12th Annual Lupus Education Day Agenda

8:30 – 9:00 am	Sign-in / Refreshments
9:00 – 9:05 am	Introduction / Logistics
9:05 – 9:30 am	Dr. Jennifer Anolik: What's New in the World of Lupus
9:30 – 10:00 am	Dr. Christopher Richardson: How Lupus Affects the Skin
10:00 – 10:15	Refreshment Break
10:15 – 11:15	Patient Panel
11:15 – 12:00	Break-out Sessions: Yoga, Nutrition, Mindfulness & Complementary Therapies
12:00 – 12:30	Questions and Wrap-up

12th Annual Lupus Education Day Agenda

Faculty:

Jennifer Anolik, MD, PhD

Christopher Richardson, MD, PhD

Ummara Shah, MD

Rev. Imani Dodley: Yoga break-out session

Aubree Guiffre, PhD: Mindfulness break-out session

Margaret-Mary Holyst, MD: Complementary therapies break-out session

Lynn Moll, registered dietician: Nutrition break-out session

What's New in the World of Lupus

Jennifer H. Anolik, MD, PhD

Associate Professor of Medicine, Pathology, and Microbiology/Immunology

Division of Allergy, Immunology & Rheumatology

University of Rochester Medical Center

Oct 2018 12th Annual Lupus Education Day

Research in Lupus

- **The more that is known about clinical outcomes and immune abnormalities associated with lupus, the better equipped we are to fight the disease!**

What we're doing at the U of R:

- NIH funded networks and other basic research to understand mechanisms of disease
  - Accelerating Medicines Partnership
- Clinical Cohorts/Consortiums
  - LuCIN (Lupus Clinical Investigators Network- LRI/ALR collaboration, repurposing drugs)
- Clinical Trials
- Outcomes research and new patient centered care delivery models

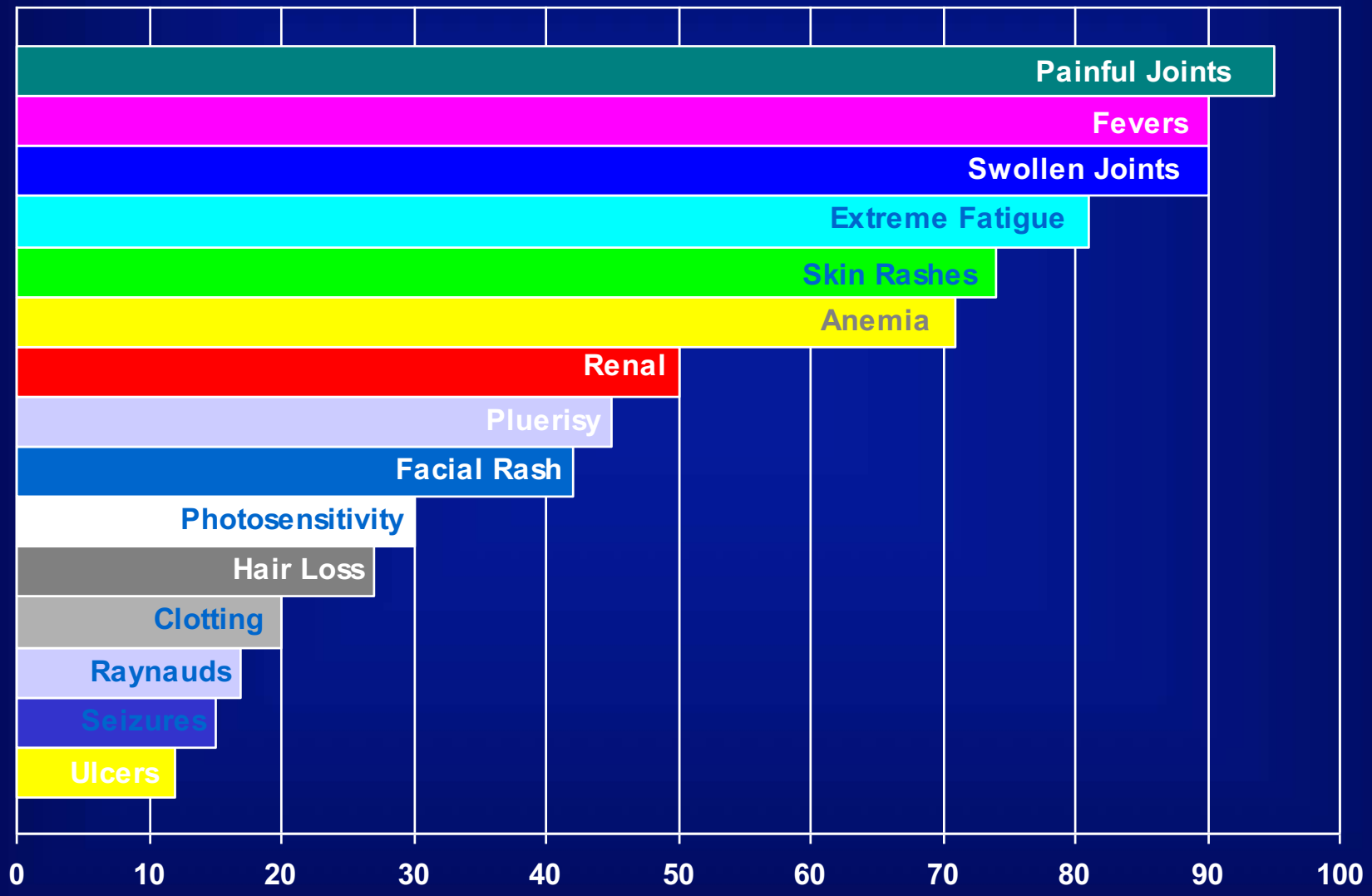
Let's start with the basics

- Lupus is a systemic inflammatory disease of autoimmune etiology and unknown cause.
- Chronic disease characterized by unpredictable exacerbations and remissions.
- It can affect virtually any organ, singly or in combinations that change from patient to patient.
- Its severity ranges from mild in some cases to life-threatening in others.

Who develops lupus?

