NASEM

Committee for the Assessment of NIH Research on Autoimmune Diseases

February 1, 2021

Autoimmune Disease Research at the National Institute of Arthritis and Musculoskeletal and Skin Diseases

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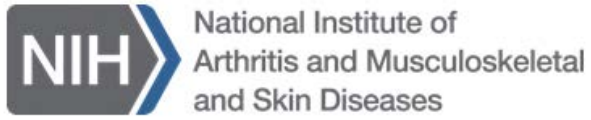
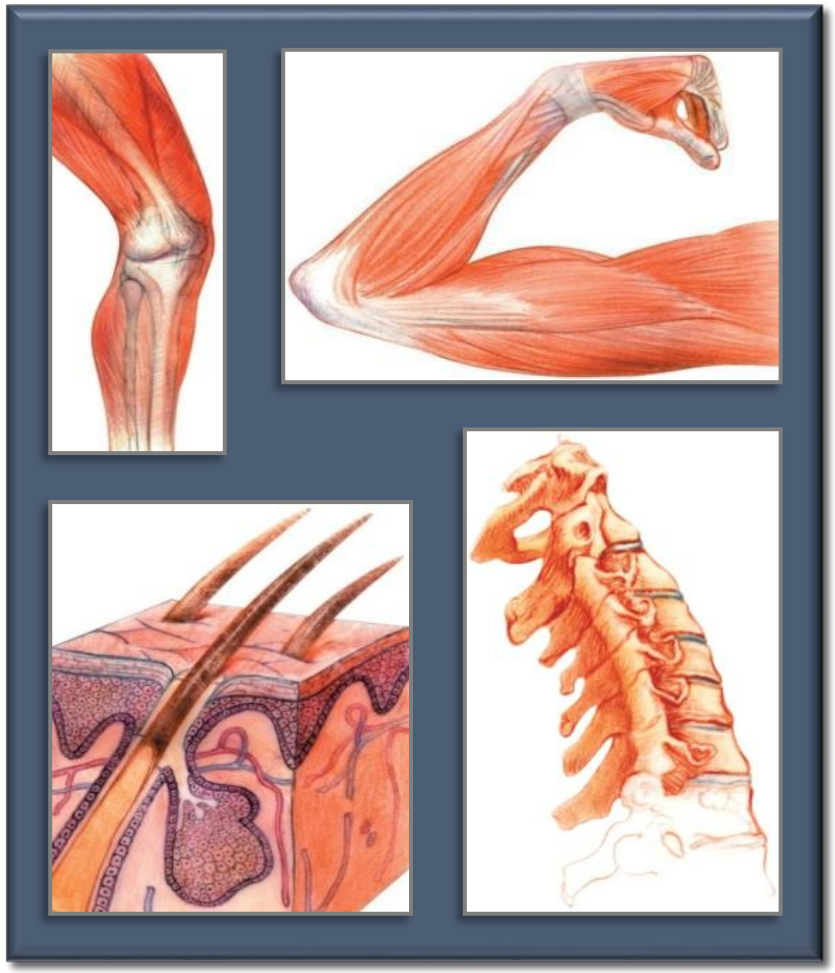
NIAMS/NIH



Outline

- **NIAMS Overview**
- **Strategic Planning**
- **Trans-NIH Collaborations and Initiatives**
- **NIAMS-supported Advances**
- **Questions/Discussion**

NIAMS Mission



To support:

- **Research** into the causes, treatment, and prevention of arthritis and musculoskeletal and skin diseases
- **Training** of basic and clinical scientists to carry out this research
- **Dissemination** of information on research progress in these diseases

