Lupus Treatments and Research Updates

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Last Saturday in Athens

Challenges in Developing SLE Treatments

- Waxing and waning course
- Heterogeneity of manifestations
- Variety of immunomodulating medications
- Each validated assessment instrument has strengths and limitations
  - Composite endpoint can rigorously demonstrate reduction in disease activity

Current Standard of Care

- Mild to moderate disease (rash, arthritis, serositis):
  - NSAIDs
  - Hydroxychloroquine (Plaquenil), DHEA (prasterone), corticosteroids
  - Azathioprine (Imuran), Methotrexate (Rheumatrex or Trexall), Mycophenolate mofetil
- Severe disease (renal, CNS):
  - Cyclophosphamide (Cytoxan) + steroids
  - Mycophenolate mofetil (Cellcept) + steroids
  - Rituximab (Rituxan) + steroids
- Refractory severe disease:
  - Pheresis
  - Bone marrow ablation +/- stem cell transplant

Things we do know

- Every lupus patient should be on an anti-malarial (i.e. plaquenil)
  - Multiple trials have shown
    - Improved survival of patients on plaquenil
    - Fewer flares in patients on plaquenil
    - Less prednisone use
    - Decreased progression of disease
    - Improved outcomes in pregnancy with APL
    - ? Protection against cardiovascular disease

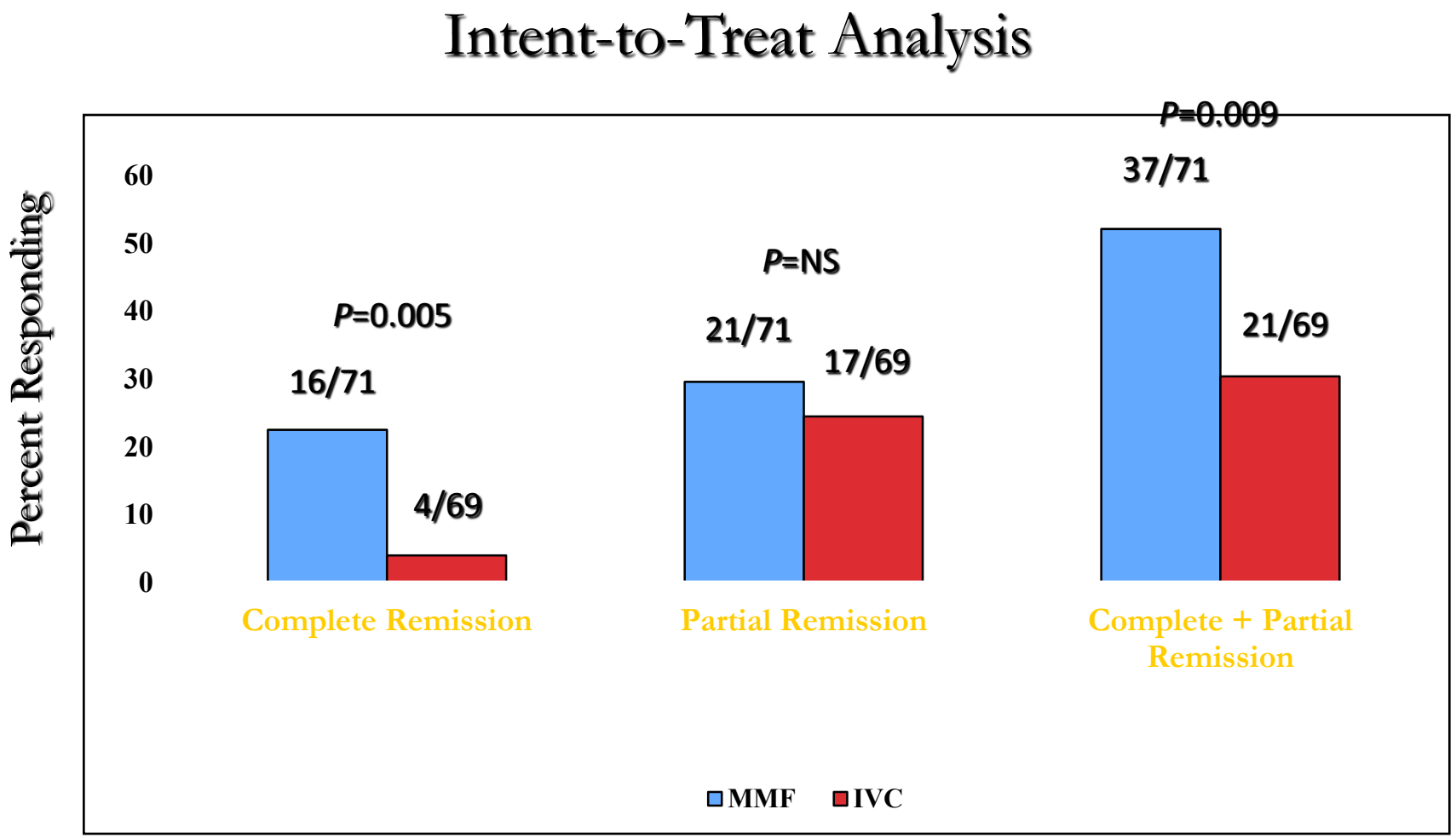
Things we do know (continued)

- In lupus nephritis, cellcept is equivalent to cytoxan in inducing improvement/remission
  - Cellcept appears more effective than CTX in African Americans

In lupus nephritis, cellcept is superior to imuran in maintaining remission/ renal function

In lupus nephritis the Eurolupus low dose CTX regimen is equivalent to high dose CTX (? AAs)

Remission Rates: MMF vs. IVC

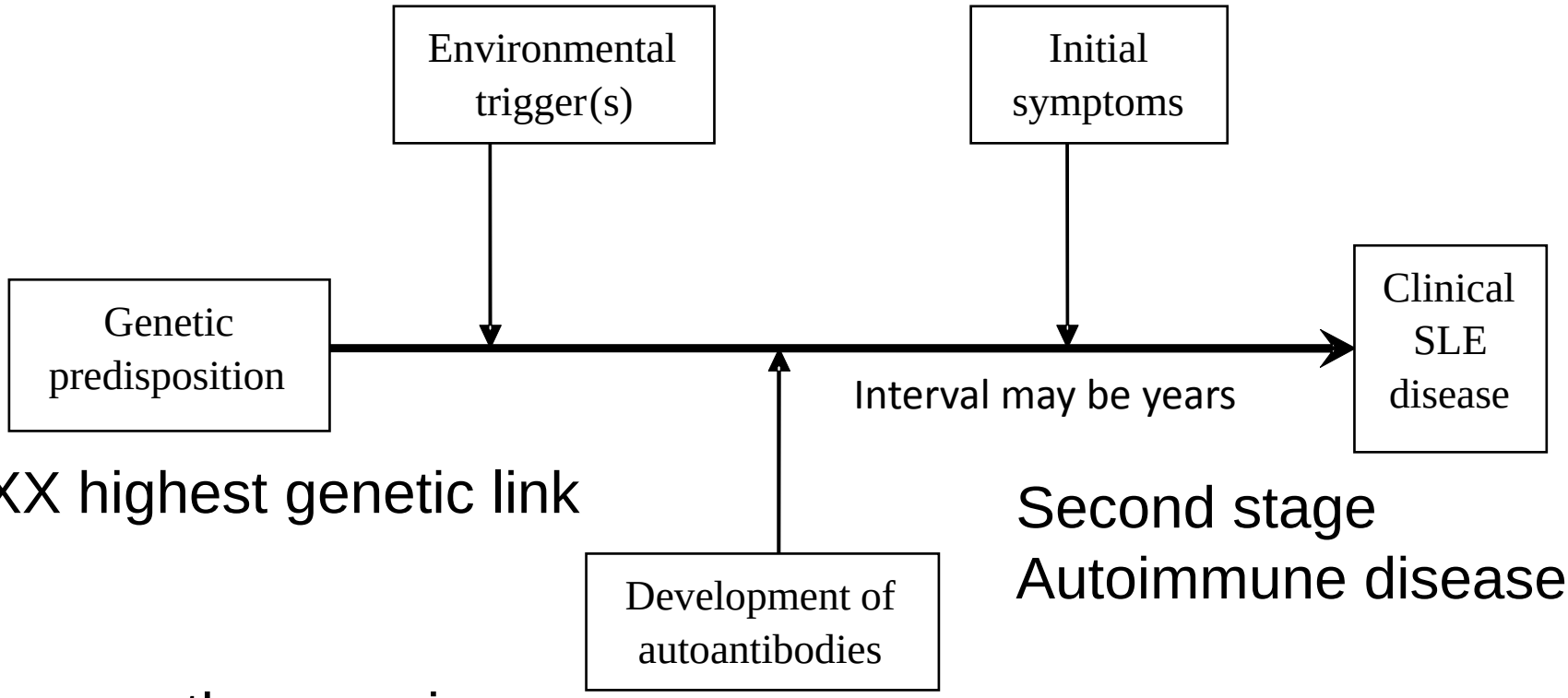


Ginzler et al: NEJM 2005

New Targets for Treatment in Lupus

- Predisease state
- B cells
- Alpha interferon
- Cell Based Therapies
- TLRs
- Neutrophil Nets

