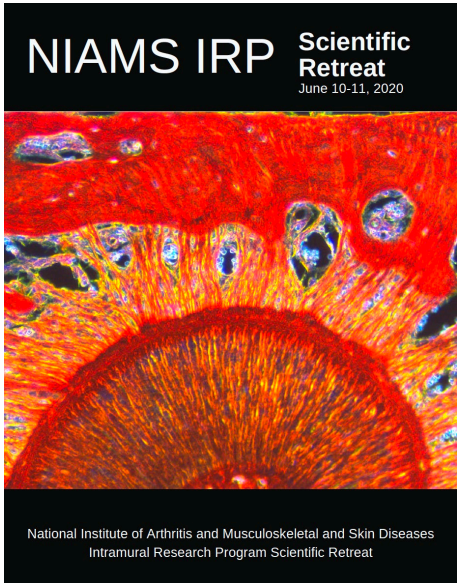

NIAMS IRP 101

- NIAMS = 1.4% of NIH budget
- NIAMS IRP
  - 11% of total NIAMS budget
  - 1.4% of NIH IRP budget
- 20 Principal Investigators
  - Tenured Senior Investigators (11)
  - Tenure Track Investigators (4)
  - Assistant Clinical Investigators (4)
  - Contract Orthopaedic Surgeon (1)
- Clinical: Rheumatologists, Dermatologists, Neurologist
- Basic – muscle, bone, skin, immunology, structural biology, chromatin and RNA biology
- Reviewed every 4 years, largely retrospective, not prospective grants
- We train and invest in people – long term (often decades)

A Bit of History

- 1950 – National Institute of Arthritis and Metabolic Disease created by Harry Truman

THE JOURNAL
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SIMPLE, RAPID DIAGNOSTIC TEST FOR RHEUMATOID ARTHRITIS—BENTONITE FLOCCULATION TEST

Kurt J. Bloch, M.D.
and
Joseph J. Bunim, M.D., Bethesda, Md.

Joseph Bunim
NIAMD Clinical Director

JAMA, 1964

Methotrexate Therapy in Psoriatic Arthritis

Double-Blind Study on 21 Patients

Roger L. Black, MD, William M. O'Brien, MD, Eugene J. Van Scott, MD, Robert Auerbach, MD, Arthur Z. Eisen, MD, and Joseph J. Bunim, MD,† Bethesda, Md

NIAMS and Lupus

1985 – National Institute of Arthritis, and Musculoskeletal and Skin Diseases created

THERAPY OF LUPUS NEPHRITIS

Controlled Trial of Prednisone and Cytotoxic Drugs

HOWARD A. AUSTIN, III, M.D., JOHN H. KLIPPEL, M.D., JAMES E. BALOW, M.D., NICOLE G.H. LE RICHE, M.D., ALFRED D. STEINBERG, M.D., PAUL H. PLOTZ, M.D., AND JOHN L. DECKER, M.D.

THE LANCET

Vol 340 Saturday 26 September 1992 No 8822

ORIGINAL ARTICLES

Controlled trial of pulse methylprednisolone versus two regimens of pulse cyclophosphamide in severe lupus nephritis

DIMITRIOS T. BOUMPAS HOWARD A. AUSTIN III
ELLEN M. VAUGHN JOHN H. KLIPPEL ALFRED D. STEINBERG
CHERYL H. YARBORO JAMES E. BALOW

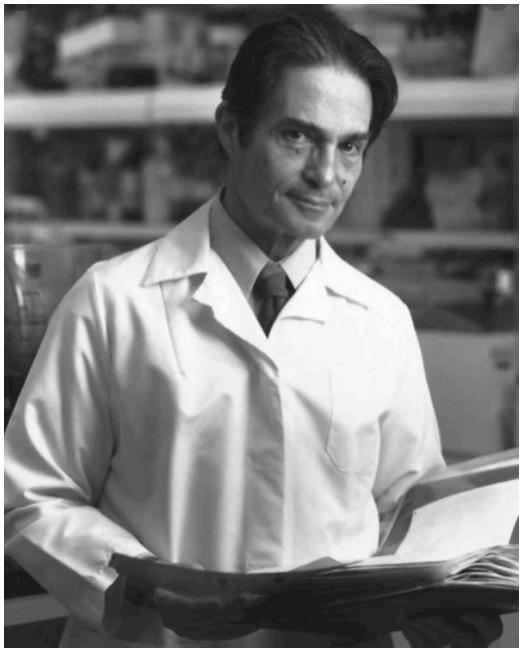
Methylprednisolone and Cyclophosphamide, Alone or in Combination, in Patients with Lupus Nephritis