Autoimmune Disease Research Relevant to NIAMS

- Rheumatic Diseases/Conditions:
  - Systemic Lupus Erythematosus (SLE)
  - Cutaneous Lupus Erythematosus (CLE)
  - Inflammatory Arthritis
    - Rheumatoid Arthritis
    - Ankylosing Spondylitis
    - Gout
    - Lyme Disease
    - Psoriatic Arthritis
  - Inflammatory Myopathies
  - Scleroderma
  - Sjögren's Syndrome
  - Antiphospholipid Syndrome
  - Vasculitis
    - Giant Cell Arteritis
    - ANCA-Associated Vasculitis
    - Granulomatosis with Polyangitis
    - Behçet's disease

- Skin Diseases/Conditions:
  - Psoriasis
  - Pemphigus
  - Bullous Pemphigoid
  - Atopic Dermatitis (Eczema)
  - Alopecia Areata
  - Vitiligo
  - Hidradenitis suppurativa (HS)

- Autoinflammatory Syndromes:
  - Tumour necrosis factor receptor-associated periodic fever syndrome (TRAPS)
  - Cryopyrin-associated periodic syndromes (CAPS)
  - Systemic Juvenile Idiopathic Arthritis (sJIA)

(not a complete list!)

NIAMS and Autoimmune Disease Research

- Basic, translational, and clinical research, including clinical trials and observational and mechanistic studies
- Focus on mechanisms of disease:
  - Immunologic
  - Inflammation, end-organ damage and repair
  - ‘Omics (genomics, proteomics, etc.)
  - Pain and fatigue
  - Behavioral and biopsychosocial factors contributing to disease severity and QOL
  - Patient Reported Outcomes (PROs)
  - Health disparities and special populations (e.g. pediatrics, pregnancy)

NIAMS Strategic Planning

NIAMS Strategic Plan (FY2020-2024): Turning Discoveries into Health

- **Plan development involved a large consultation process with the community (RFIs, multiple listening sessions)**
- Conveys both the potential of the current research trajectory and the NIAMS aspirational vision
- Not intended to be a rigid roadmap for investigators to follow
- Encourages investigators to collaborate across disciplines

- **Cross-cutting Scientific Themes:**
  - Precision medicine for arthritis and musculoskeletal and skin diseases
  - Shared mechanisms in health and among diseases
  - Patient-centric approaches to health and disease
  - Health and disease in diverse populations
- **Disease and Tissue-Specific Goals:**
  - Enhancing systemic rheumatic and autoimmune diseases research
  - Advancing skin biology and diseases research
  - Accelerating bone biology and diseases research
  - Strengthening muscle biology and diseases research
  - Furthering joint biology, diseases, and orthopaedics research

NIAMS Strategic Planning and Implementation

- Strategic planning helps inform:
  - Funding decisions under select pay process
  - Development of Initiatives, special grant mechanisms (e.g. P30 Resource Core; Consortia)
- Stakeholder input on research gaps and opportunities
  - Listening sessions with researchers and NIAMS Coalition members
  - Input from the Advisory Council
  - Host Roundtables, Workshops
    - Subset Analysis in Clinical Studies (2020); Psoriatic Arthritis Research (2017)
    - Annual Clinical Mentored K Forum

NIAMS and Trans-NIH Collaborations and Initiatives

- **NIAMS leads Lupus Federal Working Group**
  - Includes representatives NIH ICs, from DHHS agencies and other federal departments, and voluntary and professional organizations
  - Meets twice annually
  - At the request of the Congressional Lupus Caucus, the NIAMS led a trans-NIH effort to develop a new NIH Action Plan for Lupus Research, released Jan. 2016.

- Participate in the Autoimmune Disease Coordinating Committee
  - Led by NIAID

AMP: Accelerating Medicines Partnerships: RA/SLE Program

- Partnership of NIH (NIAMS and NIAID), pharmaceutical companies and non-profit organizations
- Goal: To ascertain and define shared and disease-specific biological pathways in order to identify relevant drug targets for the treatment of autoimmune diseases

Multi 'omic' (protein, mRNA, open chromatin) characterization of thousands of single cells in >100 synovial biopsies in rheumatoid arthritis and >200 renal biopsies in lupus nephritis

