Lupus and Clinical Trials: an update 2020

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Systemic Lupus Erythematosus

- Autoimmune inflammatory multisystem disease
- 1.5 million cases
- Women>Men- 9:1 ratio (90% cases are women)
- African-Americans > Caucasians (3x)
  - Caucasian women (15-64 years of age): 1/700
  - African-American women (15-64): 1/245
- Onset usually between ages 15 and 45 years, but can occur in childhood or later in life
- Highly variable course and prognosis, ranges from mild to life threatening
- Characterized by flares and remissions
- Associated with characteristic autoantibodies- ANA, dsDNA

Symptoms of lupus

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

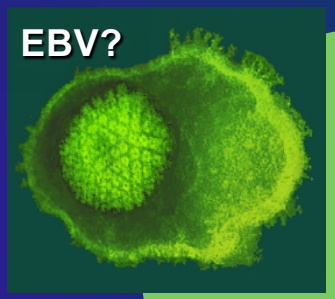
- Painful swollen joints
- Unexplained fever
- Extreme fatigue
- Rashes

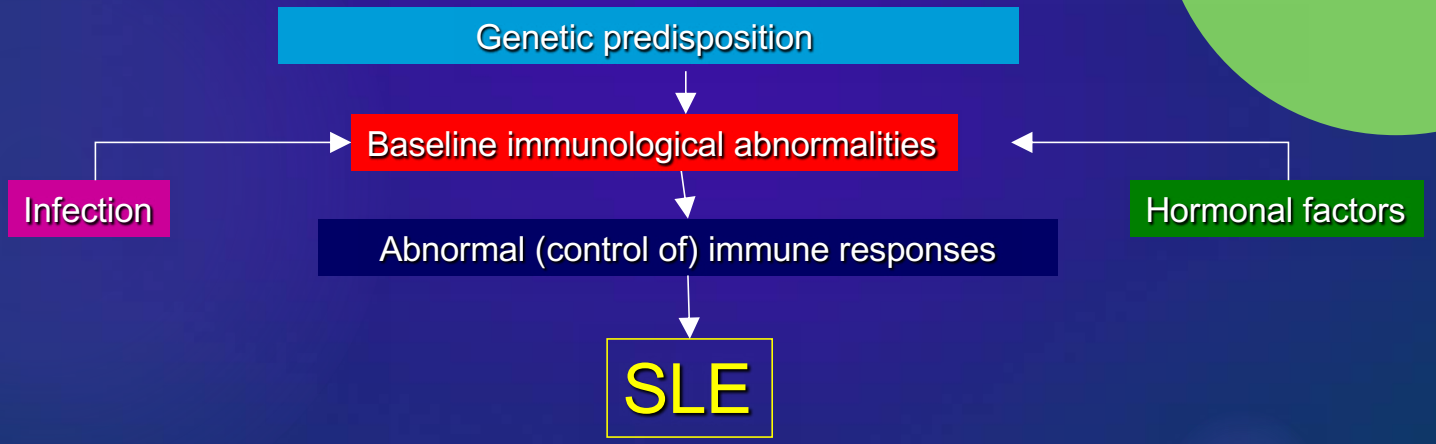
Internal organ involvement in lupus

- Repeated Miscarriages
- Disease in organs
  - Kidney- Lupus Nephritis
  - Heart – Cardiomyopathy, pericarditis, valve disease
  - Lungs- interstitial lung disease, shrinking lung syndrome
  - Brain and nerves – neuropathy, cerebritis

