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Enpatoran reverses established kidney disease in the IFN- α accelerated NZB/W model of lupus

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Disclosure information

We have the following relevant financial relationships to disclose:

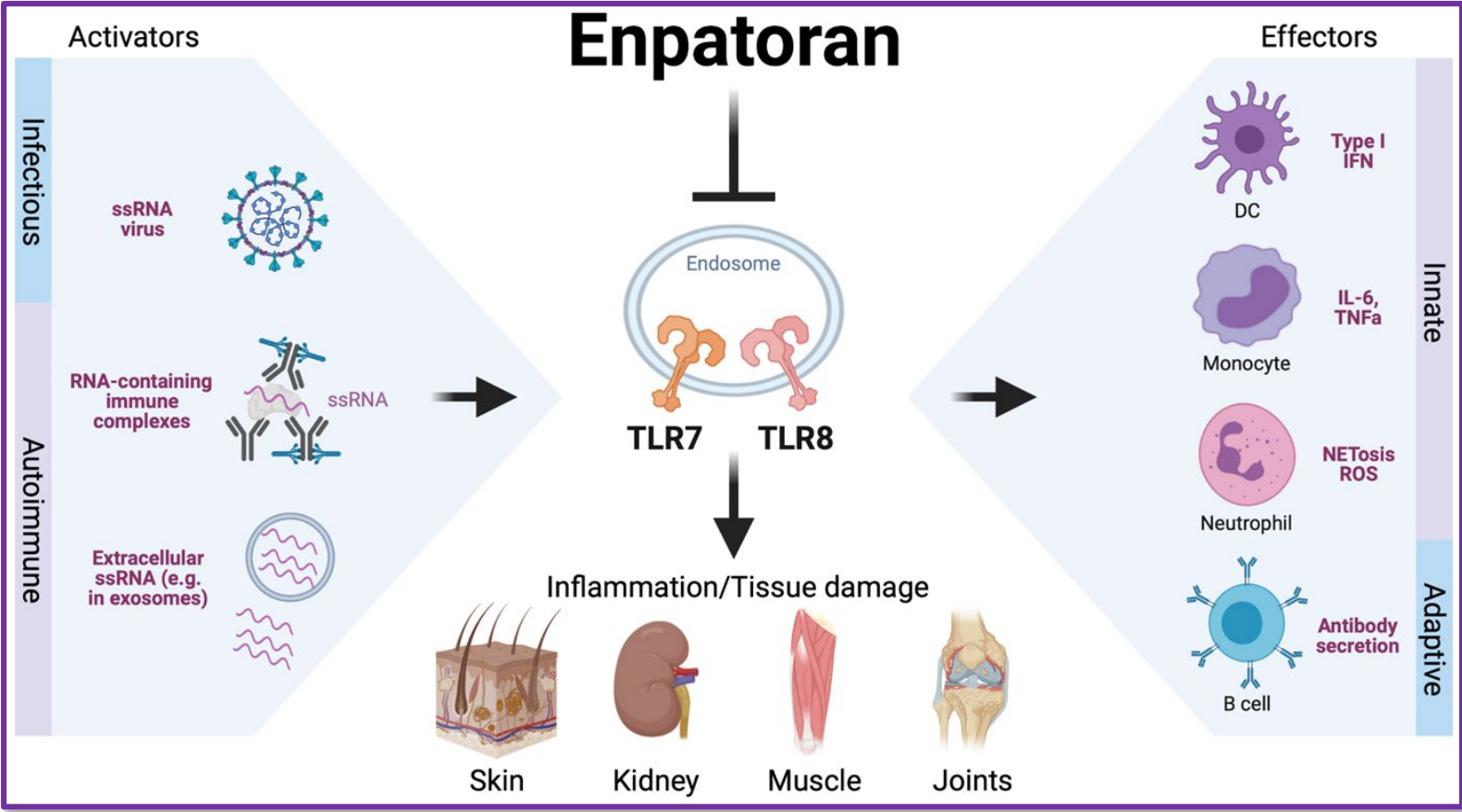
Amy Kao and I are employees of EMD Serono, Billerica, MA, USA

Julia Bruttger, Sonja Reissig and Philipp Haselmayer are employees of the healthcare business of Merck KGaA, Darmstadt, Germany

All of the relevant financial relationships listed have been mitigated

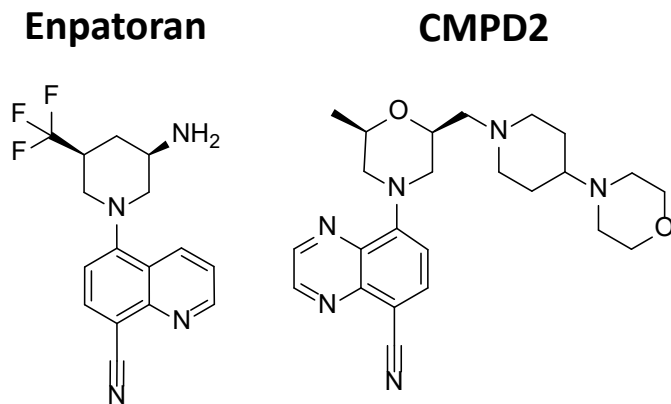
Background

TLR7 and TLR8 are ssRNA-sensing receptors that can drive inflammation and have the potential to contribute to autoimmunity and inflammatory disorders