A Randomized, Controlled Trial

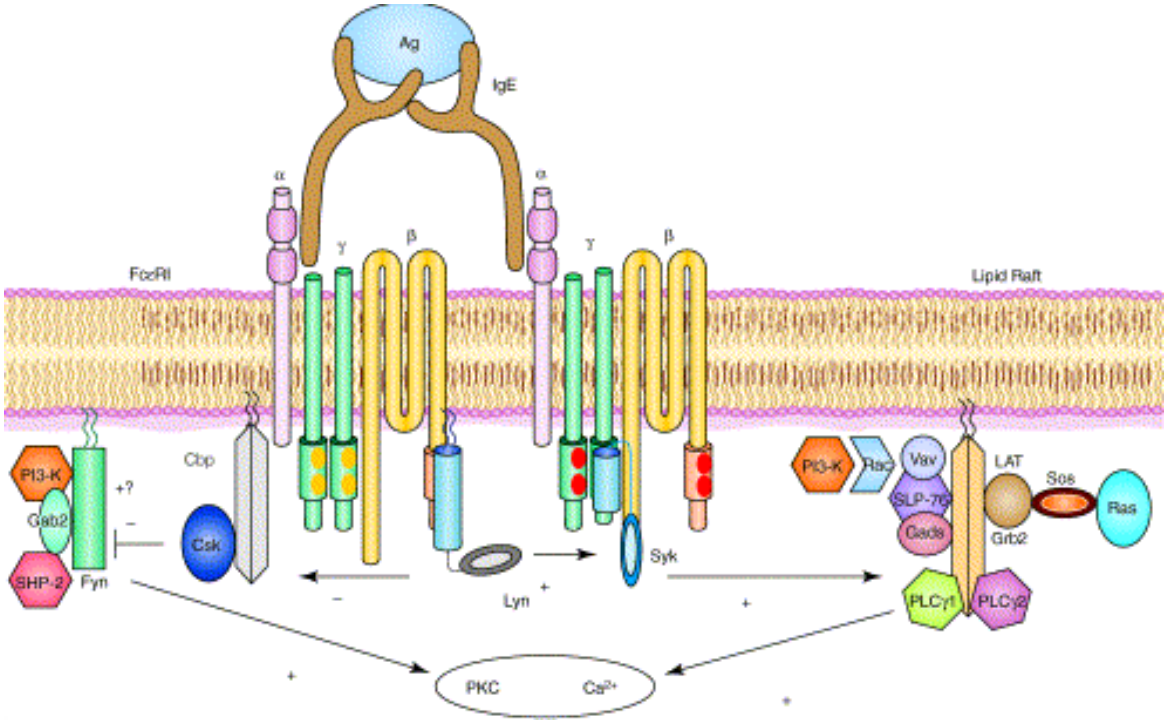
Mark F. Gourley, MD; Howard A. Austin III, MD; Dorothy Scott, MD; Cheryl H. Yarboro, RN; Ellen M. Vaughan, RN; Joanne Muir, RN; Dimitrios T. Boumpas, MD; John H. Klippel, MD; James E. Balow, MD; and Alfred D. Steinberg, MD

Ann Intern Med. 1996;125:549-557.

