Recent Advances in SLE Therapy: Development of targeted therapies

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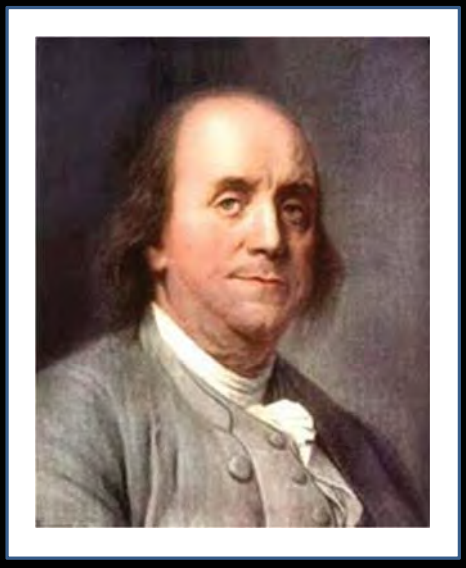
"I didn't fail the test, I just found 100 ways to do it wrong."



Lupus Clinical Trials

SLE: 3 successes *versus* lots of studies that did not work (BLISS-52, BLISS-76, ALMS maintenance)

SLE: Treatment Highlights 1996-2016

Mycophenolate Mofetil

MMF vs. CYC LN Induction — CR

	MMF	CYC
– Chan[1]: 64 class IV	73%	74%
– Ginzler[2]: 140 class III-V	23	6
– Appel[3]: 370 class III-V	9	8

MMF vs. AZA LN Maintenance — 1°

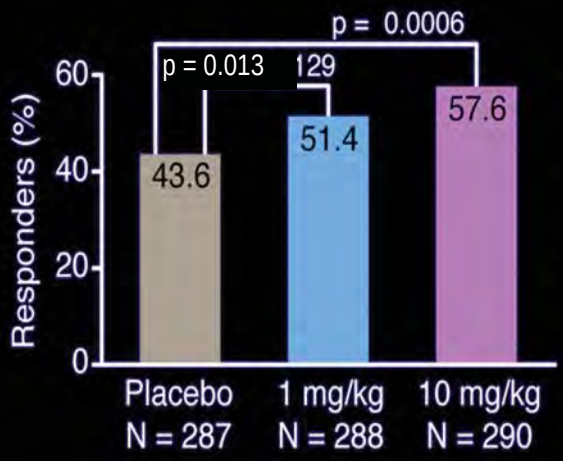
	MMF	AZA
– Dooley[4]:	82	63

1. Chan TM, et al. *J Am Soc Nephrol* 2005; **16**(4): 1076-84. 2. Ginzler EM, et al. *N Engl J Med* 2005; **353**(21): 2219-28.
3. Appel GB, et al. *J Am Soc Nephrol* 2009; **20**(5): 1103-12. 4. Dooley MA, et al. *N Engl J Med* 2011; 365:1886-1895.

2011: FDA Approval of Belimumab

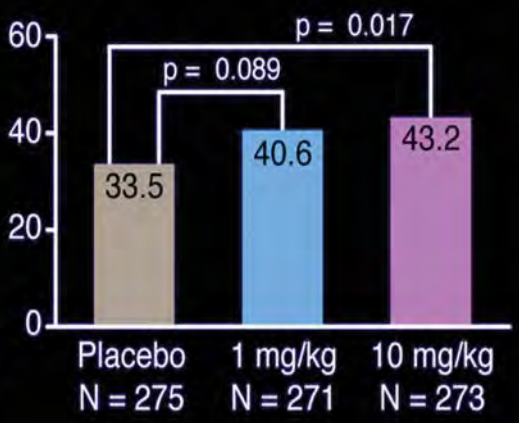
BLISS Phase III Summary

BLISS-52



Navarra SV, et al. *Lancet* 2011; **377**(9767): 721-31.

BLISS-76



Furie R, et al. *Arthritis Rheum* 2011; **63**(12): 3918-30.

Hydroxychloroquine: Old Drug, New Understanding

Recommended for all:

- Improves rash and arthritis
- Increased survival: LUMINA cohort[1]
- Reduced lipid levels (TC: -8%; LDL: -14%)[2]
- Anti-thrombotic effects[3]
- Reduced risk of early cumulative damage[4]
- Flare prevention[5]

[1]Alarcón GS et al. Ann Rheum Dis 2007; [2]Cairoli E et al. Lupus 2012; [3]Petri M Curr Rheumatol Rep 2011; [4]Akhavan PS et al. J Rheumatol 2013; [5]N Engl J Med 1991.

Current SLE Therapies

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

How Are We Performing Now?

Drug Study	Study Type	Year	Endpoint	Placebo Response Standard of Care!!
Belimumab	SLE	2011	SRI	43.6% (B-52); 33.5% (B-76)
Tabalumab	SLE	2014	mSRI(5)	28%
Sifalimumab	SLE	2014	SRI	45%
Rituximab	SLE	2010	Major Clinical	16%
Epratuzumab	SLE	2014	BICLA	21%
Rituximab	LN	2012	CR	31%
MMF	LN	2009	CR	9%
Abatacept	LN	2014	CR	3%; 12% (CRrev)
Abatacept	LN	2014	CR	30%

SLE: Unmet Needs

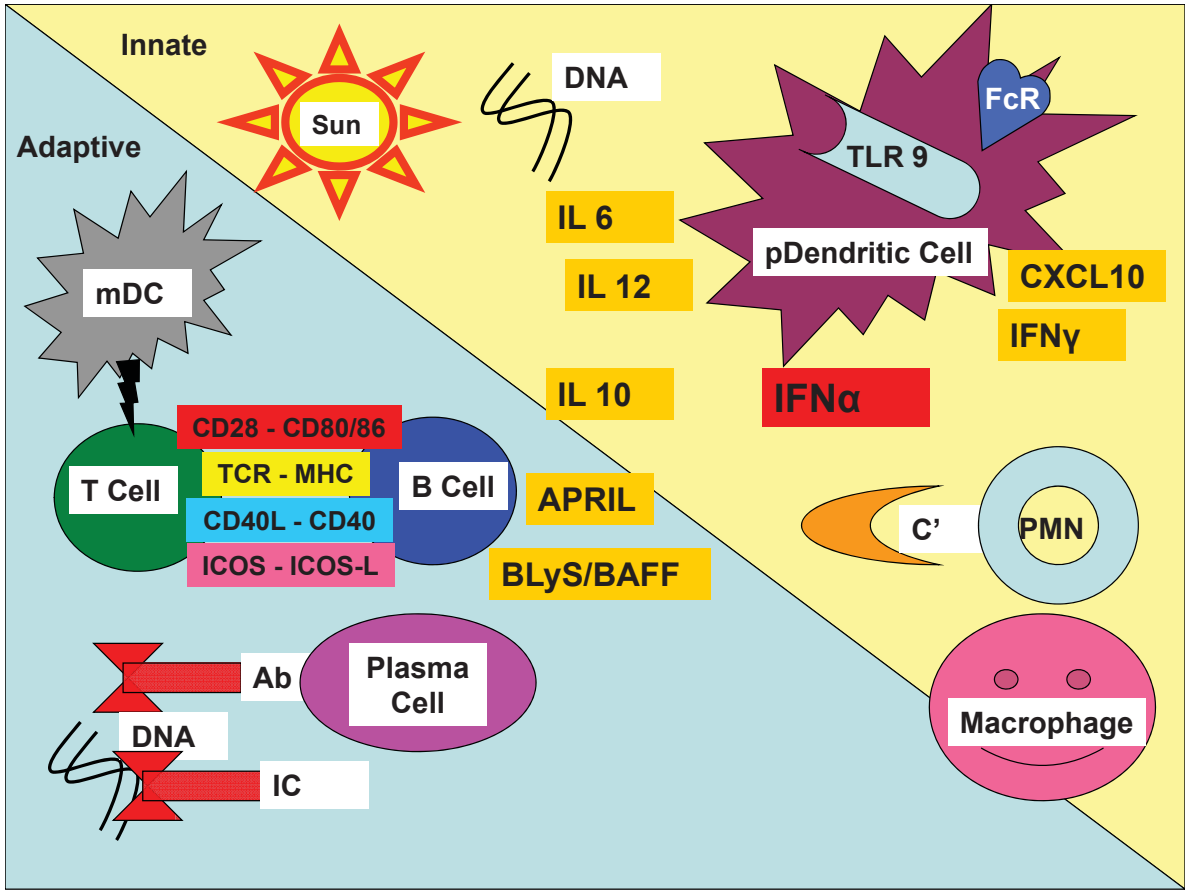
- Lupus nephritis
- Severe extra-renal disease
- Damage prevention
  - Flare prevention
  - Steroid- and immunosuppressive-sparing
- Remission induction

What Does the Future Hold?

