From the Manhattan Project to Autoimmune therapy

Fred Ramsdell

Disclosures

- Founder and Advisor:
  - Sonoma Biotherapeutics
- Scientific Advisory Boards:
  - Equillium, Inc; Georgiammune; AbilitaBio; SelectIon; HelixNano

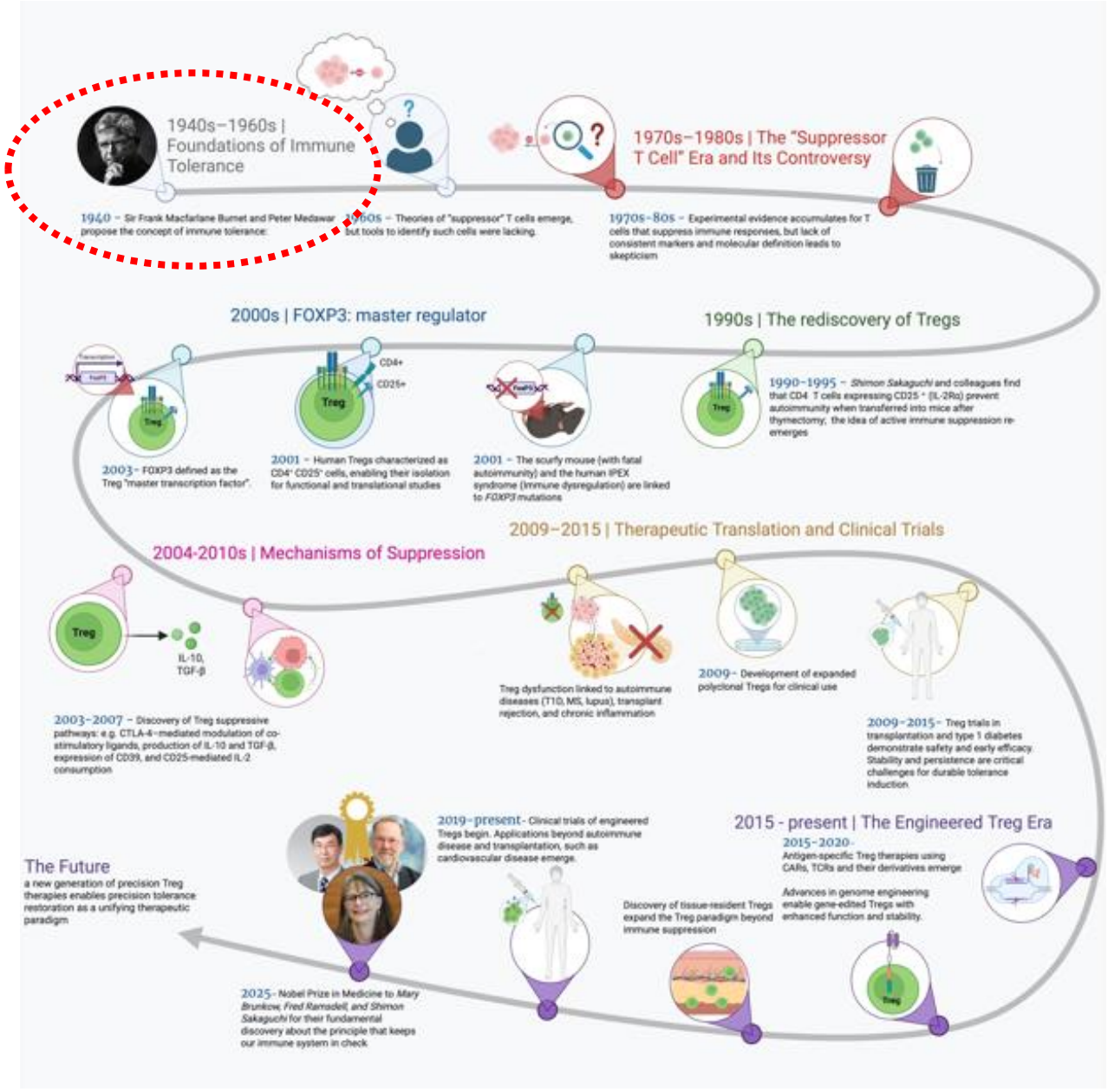
Art meets Science

Nobel Museum:

YoU:

Odessa Calloway and Lovisa Schmidt
(Beckmans design group)

