

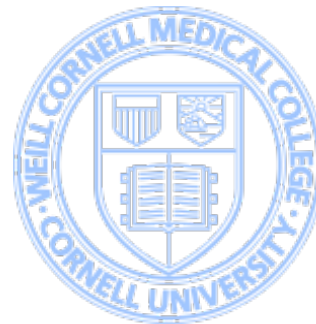
Autoimmune Arthritis

- Impact
- Advances
- Opportunities

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Arthritis characterizes many immune-mediated diseases

➤ Systemic sclerosis

- 240/million in U.S
- Enriched in Choctaw



➤ Systemic lupus erythematosus

- >200,000 in U.S.
- Most severe in African Americans



➤ Rheumatoid arthritis

- 1.5 million in U.S.

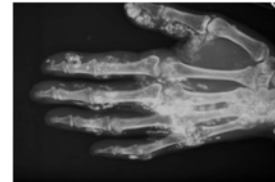


➤ Psoriatic arthritis

- 0.05-0.25% of U.S



➤ Dermatomyositis



➤ Vasculitis



Plus –

-Undifferentiated
Connective Tissue
Disease

- Overlap
- Incomplete
- Pre-

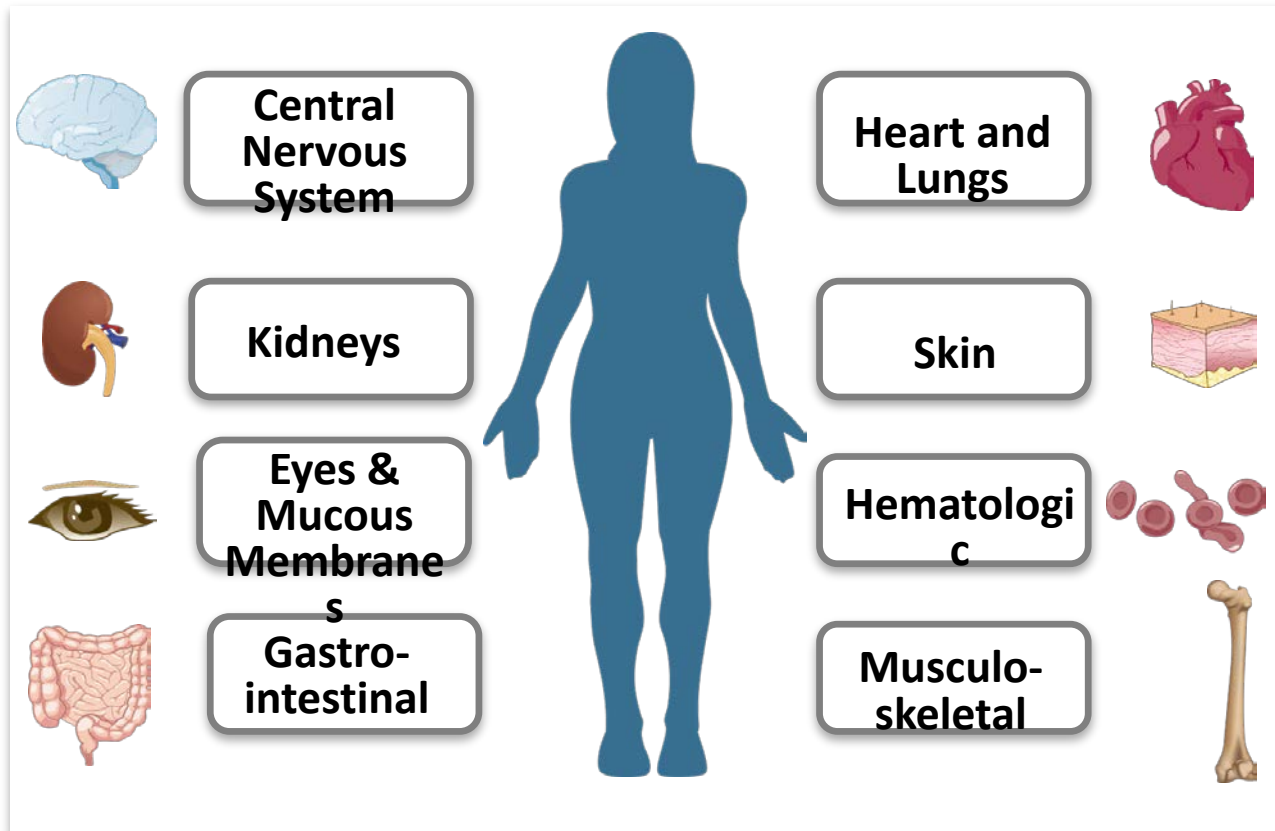
-Sjogren's syndrome
-Ankylosing spondylitis
-Lyme arthritis
-Sarcoidosis
-Anti-phospholipid syndrome

