What's New in Lupus

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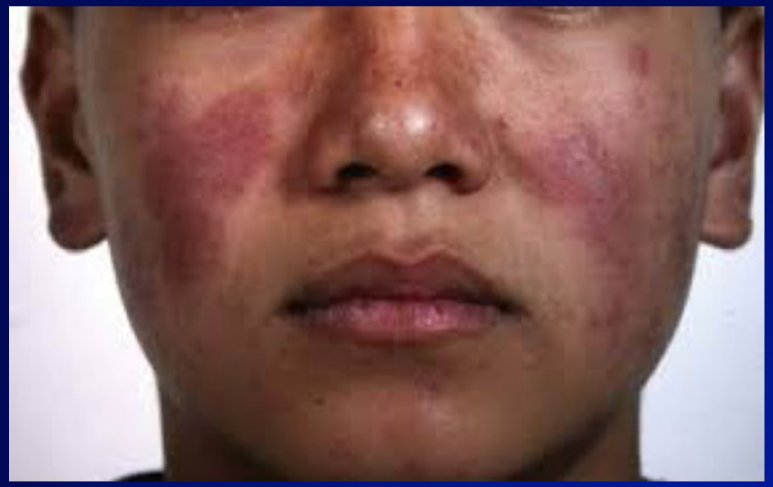
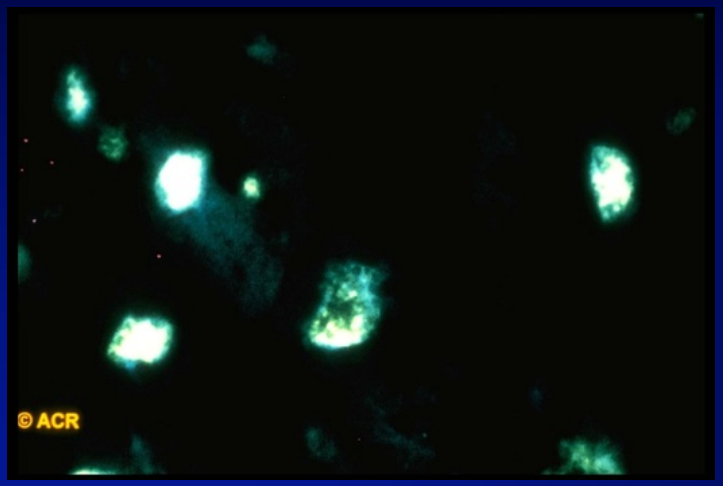
What is lupus? %

- 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.

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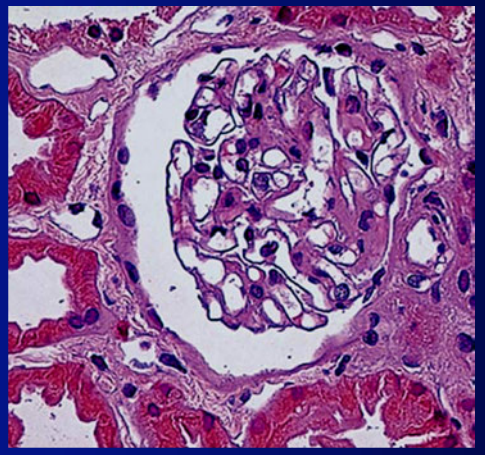
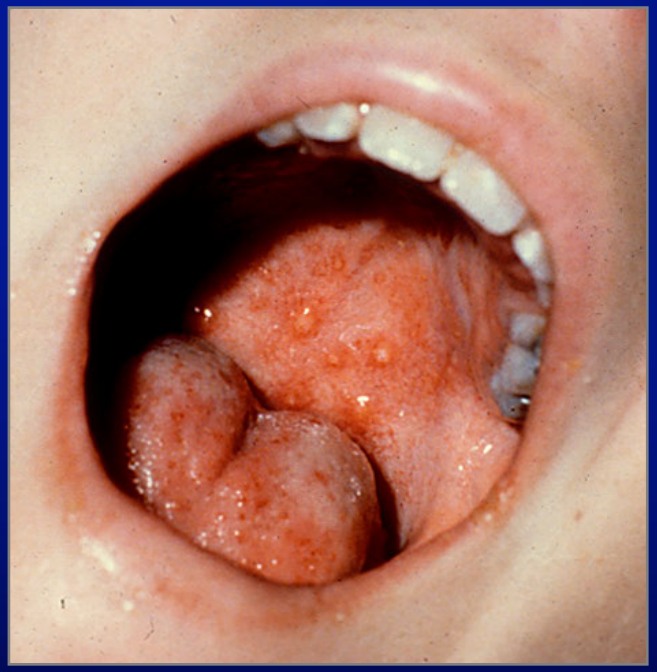
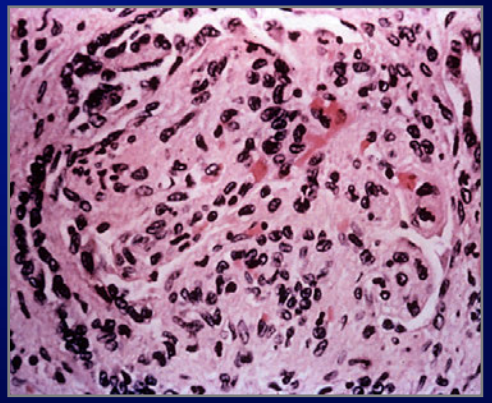