Discovery of TLR7/8 inhibitors Enpatoran (M5049) is a selective and potent dual TLR7/8 inhibitor

- **Enpatoran**, a clinical stage molecule, and **CMPD2**, a tool molecule, are both reversible and competitive inhibitors of TLR7 and TLR8

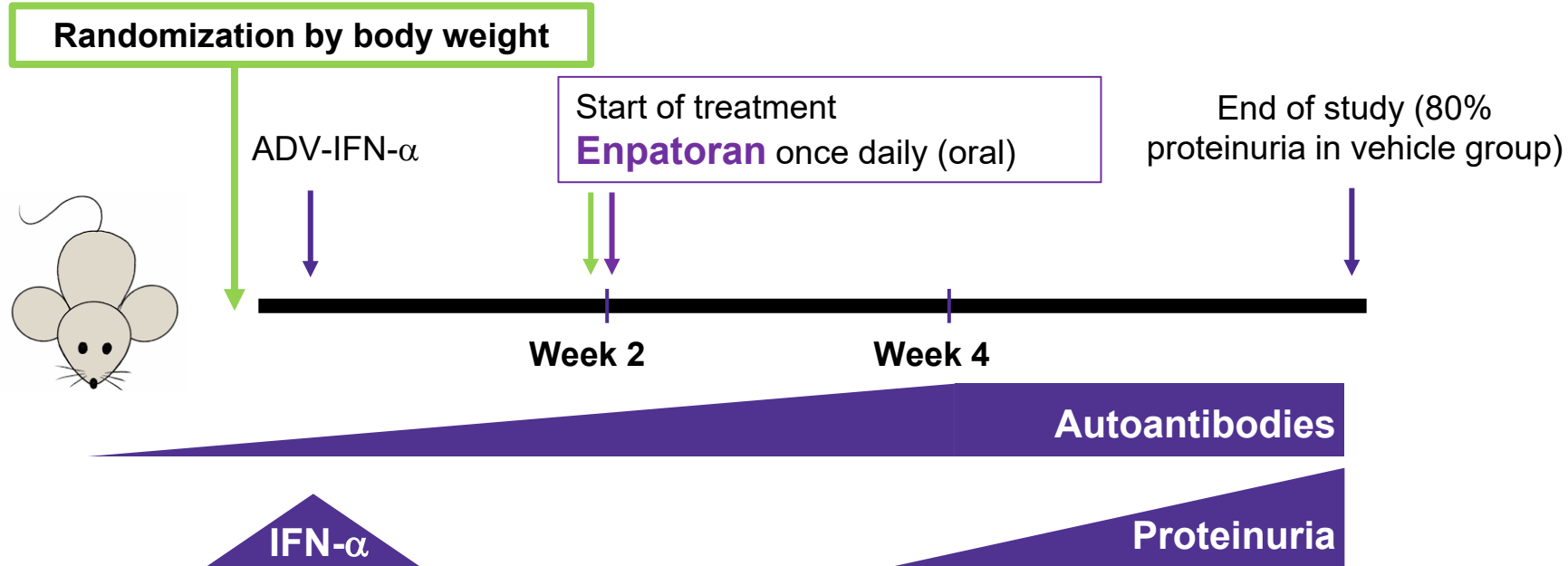


Highly selective and potent activity

TLR	Stimulus	Cells	Endpoint	Enpatoran IC ₅₀ (nM)	CMPD2 IC ₅₀ (nM)
TLR7	R848	HEK	NF-κB Luc	11.1 ± 9.94	26 ± 10.6
TLR8	R848	HEK	NF-κB Luc	24.1 ± 9.16	3.6 ± 1.06
TLR7	TLR7 ligand	PBMC	IL-6	68.3 ± 59.8	80 ± 28
TLR8	TLR8 ligand	PBMC	IL-6	620 ± 628	8.9 ± 6.2
TLR7	TLR7 ligand	WB	IL-6	2.2 ± 2.6	0.58 ± 0.27
TLR8	TLR8 ligand	WB	IL-6	120 ± 34	0.81 ± 0.31

- We investigated the ability of TLR7/8 inhibition to reverse established kidney disease in mouse models, as an indicator for effects in **lupus nephritis** patients