NIAMS and Immune Cell Signaling



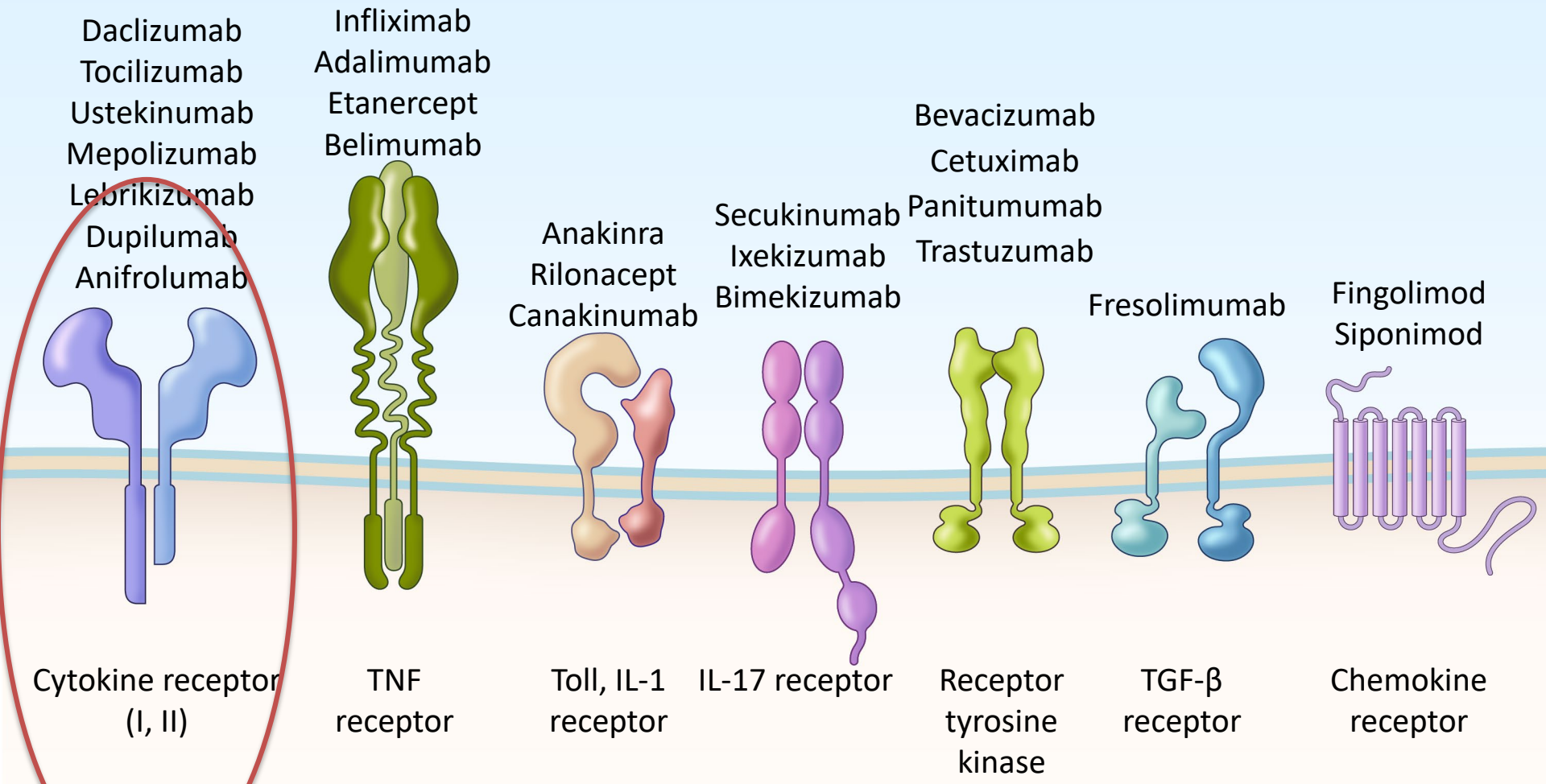
NIAMS First Scientific Director
Henry Metzger