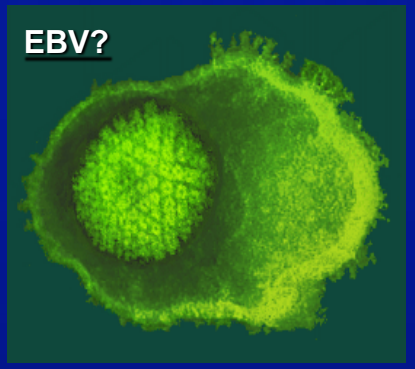


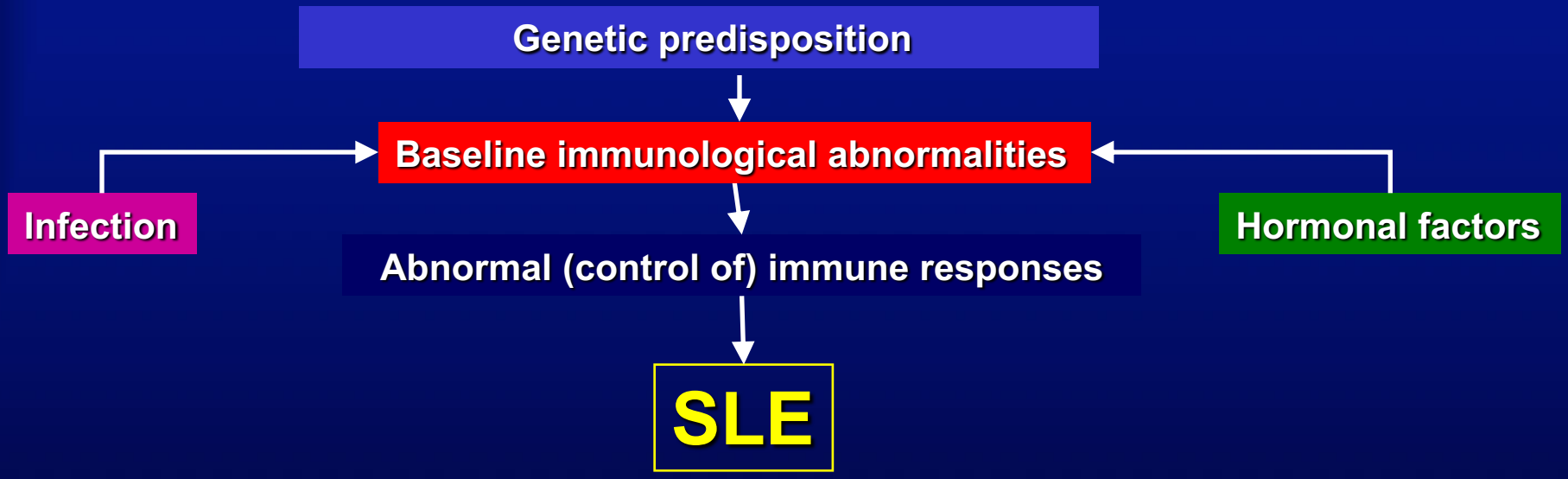
Who develops lupus? $

- 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 - Cause $

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





‘A genetic component’

