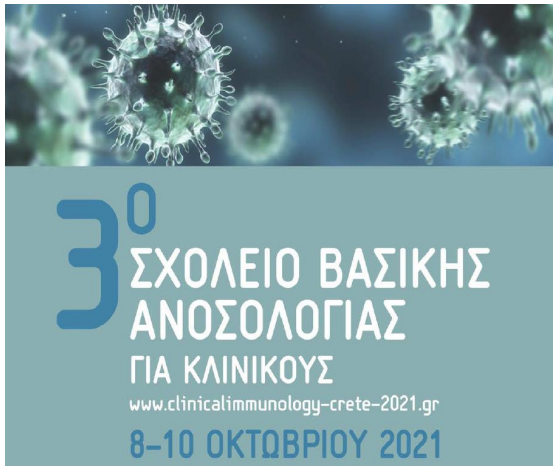
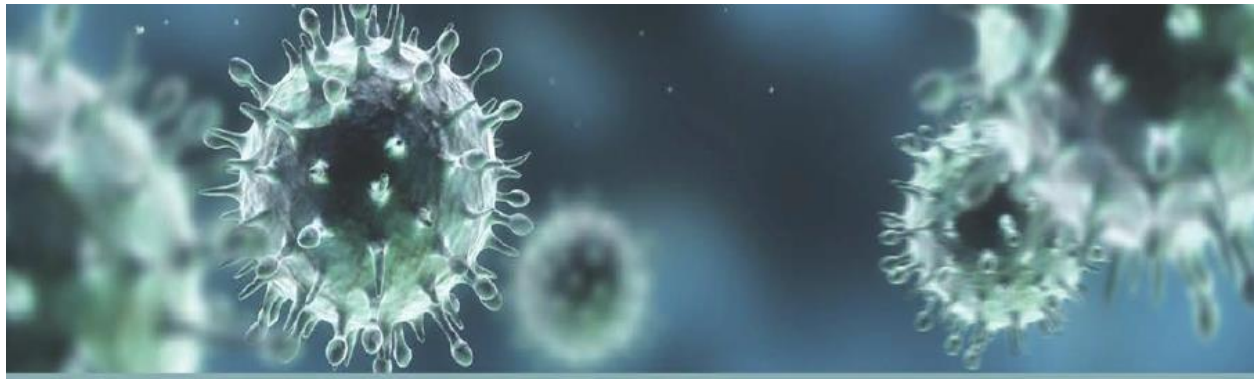


Immunoregulatory therapies in autoimmunity

Αντώνης Φανουριάκης

Ρευματολογική Κλινική, Γ.Ν. Ασκληπιείο Βούλας

Ηράκλειο, 9/10/2021



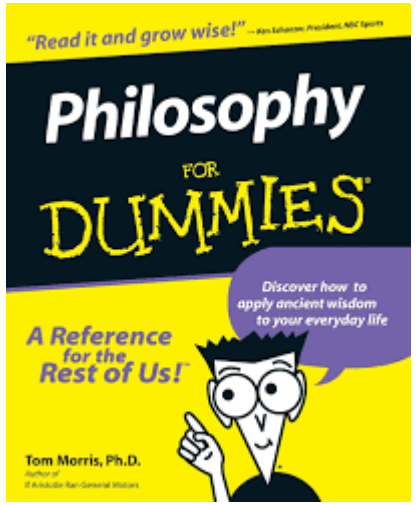
3ο ΣΧΟΛΕΙΟ ΒΑΣΙΚΗΣ ΑΝΟΣΟΛΟΓΙΑΣ

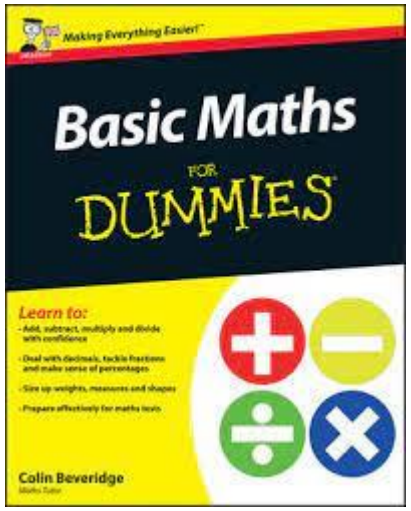
ΓΙΑ ΚΛΙΝΙΚΟΥΣ

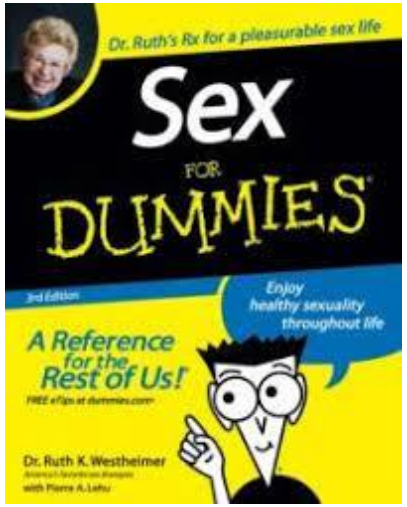
www.clinicalimmunology-crete-2021.gr

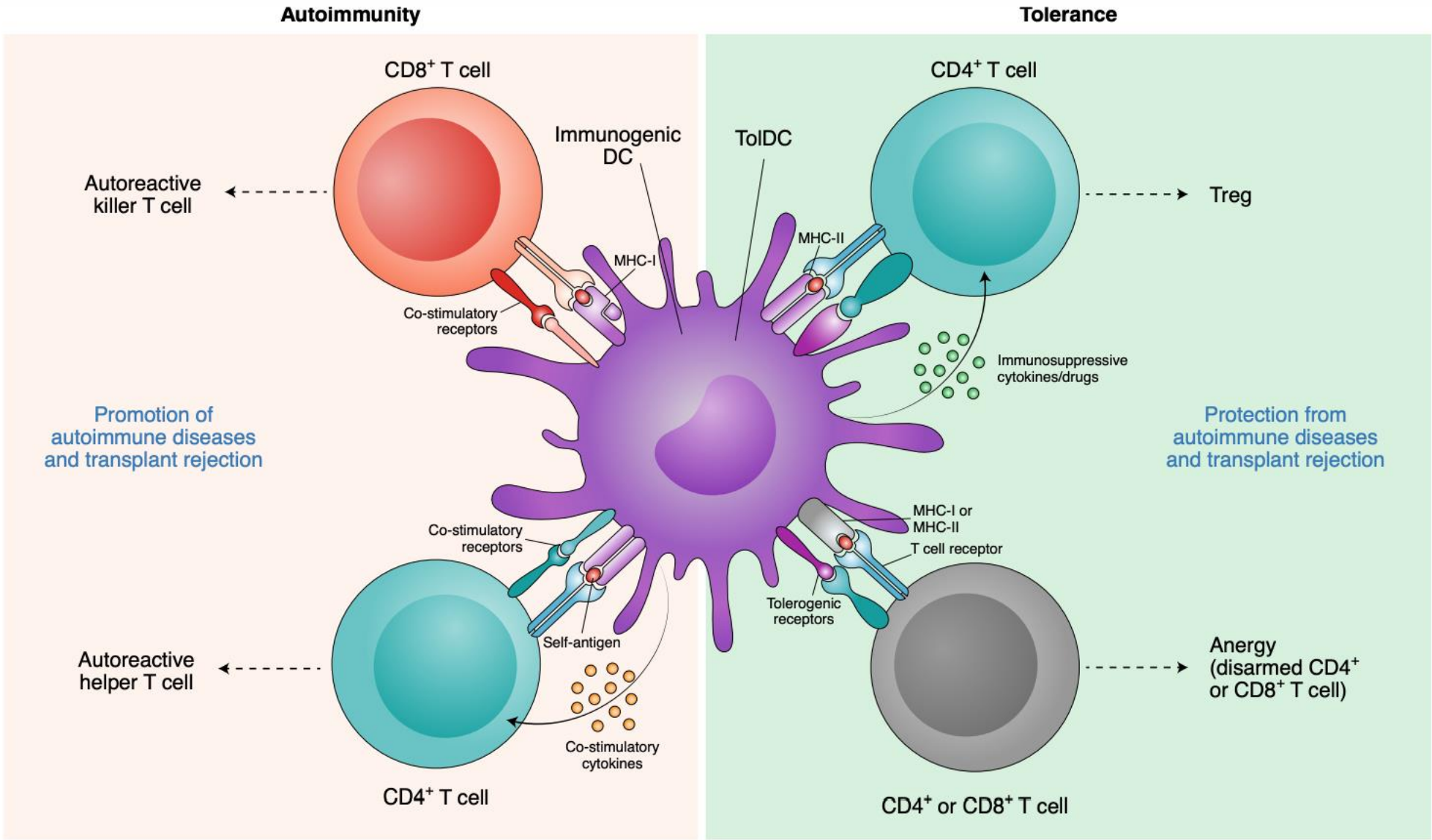
8-10 ΟΚΤΩΒΡΙΟΥ 2021

Για κλινικούς ή For dummies…



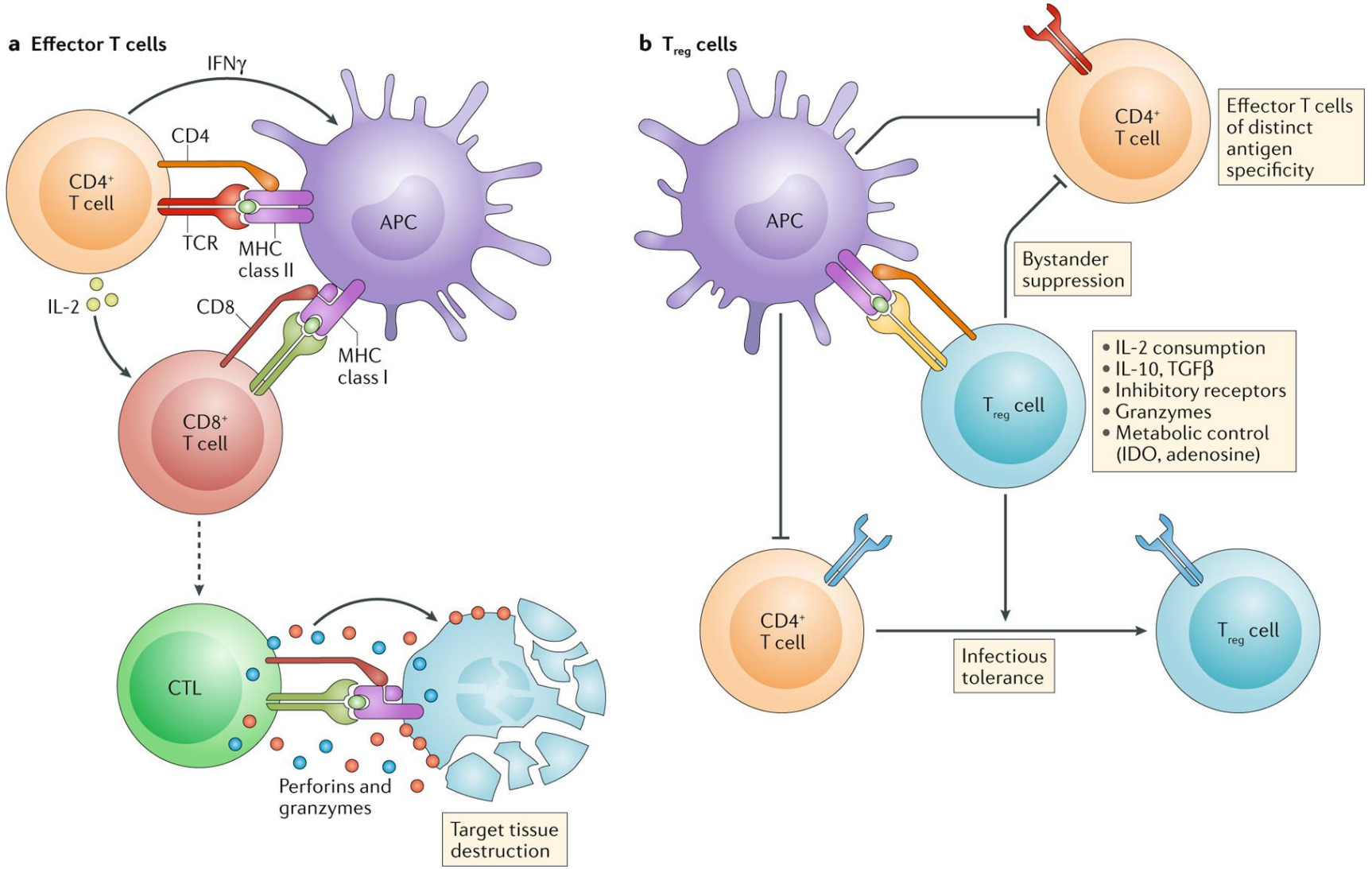






Cifuentes-Rius A, et al. Nat Nanotechnol. 2021;16(1):37-46

Mechanisms of action of effector T cells versus Treg cells



Raffin C, et al. Nat Rev Immunol 2020;20(3):158-72

The rationale behind immunoregulatory therapies

- Systemic autoimmune diseases are caused by a failure of endogenous mechanisms of immune tolerance.