Fc receptor – prototype for multi-chain immune recognition receptors

Henry's hires

The Cytokine and "Biologics" Revolutions



Despite success of biologics – incomplete responses/complete remission

Limited efficacy (thus far) in lupus

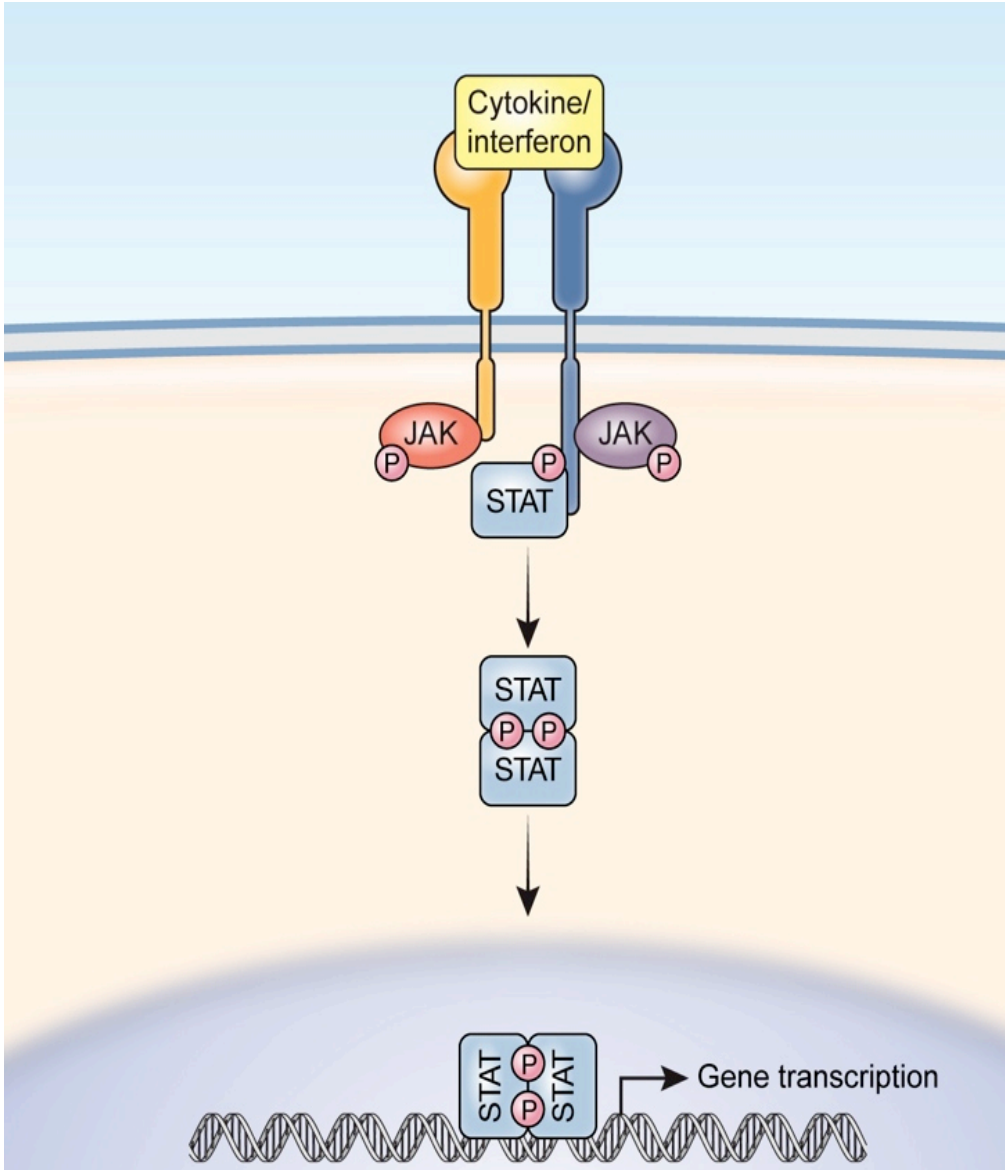
Other options?

How do cytokines signal?

Can signaling molecules be targeted therapeutically?

Discovery of JAK-STAT pathway

- Jaks
  - Screening libraries for kinases
- STATs
  - Identification of complexes bound to promoters of IFN-induced genes
- Used by 57 cytokines and growth factors
- In vivo criticality?



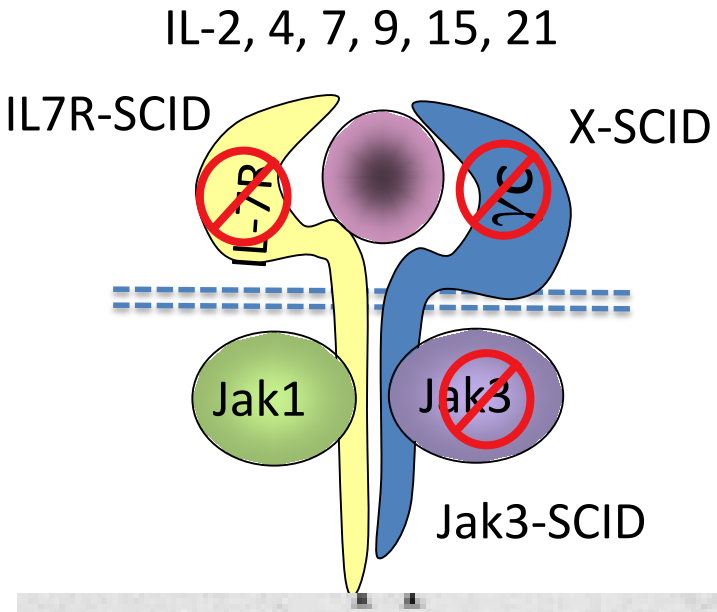
Jaks essential for Type I/II cytokine signaling – genetic evidence