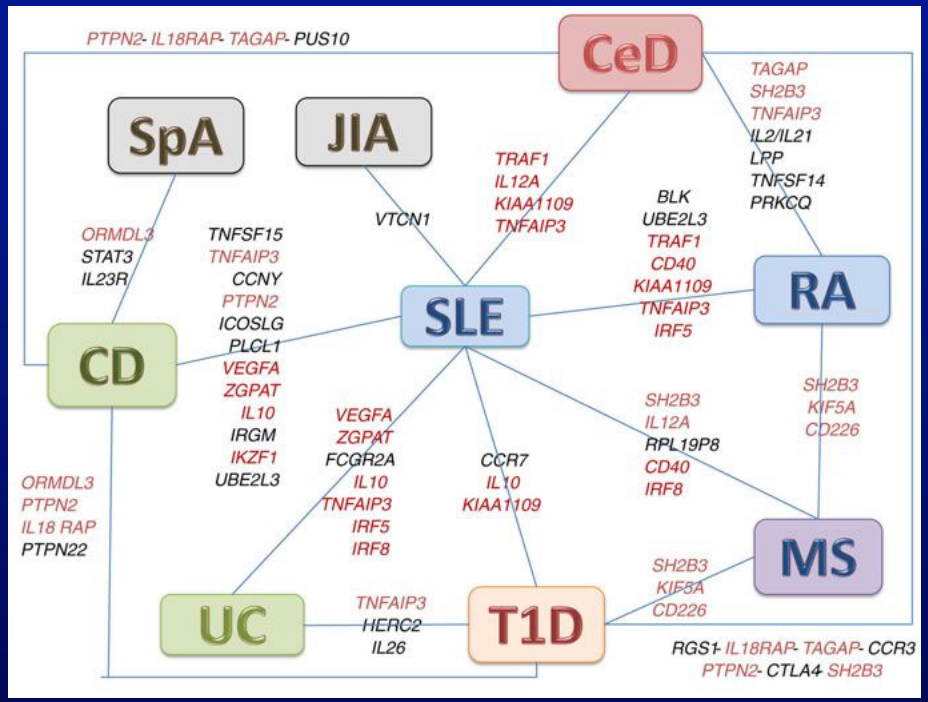
- **Strong genetic component suggested by:**
  - **High concordance in identical twins (15-40%)**
  - **Higher incidence in families (2-10%) (10-fold increased risk in first degree relatives) (instead of 1:400 chance increased to 1:25)**

- **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

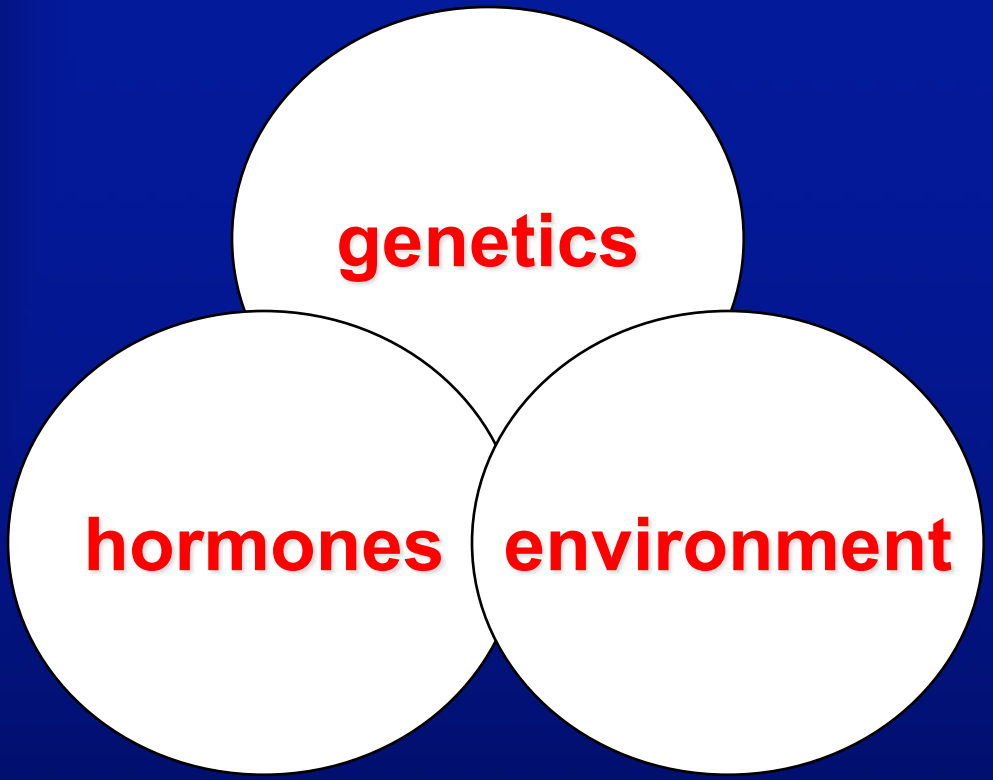
Overlap in genetic risk between autoimmune diseases (