- **Regulatory T cells (Treg),** expressing the transcription factor Foxp3, are pivotal for maintaining peripheral self-tolerance and controlling autoimmunity by suppressing the activation and expansion of autoreactive T cells and other pathogenic immune cells

Setoguchi R, et al. J Exp Med 2005;201:723–35; Fontenot JD, et al. Nat Immunol 2005;6:1142–51.

Key properties of Treg cells

- Treg cells: ~ 5% of circulating CD4+ T cells
- Dominance and durability of Treg cell- mediated immune tolerance:
  - **Bystander suppression**: Treg cells activated by one antigen suppress immune responses against other antigens.
  - **Infectious tolerance**: Suppressive capacity is transferred from one cell population to another
    - Inhibitory cytokines that inhibit DC maturation

The rationale behind immunoregulatory therapies

- The survival, growth and homeostasis of Treg fundamentally depend on the availability of the cytokine interleukin-2 (IL-2)

- IL-2 deficiency results in a profound disturbance of Treg homeostasis and the development of a severe systemic autoimmune disease due to uncontrolled hyperactivity of T and B cells.

- While expressing high levels of IL2R (CD25), Tregs are unable to produce IL2 themselves - in the absence of IL-2 produced by other cell subtypes, or signalling by its receptor, there is a decrease in the number and functional activity of the Treg cells

Setoguchi R, et al. J Exp Med 2005;201:723–35; Fontenot JD, et al. Nat Immunol 2005;6:1142–51; Chinen T, et al. Nat Immunol 2016;17(11):1322-33

Ways currently used to exploit Treg cells

- Exogenous administration of IL-2 to expand Tregs
- Adoptive Treg cell transfer
  - Ex vivo polyclonal expansion of autologous Tregs and reinfusion into patient
  - Next-generation Treg cell therapy

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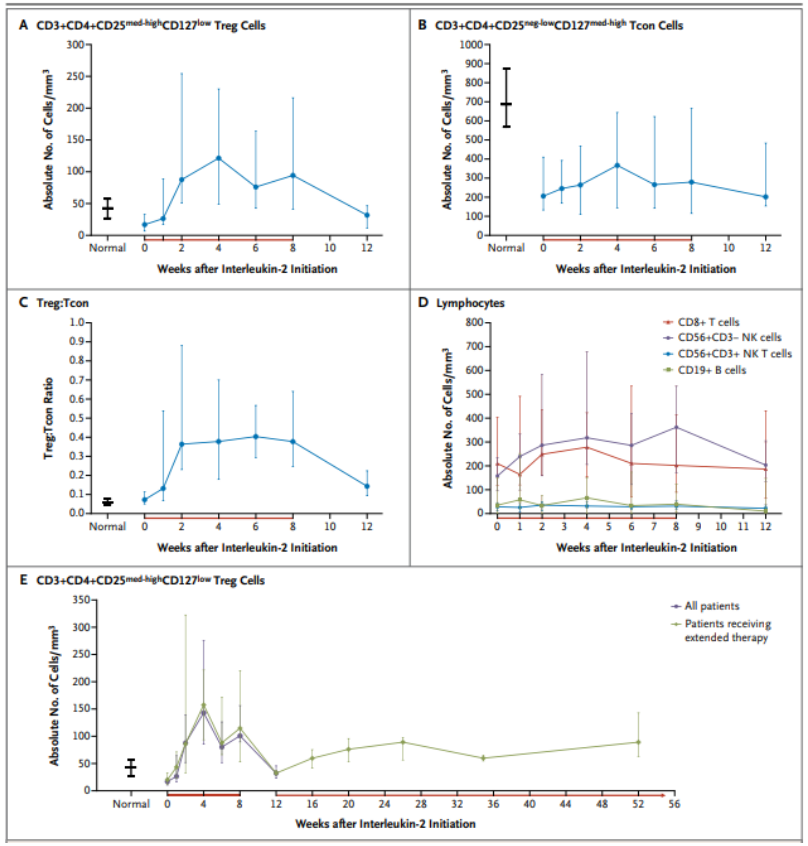
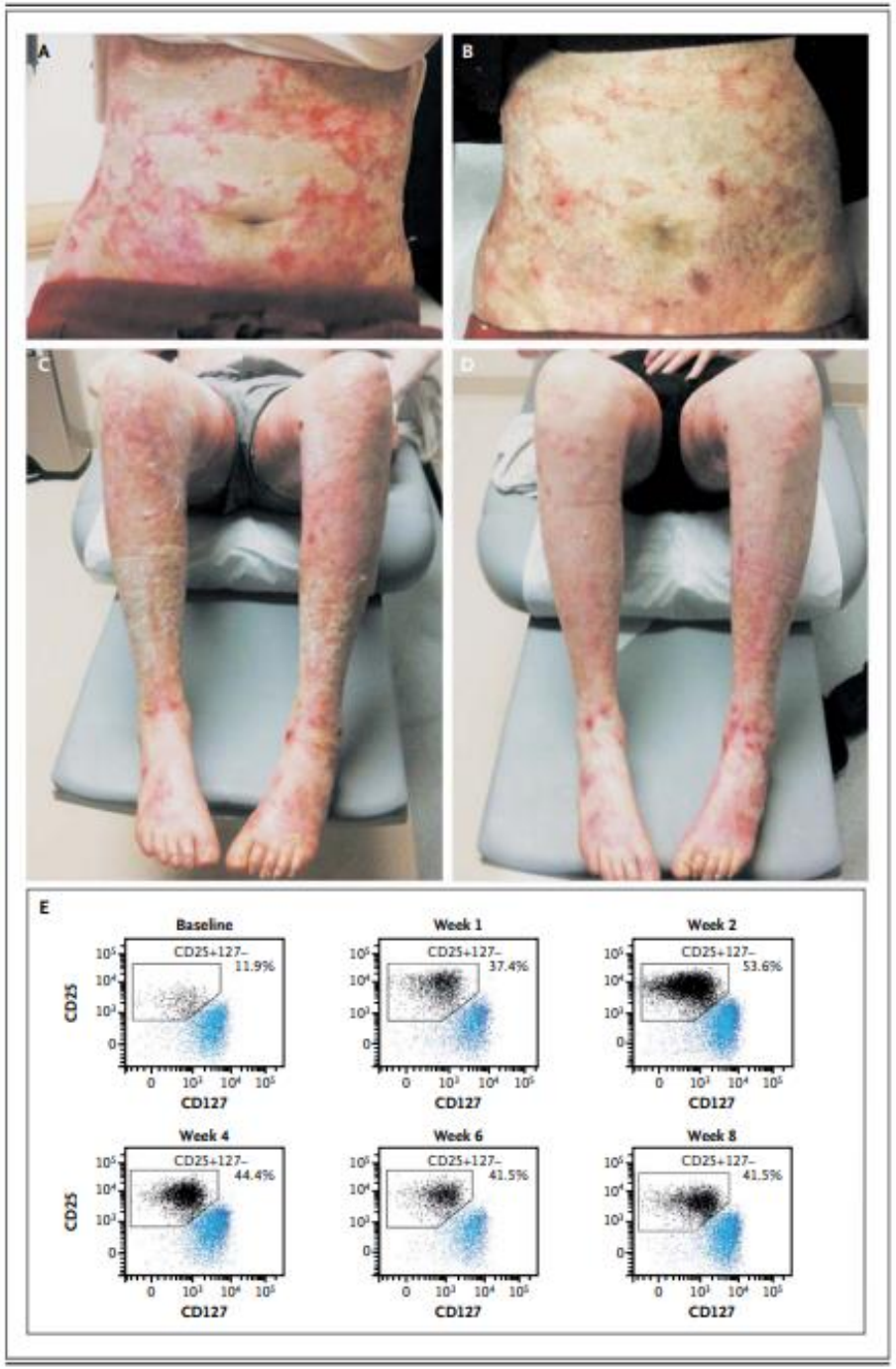
The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 DECEMBER 1, 2011 VOL. 365 NO. 22

Interleukin-2 and Regulatory T Cells in Graft-versus-Host Disease

29 ασθενείς με χρόνια graft-versus-host disease
ανθεκτική στα κορτικοειδή



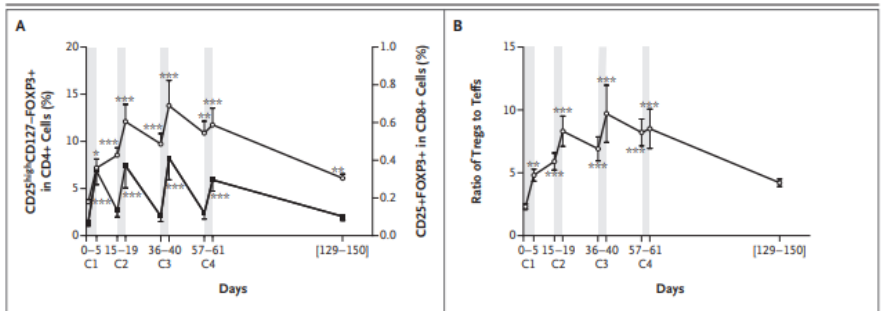


No major safety signals

Koreth J, et al. N Engl J Med 2011;365(22):2055-66

Regulatory T-Cell Responses to Low-Dose Interleukin-2 in HCV-Induced Vasculitis

10 ασθενείς με HCV-σχετιζόμενη κρυοσφαιριναιμική αγγειίτιδα ανθεκτική σε αντιική θεραπεία και rituximab