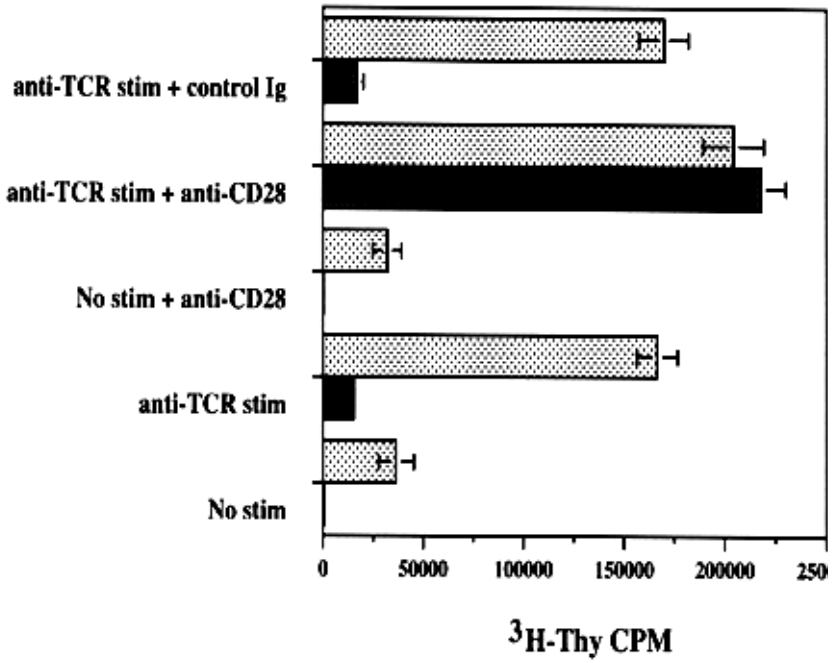
Timeline: From *Scurfy* to therapies



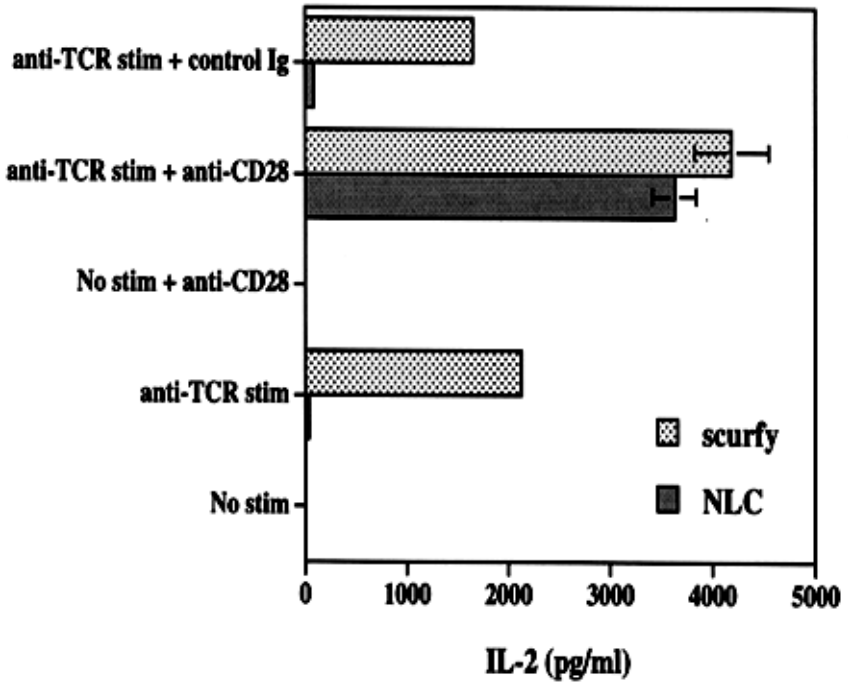
Bluestone, Levings & Fung

The *Scurfy* immune system is hyper-active

T cell Proliferation



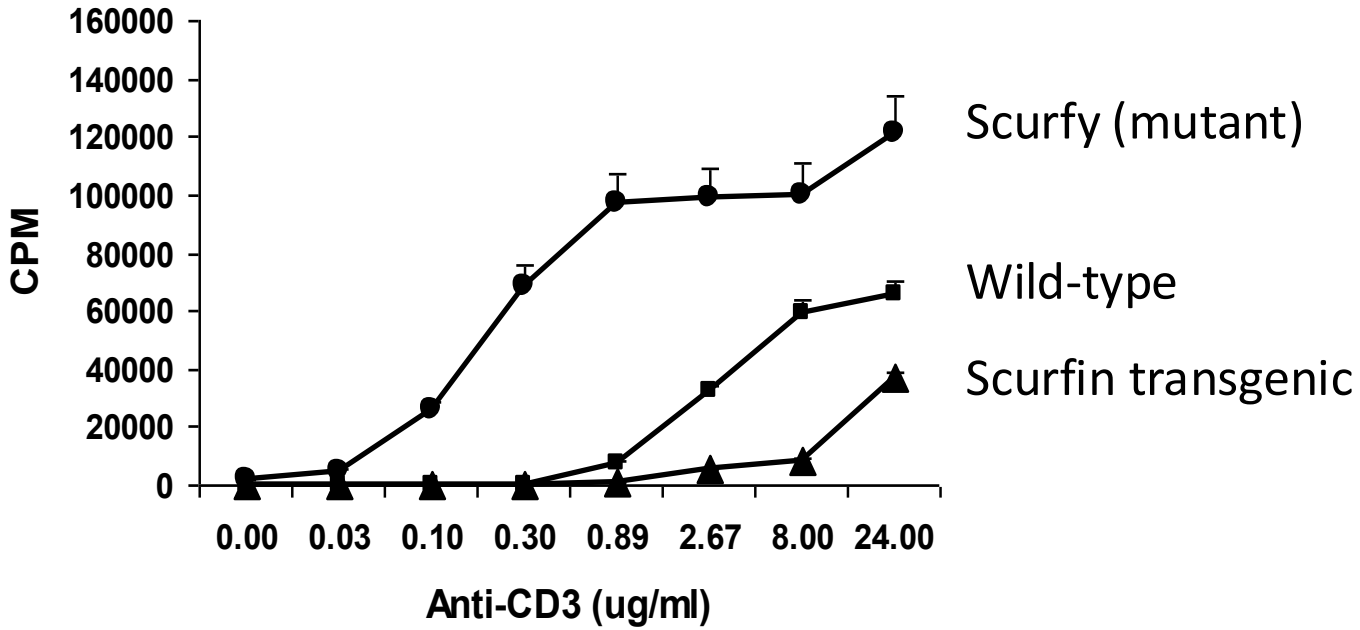
Cytokine Production



Lisa Clark

DARWIN MOLECULAR CELLTECH

Scurfin over-expressing T cells are hypo-active



Roli Khattri

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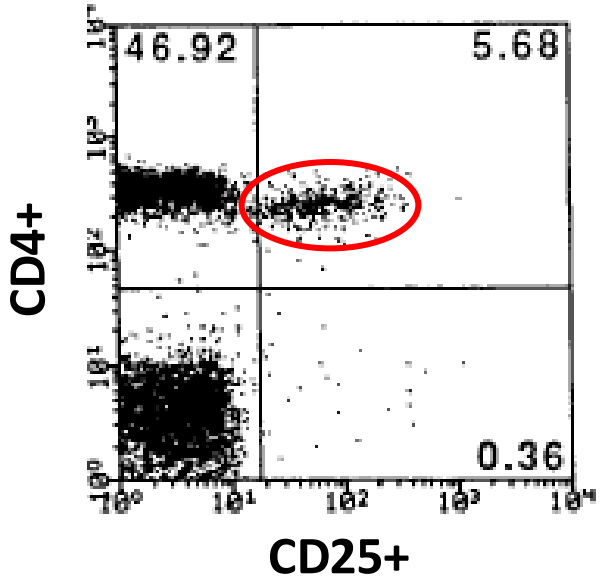
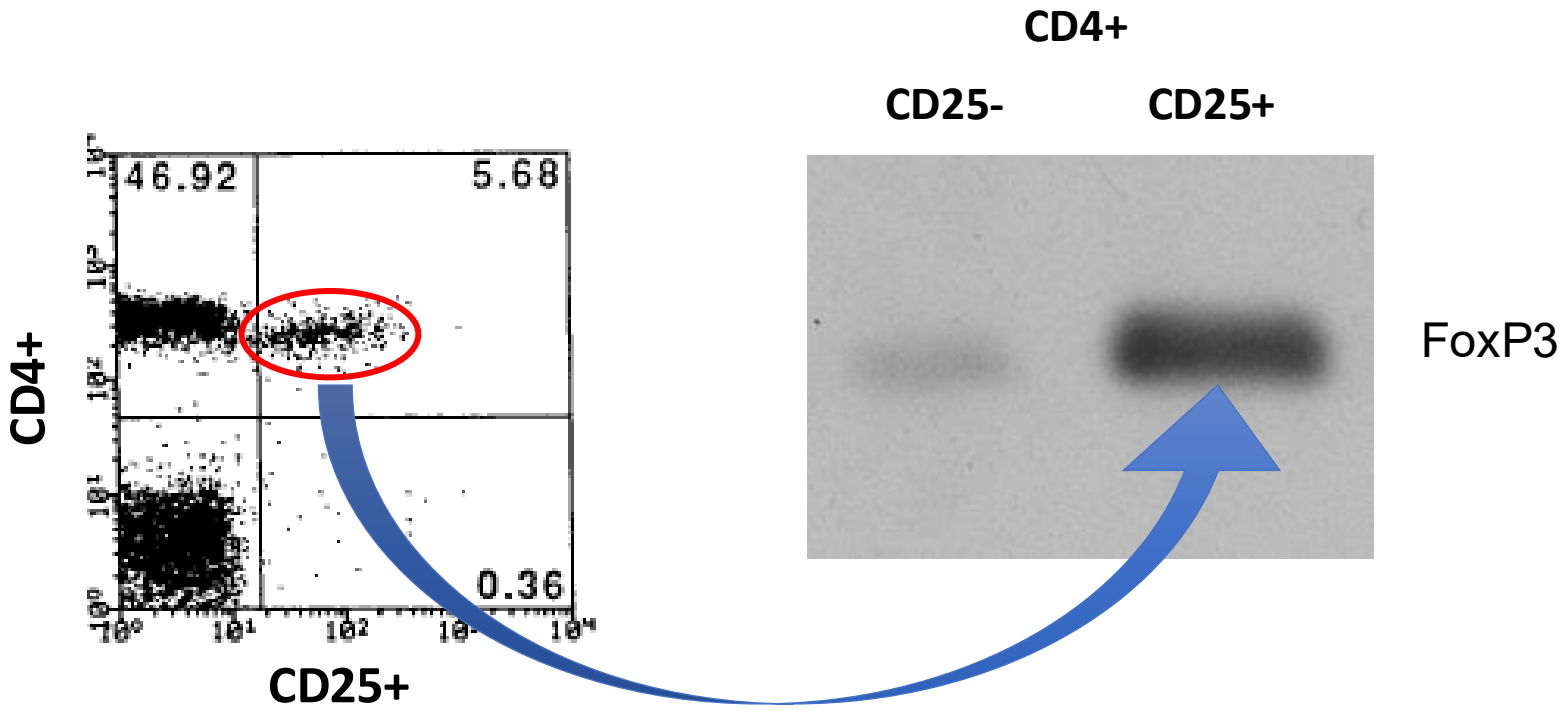
T_{reg} cells uniquely express FoxP3



Sakaguchi et.al. 1995

T_{reg} cells uniquely express FoxP3



Roli Khattri

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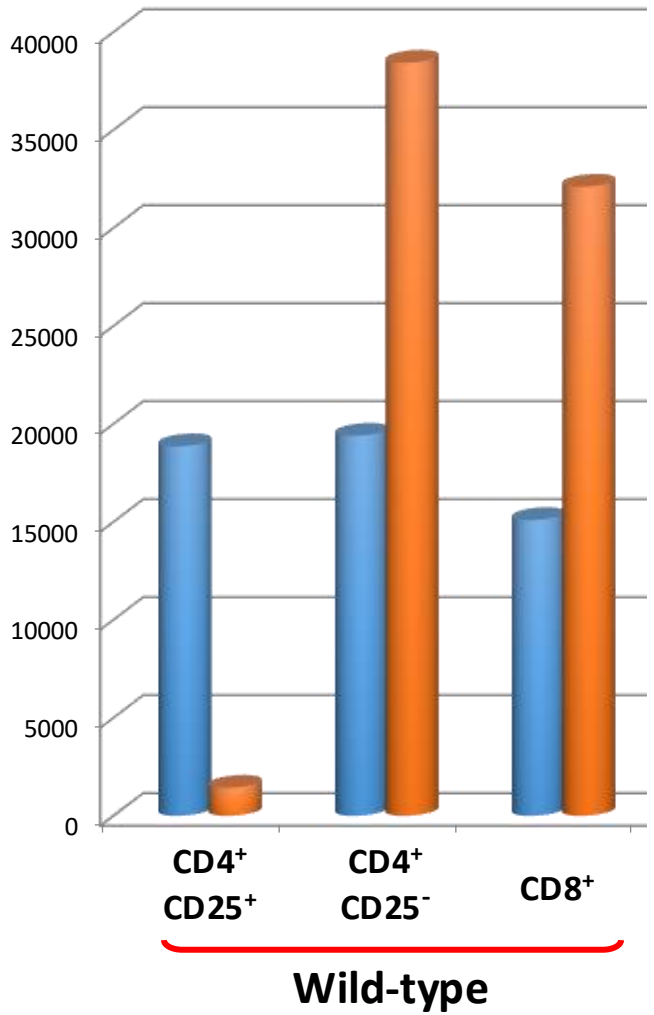
Aug 8, 1998

Foxp3 expression drives T_{reg} activity



Blue: responding cells only

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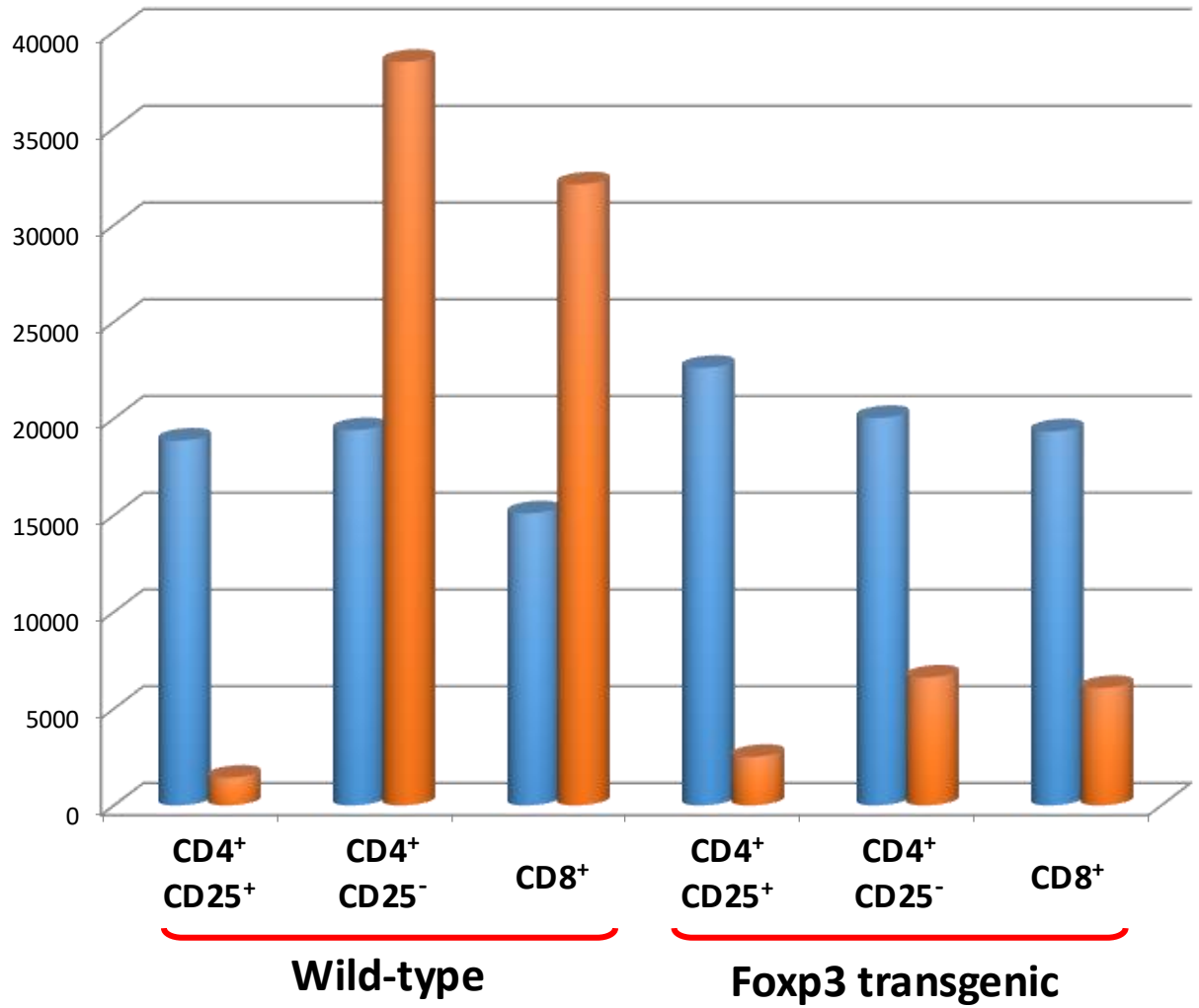
Foxp3 expression drives T_{reg} activity



Blue: responding cells only

Roli Khattri

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Thymic only expression of Foxp3 is insufficient to prevent disease in *scurfy* mice

Table II. *Expression of* Foxp3 *in the thymus is insufficient to prevent disease in* sf/*Y mice*[a]