*All images ACR Rheumatology
Image Collection*

*Prevalence numbers:
Arthritis Foundation and
Izmirly P et al., doi:
10.1002/ART.41632*

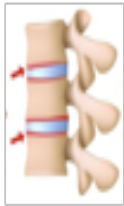
Diseases characterized by immune-mediated arthritis are **systemic diseases**

- potential for significant organ involvement and damage
- 31% excess cardiovascular deaths in RA patients (Arthritis Foundation)
- Interstitial lung disease and chronic nephritis
- Heterogeneity in manifestations in individual patients



Systemic autoimmune diseases particularly impact women

Arthritis Foundation: 1 in 12 women will develop an Inflammatory autoimmune rheumatic disease in their lifetime



1:3

*Ankylosing
spondylitis*



2:1

*Rheumatoid
arthritis*



4:1

*Systemic
sclerosis*



7:1

*Hashimoto
Thyroiditis*



7:1

*Primary
Biliary
Cholangitis*



9:1

*Sjögren's
syndrome*

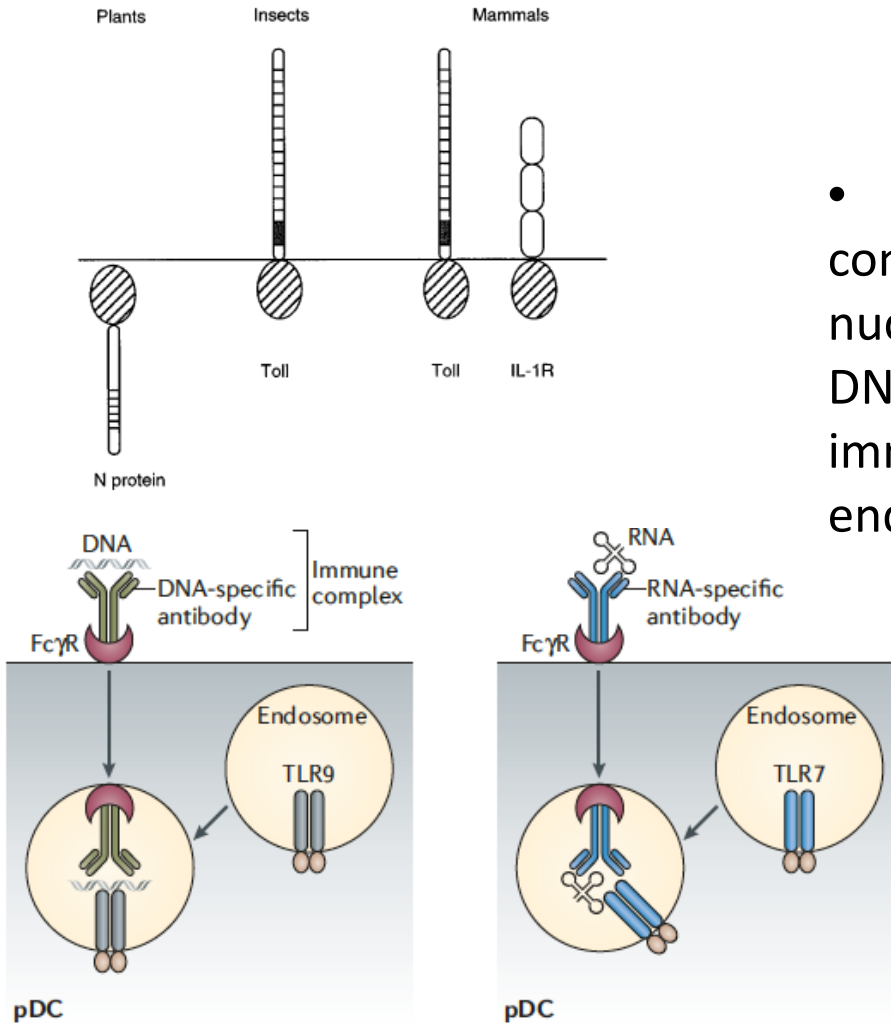


9:1

*Systemic
lupus
erythematosus*

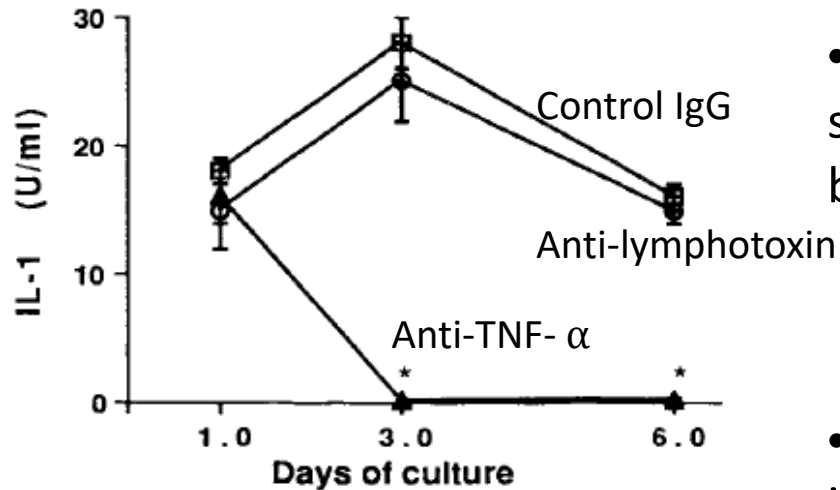


Big Picture Advances: Translation of discovery of Toll-like receptors to the role of the innate immune response in autoimmune disease



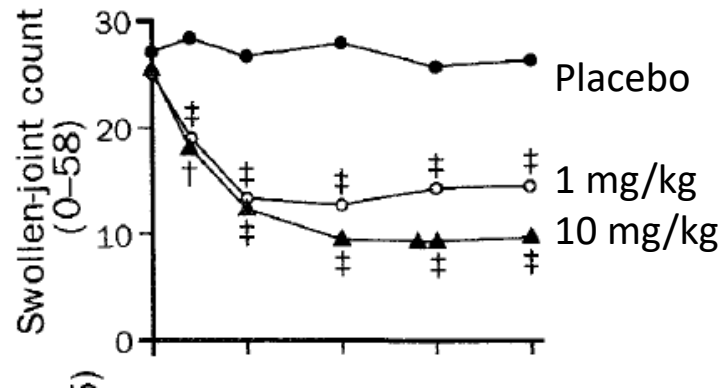
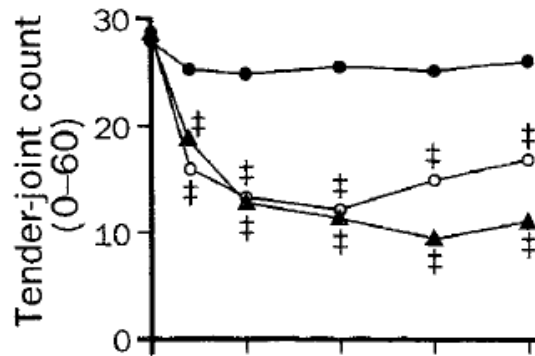
- Nucleic acid-containing immune complexes, neutrophil-derived nuclear material and circulating DNA can trigger an innate immune response through endosomal Toll-like receptors