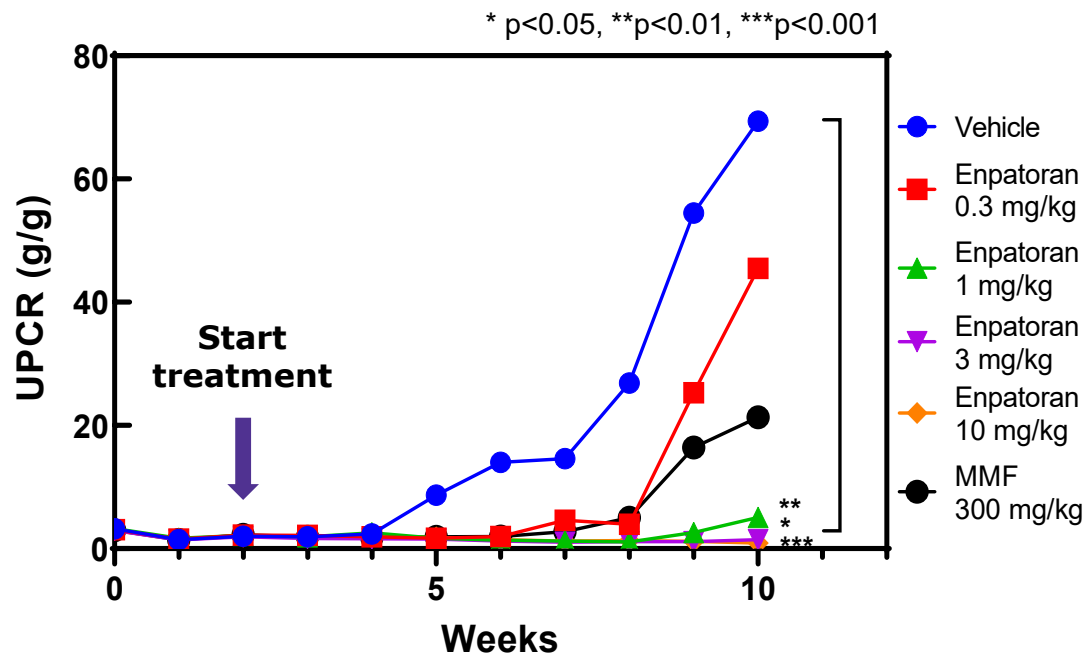
Prophylactic treatment Study design of the IFN- α -accelerated NZB/W F1 lupus mouse model



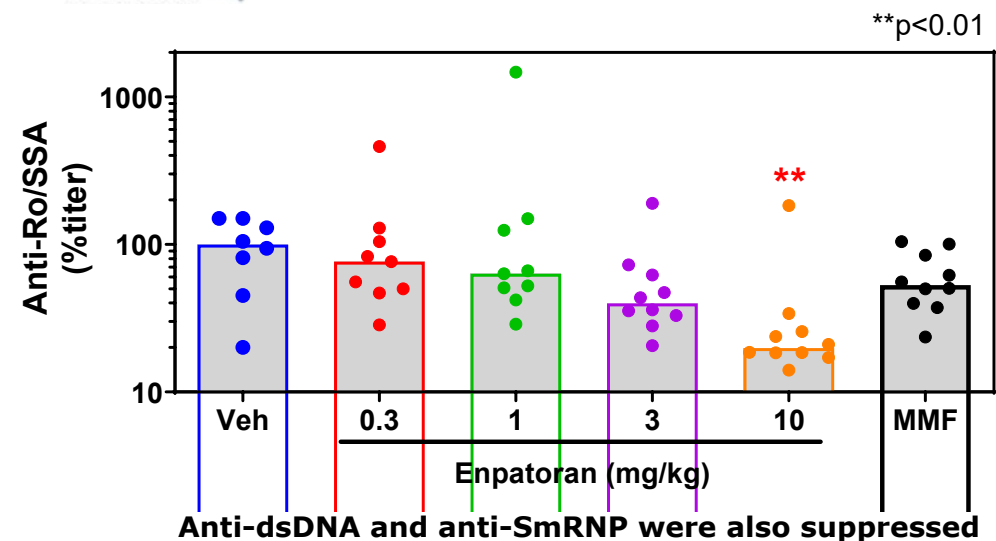
- NZB/W F1 mice spontaneously develop SLE-like symptoms
- Application of IFN- α at 10 weeks of age accelerates and synchronizes disease development
- IFN- α expression was transient and no increase in systemic IFN- α levels was detectable 14 days post-application

Prophylactic treatment Enpatoran treatment is efficacious when dosed early before proteinuria onset