Conceptual 2 Step Model of SLE Pathogenesis



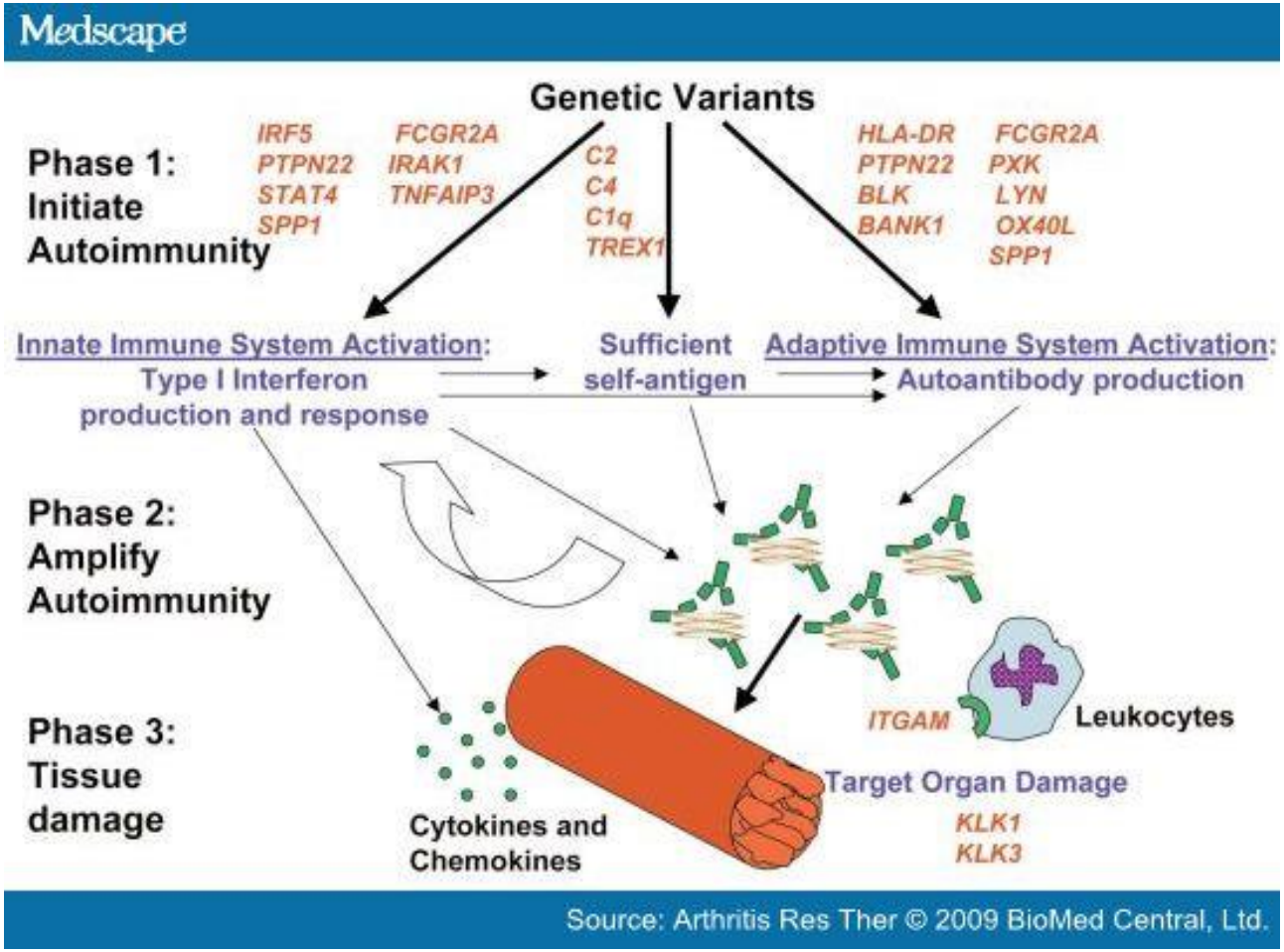
XX highest genetic link

Second stage Autoimmune disease

2 stage pathogenesis

First stage- autoimmunity

Genetic risk factors act at different stages of lupus



Environmental factors in lupus

EBV

Silica

pesticides/heavy metals

Smoking- current not past

Sunlight- flares

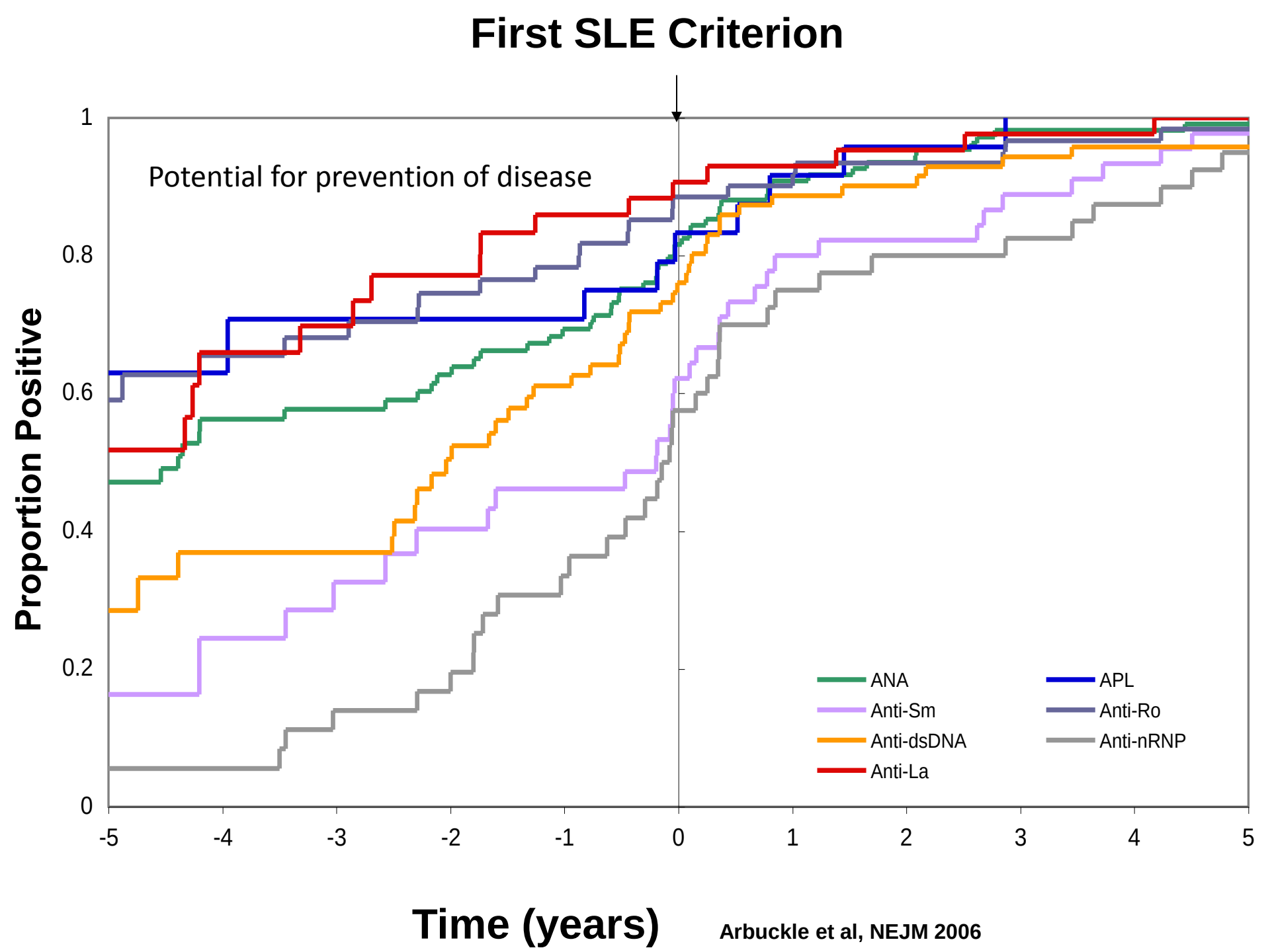
Drugs- anti-TNFs, hydralazine

Vitamin D deficiency

New Targets for Therapy

Target #1-Predisease state

- Can we identify individuals predisease who are going to develop lupus?
- If we can, can we treat them with something to prevent disease?


First SLE Criterion
Potential for prevention of disease
Proportion Positive
1
0.8
0.6
0.4
0.2
0
-5
-4
-3
-2
-1
0
1
2
3
4
5
ANA
APL
Anti-Sm
Anti-Ro
Anti-dsDNA
Anti-nRNP
Anti-La
Time (years)
Arbuckle et al, NEJM 2006

Autoantibodies in First Degree Relatives

	All SLEIGH FDRs (N=144)	Female SLEIGH FDRs (N=111)	Male SLEIGH FDRs (N=33)	All LMRR FDRs (N=836)	LMRR AA Female FDRs (N=600)	LMRR AA Male FDRs (N=236)	p-value
ANA Positivity ≥1:40	47.9%	52.3%	33.3%	50.2%	54.7%	36.9%	0.61
ANA Positivity ≥1:120	34.7%	38.7%	21.2%	38.6%	42.5%	27.1%	0.37
ANA Titer > 1:1000	4.9%	5.4%	3.0%	6.9%	7.2%	5.5%	0.37
ANA Titer > 1:3000	2.8%	2.7%	3.0%	1.4%	1.0%	2.5%	0.22
Cardiolipin IgG > 20	6.9%	7.2%	6.1%	8.2%	8.6%	7.1%	0.60
Cardiolipin IgM > 20	0.7%	0.0%	3.0%	2.1%	1.9%	2.6%	0.26
dsDNA positive	1.4%	1.8%	0.0%	0.48%	0.7%	0.0%	0.21
Sm positive	0.7%	0.9%	0.0%	0.2%	0.3%	0.0%	0.29
RNP positive	2.8%	3.6%	0.0%	2.6%	2.5%	3.0%	0.89
Ro (SSA) positive	2.1%	2.7%	0.0%	2.8%	3.2%	1.7%	0.63
La (SSB) positive	0.0%	0.0%	0.0%	0.8%	1.2%	0.0%	0.28