Warren Leonard

Gigi Notarangelo

Fabio Candotti

Rebecca Buckley



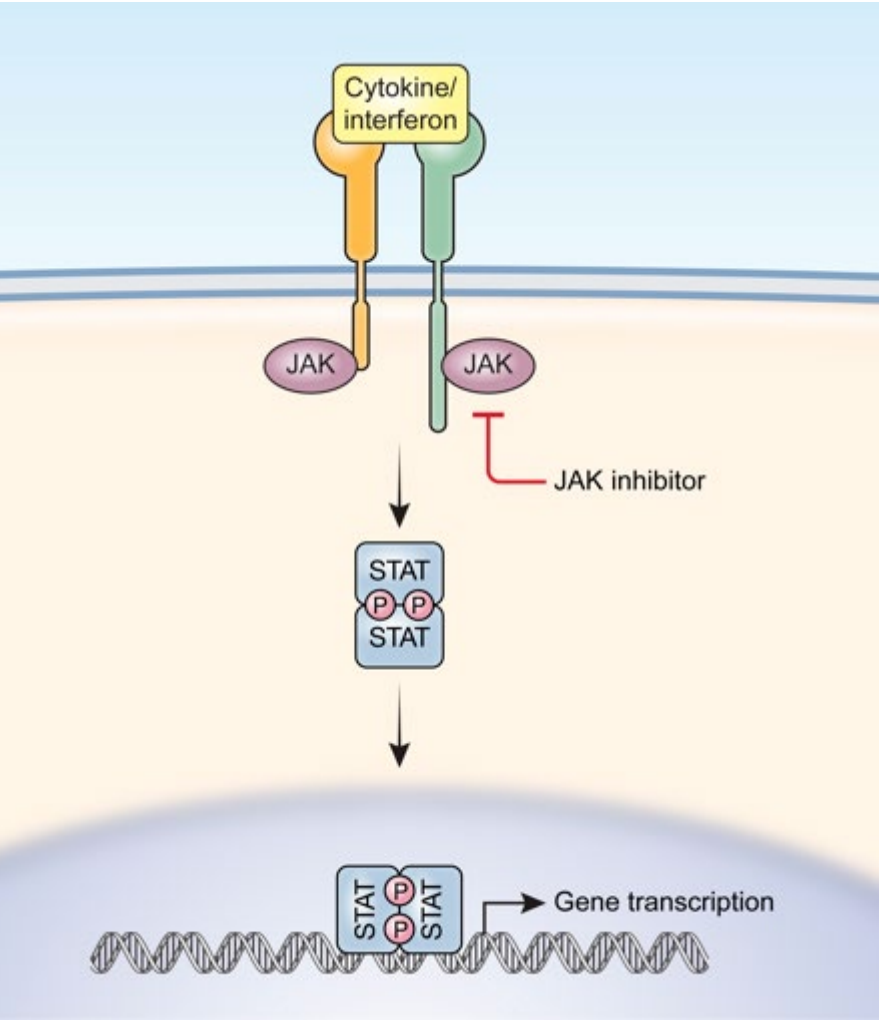
- Human primary immunodeficiency

  Macchi P et al, Nature, 1995

  Russell et al, Science 1995
- First “knockout” in JAK-STAT pathway
- How a very rare disease can inform common disease

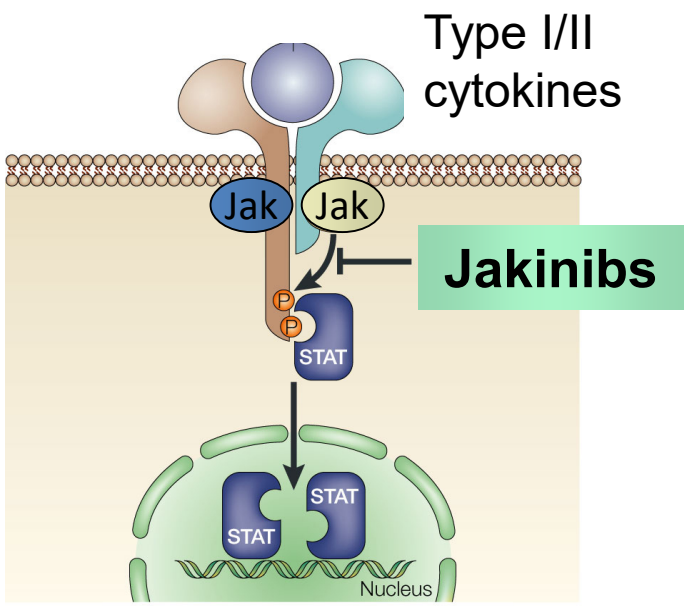
The current study further suggests that any agents that inactivate Jak3 function may be potent immunosuppressants. Moreover, the