Reduction in proteinuria

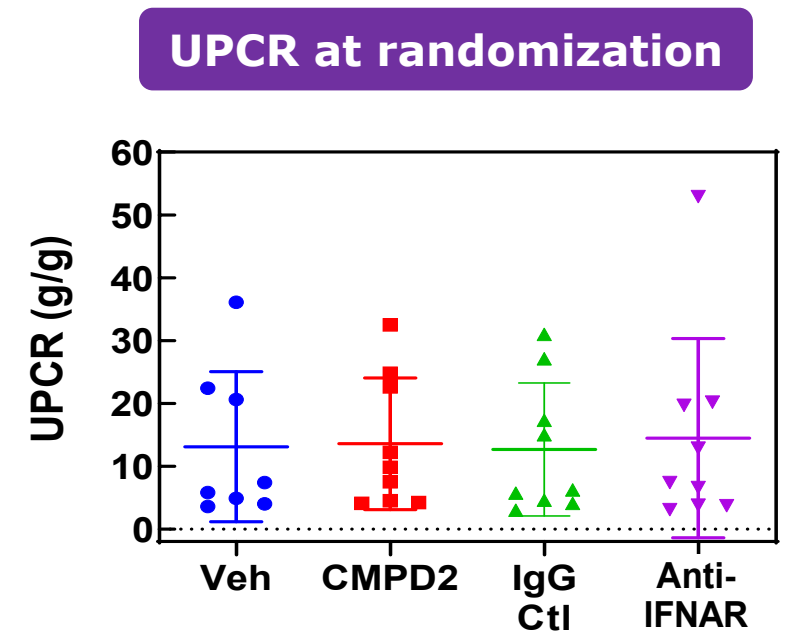
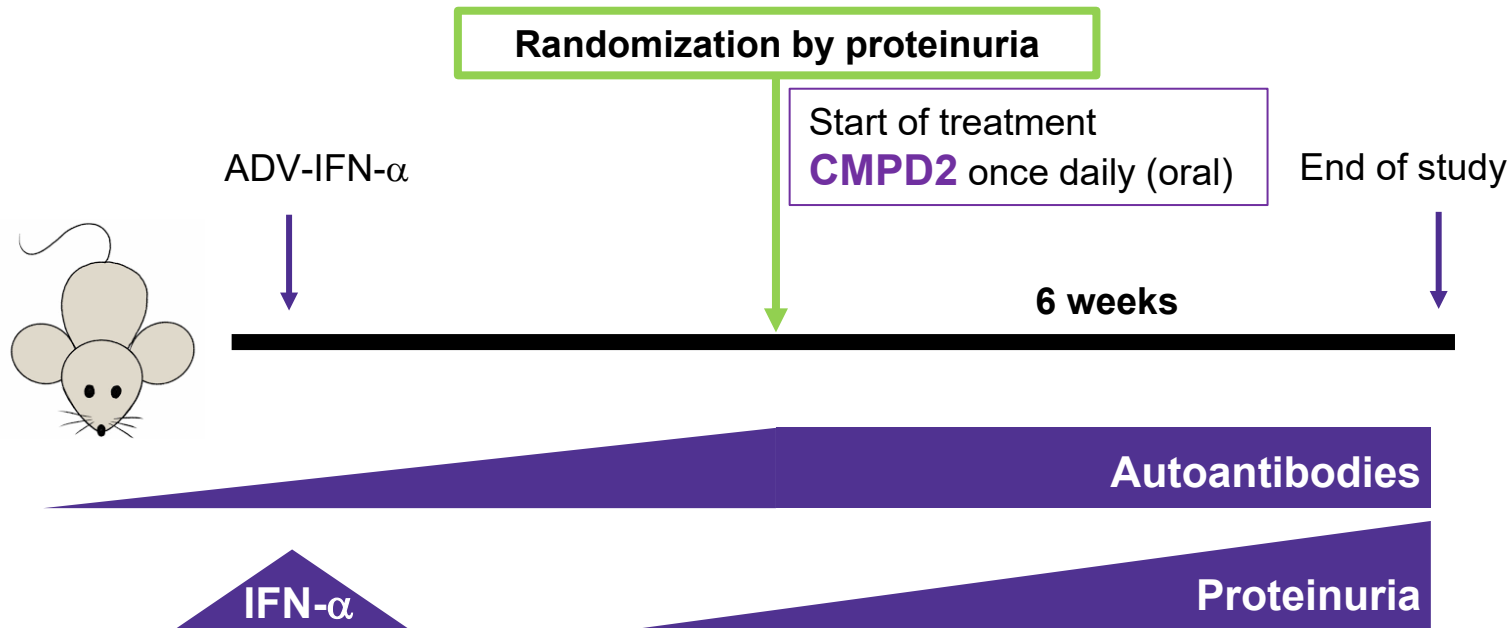