Big Picture Advances: Application of *in vitro* study of human tissue for therapeutic target identification



- Production of IL-1 by rheumatoid arthritis synovial membrane cells inhibited by anti-TNF- α

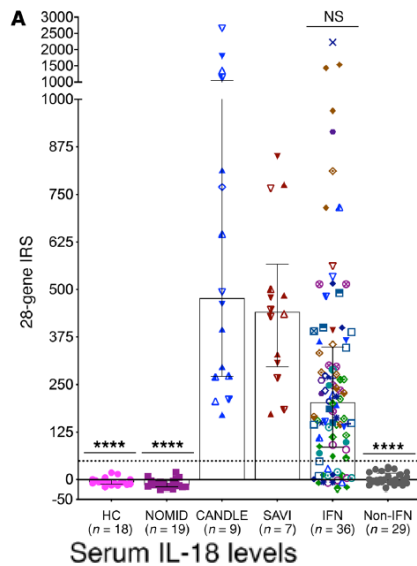
- Randomized controlled trial of anti-TNF- α in rheumatoid arthritis



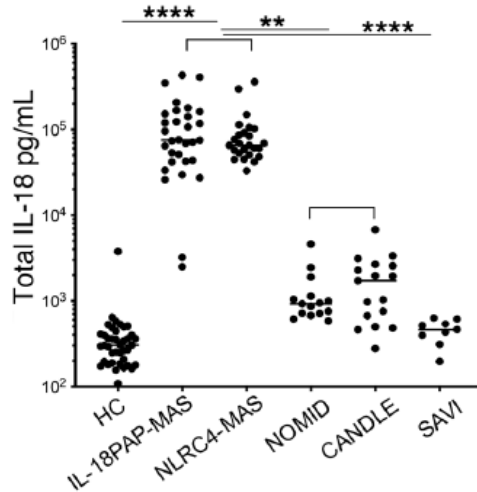
Brennan FM et al., Lancet 2 (8657), 1989

Elliott MJ et al., Lancet 344 (8930), 1994

Selected Recent Advances: Dissection of clinical features and molecular pathways associated with monogenic diseases inform studies of polygenic disorders



- Type I interferon-dominant syndromes

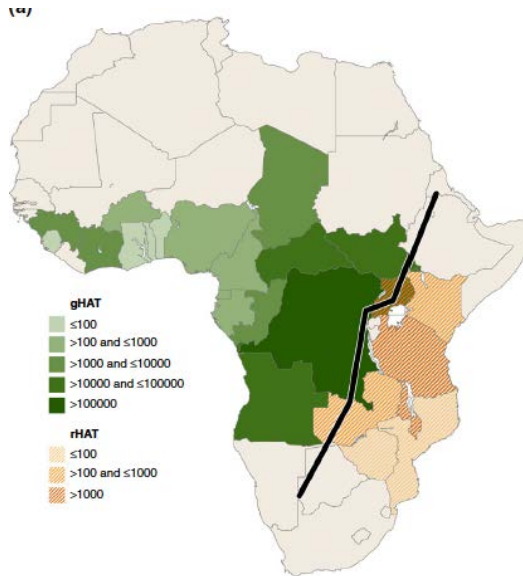


- IL-18-dominant syndromes

Selected Recent Advances: Identification of single gene variants and pathways associated with disease in African Americans

Arthritis Rheumatol. 2014 February ; 66(2): 390–396. doi:10.1002/art.38220.