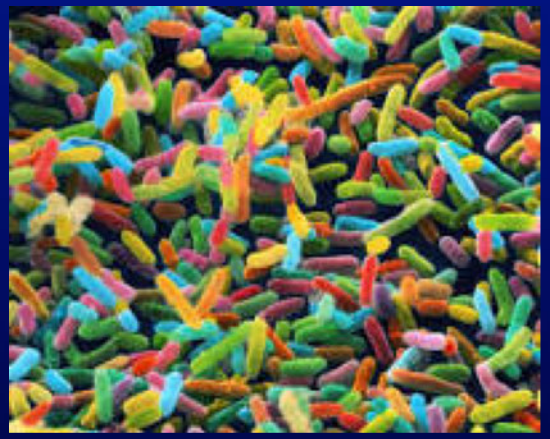
- Surprising degree of overlap in genetic loci among autoimmune diseases



Farh et al. Nature 2015

A lot more than genetics .





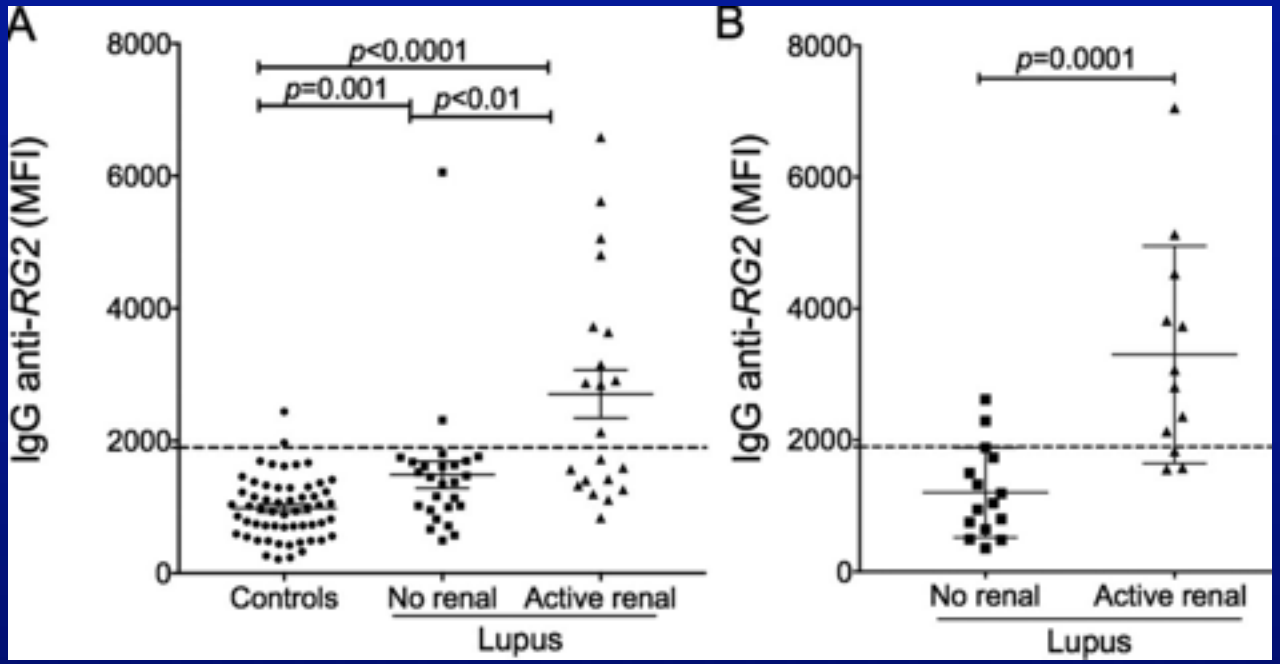
The ‘exposome’ .

Environmental factors

- The ‘microbiome’
- Findings: certain gut bacteria and immune response correlated with disease activity and nephritis
- Implications for clinical practice:
  - Development of bioassays with prognostic values for risk of development of nephritis
  - Paves the way for altering the microbiome

Azzouz et al. Annals of rheumatic disease 2019[1]

Microbiome



Azzouz et al. Annals of rheumatic disease 2019

What's new in treatment? '

Treating inflammation or autoimmunity

- Anti-inflammatory agents
- Antimalarials
- Immunosuppressive/cytotoxic agents

Other

- Prevention: management of cardiovascular risk, immunization, etc.
- Anti-thrombotic therapy
- Dialysis and kidney transplantation

The 'traditional treatment armamentarium'

FDA Approved drugs

- glucocorticoids
- hydroxychloroquine
- low dose ASA

Benlysta

'Off-label' but standard of care

- azathioprine
- cyclophosphamide
- NSAIDs

Immunosuppressives developed for other diseases

- mycophenolate mofetil
- cyclosporin
- tacrolimus

methotrexate
leflunomide
fludarabine

Treat to target '

- Defined a lupus low disease activity state (LLDAS)- includes “no activity in major organ systems” and “prednisone use of less than 7.5mg a day”

- Patients who reach LLDAS do better:
  - 78% of the patients (n=1700) could reach LLDAS goals at least once
  - Patients who reached the LLDAS targets 50% of the time had fewer disease flares and were less likely to have further damage to their kidneys or other organs.

