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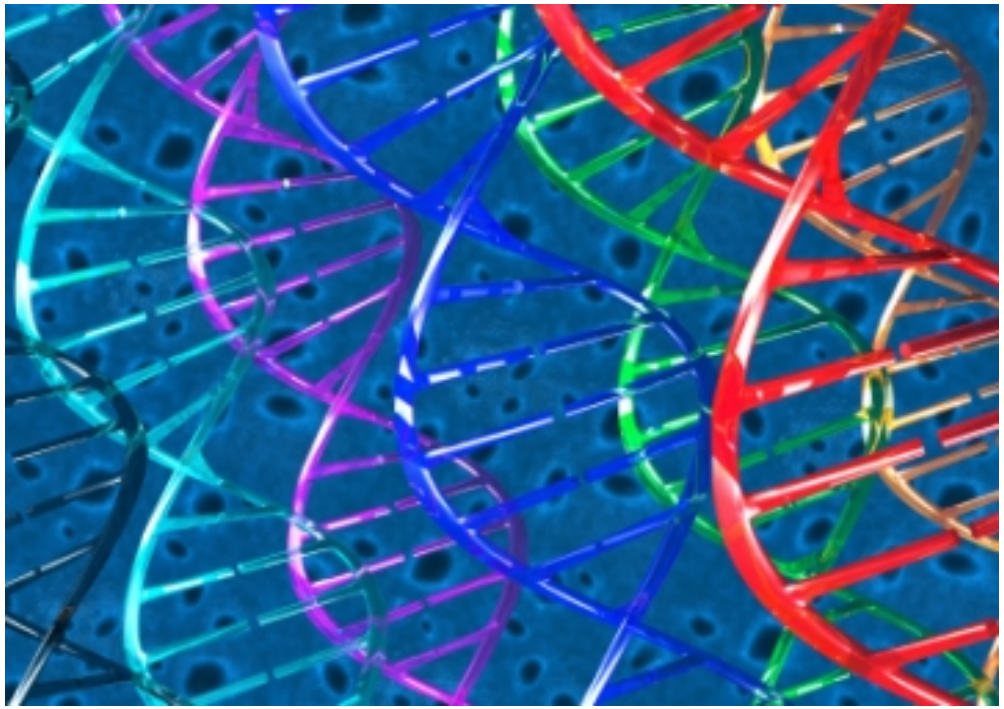
Blockbuster drugs for niche markets

Lupuzor Presentation
Phase IIb Abstract / Clinical Paper
2012 Annual ACR Meeting



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Lupuzor ™
Treatment of Lupus

A novel drug specific for the treatment of Lupus with multi-billion sales potential

Mechanism that modulates the immune system specifically to correct the abnormality in Lupus

Leaves the rest of the immune system intact to defend the body

Significant advantages vs other treatments

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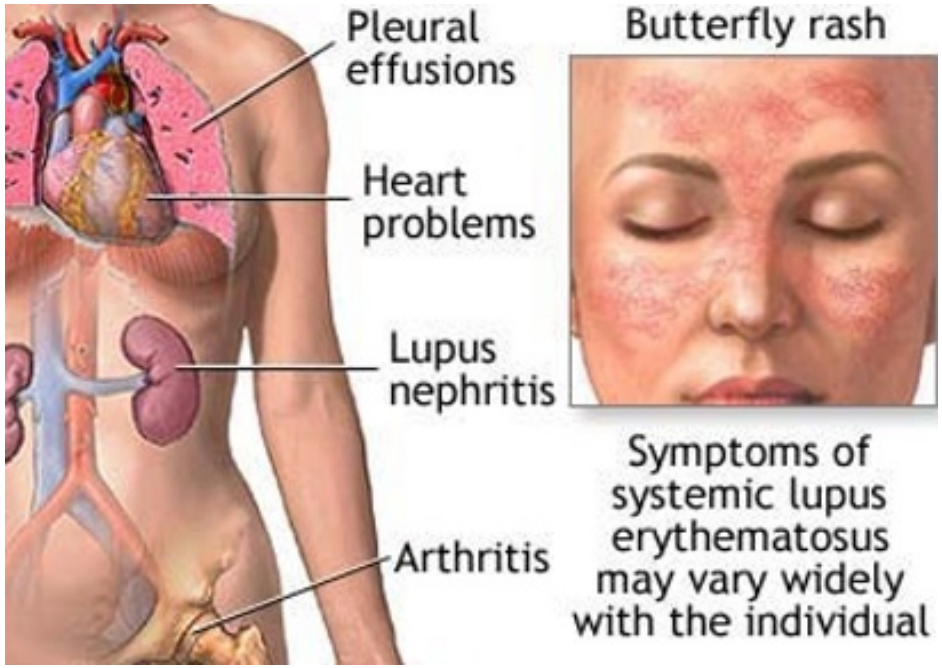
Commercial Opportunity