Males and females similar rates of autoimmunity

Kamen, A and R, 2008

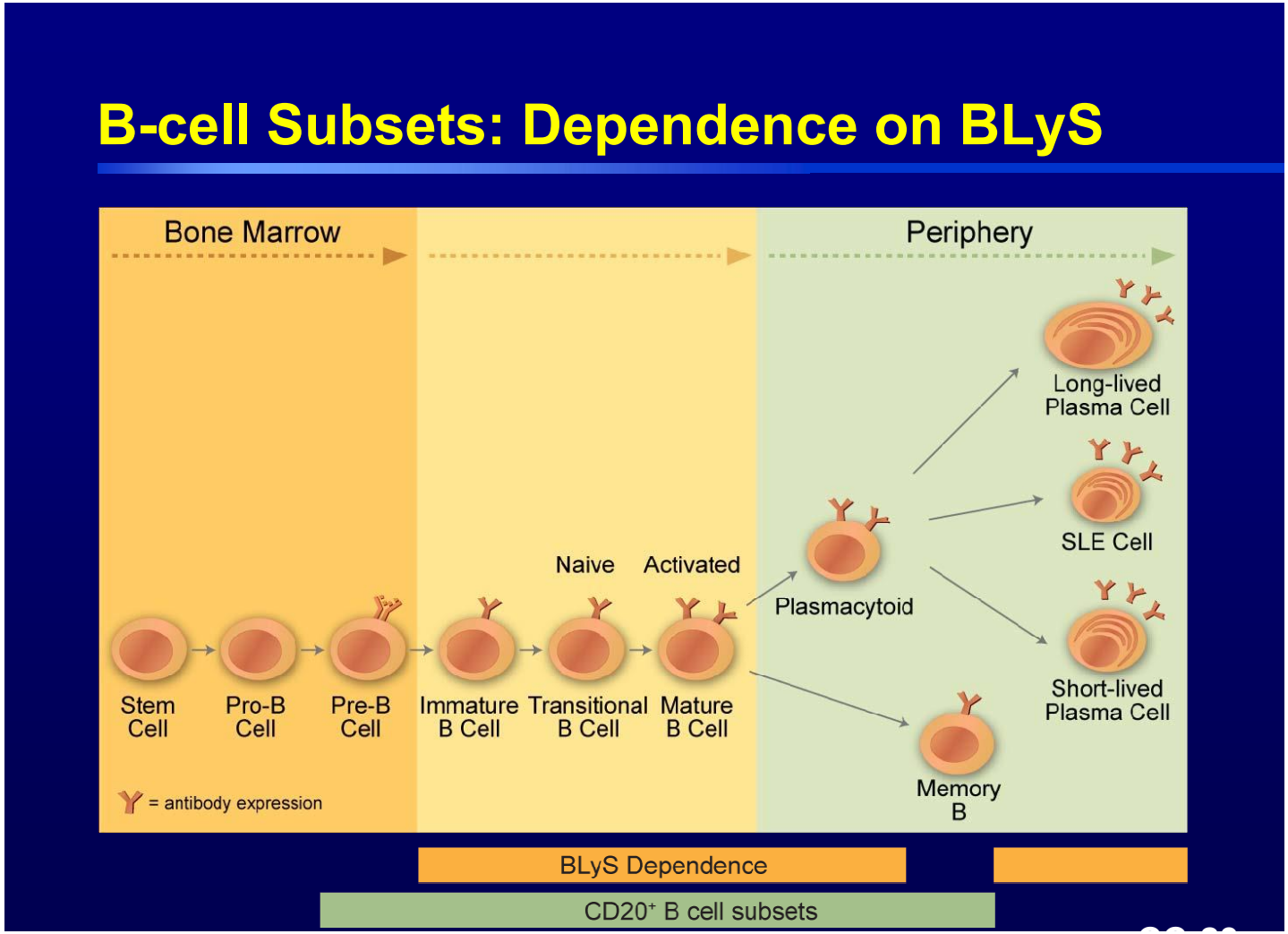
Predicting progression to lupus

- LAUREL study following FDRs over time
- 448 FDRs were followed average of 5 years
- 19 developed 4/11 criteria
- Predictors of progressing
  - Baseline CSQ score
  - Autoantibody progression
  - Markers of inflammation (high Blys, low APRIL)

Therapies to Prevent Disease

- If so, can we prevent progression to disease?
  - Plaquenil- clinical trials indicate patients on plaquenil have decreased progression of disease
  - Vitamin D- vitamin D deficiency associated with higher disease activity

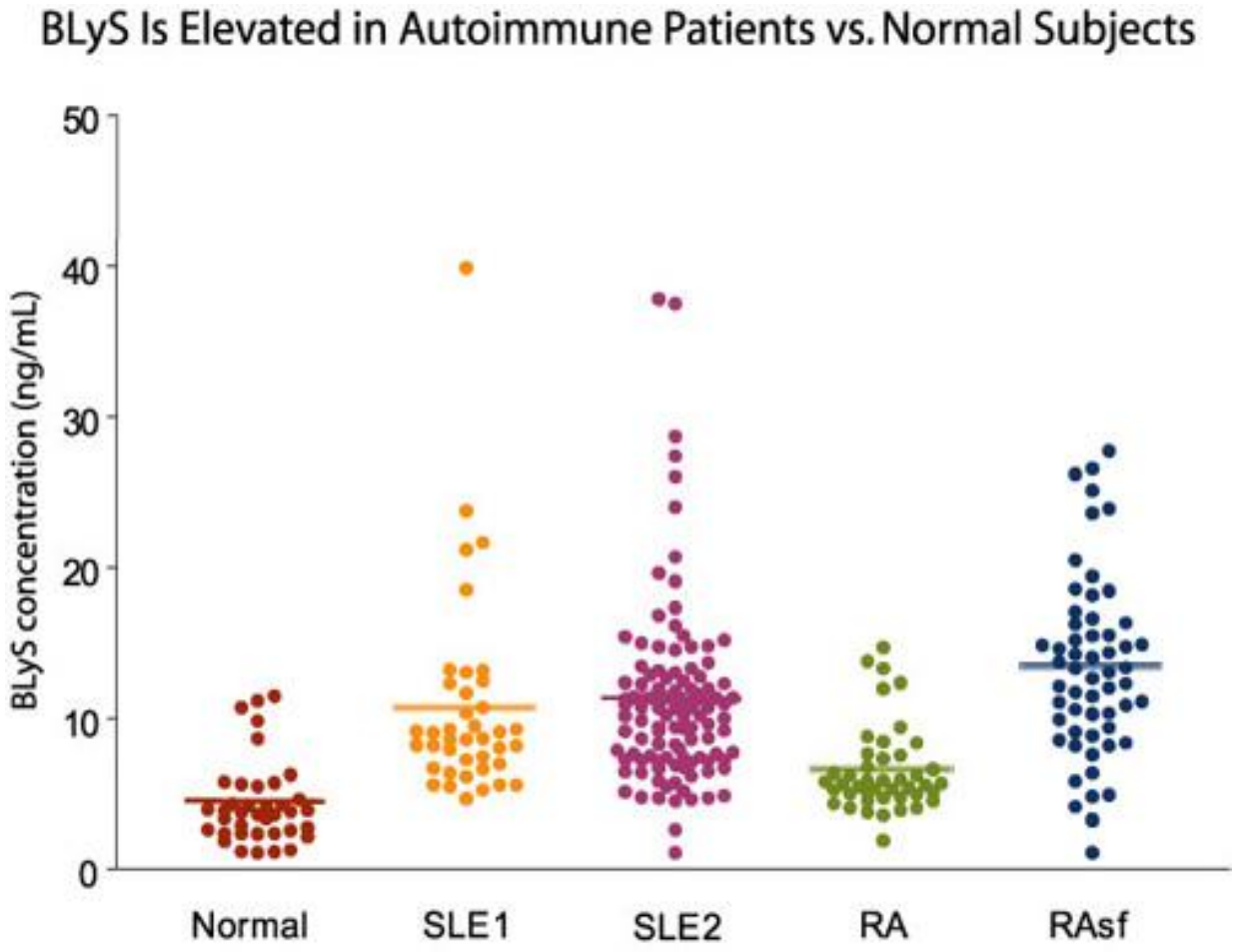
Targeting B cells in Lupus



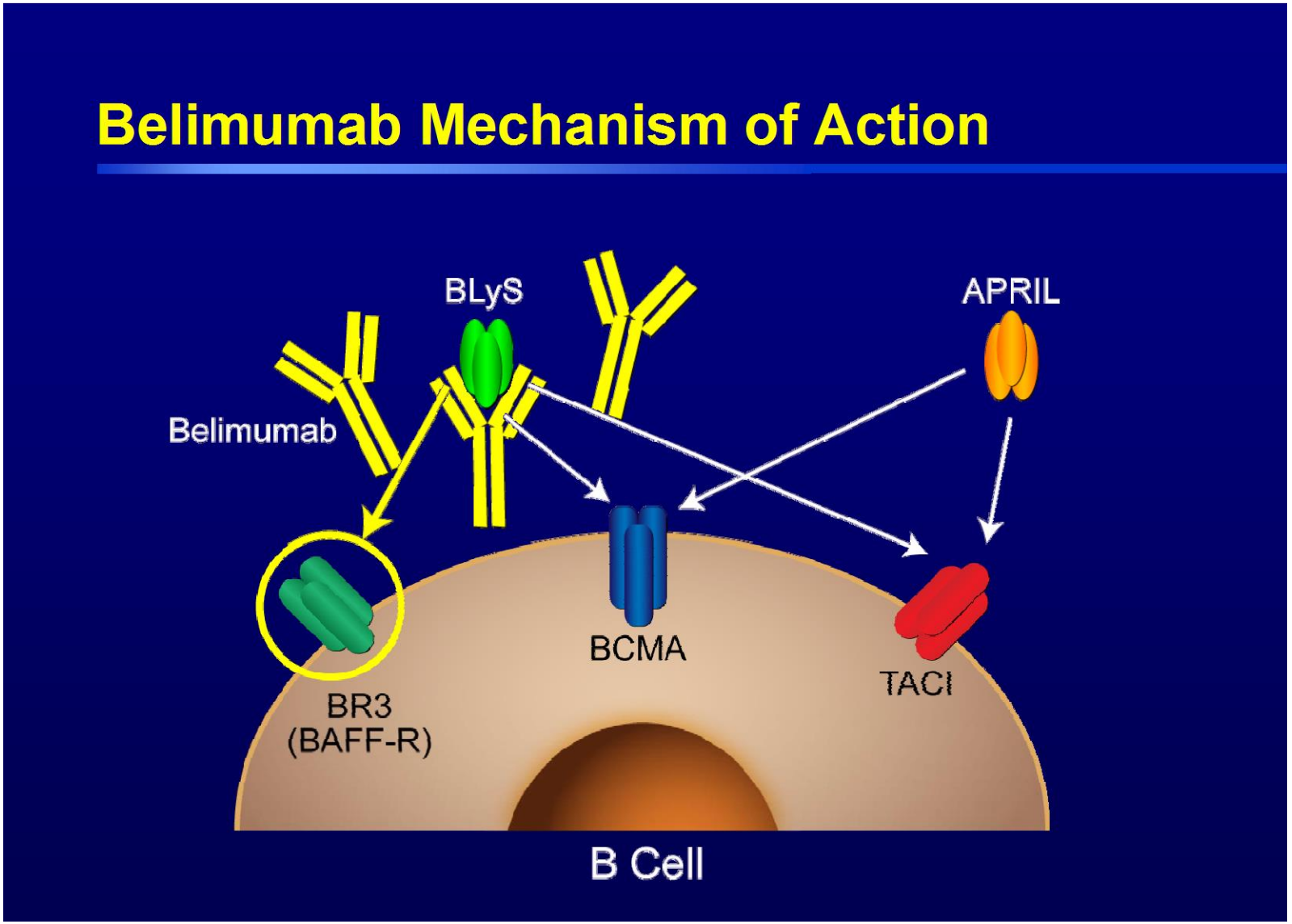
B cell depletion as therapy in lupus

- Rituxan did not meet its endpoints for the treatment of lupus or lupus nephritis
  - ? B cells are not a good target in lupus
  - ? Wrong antibody isotype- proinflammatory IgG1
  - ? Study design- concomitant meds
    - All patients got IV medrol
    - Study only 52 weeks
  - ? Don’t want to deplete all B cells
    - Breg cells make IL10 and may be important