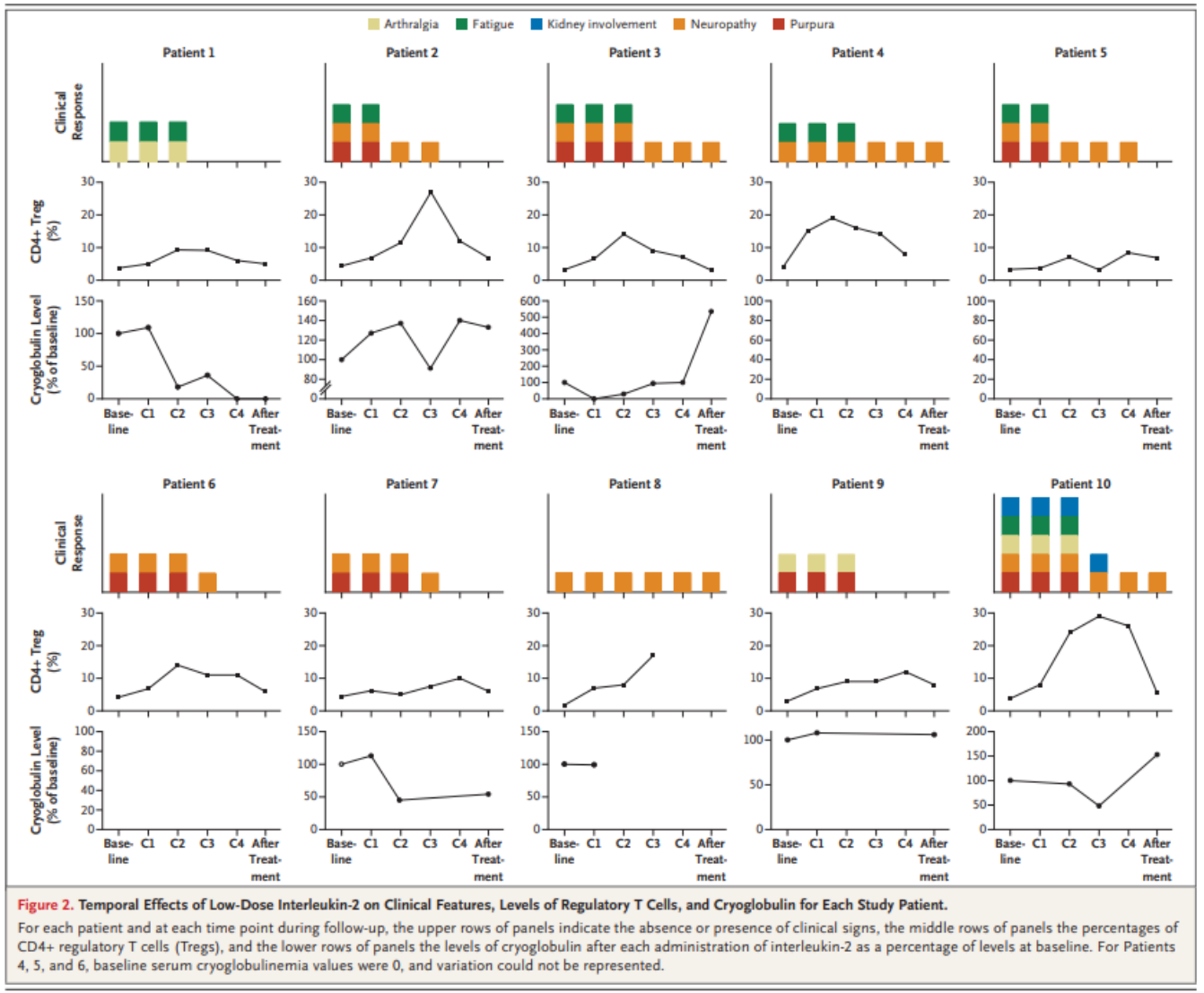


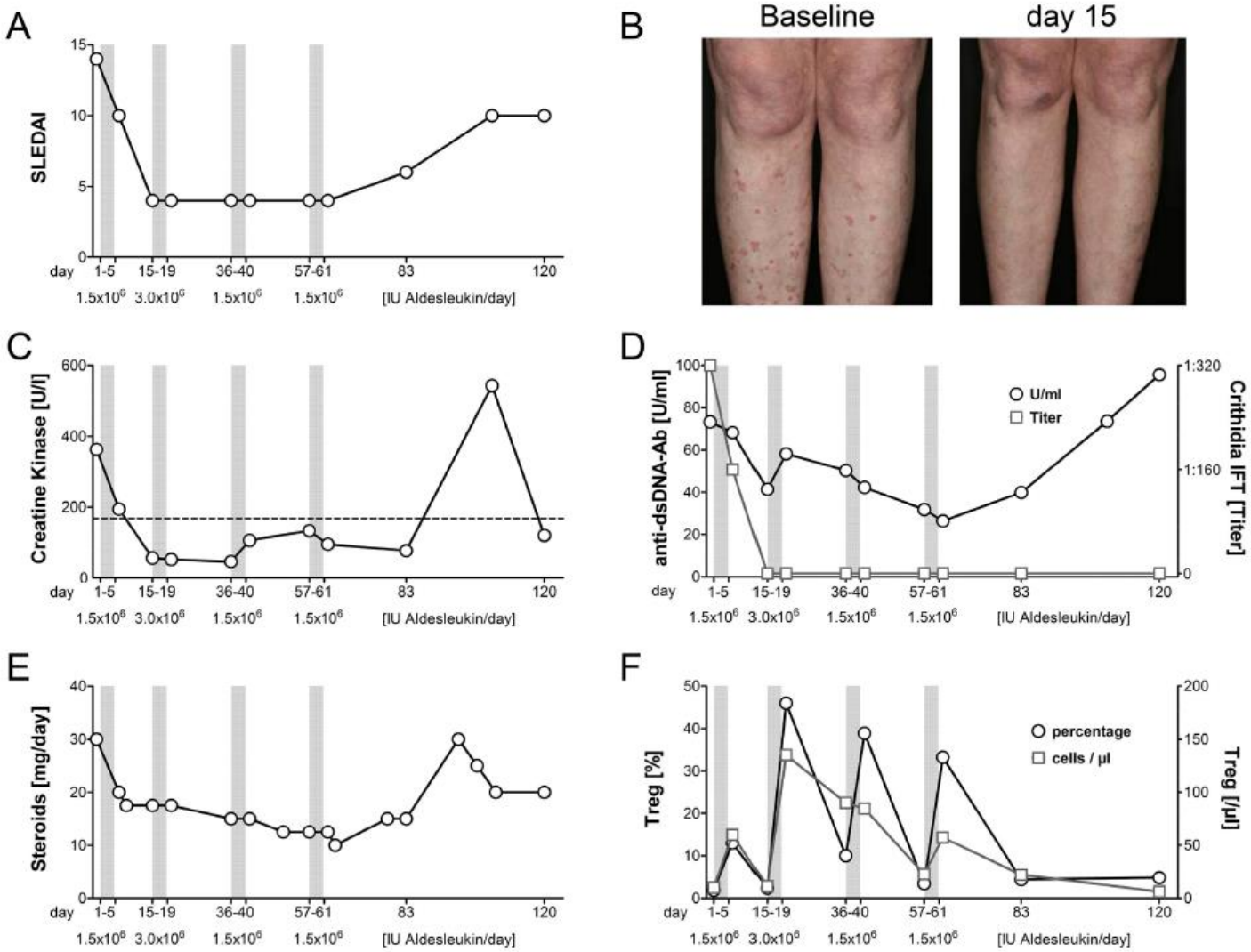
Figure 2. Temporal Effects of Low-Dose Interleukin-2 on Clinical Features, Levels of Regulatory T Cells, and Cryoglobulin for Each Study Patient.

For each patient and at each time point during follow-up, the upper rows of panels indicate the absence or presence of clinical signs, the middle rows of panels the percentages of CD4+ regulatory T cells (Tregs), and the lower rows of panels the levels of cryoglobulin after each administration of interleukin-2 as a percentage of levels at baseline. For Patients 4, 5, and 6, baseline serum cryoglobulinemia values were 0, and variation could not be represented.

Saadoun D, et al. N Engl J Med 2011;365(22):2067-77

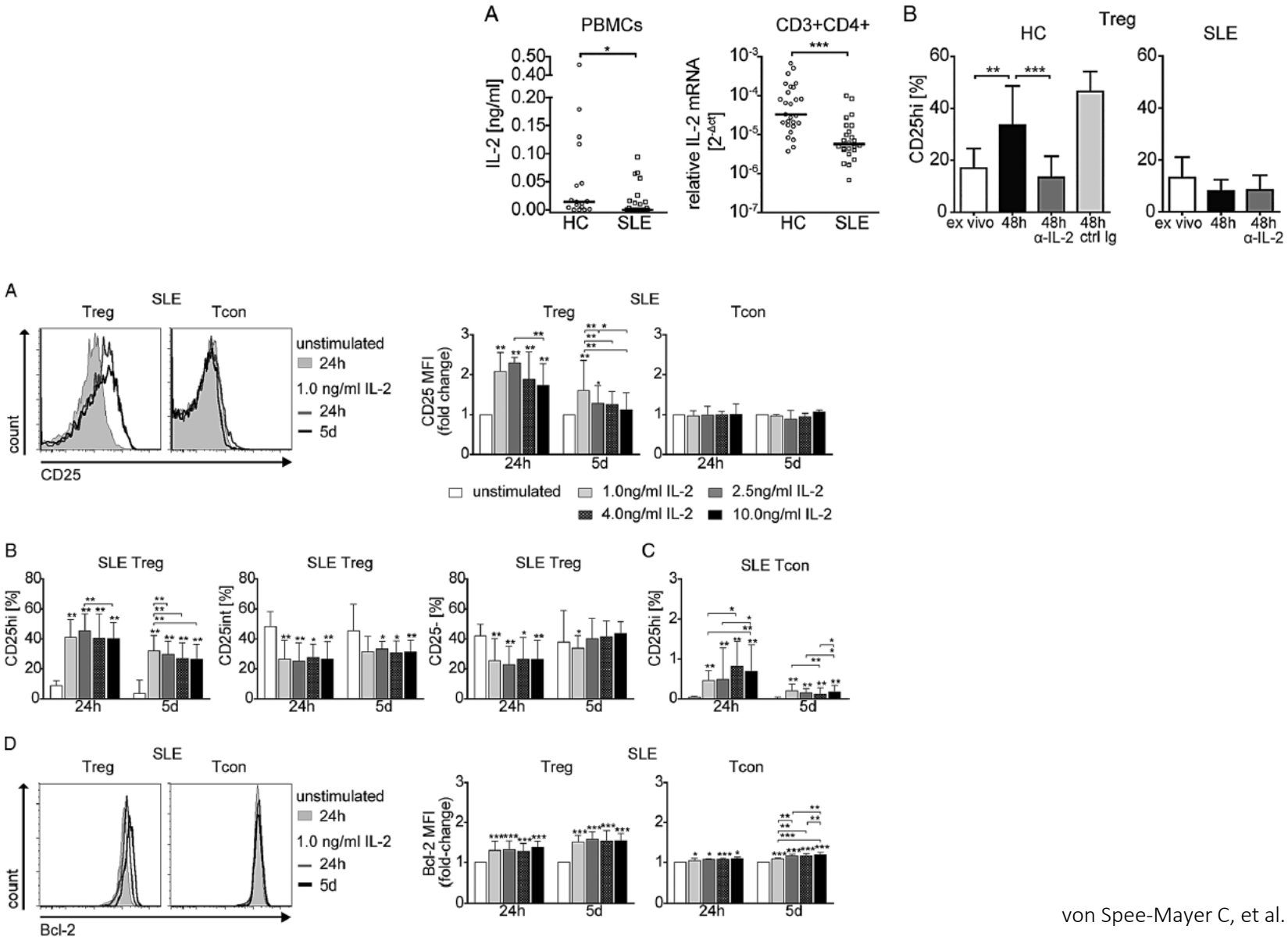
Case report of low-dose IL-2 therapy in a SLE patient

Clinical parameters and Treg cells



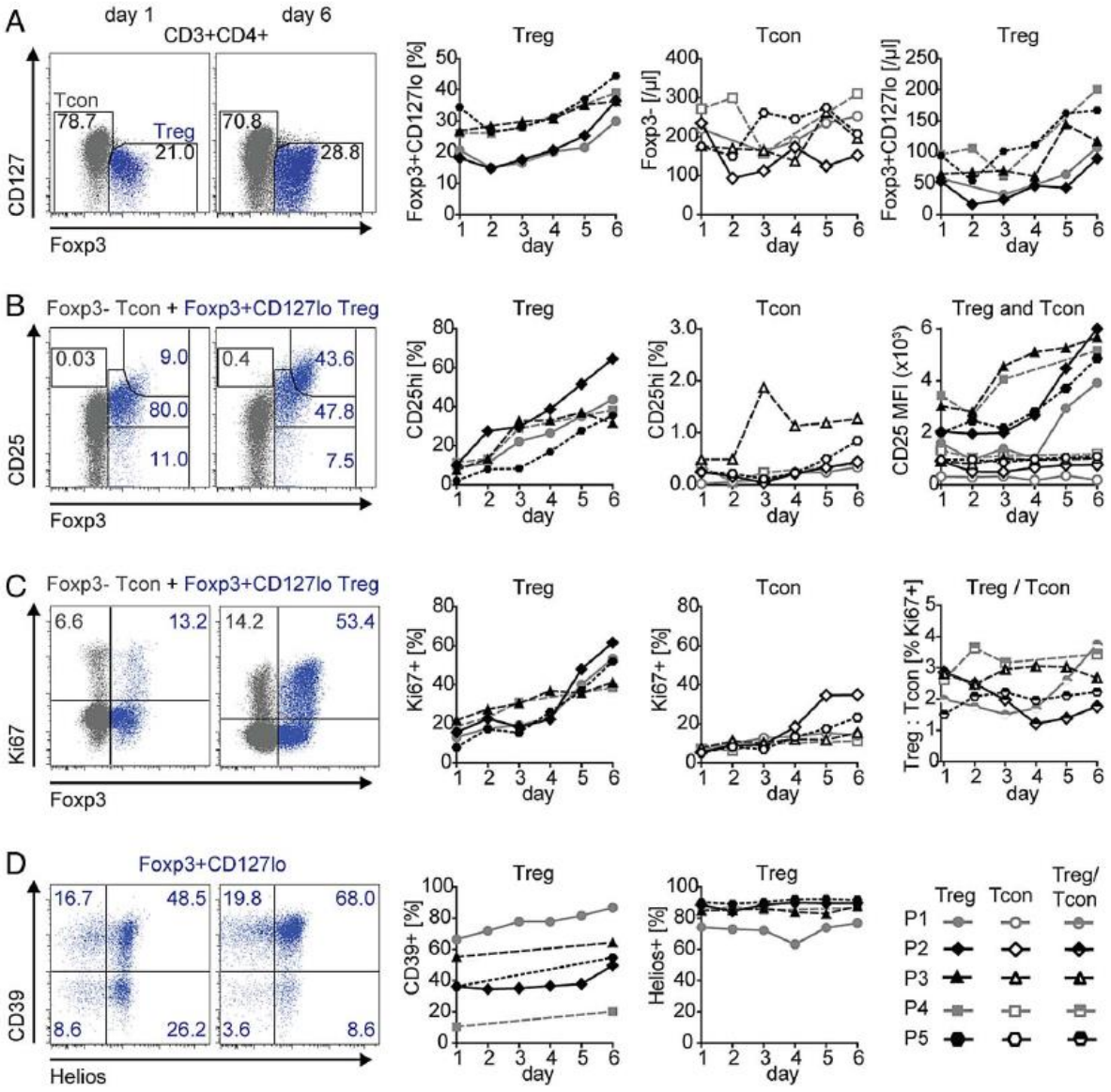
Humrich JY, et al. Ann Rheum Dis 2015;74(4):791-2