Current drugs either have serious side effects or have limited effectiveness

Benlysta's approval paves the way for Lupuzor

1.5m estimated patients in US, Europe and Japan. Target price per patient $10,000 - $20,000 per year



Lupuzor ™
Substantial progress

FDA granted Lupuzor™' Fast Track designation in December 2010

FDA granted approval to start phase III based on ImmuPharma phase IIb data, with a Special Protocol Assessment in August 2011

Active ingredient already manufactured for phase III

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2012 ACR Conference

- Lupuzor data presented on Wednesday 14 November at the 2012 Annual American College of Rheumatology Meeting
- The ACR **Annual Scientific Meeting** is the premier scientific meeting devoted to rheumatic diseases
- The title of the session was called “Systemic Lupus Erythematosus – Clinical Aspects and Treatment”

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Abstract Authors

- Dr. Robert Zimmer
  - President and Chief Science Officer, ImmuPharma

- Prof. Daniel J. Wallace
  - Associate Director, Rheumatology Fellowship Program, Cedars-Sinai Medical Center, Los Angeles
  - Leading practicioner within the field of Lupus

- Sylviane Muller
  - Research Director at CNRS, Strasbourg, France
  - Key inventor of Lupuzor

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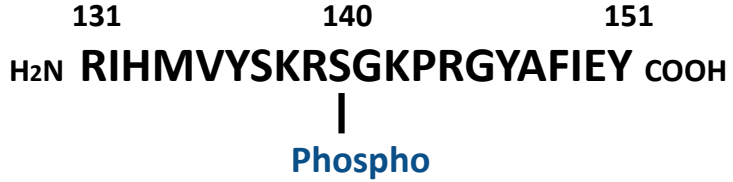
Definitions

- P140 (Drug substance): peptide 131-151 issued from the U1-70K snRNP protein with a phosphorylated serine in position 140 (hence P140)



- Drug products:
  - Original formulation is P140 formulated with mannitol as a lyophilizate (200µg/vial) for sc administration
  - Cephalon tested also another formulation - P140 formulated with trehalose as a lyophilizate (200µg/vial) for sc administration

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P140 Pre-clinical studies

- P140 is recognized by CD4+ cells of both Lupus patients and MRL/lpr lupus-prone mice
- P140 does not induce ex vivo proliferation of Lupus patients T cells
- P140 induces secretion of pro-toleragenic cytokine Il-10 in Lupus patients

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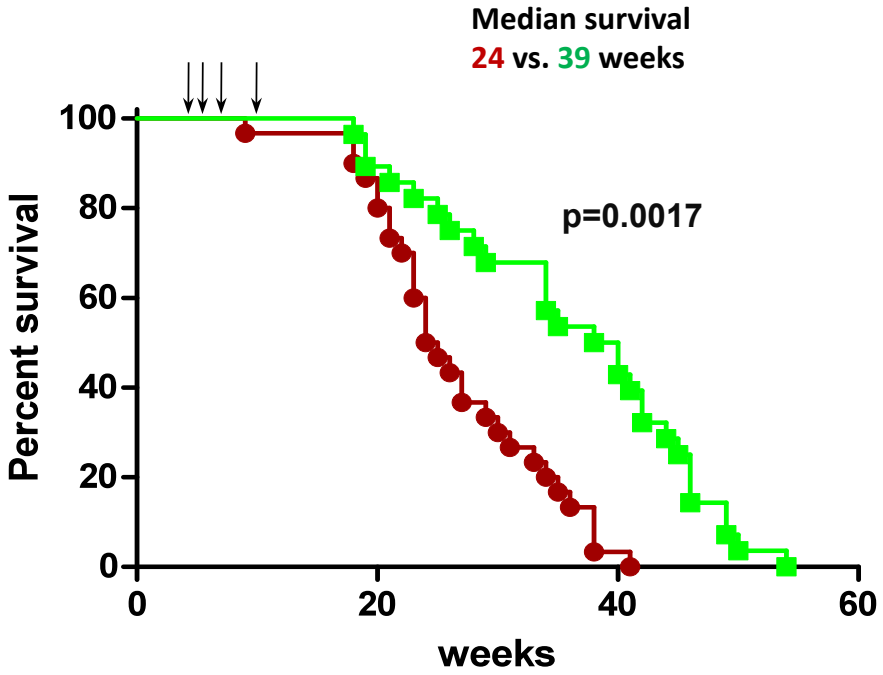
Administration of peptide P140 improves lupus disease in MRL/lpr mice