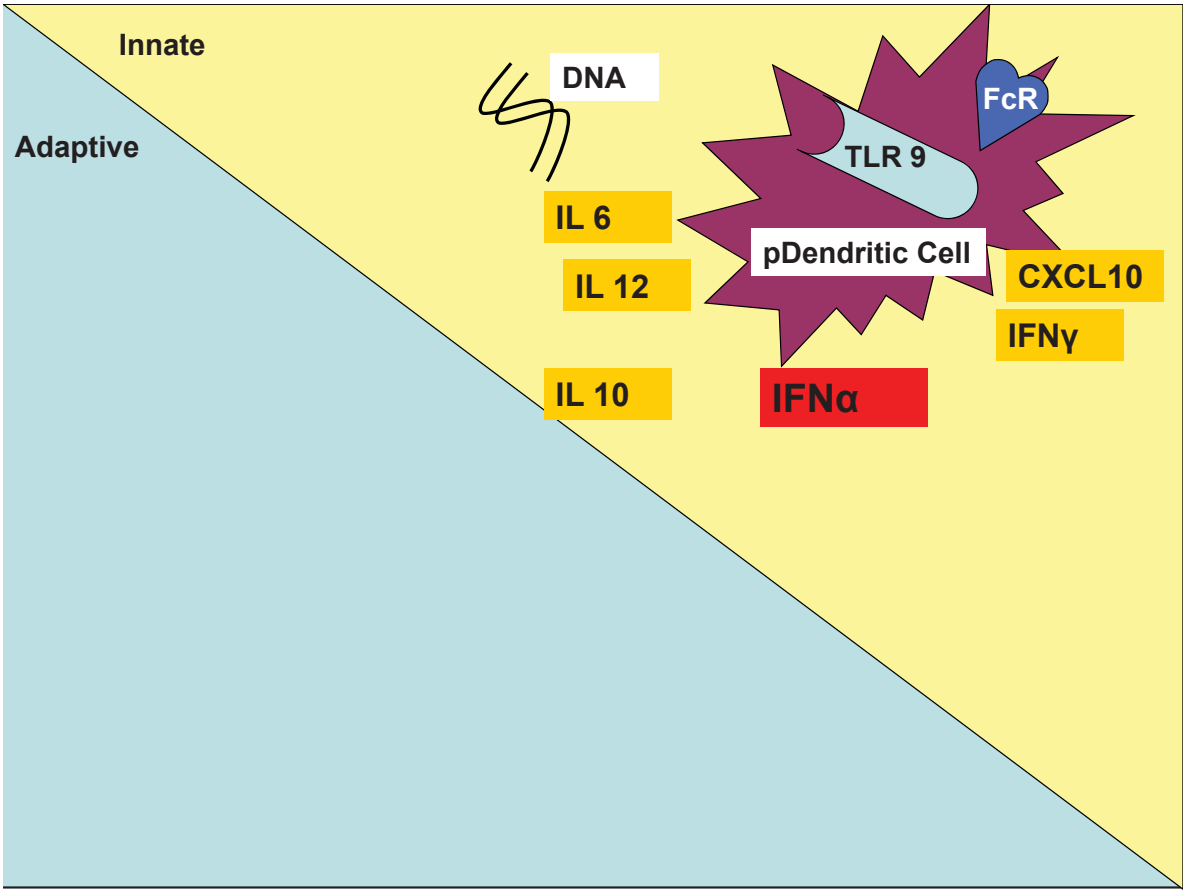
Linking Pathogenesis to SLE Drug Development

"It is difficult to make predictions, especially about the future."

Neils Bohr or Yogi Berra



Linking Pathogenesis to SLE Drug Development



Linking Pathogenesis to SLE Drug Development Strategies: Targeting "Early" Events

1. DNA (DNase)
2. RNA (RNase Fc conjugate: RSLV-132)
3. TLR
4. Type I Interferons
5. pDC

Targeting TLRs

- DV1179 (TLR 7/9 inhibitor):
  - Entry criteria: IFN signature
  - N= 52
  - Treatment up to 60 mg for 8 weeks
  - Endpoint: IFN signature inhibition
  - Failed pharmacodynamic endpoint (IFN GS)
- IMO-8400 (oligonucleotide inhibitor of TLR 7,8,9)
  - Psoriasis, DM, Waldenstrom's

Interferons

- Type I
  - IFN-α, -β, -ω, -ε, -κ
  - Bind to IFNAR
- Type II
  - IFN-γ
  - Binds to IFNGR
- Type III

Interferon alpha in SLE

- 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?

Targeting Type I IFNs: Strategies

- IFNα-Kinoïd: vaccine (inactive IFNα-KLH)[0]
- Ab to IFN alpha
  - 3 Ab (sifalimumab; rontalizumab; AGS-009)
  - 2 diseases (myositis[1], SLE[2-5])
- Ab to type I IFN receptor (IFNAR)
  - 1 Ab (anifrolumab)
  - 2 diseases (scleroderma[6]; SLE[7,8])
- Ab to IFN omega[9]

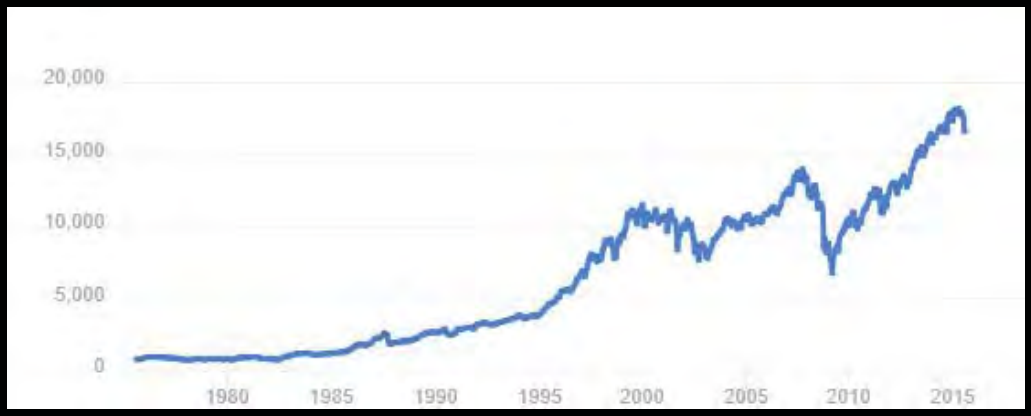
[0]Lauwerys BR, et al. Arthritis Rheum 2013;[1]Higgs BW, et al. Ann Rheum Dis 2013; [2]Merrill JT, et al. Ann Rheum Dis 2011; [3]Petri M, et al. Arthritis Rheum 2013; [4]Khamashta M, et al. ACR 2014; [5]Kalunian KC, et al. Ann Rheum Dis 2015; [6]Goldberg A, et al. Arthritis Res Ther 2014; [7]Morehouse C, et al. ACR 2014; [8]Furie R, et al. ACR 2015; EULAR 2016; [9]Jordan J et al. ACR 2014.