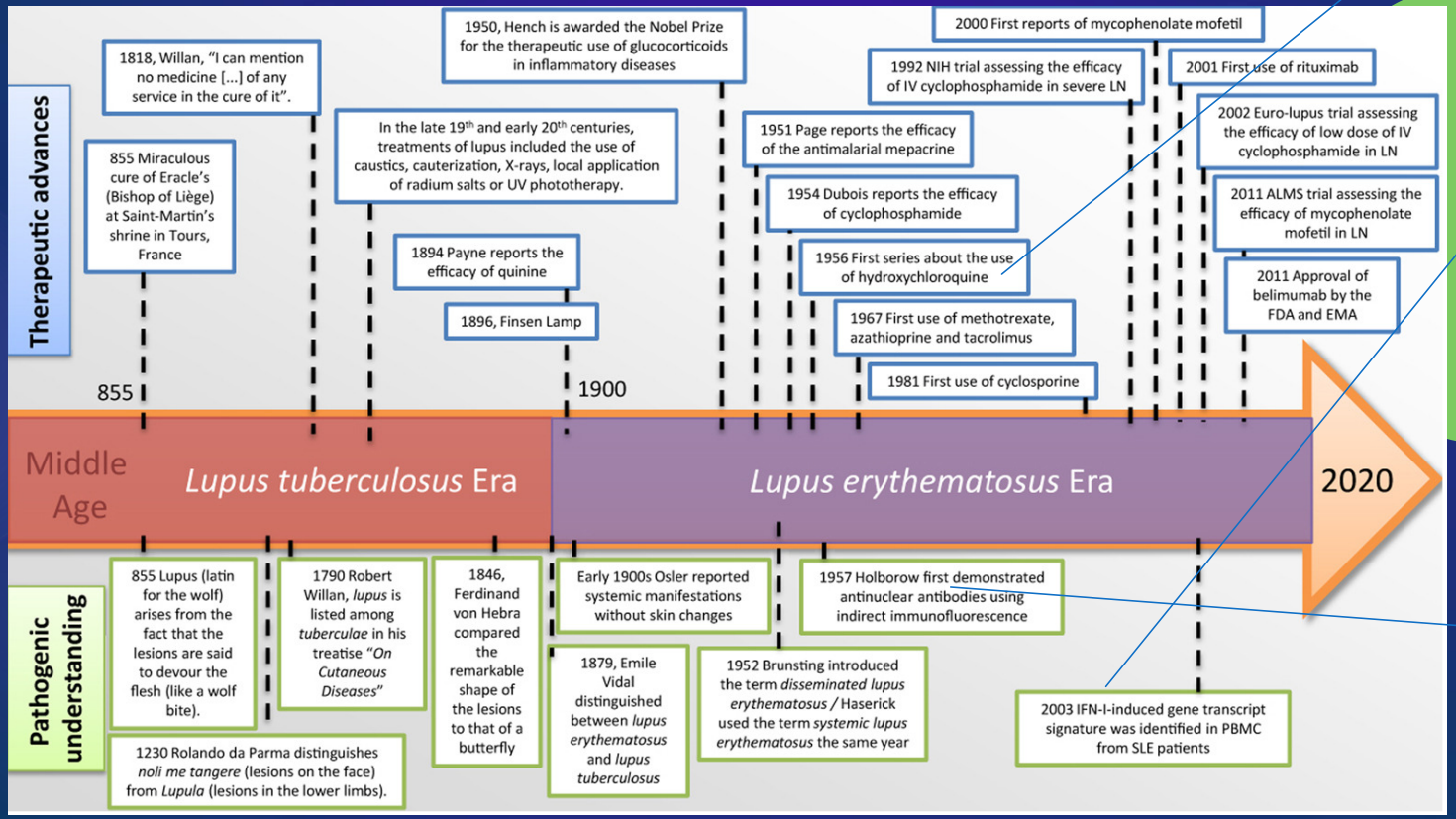
SLE - Cause

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





Lupus History: We've come a long way



1955: Hydroxychloroquine!