4-wk-old pre-autoimmune mice
i.v. injections at wks 4, 6, 8 and 12
100 µg in saline/mouse/injection



At week 24 :

↓ **proteinuria : 25% vs. 75%**
↓ **anti-dsDNA Abs: 29% vs. 75%**

↓ **dermatitis appearance**
↓ **vasculitis with less perivascular inflammatory infiltrates**

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Clinical Studies
Mannitol / Trehalose Protocols Phase IIb

Original formulation with mannitol

- **double-blind, randomized, multi center**
- **s.c. administrations**
- **3 arms standard of care + P140 in mannitol**
  1. **200µg 1x/4w**
  2. **200µg 2x/2w**
  3. **placebo**
- **12-week treatment + 12-wk observation period (total study duration 24 weeks)**

Cephalon's test of a formulation with trehalose

- **double-blind, randomized, multi center**
- **s.c. administrations**
- **2 arms standard of care + P140 in trehalose**
  1. **200µg 1x/4w**
  2. **placebo**
- **24-week treatment**

Inclusion

- SLE as defined by ACR criteria (1997)
- Age 18 – 70
- Cumulative weekly steroid dose < 80mg prednisone/week
- Patients on stable standard of care (antimalarials, methotrexate, leflunomide, mycophenolate mofetil, azathioprine)

Target population: clinical SLEDAI score ≥ 6

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P140 in mannitol / trehalose Protocols Phase IIb

End-points

Combined score (SRI) =

- A reduction from baseline in the SLEDAI-2K score of at least 4 pts
- No worsening in Physician's Global Assessment (PGA) (1)
- No new BILAG A score (2) and no more than one new BILAG B score from baseline

(1) Worsening defined as an increase in PGA of more than 0.30 point from baseline

(2) BILAG A: very active disease requiring immunosuppressive drugs and/or prednisolone dose of > 20 mg daily (or equivalent); BILAG B: moderate flare of disease activity

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Phase IIb results
ITT target populations (SRI responders)

Treatment	200 µg/4w	200 µg/2w	Placebo	p
P140 mannitol 12 w n = 136	26 (62%)	23 (50%)	17 (37%)	p < 0.025
P140 mannitol 12 w follow-up	29 (69%)	30 (62%)	26 (56%)	ns
P140 trehalose n = 183	31 (34%)	--	37 (40%)	ns

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Interim analysis for Lupuzor (n = 114)

		200µg/4w	200 µg/2w	Placebo	p
W 12	n total	34	39	41	
	Nb responders (%)	23 (68%)	20 (51%)	17 (42%)	p < 0.025
W 24	n total	19	21	24	
	Nb responders (%)	16 (84%)	14 (67%)	11 (46%)	p < 0.025

Responder : decrease of SLEDAI-2K > 4 points, omitting component 20 (low complement) and 21 (increased DNA binding)

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Comparison

	P140 in mannitol	P140 in trehalose	Benlysta (1)
Duration of treatment	3 months	6 months	12 months
Drop-out rate % (active/ placebo)	8% / 16%	22% / 23%	23% / 25%
Responder rate % (active/placebo)	62% / 38% $p < 0.025$	34% / 40%	43% / 33% $p < 0.025$
Clinical impact	+ 24%	0%	+ 10%

(1) published Benlysta data as reference (Furie et al. 2011)

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How does P140 work ?

