15th Annual Lupus Education Day Agenda

Breakthroughs in Lupus 2021

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What are the different forms of lupus?

Systemic Lupus Erythematosus

Discoid or Cutaneous Lupus

Drug-Induced Lupus

Neonatal Lupus

SLE

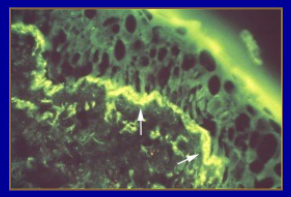
- Lupus is a systemic inflammatory disease of autoimmune etiology.
- Chronic disease characterized by unpredictable exacerbations and remissions.
- It can affect virtually any organ, singly or in combinations that change from patient to patient.
- Its severity ranges from mild in some cases to life-threatening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

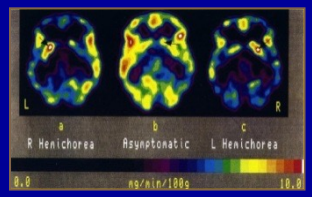
What are the symptoms of lupus?

- Painful swollen joints
- Unexplained fever
- Extreme fatigue
- Rashes

- Sensitivity to the sun
- Mouth Sores
- Hair loss
- Pale or purple fingers or toes from cold
- Swollen glands
- Headache and/or Depression
- Chest pain with deep breathing
- Low blood count

SLE: Clinical Heterogeneity

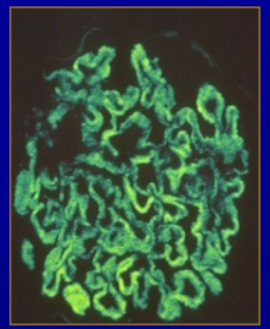


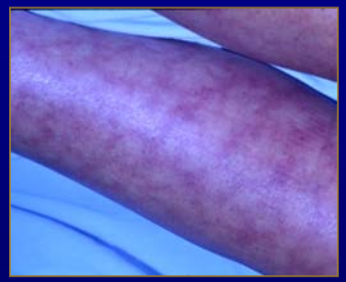


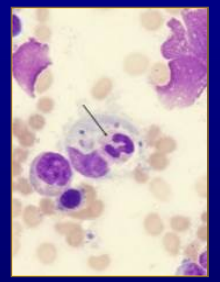
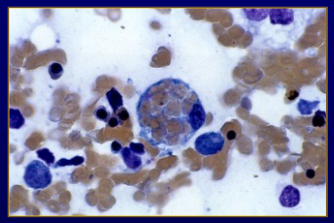


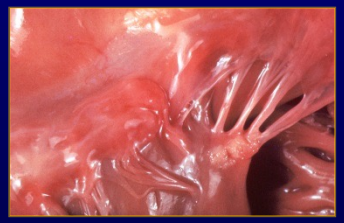
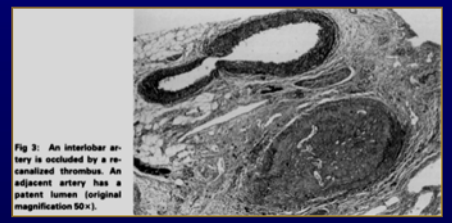






How do we treat lupus?
Circa 2016
At the 10th Annual Lupus Education Day

- NSAIDs
- Steroids (low dose to “pulse”)
- Antimalarials (hydroxychloroquine; quinacrine)
- Immunosuppressives
  - (MMF; AZA, MTX; calcineurin inh)
- Chemotherapy (cyclophosphamide)
- Biologics (belimumab; rituximab; abatacept)
- Adjunctive therapies (ACEi; bisphosphonates)

Let's Make this Era the Golden Era of SLE Drug Development

Rheumatoid Arthritis, Psoriatic Arthritis, Psoriasis, Crohn's Disease, Ulcerative Colitis, Multiple Sclerosis collectively have had over 2 dozen drugs approved since the late 1990's.

SLE had just one!!

(as of 2020)

Do we need new treatments?

ABSOLUTELY!