Low-dose IL2 therapy corrects Treg cell defects in SLE



von Spee-Mayer C, et al. Ann Rheum Dis 2016;75(7):1407–15

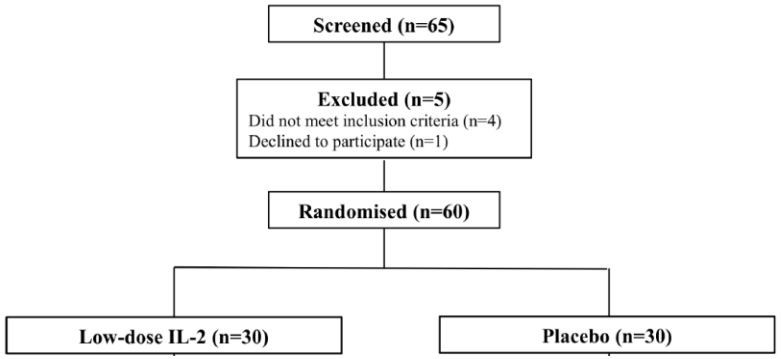
Low-dose IL2 therapy corrects Treg cell defects in SLE

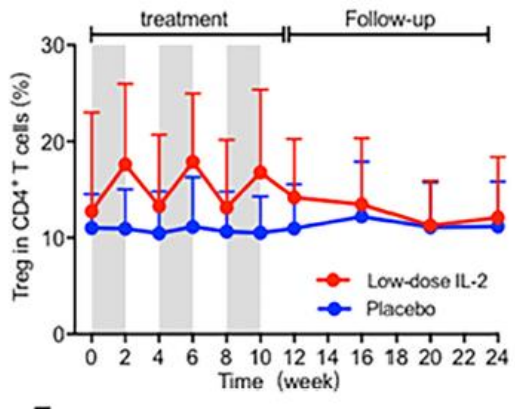


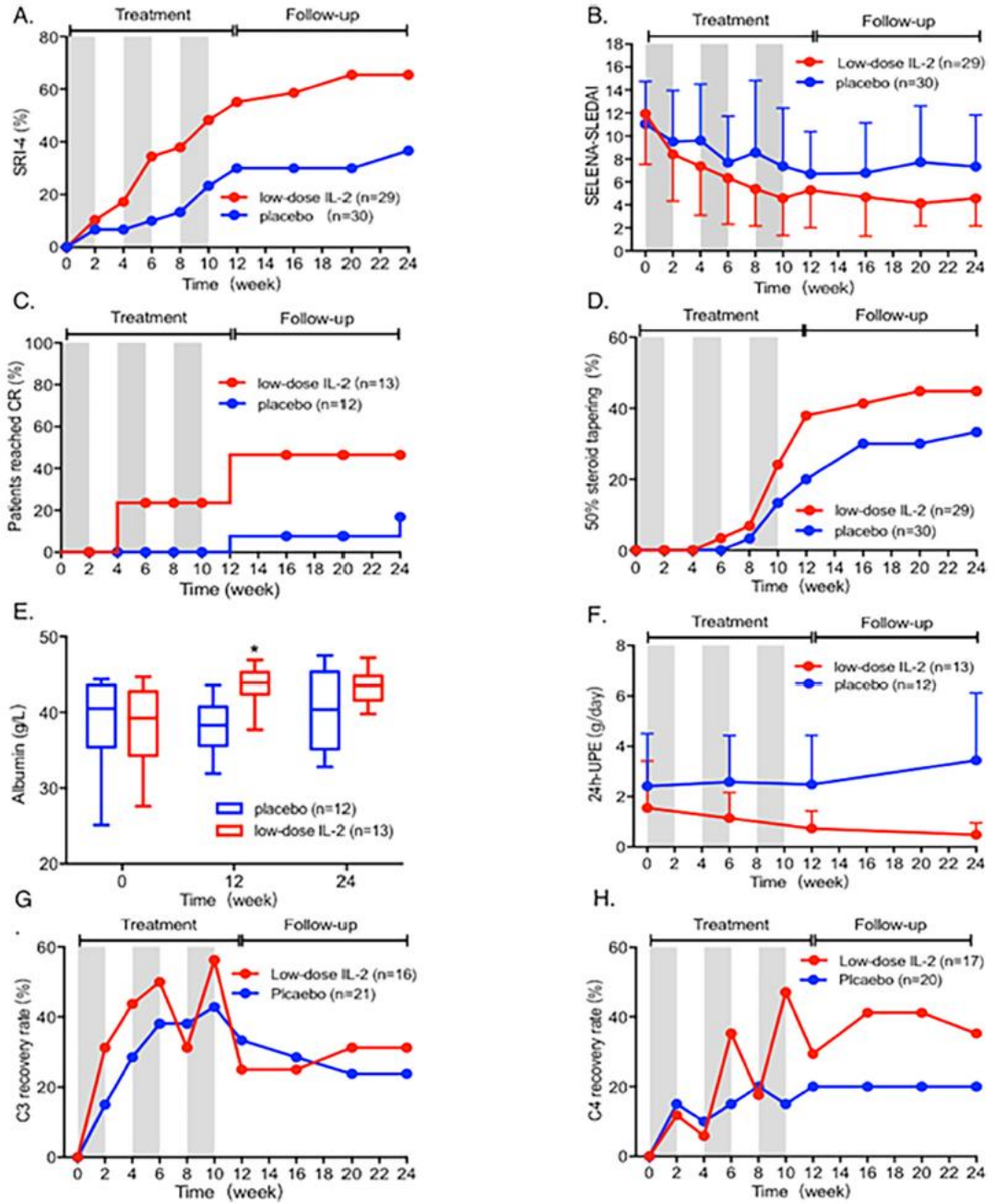
5 patients with SLE

von Spee-Mayer C, et al. Ann Rheum Dis 2016;75(7):1407–15

Efficacy and safety of low-dose IL-2 in the treatment of systemic lupus erythematosus: a randomised, double-blind, placebo-controlled trial







He J, et al. Ann Rheum Dis 2020;79(1):141-49

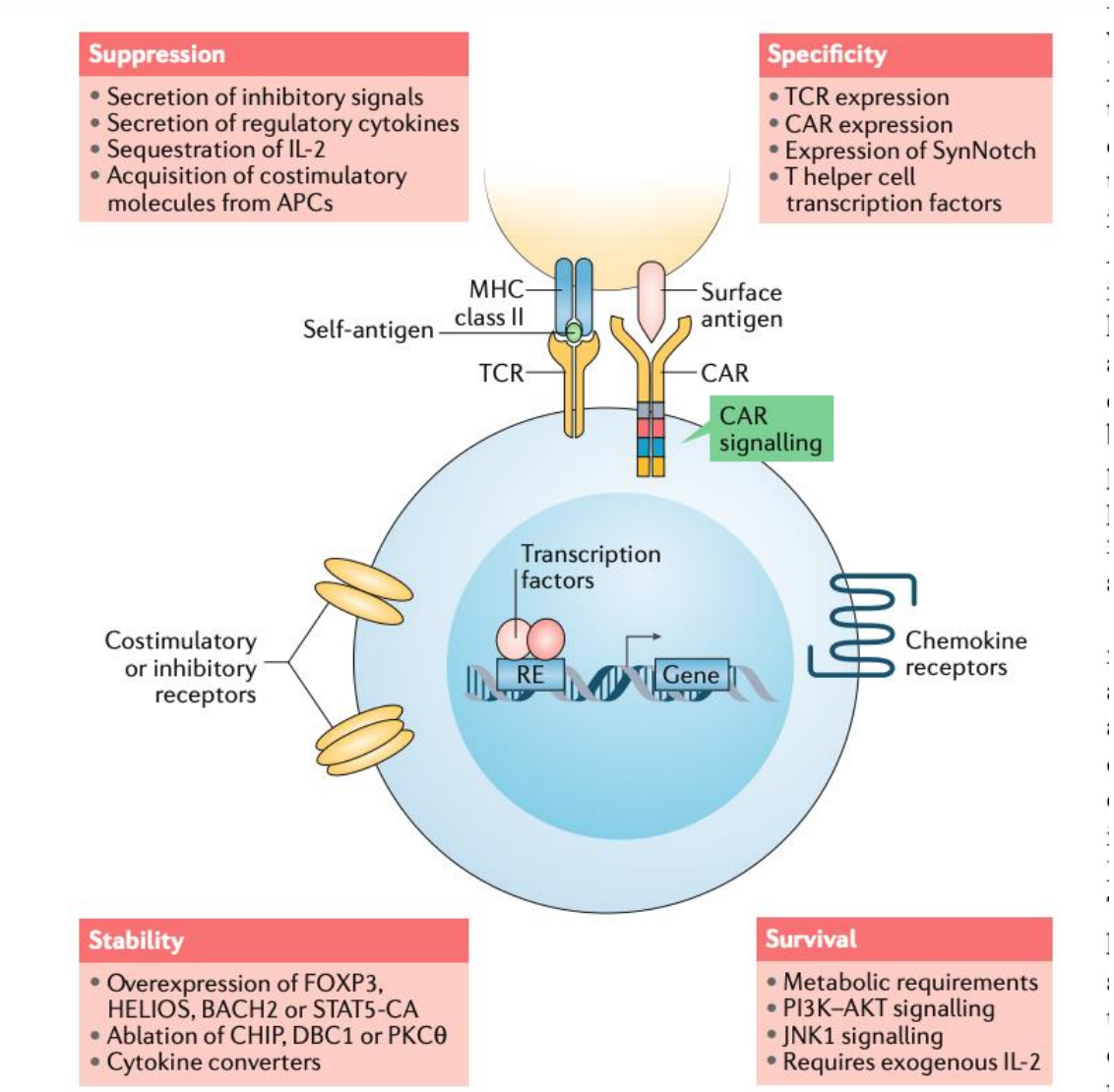
Ways currently used to exploit Treg cells

- Exogenous administration of IL-2 to expand Tregs
- Adoptive Treg cell transfer
  - Ex vivo polyclonal expansion of autologous Tregs and reinfusion into patient
  - Next-generation Treg cell therapy

Key properties needed to successfully use Tregs as living drugs

The 4 “S”

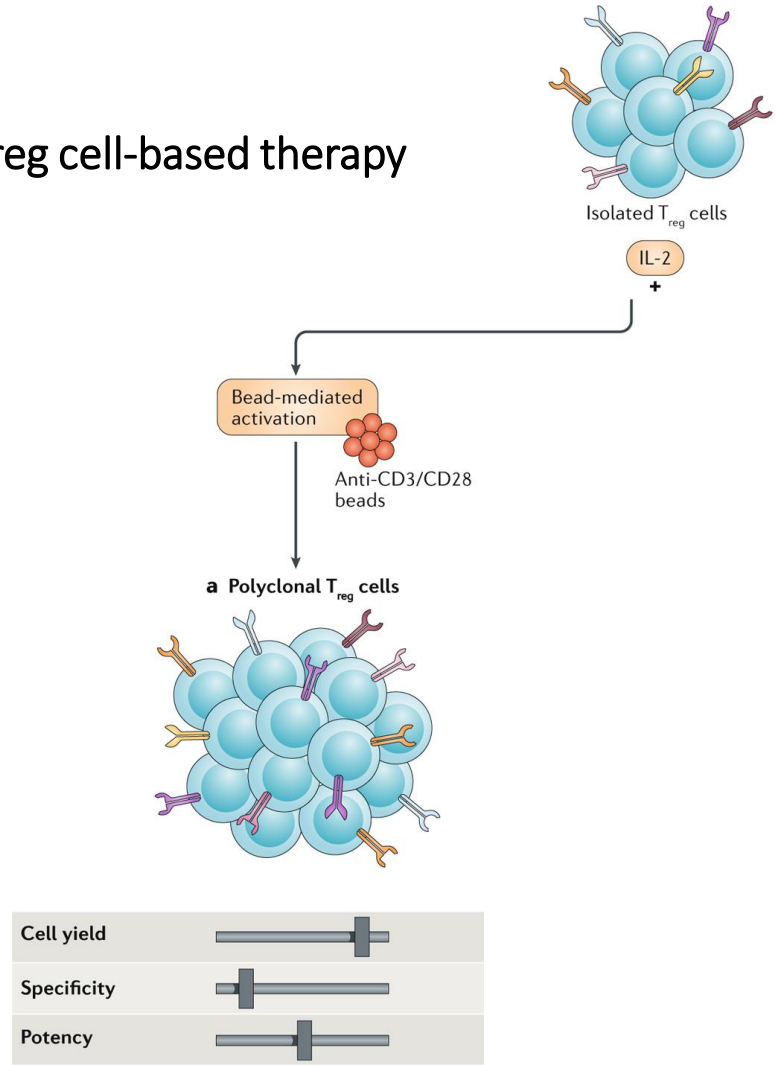
1. Suppression
2. Stability
3. Survival
4. Specificity