End-Stage Renal Disease in African Americans With Lupus Nephritis Is Associated With *APOL1*



- Genetic variants in *APOL1* that conferred protection from *Trypanosoma brucei* are enriched in populations from Sub-Saharan Africa and contribute to organ pathology
- Case fatality rate 14 x higher in *APOL1* high risk genotype Ghanaian SLE patients
- Gene expression analysis determined that patient ancestry contributes to molecular heterogeneity of systemic autoimmune disease including predisposition to express particular autoantibodies

Rotimi CN et al., *Current Opin Genet Dev.*, 41, 2016

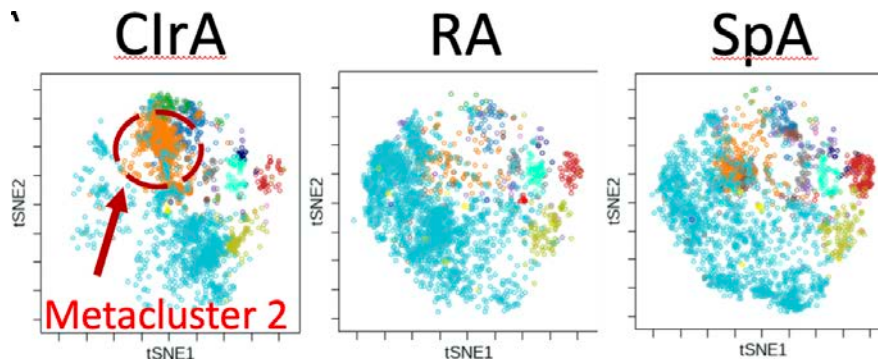
Blazer A et al., *Lupus Science Medicine*, 2021

Catalina MD et al., *JCI Insight.*, 5, 2020

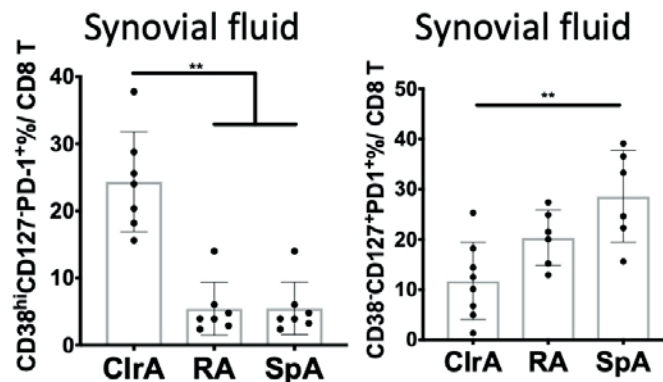
Selected Recent Advances: Checkpoint inhibitor therapy-induced inflammatory arthritis may provide new insights into mechanisms

