16th Annual Lupus Education Day

Lupus in the Year 2022

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MEDICINE OF THE HIGHEST ORDER

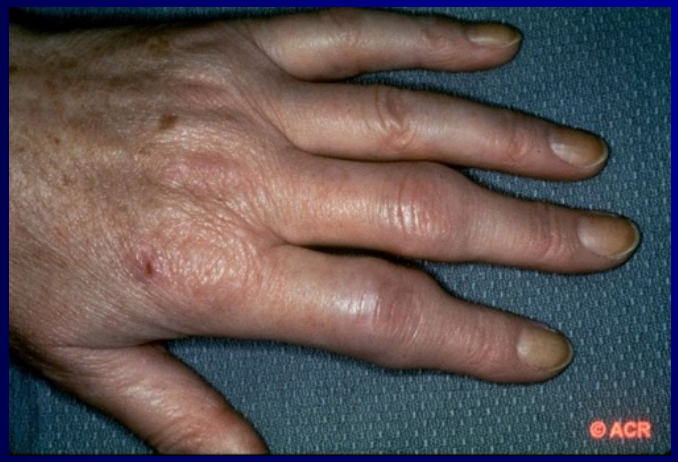
UNIVERSITY of ROCHESTER MEDICAL CENTER

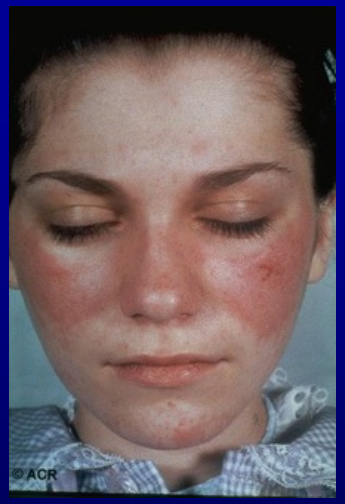
SLE

- 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?

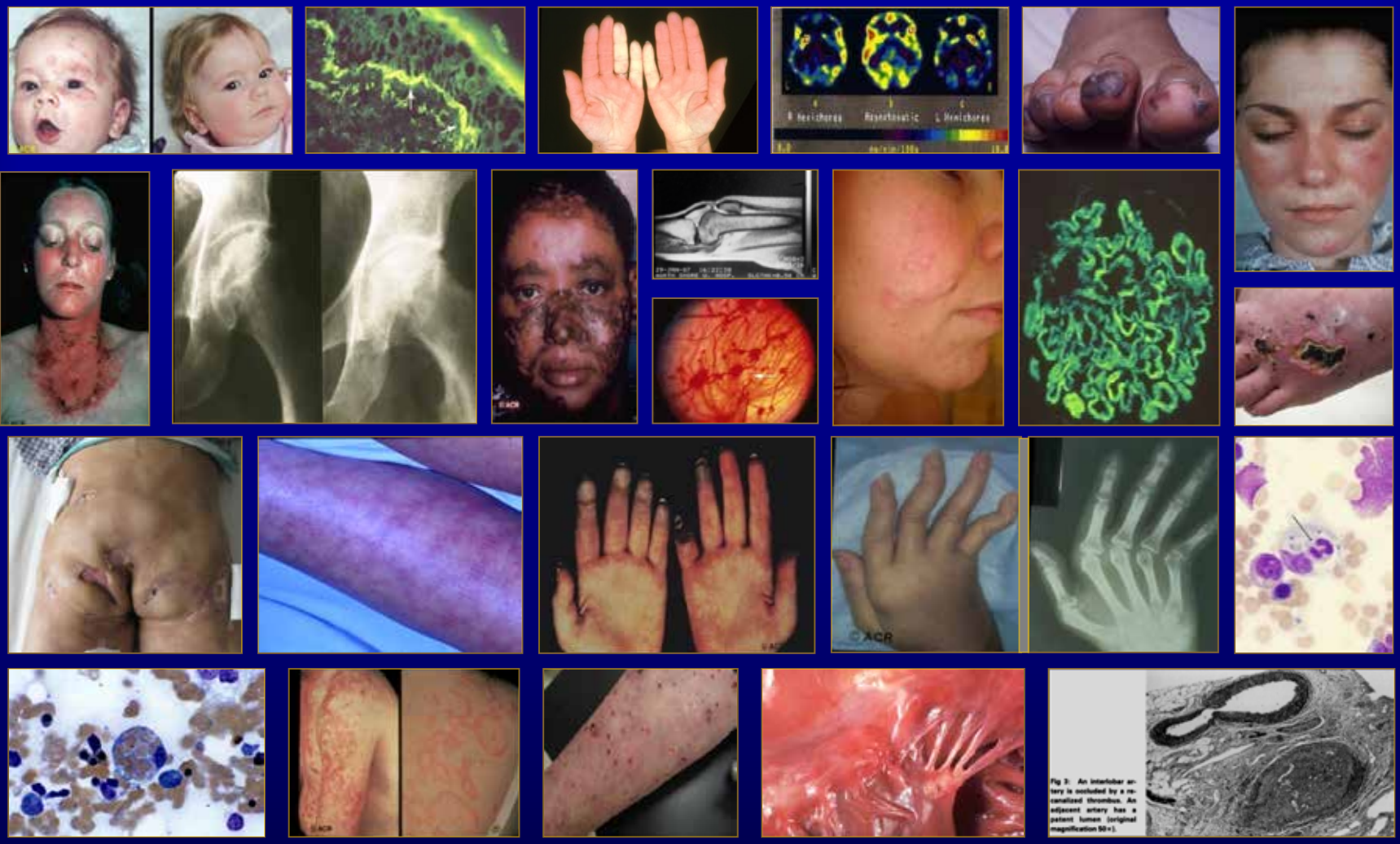
- Painful swollen joints
- Unexplained fever
- Extreme fatigue
- Rashes





- 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:

2011 Benlysta approval

2021 Voclosporin for nephritis

2021 Anifrolumab approval

Do we need new treatments?

ABSOLUTELY!