- African-Americans > Caucasians (3x)
  - Caucasian women (15-64 years of age): 1/700
  - African-American women (15-64): 1/245
- Age at diagnosis:
  - 16-55 years of age: 65% of cases
  - < 16: 20%;
  - > 65: 15%
- Female/male ratio:
  - Age 14-65: 6-10 / 1
  - Age <14 or >65: 2-3 / 1

Lupus presenting symptoms



How do we diagnose lupus?:

American College of Rheumatology (ACR) criteria

Skin criteria

1. Malar rash
2. Discoid Rash
3. Photosensitivity
4. Oral Ulcers

Systemic criteria

5. Arthritis
6. Serositis
7. Kidney
8. Neurologic

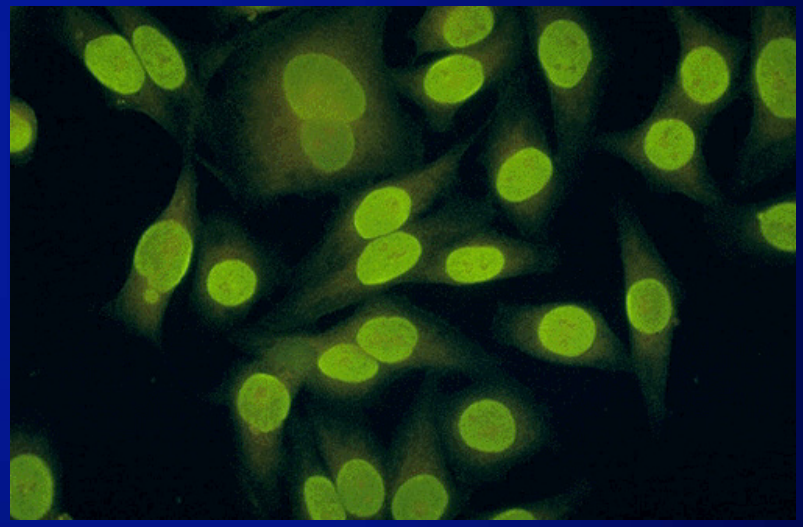
Lab criteria

9. Anti-nuclear antibody
10. Immunologic
11. Hematologic

For the purpose of identifying patients in clinical studies, a person shall be said to have SLE if any **4 or more of the 11 criteria** are present, serially or simultaneously, during any interval of observation.

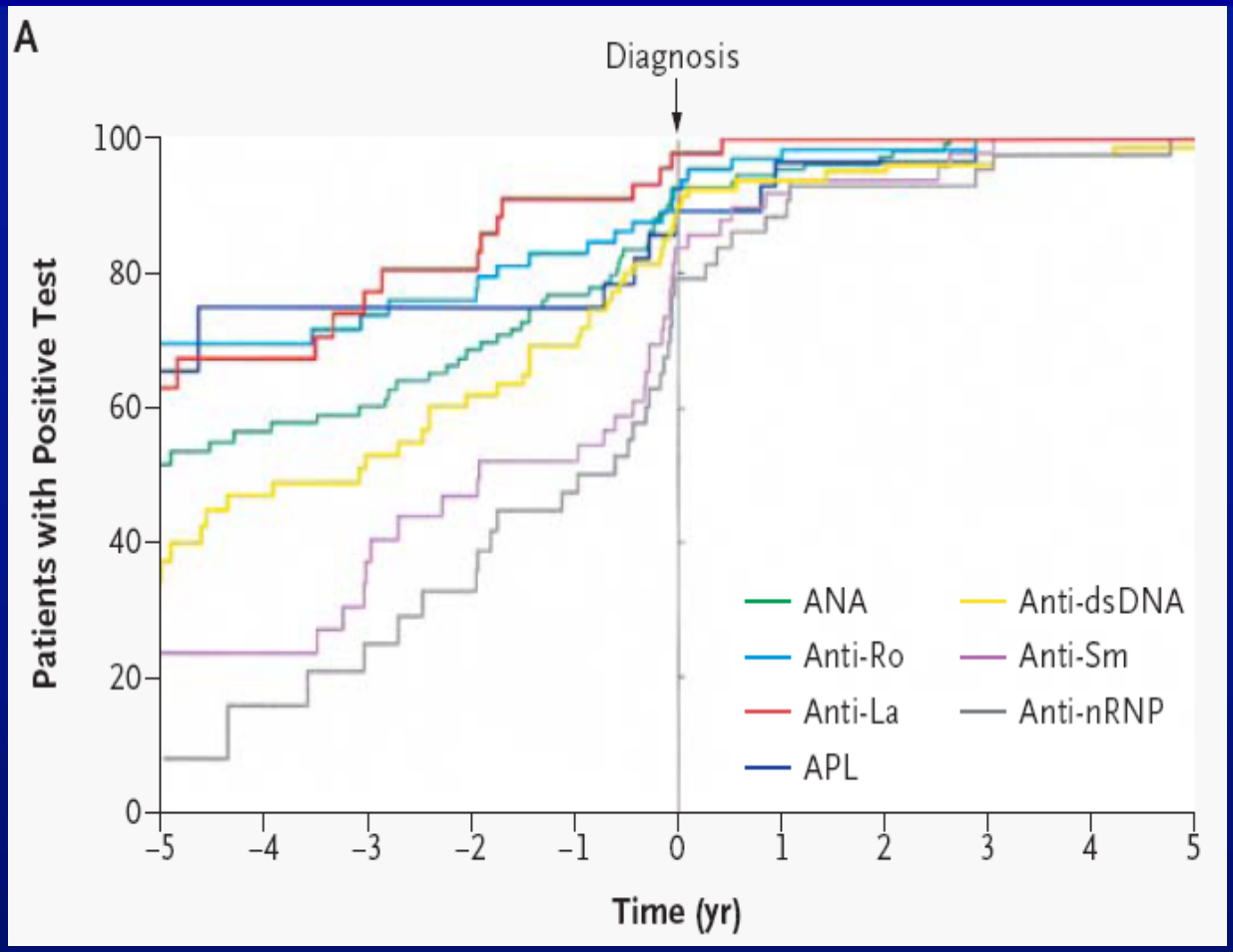
SLE Diagnosis: Autoantibodies

- ANA
  - Seen in 99% of SLE
  - Not specific for SLE
  - Seen in many inflammatory, infectious, and neoplastic diseases
  - Seen in 5% to 15% of normal persons



- Other more specific autoantibodies- antiDNA, antiSmith

Autoantibodies precede diagnosis



- **Recent research focus on identifying 'at risk' individuals and trying to prevent disease**

Arbuckle…Harley. NEJM 349: 1526, 2003
Judith James and colleagues: Ann Rheum Dis 2011, Ann Rheum Dis 2016, A and R 2017