- Analysis of associated samples (peripheral blood, urine) from the same patients is underway

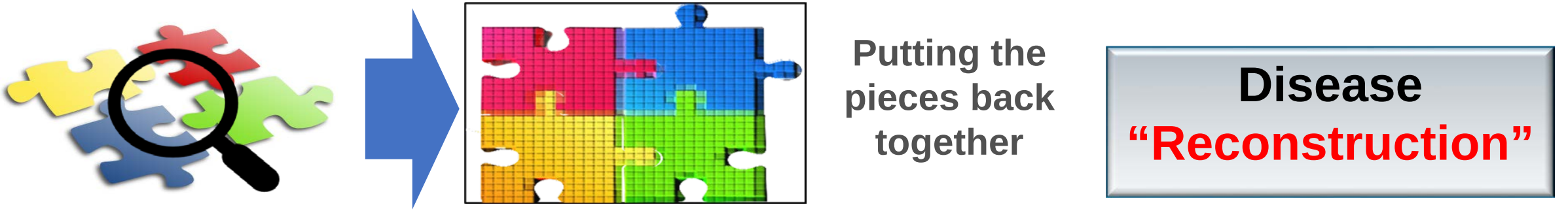
These studies have led to the discovery of new cell populations and states, biomarkers and new pathways and targets for drug development

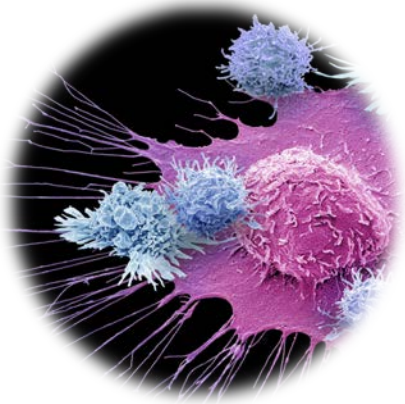
Thorough phenotyping and longitudinal follow-up of patients will allow discovery on linkages between patients, mechanisms and responses to treatments

Changed the research landscape for RA and lupus

AMP Autoimmune and Immune-mediated Diseases (AMP AIM)

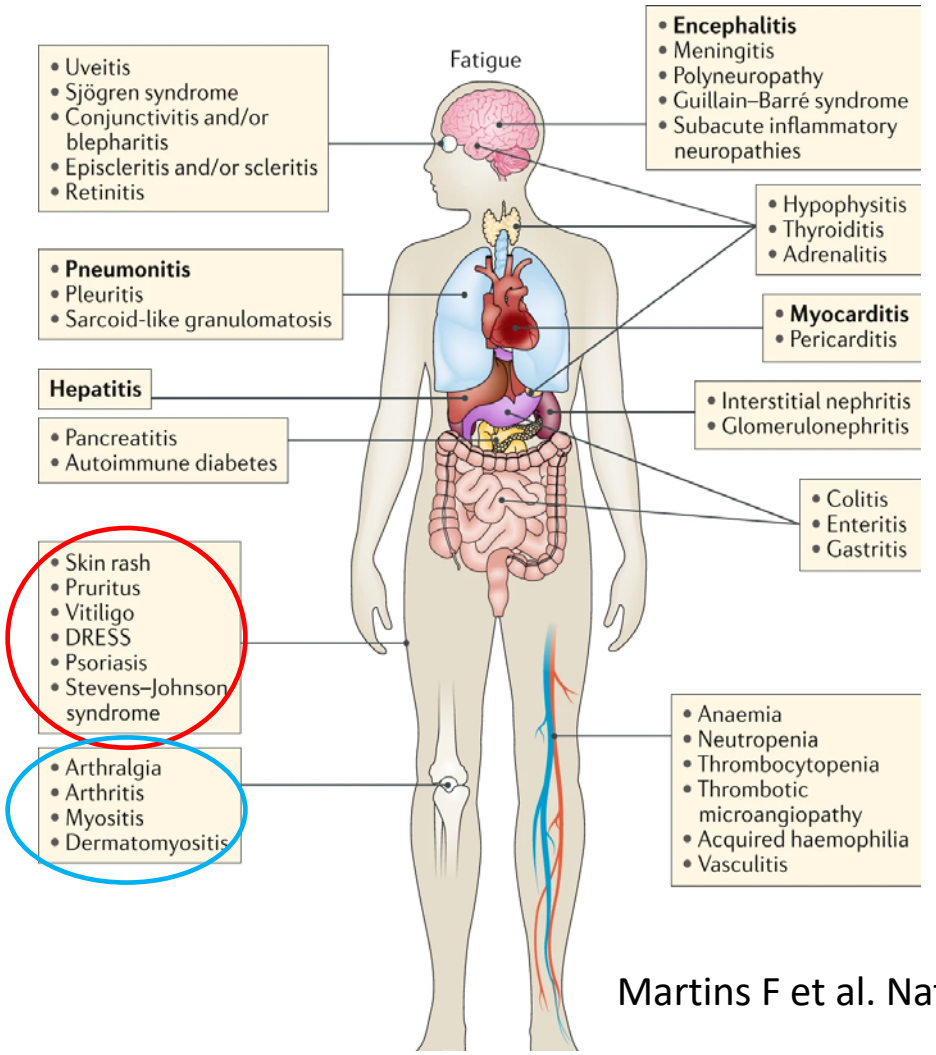
- AMP AIM Builds on Key Outcomes of AMP RA/SLE
  - Will extend disease deconstruction and mapping of cells and pathways in RA and lupus to include Sjögren's syndrome and psoriasis/psoriatic arthritis.
- The cornerstone is the concept of disease reconstruction based on high dimensional study of cell interactions