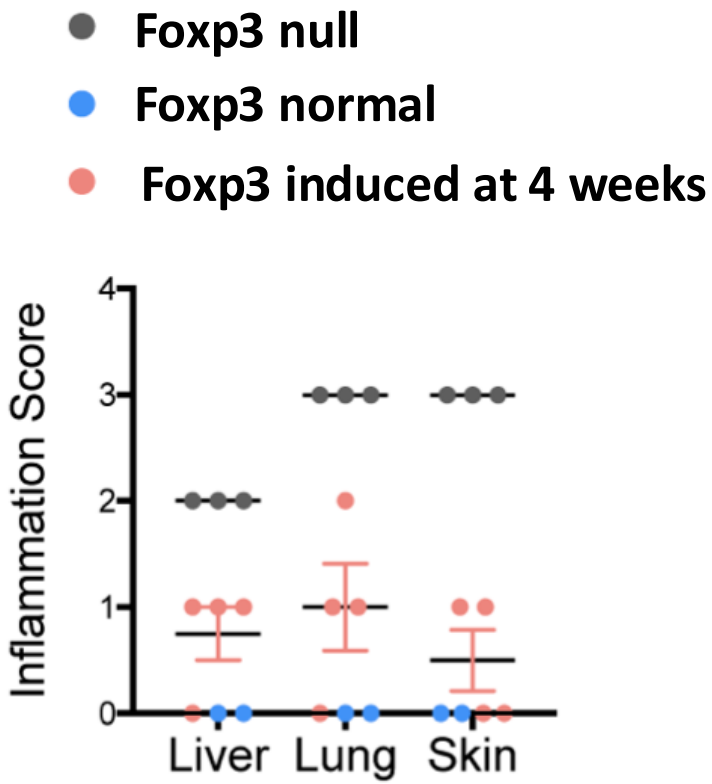
Genotype	Disease in *sf*/Y Mice?	Cell Number ($\times 10^6$)	
		Thymus	Lymph node
NLC	NA	79.0	2.9
2826	No	100.1	2.2
16.5	Yes	110.4	2.7
8.3	Yes	32.2	2.9

Note: Thymic expression (16.5 & 8.3 mice) generated via the pLck promoter

Induction of Foxp3 in T_{reg} 'wannabe' cells can reverse autoimmunity in mice

Foxp3 null mice

Foxp3 induced at 4 weeks

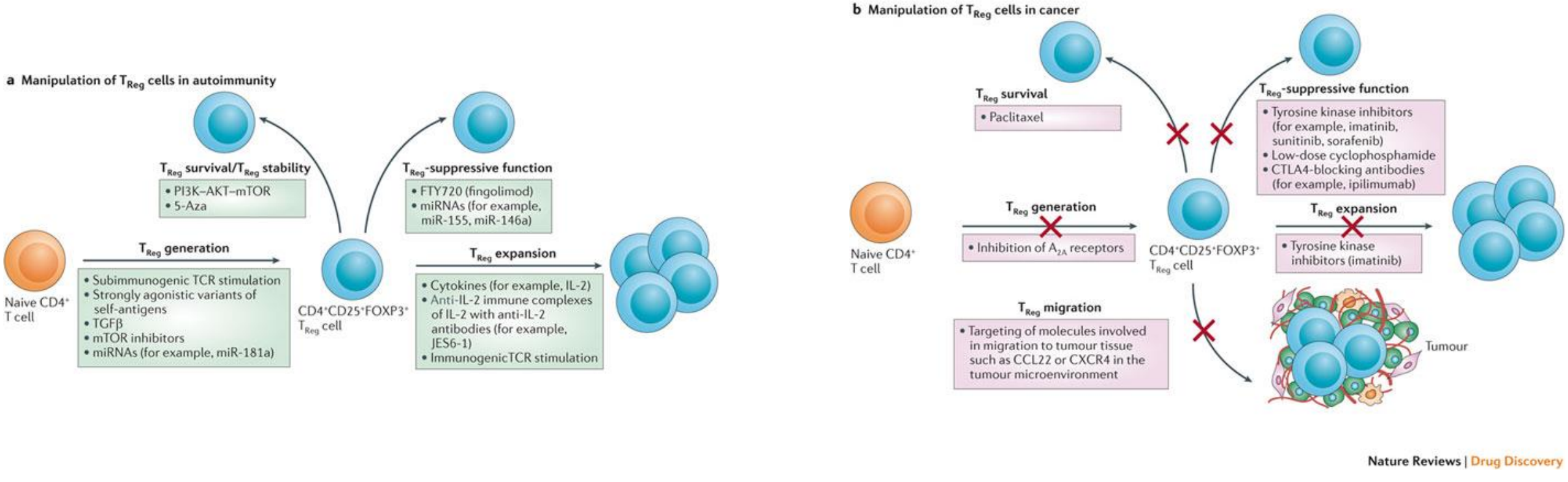


Hu, W … A. Rudensky, Nat. Immunol. 2021

Summary

- Foxp3 is the master regulator for T_{reg} cell development and function
- The absence of a functional *Scurfin* protein results in lethal autoimmunity in mice and humans
  - Expression of this protein can reverse ongoing autoimmune pathology
- Foxp3 thus defines a necessary gene for the generation, activity and maintenance of peripheral tolerance

Therapeutic implications:



Nature Reviews | Drug Discovery

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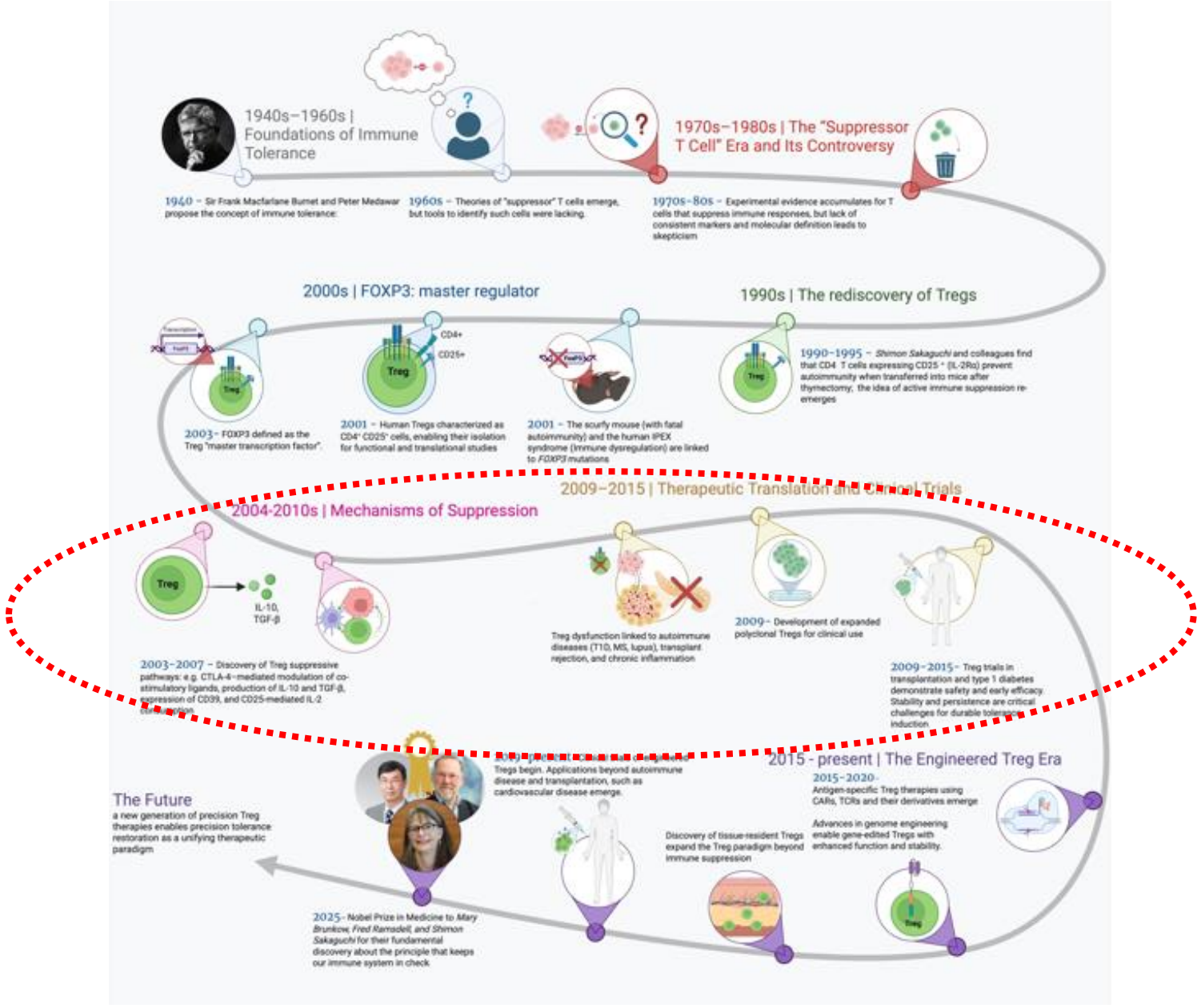
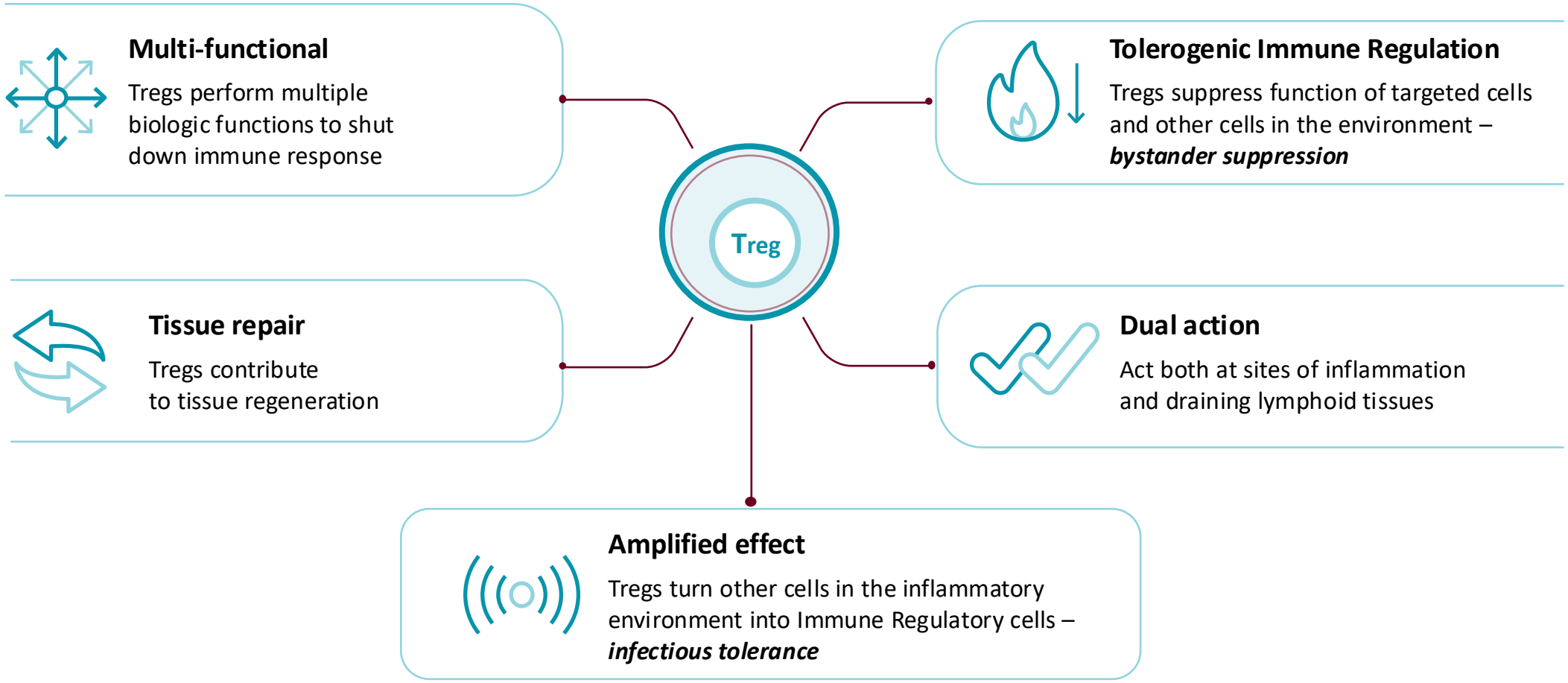
FoxP3: The missing years