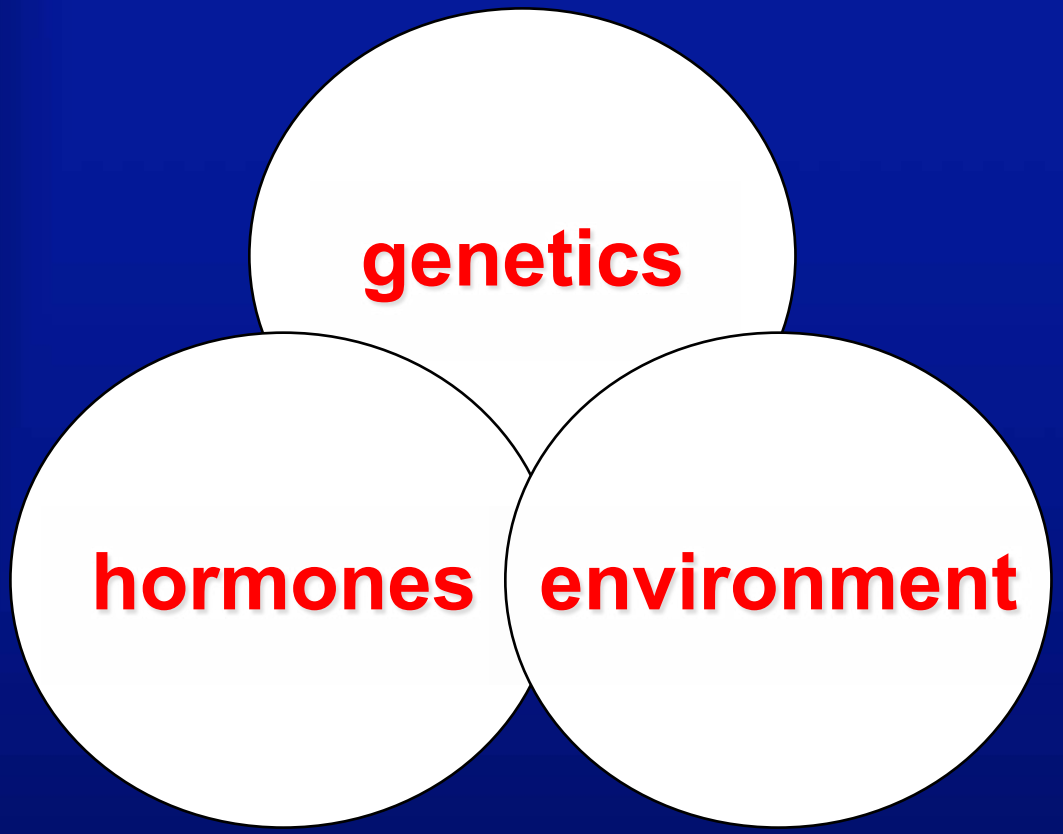
The Future of Diagnosis

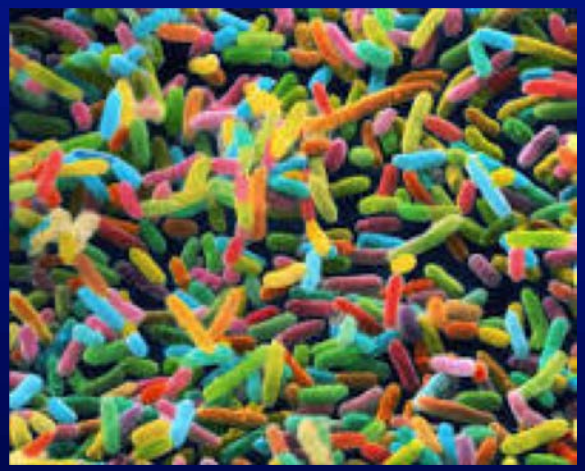
- Identify and detect more lupus specific autoantibodies

- Combine autoantibodies with other measurements of immune abnormalities: e.g. detection of interferon or complement activation

Stanford- Scientific Reports 2016; Nature Medicine 2012
Duffy and Yanick Crow, J Exp Med 2017

Cause/Pathogenesis





The ‘exposome’

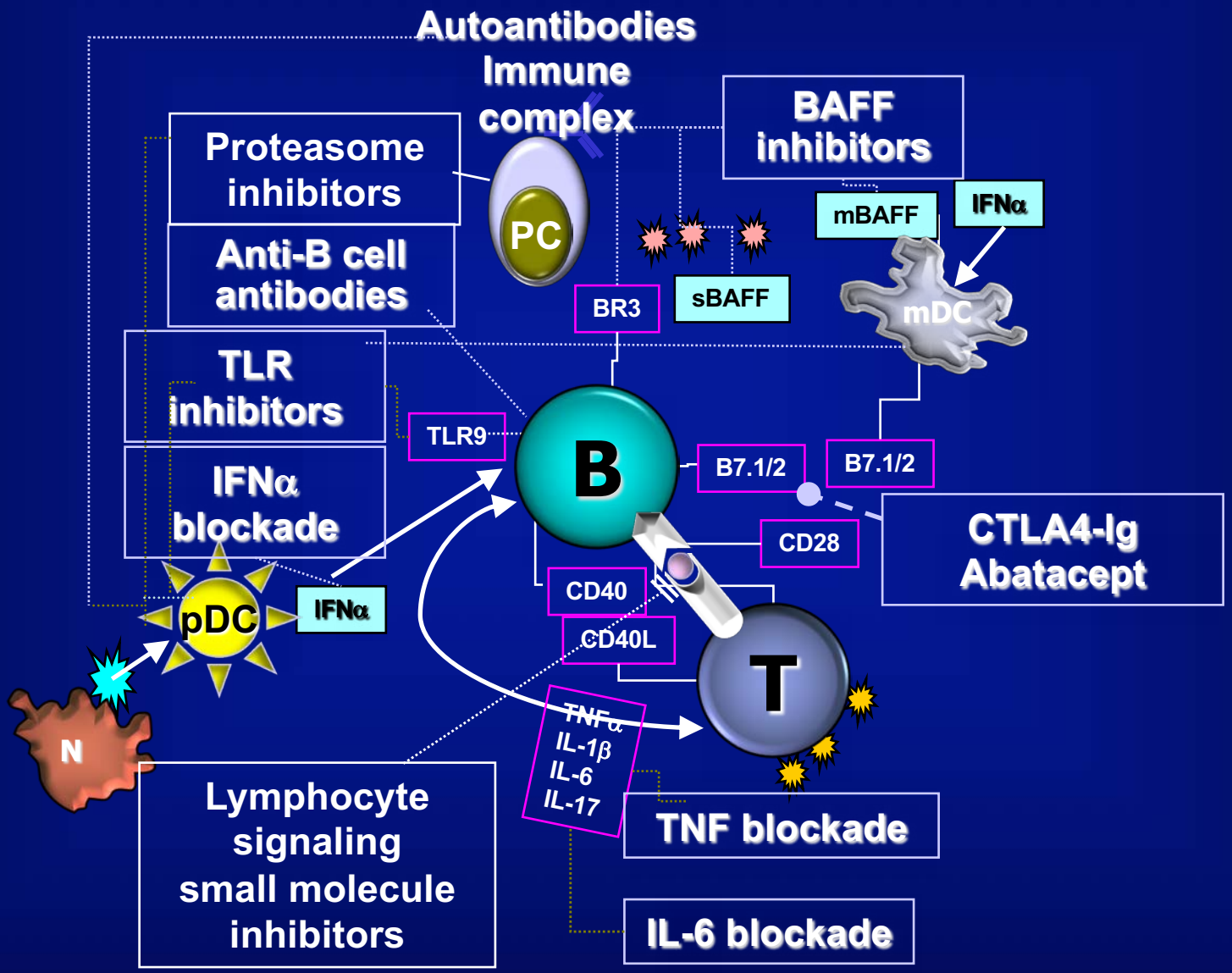
Updates from ACR 2018

- Association of diet and risk of SLE in the Nurse's Health Study
  - >230,000 female nurses followed for 29 years
  - Various definitions of a healthy or anti-inflammatory diet (vegetables- dark yellow and leafy greens, whole grains, nuts/legumes, omega-3-fats/fish)
  - No association between long-term adherence to four different dietary quality scores/indices and incident SLE within this large prospective cohort of women
  - Though diet may have an impact on SLE, a large effect on developing SLE may be unlikely