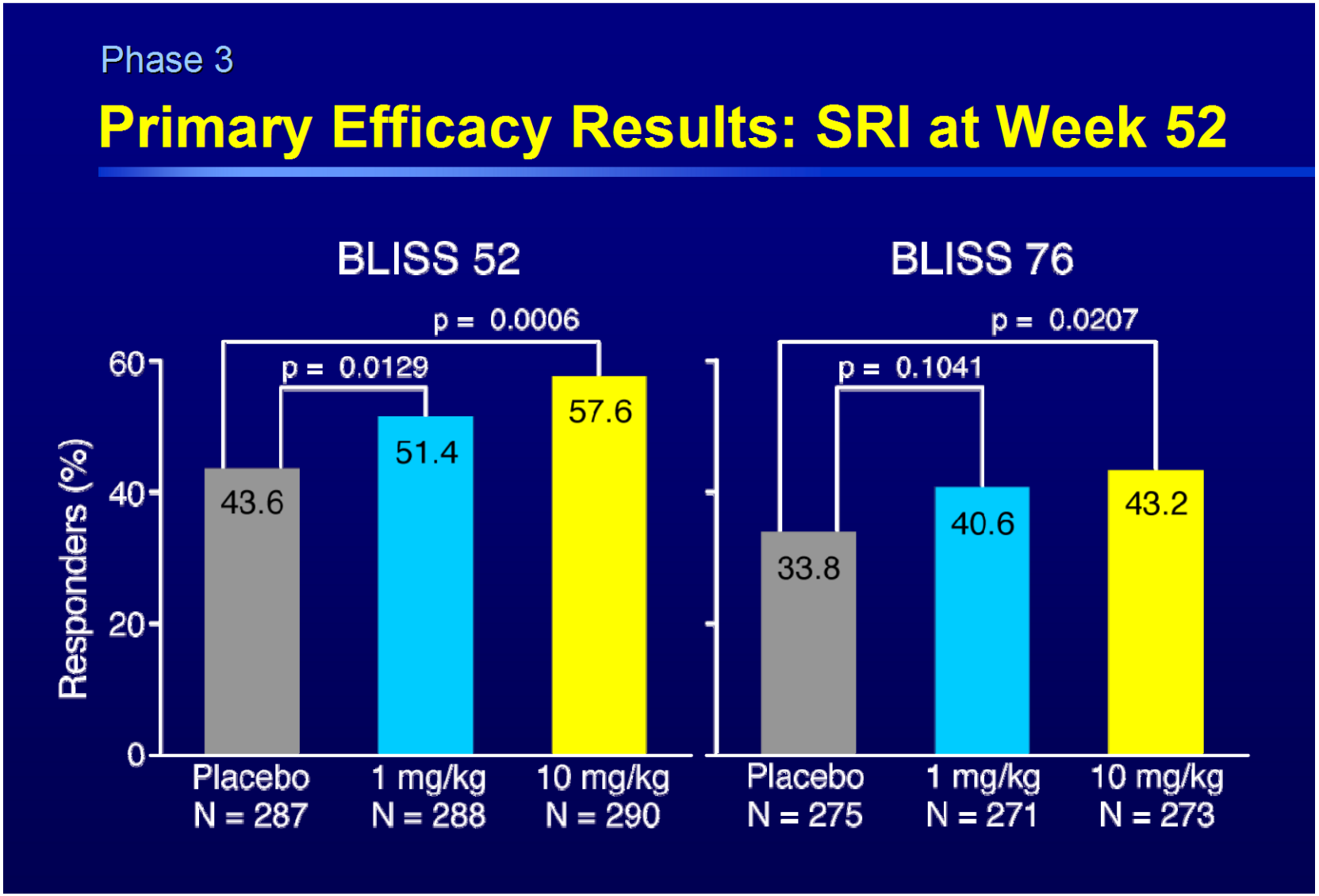
BLyS


BLyS Is Elevated in Autoimmune Patients vs. Normal Subjects
BLyS concentration (ng/mL)
50
40
30
20
10
0
Normal
SLE1
SLE2
RA
RAsf

Targets in the Blys/April Pathway



Efficacy of Benlysta



Other B cell directed therapies

Future Directions

- B cell depletion
  - Anti-CD19 antibodies deplete early B cell progenitors (pre-B cells)
- B cell costimulatory blockade
  - BAFF/BLyS blockade, antibodies to the BAFF-R, TACI:Fc,
  - anti-CD40,
  - anti-CD22 (epratuzamab)

Target #3- Interferons and Lupus

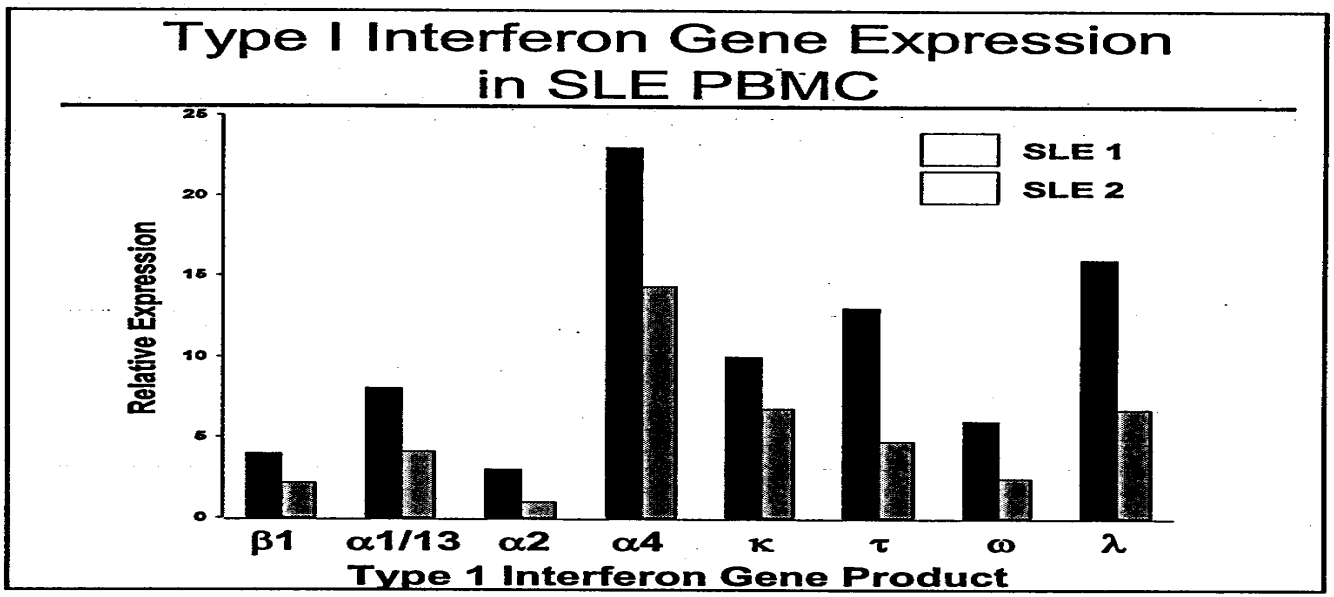
Interferon alpha in lupus

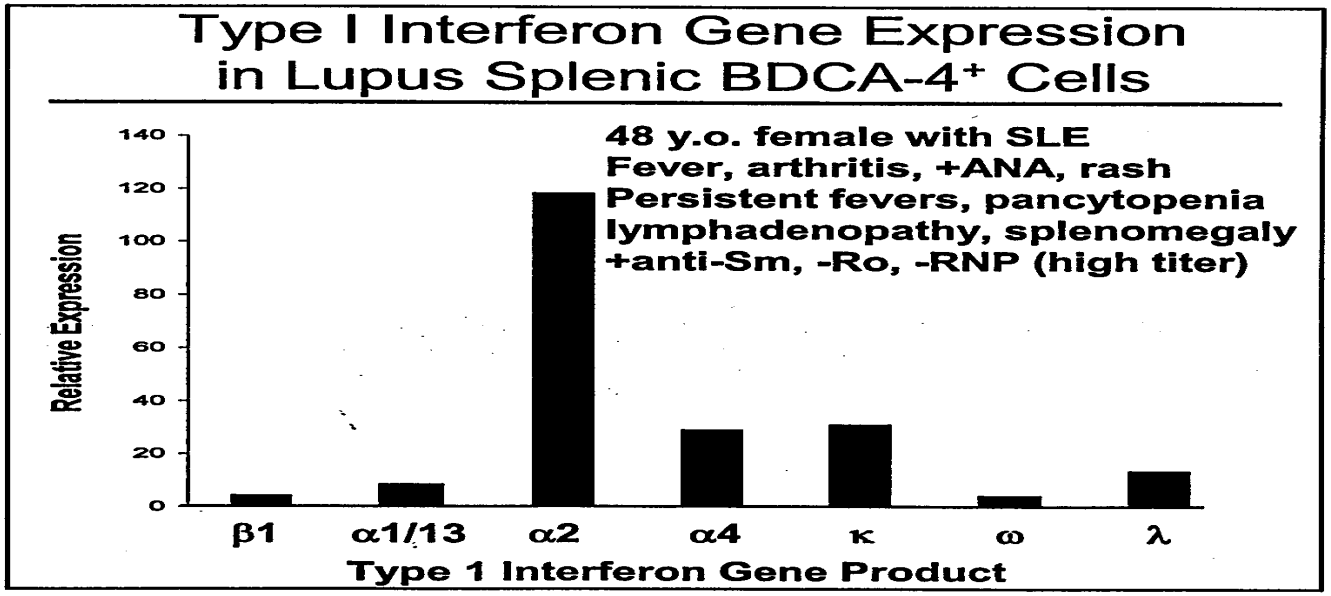
High serum IFNα levels demonstrated in lupus patients in the 1970s

IFNα given for hepatitis C induces lupus in some individuals

Multiple groups demonstrate an “IFN signature” in PBMC gene expression in lupus patients