Bluestone, Levings & Fung

The intrinsic polypharmacy of T_{reg} cells underscores their appeal as a versatile therapeutic modality



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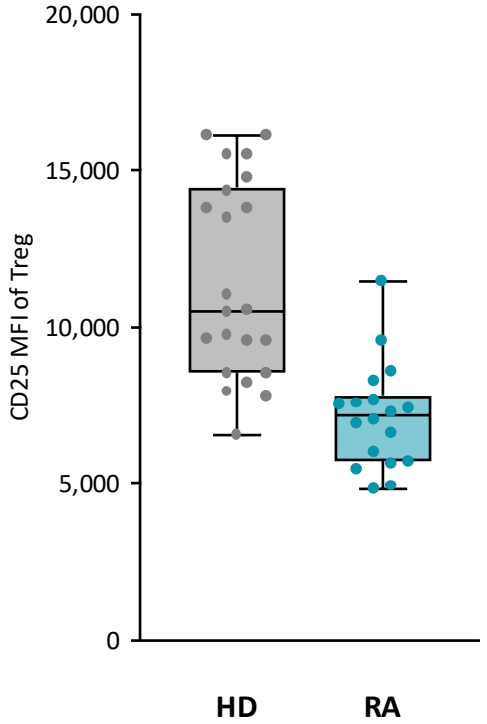
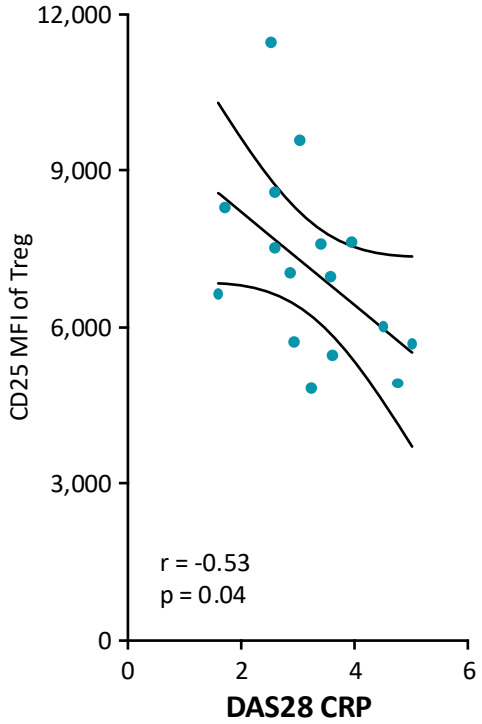
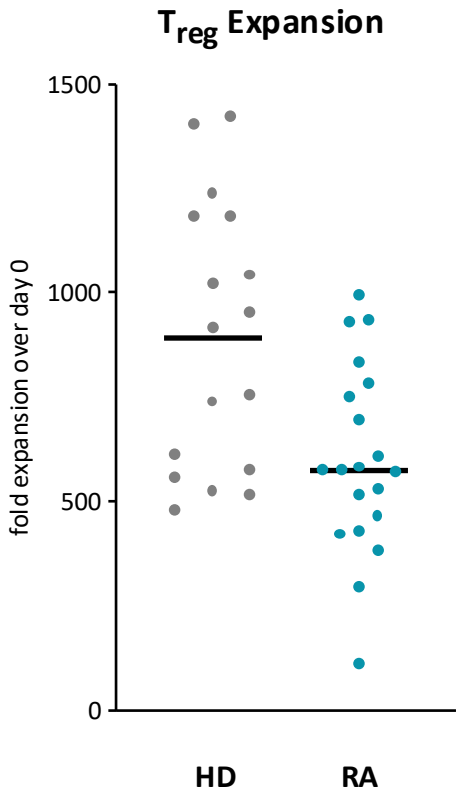
T_{reg} cells are defective in RA patients but can be engineered and expanded

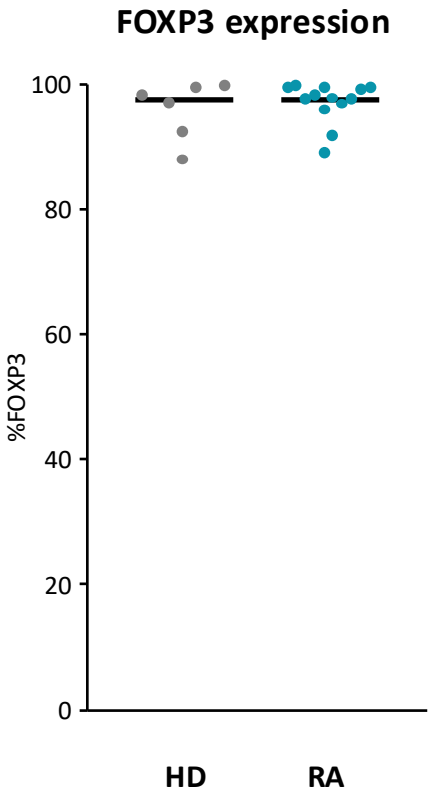
RA patient T_{reg} cells have less CD25 than Healthy Donors





Patient T_{reg} expand normally and have high levels of FOXP3





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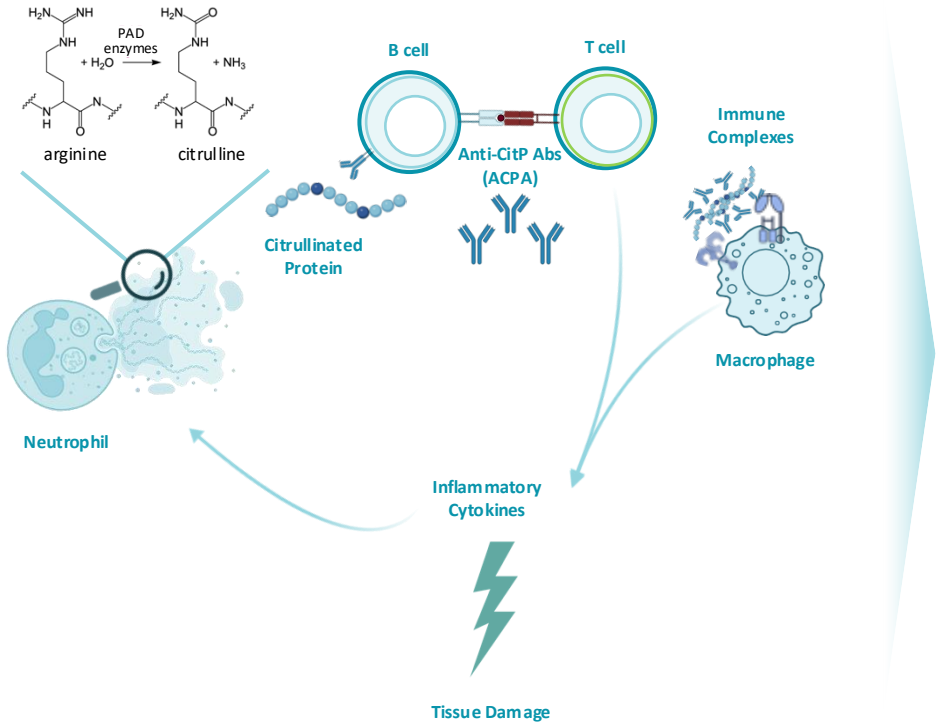
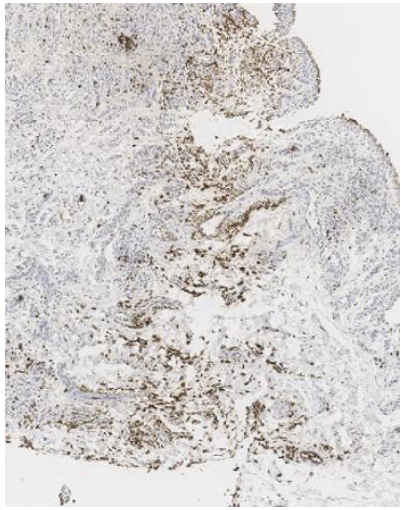
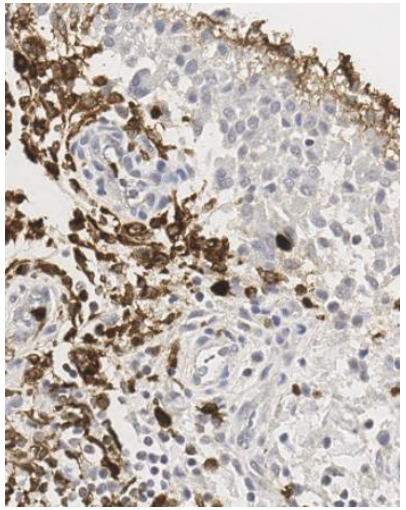
Citrullinated autoantigens are generated by NETosis and function as a pathogenic marker of RA



CitP reactivity in joint of RA patient





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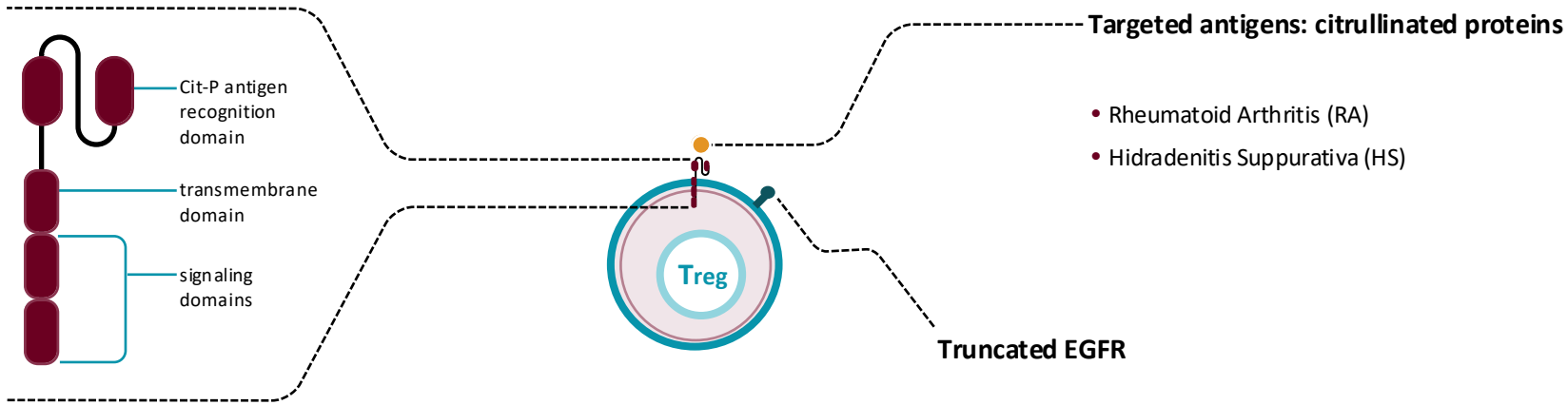
SBT-77-7101 is a Citrullinated Protein-specific CAR-T_{reg} to treat RA and other autoimmune diseases.