- Stress and lupus
  - Prior studies: probable PTSD and trauma associated with nearly 3-fold increased risk of incident SLE among women exposed to any traumatic event compared to unexposed
  - Black women's health study: 59,000 black women, ages 21-69 years (median 38 years) enrolled in 1995 and followed through 2015
    - Childhood physical and sexual abuse associated with an increased risk of developing lupus among adult black women

Barbhaiya ACR 2018

The immune system and lupus



Why do we need new treatments?

- The more that is known about clinical outcomes and immune abnormalities associated with lupus, the better equipped we are to fight the disease!

- Current treatments do not always work
- Current treatments can have toxicity
- We have no cure for lupus

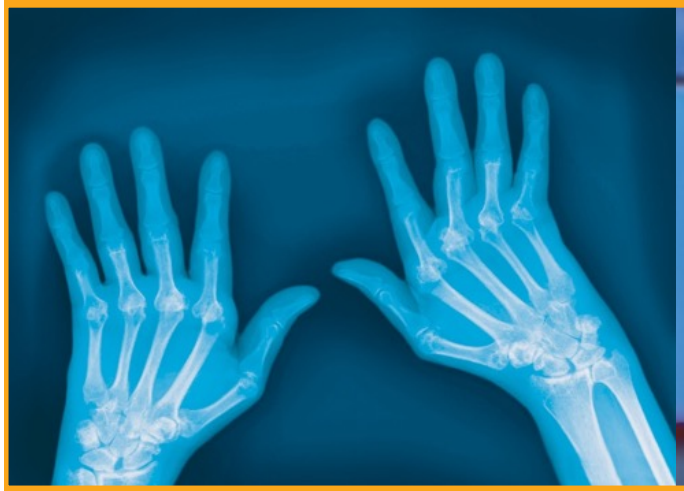
Identifying new treatment targets and biomarkers

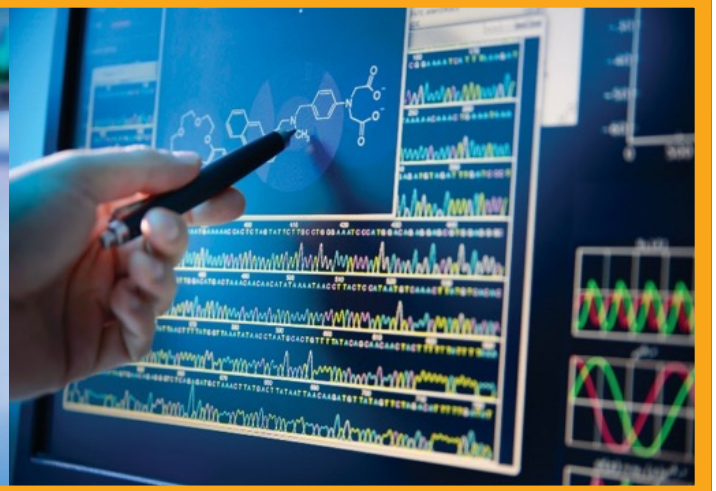
Accelerating Medicines Partnership (AMP) Initiative

First-of-its-kind partnership and study

Goal: To evaluate the molecular pathways and relevant drug targets of autoimmune diseases to help develop new therapies

Learn more: fnih.org/AMP-RA-Lupus





Boosting Success by Improving Efficacy: Phase II Clinical Trials

Current targets

- Animal models
- Cell lines

AMP targets

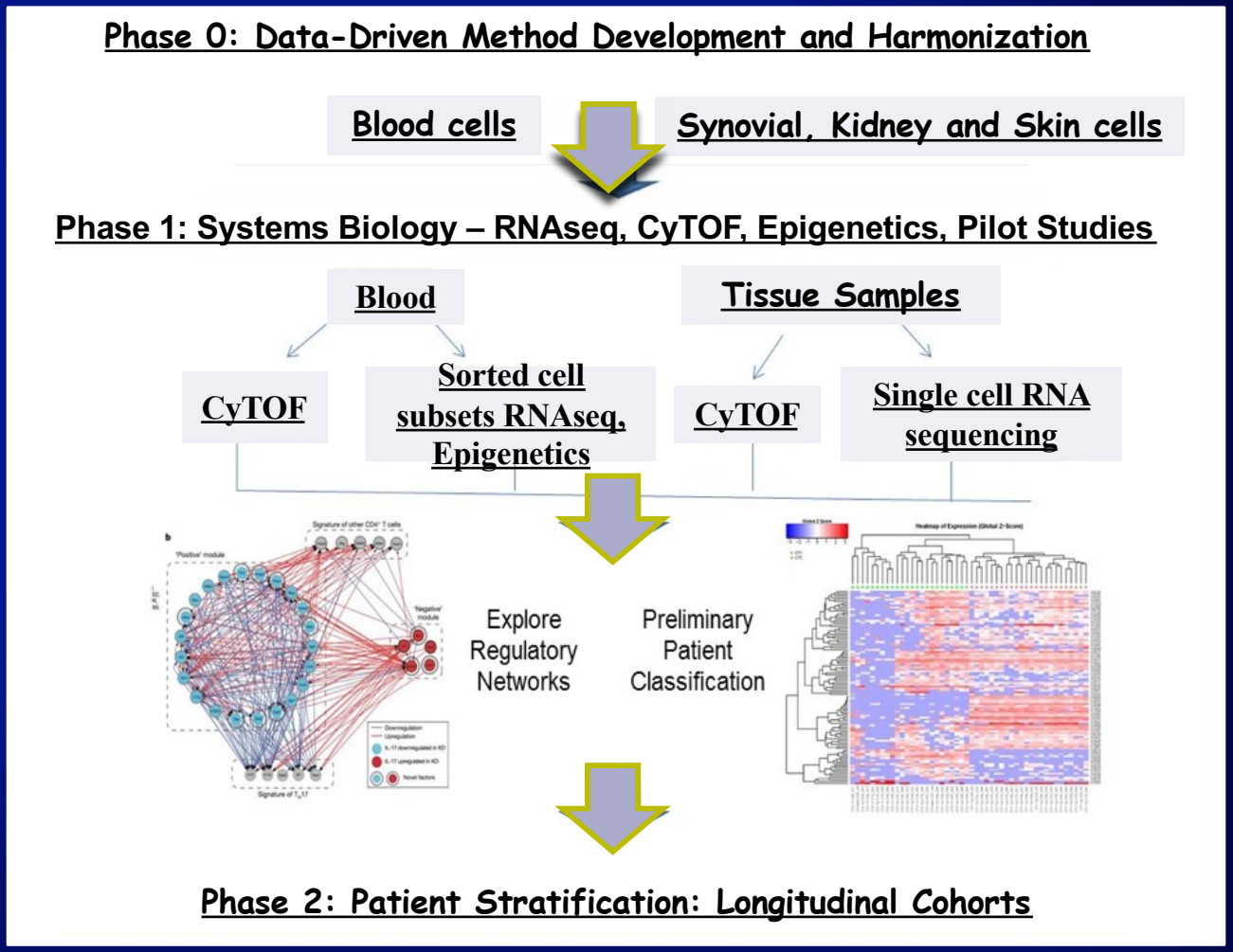
- Emerging Technologies
  - DNA sequencing
  - Proteomics
  - Single-cell analysis
  - Bioengineered cells
  - Imaging
- Extensive Human Data
  - Tissue/blood samples
  - Clinical information
  - Demographics
- Big Data Tools

