Autoimmune Disease Research Supported by Extramural NIAID

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NIAID's Mission

- Conduct and support basic and applied research to better understand, treat, and ultimately prevent infectious, immunologic, and allergic diseases

NIAID's Mission in Autoimmunity

- Examine role of the immune system in autoimmunity, highlighting
  - Basic immune mechanisms
  - Role of the microbiome
  - Development of novel immune strategies for earlier detection, diagnosis, treatment, and prevention
  - Application of knowledge of immune mechanisms to develop immunotherapies
  - Improved animal models of disease
- Support clinical trial networks and investigator-initiated clinical trials to evaluate immune-based treatment, including cellular therapies, tolerance approaches, and other strategies, each with integrated mechanistic studies

Significant Clinical Achievements

- **RAVE Trial:** Single course of rituximab for severe ANCA-associated vasculitis (AAV) shown to be as effective as the standard-of-care used for 40 years (*NEJM*, 2010; *NEJM,* 2013)
- **SCOT Trial:** Autologous hematopoietic stem cell transplant (HSCT) for severe systemic sclerosis achieved long-term benefit including survival, event free survival, and quality of life compared to CYC, with benefits durable for up to 11 years (*NEJM,* 2018)
- **HALT-MS:** Single arm study evaluated efficacy, safety and durability of autologous HSCT for treatment of relapsing remitting MS (*JAMA Neurol,* 2015; *Neurology,* 2017)
  - Basis for ongoing Phase 3 BEAT-MS trial, comparing best available therapy to HSCT

NIAID Achievements in Basic Autoimmunity (1)

- **Autoantibodies Drive Neuropsychiatric Symptoms in Systemic Lupus Erythematosus** (*Nat Commun.*, 2020)
  - Identified anti-double stranded DNA autoantibodies in patients with SLE that cross-react with the NMDA receptor
  - Suggests selective NMDA receptor antagonists or modulators as potential therapeutics in SLE patients with nervous system dysfunction
- **Single Cell Analysis Identifies Resistance to anti-TNF Therapy in Crohn's disease** (*Cell*, 2019)
  - Identified two distinct subsets of ileal Crohn's disease with distinct responses to anti-TNF therapy
  - Identified unique module of immune cells that correlated with failure to achieve durable corticosteroid-free remission upon anti-TNF therapy

NIAID Achievements in Basic Autoimmunity (2)

- **Gut Commensal Microbe Contribution to Autoimmunity**

  (*Science,* 2018; *Cell Host Microbe,* 2019)

  – Translocation of gut bacterium, *E. gallinarum,* to the liver triggers autoantibodies, autoimmunity, and mortality in autoimmune-prone mice

  – *E. Gallinarum* found in liver biopsies and *E. gallinarum* antibodies found in sera from lupus patients but not healthy controls, suggesting breakdown of gut barrier may play a role in human autoimmune disease

- **Molecular Signature of Autoimmune Disease Activity**

  (*J. Exp. Med.,* 2003; *Cell,* 2016; *Immunity,* 2008; *NEJM,* 2020)

  – SLE patients display unique blood transcriptional signatures linked to type I interferon (IFN) and granulocytes

  – Clinical and transcriptional profiling over time revealed molecular correlates of disease activity and progression

  – This molecular classification system may represent a first step toward a personalized approach for lupus treatment

NIAID Clinical Trial Networks in Autoimmunity

- **Immune Tolerance Network (ITN):** Established in 1999 to study tolerance induction in asthma and allergic diseases, autoimmune diseases, and solid organ transplantation
  - 25 studies in autoimmunity, concluded or ongoing; 3 in advanced development
  - Diseases currently under study: SLE, RA, T1D, MS, systemic sclerosis, vitiligo, membranous nephropathy
- **Autoimmunity Centers of Excellence (ACE):** Established in 1999 to accelerate the understanding, prevention, and treatment of autoimmune diseases
  - Collaboration of basic and clinical scientists
  - 20 studies in autoimmunity, concluded or ongoing; 4 in advanced development
  - Diseases currently under study: SLE, RA, MS, pemphigus, IgG4-related disease

Clinical Research Informing Autoimmunity

- **Human Immunology Project Consortium (HIPC):** Established in 2010 to provide foundational knowledge of human immune responses in well-characterized human cohorts (healthy, and after infection and vaccination)
  - High-throughput, systems-based approaches coupled with detailed clinical phenotyping
- **Development of Sample Sparing Assays for Monitoring Immune Responses:** Initiated in 2015 to accelerate the development and validation of sample sparing assays that can be applied for study of the human immune system in health and disease
- **Large-Scale T Cell Immune Epitope Discovery:** Initiated in 2004 for discovery of T cell epitopes associated with infectious or autoimmune diseases, commensal organisms, or alloantigens, as well as validation of these epitopes' role in immune protection or immune-mediated pathogenesis in humans

Development of NIAID Solicited Research Programs - 2 Year Process

- Identification of research needs by NIAID staff and the scientific community that align with NIAID Strategic Plan
- Identification of available funding
- Development of a “Concept”
  - Communication with other NIH Institutes
  - Brief description of research sent to NIAID Council for review and approval
  - Approved “Concept” published on NIAID web site
- Development and publication of Request for Application
- Receipt of applications, review, and award