Synovial fluid from patients with checkpoint inhibitor-associated arthritis

- Expanded CD38^{hi} CD127⁻ PD1⁺ T cells
- Reduced CD38⁻ CD127⁺ CD8 T cells

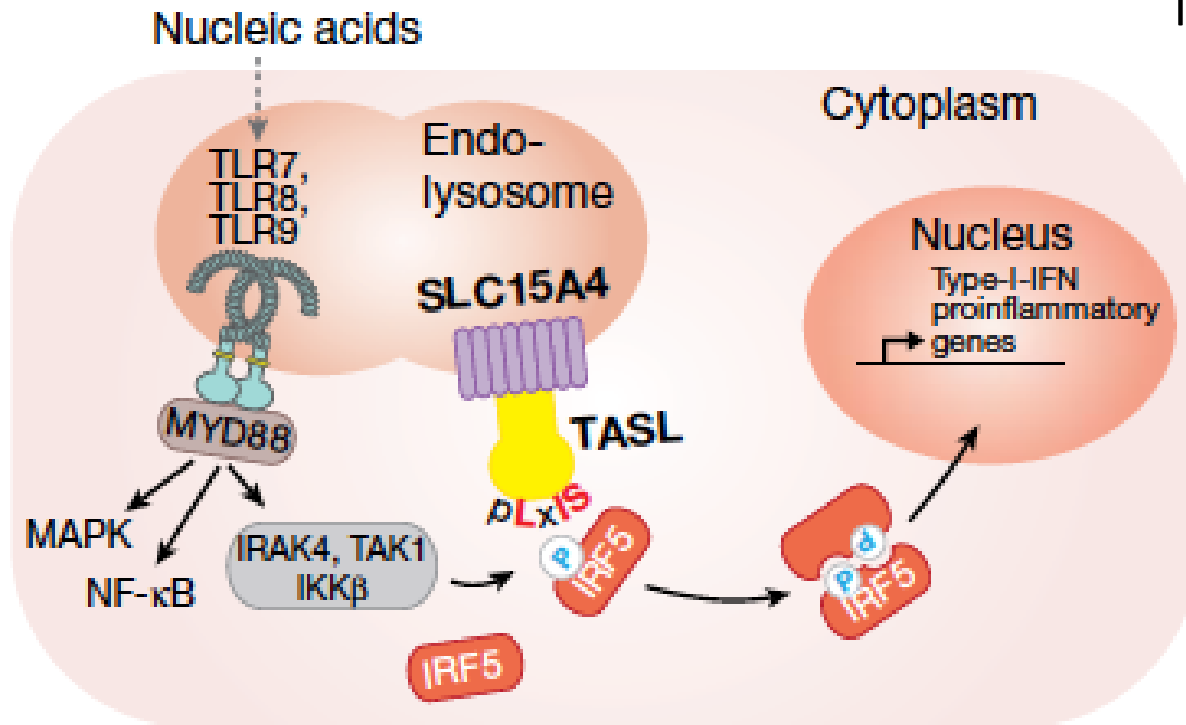


- An expanded CD8 population not shared by RA or SpA
- Expresses a type I interferon signature

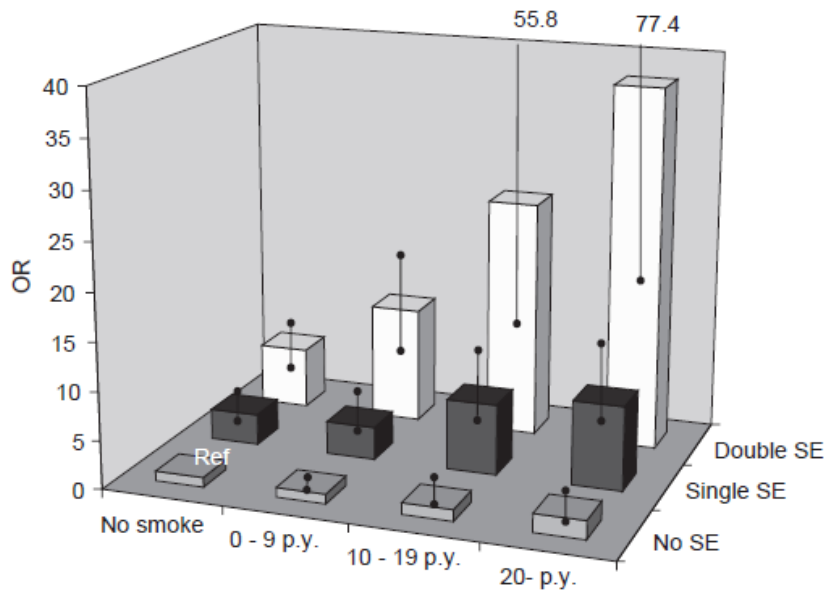


Selected Recent Advances: Insights into mechanisms of female skewing of systemic autoimmune diseases

- X chromosome-encoded *CXORF21* (*TASL*) amplifies TLR signaling



Selected Recent Advances: Impact of environment on development of rheumatoid arthritis – passive smoking



What is the mechanism?