Adapted from: Arrowsmith J, Miller P. *Nat. Rev. Drug Discov.* **12,** 569, August 2013

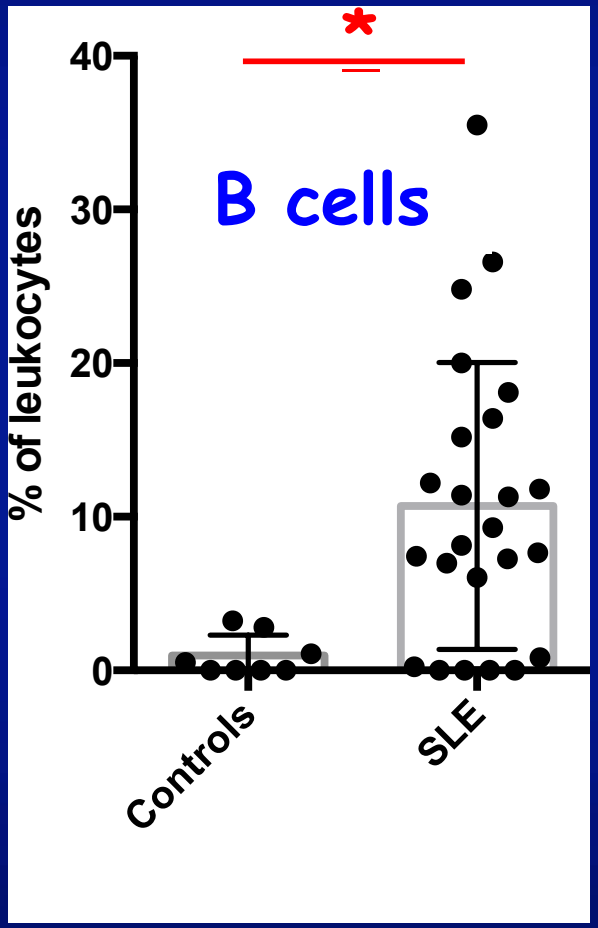
Focus on target tissue

Getting towards precision medicine

- Clinical/transcriptional profiling of 72 lupus patients
- Molecular and cellular stratification may improve outcomes in SLE and help identify new treatment targets



What have we found so far?
More B cells in lupus kidney



Including activated B cells

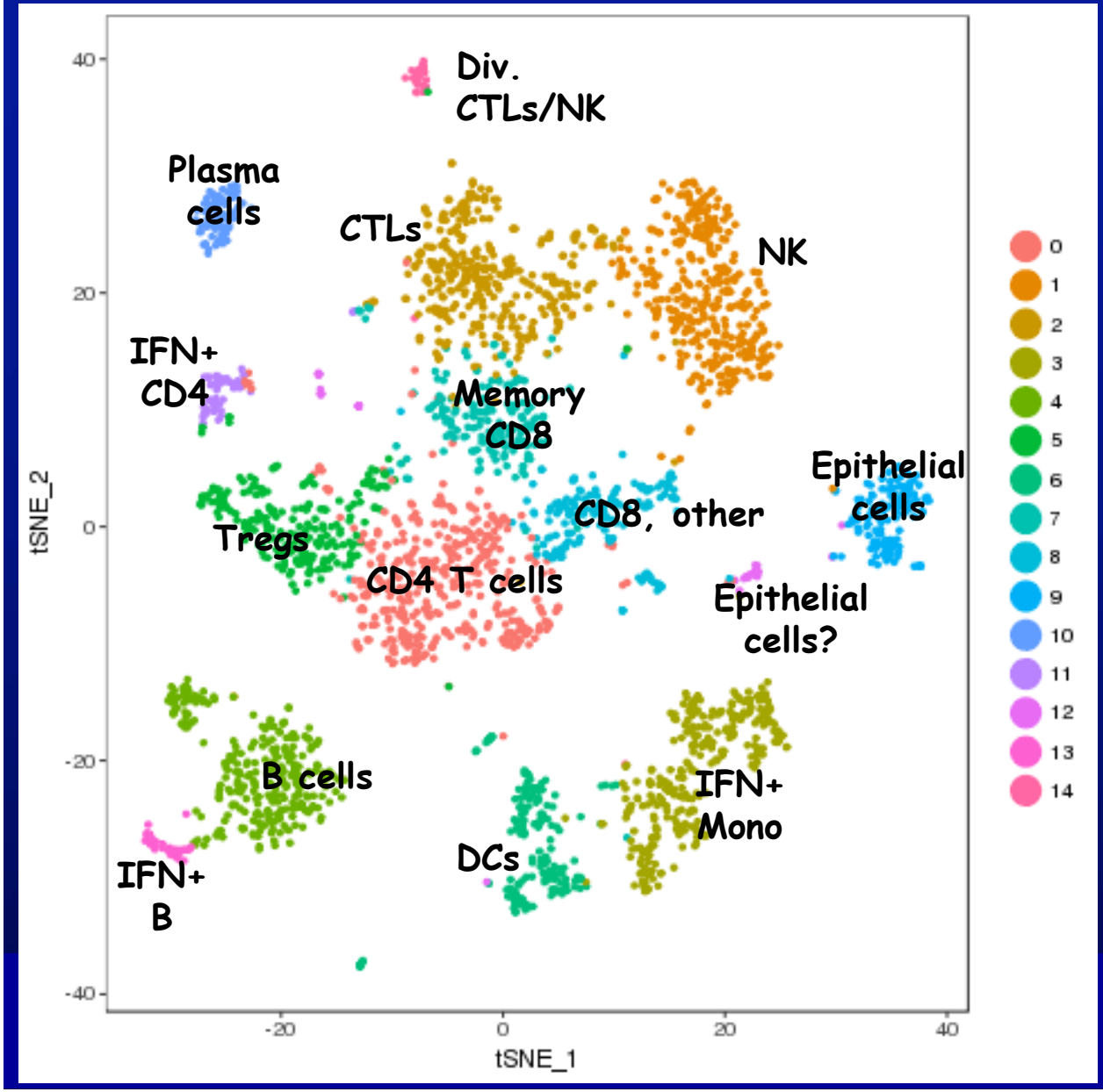
Arazi et al. for the AMP; bioRxiv preprint first posted online Jul. 7, 2018; doi: http://dx.doi.org/10.1101/363051.

