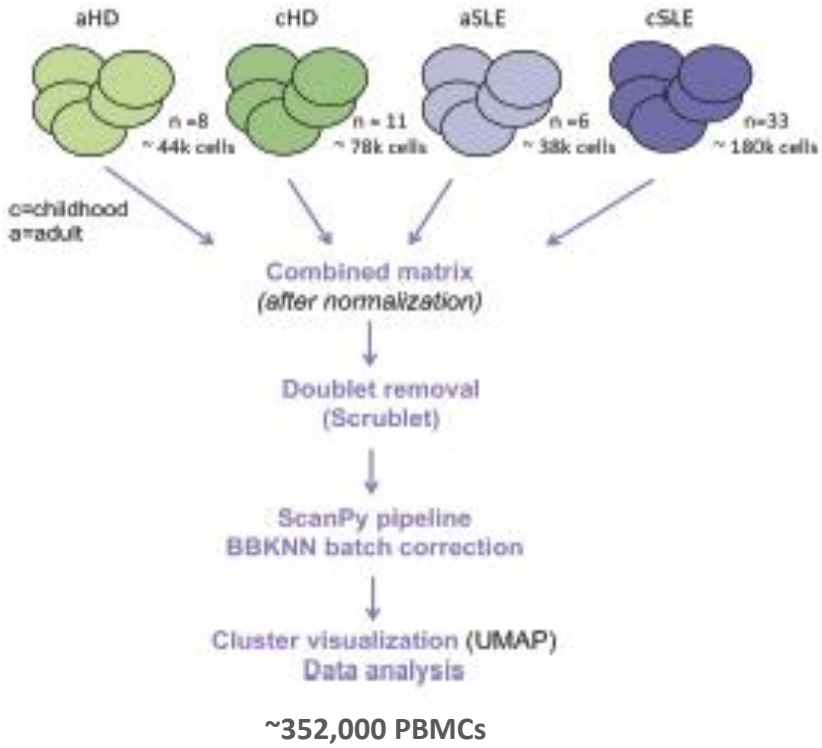
Link between Innate and Adaptive Immunity at the core of SLE:

Novel pathways contributing to antibody production and tissue damage: TH10

Rational Trial Design based on

Molecular Stratification of Lupus

Increasing the Resolution of SLE Molecular Signatures
(From Whole Blood to scRNAseq)



~352,000 PBMCs

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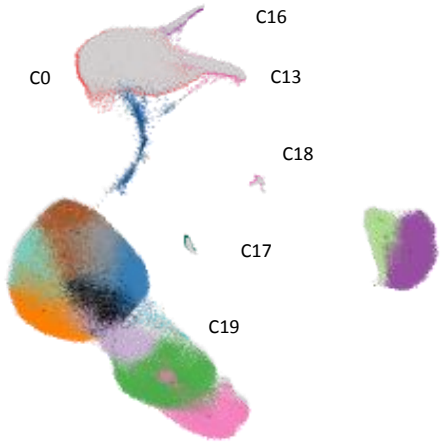
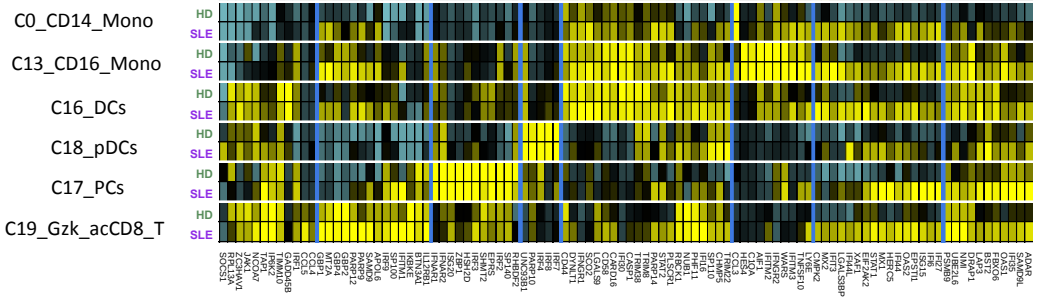
Nehar-Belaid et al., Submitted

From Whole Blood to Single Cells to unravel the origin of the SLE IFN Signature

A fraction of PBMC Clusters Contribute Disproportionately to the SLE Interferon Signature





Nehar-Belaid et al., Submitted

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