Ferreira LMR, et al. Nat Rev Drug Discov 2019;18(10):749-69

Adoptive cell transfer of Tregs

Treg cell products for Treg cell-based therapy



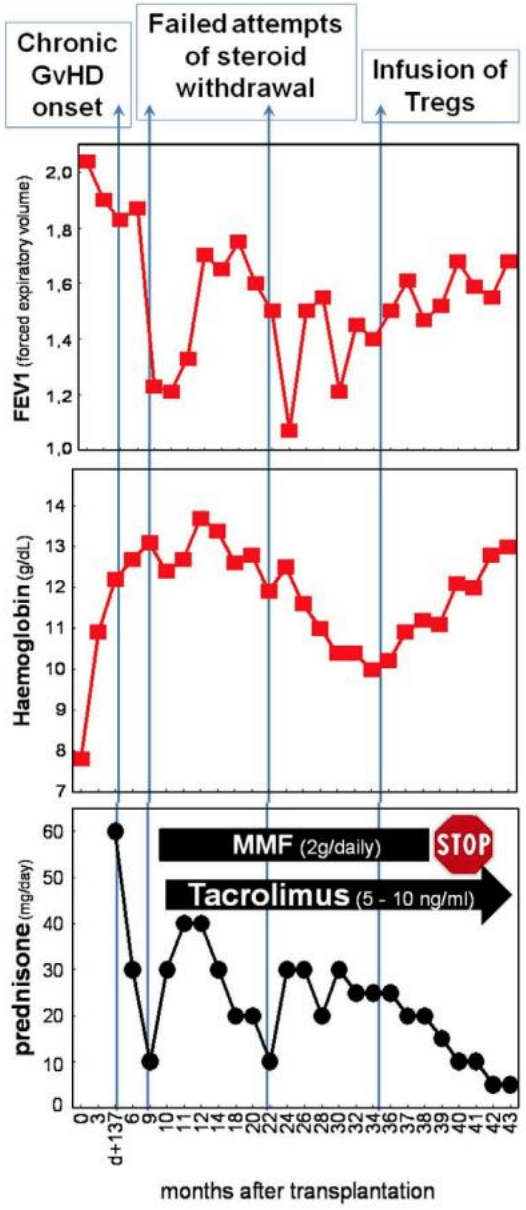
Raffin C, et al. Nat Rev Immunol 2020;20(3):158-72

RAPID COMMUNICATION

First-in-man clinical results of the treatment of patients with graft versus host disease with human ex vivo expanded CD4+CD25+CD127− T regulatory cells

1 acute GvHD - 1 chronic GvHD

Gdansk, Poland



Trzonkowski P, et al. Clin Immunol 2009;133(1):22-6

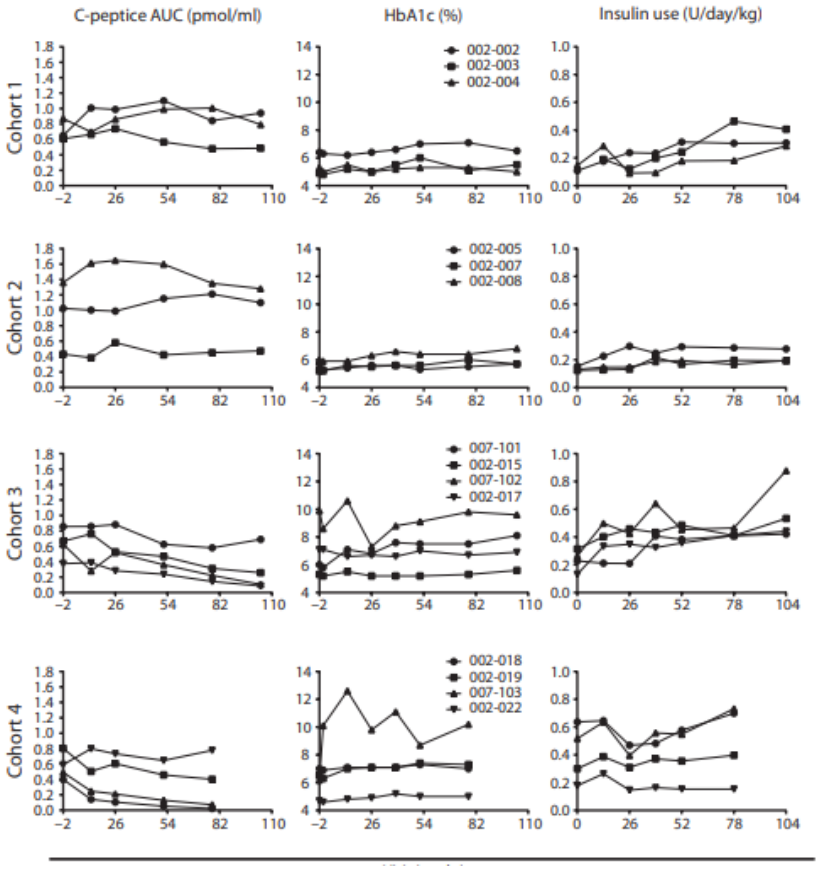
RESEARCH ARTICLE

IMMUNOTHERAPY

Type 1 diabetes immunotherapy using polyclonal regulatory T cells

Jeffrey A. Bluestone,[1]* Jane H. Buckner,[2] Mark Fitch,[3] Stephen E. Gitelman,[4] Shipra Gupta,[2] Marc K. Hellerstein,[3] Kevan C. Herold,[5] Angela Lares,[1] Michael R. Lee,[1] Kelvin Li,[6] Weihong Liu,[1] S. Alice Long,[2] Lisa M. Masiello,[1] Vinh Nguyen,[7] Amy L. Putnam,[1] Mary Rieck,[1] Peter H. Sayre,[8] Qizhi Tang[7]

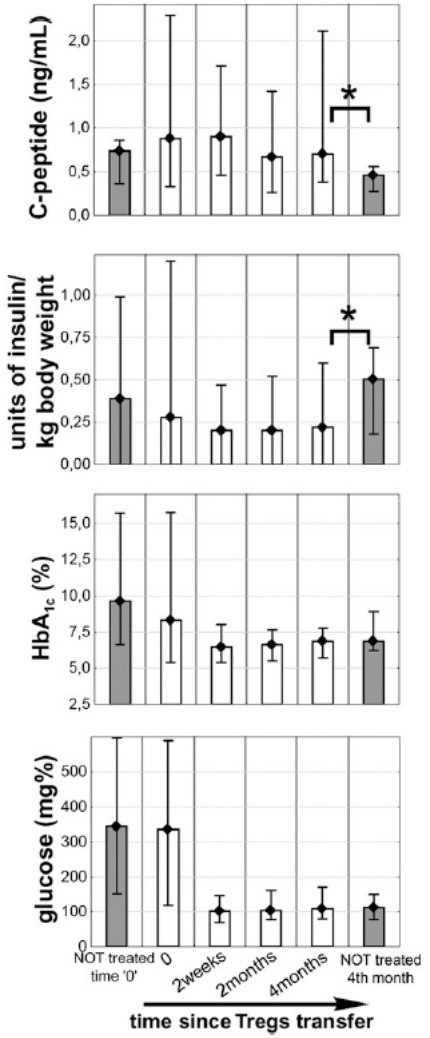
14 ενήλικες με T1DM



Bluestone JA, et al. Sci Transl Med 2015;7(315):315ra189

Administration of CD4+CD25highCD127− Regulatory T Cells Preserves β-Cell Function in Type 1 Diabetes in Children

10 παιδιά με T1DM εντός 2 μηνών από τη διάγνωση



Marek-Trzonkowska N, et al. Diabetes Care 2012;35(9):1817-20

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ORIGINAL ARTICLE

An Anti-CD3 Antibody, Teplizumab, in Relatives at Risk for Type 1 Diabetes

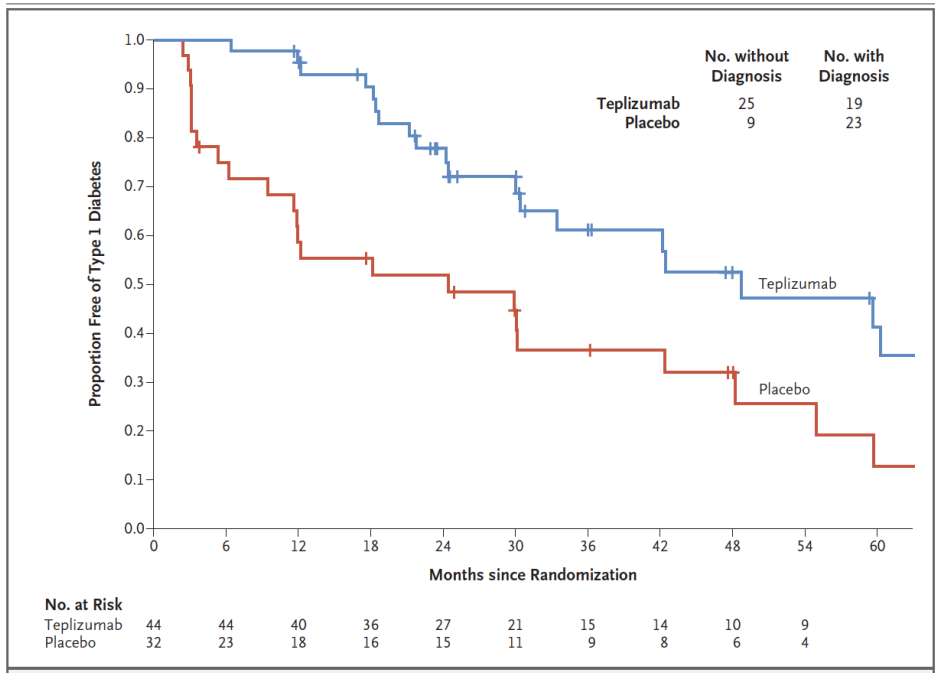
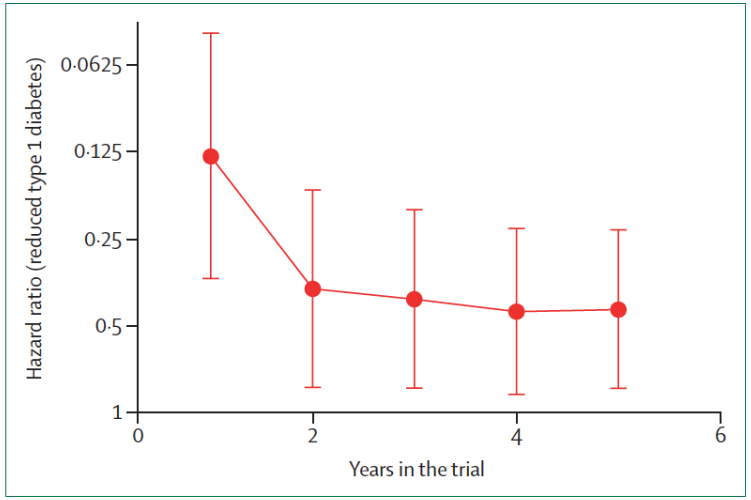


Figure 1. Effects of Teplizumab on Development of Type 1 Diabetes.
Shown are Kaplan–Meier estimates of the proportions of participants in whom clinical diabetes was not diagnosed. The overall hazard ratio was 0.41 (95% confidence interval [CI], 0.22 to 0.78; two-sided P=0.006 by adjusted Cox proportional-hazards model). The median time to diagnosis of type 1 diabetes was 48.4 months in the teplizumab group and 24.4 months in the placebo group. The numbers of participants with or without a diagnosis of clinical type 1 diabetes (upper right) represent data at the conclusion of the trial. Tick marks indicate censored data.