Trigger for lupus identified

- A subset of B cells called ‘Age-associated B cells’ (ABCs) may drive lupus
- A transcription factor called T-bet drives the development of these B cells
- Deletion of T-bet inside B cells in mice prone to develop autoimmune disease remain healthy
- Recent studies enumerating these cells in human lupus

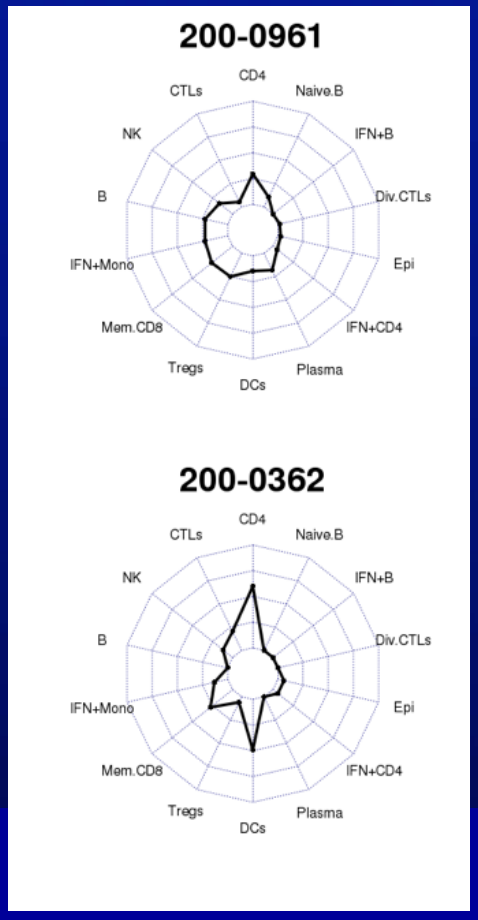
Rubtsova..Marrack, JCI 2017
Ettinger and colleagues Nat Comm 2018
Sanz and colleagues Immunity 2018

Many different kinds of cells in the lupus kidney



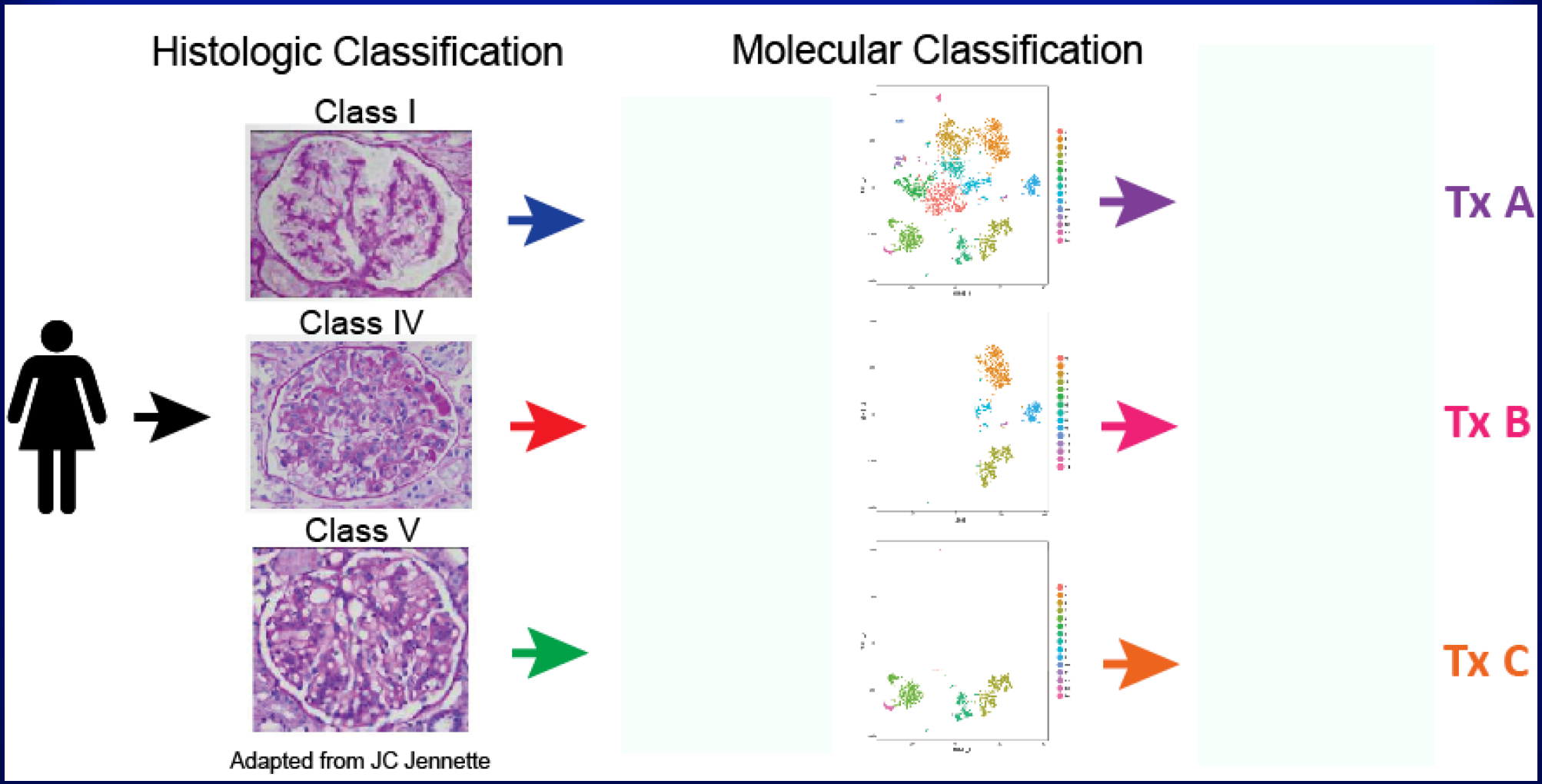
Patients vary:

- **-types of infiltrating cells**
- **-gene expression across corresponding clusters**



Aims for Phase 2

Identify molecular + cellular features that define pathologically distinct subsets of nephritis