Type I IFN Antagonists: SLE

- Rontalizumab phase II trial (n=238): failed[1]
- Sifalimumab phase IIb trial (n = 431)[2]
  - 4 treatment arms
  - 60% SRI response (1200 mg q4wk) vs 45% (placebo)
  - No significant toxicities
- Anifrolumab trials:
  - Japanese study: 50% greater IFN GS suppression with anifrolumab (97%) than with sifalimumab[3]
  - Phase II: 300 patients, 3 arms[4]

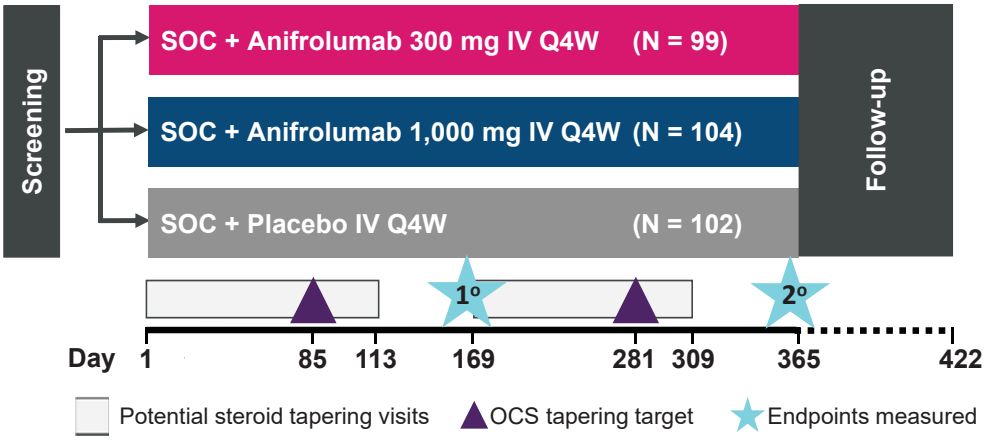
[1]Kalunian KC, et al. Ann Rheum Dis 2015; [2]Khamashta M, et al. Ann Rheum Dis 2016; [3]Morehouse C et al. ACR 2014; [4]Furie R et al. ACR 2015.

Dow Jones Industrial Average or Enthusiasm for IFN Inhibition as an SLE Treatment Strategy?



Dow Jones Industrial Average or Enthusiasm for IFN Inhibition as an SLE Treatment Strategy?

Anifrolumab Phase II: Study design



Primary efficacy measure

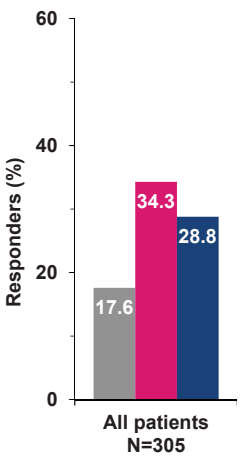
- SLE Responder Index [SRI(4)] at Day 169 with a sustained reduction of oral corticosteroid to <10 mg/day prednisone and ≤Day 1 dose, between Days 85 and 169

Q4W, every 4 weeks; SOC, standard of care; SRI, SLE responder index

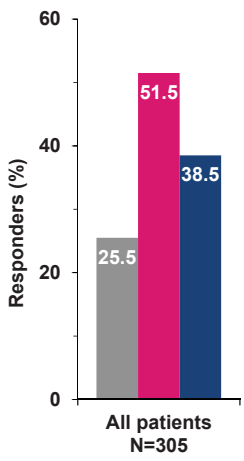
Furie R et al. ACR 2015

NCT01438489

Primary endpoint: SRI(4) including OCS taper



	300 mg	1,000 mg
Delta:	16.7%	11.2%
OR:	2.38	1.94
90% CI:	(1.33, 4.26)	(1.08, 3.49)
P:	0.014	0.063



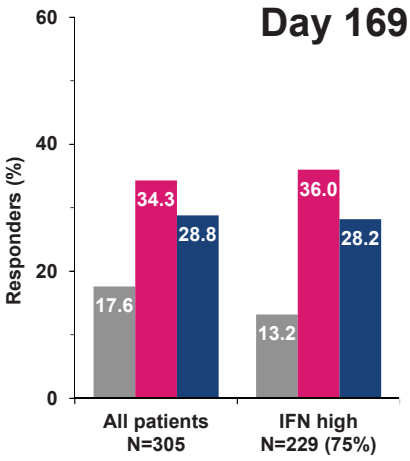
	300 mg	1,000 mg
	26.0%	13.0%
	3.08	1.84
	(1.86, 5.09)	(1.11, 3.04)
	<0.001	0.048

Placebo Anifrolumab 300 mg Q4W Anifrolumab 1,000 mg Q4W

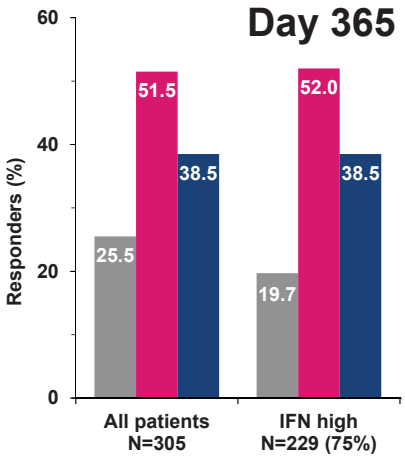
Dropouts and patients whose medication use exceeded protocol threshold were imputed as failures

Delta=dosage vs. placebo

Primary endpoint: SRI(4) including OCS taper



	300 mg	1,000 mg	300 mg	1,000 mg
Delta:	16.7%	11.2%	22.8%	15.0%
OR:	2.38	1.94	3.55	2.65
90% CI:	(1.33, 4.26)	(1.08, 3.49)	(1.72, 7.32)	(1.27, 5.53)
P:	0.014	0.063	0.004	0.029



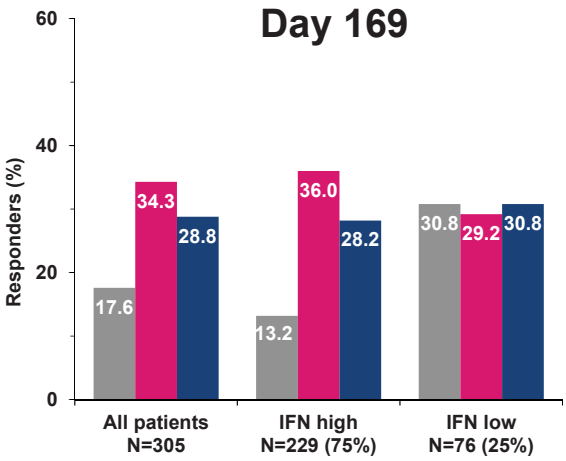
	300 mg	1,000 mg	300 mg	1,000 mg
Delta:	26.0%	13.0%	32.3%	18.8%
OR:	3.08	1.84	4.30	2.52
90% CI:	(1.86, 5.09)	(1.11, 3.04)	(2.34, 7.91)	(1.37, 4.64)
P:	<0.001	0.048	<0.001	0.013

Placebo Anifrolumab 300 mg Q4W Anifrolumab 1,000 mg Q4W

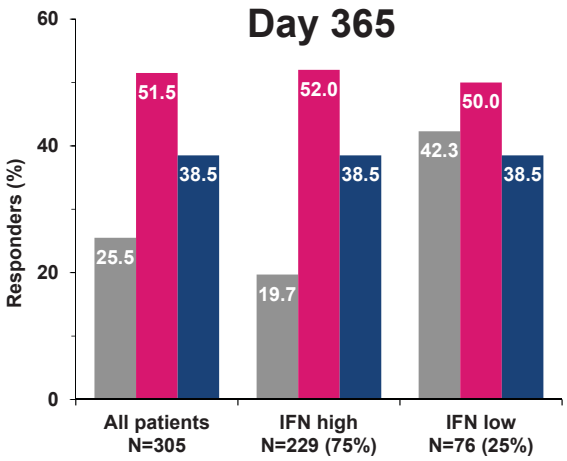
Dropouts and patients whose medication use exceeded protocol threshold were imputed as failures