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

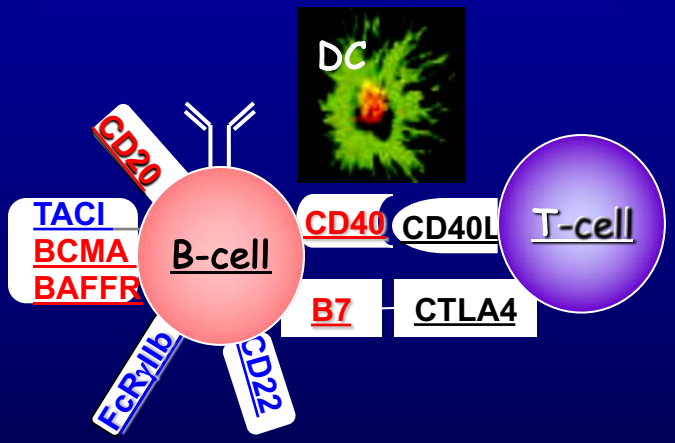
How do we get new treatments? Research

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

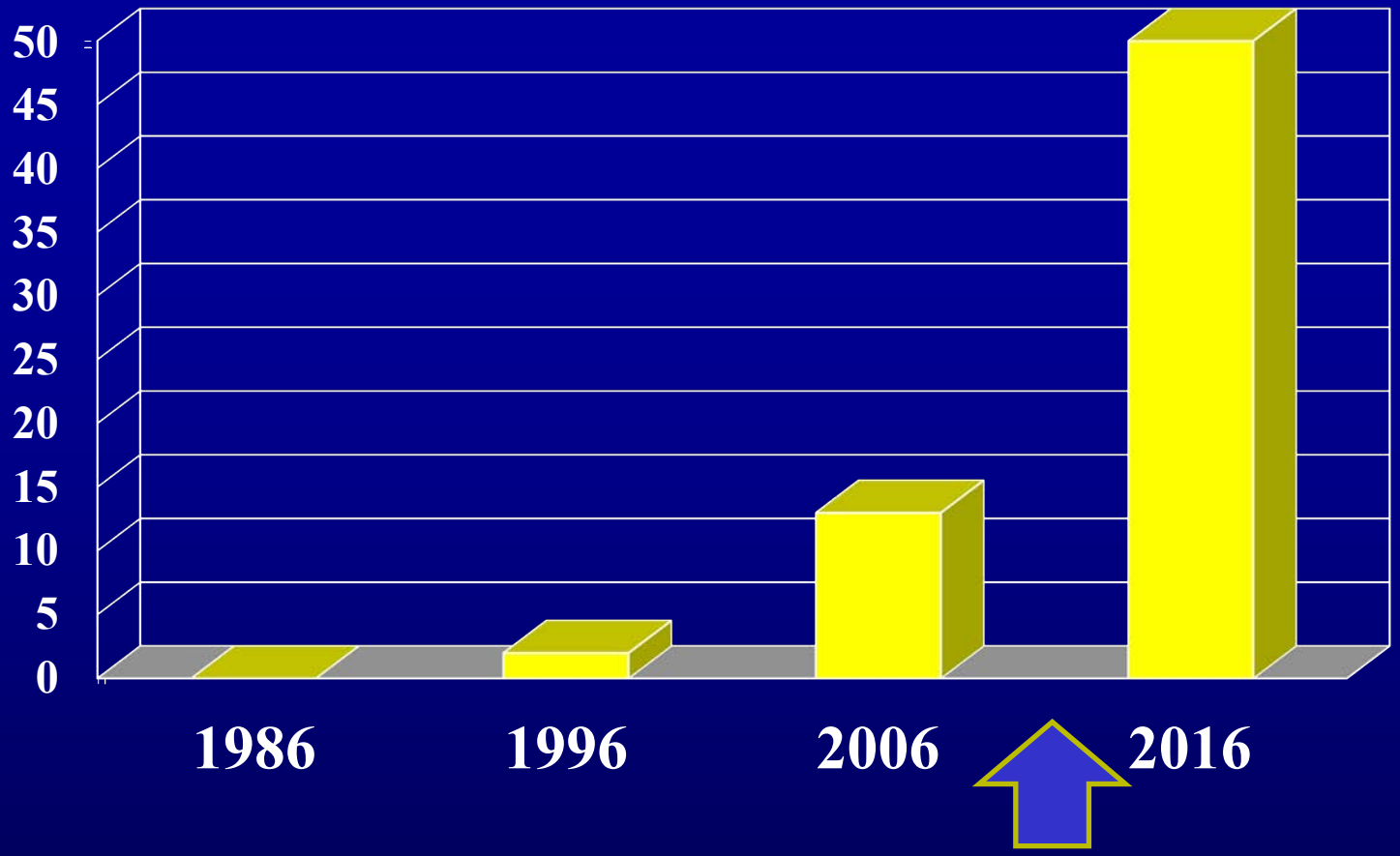
What we're doing at the U of R:

- Observational studies:
  - Clinical Cohorts: Lupus Clinical Trials Consortium 20 centers
  - Outcomes: IQ-Lupus Program
- Basic and translational science research
  - NIH funded international networks-Accelerating Medicines Partnership
  - Translational studies of disease mechanisms using biologic specimens -
  - Mouse models of disease
- Clinical Trials
  - The AIR unit has an active program in clinical trials in SLE
    - Pharma
    - LUCIN
  - Investigation of new, targeted biological interventions in SLE