Why is P140 in trehalose not active?

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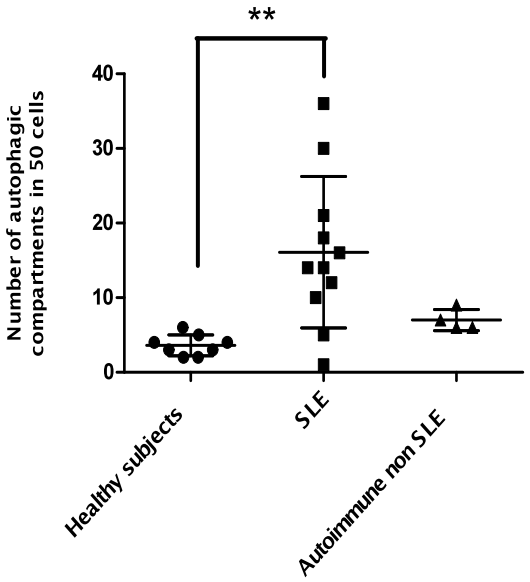
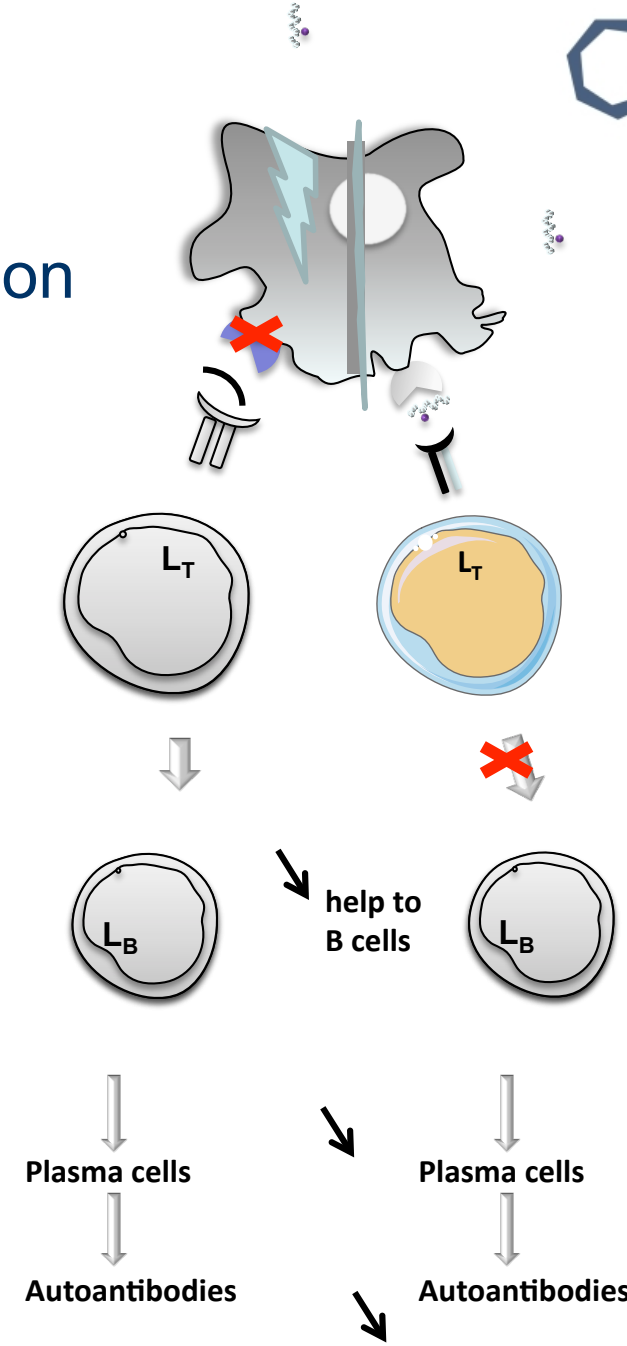
P140 mode of action



(1)

-Autophagy is increased in lupus.
-P140 controls autophagic flux,
➔ decrease of
- MHCII stability
- self antigen processing
- autoreactive T cell priming



(2)