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

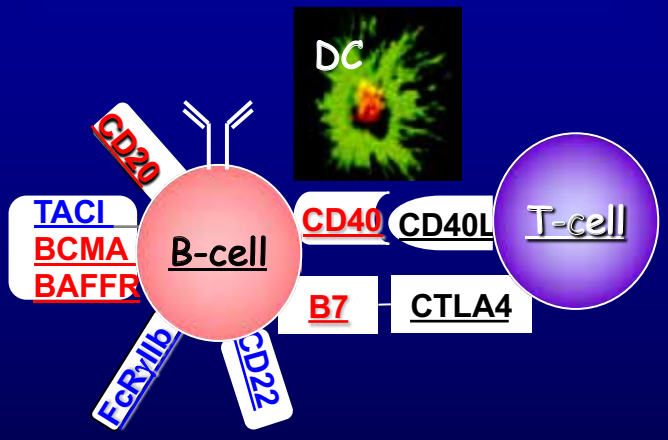
How do we get new treatments? Research

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

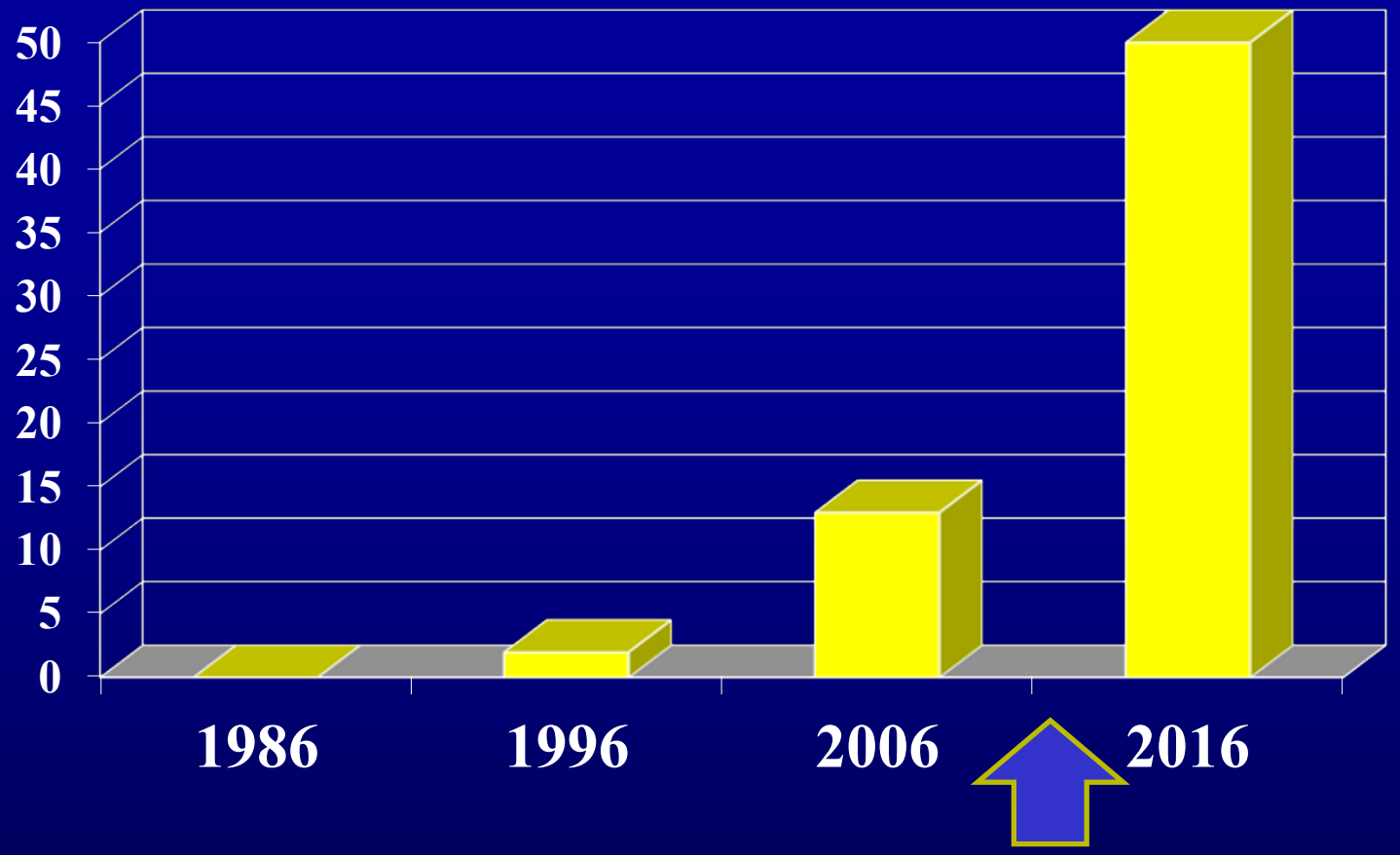
What we're doing at the U of R:

- 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

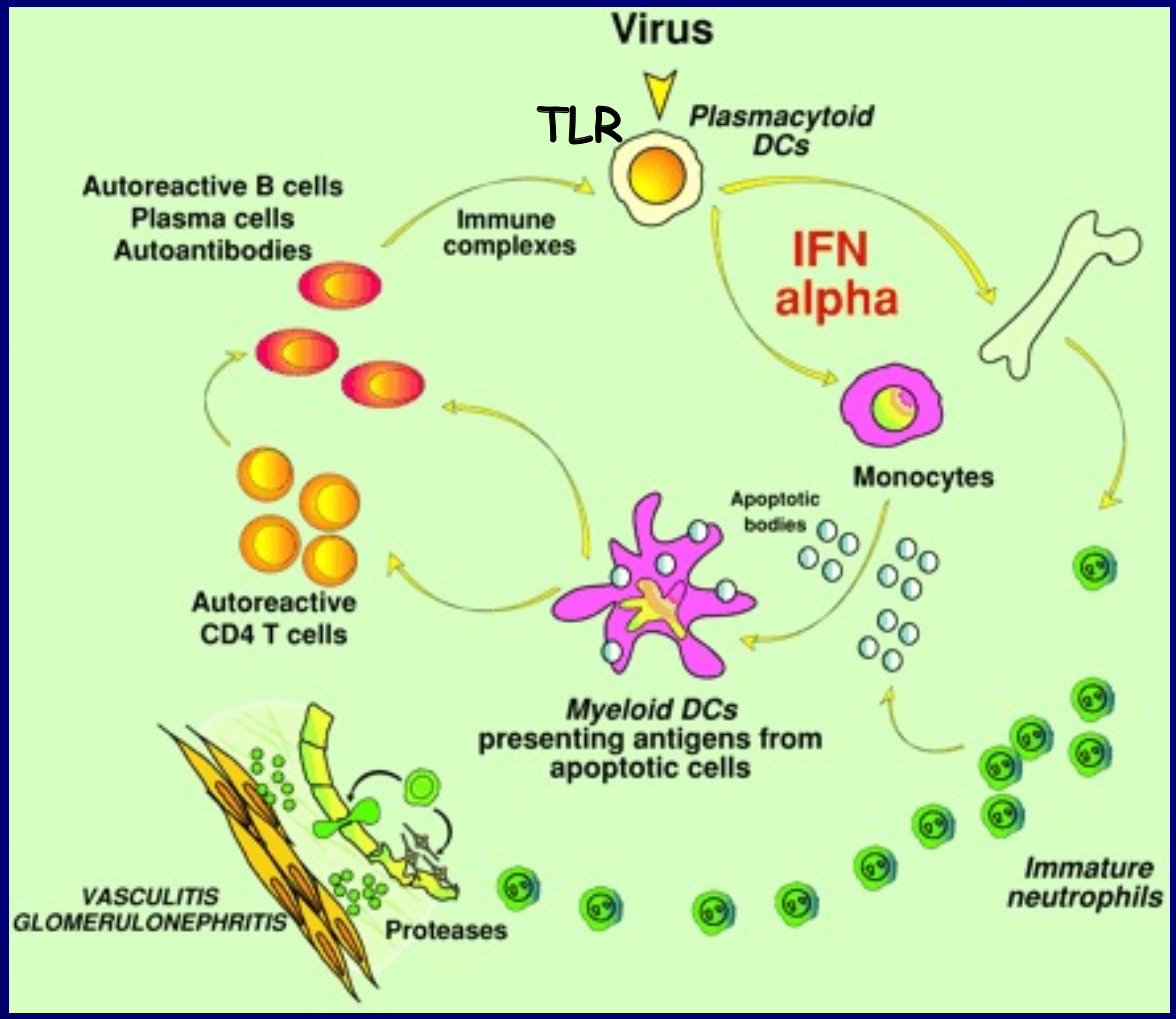
Much research focused on identifying biologic molecules critical to the lupus disease process and strategies to remove or neutralize them: 'targets'