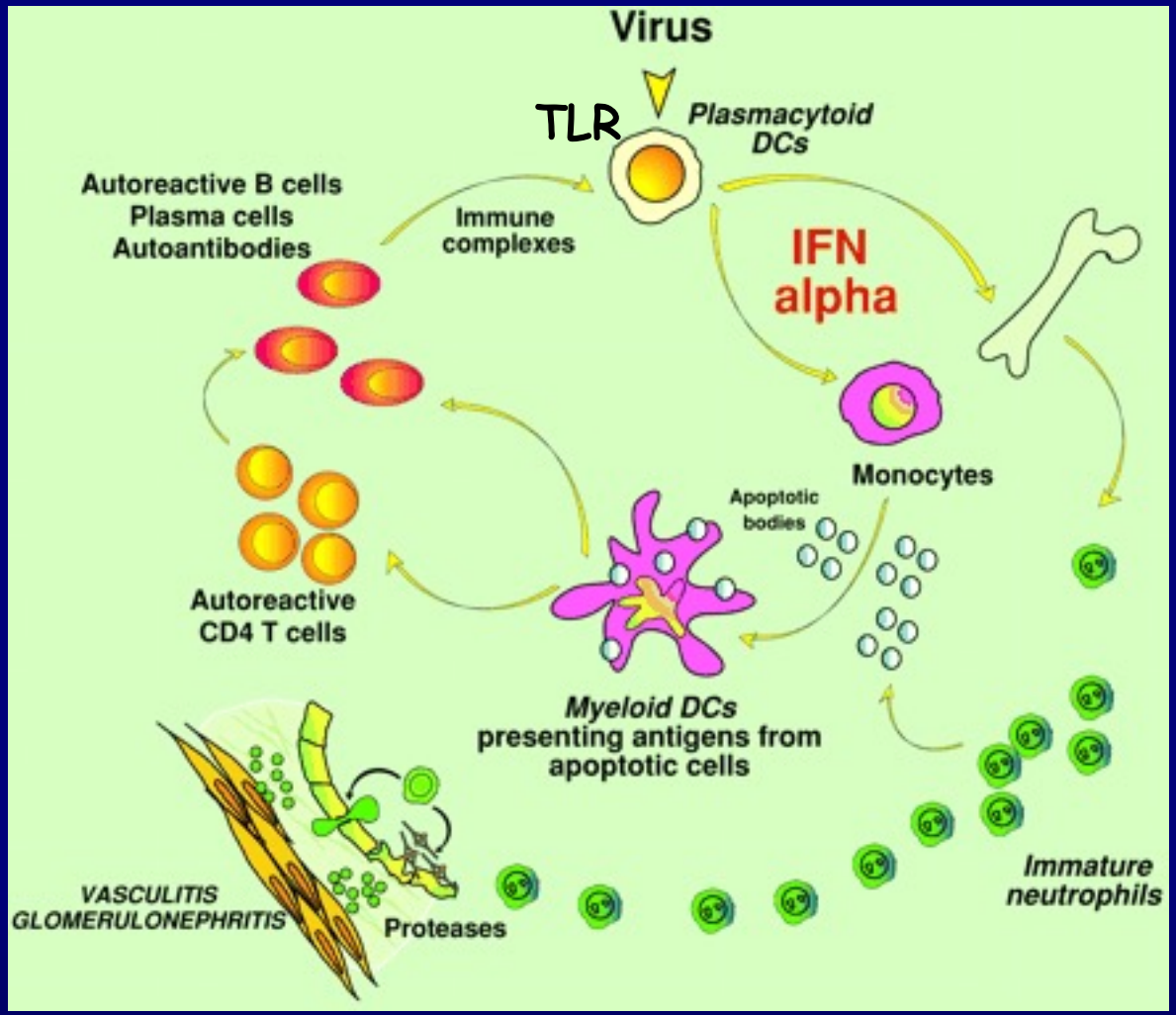
Much research focused on identifying biologic molecules critical to the lupus disease process and strategies to remove or neutralize them: 'targets'



Drugs in Development for SLE



An example of targeted drug development: Blocking Interferon



Current Opinion in Rheumatology 2003 Pascual

Interferon in SLE

- Family of cytokines important in viral immunity
- SLE patients:
  - Elevated IFN-α levels
  - SLE sera induce IFN gene signatures
  - 60%-75% have IFN gene signatures in PBMC
  - Clinical and serologic activity correlate with IFN gene expression
- Can IFN inhibitors reduce SLE clinical activity?

Clinical Trials with IFN blockade

- Phase 2 (~300 patients)
  - MUSE (published 2016)
- Phase 3 (~400 patients in each)
  - TULIP1 (published Dec 2019)
  - TULIP2 (published Jan 2020)


BREAKING NEWS
LUPUS


FDA APPROVED
FDA APPROVED
FDA APPROVED

Exciting news in 2021!!!

Two new drug approvals!

-Blocking interferon- anifrolumab/saphnelo
July 2021

-Voclosporin/lupkynis
January 2021

-Benlysta
Approved 2011
Approved for lupus nephritis December 2020

Other clinical trials

- B cells:
  - Phase 2 NOBILITY trial of a new B cell depleting therapy (anti-CD20 obinutuzumab) met endpoints in LN
  - Phase 3 REGENCY study underway
- Mesenchymal stem cell transfer

Other research updates on lupus

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

SLE – Epidemiology: ethnic disparities

- LUMINA cohort: LUpus in MInorities, NAture versus nurture
- Longitudinal study of patients with SLE
- Hispanic and African American patients have more serious disease at a younger age and worse outcomes

- CONCLUSION:

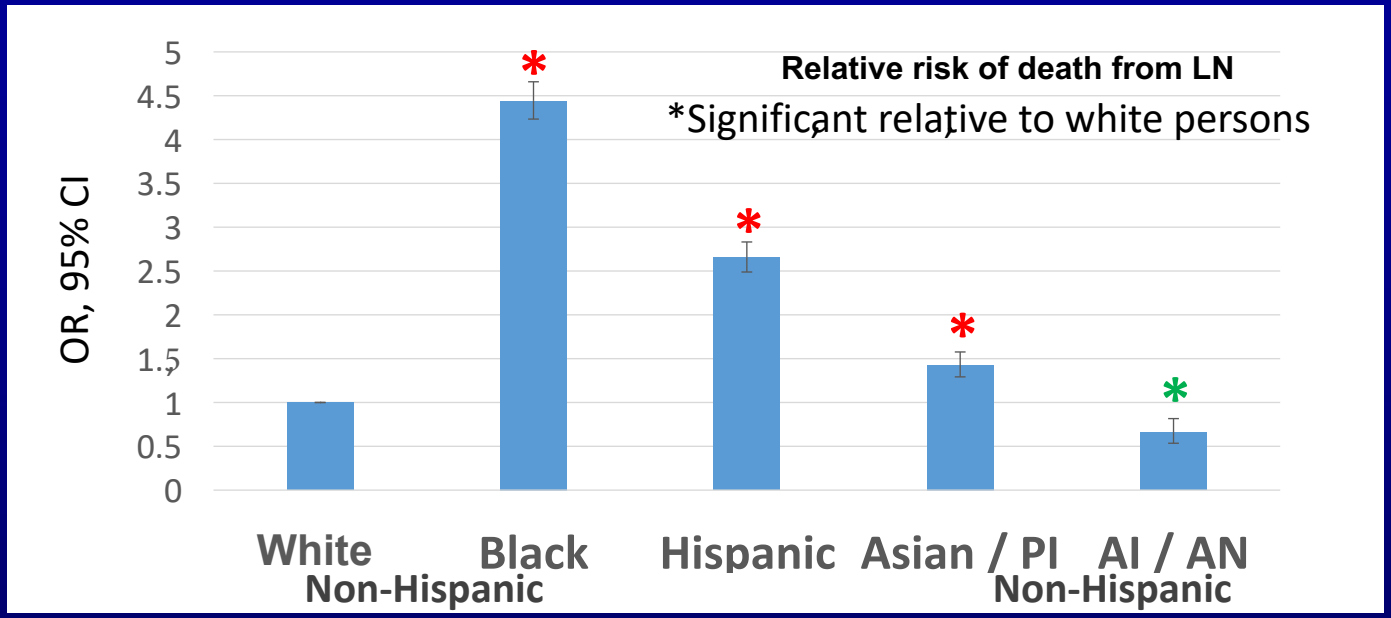
-Ethnic disparities occur in SLE

-Emerging role of environmental and socioeconomic/ demographic factors

Fernandez et al. Arthritis Care and Research 57:576, 2007

Ethnic disparities

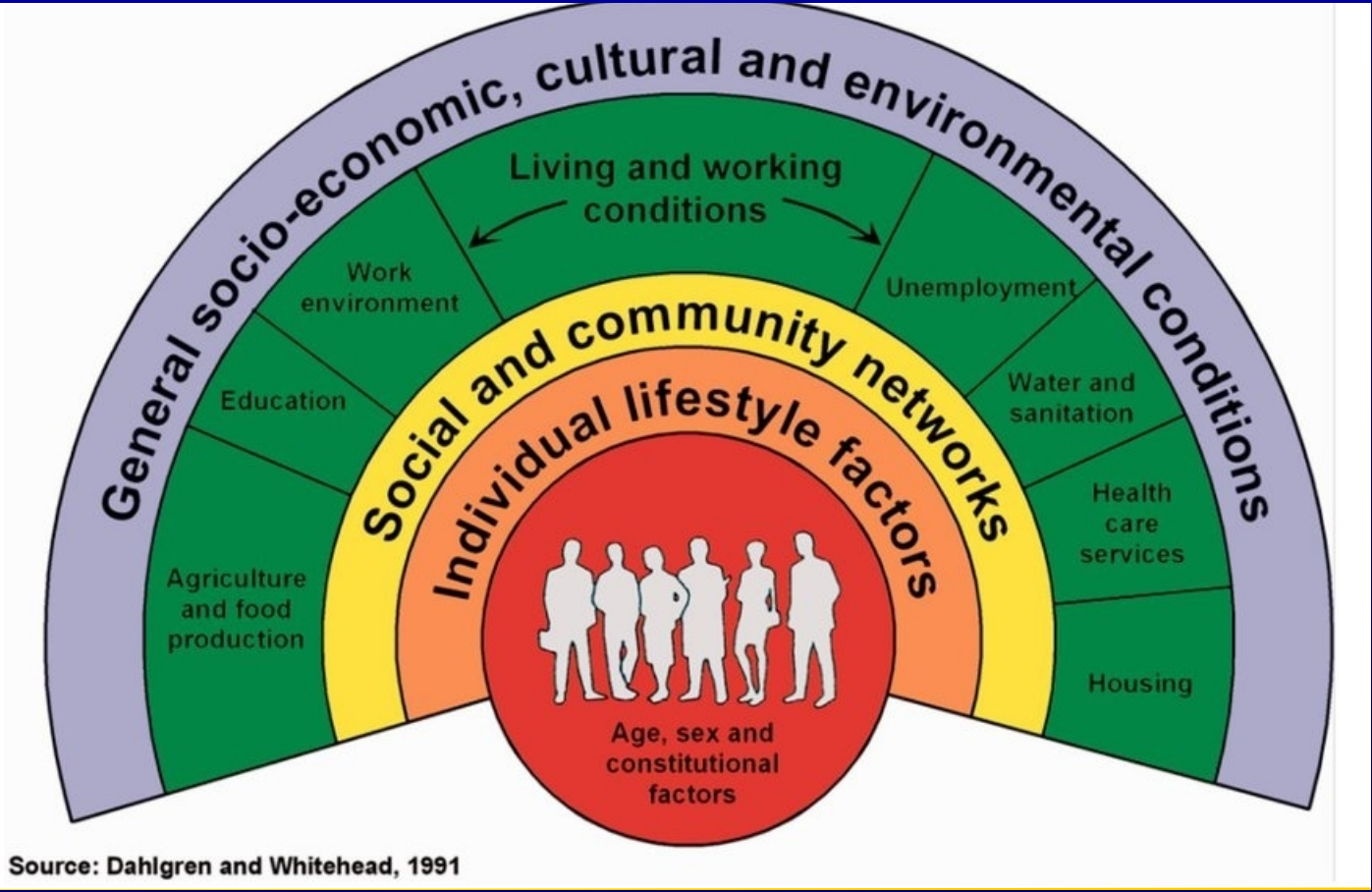
- LN mortality has decreased-that's good
- BUT, outcomes are worse for blacks and those living in urban areas



- Race and where you live can impact your health!!