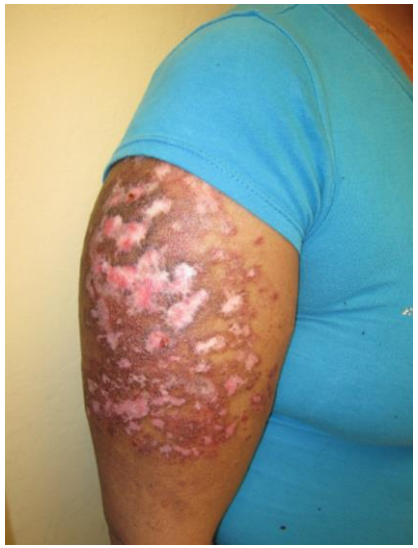
Hazard ratio over time in the TN-10 teplizumab prevention trial

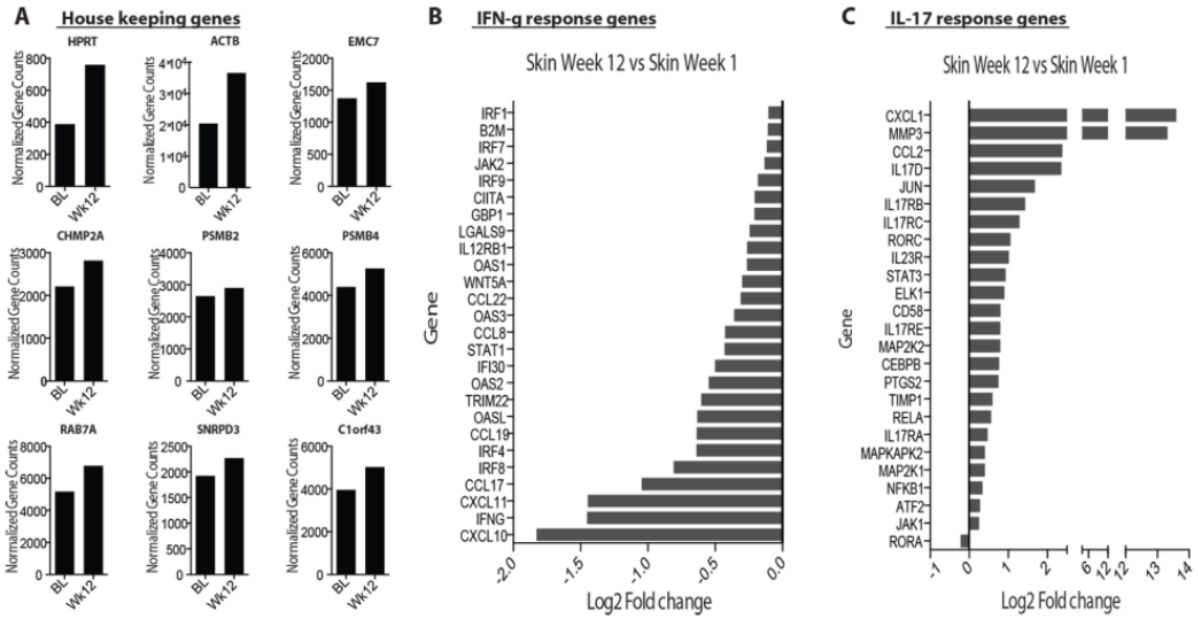


The largest effect of teplizumab treatment was in the first year: only 3/44 (6·8%) of 44 participants had developed diabetes compared with 14/32 (43·8%) in the PBO group (**unadjusted HR 0·129**)

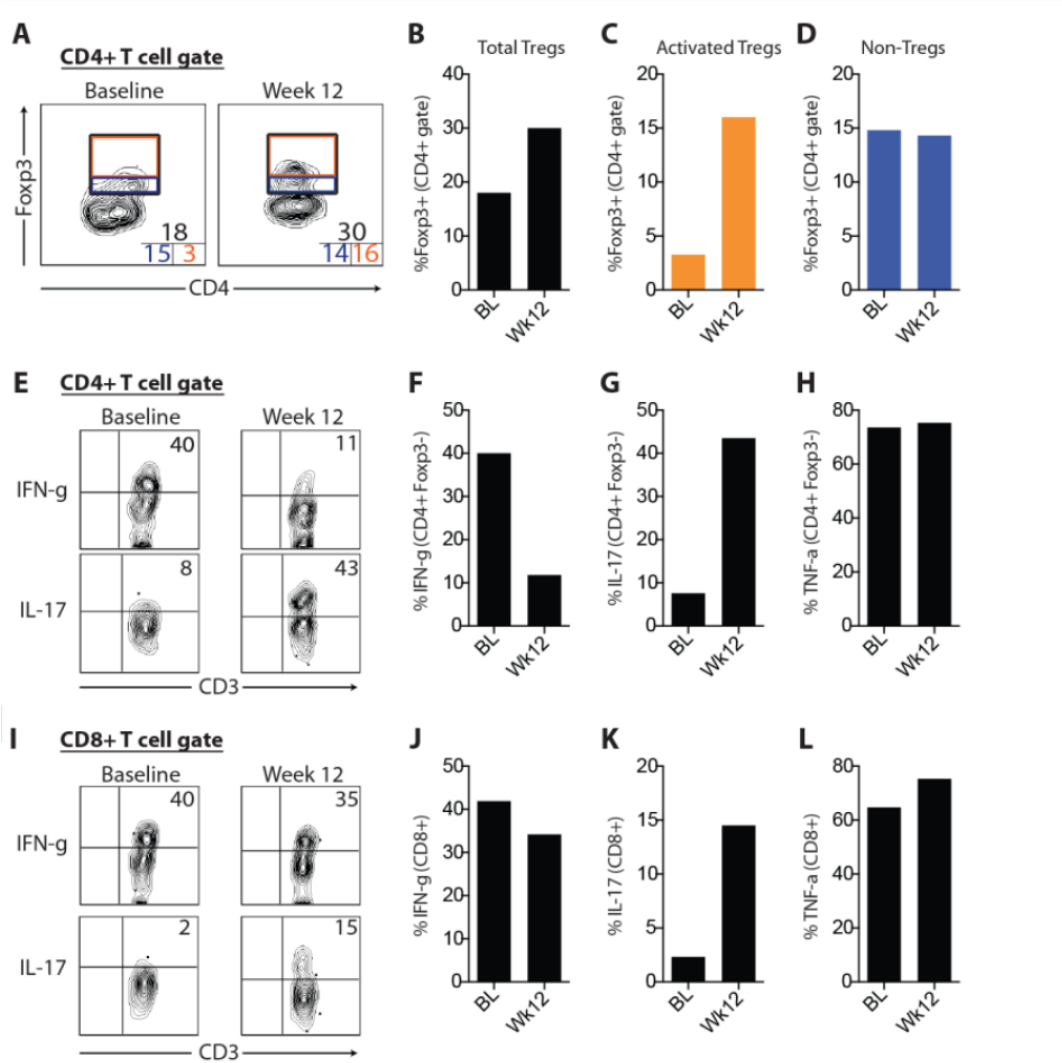
Herold KC, et al. N Engl J Med 2019; 381: 603–613; Dayan CM, et al. Lancet 2019 Sep 15;

The first patient with SLE treated with ex vivo expanded Tregs



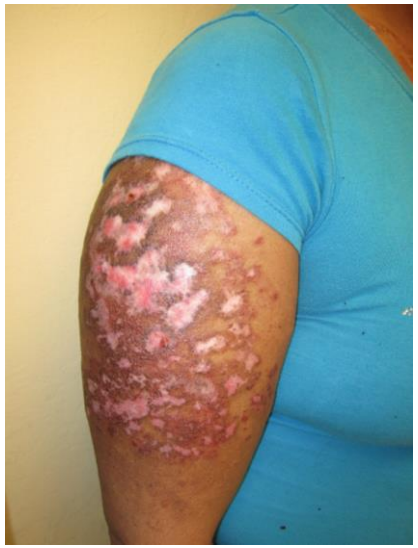


Whole transcriptome analysis of skin tissue pre - and post -adoptive Treg cell therapy



Accumulation of activated Tregs, attenuation of IFNγ production and increased IL -17 production in skin after adoptive Treg cell therapy

Dall'Era M, et al. Arthritis Rheumatol 2019;71(3):431-440



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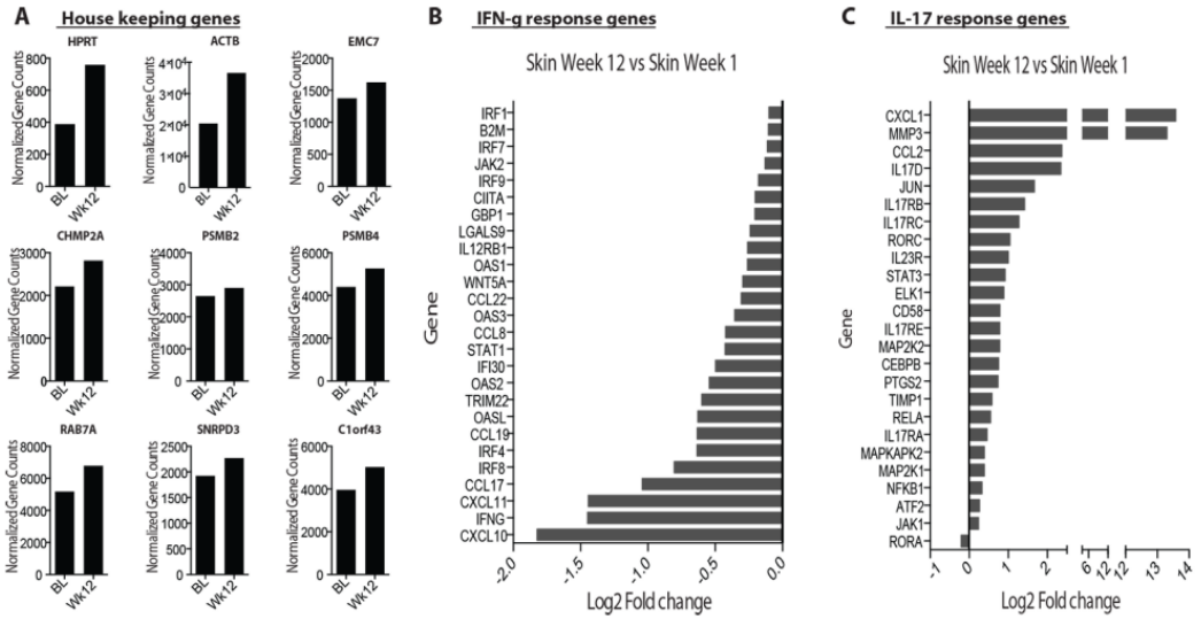
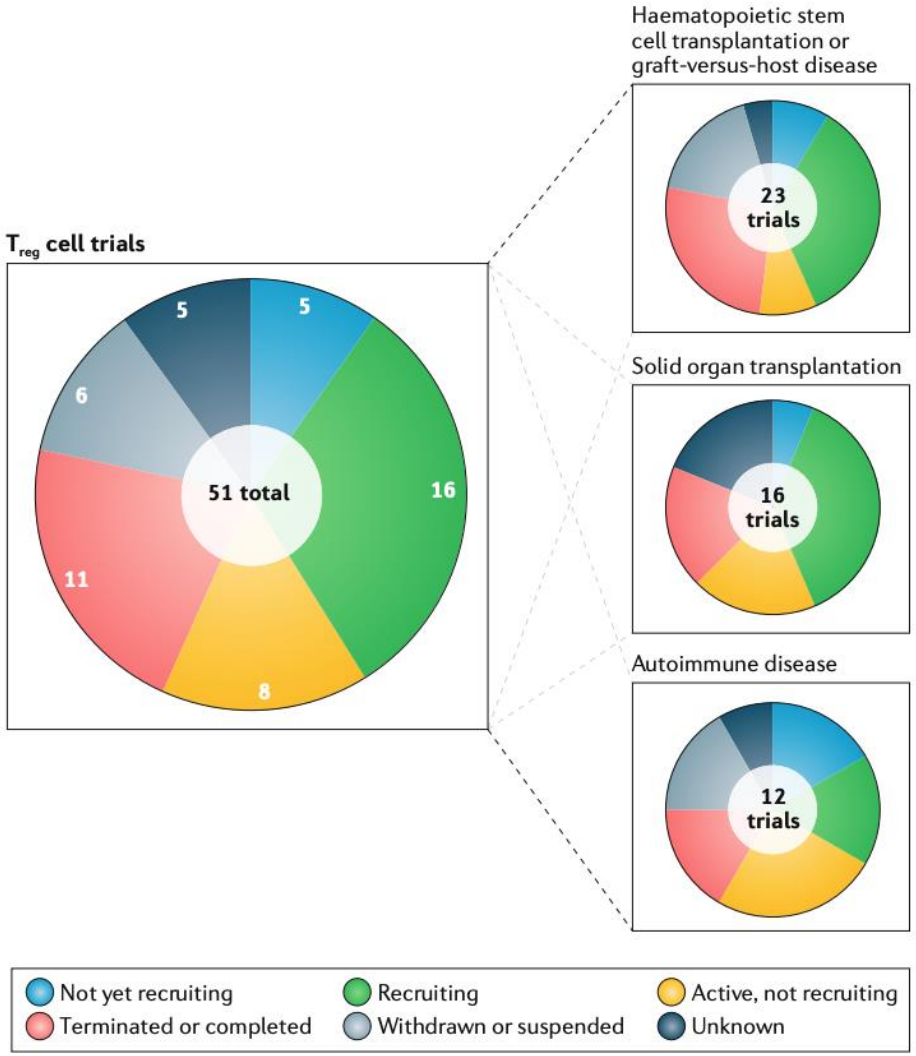