IFNα induces a lupus like disease in some





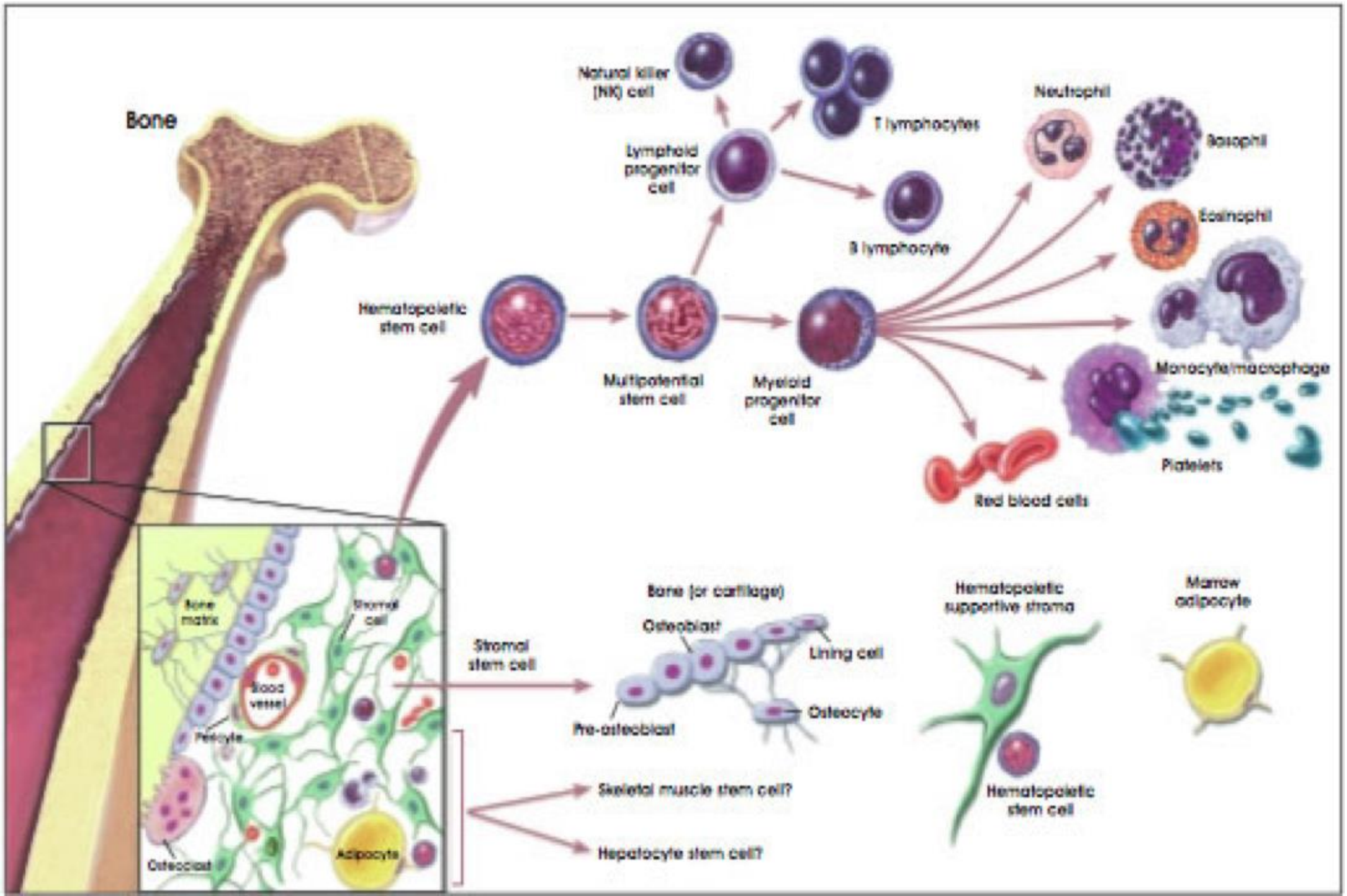
Crow et al, Arth Rheum 2005

Clinical trials in IFNγ

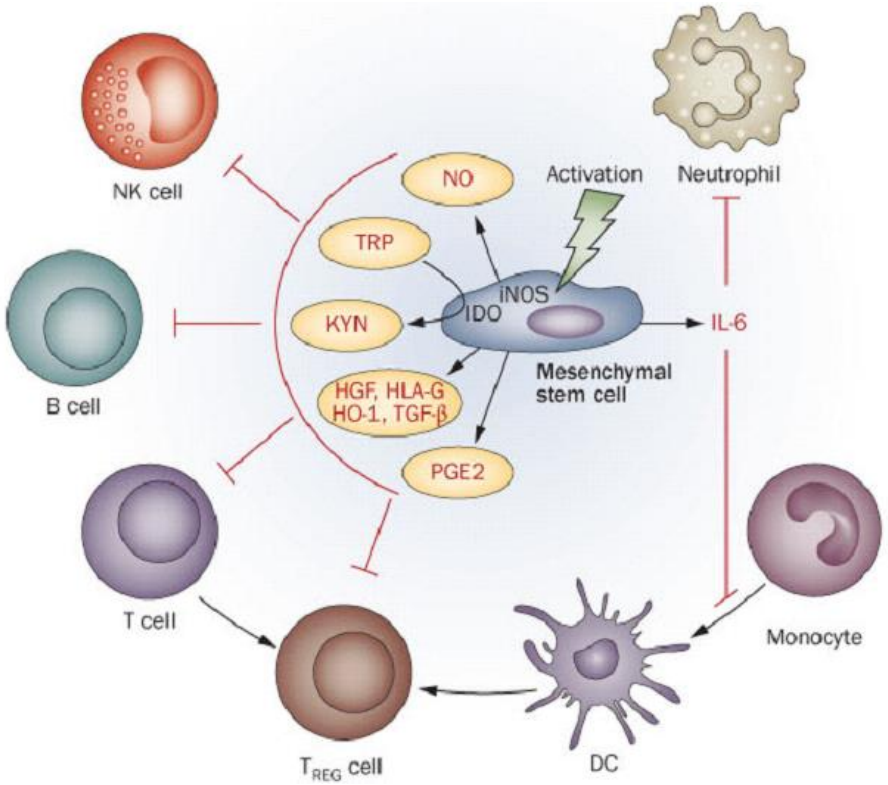
- Two different companies have ongoing phase III trials of anti-IFNα antibodies in lupus
- The antibodies do not bind all IFNα and likely bind different subsets
- Patients were not selected based on IFNα expression
- Trends, but not significant improvement
- No significant safety signal to this point

Target #4- Cell based therapies in Lupus

Stem cell therapy



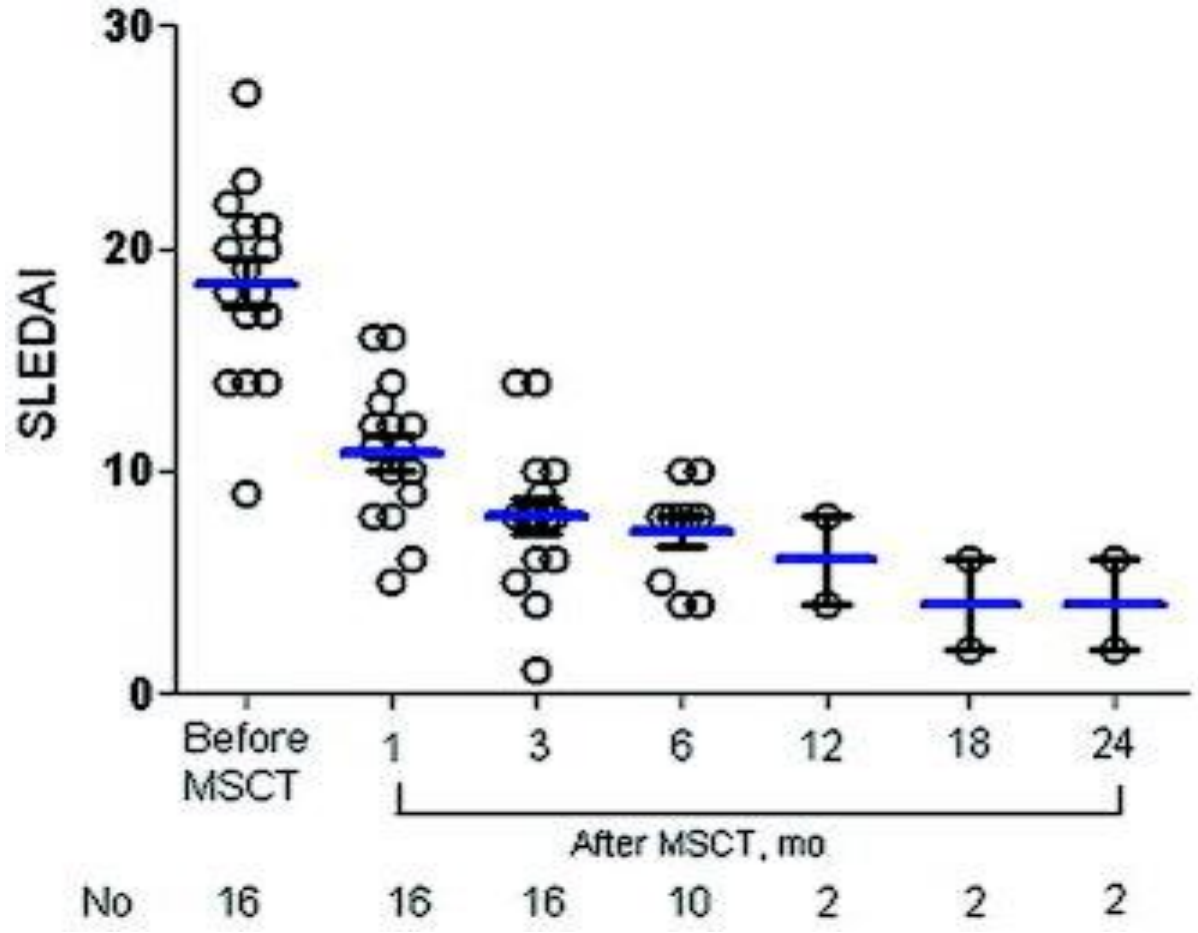
Mesenchymal Stem Cells (MSCs)