Decrease in autoreactive B cells and autoantibodies



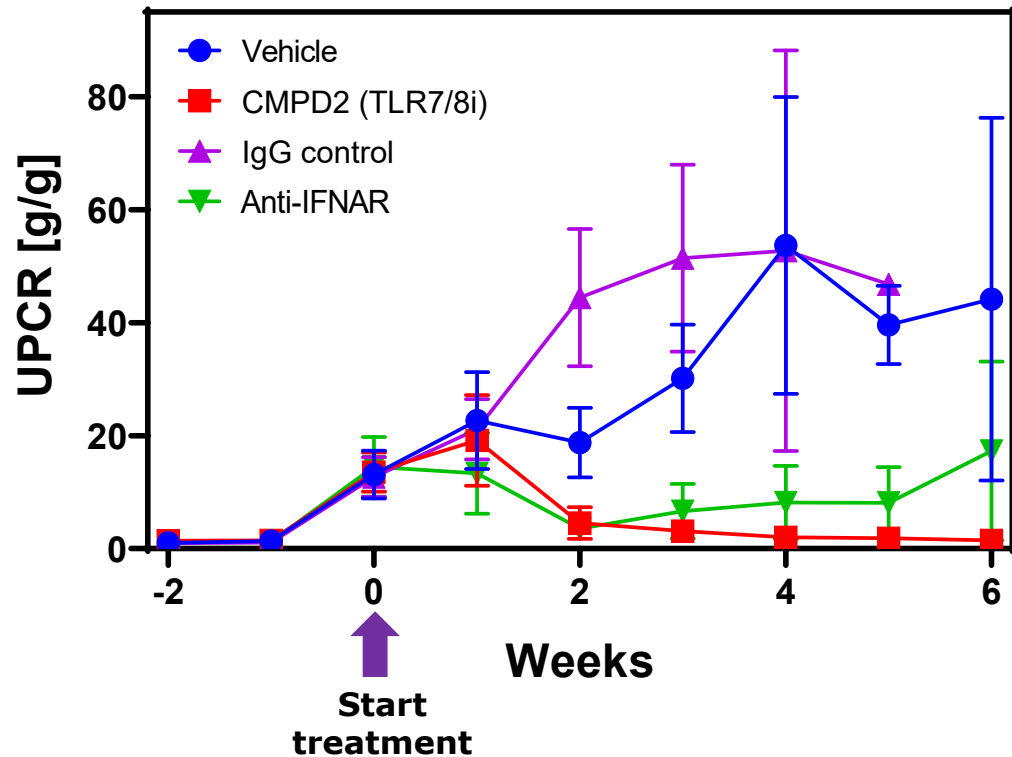
Enpatoran prevented proteinuria, reduced B cell numbers, and lowered autoantibody titers

Therapeutic intervention Randomization and treatment initiation after proteinuria onset

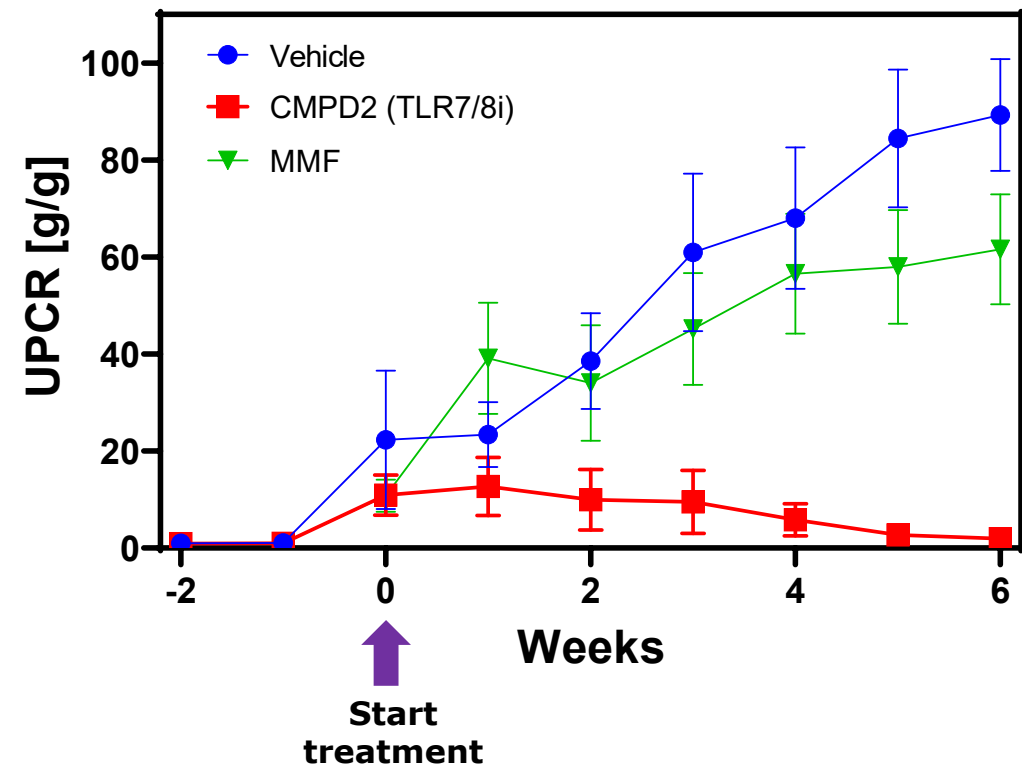


Therapeutic intervention TLR7/8 inhibition was efficacious when dosed even after proteinuria onset