Drugs in Development for SLE



An example of targeted drug development: Blocking Interferon

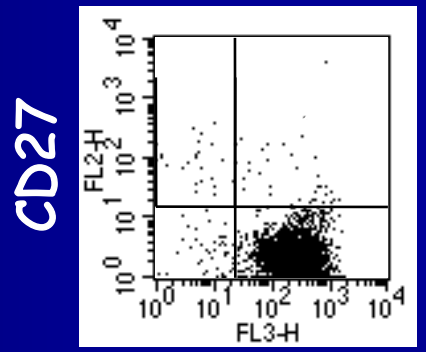


Current Opinion in Rheumatology 2003 Pascual

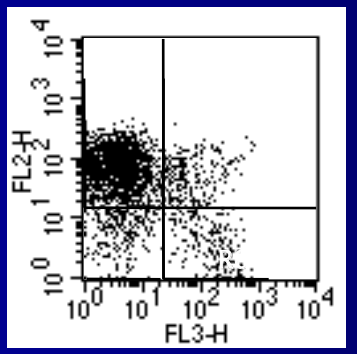
Another example: B cells behaving badly

(Auto)-antibody production

SLE Controlled



SLE Active

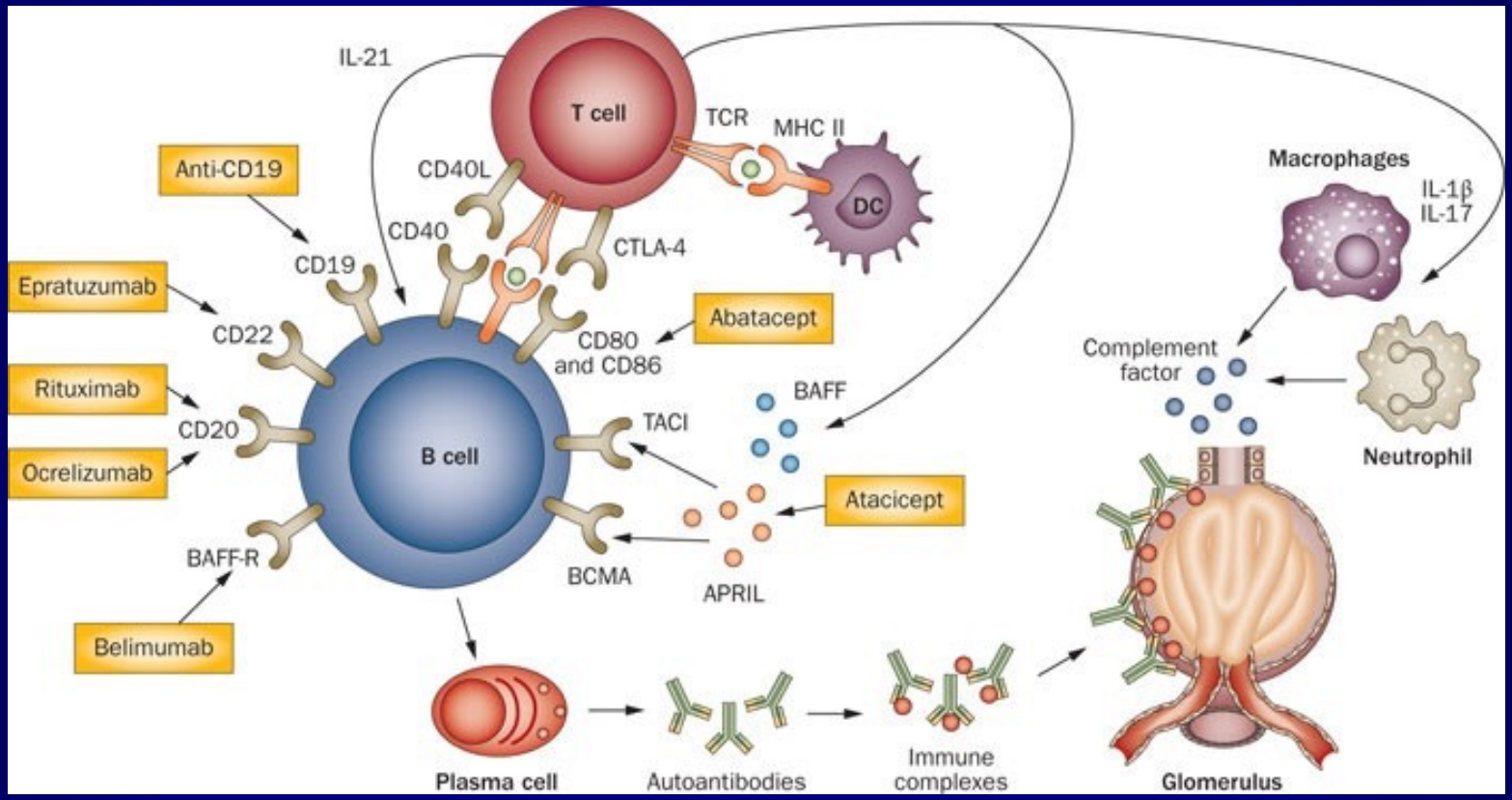


Protective B cell functions

Bad B cell functions

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

Another example : Targeting B cells



Current Opinion in Rheumatology 2003 Pascual

New Targets and Approaches 2022

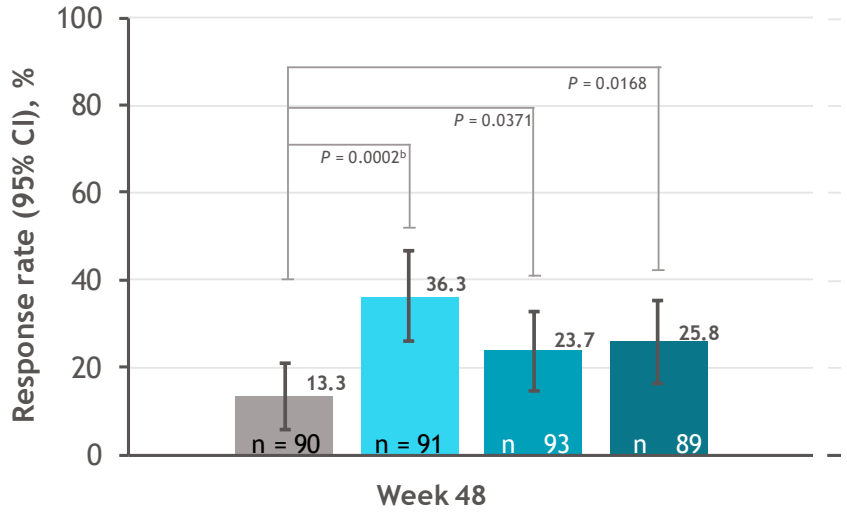
- Deucravacitinib- an oral TYK2 inhibitor
  - Cytokine blocking in a different way
  - Phase 2 study safe and beneficial presented at ACR 2022 plenary
  - We are considering joining the Phase 3 study

- Better B cell targeting
  - CAR-T therapy (NEJM 2022)
  - Chimeric Autoantigen-T Cell Receptor (CATCR)-T Cell Therapies to Selectively Target Autoreactive B Cells
  - Phase 3- Combination of BAFF and APRIL blockade (ACR 2022)

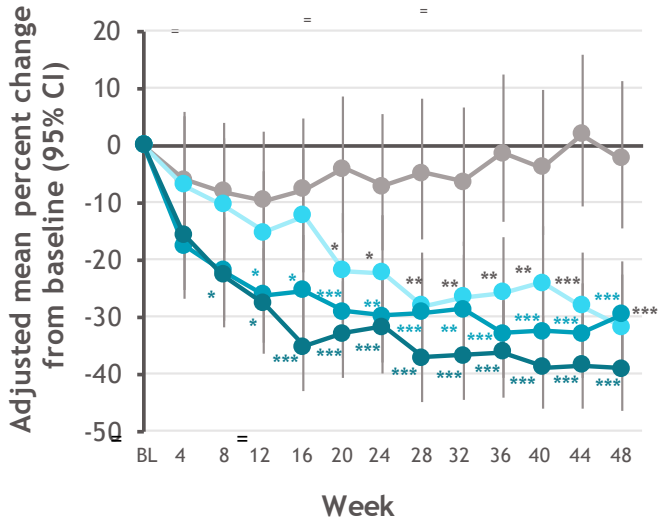
New cytokine blocking approaches: TYK2

Secondary endpoints: LLDAS and CLASI-50 at week 48[a]