MSC Efficacy in Animal Models of Disease

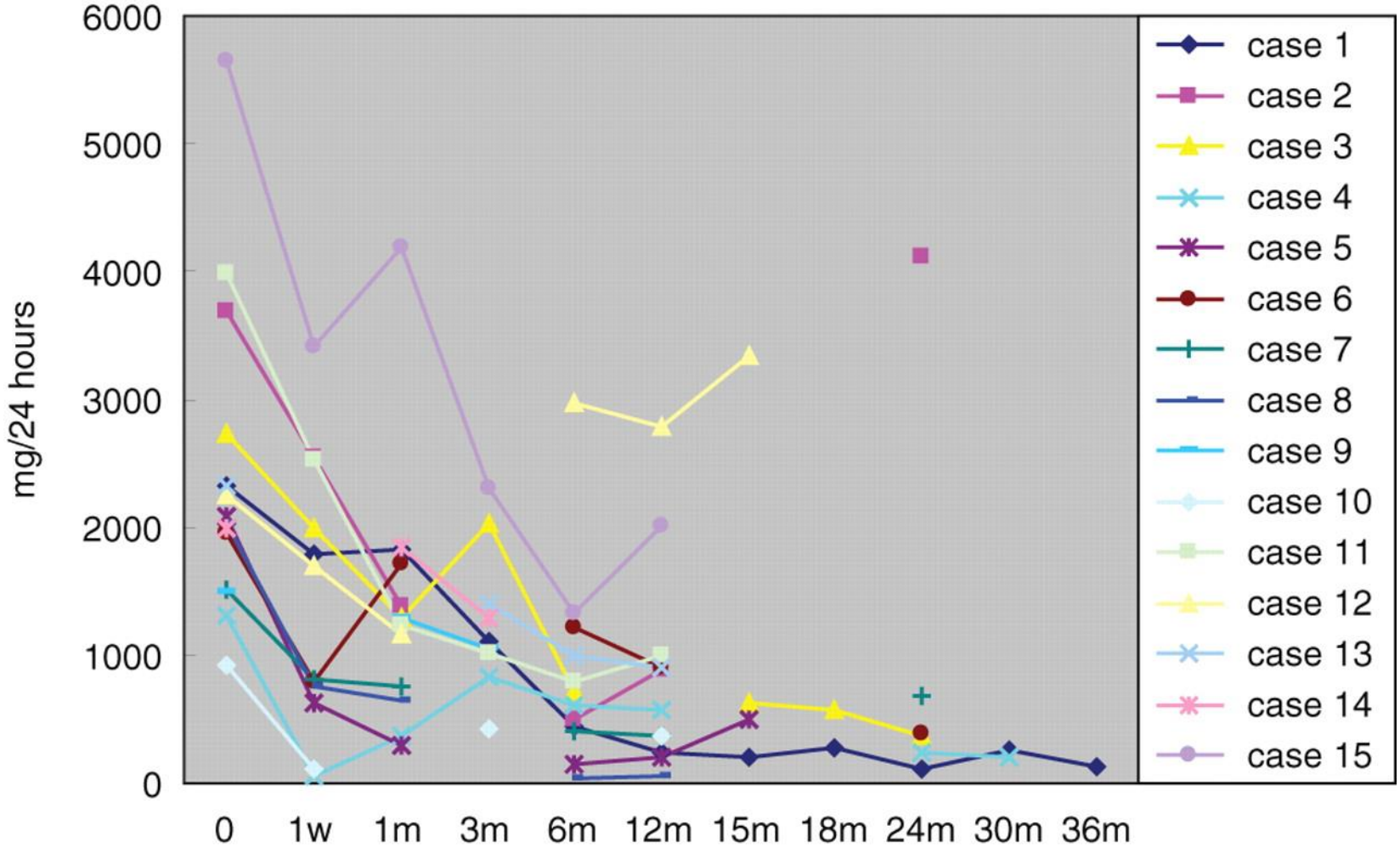
- Arthritis
- MS
- IBD
- Asthma
- GVH disease
- Type I diabetes

Umbilical cord mesenchymal stem cell transplantation in severe and refractory systemic lupus erythematosus



Arthritis & Rheumatism
Volume 62, Issue 8, pages 2467-2475, 6 MAY 2010 DOI: 10.1002/art.27548
http://onlinelibrary.wiley.com/doi/10.1002/art.27548/full#fig1

Results for 24-h proteinuria in 15 patients with refractory systemic lupus erythematosus before and after mesenchymal stem cells transplantation (MSCT).



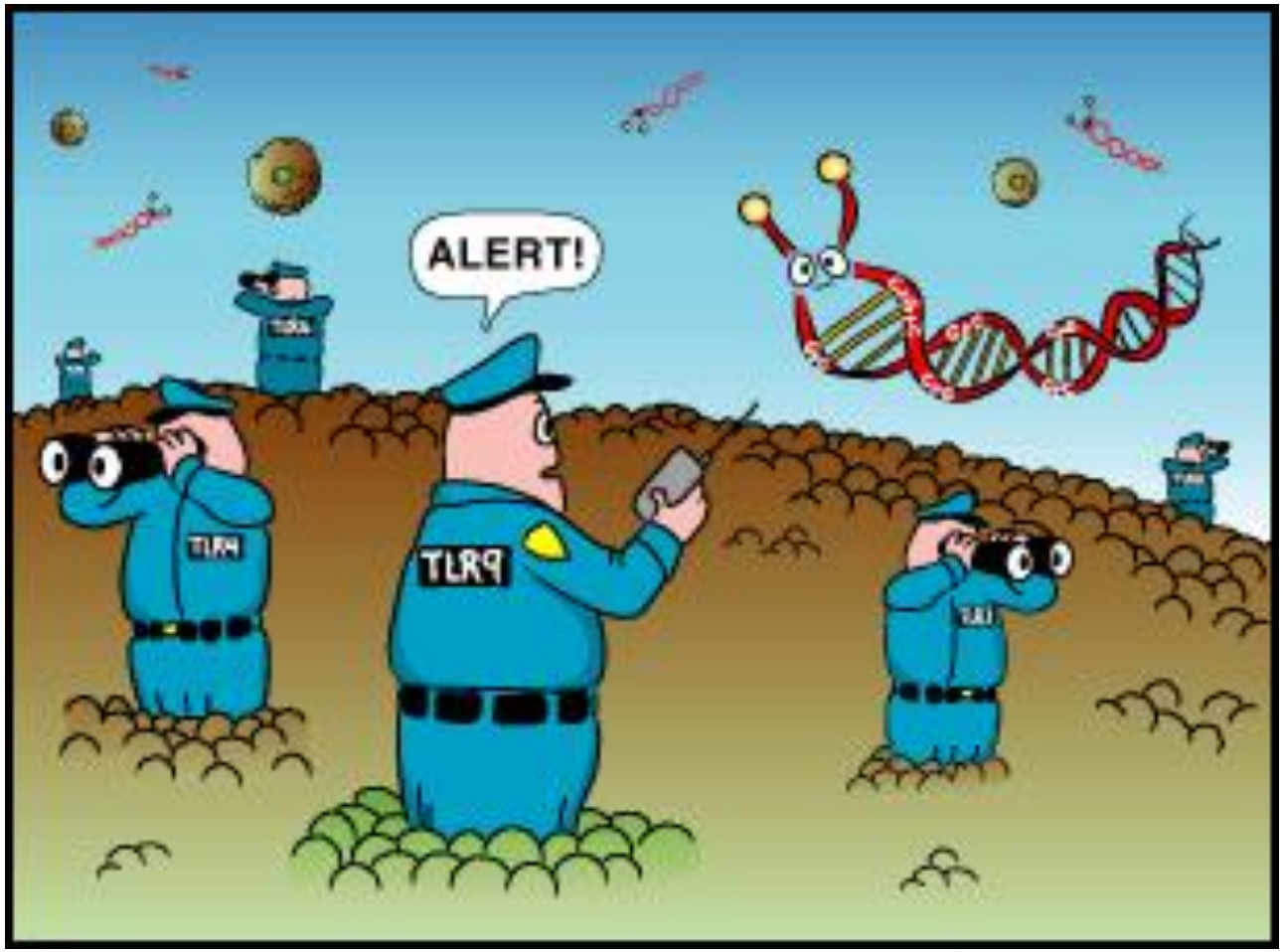
Liang J et al. Ann Rheum Dis 2010;69:1423-1429