TLR7/8 inhibition and anti-IFNAR
reduced proteinuria

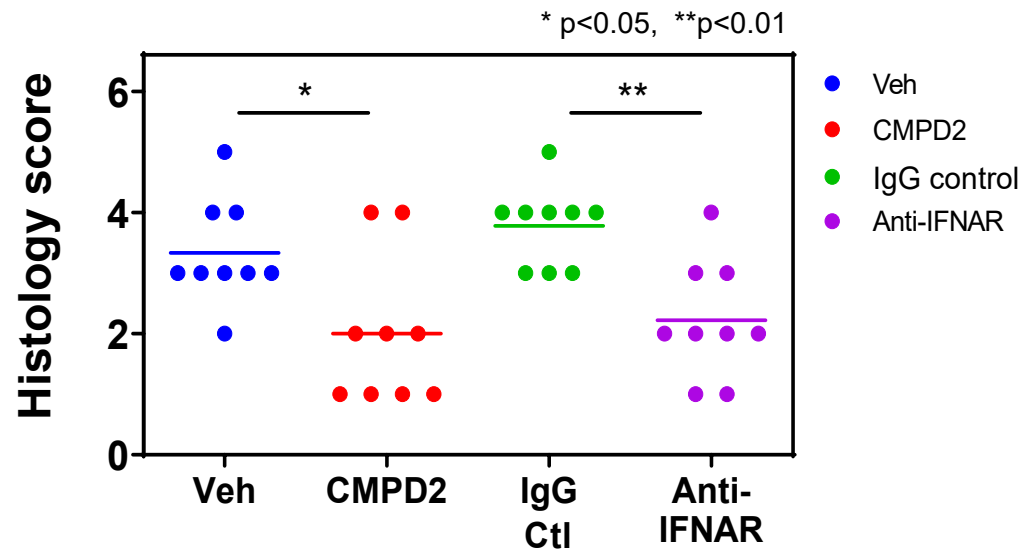


MMF was much less effective
than TLR7/8 inhibition

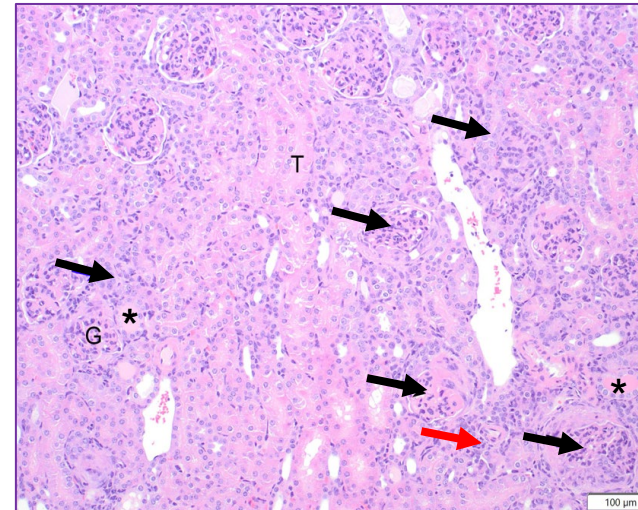


TLR7/8 inhibitor treatment rescued mice from established proteinuria

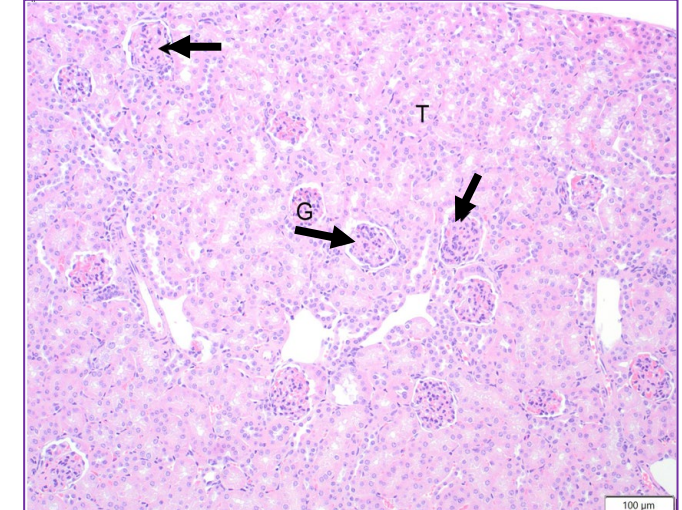
Renal histological score was improved with TLR7/8 inhibition



Moderate/marked score (vehicle control)