Lancet Rheum 2019 '

What's new in treatment? '

- **WHY DO WE NEED NEW TREATMENTS? '**

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

What's new in treatment? '

- **HOW DO WE FIND THE RIGHT TREATMENTS:**

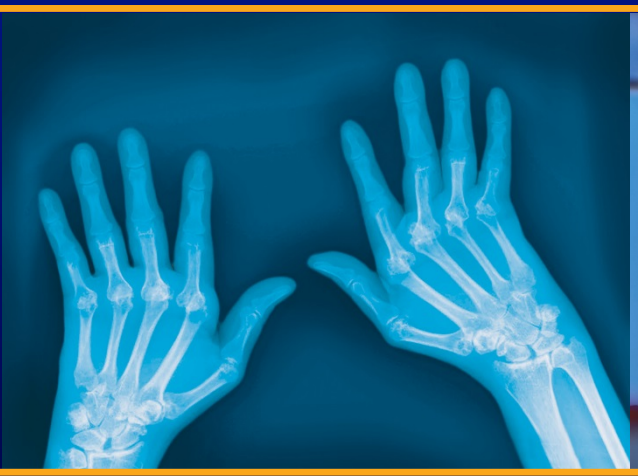
The more that is known about clinical outcomes and immune abnormalities associated with lupus, the better equipped we are to fight the disease!

If we have a good target and drug, we need to test it in clinical trials

Identifying new treatment targets and biomarkers *

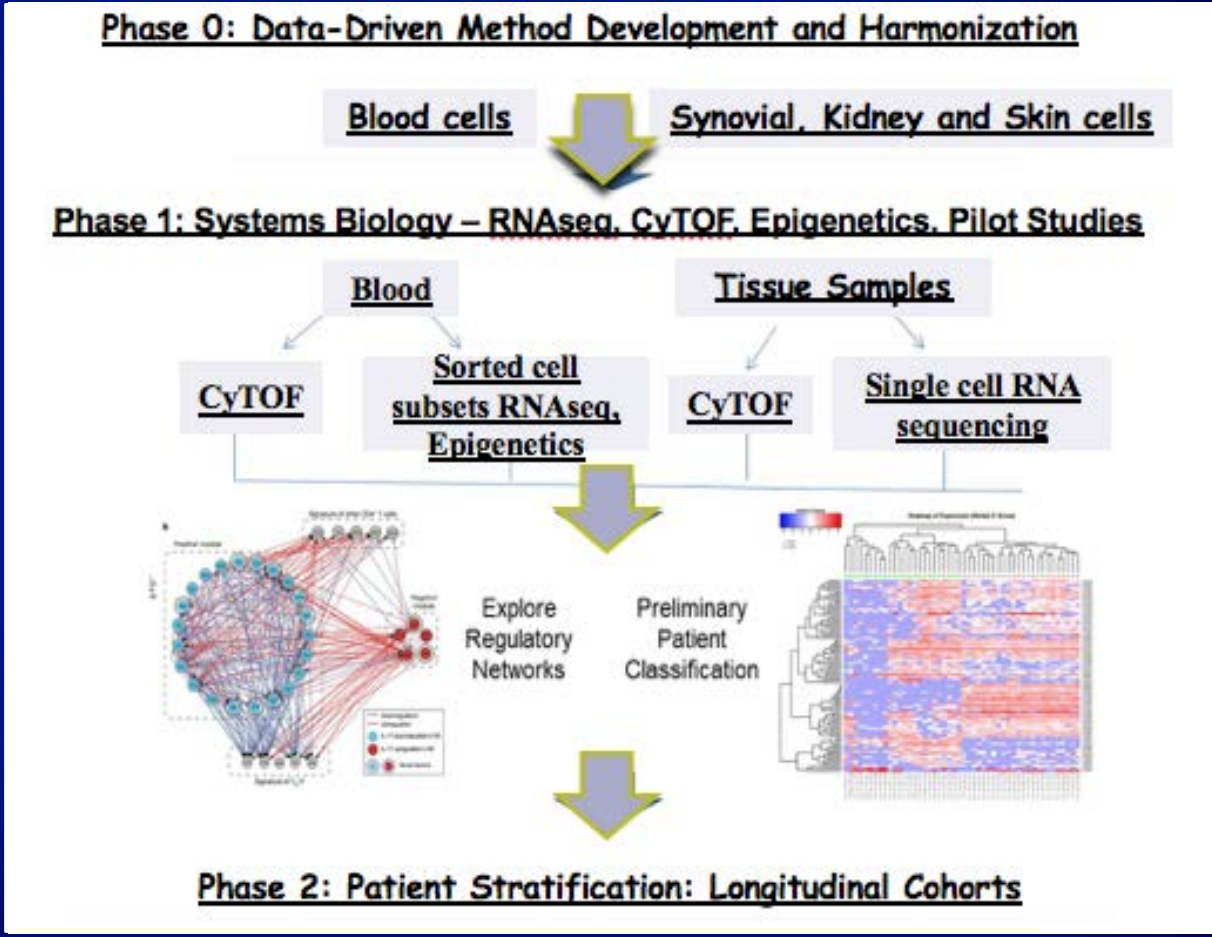
Accelerating Medicines Partnership (AMP) Initiative *