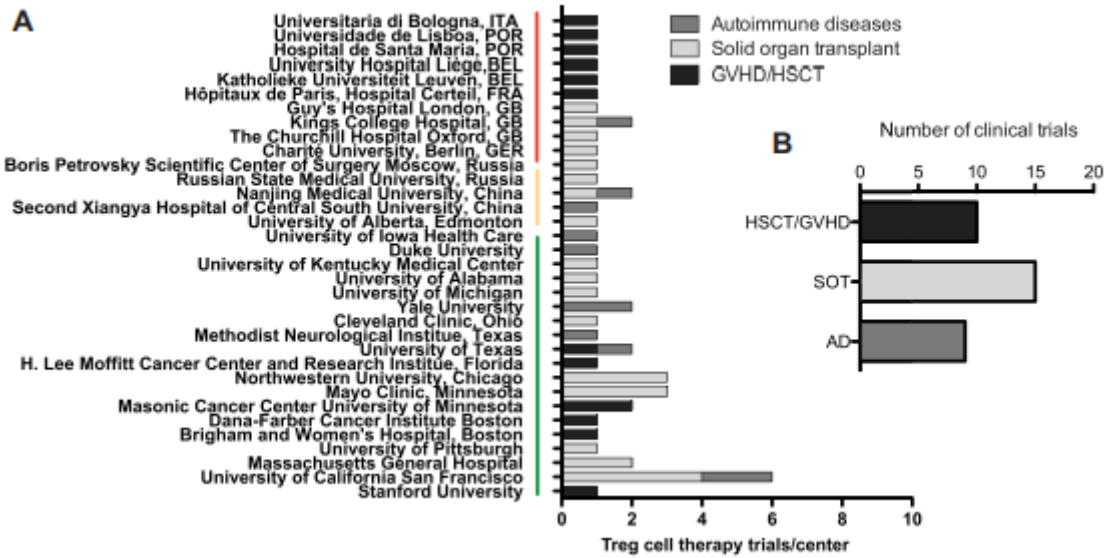
Whole transcriptome analysis of skin tissue pre - and post -adoptive Treg cell therapy

Dall'Era M, et al. Arthritis Rheumatol 2019;71(3):431-440

No demonstrable clinical benefit

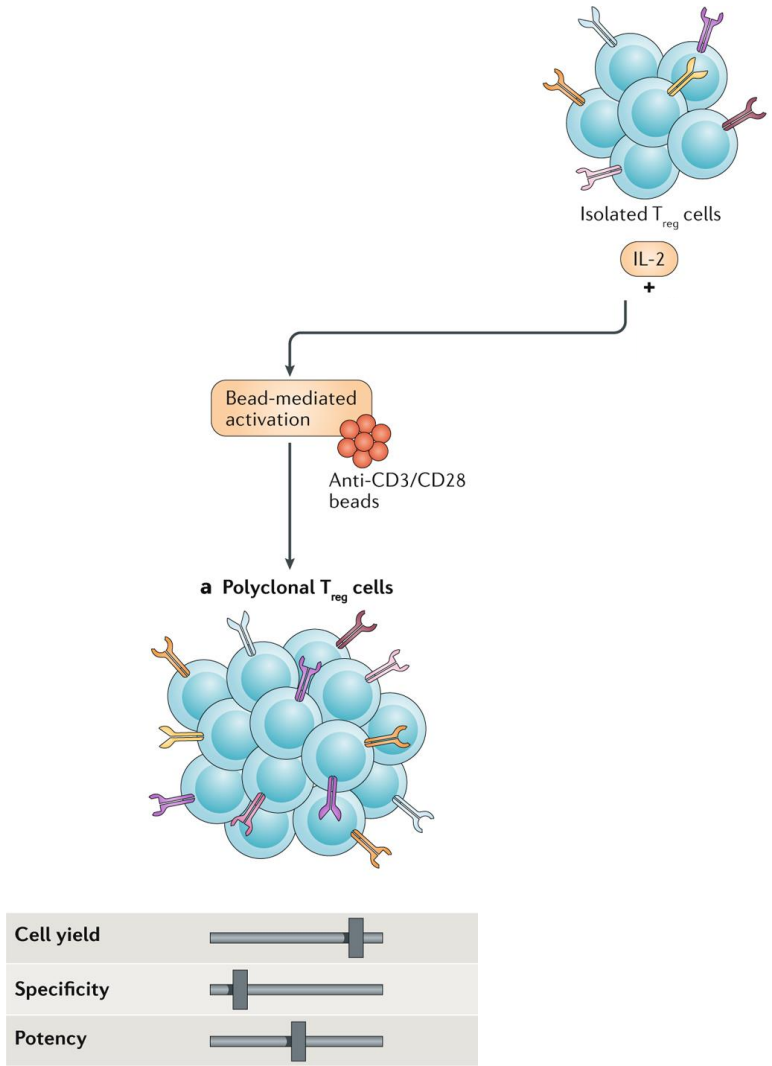
Registered clinical trials using regulatory T-cells





Ferreira LMR, et al. Nat Rev Drug Discov 2019;18(10):749-69; Esensten JH, et al. J Allergy Clin Immunol 2018;142(6):1710-1718

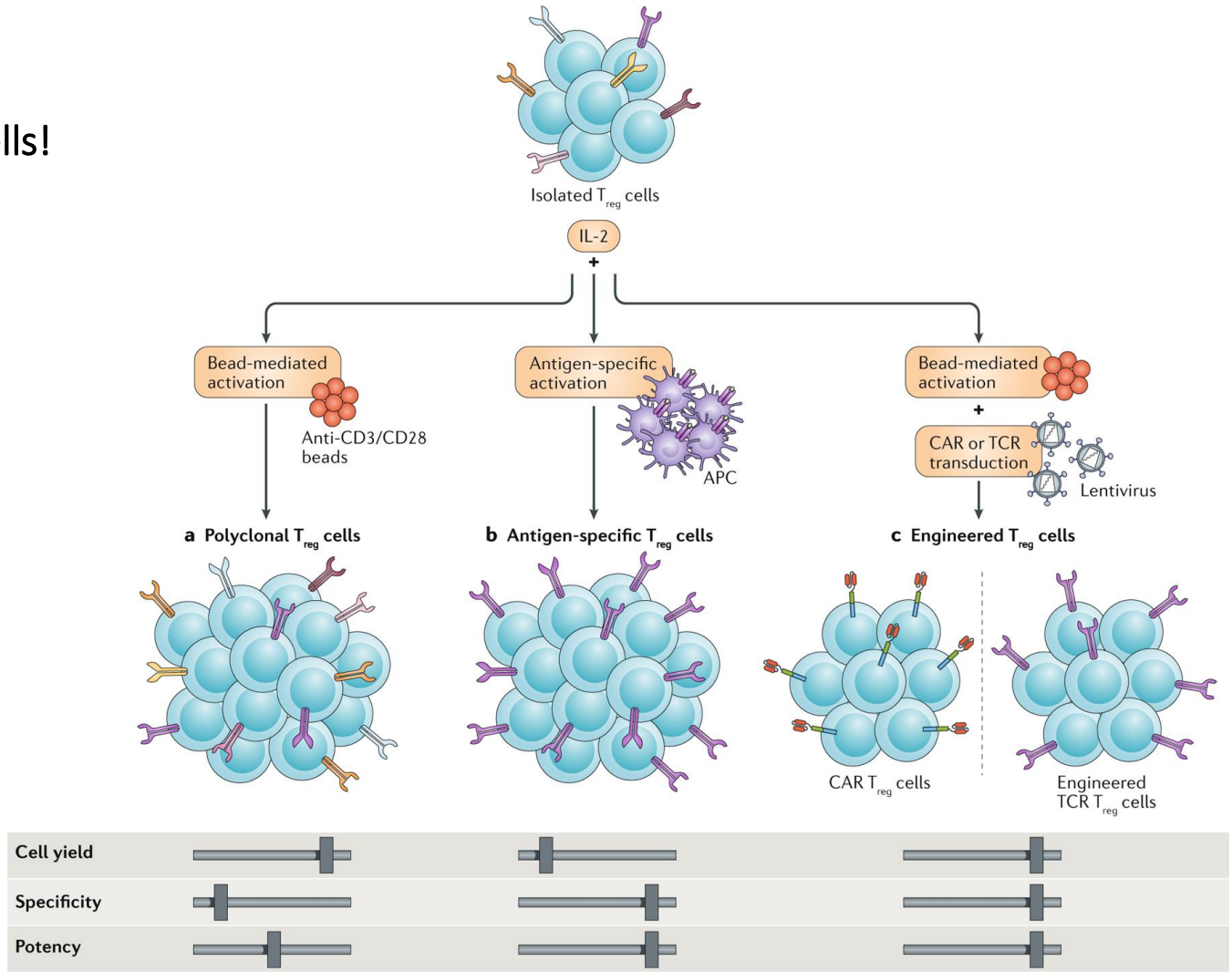
Adoptive cell transfer of Tregs



Raffin C, et al. Nat Rev Immunol 2020;20(3):158-72

Adoptive cell transfer of Tregs

Antigen-specific Treg cells!



Antigen-specific Treg cells!

Raffin C, et al. Nat Rev Immunol 2020;20(3):158-72

Next-generation regulatory T-cell therapy

Pitting cell against cell

Biotechnology companies are engineering regulatory T cells to help the cells guard the body against friendly fire. By Eric Bender

Nature Outlook (Autoimmune disease) 15 July 2021

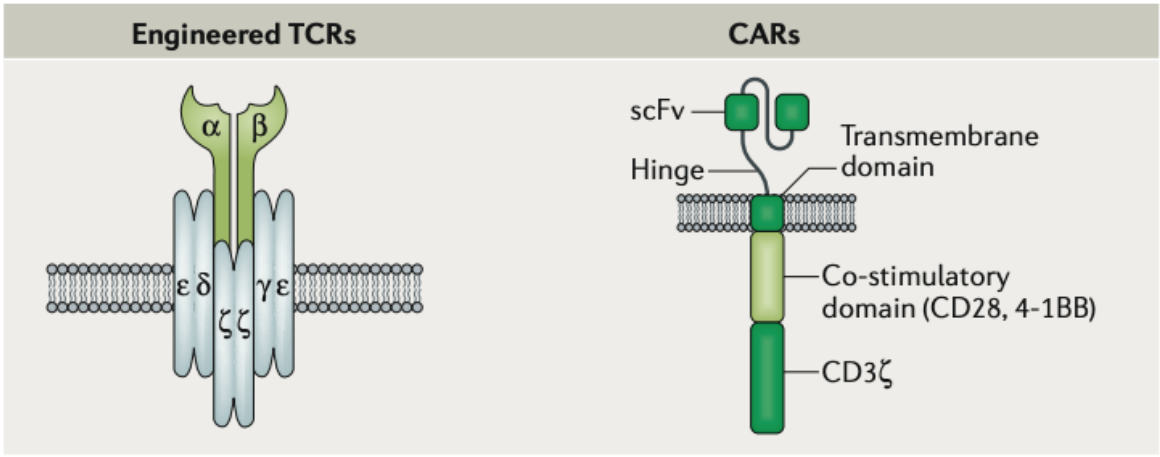
Two rapidly advancing technologies:

1) chimeric antigen receptor (CAR) T-cell manipulation (provides T cells with receptor proteins matched to specific cell targets)
2) CRISPR–Cas9 genome-editing tools

Aim: Enhance the specificity and functionality of Treg cells

Multiple Start-ups!!!