2003: Interferon signature

1957: ANA testing

Felten et al. Journ of American Academy of Dermatology May 2020

Current Lupus Treatments

- FDA approved Drugs:
  - Steroids (1950s)
  - Low Dose Aspirin (1948)
  - Hydroxychloroquine (1956)
  - Belimumab (2011)

- Immune suppressive drugs "borrowed" from other diseases but also standard of care
  - Cyclophosphamide
  - Azathioprine
  - Mycophenolate Mofetil
  - Methotrexate
  - Tacrolimus
  - Cyclosporine
- Biologic Drugs:
  - Rituximab
  - Belimumab

Goals of treatment: 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

Unmet needs in Lupus

- The "other" symptoms of lupus
  - Fatigue
  - Concentration difficulties
  - Depression
- Cardiovascular risk
- Refractory disease
- Personalised Medicine: Tailored therapy

We need new treatments in lupus

- Safer and more effective therapies with less side effects
- Replace steroids
- Replace immune-suppressives and chemotherapy with more targeted treatment
- Improve quality of life
- Prevent flares
- Cure!

Biologic Era

- Potential Targets:
  - Type I Interferon
  - Jak Pathway
  - BTK
  - Proteosome inhibitor

Rituximab

Anifrolumab

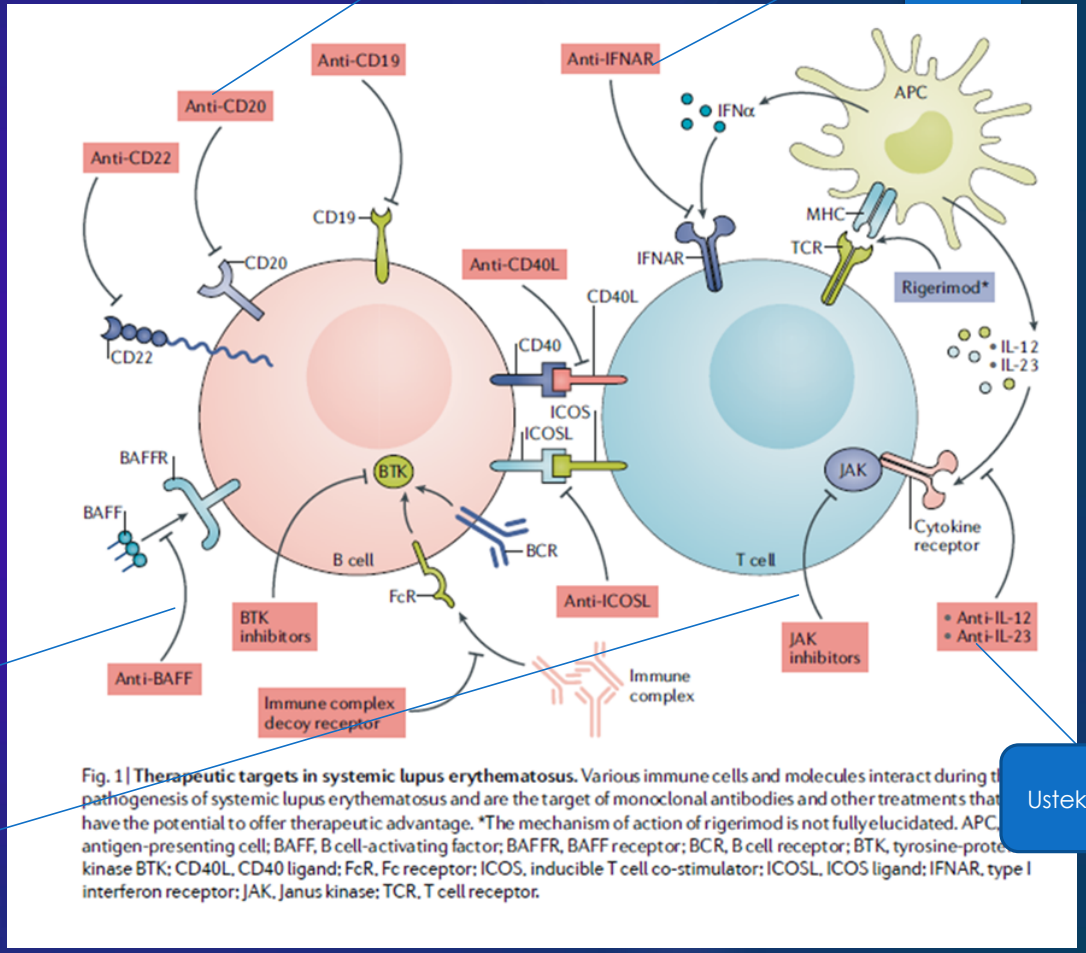


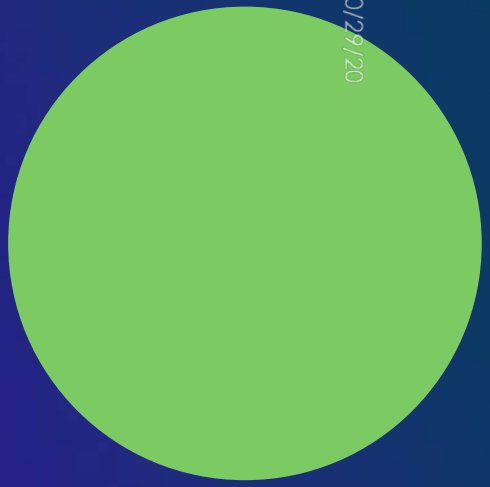
Fig. 1 | **Therapeutic targets in systemic lupus erythematosus.