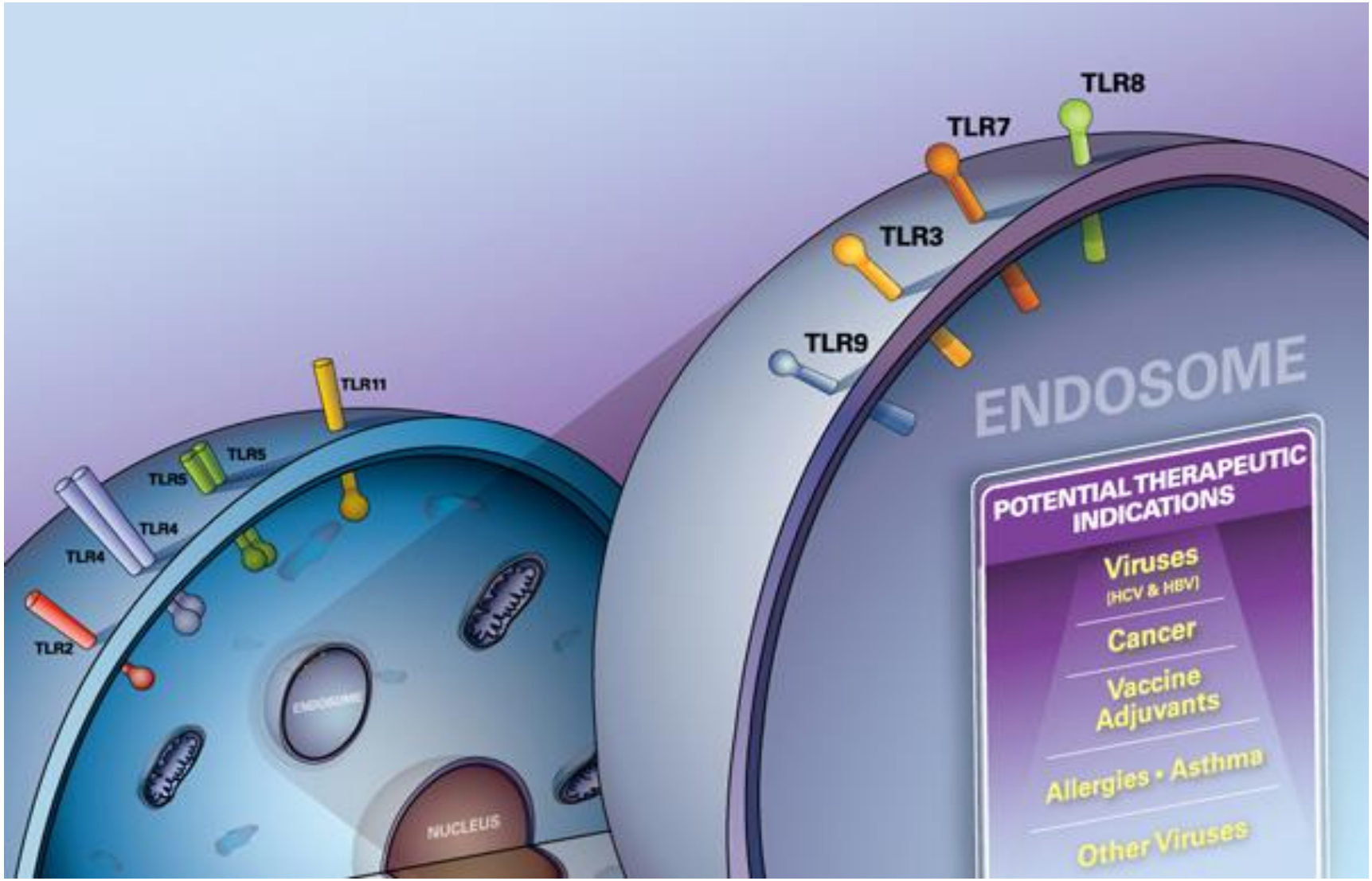
ARD

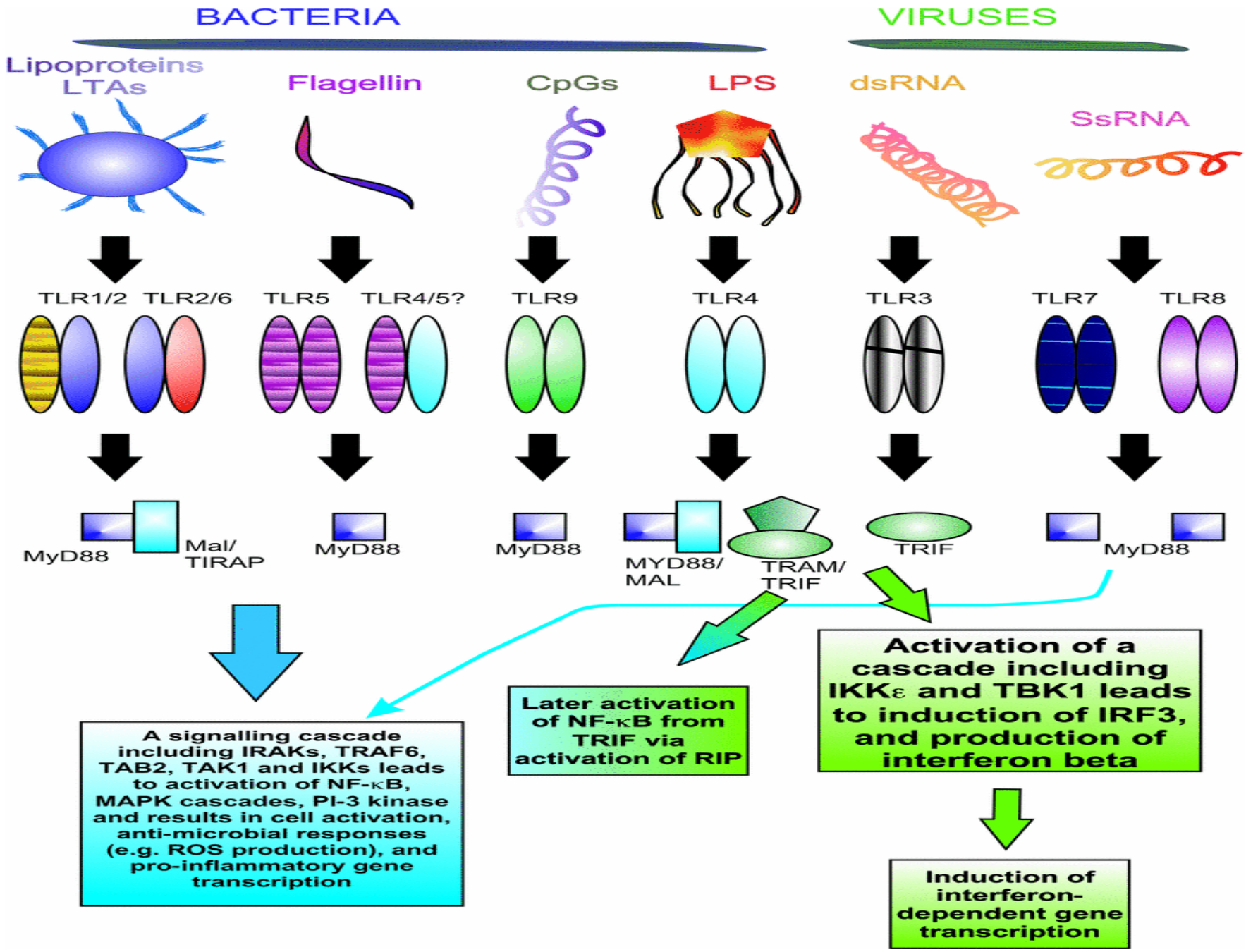
MSC issues

- Studies are uncontrolled and patients were all receiving concomitant meds
- MSCs cannot be mass produced and frozen as this processing decreases biologic activity
- Unclear if autologous or allogenic transplant is the best approach at this time- are lupus MSCs defective?

Target #5- Toll Like Receptors



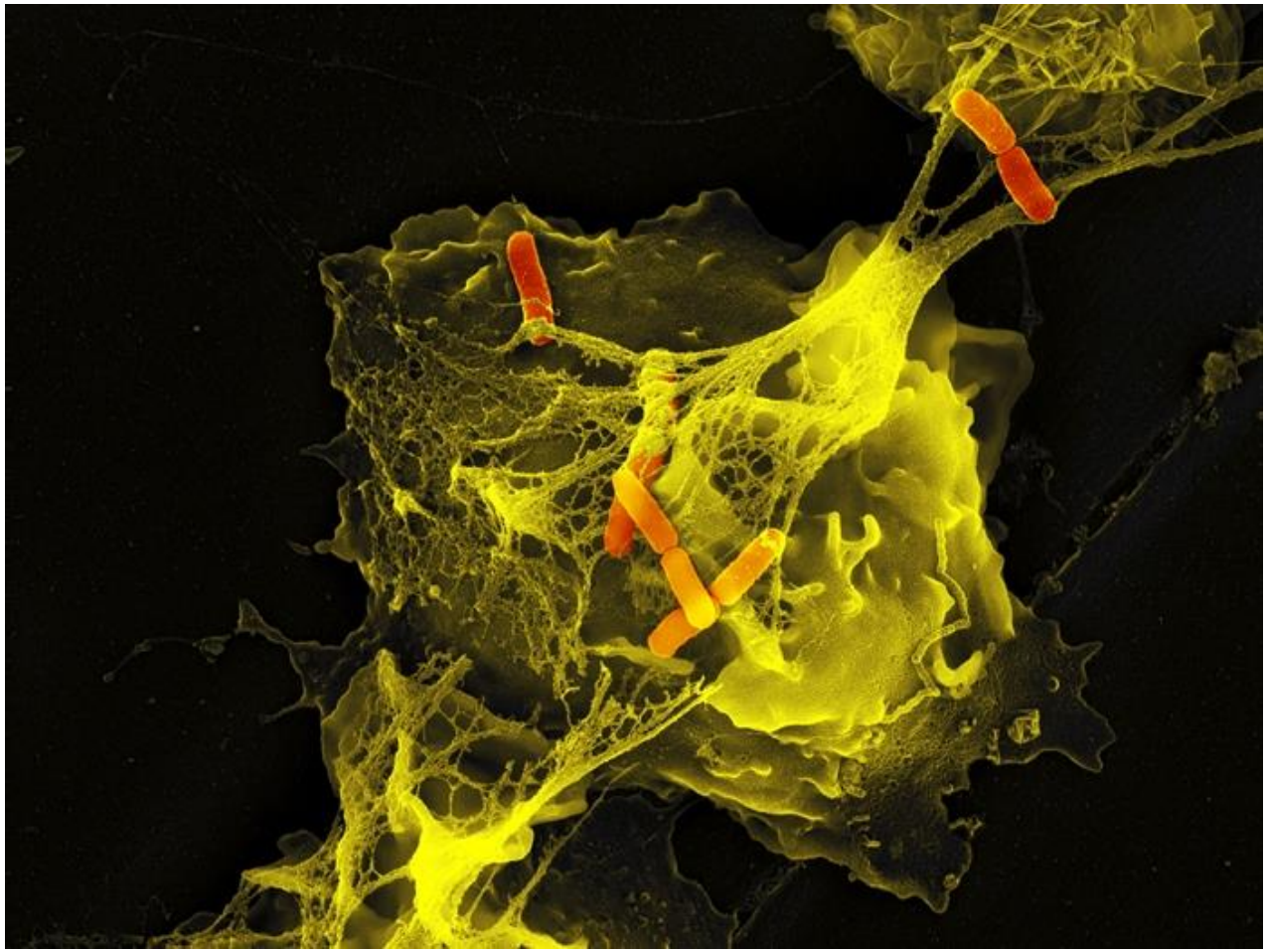

TLR8
TLR7
TLR3
TLR9
ENDOSOME
POTENTIAL THERAPEUTIC INDICATIONS
Viruses
(HCV & HBV)
Cancer
Vaccine Adjuvants
Allergies • Asthma
Other Viruses
TLR11
TLR5
TLR5
TLR4
TLR4
TLR2
ENDOSOME
NUCLEUS