NIAMS and NCI's Cancer Moonshot Program: Immuno-Oncology Translational Network (IOTN)

- Cancer Moonshot Program authorized $1.8B in funding, over 7 years
- IOTN: Goal is to extend early success in cancer immunotherapy through improved understanding of mechanism that enable and limit immunotherapy
- An obstacle to the success of immune checkpoint inhibitor treatment is the occurrence of immune-related adverse events (IrAEs)



Martins F et al. Nature Rev. 2019

NIAMS and NCI's Cancer Moonshot Program: Immuno-Oncology Translational Network (IOTN) (con't)

- Activities to Promote Research Collaborations on Immune-Related Adverse Events (APRC-irAEs) Associated with Cancer Immunotherapy (Admin Supp) (PA-17-248):
  - NIAMS supported 2 collaborative supplements (with NCI co-funding)
- Advancing Cancer Immunotherapy by Mitigating Immune-Related Adverse Events (irAE) (U01 Clinical Trial Not Allowed) (RFA-CA-19-044):
  - NIAMS supporting (with NCI-co-funding) one U01, focused on cutaneous irAEs

- NIAMS a co-sponsor of the NIH-AACR Cancer, Autoimmunity and Immunology (CAI) Conference
  - Held 2018, 2019, and 2020

NIAMS and the INCLUDE Project (Investigation of Co-occurring conditions across the Lifespan to Understand Down SyndromE)

- **INCLUDE:** trans-NIH research initiative on critical health and quality-of-life needs for individuals with Down syndrome, launched 2018, led by NICHD
  - Allows NIH to build an integrated effort across NIH that is truly transformative
- Individuals with Down syndrome have a unique clinical profile, including higher rates autoimmune disorders
- **NIAMS funding priorities**: Examining arthritic (and other rheumatic), musculoskeletal, and skin anomalies and disorders in Down syndrome, and causes, treatment and prevention of arthritic (and other rheumatic), musculoskeletal, and skin complications throughout the lifespan in individuals with Down syndrome
- 2019-2020: NIAMS supports a training slot for a pediatric rheumatology trainee to study rheumatic and autoimmune diseases in individuals with Down syndrome
- 2019-2021: NIAMS supports R61/R33 (Exploratory/Developmental Phased Innovation Award): “JAK Inhibition in Down Syndrome”
  - Evaluate the safety and therapeutic effects of tofacitinib on immune-mediated dermatological conditions in young adults with Down syndrome