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 ,

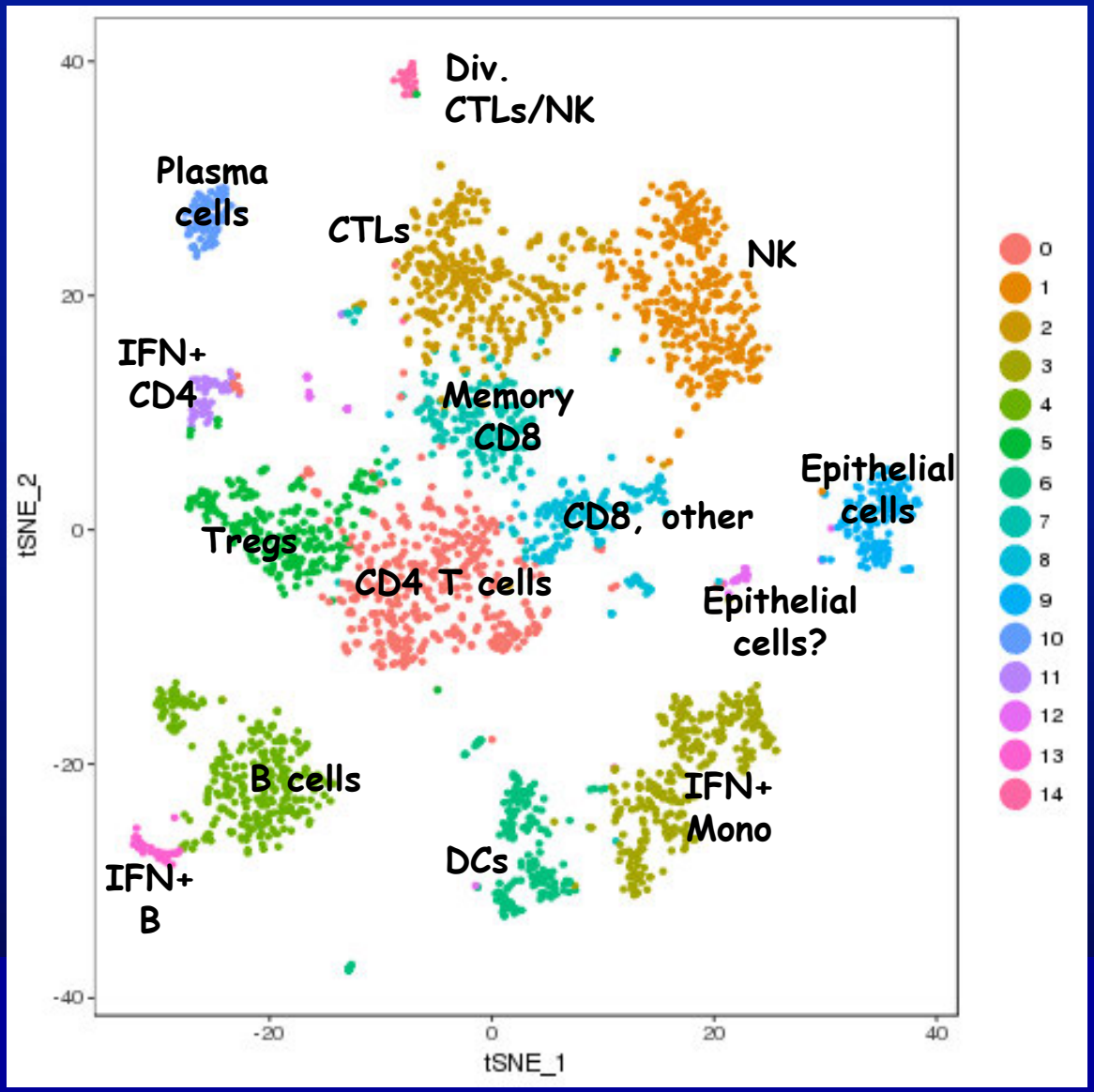


Getting towards precision medicine '