** Various immune cells and molecules interact during t pathogenesis of systemic lupus erythematosus and are the target of monoclonal antibodies and other treatments that have the potential to offer therapeutic advantage. *The mechanism of action of rigerimod is not fully elucidated. APC, antigen-presenting cell; BAFF, B cell-activating factor; BAFFR, BAFF receptor; BCR, B cell receptor; BTK, tyrosine-prote kinase BTK; CD40L, CD40 ligand; FcR, Fc receptor; ICOS, inducible T cell co-stimulator; ICOSL, ICOS ligand; IFNAR, type I interferon receptor; JAK, Janus kinase; TCR, T cell receptor.

Belimumab

Ustekinumab

Baricitinib

What are the Different Types of Clinical Research?



- Observational studies
  - "Non-invasive" collection of information
  - Questionnaires
  - Epidemiology
  - Registries
- Tissue acquisition studies
  - Provide materials for basic science research
- Clinical trials
  - Interventions with experimental therapies performed with the goal of improving clinical outcomes

What is a Clinical Trial?

- A study designed to yield information about an experimental therapy in development
- Generally sponsored by pharmaceutical or biotechnology companies
- Highly regulated with oversight by FDA and local authorities (IRB: Institutional Review Board) to assure patient protection and safety
- Necessary for new drug development
- Different phases (I-IV)
- Most always placebo controlled and double-blinded for stronger results
- Successful completion generally means a drug approval

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?

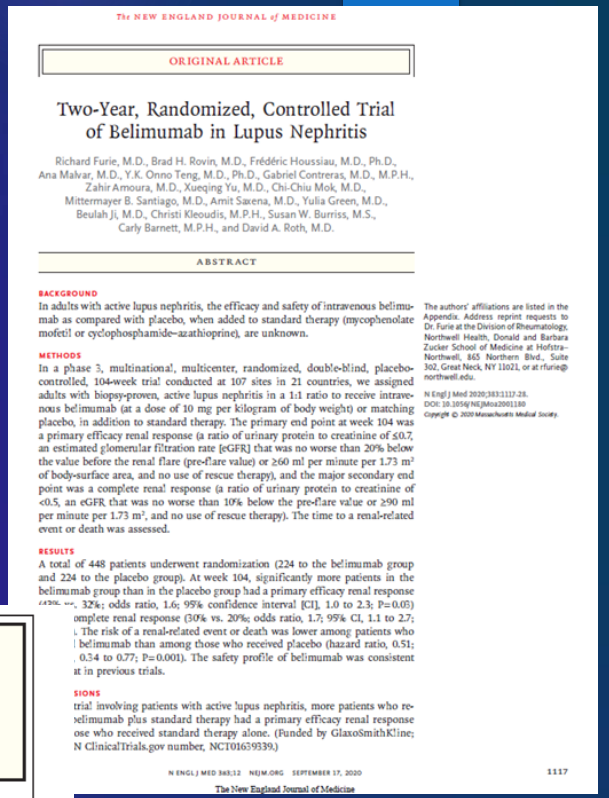
What's new in treatment?