Approved Jakinibs



- **Ruxolitinib (JAK1/2 inhibitor)**
  - polycythemia vera/myelofibrosis
  - Acute GVHD
- **Tofacitinib (JAK1/3 > 2 inhibitor)**
  - RA, PsA, JIA, UC
- **Baricitinib (JAK1/2 inhibitor)**
  - RA (US and EMA)
  - Atopic dermatitis (EMA)
- **Peficitinib (Pan-JAK)**
  - RA (Japan)
- **Fedratinib (JAK2 V617F-FLT3)**
  - myelofibrosis
- **Upadacitinib (JAK1 inhibitor)**
  - RA
  - PsA, AS - EMA
- **Filgotinib (JAK1 inhibitor)**
  - RA (EMA)
- **Delgocitinib (Pan-JAK)**
  - Atopic Dematitis (Japan) – topical
- **Oclacitinib (JAK1/2/3 inhibitor)**
  - Atopic Dermatitis (in dogs)

Ongoing Jakinib Trials



Rheumatologic
- Juvenile Arthritis
- Spondyloarthritis
- Dermatomyositis
- Inherited interferonopathies, Down syndrome
- Autoinflammatory disease

Dermatologic
- Chronic graft versus host disease
- Psoriasis
- Atopic Dermatitis
- Alopecia areata
- Drug Induced Hypersensitivity
- Scleroderma
- Vitiligo
- Sarcoidosis

GI
- IBD, UC, CD

Oncologic
- MPN
- leukemia/lymphoma
- solid organ cancers

NIAMS IRP
Current Areas of Investigation

Basic – epigenomics, chromatin and RNA biology, gene expression, cell biology, structural biology, immunology

Rheumatology

Lupus - role of neutrophils, genetics, cardiovascular disease, mechanism of action of steroids therapy – Jakinibs, metabolic regulation (PPARg, diet)

Sjogren's syndrome – therapy - Jakinibs

Vasculitis – imaging, genetics

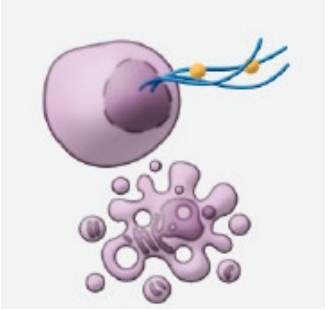
Relapsing Polychondritis – somatic mutations, VEXAS

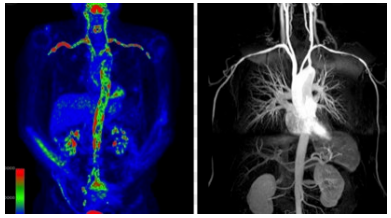
Spondyloarthritis – imaging, genetics, mechanisms

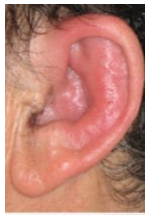
Myositis – mechanisms, therapy – jakinibs, eculizumab

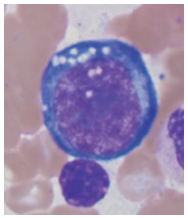
Juvenile Arthritis - genetics

Scleroderma – genetics, epigenetics









NIAMS IRP
Current Areas of Investigation

Dermatology

- Wound healing
- Skin microbiome
- Skin cancer
- Graft vs host disease
- Drug-induced hypersensitivity

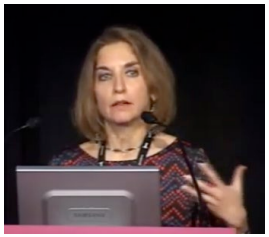
Orthopaedics – outcomes research, somatic mutations

Viral structural biology

Dental-oral-craniofacial development

How we think of “autoimmunity” versus Joe and Henry?

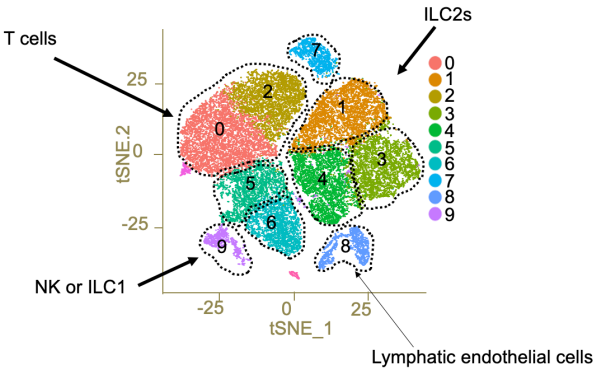
- Is the concept of “autoimmunity” *per se* still useful?
- Innate and adaptive immunity intertwined
  - Neutrophils - classically “non-specific” immunity
    - Kaplan – neutrophils fundamental part of lupus
    - Fever and lupus
    - innate mechanisms initiating factors