-P140 acts as an altered peptide ligand for the TCR of P140 reactive T cells
deviates the cytokine secretion of these T cells ➔
(Th1 to Th2 cytokines)

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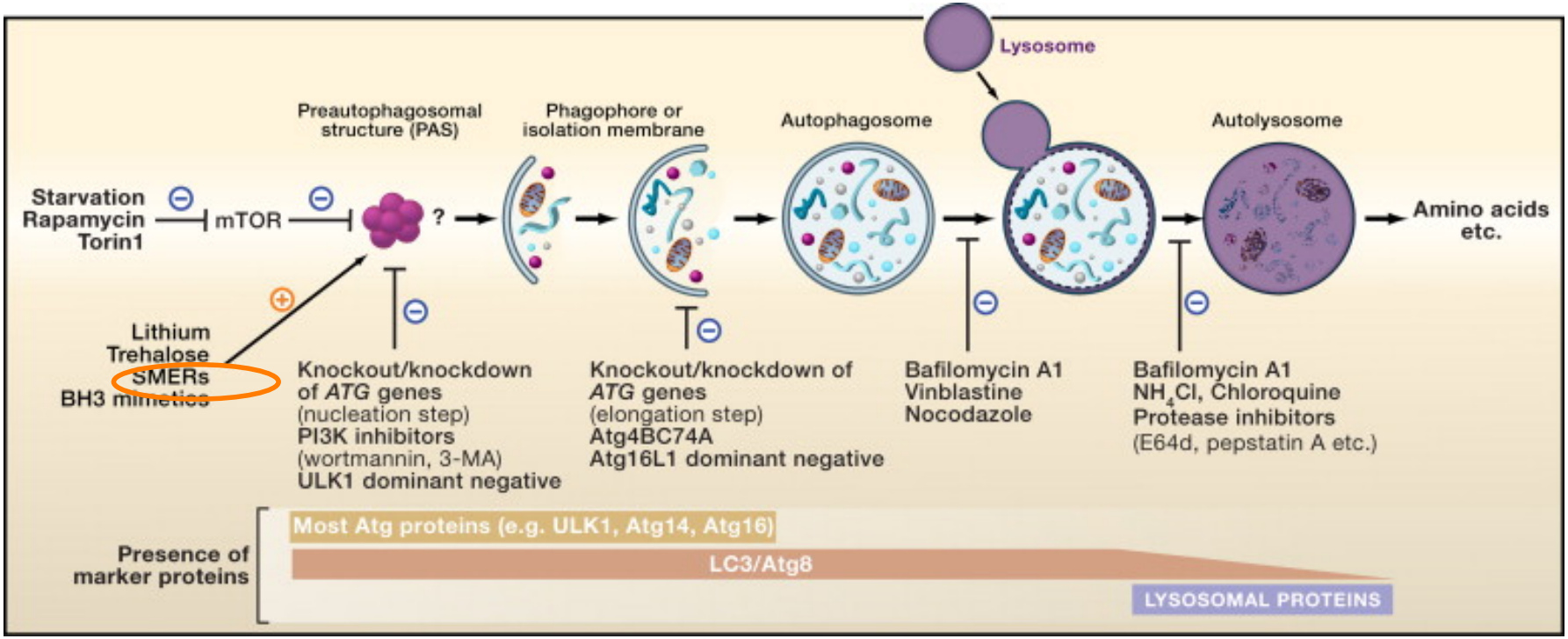
Why is P140 in trehalose not active ?

- Autophagy is increased in Lupus (Gros et al. 2012)
- Trehalose is known as an activator of autophagy and as such it counteracts the P140 effect on the control of lupus hyperautophagy