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

Latest clinical trial results

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



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Two-Year, Randomized, Controlled Trial of Belimumab in Lupus Nephritis

Richard Furie, M.D., Brad H. Rovin, M.D., Frédéric Houssiau, M.D., Ph.D., Ana Malvar, M.D., Y.K. Onno Teng, M.D., Ph.D., Gabriel Contreras, M.D., M.P.H., Zahir Amoura, M.D., Xueqing Yu, M.D., Chi-Chiu Mok, M.D., Mittermayer B. Santiago, M.D., Amit Saxena, M.D., Yulia Green, M.D., Beulah Ji, M.D., Christi Kleoudis, M.P.H., Susan W. Burriss, M.S., Carly Barnett, M.P.H., and David A. Roth, M.D.

ABSTRACT

BACKGROUND

In adults with active lupus nephritis, the efficacy and safety of intravenous belimumab as compared with placebo, when added to standard therapy (mycophenolate mofetil or cyclophosphamide–azathioprine), are unknown.

METHODS

In a phase 3, multinational, multicenter, randomized, double-blind, placebo-controlled, 104-week trial conducted at 107 sites in 21 countries, we assigned adults with biopsy-proven, active lupus nephritis in a 1:1 ratio to receive intravenous belimumab (at a dose of 10 mg per kilogram of body weight) or matching placebo, in addition to standard therapy. The primary end point at week 104 was a primary efficacy renal response (a ratio of urinary protein to creatinine of ≤0.7, an estimated glomerular filtration rate [eGFR] that was no worse than 20% below the value before the renal flare (pre-flare value) or ≥60 ml per minute per 1.73 m² of body-surface area, and no use of rescue therapy), and the major secondary end point was a complete renal response (a ratio of urinary protein to creatinine of <0.5, an eGFR that was no worse than 10% below the pre-flare value or ≥90 ml per minute per 1.73 m², and no use of rescue therapy). The time to a renal-related event or death was assessed.

RESULTS

A total of 448 patients underwent randomization (224 to the belimumab group and 224 to the placebo group). At week 104, significantly more patients in the belimumab group than in the placebo group had a primary efficacy renal response (43% vs. 32%; odds ratio, 1.6; 95% confidence interval [CI], 1.0 to 2.3; P=0.03) omplete renal response (30% vs. 20%; odds ratio, 1.7; 95% CI, 1.1 to 2.7; . The risk of a renal-related event or death was lower among patients who belimumab than among those who received placebo (hazard ratio, 0.51; 0.34 to 0.77; P=0.001). The safety profile of belimumab was consistent at in previous trials.

SIONS

trial involving patients with active lupus nephritis, more patients who re- belimumab plus standard therapy had a primary efficacy renal response ose who received standard therapy alone. (Funded by GlaxoSmithKline; N ClinicalTrials.gov number, NCT01639339.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Furie at the Division of Rheumatology, Northwell Health, Donald and Barbara Zucker School of Medicine at Hofstra–Northwell, 865 Northern Blvd., Suite 302, Great Neck, NY 11021, or at rfurie@northwell.edu.