Lars Klareskog, Vivianne Malmstrom
Karolinska Institute

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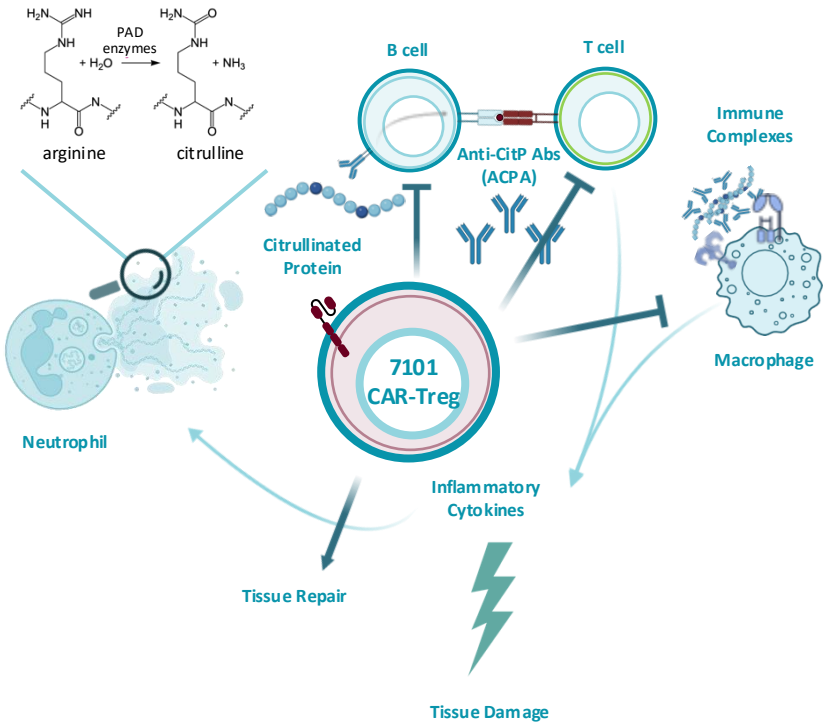
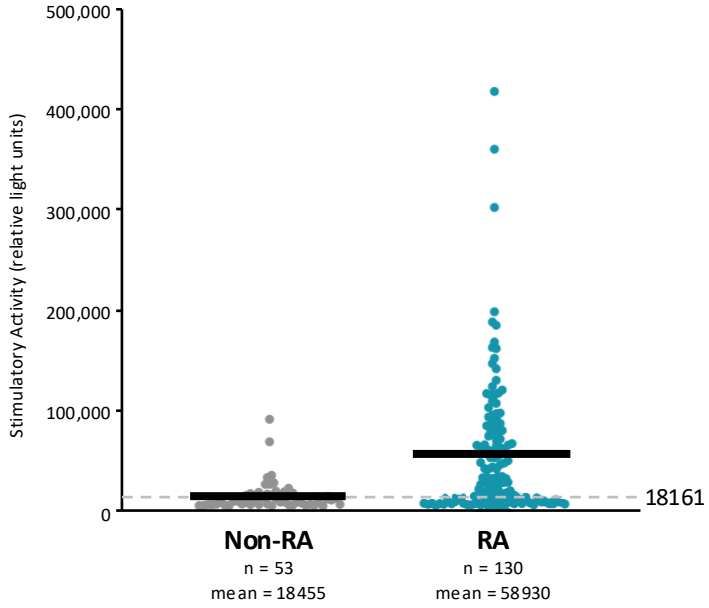
CitP-reactivity is present in the joints of rheumatoid arthritis patients

SBT77-7701 is directed to CitP



CitP in RA patient synovial fluid selectively activates anti-CitP CAR T_{reg}



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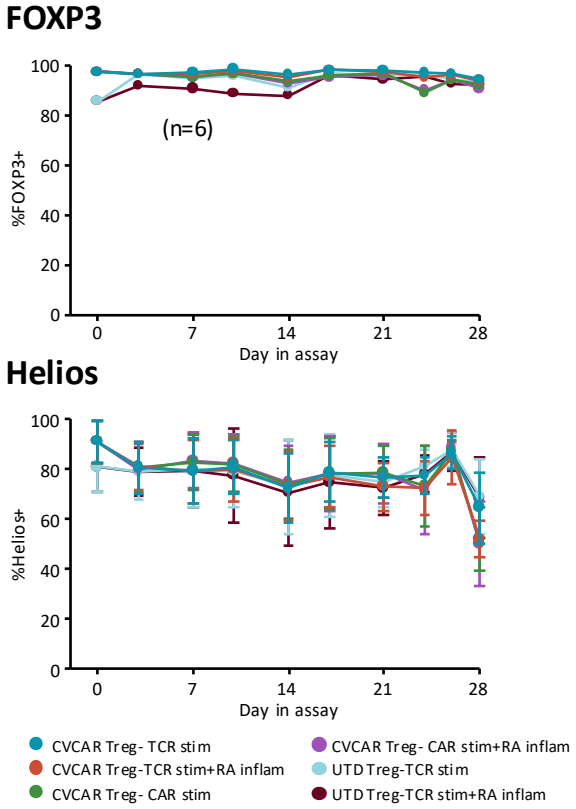
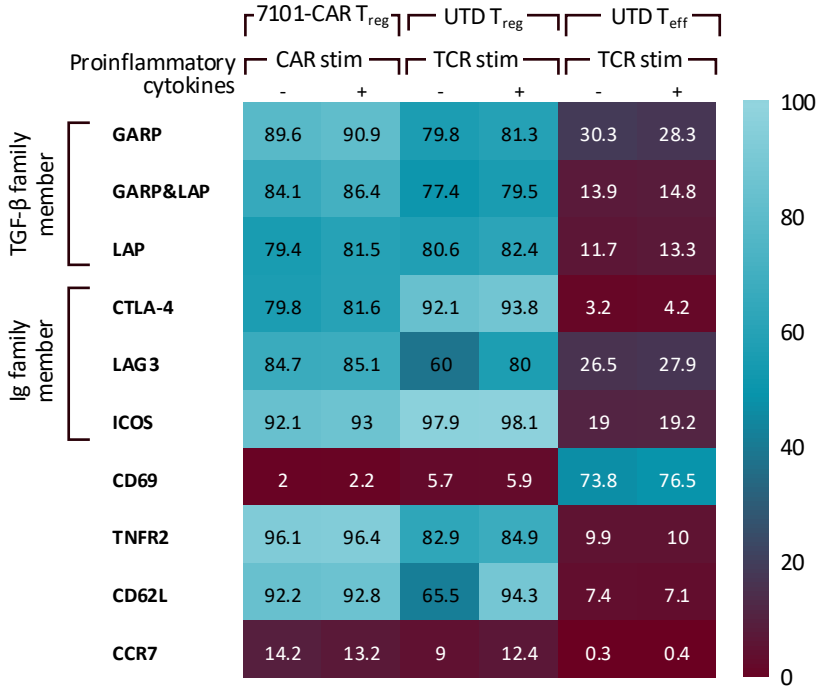
CitP-CAR T_{reg} cells retain expression of key identity genes in the presence of proinflammatory cytokines





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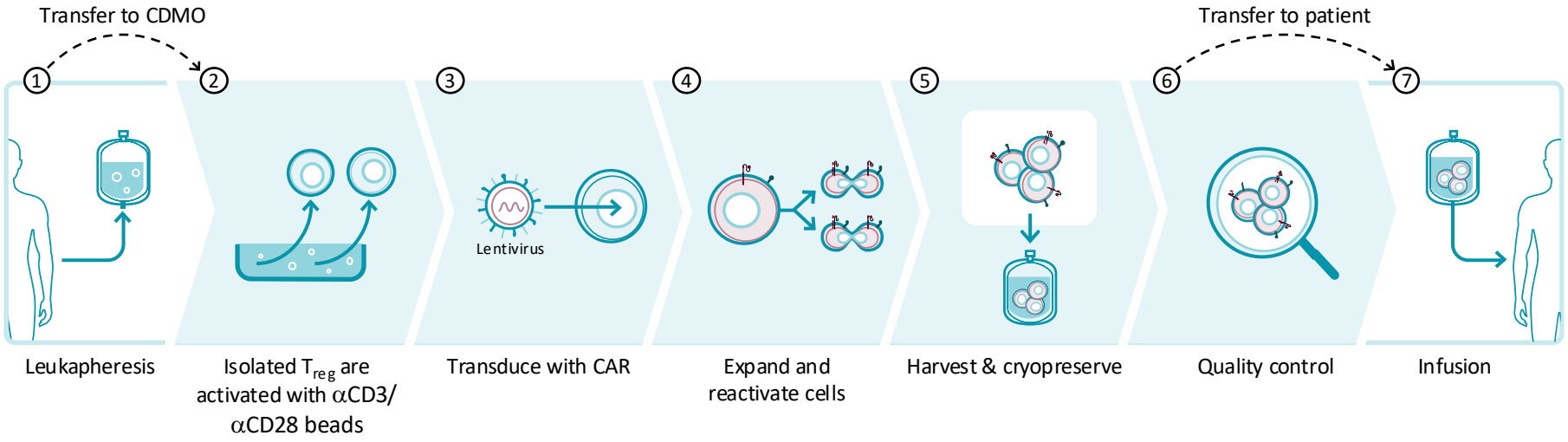
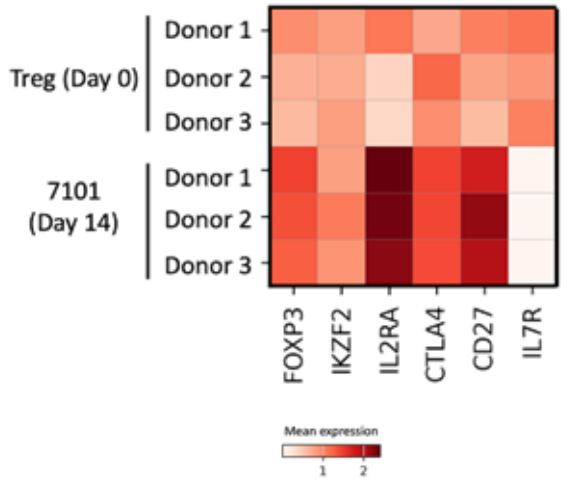
Manufacturing Engineered T_{reg} cells



Manufactured SonomaBio T_{reg} product demonstrates increased potency based on expression of key T_{reg} function genes