Delta=dosage vs. placebo

Primary endpoint: SRI(4) including OCS taper



	300 mg	1,000 mg	300 mg	1,000 mg	300 mg	1,000 mg
Delta:	16.7%	11.2%	22.8%	15.0%	-1.6%	0.0%
OR:	2.38	1.94	3.55	2.65	0.96	1.04
90% CI:	(1.33, 4.26)	(1.08, 3.49)	(1.72, 7.32)	(1.27, 5.53)	(0.34, 2.74)	(0.37, 2.88)
P:	0.014	0.063	0.004	0.029	0.946	0.953



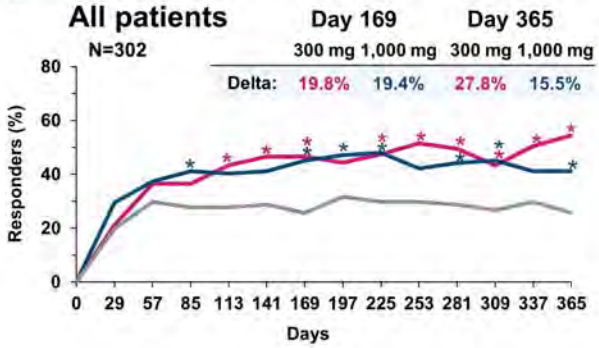
	300 mg	1,000 mg	300 mg	1,000 mg	300 mg	1,000 mg
Delta:	26.0%	13.0%	32.3%	18.8%	7.7%	-3.8%
OR:	3.08	1.84	4.30	2.52	1.47	0.89
90% CI:	(1.86, 5.09)	(1.11, 3.04)	(2.34, 7.91)	(1.37, 4.64)	(0.55, 3.93)	(0.34, 2.35)
P:	<0.001	0.048	<0.001	0.013	0.514	0.849

Placebo Anifrolumab 300 mg Q4W Anifrolumab 1,000 mg Q4W

Dropouts and patients whose medication use exceeded protocol threshold were imputed as failures

Delta=dosage vs. placebo

BICLA response

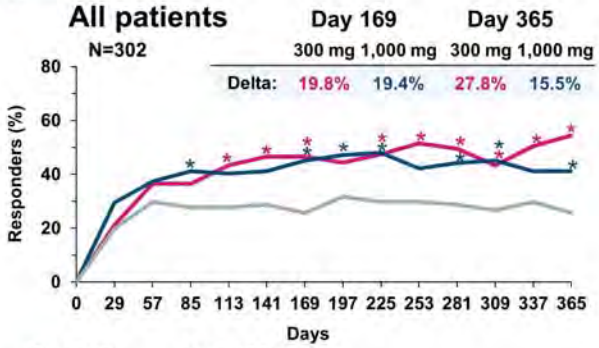


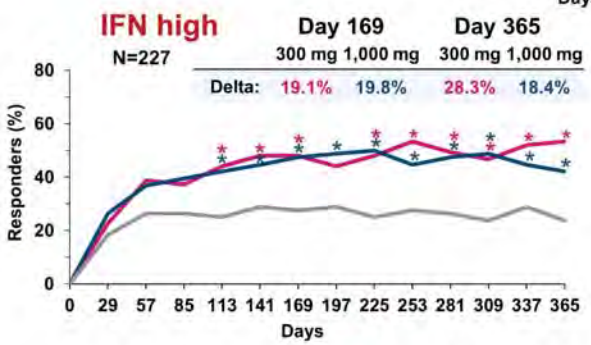
Placebo Anifrolumab 300 mg Q4W Anifrolumab 1,000 mg Q4W

*p≤0.05 compared with placebo

Delta=dosage vs. placebo

BICLA response



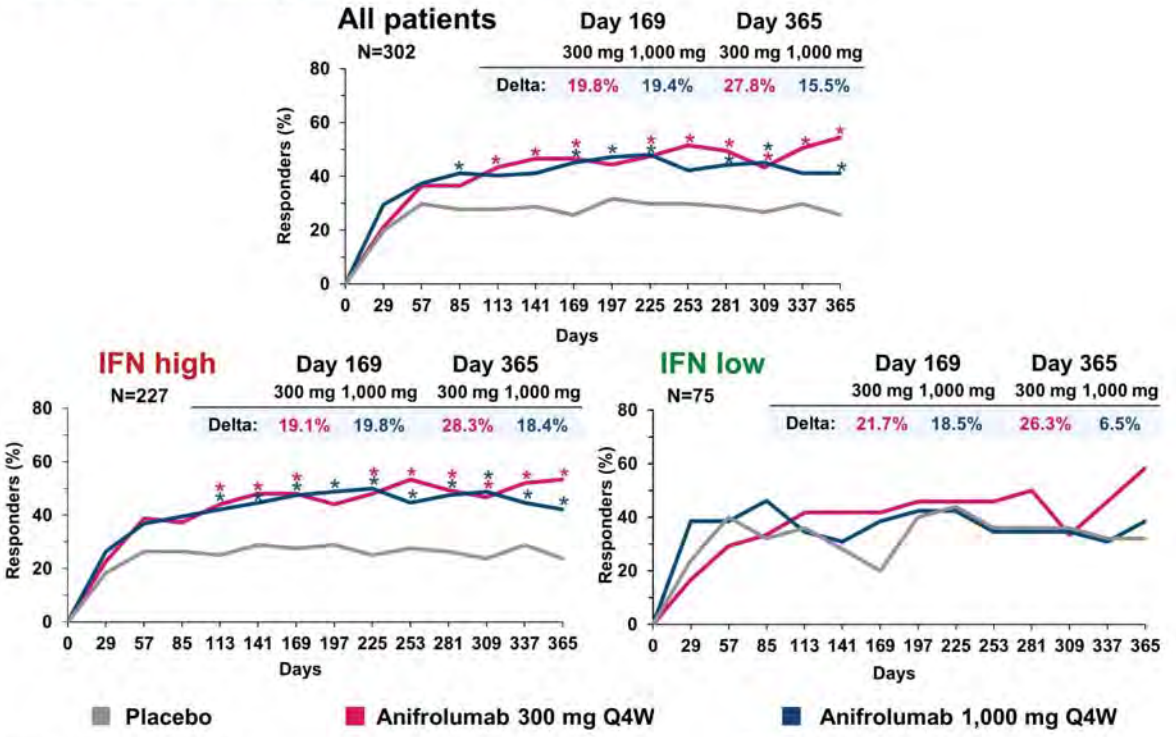


Placebo Anifrolumab 300 mg Q4W Anifrolumab 1,000 mg Q4W

*p≤0.05 compared with placebo

Delta=dosage vs. placebo

BICLA response



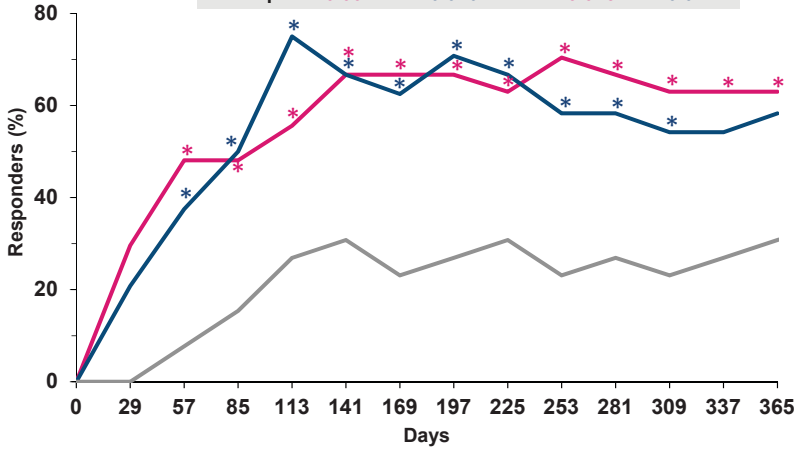
*p≤0.05 compared with placebo

Delta=dosage vs. placebo

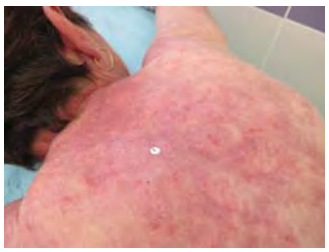
Reduction in CLASI activity

≥50% improvement in patients with CLASI activity score ≥10 at baseline (N=77)