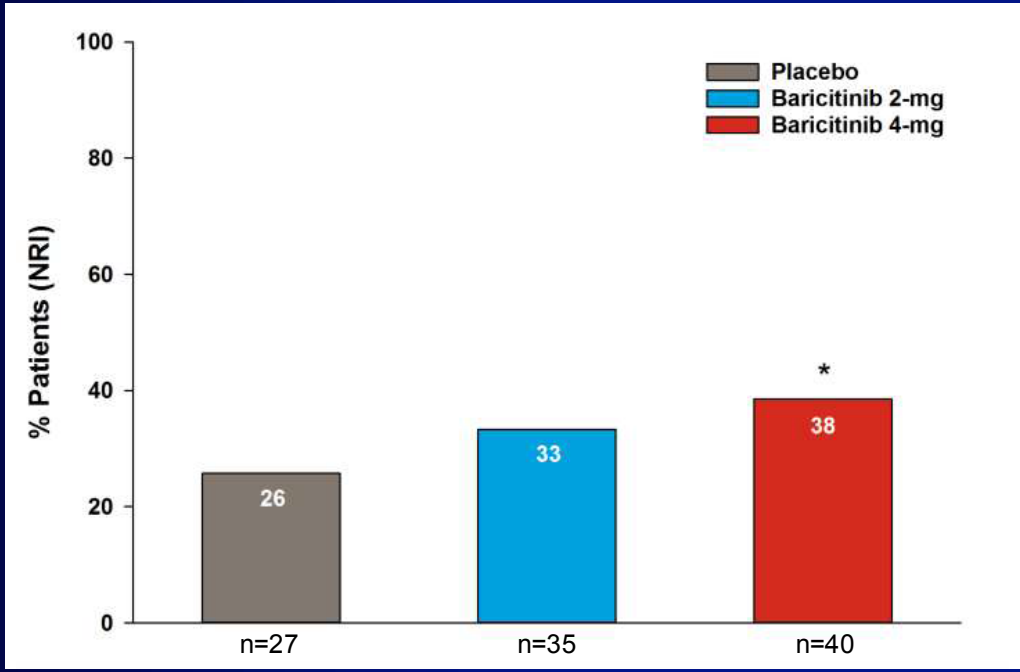
What's new in clinical trials?

- Two Phase 2 clinical trials reported success at ACR 2018
- Barcitinib- an oral JAK inhibitor approved to treat RA
  - Once-daily baricitinib 4-mg was associated with significant clinical improvements compared to placebo
- Ustekinumab (IL12/23 inhibitor) approved for psoriasis, PsA, Crohn's

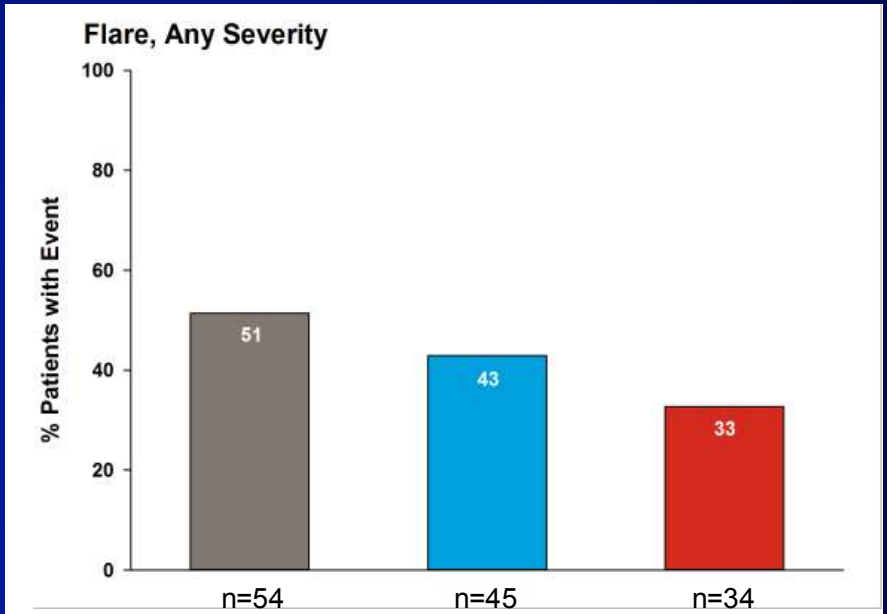
Wallace ACR 2018
Van Vollenhoven ACR 2018