Yen..Singh ACR 2021

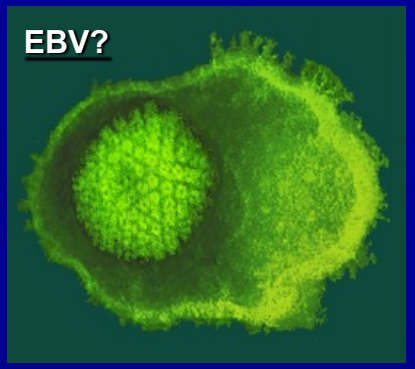
Ethnic disparities

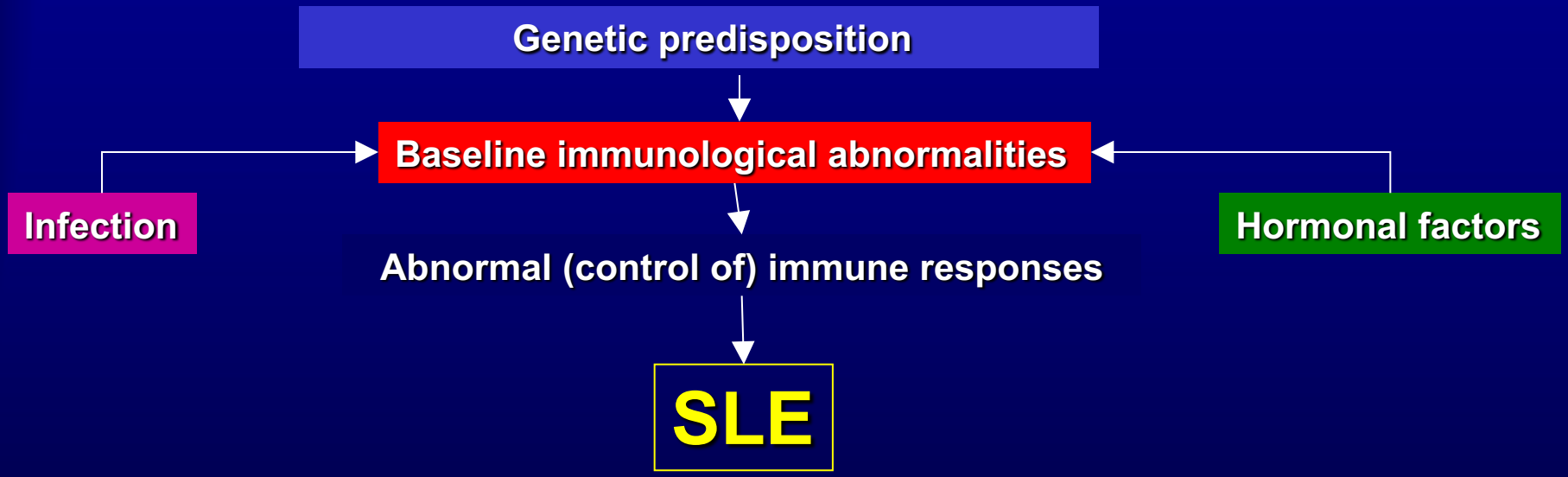


Yen..Singh ACR 2021

SLE - Cause

- The etiology of SLE remains unknown
- Yet, SLE is clearly multifactorial:
  - Genetic factors
  - Immunologic factors
  - Hormonal factors
  - Environmental factors





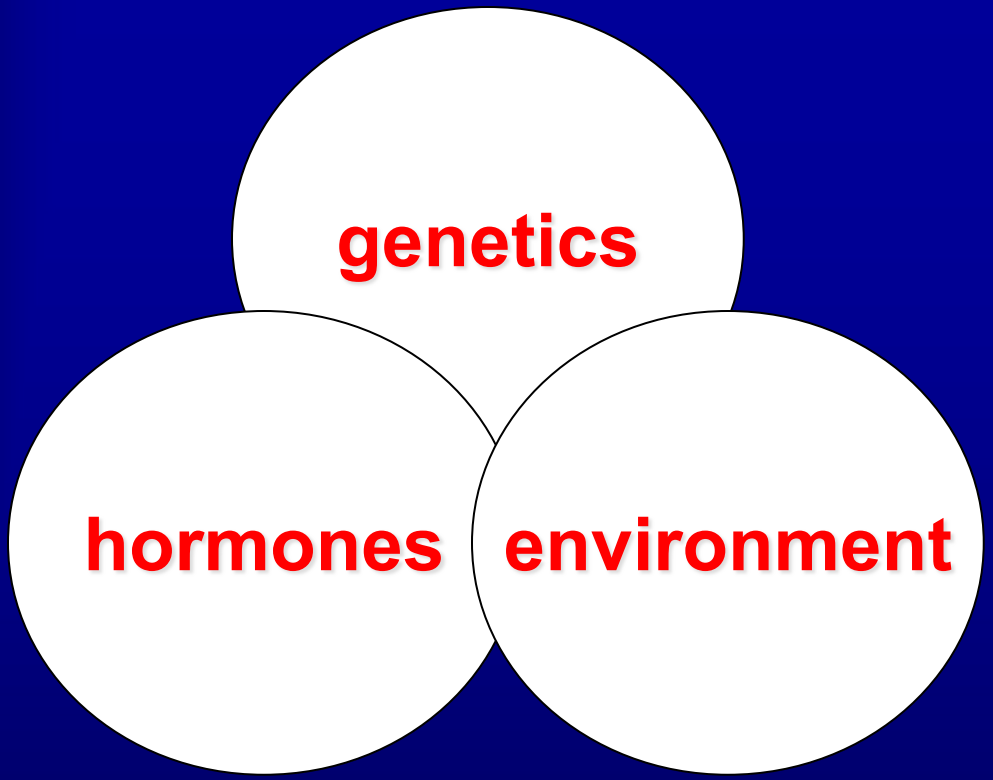
‘A genetic component’