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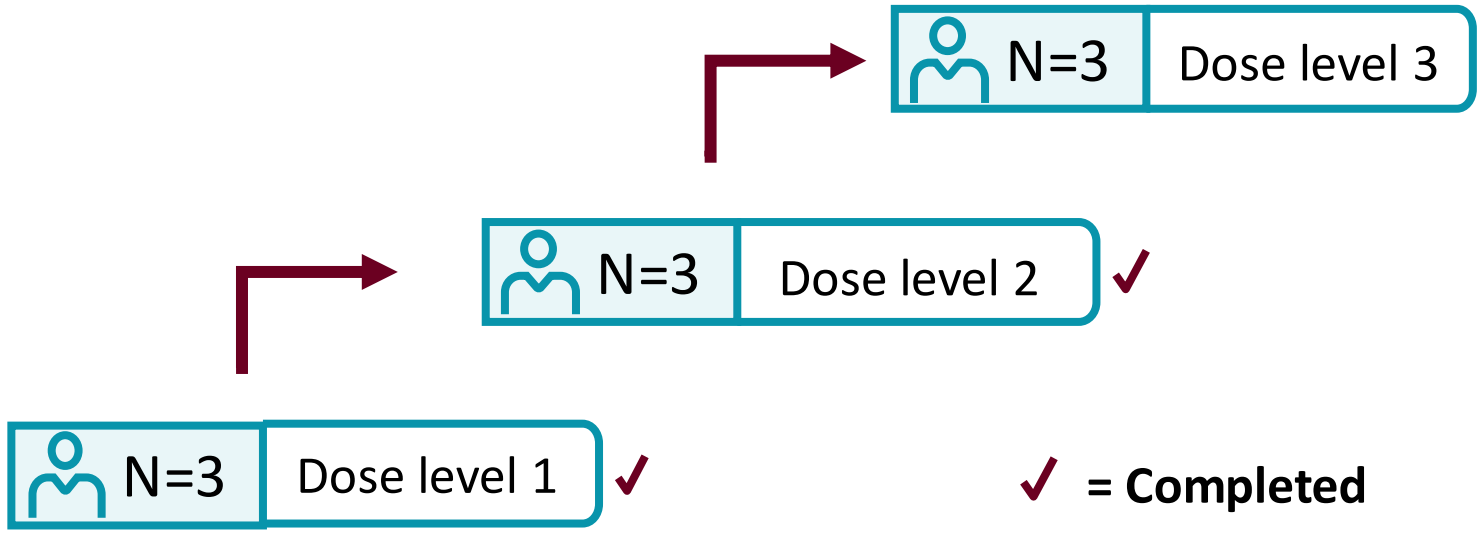
Regulate-RA is a phase 1, first-in-human study to evaluate the safety and clinical activity of SBT-77-7101 in RA patients with highly refractory disease

Patient population

- Adults with RA
- Moderate-to-severe active disease
- Failure of at least three therapies of **different** mechanisms of action

Dose escalation



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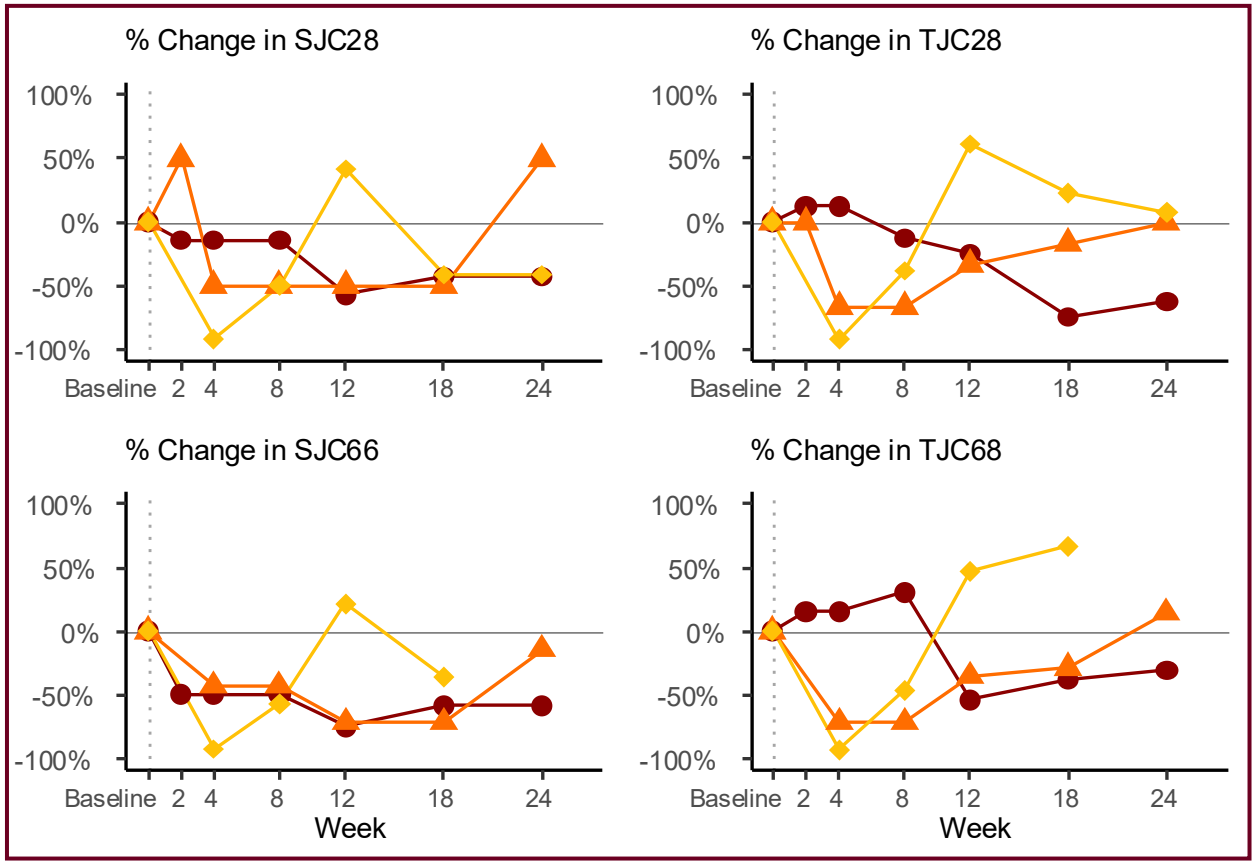
Regulate-RA participants in Cohorts 1 and 2 have active and highly refractory disease

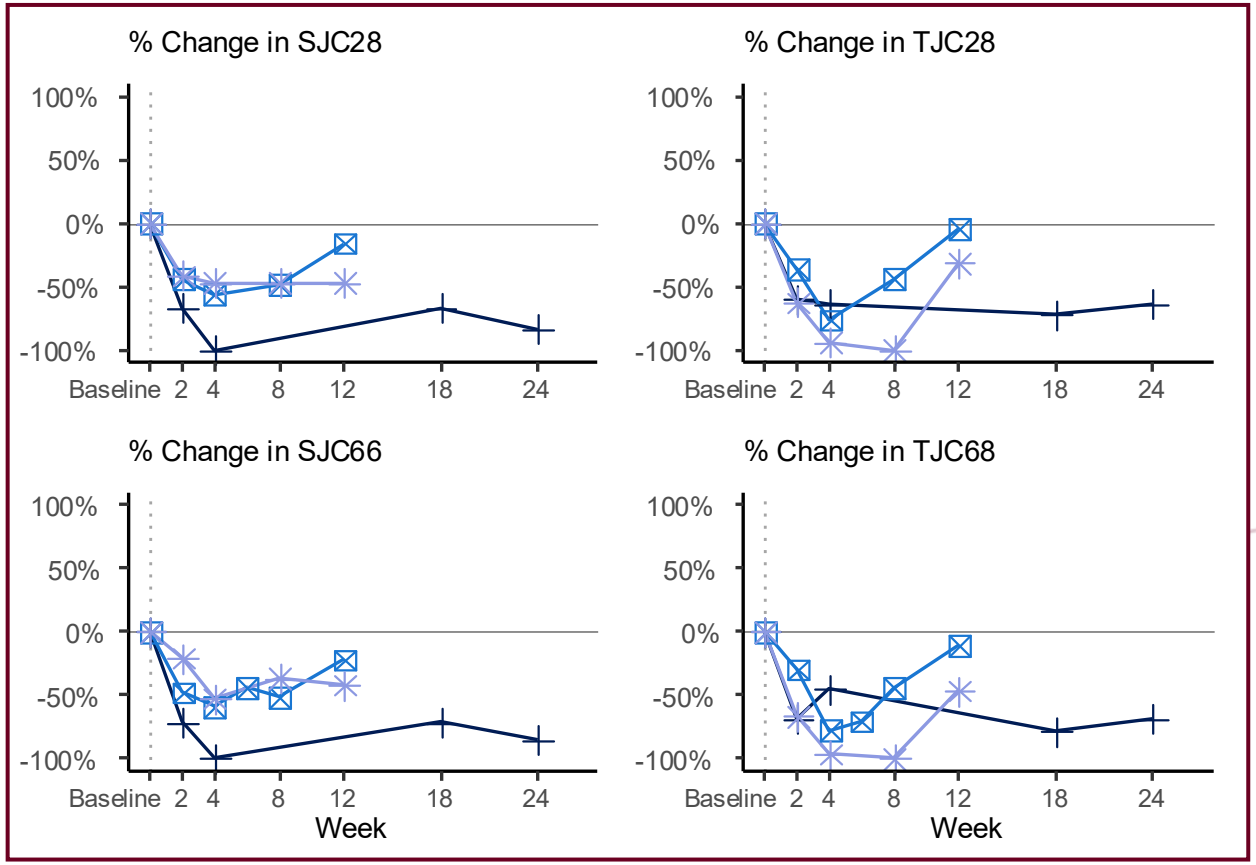
	Pt 1	Pt 2	Pt 3	Pt 4	Pt 5	Pt 6
	Cohort 1 (dose level 1)			Cohort 2 (dose level 2)		
Sex at birth	F	F	F	F	F	F
Age (years)	68	42	58	64	51	52
Race/Ethnicity	White, Hispanic	White, Hispanic	White, Hispanic	White, not Hispanic	White, not Hispanic	White and Nat Am, not Hispanic
Disease duration (years)	2.3	18.1	4.8	28.1	7.5	14.7
RF status (titer)	+	+	+	+	+	+
ACPA status (titer)	+	+	+	+	+	+
DAS28-CRP	4.5	3.7	6.5	6.2	7.6	5.4
CDAI	25	18	58	41	66	44
Swollen joints – 28 joint count	5	7	20	6	20	11
Tender joints – 28 joint count	7	4	21	22	27	17
Total number of prior DMARDs	6	10	12	14	9	8
Number of prior b/ts DMARDs total (**Number of Mechanisms of Action**)	4 (**4**)	6 (**5**)	8 (**5**)	12 (**6**)	7 (**4**)	9 (**5**)

Higher dose levels show a deep and consistent reduction in joint counts

Cohort 1 (Dose level 1)



Cohort 2 (Dose level 2)