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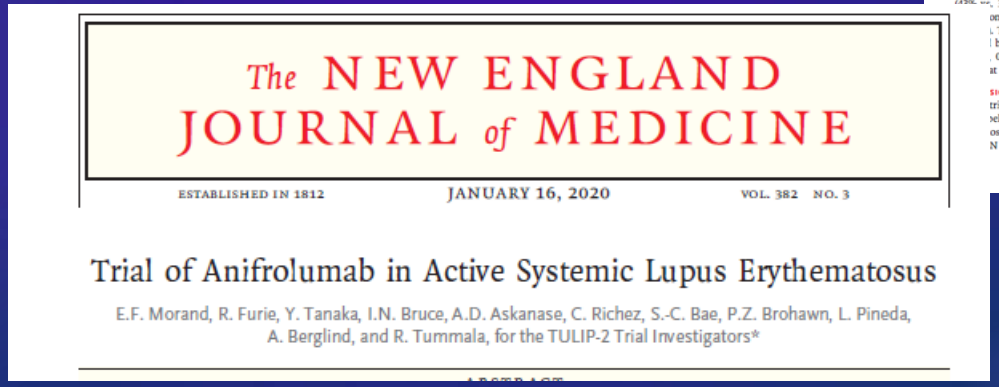
The New England Journal of Medicine



The NEW ENGLAND JOURNAL of MEDICINE

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Trial of Anifrolumab in Active Systemic Lupus Erythematosus

E.F. Morand, R. Furie, Y. Tanaka, I.N. Bruce, A.D. Askanase, C. Richez, S.-C. Bae, P.Z. Brohawn, L. Pineda, A. Berglind, and R. Tummala, for the TULIP-2 Trial Investigators*

ABSTRACT

Current Clinical Trials in SLE

Table 2 | **Ongoing clinical trials of new therapies for systemic lupus erythematosus**

Therapy	Target(s)	Trial phase	Status	Size	Primary outcome	Refs
Obinutuzumab	CD20	II	Active, not recruiting	127 participants	Percentage of patients with complete renal response at 52 weeks	36
Combination therapy with rituximab and belimumab	CD20 and BAFF	II	Recruiting	Target of 30 participants	Reduction in disease-relevant autoantibodies at 28 weeks	41
		III	Recruiting	Target of 200 participants	Proportion of patients with a SLEDAI-2K score of <2 without the use of additional immunosuppression	40
		II	Active, not recruiting	Target of 50 participants	Reduction in anti-dsDNA antibodies at 52 weeks	42
GDC 0853	BTK	II	Active, not recruiting	240 participants	SRI-4 response at 48 weeks	49
Dapirolizumab pegol	CD40L	II	Active, not recruiting	182 participants	Proportion of patients with a BICLA response at 24 weeks	59
Anifrolumab	IFNAR	II	Recruiting	Target of 150 participants	Relative change from baseline in urine protein-to-creatinine ratio	82
IFNα kinoid	B cells to stimulate the production of anti-IFNα antibodies	II	Active, not recruiting	178 participants	• Change from baseline in expression of IFN-induced genes at 36 weeks • Treatment response as assessed by BICLA at 36 weeks	85
Baricitinib (BRAVE I)	JAK1 and JAK2	III	Recruiting	Target of 750 participants	Percentage of patients achieving an SRI-4 response at 52 weeks	90
Baricitinib (BRAVE II)	JAK1 and JAK2	III	Recruiting	Target of 750 participants	Percentage of patients achieving an SRI-4 response at 52 weeks	91
Tofacitinib	JAK1 and JAK3	I/II	Complete	34 participants	Safety of tofacitinib in patients with mild-to-moderate disease activity	96
Ustekinumab	IL-12 and IL-23	III	Recruiting	Target of 500 participants	Percentage of patients achieving an SRI-4 response at 52 weeks	95

BAFF, B cell-activating factor; BICLA, BILAG-based Composite Lupus Assessment; BTK, tyrosine-protein kinase BTK; CD40L, CD40 ligand; dsDNA, double-stranded DNA; IFN, interferon; IFNAR, type I interferon receptor; JAK, Janus kinase; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000; SRI-4, SLE Responder Index 4.