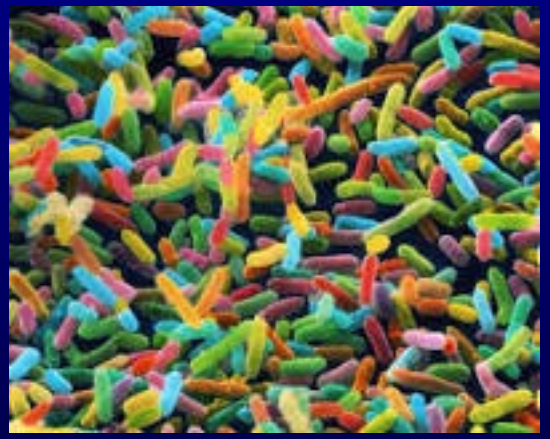
- **Strong genetic component suggested by:**
  - **High concordance in identical twins (15-40%)**
  - **Higher incidence in families (2-10%) (10-fold increased risk in first degree relatives) (instead of 1:400 chance increased to 1:25)**

- **Multiple loci (probably >100) may contribute to SLE:**
  - **Multiple risk variants each conferring tiny increase risk**
  - **Many immune related genes**

Recent insights into the genetic basis of SLE. Moser et al. Genes Immun 2009

A lot more than genetics





The ‘exposome’

Environmental factors

- The ‘microbiome’

- Findings:

-Certain gut bacteria may be over-represented in lupus patients

-Translocation of bacteria from gut can trigger lupus in mouse models

- Future Implications for clinical practice:
  - Paves the way for altering the microbiome
  - Dietary interventions

Azzouz…Silverman. Annal of Rheum Dis 78, 2019
Vieira…Kriegel. Science 359, 2018
Zegarra-Ruiz…Kriegel, Cell Host and Microbe 25, 2019

Diet

- Vitamin D and fish oil for the prevention of autoimmune disease- VITAL study

- Background:

-We don't have any way to prevent autoimmune disease

- Findings/Implications:
  - Up to 5 years of f/u vitamin D provides protection
  - .NS trend for omega-3
  - Limitations- older cohort- mostly rheumatoid and PMR, don't know about lupus

ACR 2021- Karen Costenbader

Identifying new treatment targets and biomarkers

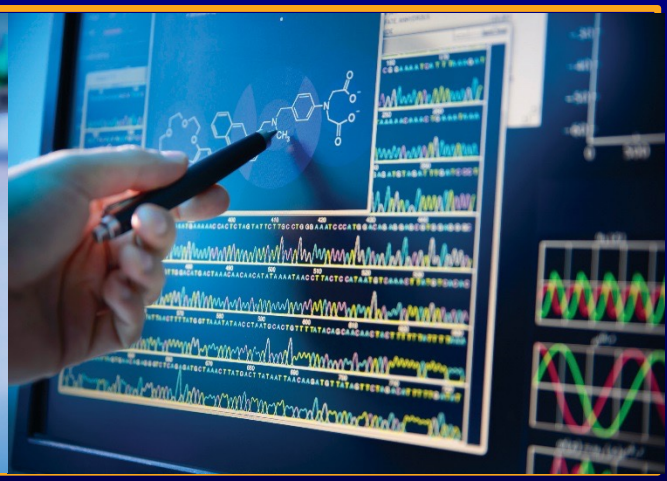
Accelerating Medicines Partnership (AMP) Initiative