BACTERIA
VIRUSES
Lipoproteins
LTAs
Flagellin
CpGs
LPS
dsRNA
SsRNA
TLR1/2
TLR2/6
TLR5
TLR4/5?
TLR9
TLR4
TLR3
TLR7
TLR8
MyD88
Mal/
TIRAP
MyD88
MyD88
MYD88/
MAL
TRAM/
TRIF
TRIF
MyD88
A signalling cascade including IRAKs, TRAF6, TAB2, TAK1 and IKKs leads to activation of NF-κB, MAPK cascades, PI-3 kinase and results in cell activation, anti-microbial responses (e.g. ROS production), and pro-inflammatory gene transcription
Later activation of NF-κB from TRIF via activation of RIP
Activation of a cascade including IKKε and TBK1 leads to induction of IRF3, and production of interferon beta
Induction of interferon-dependent gene transcription

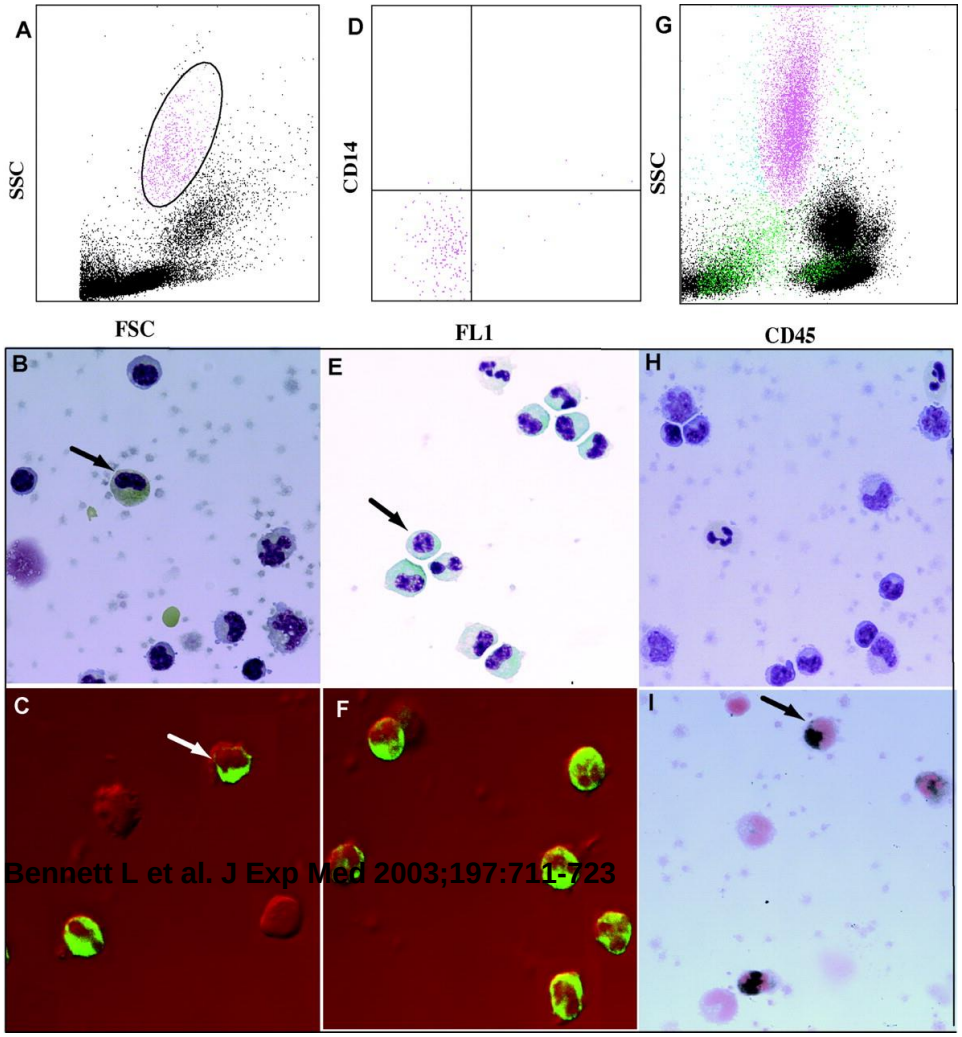
TLRs in Lupus

- Deletion of TLR7 in lupus mice prevents production of anti-RNP autoantibodies and decreases disease
- Deletion of TLR9 in lupus mice diminishes production of anti-DNA antibodies but worsens disease
- Self DNA, RNA, HSPs and Hyaluronin can trigger TLRs
- TLR7/TLR9 inhibitor is in Phase I trials in lupus

Target #6- Neutrophil Nets

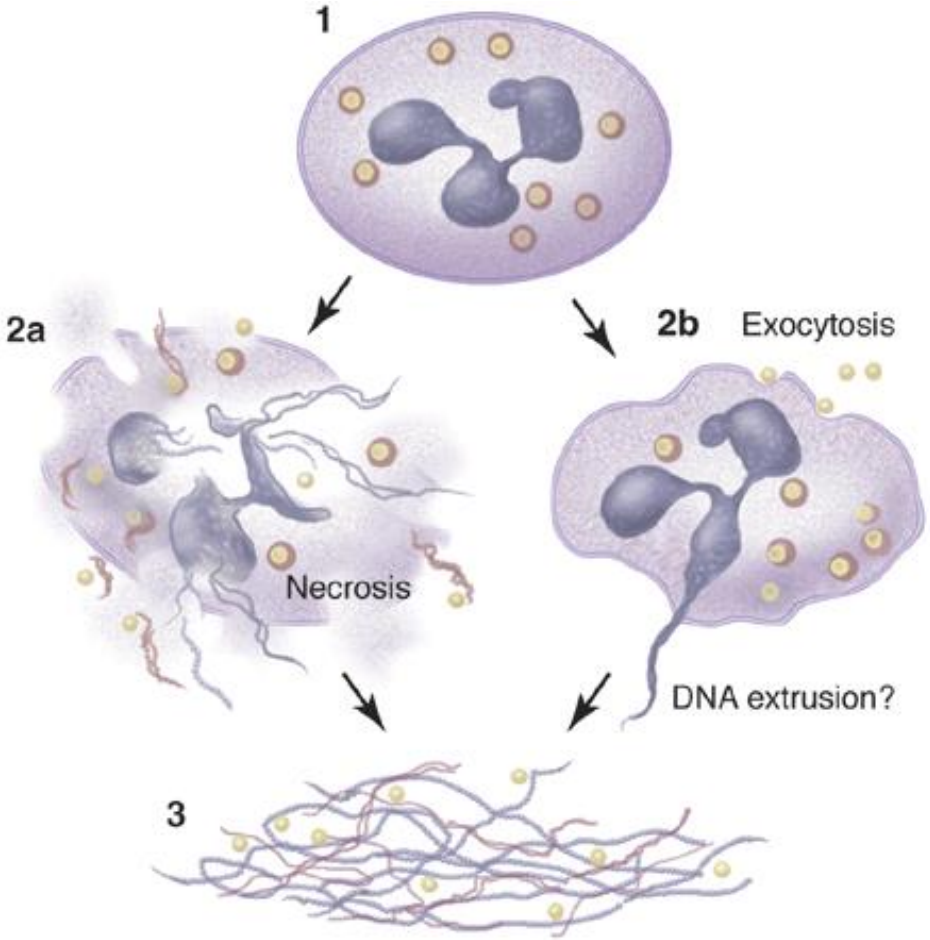


Low Density immature PMNs are detected in increased numbers in patients with lupus
The low density PMNs were shown to be high producers of IFNα

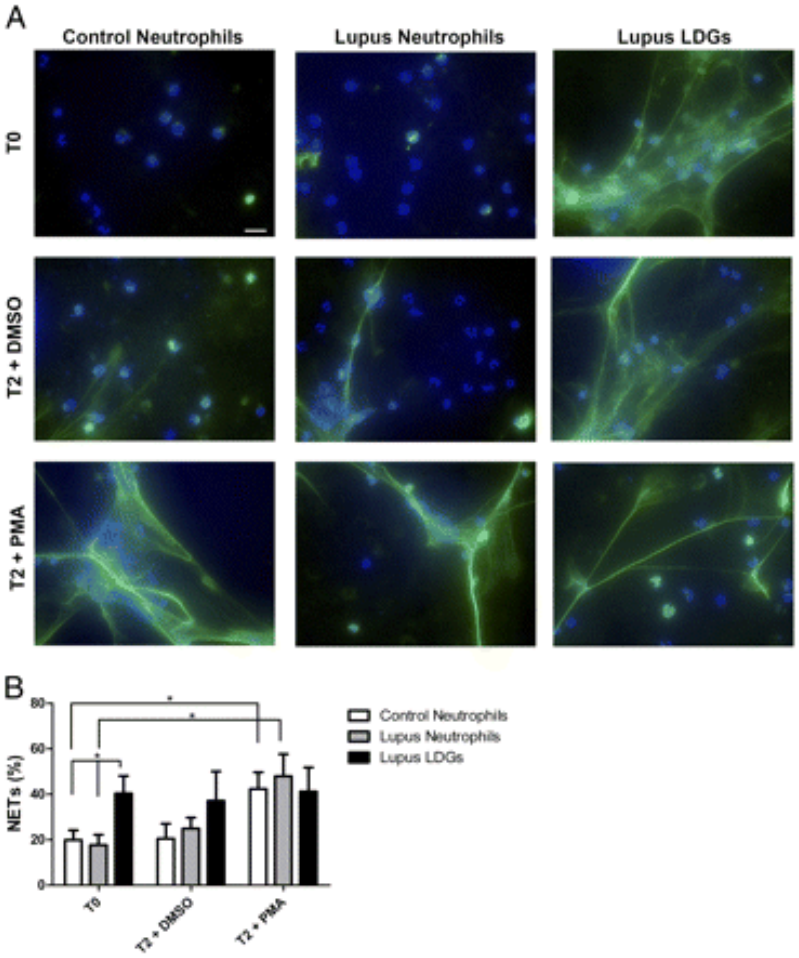


Bennett L et al. J Exp Med 2003;197:711-723

Neutrophil Nets are composed of nuclear material and anti-microbials



Low density PMNs from lupus make neutrophil nets without stimuli



Treatment strategies for NETs

- Enhance nuclease activity (DNAse)
- Block interferon alpha
- Block TLRs
- Inhibit oxidative stress
- Block anti-LL37/anti-RNP antibody production
- Balance the positive with the negative

SUMMARY

- Multiple pathways lead to lupus
- Multiple targets are being studied and over 15 drugs are in clinical trials in humans in lupus
- Most of the genes/environmental triggers and disease mediators are not specific for lupus but are pathogenic in other immune diseases
- Most therapies for lupus will likely be effective in other diseases
- ? Best strategy is to determine individual patients genetics/gene expression to determine optimum therapy.