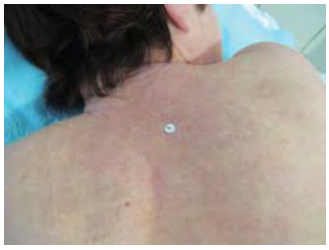
	Day 169		Day 365	
	300 mg	1,000 mg	300 mg	1,000 mg
Delta:	43.6%	39.4%	32.2%	27.5%
OR:	7.31	5.16	4.49	2.97
90% CI:	(2.56, 20.86)	(1.81, 14.73)	(1.67, 12.12)	(1.08, 8.19)
p:	0.002	0.010	0.013	0.077



Day 1



Day 281

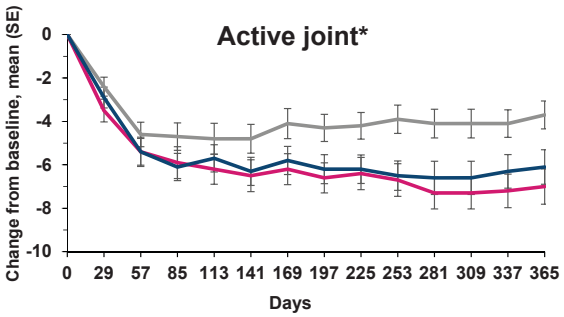


Patient was receiving anifrolumab 300 mg Q4W

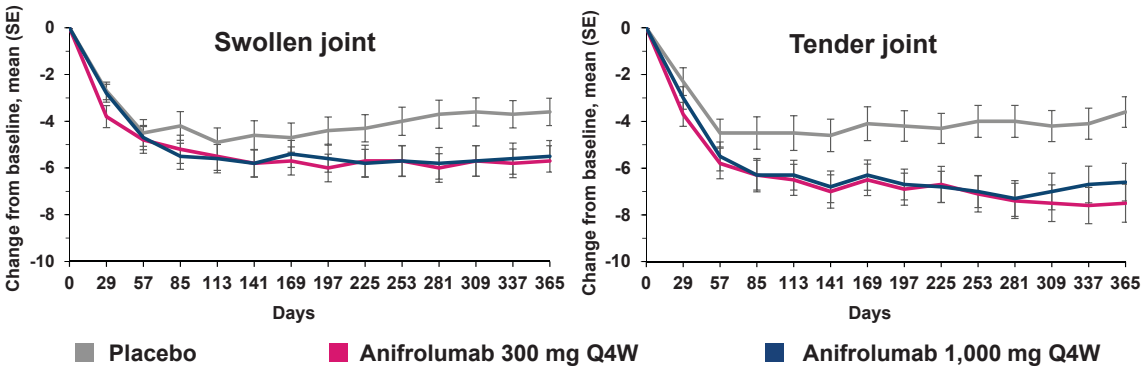
*p≤0.05 compared with placebo

Delta=dosage vs. placebo

Reduction in joint scores



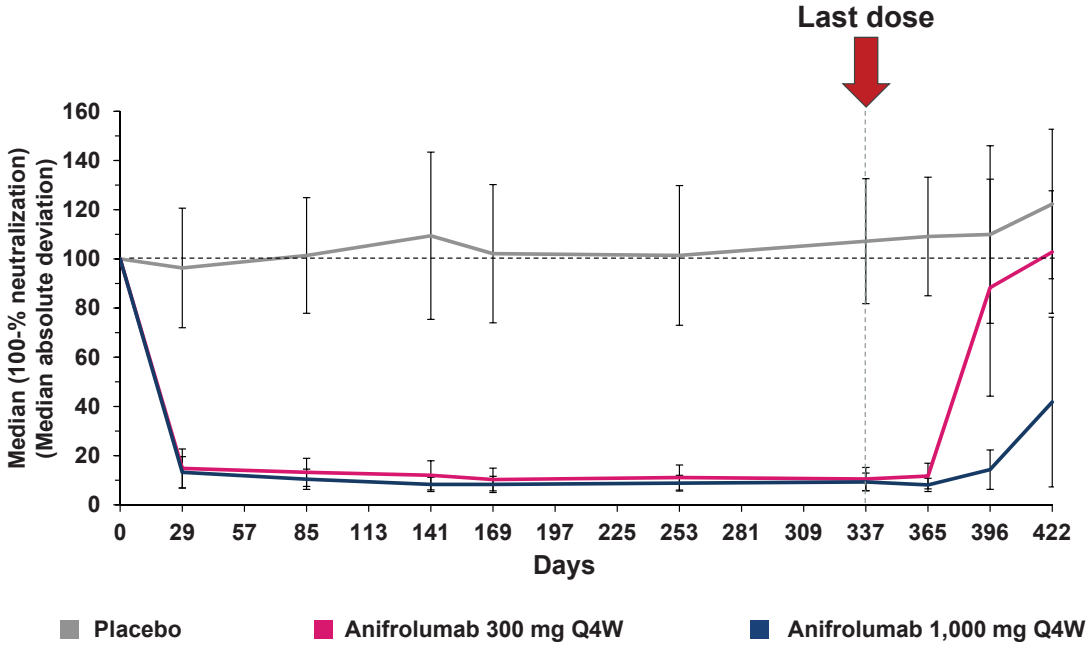
*Defined as a joint with pain and signs of inflammation



SE, standard error

Furie RA et al EULAR 2016

Neutralization of 21-gene type I IFN signature*



*Based on patients with positive gene signature at baseline.
Positive is defined as baseline 21-gene signature ≥2

The Interferon High vs Low Patient

	Rontalizumab[1]		Sifalimumab and Anifrolumab[2]	
	N=238		N=736	
	High	Low	High	Low
BILAG ≥2A	9%	16%		
SLEDAI mean	10	10		
SLEDAI ≥ 10			63%	52%
CLASI ≥ 10			32%	13%
DNA Ab	71%	35%	85%	58%
ENA Ab	74%	19%		
Sm Ab			30%	5%
RNP Ab			34%	8%
Low C3	43%	16%	48%	19%
Low C4	39%	11%	31%	7%

[1]Kalunian KC, et al. Ann Rheum Dis 2015; [2]Ranade K, et al. ACR 2015

Targeting pDCs

- BDCA2:
  - Uniquely expressed lectin on pDCs
  - Ligation of BDCA2 suppresses IFN production in pDCs
  - Anti-BDCA 2 (BIIB059)[1]:
    - BDCA2 internalization (Fc-independent)
    - Down-modulation of CD32a (FcγRIIa; Fc-dependent)
    - Inhibits TLR-induced IFN by pDCs in vitro using healthy and SLE blood
  - Phase I SLE study underway