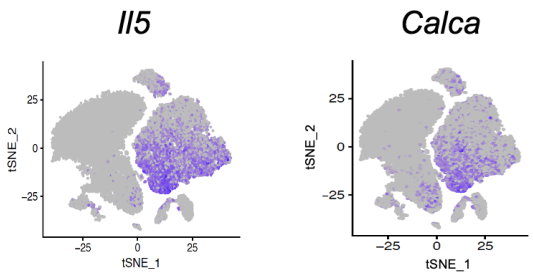


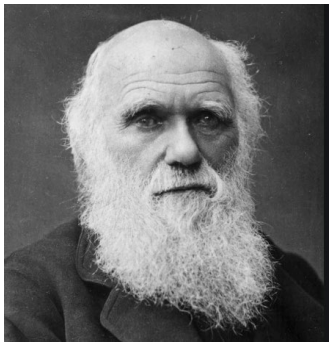
- All cells are immune cells
- Inflammation – pathogenic mechanism from nearly all diseases from
  - Inflammation independent risk for CAD; colchicine and IL-1 blockade can reduce heart attacks, strokes
  - Lupus – high risk of CVD
- Metabolism and inflammation intertwined
  - Diet restriction and lupus (collaboration with Yasmine Belkaid)

How we think of “autoimmunity” versus Joe and Henry?

- What’s a cytokine, neuropeptide, growth factor?
  - depends on who discovered it
  - Amphiregulin, GDF15
- Nervous system and immune system intertwined (Neuromedin U, CGRP)
  - Innate lymphoid cells produce CGRP
  - Lymphoid cells respond to neuropeptides- lung migraine?
  - Neurons respond to cytokines
- Pain, itch, fatigue need to be considered more broadly
  - Jakinibs rapidly reduce itch, pain > biologics
- Accelerated Medicines Partnership
- Rheumatoid arthritis starts in the lung - smoking
- scRNAseq helps breakdown silos



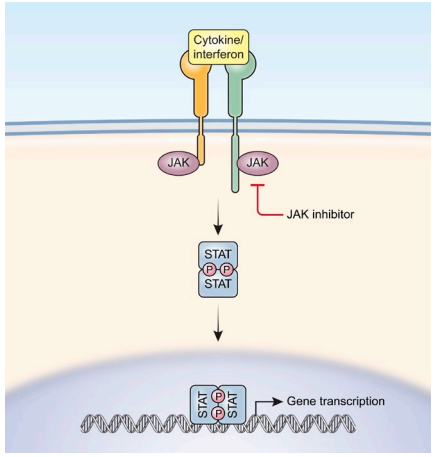




Genetics Beyond Darwin and Waddington Redux

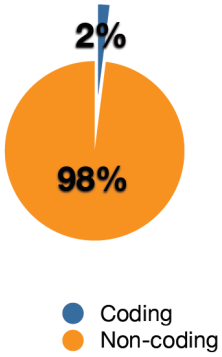
Genetic risk of immune/inflammatory disease
Single gene diseases
Somatic mutations
Genes/environment
Microbiome
Genetic risk - GWAS
    complexity of gene regulation
    beyond conventional genes
Epigenomics – immune memory

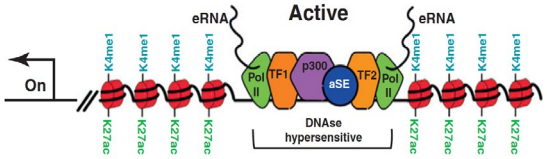
When Cytokines Met the Genome: Genome >> genes