- Molecular and cellular stratification may improve outcomes in SLE and help identify new treatment targets



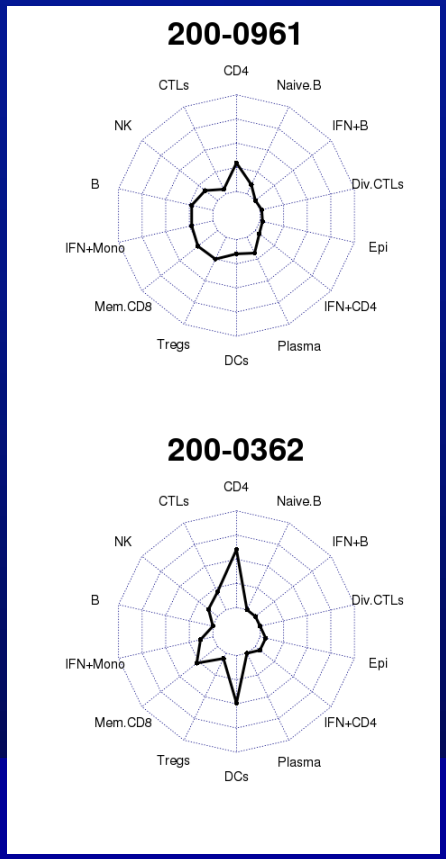
Many different kinds of cells in the lupus kidney %



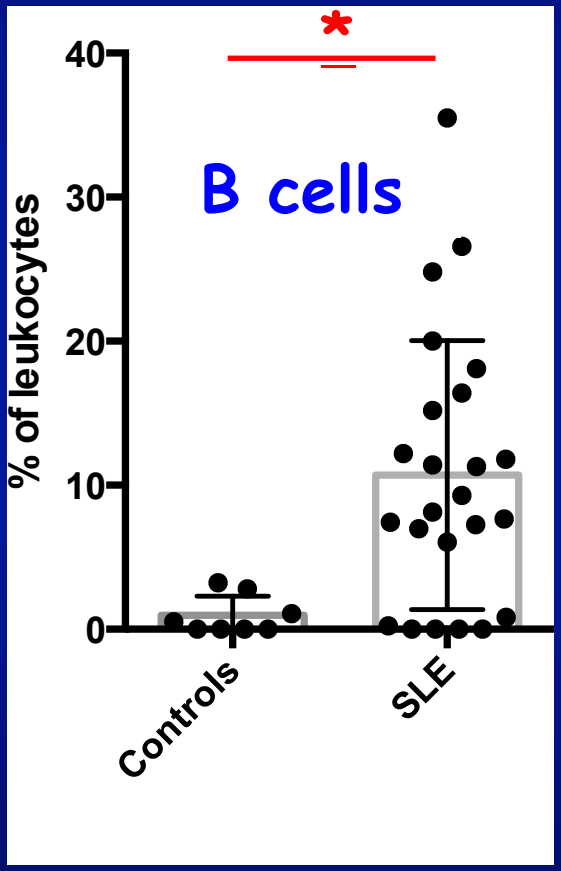
Patients vary:

-types of infiltrating cells

-gene expression across corresponding clusters



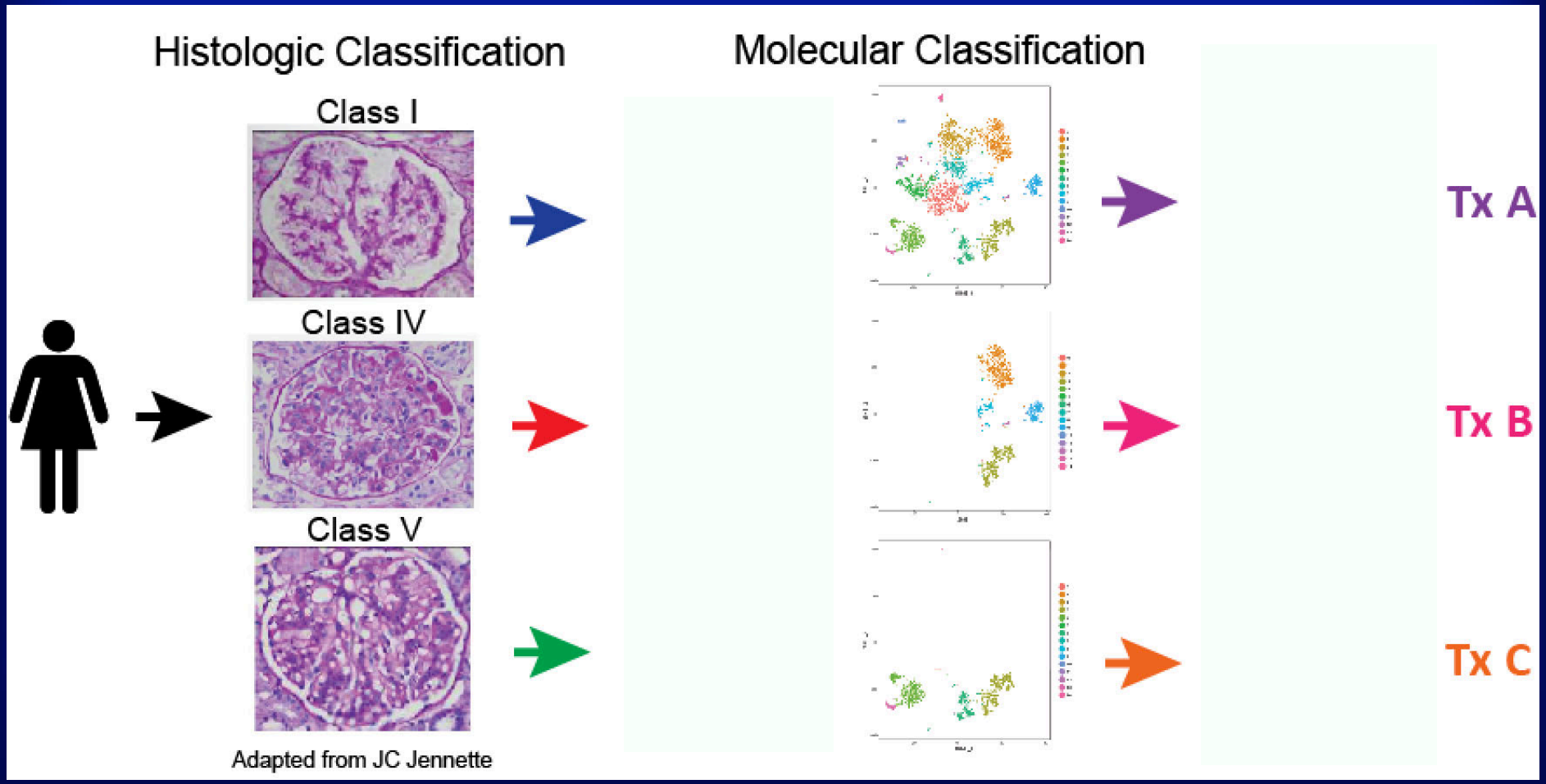
Dominant cells may allow precision medicine (



Arazi et al. for the AMP; Nature Immunology 2019 (

Aims for Phase 2

Identify molecular + cellular features that define distinct subsets of nephritis



What's new in treatment? $

The importance of clinical trials

- We need to know what works
- We need better medications for lupus
- We need FDA approval
- We need to get insurance companies to pay for medications

Steps for drug approval &

- Pre-clinical studies – Non-Human
- Phase I studies – 1st time in humans <100 people *
  - *What are the side effects and what dose should be given?
- Phase II studies – 100+ people
  - Does the drug work and are there other side effects?
- Phase III studies – 1000+ people
  - *Does the drug work and is it safe long term?

Latest clinical trial results &

- B cells: #
  - #Phase 2 NOBILITY trial of a new B cell depleting therapy (anti-CD20 obinutuzumab) met endpoints
  - #Belimumab: SQ use approved, trial in black SLE patients (EMBRACE) did not meet primary endpoints- is there a silver lining?

- #Cytokines:
  - #Ustekinumab (approved for Ps, PsA, Crohn's) Phase 2 trial: 1 yr improvement in disease activity drug 62%> placebo 33%. Phase 3 underway.
  - #Blocking interferon- Phase 3 TULIP 2 study meets endpoints (anifrolumab)

- Other: Phase 2 barcitinib #

Currently enrolling trials at UR)

- %Cell based therapies
  - %Mesenchymal stem cell transfer
- %Krill oil (omega-3-fatty acids) (through LUCIN: Lupus Clinical Investigators Network; other LUCIN studies include anti-CD38
- %Proteasome inhibitors (approved for myeloma) (Kezar)

Concluding points *

-) Therapy will attempt to target specific pathways in the body
-) Despite failed trials, 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!

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