LLDAS



Anti-dsDNA Antibodies



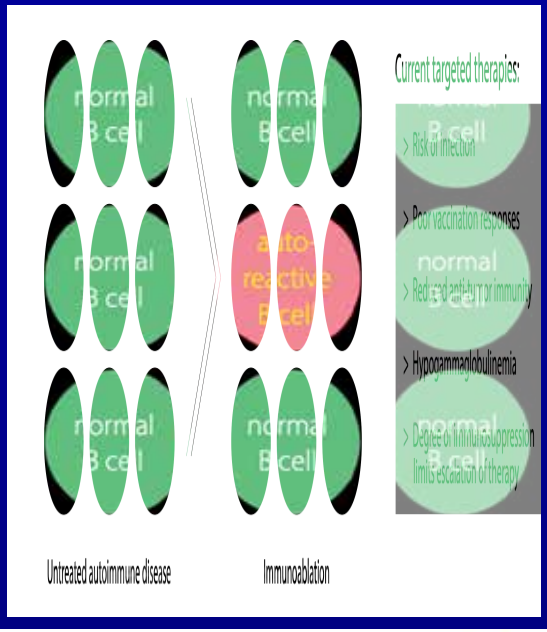
Placebo | Deucravacitinib 3 mg BID | Deucravacitinib 6 mg BID | Deucravacitinib 12 mg QD

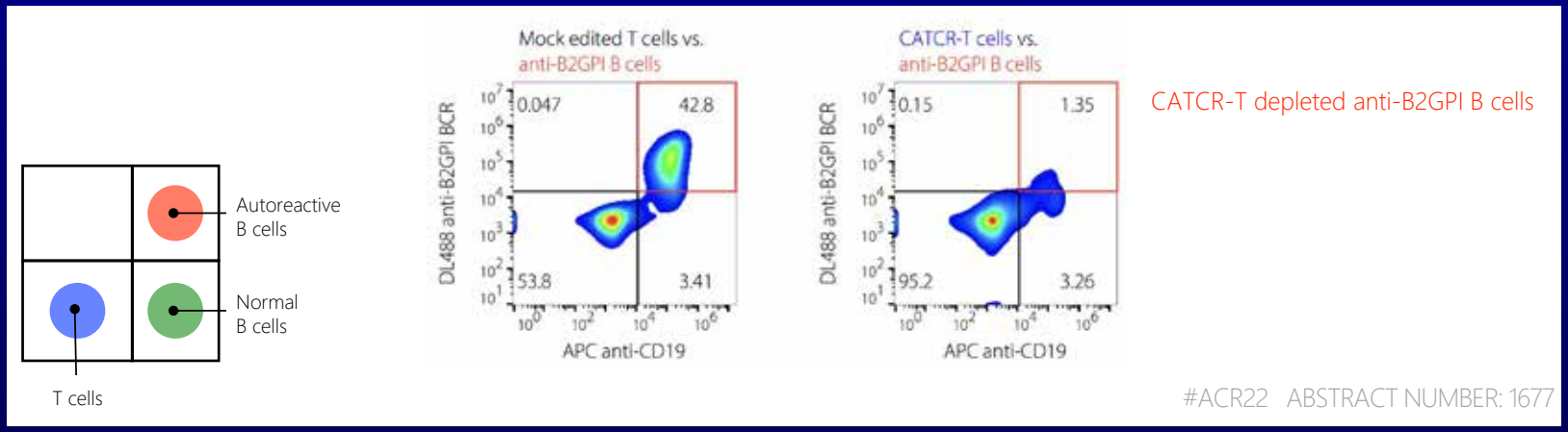
[a]Assessed by nonresponder imputation. All randomized patients assessed; missing data, prohibited medication use, or early discontinuation analyzed as a nonresponse. [b]*P* value was significant vs placebo in multiplicity-controlled prespecified analysis. [c]No *P* values calculated for this exploratory endpoint.
BID, twice daily; CI, confidence interval; CLASI-50, decrease of ≥ 50% from baseline in CLASI-A; CLASI-A, Cutaneous Lupus Erythematosus Disease Area and Severity Index Activity; LLDAS, Lupus Low Disease Activity State; QD, once daily; SD, standard deviation.

ACR 2022 Pike et al

New B cell approaches

- Culture systems
- Not in humans yet





ACR 2022 Konig et al

nature medicine

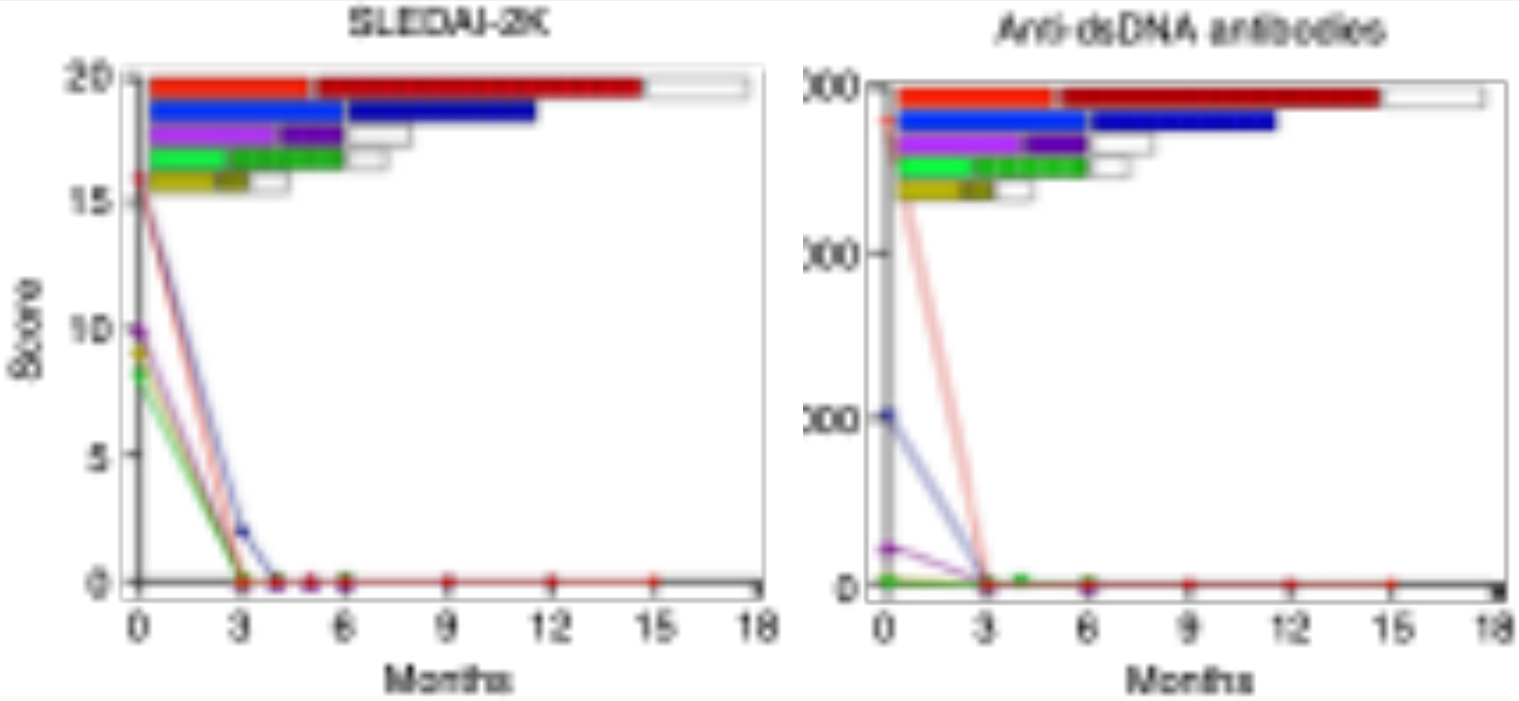
ARTICLES

https://doi.org/10.1038/s41591-022-02017-5

Check for updates

Anti-CD19 CAR T cell therapy for refractory systemic lupus erythematosus

‘Conceptually, a deep depletion of CD19+ B cells and plasmablasts in the tissues could trigger an immune reset in SLE that could allow the cessation of immunosuppressive treatment’.