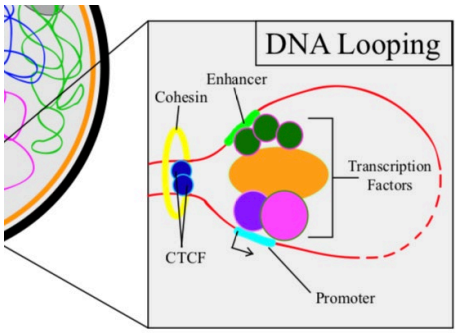


20th century view of signaling and transcription

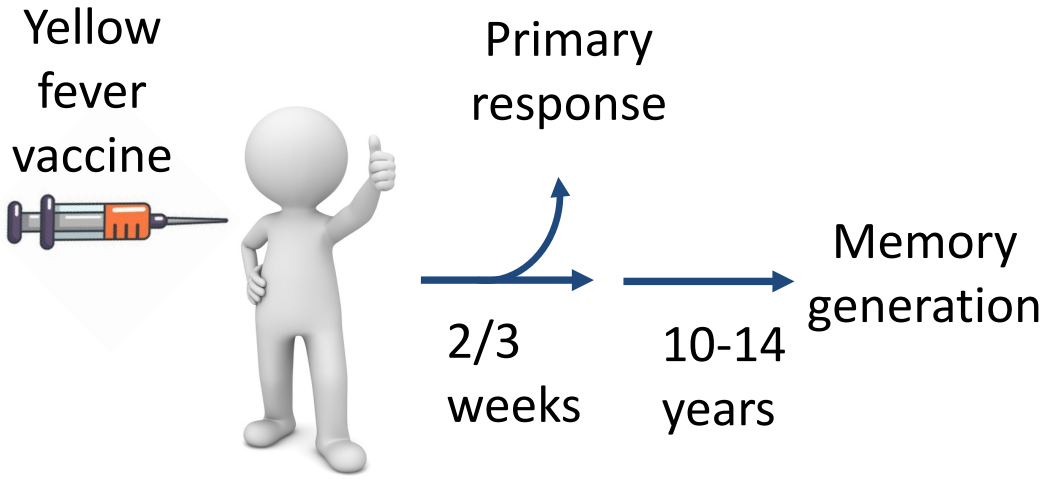
- Transcription > transcription factors and promoters
- Much of genome is transcribed
- Much of genome is active in cell-specific manner
- Thousands of cell-specific enhancers
  - Superenhancers vs typical enhancers
  - Long-noncoding RNAs > conventional genes
- Genetic links to human dz – regulome not genes

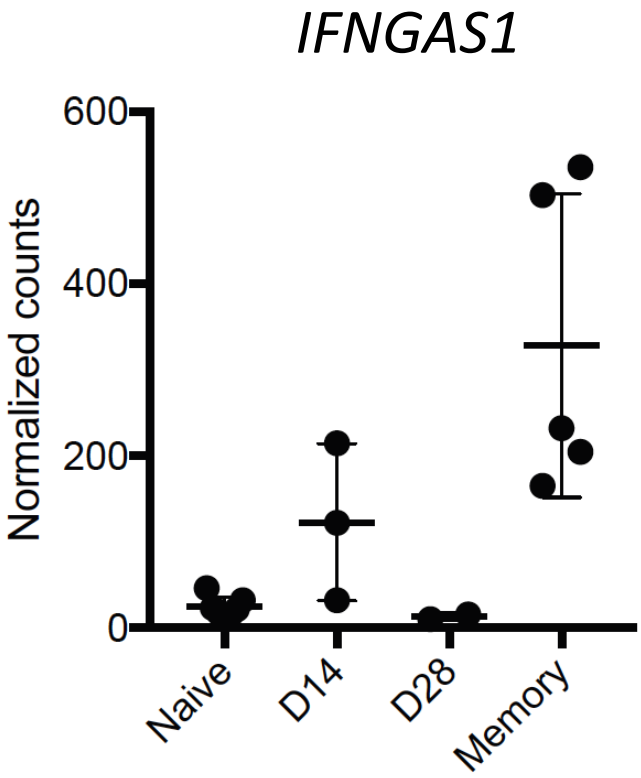






IFNG-AS1 expressed in antigen-specific memory T cells 10 years after vaccination





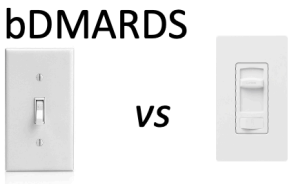
IFNG-AS1 expression

Tcm > Tem, Teff

IFNg and IFNG-AS1 discoordinately regulated

Next step in therapies?

- Targeted therapies -amazing advances, but….
  - Combination therapy likely essential
  - TsDMARDs + bDMARDs?
- But need to be rationally targeted
  - Better understanding of pathways
  - Better measurements
  - Individual variation, heterogeneity of disease, phases of disease
  - How?



Autoimmunity post-pandemic

- Lots to say
- Single gene diseases revealed in previously asymptomatic individuals
- Impact of anti-cytokine antibodies
- Long-haulers - mechanisms
- How does infection reset immune system
  - Adults and children
- Immunization, viral infection in patients with autoimmunity, on immunodulatory drugs

What can we do at NIH-IRP that's harder to do elsewhere?

- Longterm commitment to problem
- High risk/high reward
- Rare diseases – clues to common disease
  - Immunodeficiency and autoinflammatory diseases illustrate mechanisms and therapeutic targets
- Lupus at NIH - > 50 years
  - Cancer drugs to jakinibs
  - Genetics to help unravel heterogeneity
  - Metabolic intervention (drugs, diet)