Selected Research Advances

Collaborative Study Identifies Early Indicators of Pregnancy Complications in Women with Lupus

- Adverse pregnancy outcomes occur in over 20 percent of women with SLE and/or aPL. The goal of the study was to identify early changes that could be used to determine the likelihood of developing pregnancy complications, in order to inform treatment and decrease morbidity and mortality in lupus patients.
- By analyzing gene expression patterns from pregnant lupus patients or healthy pregnant women, the team identified a unique immune signature that could predict the development of preeclampsia more accurately than existing clinical factors.

- Ref: Longitudinal profiling of human blood transcriptome in healthy and lupus pregnancy. Hong S. et al., *J Exp Med.* 2019
- Grant Support: R01AR049772 (Salmon, Jane) Predictors of Pregnancy Outcome in SLE and APS; P50AR070594 (Pascual, Maria Virginia) Center for Lupus Research

Selected Research Advances (con't)

Sex Differences in Neutrophil Biology affect Response to Type Interferons (IFNs) and Cellular Metabolism

- The underlying mechanisms that drive the differences between the male and female immune system remain insufficiently characterized
- This work showed that female neutrophils have striking upregulation of type I IFN stimulated genes, suggesting an enhanced response to type I IFNs
- The researchers also identified differences in the cellular metabolism of female and male neutrophils, driven by driven by sex hormones, such as estradiol.
- Several novel subsets of neutrophils in the peripheral blood of healthy young adults were identified, suggesting that neutrophils are significantly more heterogeneous than previously appreciated.

- Ref: Sex differences in neutrophil biology modulate response to type I interferons and immunometabolism. Gupta S. et al., *Proc Natl Acad Sci U S A*. 2020
- Grant Support: 1ZIAAR041199-06 (Kaplan, Mariana) Systemic Autoimmunity (Intramural NIAMS)

Selected Research Advances (con't)

Lung Diseases Are Associated with Increased Risk for Rheumatoid Arthritis

- Patients with RA are prone to lung diseases and have excess respiratory mortality.
- The researchers investigated whether lung diseases, such as asthma or chronic obstructive pulmonary disease (COPD), increase risk for developing RA.
- The study demonstrated that individuals with lung diseases such as asthma and COPD indeed are more likely to develop RA.
- This advance was the first prospective study of lung diseases and RA with robust statistical power. These findings have implications in informing the clinical care of asthma and COPD patients to allow for early detection of RA and lowering the risk of negative long-term outcomes.

- Ref: Asthma, chronic obstructive pulmonary disease, and subsequent risk for incident rheumatoid arthritis among women: A prospective cohort study. Ford et al., *Arthritis Rheumatol*. 2020
- Grant Support: R03AR075886 (Sparks, Jeffrey) Respiratory Diseases, Genetics, and Rheumatoid Arthritis Risk; K23AR069688 (Sparks, Jeffrey) Rheumatoid Arthritis and Respiratory Outcomes in Prospective Cohorts

Resources/Links

- NIAMS Website: https://www.niams.nih.gov/
- NIAMS Strategic Plan FY2020-2024: https://www.niams.nih.gov/sites/default/files/pdf
- Lupus Federal Working Group: https://www.niams.nih.gov/about/working-groups/lupus-federal
- AMP RA/SLE: https://www.niams.nih.gov/grants-funding/funded-research/accelerating-medicines
- Cancer Moonshot/Immuno-Oncology Translational Network (IOTN): https://www.iotnmoonshot.org/en/
- NIH INCLUDE Project: https://www.nih.gov/include-project

Questions?

Thank you!

National Institute of
Arthritis and Musculoskeletal
and Skin Diseases