[1]Pellerin A et al. EMBO 2015

Targeting pDCs

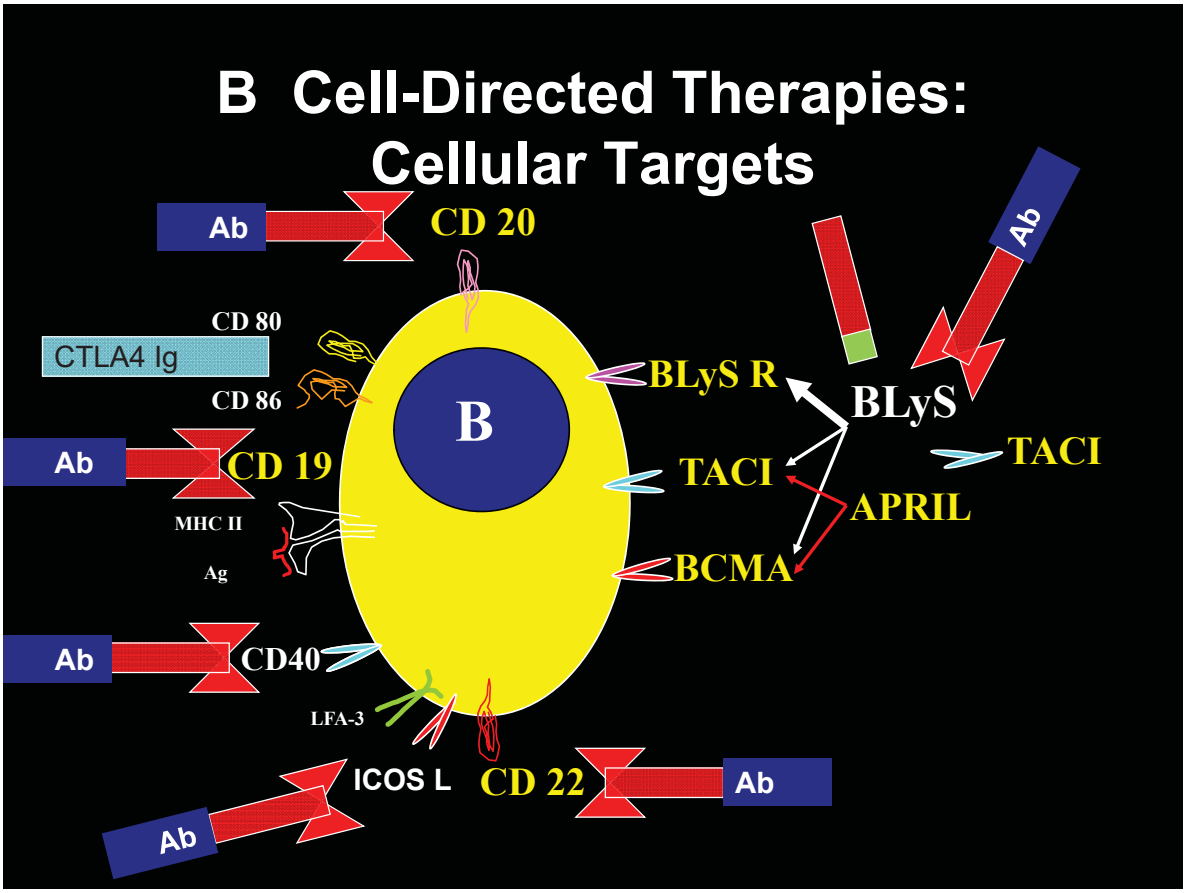
- Anti-IL-3Rα [CD123] (JNJ 473)[1,2]
  - Depletes IL-3Rα-expressing cells
  - SLE in vitro studies
    - Average depletion 86% for pDCs; 59% for basophils
    - Mechanism: ADCC
    - 99% reduction in TLR9-stimulated IFNα production
    - Reduction in TLR9 agonist (CpG)-induced production of IP-10, ITAC and MCP-2
- Bcl-2 Antagonists: pDC depletion in NZB/NZW mice

[1]Oon S et al. EULAR 2016; [2]Monaghan KA et al. EULAR 2016

Linking Pathogenesis to SLE Drug Development Strategies: Lymphocyte Targets

1. B cells
   a. Cellular targets
      1. CD 20
      2. CD 22
   b. Extracellular targets
      1. BLyS (BAFF)
      2. APRIL
2. T cells
   a. Cellular targets
      1. CD28-CD80/86 pathway
      2. CD40L-CD40

B Cell-Directed Therapies: Cellular Targets

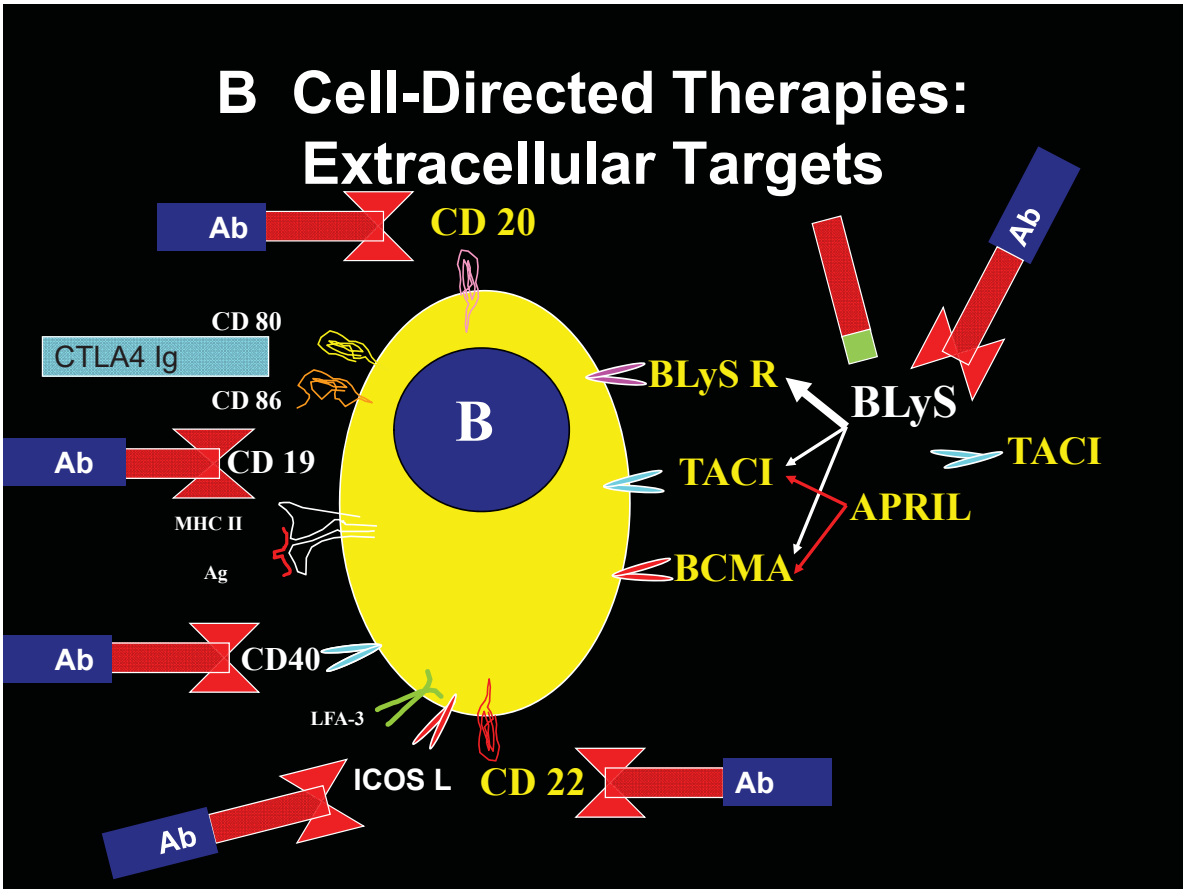


Anti-CD20 B Cell Depletion Therapy: Dead or Alive?