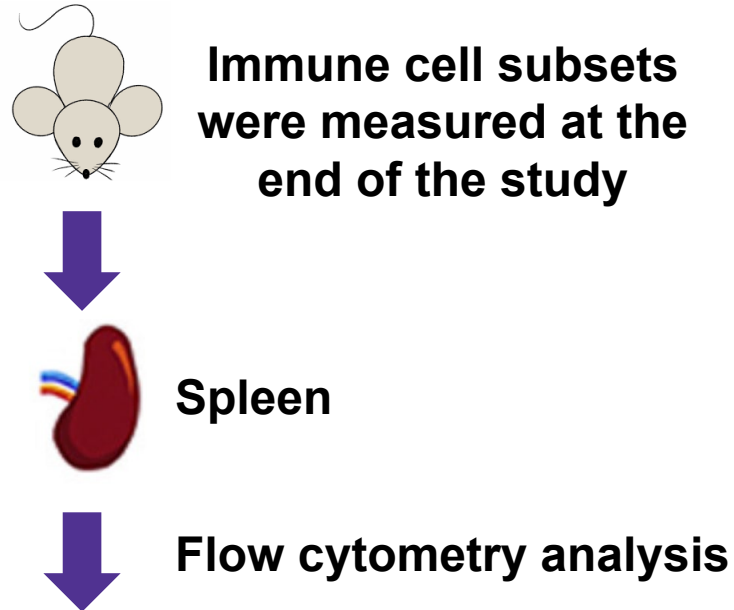


Mild score (TLR7/8 inhibitor CMPD2)

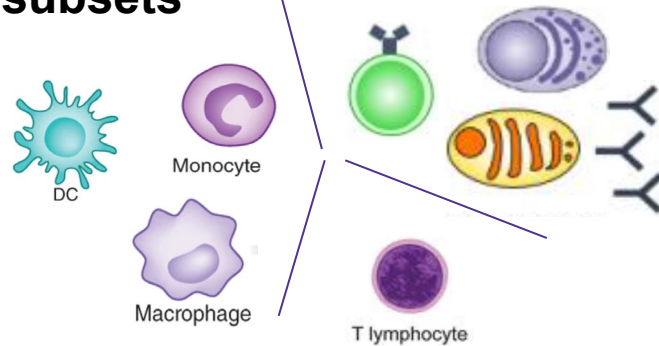


Hematoxylin and Eosin staining of the kidney. Representative images shown G, glomerulus; T, renal tubules; *, proteinaceous luminal casts.

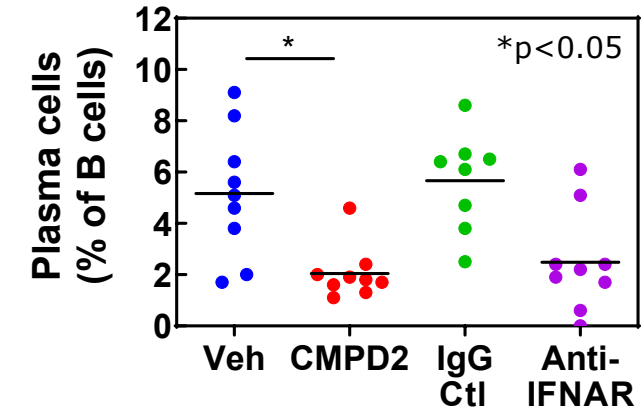
TLR7/8 inhibition reduced glomerulonephritis including tubule dilatation/casts and tubule basophilia