Mackensen…Schett. Nat Med 2022

Identifying new treatment targets and biomarkers

Accelerating Medicines Partnership (AMP) Initiative

First-of-its-kind partnership and study

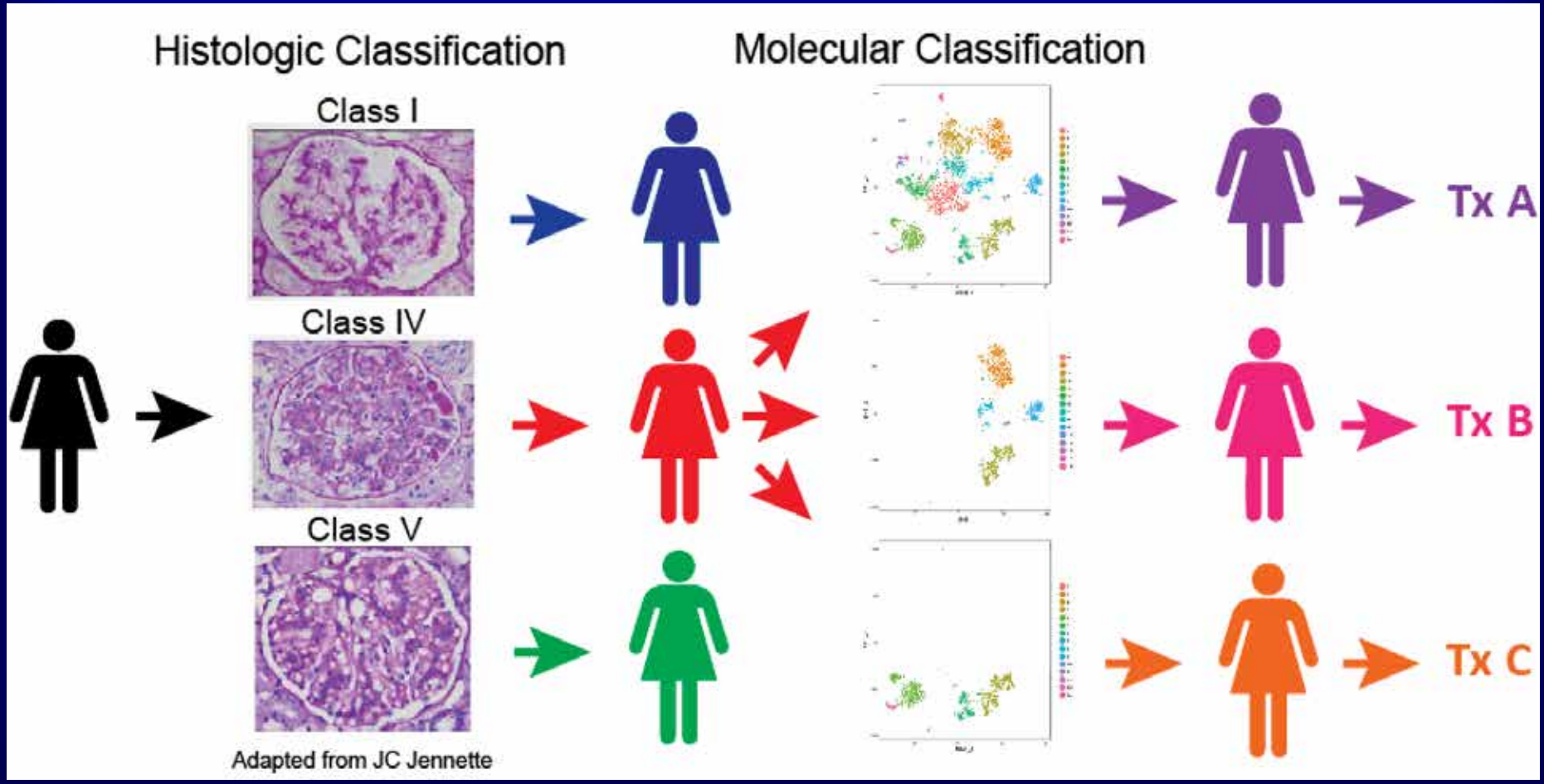
Goal: To evaluate the molecular pathways and relevant drug targets of autoimmune diseases to help develop new therapies