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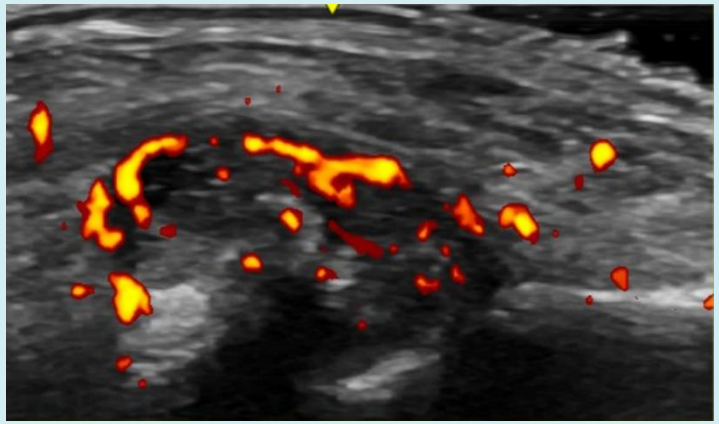
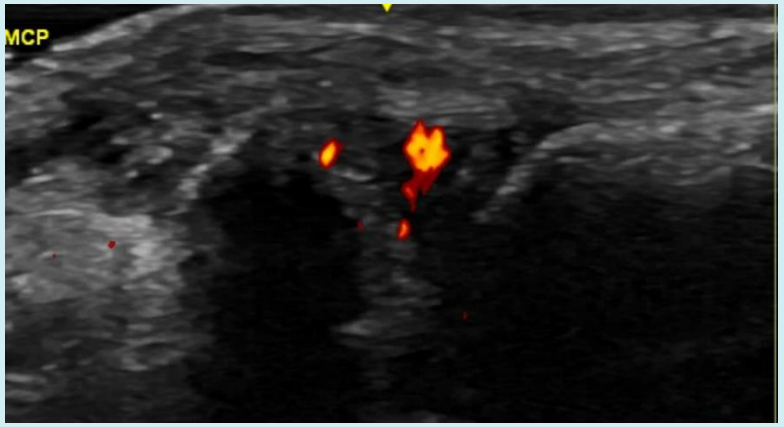
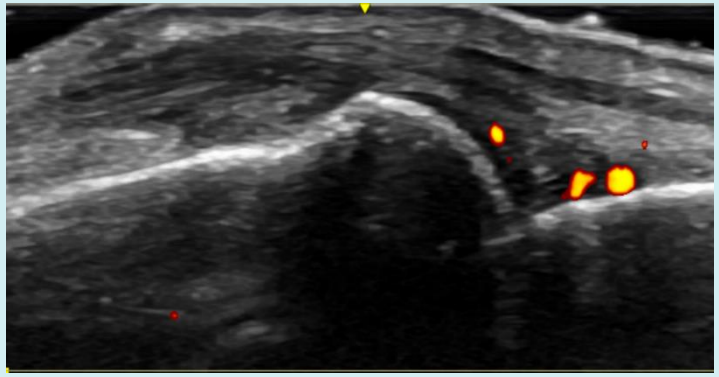
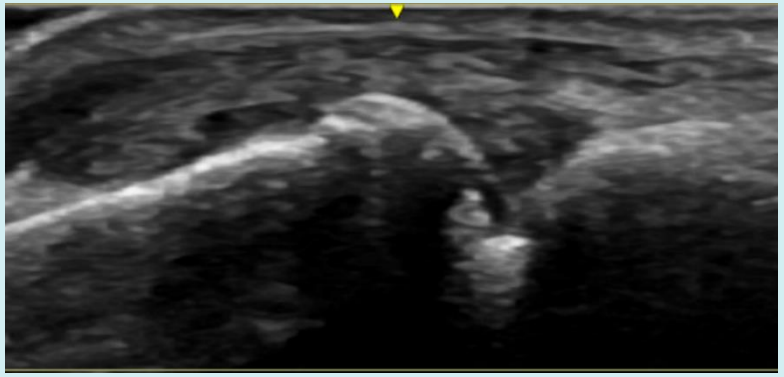
Serial ultrasounds performed in a subset of patients confirm clinical improvement

	Right 2nd MCP		Right 3nd MCP	
Pre-treatment	Score: 3		Score: 3	
Week 4 post-infusion	Score: 1		Score: 1	

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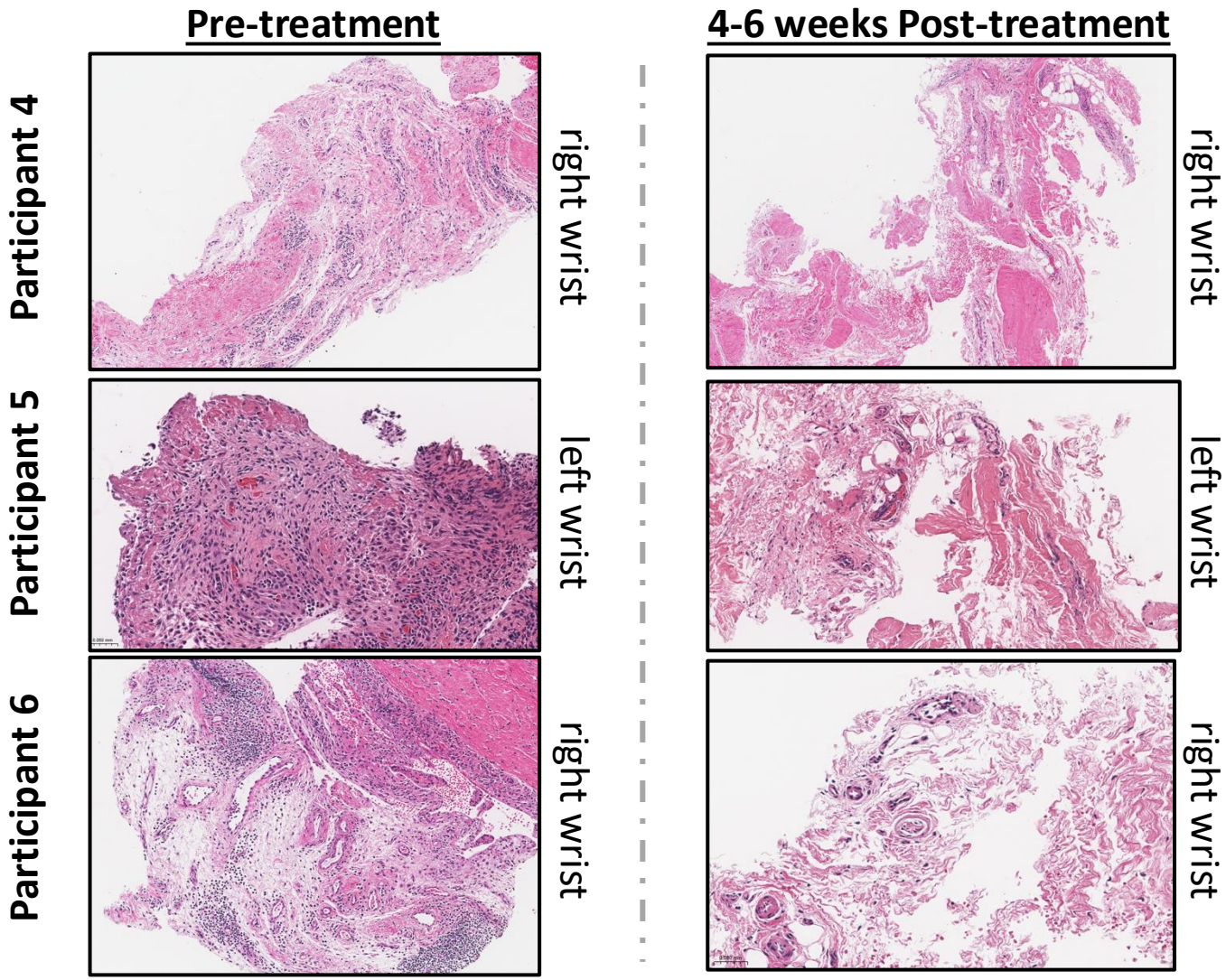
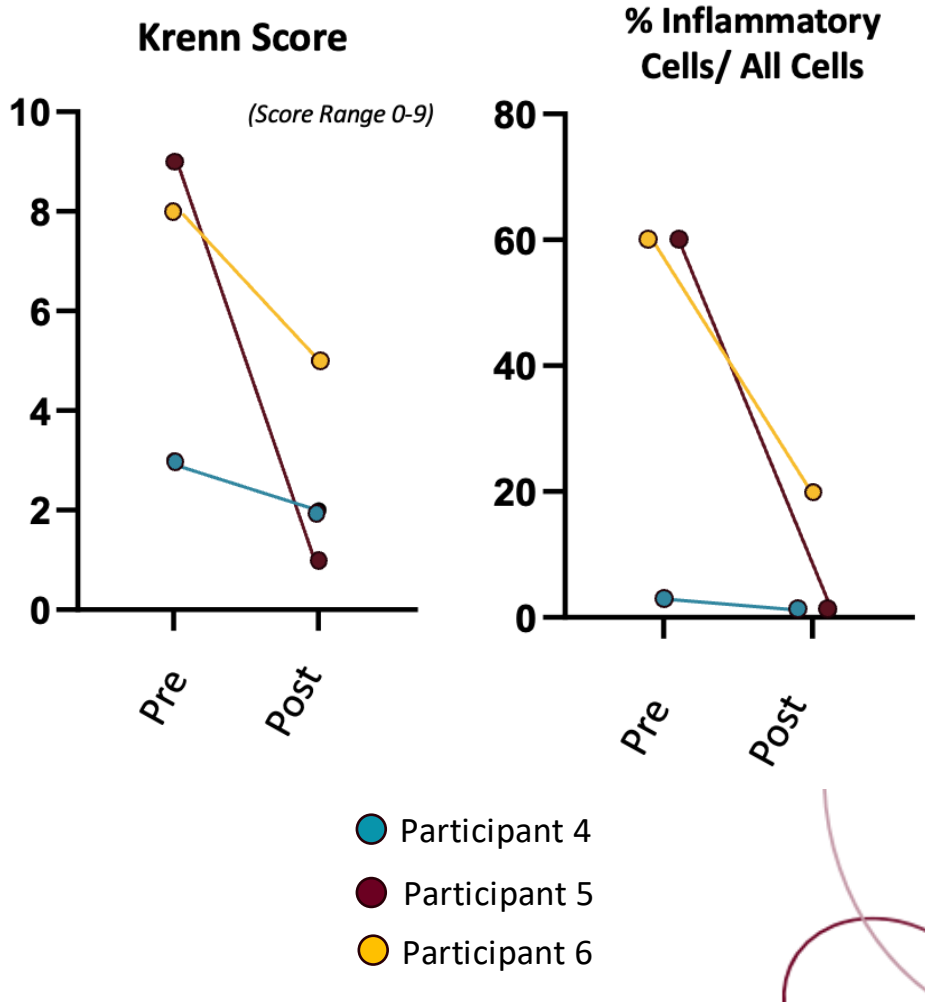
Participants showed reduced inflammation in post-treatment synovial biopsies