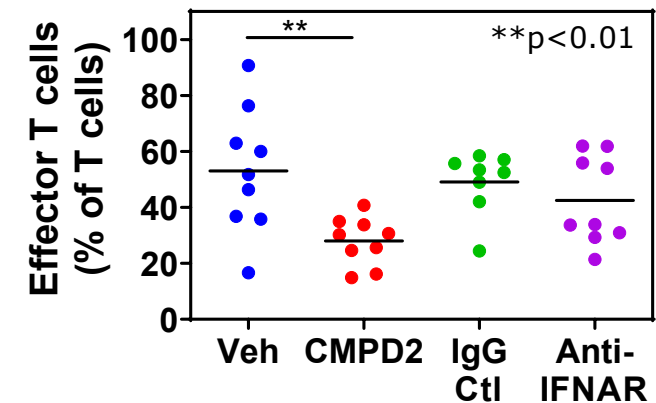
Cell subsets



Plasma cells

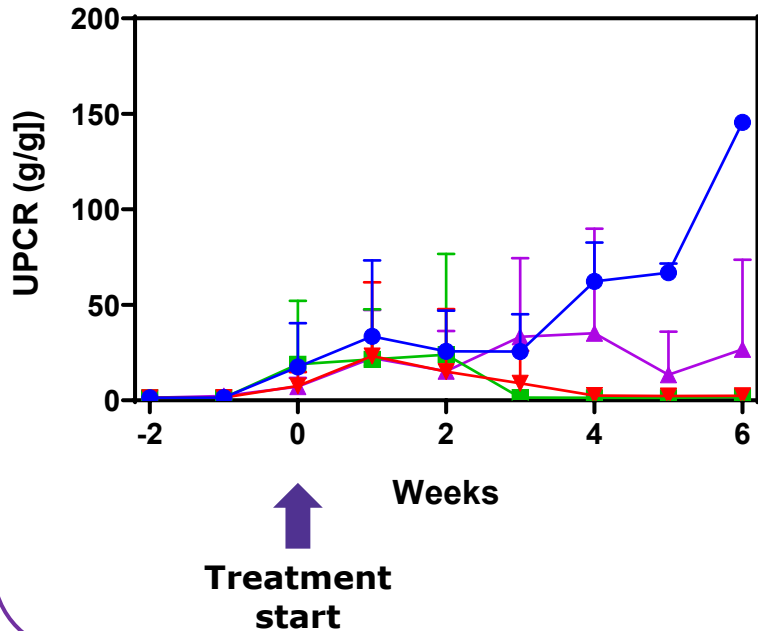


Effector T cells

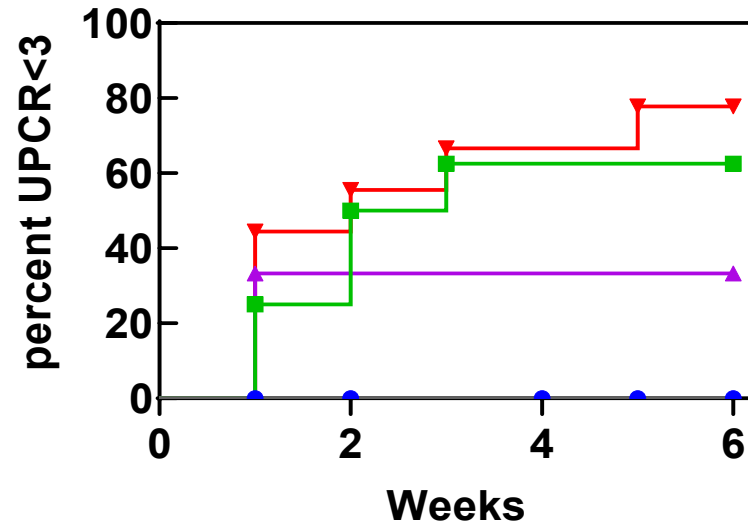


Therapeutic intervention Enpatoran reduced proteinuria and improved survival

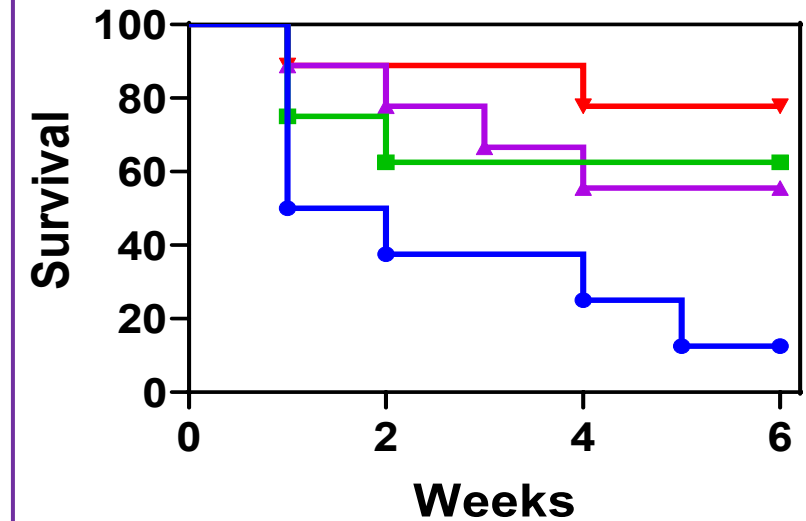
Reduced proteinuria (UPCR)



Proteinuria reduced to UPCR <3 g/g



Improved survival



● Veh ■ CMPD2 ▲ Enpatoran (0.5 mg/kg) ▼ Enpatoran (5 mg/kg)

Conclusions

TLR7/8 inhibition is efficacious when dosed before or after proteinuria onset in mouse lupus models

- In the NZB/W IFN- α -accelerated model, **established kidney disease was reversed** by TLR7/8 inhibition
- Both the clinical stage molecule, enpatoran, and the tool molecule, CMPD2, **significantly reduced proteinuria** even after proteinuria onset
- TLR7/8 inhibition **reduced the levels of autoantibodies, plasma cells and effector T cells**, suggesting multiple modes of action
- Our preclinical results suggest that enpatoran may be beneficial for patients with **lupus nephritis**

The ongoing Phase Ib (NCT04647708) and Phase II (WILLOW, NCT05162586)¹ studies will evaluate the safety and efficacy of enpatoran in patients with SLE and/or CLE

GET ADDITIONAL CONTENT

The **WILLOW** study design and further preclinical results are available using the QR code



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1. Morand E, et al. *Ann Rheum Dis* 2022;Suppl:AB04441

Acknowledgements

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