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

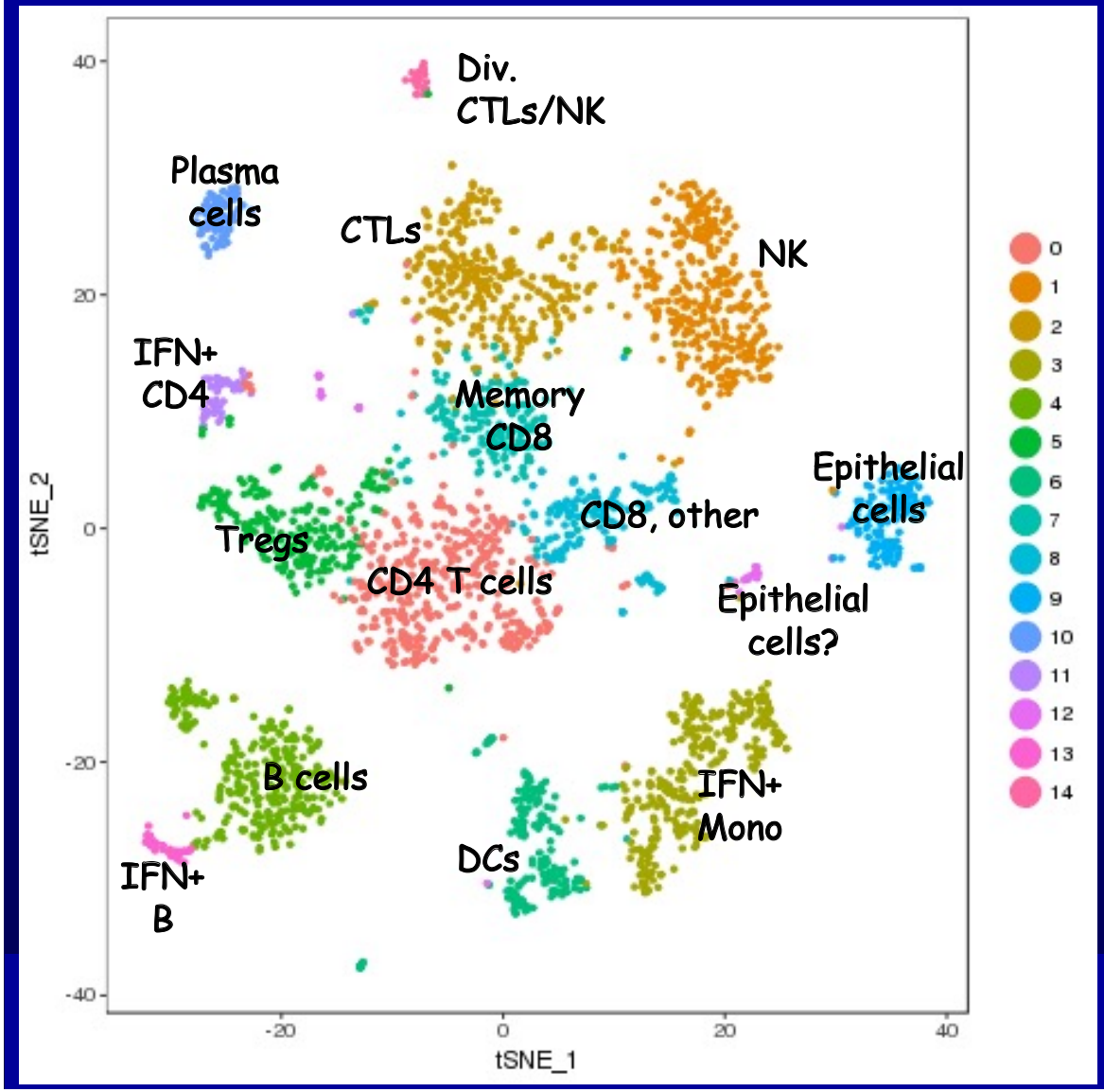


Aims for AMP

Identify molecular + cellular features that define distinct subsets of nephritis

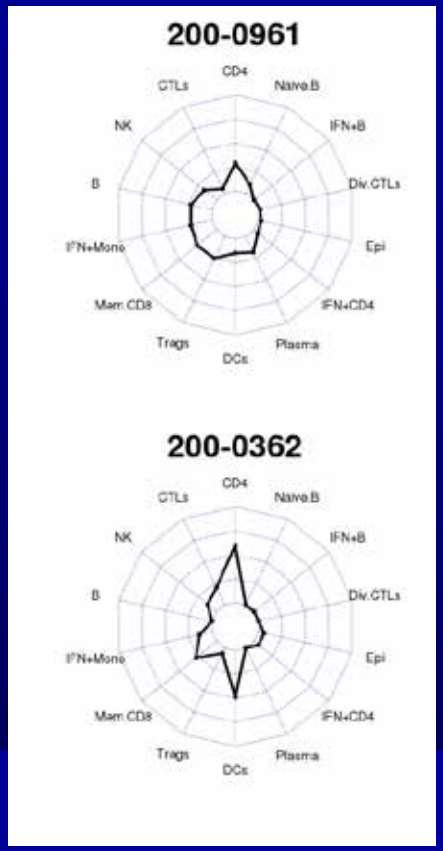


Many different kinds of cells in the lupus kidney

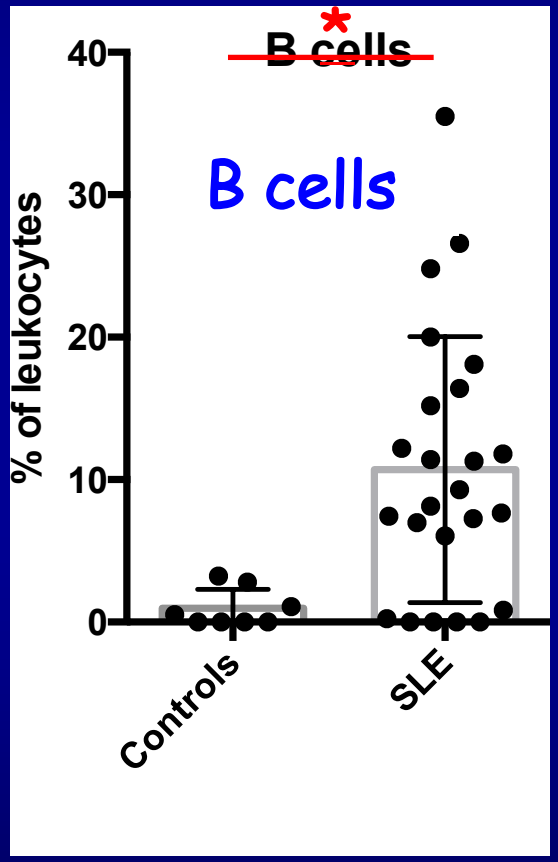


Patients vary:

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



Dominant cells may allow precision medicine



Arazi et al. for the AMP; Nature Immunology 2019

AMP AIM

Synovium

AIM for RA

Jennifer Anolik (Rochester)
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Salivary Gland

STAMP
Sjogren's Team for Accelerating Medicines Partnership

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Alan Baer (JHU)
Darise Farris (OMRF)
Blake Warner (NIDCR)

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: health care 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

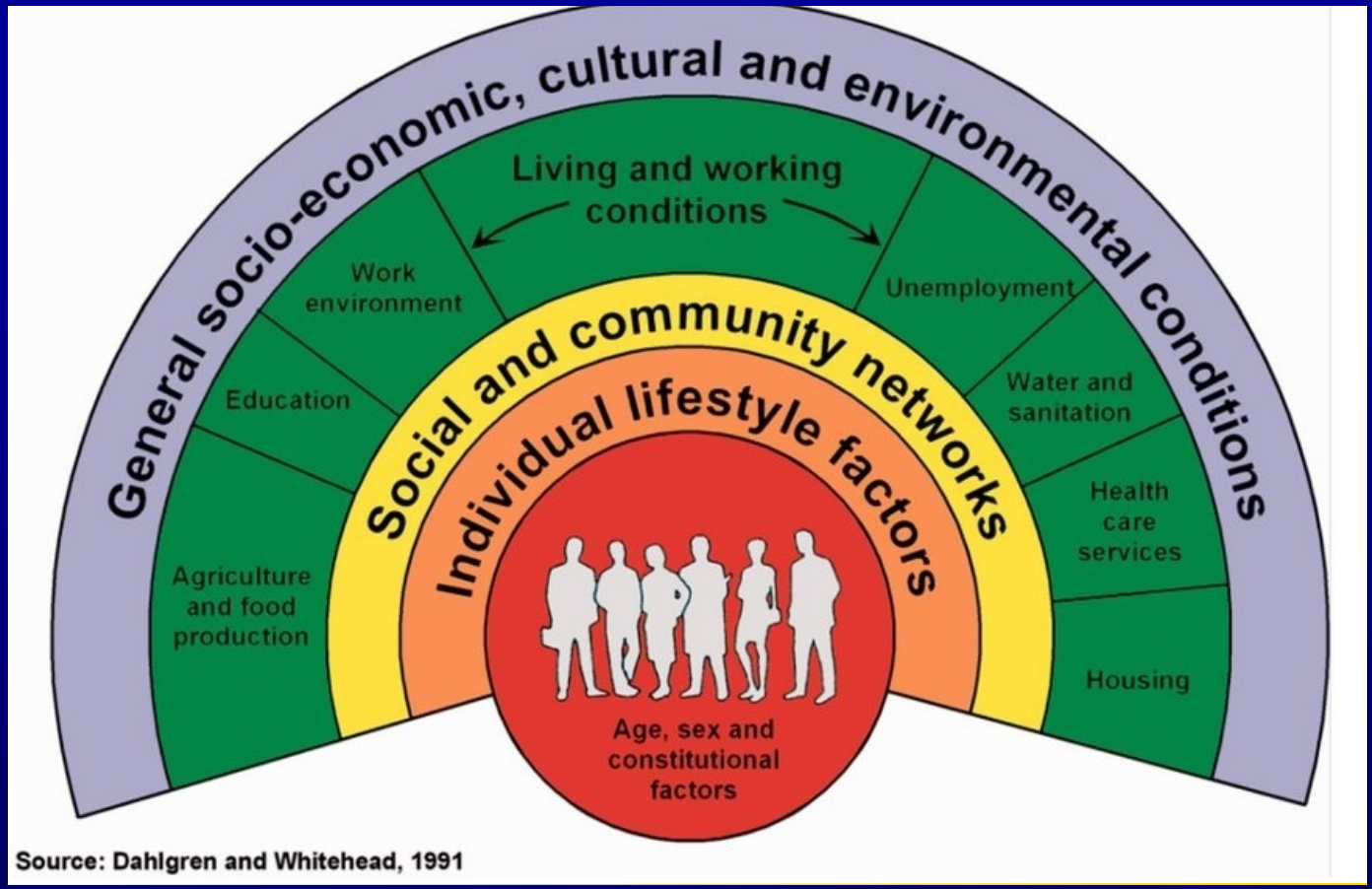
- CONCLUSION:

-Ethnic disparities occur in SLE

-Emerging role of environmental and socioeconomic/ demographic factors

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

Health care disparities



Yen..Singh ACR 2021

Black and Hispanic Americans with Lupus Experienced More Severe COVID-19 Outcomes

523 people (486 female and 37 males) with lupus and COVID-19 were included in the study. Data showed:

- 74.6% of people were not hospitalized
- 13.3% of people were hospitalized with oxygenation
- 8.3% of people were hospitalized without oxygen
- 3.8% of people died

- Black and Hispanic individuals had higher odds of more severe outcomes (2.7 fold) than White individuals
- More co-morbidities

Ugarte-Gil et al. Arthritis Care and Research 2022

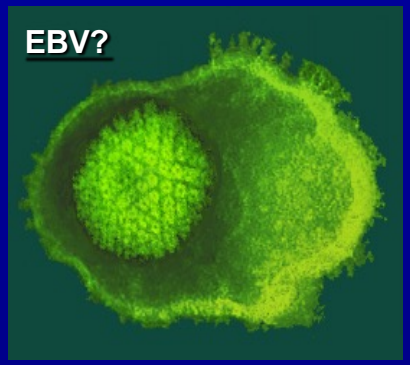
New Office of Health Equity Research at UR

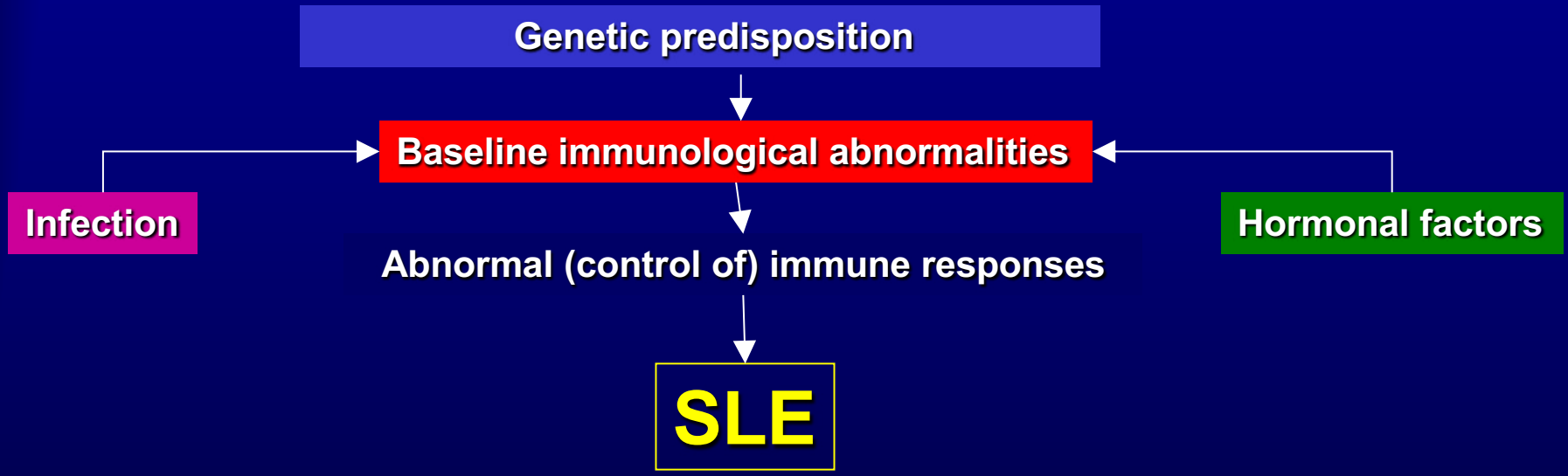
"As a Rochester native, I am overjoyed to be returning home to lead an effort focused on synergizing innovative, transdisciplinary, and impactful research to improve the health of the most vulnerable residents of Rochester and beyond."

EDITH M. WILLIAMS, PH.D.

SLE - Cause

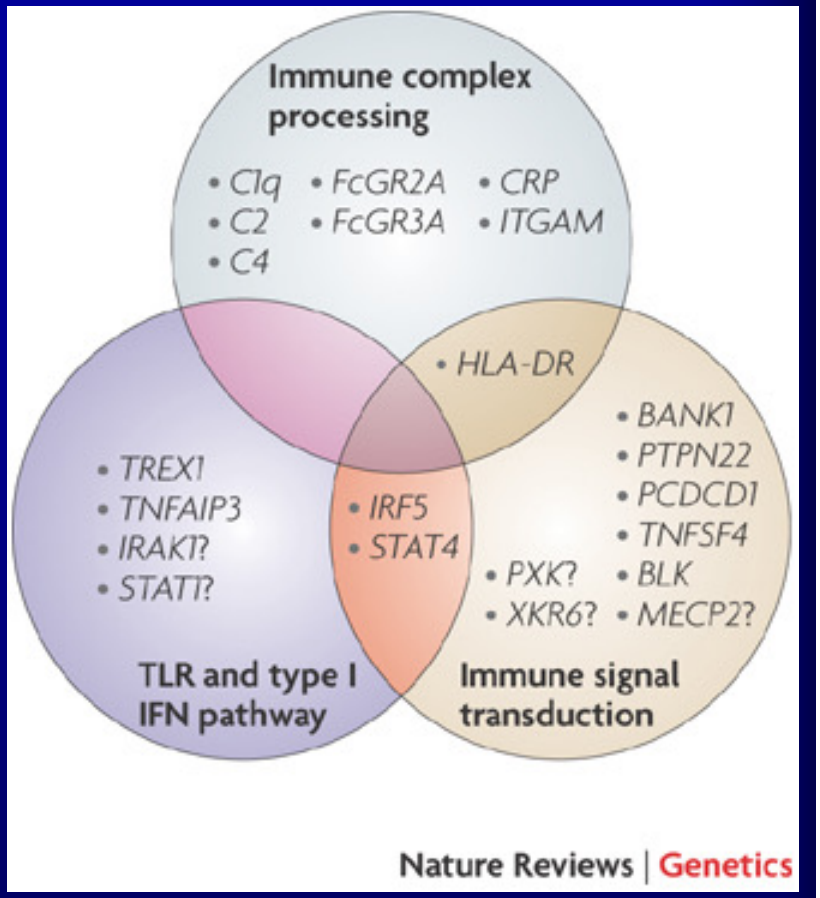
- The etiology of SLE remains unknown
- Yet, SLE is clearly multifactorial:
  - Genetic factors
  - Immunologic factors
  - Hormonal factors
  - Environmental factors





‘A genetic component’

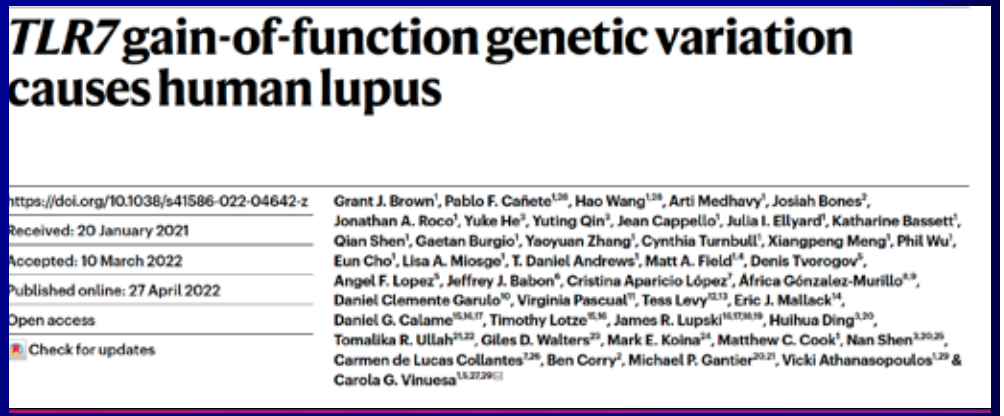
- **Strong genetic component suggested by:**
  - **High concordance in identical twins (15-40%)**
  - **Higher incidence in families (2-10%) (10-fold increased risk in first degree relatives) (instead of 1:400 chance increased to 1:25)**
- **Multiple loci (probably >100) may contribute to SLE:**
  - **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