- Clinicians still believe
  - LUNAR: wk 78 proteinuria reduction; fewer rescues[1]
  - Refractory nephritis, autoimmune cytopenias
  - CNS disease
- Interest remains high (nephritis studies)
- Will companies pursue an indication in SLE?
  - Obinutuzumab
    - 3rd generation Ab; approved for CLL in 2013
    - LN study underway

[1]Rovin BH et al. Arthritis Rheum 2012

B Cell-Directed Therapies: Extracellular Targets



Biologic Rationale for Targeting BLyS

- Crucial to B cells[1-4]
  - Maturation
  - Differentiation
  - Survival
- Murine models
  - Transgenic mice develop SLE-like disease[5-7]
  - TACI-Ig ameliorates murine lupus activity[4,8]
- Human SLE
  - Elevated levels[9] (predictive of flare)[10]

1. Moore PA et al. Science. 1999;285:260-3; 2. Schneider P et al. J Exp Med. 1999;189:1747-56; 3. Batten M et al. J Exp Med. 2000;192:1453-65;4. Gross JA et al. Nature. 2000;404:995-9; 5. Groom J et al. J Clin Invest. 2002;109:59-68; 6. Mackay F et al. J Exp Med. 1999;190:1697-1710; 7. Khare SJ et al. Proc Natl Acad Sci U S A. 2000; 97:3370-5;. 8. Ramanujam M et al. J Clin Invest. 2006;116:724-34. 9. Cheema G et al. Arthritis Rheum. 2001;44:1313-19; 10. Petri M et al. Arthritis Rheum. 2008;58:2453-9.

Inhibitors of the BLyS/APRIL Pathway

Belimumab:	FDA approval 2011[1,2]
Tabalumab:	ILLUMINATE 1: both doses failed[3a]
	ILLUMINATE 2: high dose effective[3b]
Blisibimod:	In phase III[4]
Atacicept:	Lupus Nephritis: Study terminated[5]
	Extra-renal SLE (n = 461)[6]:
	150 mg arm terminated (2 deaths)
	75 mg dosing arm ineffective

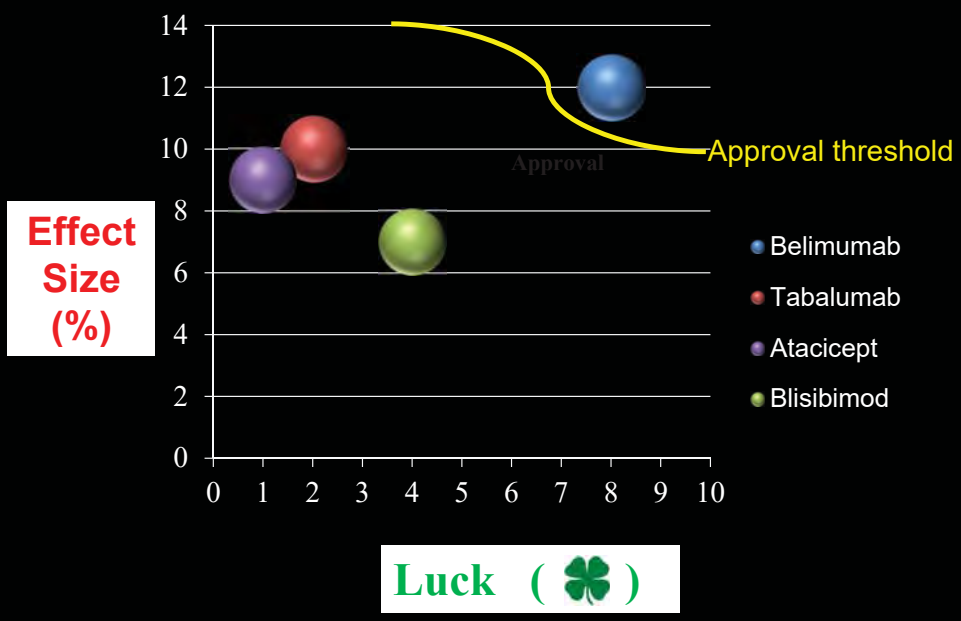
[1]Navarra SV, et al. Lancet 2011; [2]Furie R, et al. Arthritis Rheum 2011;[3a]Isenberg DA Ann Rheum Dis 2015; [3b]Merrill JT Ann Rheum Dis 2015; [4]Furie R, et al. Ann Rheum Dis 2014; [5]Ginzler EM, et al. Arth Res Ther 2012;[6]Isenberg D, et al. Ann Rheum Dis 2015

BLyS Inhibitors

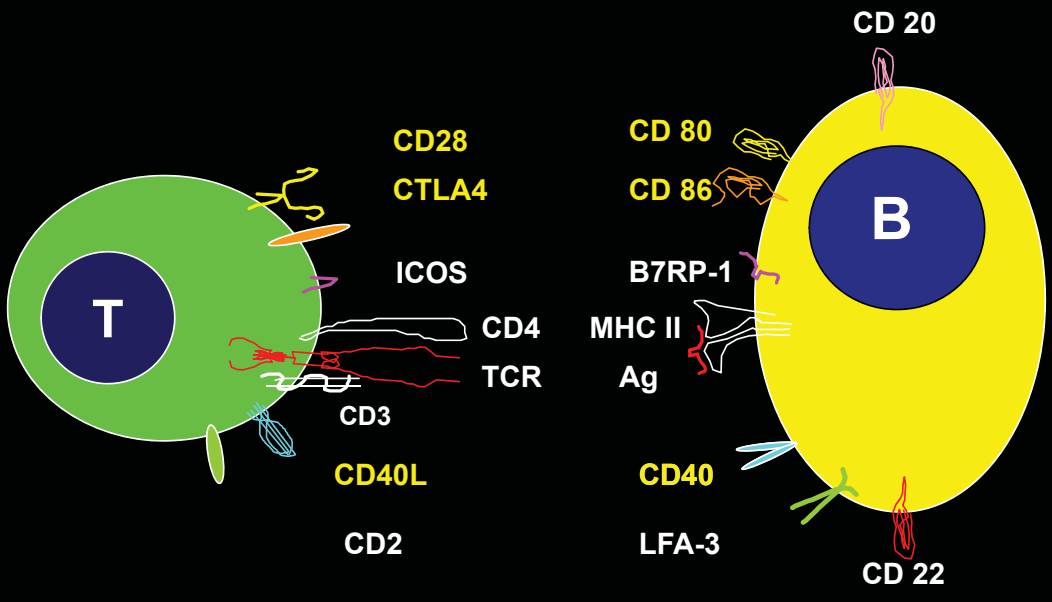
Drug	Route	KD	Highest Dose	Monthly Maintenance Dose	Endpoint
Belimumab	iv	K_D = 300 pM	10 mg/kg	~600 mg	SRI (4) Wk 52
Tabalumab	sq	K_D = 120 pM	120 mg	240 mg	SRI (5) Wk 52
Atacicept	sq	K_D = 20 pM	75 mg*	300 mg	Flare Wk 52
Blisibimod	sq	K_D = 1 pM	200 mg	800 mg	SRI (5) Wk 24

*150 mg dosing arm terminated

BLyS Pathway Inhibitors: Outcomes



Targeting T Cells and T – B Cell Interactions



Abatacept (CTLA 4 Ig)

- Binds CD80/86 on B cells
- Inhibits T cell activation
- Clinical trials
  - Extra-renal flare prevention trial (unsuccessful)[1]
  - Lupus nephritis (2 trials unsuccessful)
    - MMF background[2]
    - Eurolupus cyclophosphamide background[3]
  - Lupus nephritis (MMF) being repeated

[1]Merrill JT et al. Arthritis Rheum 2010; [2]Furie R et al. Arthritis Rheum 2014;
[3]Wofsy D et al. Arthritis Rheum 2013

Targeting T Cells and T – B Cell Interactions

- CD40L
  - IDEC phase II: ineffective
  - Biogen phase II: thrombosis
  - UCB/Biogen phase II:
    - PEG anti-CD 40L (dapirolizumab pegol)
    - Extra-renal phase II underway
- CD40
  - BI (BI 655064) : lupus nephritis underway
- CD28
  - BMS (Lulizumab): extra-renal study