Barcitinib

Lupus low disease activity at 24 wk



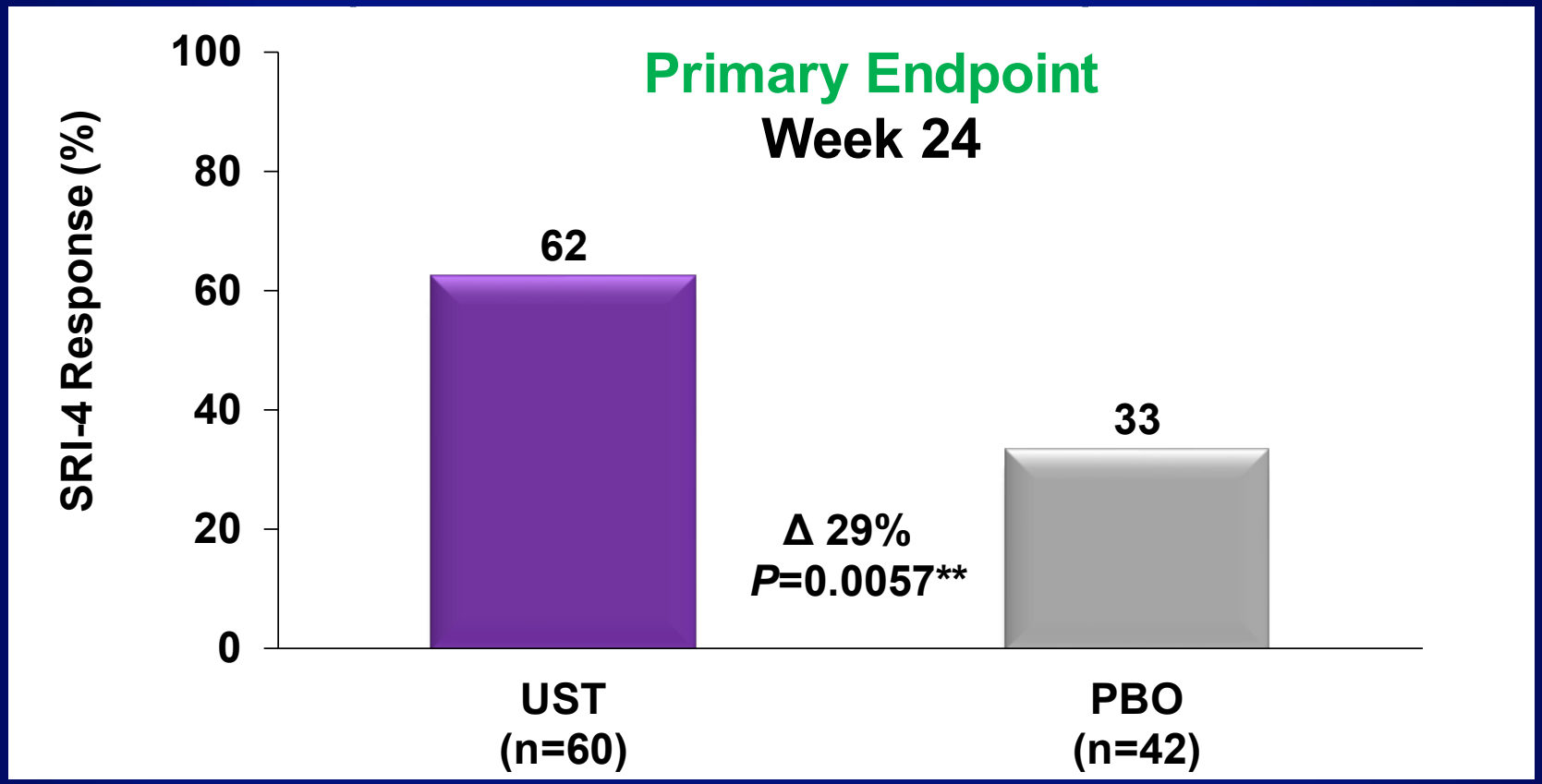
Flares



Time to first flare	Baricitinib 2-mg (N=105)	Baricitinib 4-mg (N=104)
HR (95% CI)	0.97 (0.65 to 1.45)	0.60 (0.39 to 0.92)*

Wallace ACR 2018

Ustekinumab



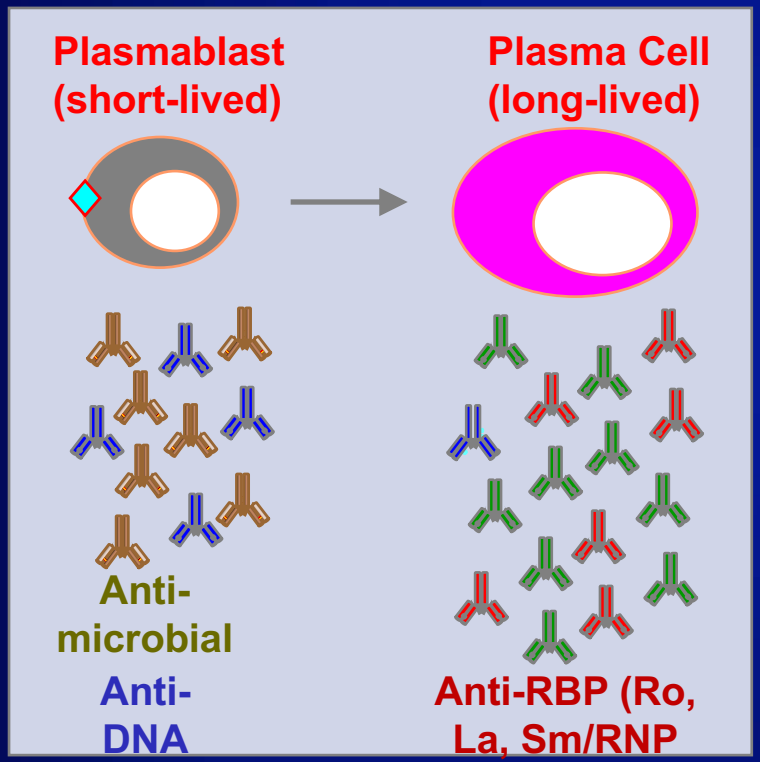
Van Vollenhoven ACR 2018

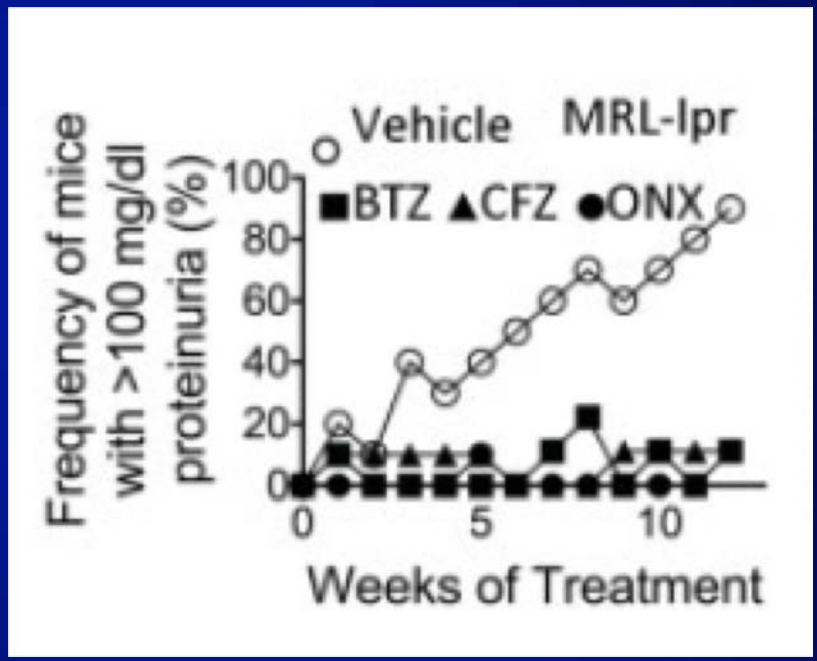
Currently (or soon) enrolling trials at UR

- Cell based therapies
  - Mesenchymal stem cell transfer
- Krill oil (omega-3-fatty acids) (through LUCIN)
- Proteasome inhibitors (approved for myeloma) (Kezar)
- Daratumumab (approved for myeloma) (Janssen)

Is it important to eliminate autoantibodies?

- Most current therapies do not effectively target autoantibodies/plasma cells





Ichikawa…Anolik; Arthritis and Rheum 2012
Alexander…Voll, Ann Rheum Dis 2015

Concluding points

- Therapy will attempt to target specific pathways in the body
- Personalized medicine
- Despite barriers, novel mechanism-based therapies are in development for SLE
- Eventual treatments may involve combination therapies, i.e., “cocktails” of targeted and semi-targeted therapies


Thank You!

Learn More

- www.lupusresearch.org/research/research_update.html
- LupusTrials.org
- www.clinicaltrials.gov
- The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) and the Office on Women's Heath have developed a strategic plan for reducing health disparities. Lupus is included as an area of research focus. Recent first-ever National Public Health Agenda for Lupus in collaboration with the National Association of Chronic Disease Directors (NACDD). Further information on disparities in lupus and educational material at:
- http://thelupusinitiative.org
- www.couldihavelupus.gov
- https://fnih.org/what-we-do/current-research-programs/amp-ra-sle