New in genetic risk

- TLR7 variant causes hyperactive signaling with accumulation of self-reactive B cells, type I IFN signature, severe lupus
- Monogenic SLE rare, but hyperactive TLR7 common in SLE
- Therapies to block TLR7 activity: HCQ, litifilimab (anti-BDCA2)



***TLR7* gain-of-function genetic variation causes human lupus**

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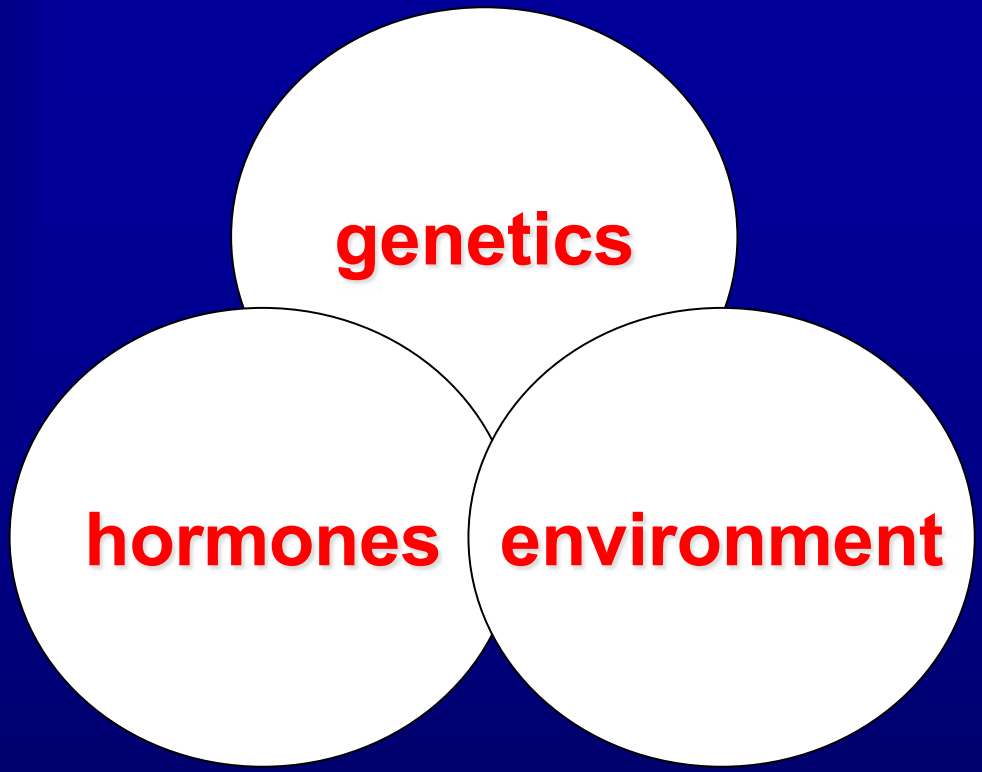
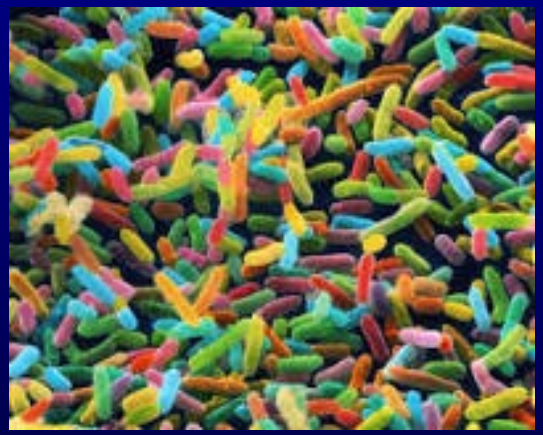
Open access
Check for updates

Grant J. Brown[1], Pablo F. Cañete[1,28], Hao Wang[1,28], Arti Medhavy[1], Josiah Bones[2], Jonathan A. Roco[1], Yuke He[3], Yuting Qin[3], Jean Cappello[1], Julia I. Ellyard[1], Katharine Bassett[1], Qian Shen[1], Gaetan Burgio[1], Yaoyuan Zhang[1], Cynthia Turnbull[1], Xiangpeng Meng[1], Phil Wu[1], Eun Cho[1], Lisa A. Miosge[1], T. Daniel Andrews[1], Matt A. Field[1,4], Denis Tvorogov[5], Angel F. Lopez[5], Jeffrey J. Babon[6], Cristina Aparicio López[7], África Gónzalez-Murillo[8,9], Daniel Clemente Garulo[10], Virginia Pascual[11], Tess Levy[12,13], Eric J. Mallack[14], Daniel G. Calame[15,16,17], Timothy Lotze[15,16], James R. Lupski[16,17,18,19], Huihua Ding[3,20], Tomalika R. Ullah[21,22], Giles D. Walters[23], Mark E. Koina[24], Matthew C. Cook[1], Nan Shen[3,20,25], Carmen de Lucas Collantes[7,26], Ben Corry[2], Michael P. Gantier[20,27], Vicki Athanasopoulos[1,29] & Carola G. Vinuesa[1,5,27,29]

Brown et al. Natture 2022

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

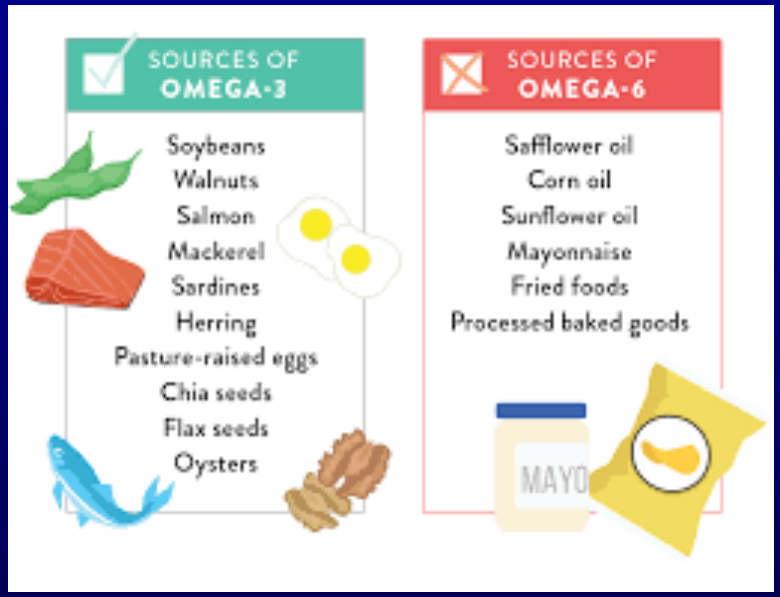
Diet and Microbiome

- Most human immune cells are located in the digestive tract
- Nutrients (vitamins, salt, fatty acids,..) may alter the permeability of the gut and/or exert a direct effect on intestinal immune cells
- Nutrients can affect the microbiome which modifies gut permeability
- Activated immune cells in the gut migrate to the joints and lymphoid tissues

Tajik Nature Comm 2020; Tourkochristou , Frontiers Immunol 2021

What's the data?

- Data on dietary interventions is limited
- Nutrition may complement conventional treatment
- Promote a balanced diet
- Omega-3 supplementation may be suggested (fatty fish)
- Mediterranean diet may be recommended for its benefits on comorbidities



Gwinnutt et al. Ann Rheum Dis 2022

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
- Diet and the microbiome are critical but more research is needed


Thank You!