Linking Pathogenesis to SLE Drug Development Strategies: Cytokine Targets

1. IL 10
2. IL 6
3. IL 21

IL-6 Inhibition

- Tocilizumab: arthritis improved; neutropenia[1]
- Sirukumab: 24 LN patients (20 vs. 4)[2]
  - 24 wk endpoint (proteinuria)
  - 15% with Pr/Cr < 0.5 (vs. 0 in P)
  - ~ 50% with SAEs, mostly infections (vs. 0 in P)
- PF-04236921: Extra-renal study[3]
  - 4 dose groups (10, 50, 200, P)
  - 24 wk endpoint (SRI)
  - 10 mg: 60%; 50 mg: 39% (vs. P: 40%; p=0.076 for 10 mg)
  - 200 mg arm terminated (3 deaths)

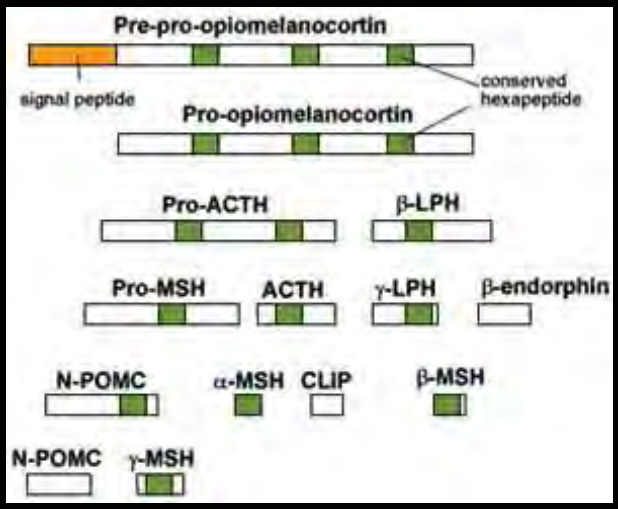
[1]Illei G, et al. *Arthritis Rheum* 2009; [2]van Vollenhoven R, et al. EULAR 2013; [3]Wallace D, et al. ACR 2014.

Linking Pathogenesis to SLE Drug Development Strategies: Melanocortin Receptors

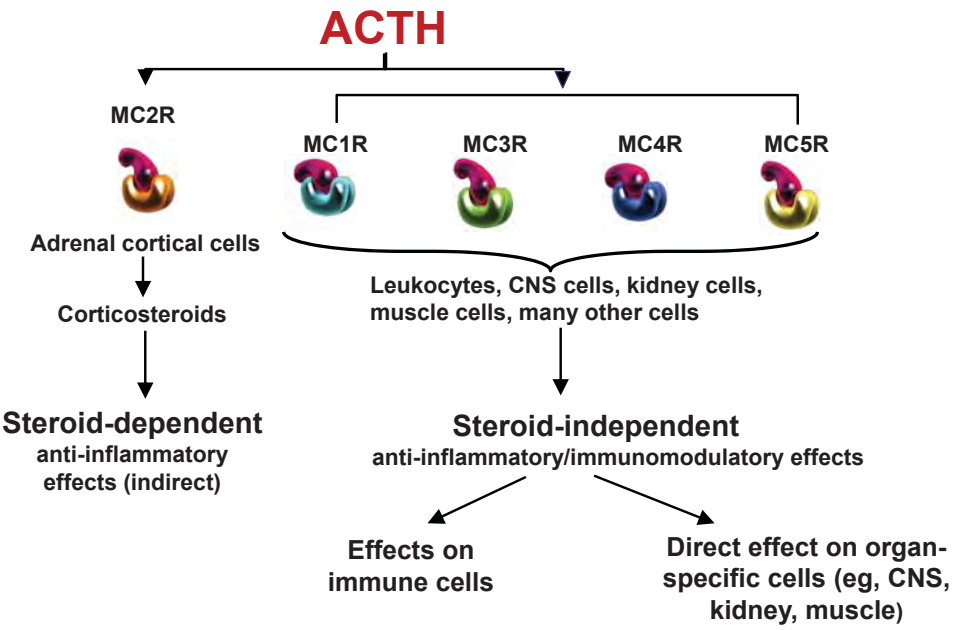
1. Repository Corticotropin Injection (Acthar)

Linking Pathogenesis to SLE Drug Development Strategies: Melanocortin Receptors

Pro-opiomelancortin Metabolism



Melanocortin Receptor Expression



Other Targets or Drugs

- Laquinimod: arthritis; lupus nephritis
- Immunoregulatory peptides: edratide; rigerimod
- CC-220: targets cereblon (E3 ubiquitin ligase coreceptor)
- Dapirolizumab pegol (anti-CD40L)
- BI 655064 (anti-CD40)
- Lulizumab (anti-CD28)
- NN8828 (anti-IL-21)
- Anti-CXCR5 Ab: B cell migration (CXCL13)
- Bortezomib: parenteral proteasome inhibitor
- Ixazomib: oral proteasome/immunoproteasome inhibitor

More Targets or Drugs

- ACT-334441 (sphingosine-1-phosphate receptor agonist KRP-203)
- Lupuzor
- Tacrolimus
- CC-11050
- ACTHar
- AMG 557 (anti-B7RP-1 (ICOSL) mAb)
- PD-0360324 (mAb to monocyte/macrophage colony stimulating factor)
- CC-930 (anti-fibrotic JNK inhibitor)
- Bruton's Tyrosine Kinase (BTK) inhibitor
- C5aR
- C5
- IL21
- ASF-1096 (a sulfated salt of R-salbutamol (affects T cells, PMNs))

More Targets or Drugs

- Anti-TWEAK: program terminated
- Milatuzumab (anti-CD74: HLA-DR)
- RSLV-132 (Rnase)
- Alitretinoin (Toctino®)
- Tacrolimus
- Sirolimus
- Lenalidomide
- Omalizumab (anti-IgE)
- Nelfinavir
- Ustekinumab
- SAR 113244, an anti-CXCR5 monoclonal antibody
- ALX-0061 – anti-IL-6R
- Paquinimod (ABR-215757: a quinoline-3-carboxamide derivative)
- Arsenic Trioxide (ATO)

More Targets or Drugs

- Fumaric Acid Esters (Fumaderm®)
- ABT-199, a potent and selective BCL-2 inhibitor
- hrIL-2
- MEDI 570 (anti-ICOS)
- ACT-334441
- GSK2586184 (JAK1 Inh)
- AMG 811 (anti-IFN gamma)
- Fulvestrant
- INV103 (ala-Cpn10) Chaperonin 10
- Baricitinib

>600 studies listed on Clintrials.gov

Lupus Trial Design

It's not just about the drug

- **Trial Design**
  - Domain-specific vs. global
  - Entry criteria
  - Background therapies
- **Endpoints**
  - Custom endpoints
  - Single endpoint *vs* composite endpoint
    - SLEDAI or BILAG changes alone
    - BICLA or SRI
    - Modified SRI requiring higher thresholds of SLEDAI response
- No consensus for extra-renal studies

Challenges to Drug Development

We need:

- Informative pre-clinical models
  - Observational studies; ? Animal models

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  - Organ-specific (rash, arthritis) designs
- Refinements in trial design
  - Lower the placebo response
  - Increase the effect size
  - Reduce the sample size

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- More trial participation by patients
  - ?
- Fewer lightning bolts: might be quicker to enroll
  - Unprecedented trial activity = competition for patients

Optimism About the Future

We will have:

- Many more medicines
  - No doubt they will become harder to pronounce
- Biomarkers
- Individualized therapy
- Better outcomes!!

The Physician-Patient Encounter in 2025

"Off hand, I'd say you're suffering from an arrow through your head, but just to play it safe, I'm ordering a bunch of tests."

As much as science and technology are integrated, treating lupus patients will remain an art.

What have trials of new therapies in SLE taught us?

They have taught us to be:

Humble

Logical

Perseverant

Thank You