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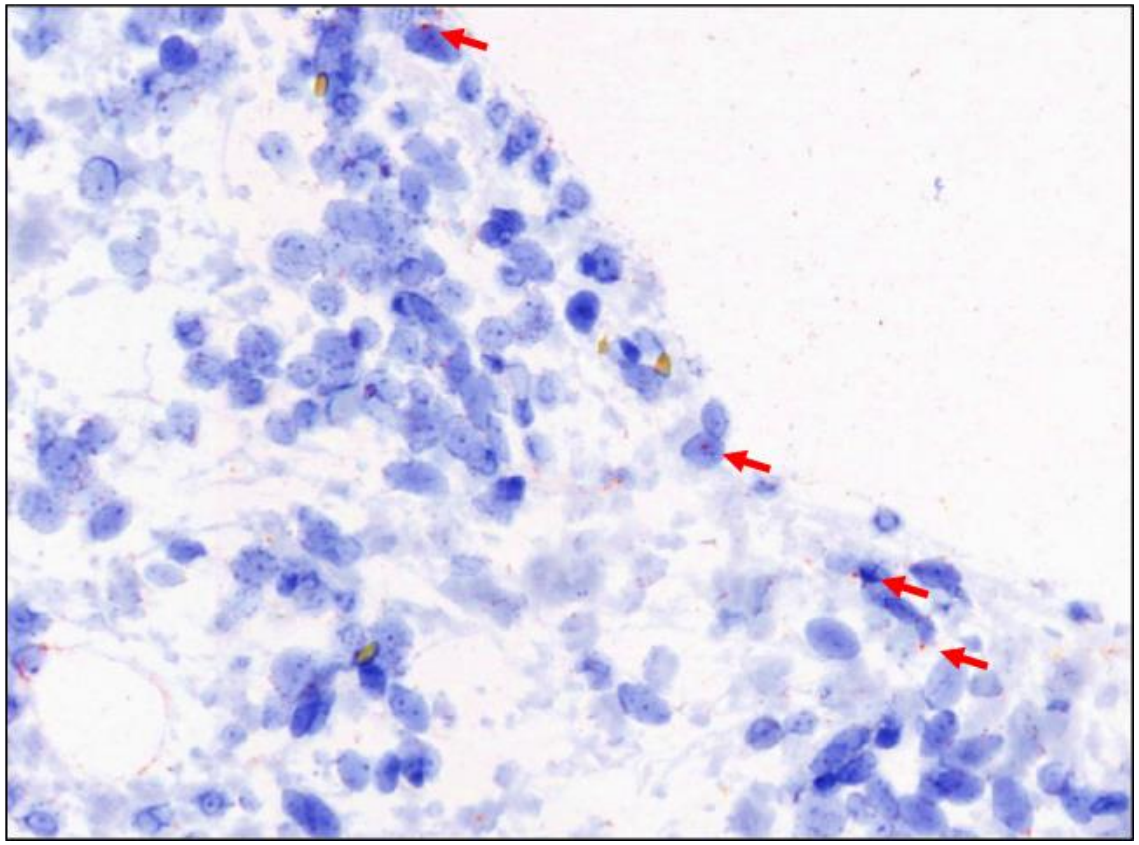
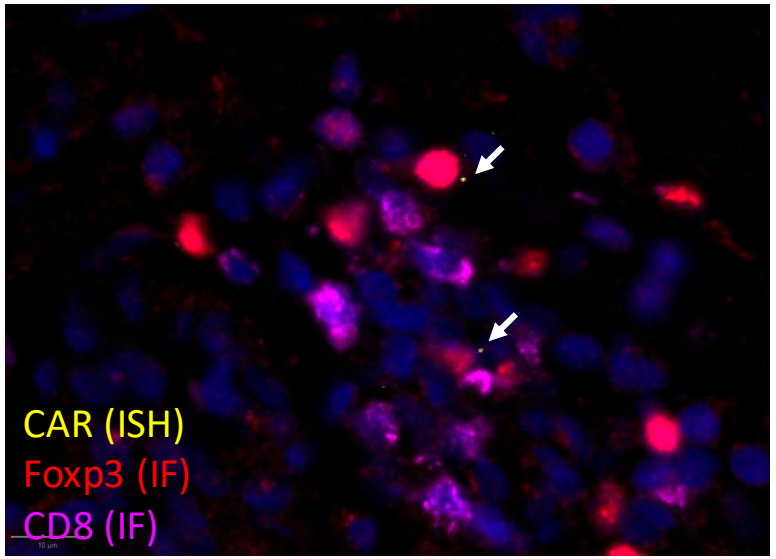
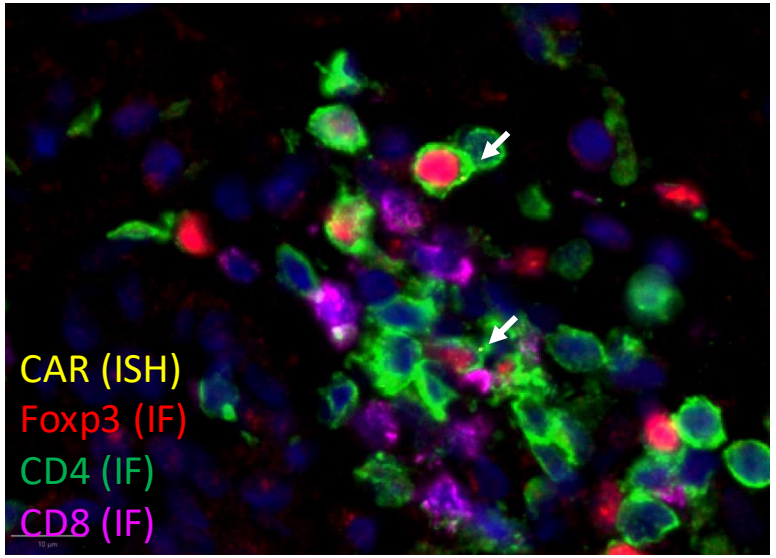
CAR+ T_{reg} cells are detectable in post-treatment synovial biopsy

ISH



ISH/mIF





Red arrows: CAR+ cells detected using in situ hybridization (ISH).

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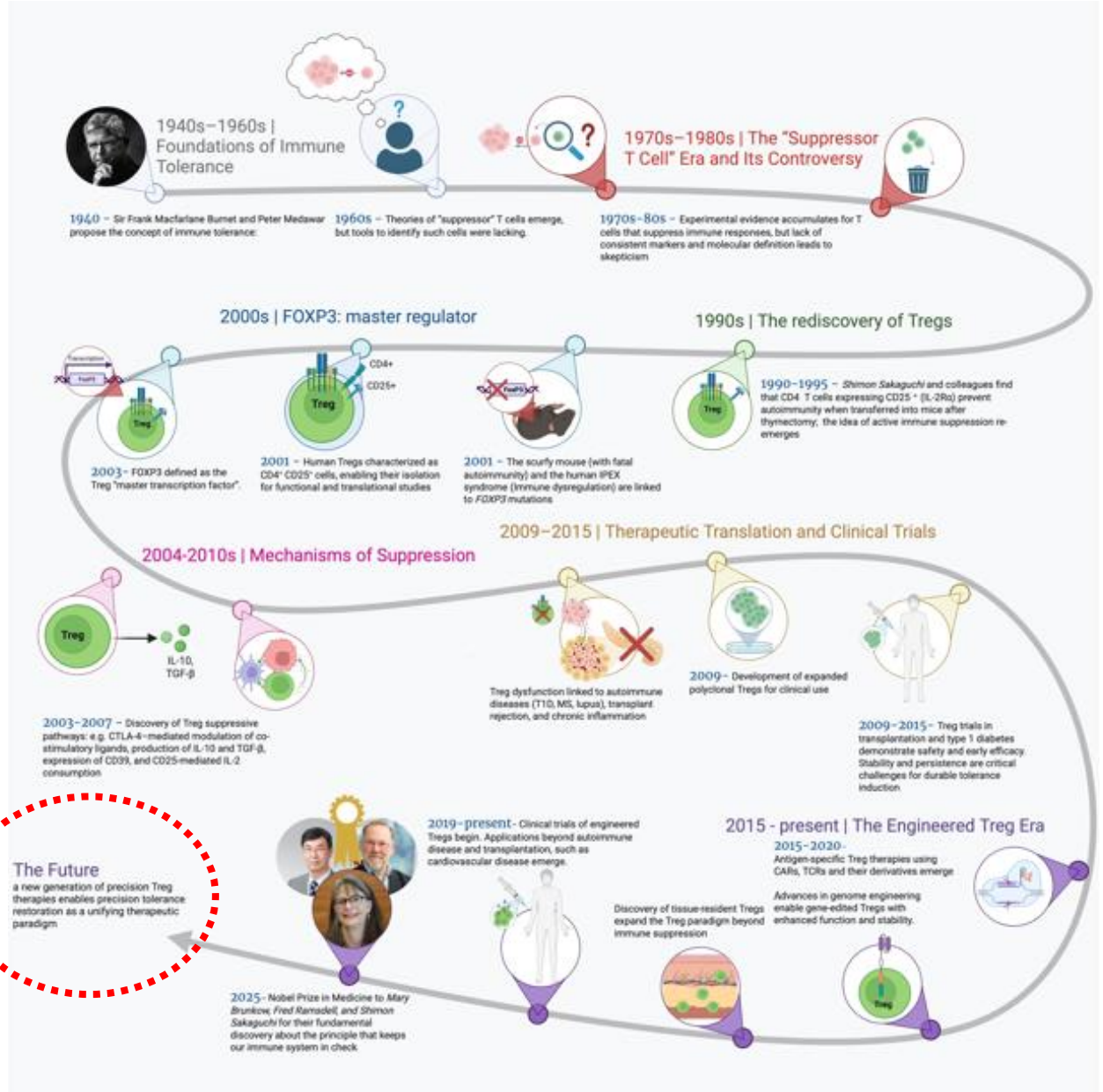
FoxP3 and T_{reg} cells are poised to deliver on the promise of peripheral tolerance



Bluestone, Levings & Fung

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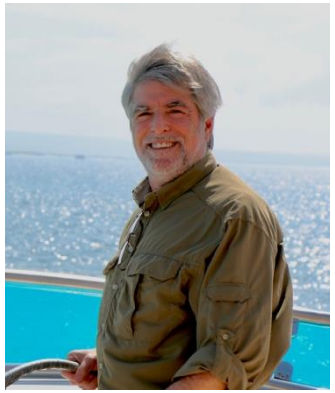
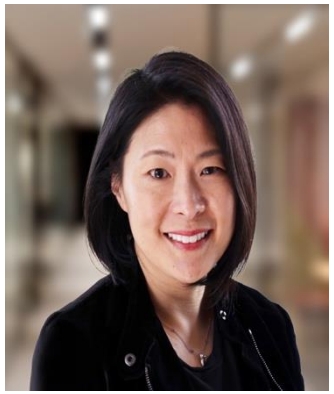
- Sameer Sivaamnuaiphorn
- Sabrina Fox-Bosetti
- Sarah Baxter

- **Clinical Investigators**

- **Patients!**





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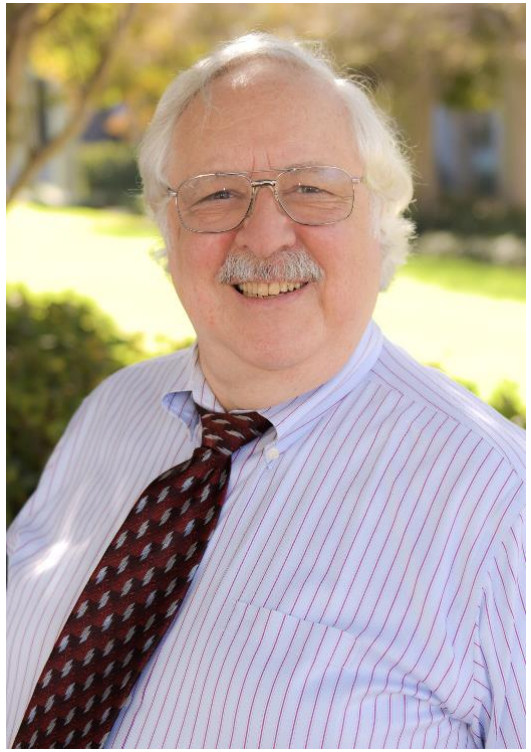
  - **NIH**



Special thank you

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The first time I was in Stockholm…