Mizushima et al. Cell 2010

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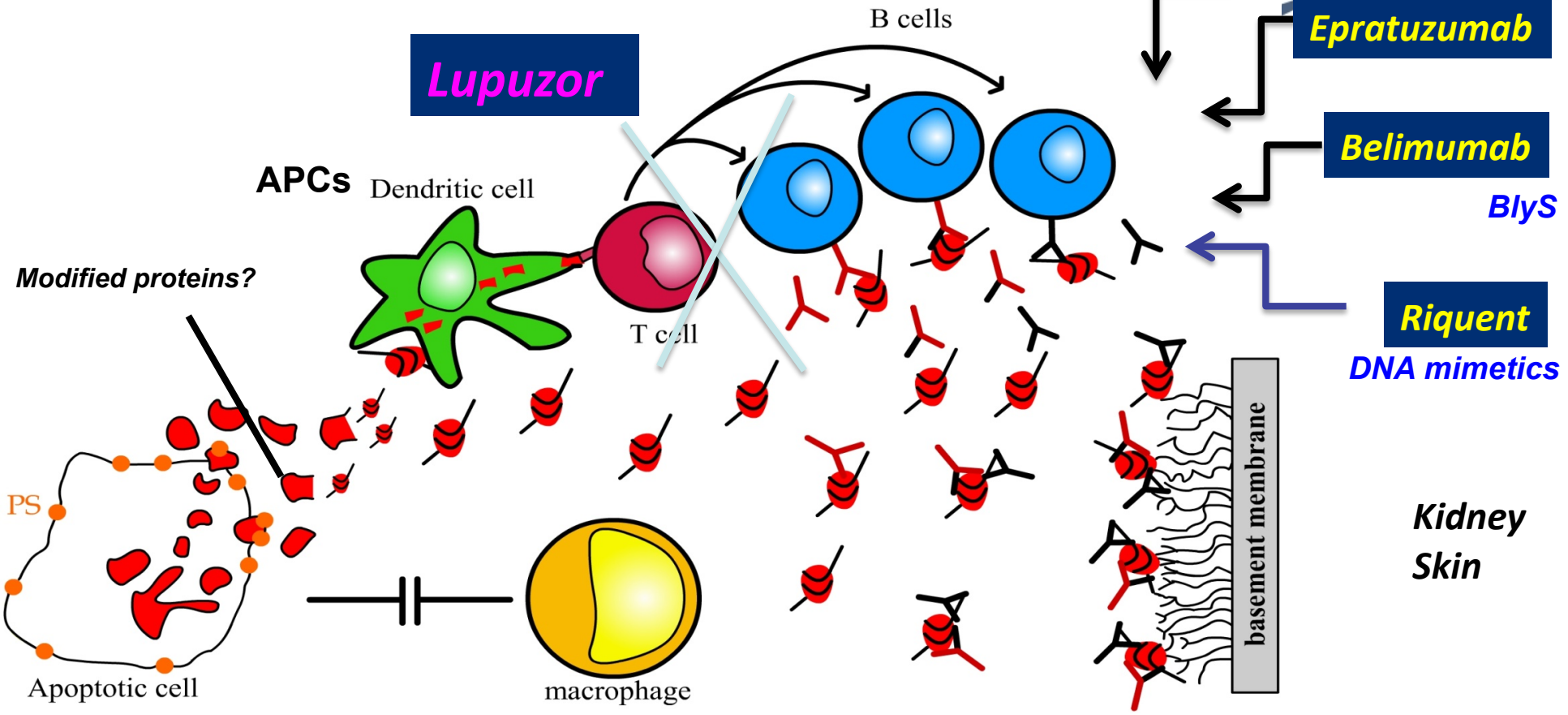
Recent treatment strategies for lupus



Lupuzor: A promising small peptide with immunomodulatory (not immunosuppressive) properties to treat Lupus via a T-cell approach. The Phase III program approved by the FDA

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Summary

- P140 has 2 different mechanisms of action
  - Normalization of hyperautophagy: fast onset of action
  - Restoration of tolerance (Altered Peptide Ligand): long term
- Lupuzor (P140 in Mannitol) is active: it demonstrates higher SRI response rates compared to published data and no safety signals

- P140 does not affect the “normal” immune system
  - It does not affect capacity of B and T cells to respond to mitogens (in contrast to prednisolone)
  - It does not affect the resistance of treated mice to an infectious (viral) agent

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Conclusion

Based on the data presented at the ACR, there is clearly no doubt with regards to the superior efficacy profile of Lupuzor™ (P140 in mannitol) when compared to either Benylsta or P140 in trehalose. We therefore see the original formulation with mannitol as being the main formulation for the peptide and will comprise the final formulation which will enter Phase III development.

More importantly, it is also the formulation on which the FDA and EMA authorities have given the green light for late-stage Phase III trials to commence.