- Longstanding observation: Smoking history and MHC class II “shared epitope” alleles contribute to risk of rheumatoid arthritis
- Recent data: Cohort study using Nurses’ Health Study II
- Maternal smoking during pregnancy and childhood parental smoking were associated with incident RA in adulthood

Nielen MMJ et al., *Arthritis Rheum* 50, 2004

Yoshida K et al., *Arthritis Rheumatol* 72 (Suppl. 10), 2020

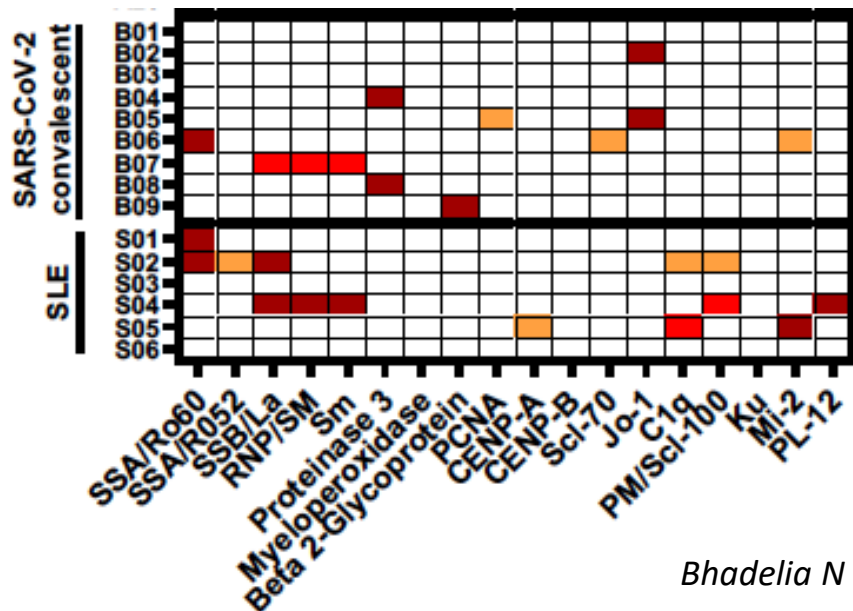
Selected Recent Advances: Infection-induced immune system activation informs mechanisms of systemic autoimmune disease

Established models:

- Lymphocytic choriomeningitis virus murine models – acute vs. chronic immune response
- Simian immunodeficiency virus primate models – African green monkey vs. rhesus macaque

New insights:

- SARS-CoV-2-induced autoimmunity and inflammation



- Autoantibodies characteristic of systemic autoimmune disease in some patients following SARS-CoV-2 infection

Opportunities - I

- Encourage a broad view of “autoimmune disease” research, incorporating investigation of disorders and their underlying mechanisms in which immune system cells or products mediate pathology
- Encourage collaborations between basic scientists making fundamental discoveries and physician scientists to accelerate advances defining pathogenic mechanisms
- Urgent need for expanded investigation of genetic and environmental risks relevant to African American and Native American populations
- Support detailed analyses of monogenic immune-mediated syndromes to amplify insights into mechanisms of complex polygenic diseases

Opportunities - II

- Aspire to define medical conditions based on common or distinguishing mechanisms rather than disease labels
 - Checkpoint inhibitor-induced inflammatory arthritis vs. rheumatoid arthritis
 - Type I interferon in SLE vs. MS
 - Rheumatoid arthritis vs. SLE vs. undifferentiated connective tissue disease
- Define biologic mechanisms through which environmental risk factors contribute to disease, e.g., smoking, obesity
- Extend focus on X chromosome-related mechanisms that impact risk for systemic autoimmune disease in women
- Leverage study of patients with post-infection autoimmunity and inflammation to gain insight into mechanisms of systemic autoimmune disease, e.g., COVID-19 convalescent patients and long-haulers