Challenges in lupus clinical trials

- Lupus is a heterogenous disease with many variable symptoms
- Challenging to capture improvements in disease activity—determining the best endpoints of a study is challenging with lupus
- Challenging to determine treatment effect on background therapy
- Large numbers of patients are needed to determine statistical effect
- Under-representation of minorities-We need better representation from minorities

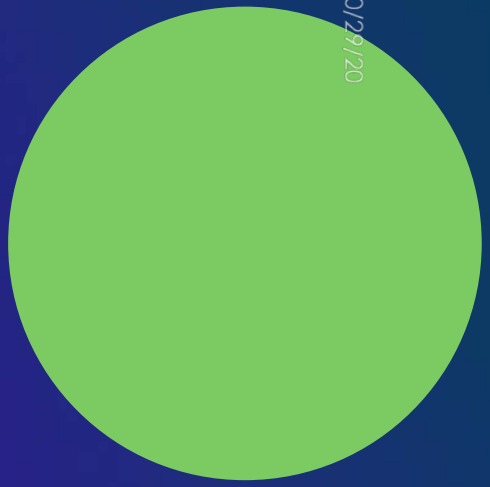
Why Participate?

1. To advance the search for better and safer therapies
2. To receive state-of-the-art medical care
3. To benefit one's self, family members, or friends
4. To receive medical care and treatment that might not be affordable

What Are the Risks and Benefits?

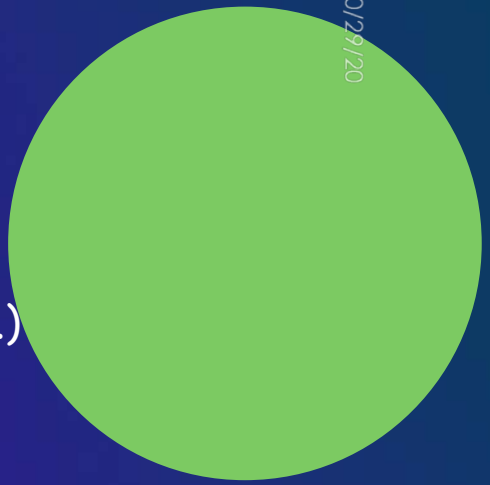
- **Risks:**
  - Time commitment
  - Treatment might not work
  - There may be side effects
  - You might get placebo (not always a bad thing)

- **Benefits:**
  - Access to state-of-the-art therapy and care
  - The investigational drug might be beneficial
  - Possible modest financial rewards



What Can a Clinical Trial Participant Expect?

- Informed consent process
- Screening
- Randomization (placebo vs. investigational drug)
- Study visits (physical exam, blood tests, surveys, etc.)
- Careful medical attention



How is Safety Ensured?

- Approval by FDA
- Approval by IRB
- Frequent visits monitored by a physician and research coordinator
- Sites are monitored by the sponsor
- Safety data are reviewed by external review boards (DSMB: Data Safety Monitoring Board)
- Safety updates provided to sites

What Happens After the Clinical Trial Ends?

- Data will be analyzed for safety and efficacy
- Investigational treatment may end or study medication is sometimes provided to all in what is called an open-label extension
- You will be eventually notified of the treatment you received during the study
- If the data are good, the drug advances to the next phase; if in phase III, probable drug approval!

Currently enrolling trials at URMC

- Cell based therapies
  - MiSLE study: Mesenchymal stem cell infusion
    - Single infusion of stem cells added on to baseline therapy (certain exclusions)

- Coming soon: Phase III Randomized Double Blind Placebo Controlled Multicenter Study to Evaluate the Efficacy and Safety of Obinutuzumab in Patients with Lupus Nephritis ---Biologic drug or placebo added on to standard of care therapy (cellcept and steroids)

Please ask your rheumatologist about research!

THANK YOU!

What we're doing at the U of R:

- NIH funded networks
  - Autoimmunity Center of Excellence for clinical trials and basic mechanisms of lupus and clinical trials
  - Accelerating Medicines Partnership
- Clinical Cohorts: Lupus Clinical Trials Consortium
  - 20 centers
  - Collaborative Longitudinal Lupus Registry
- Clinical Trials
  - The AIR unit has an active program in clinical trials in SLE
  - Investigation of new, targeted biological interventions in SLE