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

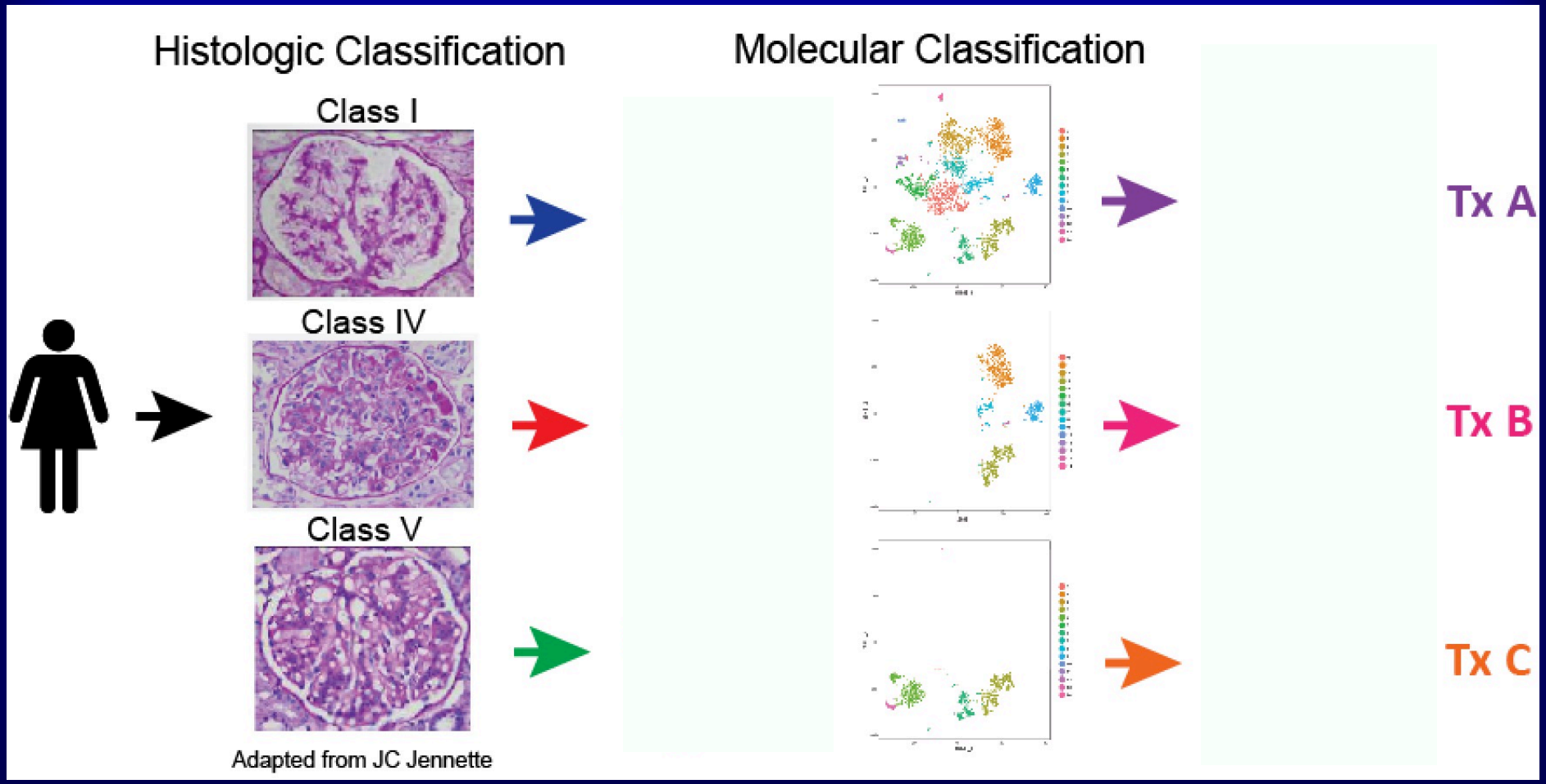
Learn more: fnih.org/AMP-RA-Lupus



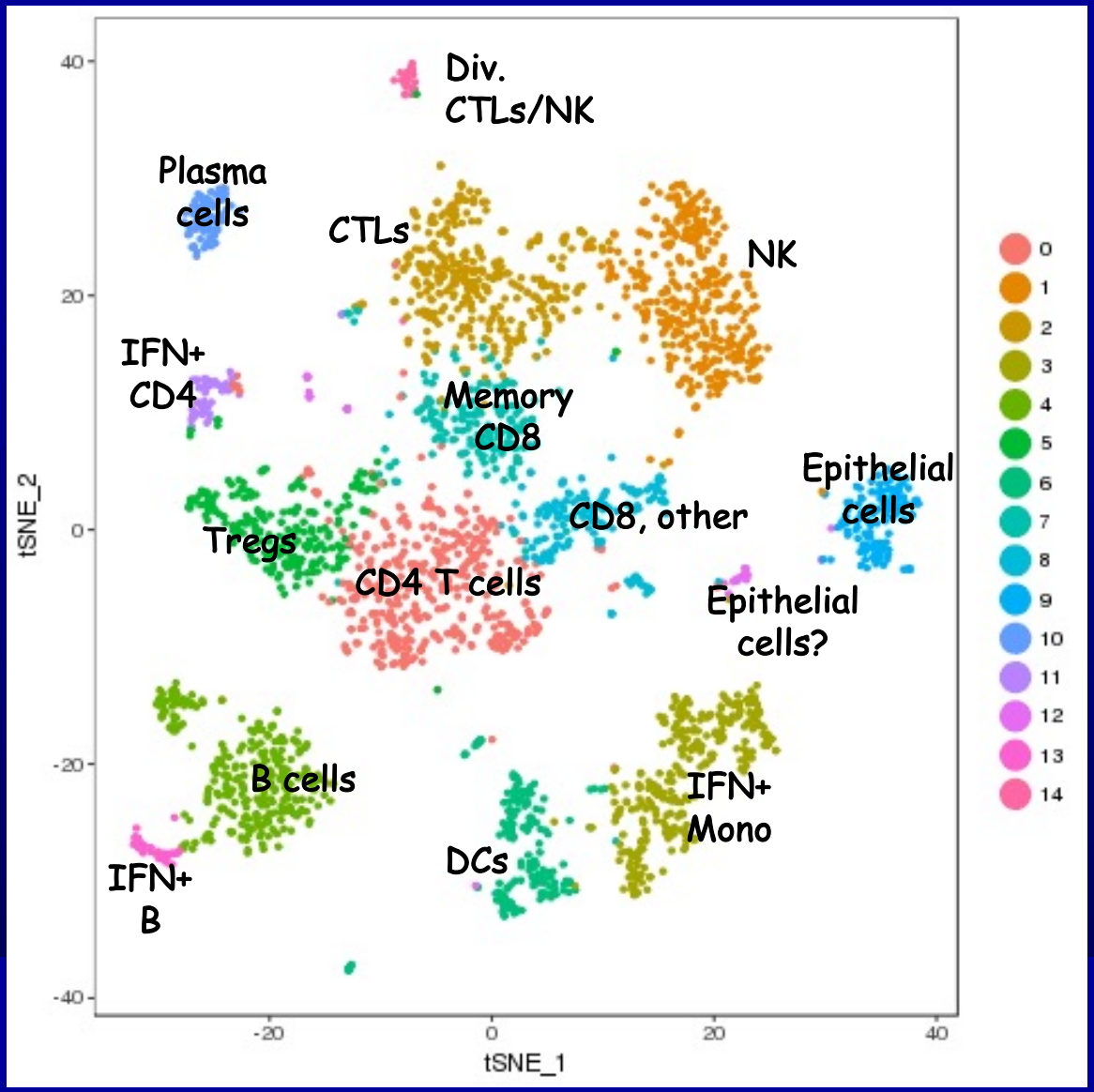


Aims for AMP

Identify molecular + cellular features that define distinct subsets of nephritis

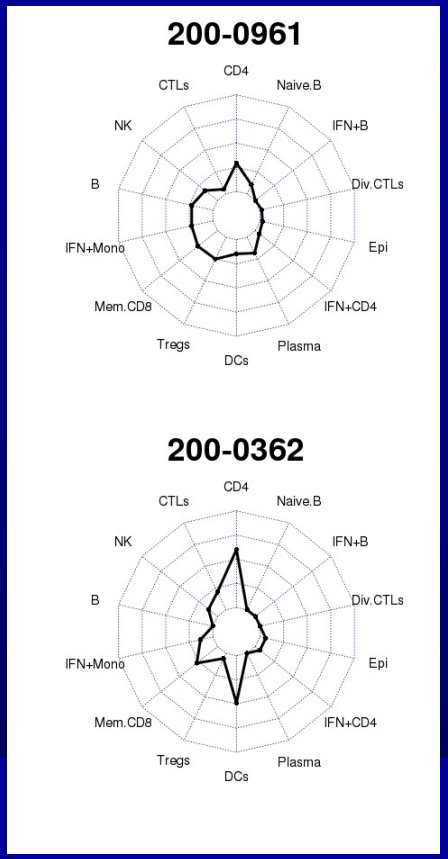


Many different kinds of cells in the lupus kidney

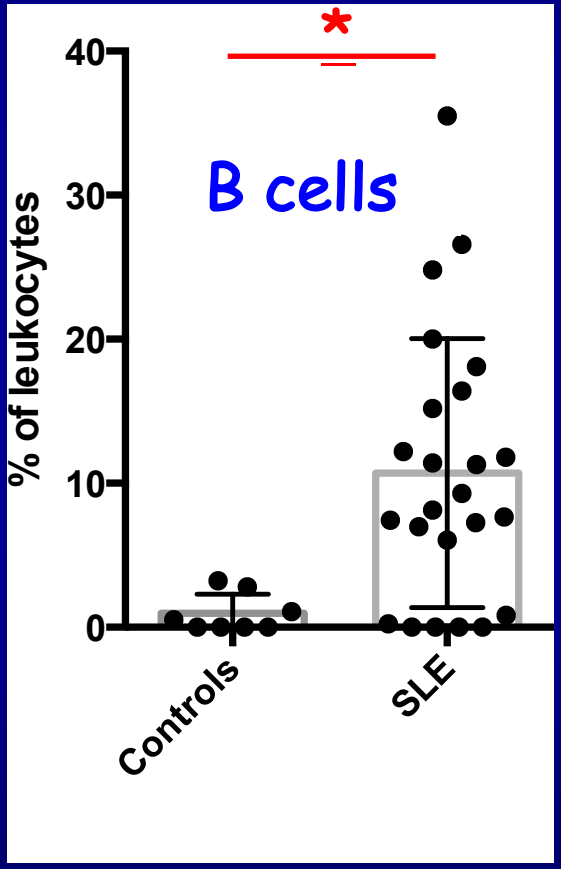


Patients vary:

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

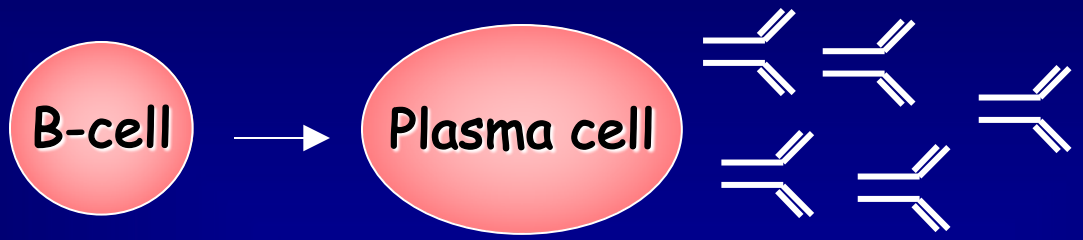


Dominant cells may allow precision medicine



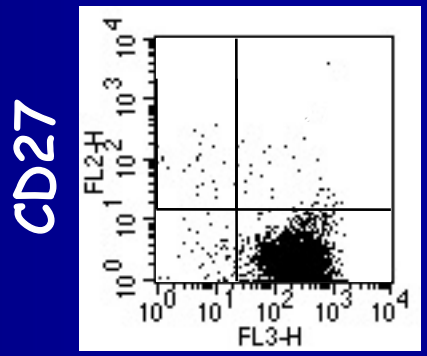
Arazi et al. for the AMP; Nature Immunology 2019

B cells behaving badly

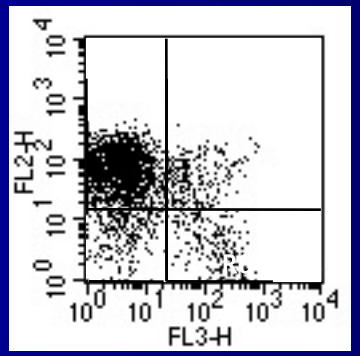


(Auto)-antibody production

SLE Controlled



SLE Active



Protective B cell functions

Bad B cell functions

Anolik et al. AR 2007
Palanichamy et al. JI 2010

Other clinical trial data from ACR

- Iberdomide – Potential Drug for Lupus and Cancer- from LuCIN Network- positive Phase 2 data
- Phase 2 Biogen investigational drug BIIB059 that inhibits production of interferon by targeting pDCs
- Phase 2 of Baricitinib Improved Disease Activity- small molecule JAK inhibitor
- BMS-986256 inhibits another part of the immune system – Toll-like Receptors 7 and 8- early mouse data. Going into lupus patient trials.

Concluding points

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


Thank You!