Engineering Tregs through TCRs and CARs

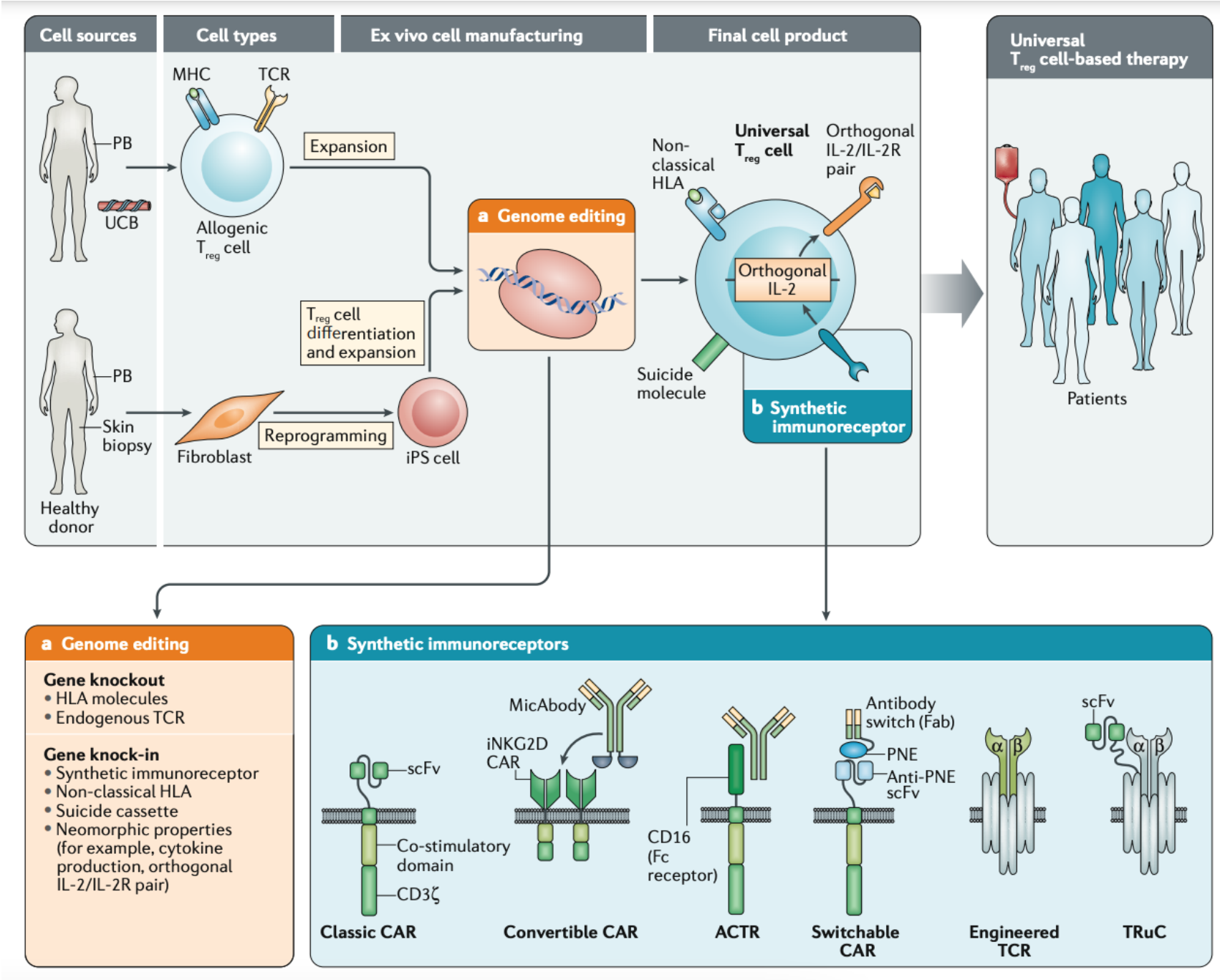


Property	TCRs	CARs
Specificity	Peptide–HLA complex	Any surface antigen or multivalent soluble antigen
HLA restriction	Yes	No
Co-receptor required	Yes (CD4 or CD8)	No
Affinity[a]	$K_D = 10^{-6}$–10^{-4} M[252]	$K_D = 10^{-10}$–10^{-6} M[253]
Sensitivity	<10 molecules per target cell[104,254]	100–10,000 molecules per target cell[105,255–257]
Signalling	Via endogenous CD3 complex (comprising six chains)	Via synthetic modular signalling domain
Expression challenges	Endogenous TCR might pair with exogenous TCR chains	Protein aggregation; aggregation of single-chain variable fragments leading to tonic signalling

Ferreira LMR, et al. Nat Rev Drug Discov 2019;18(10):749-69; Raffin C, et al. Nat Rev Immunol 2020;20(3):158-72

The future of Treg cell-based therapy

CRISPR–Cas9



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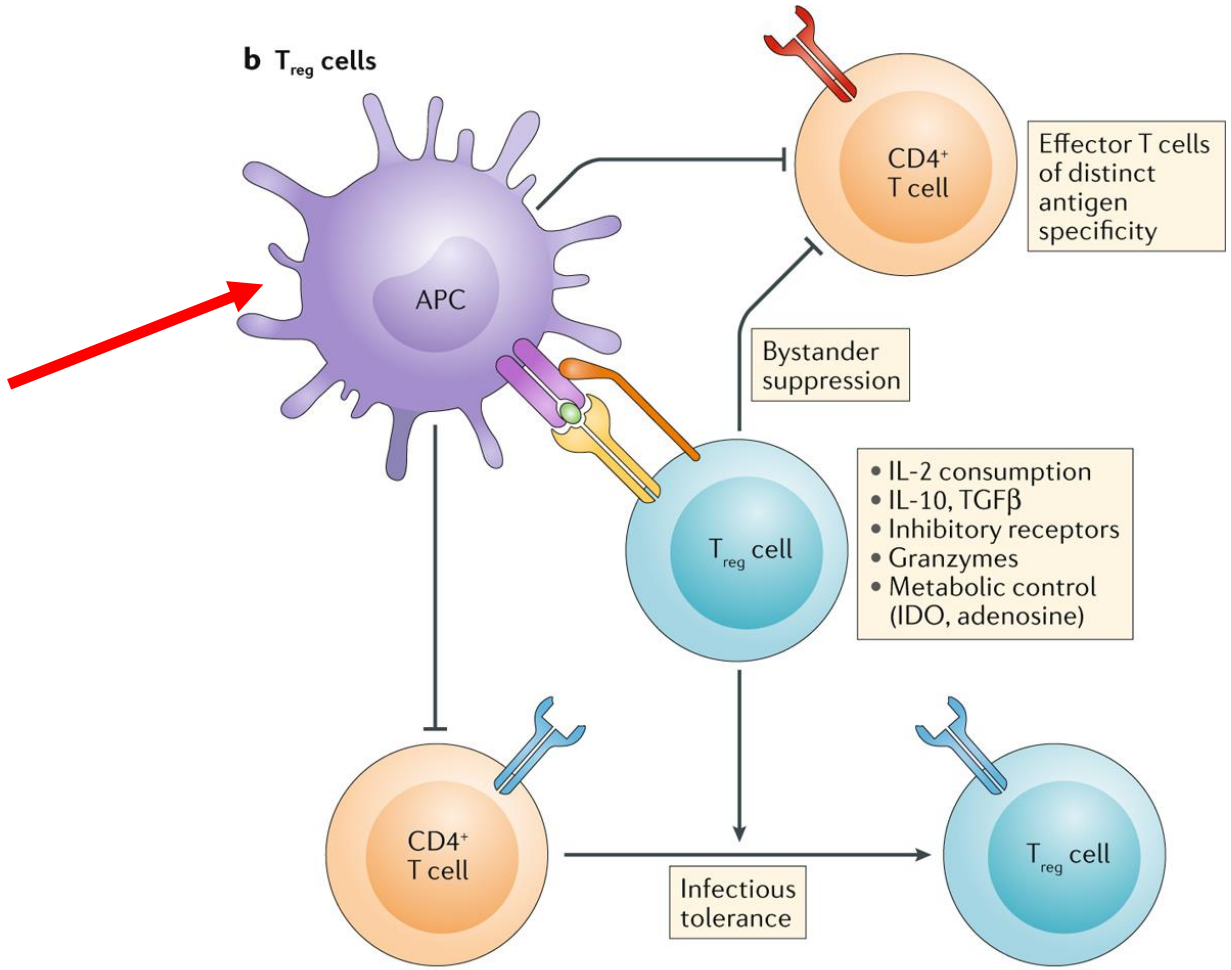
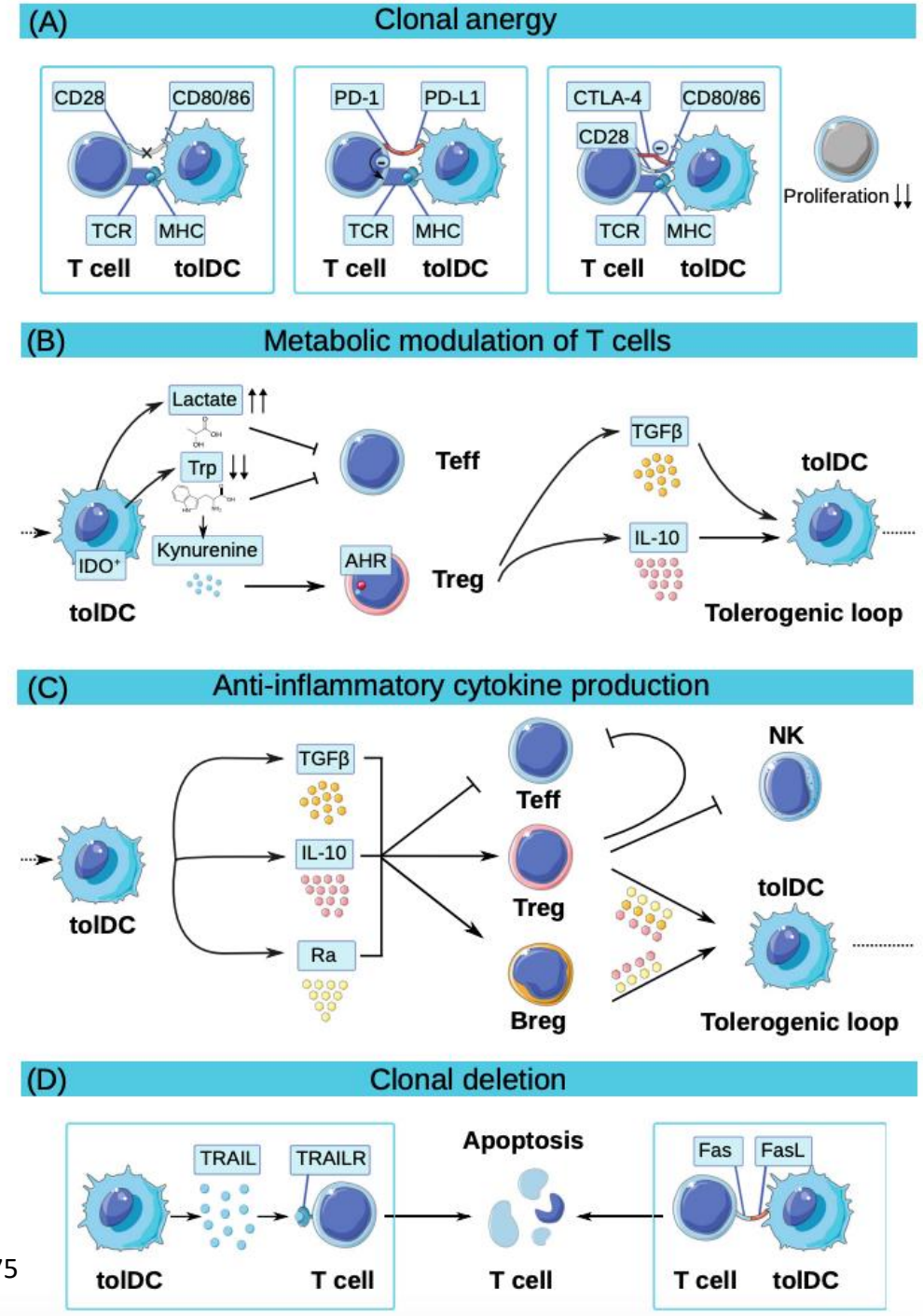
Mechanisms of action of effector T cells versus Treg cells



Raffin C, et al. Nat Rev Immunol 2020;20(3):158-72

Mechanisms of Tolerogenic Dendritic Cell Tolerogenesis



Morante-Palacios O, et al. Trends Immunol. 2021;42(1):59-75

Clinical trials with Tolerogenic Dendritic Cells

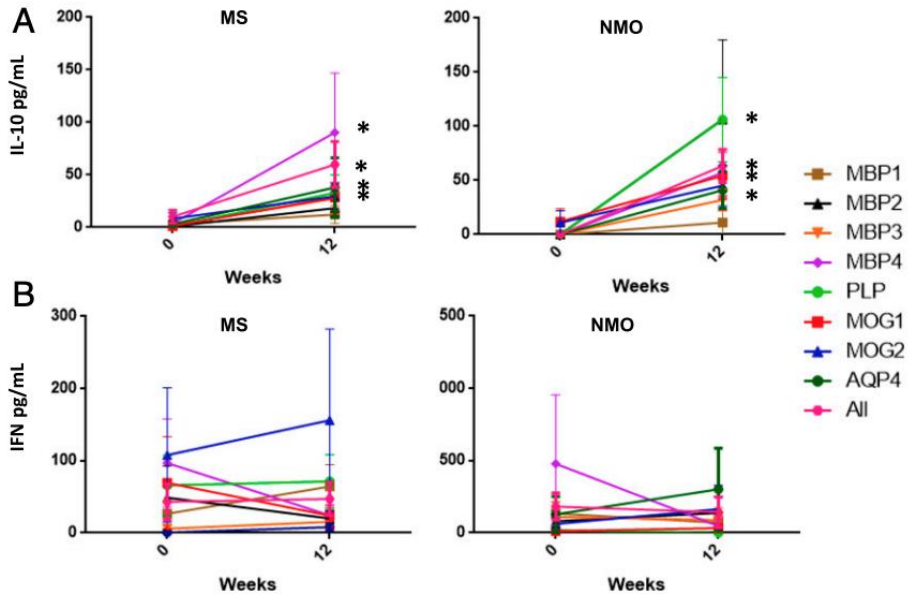
Table 1. Clinical Trials Involving tolDCs[a]

ID	Phase	Design	Status	Indication	Cell type	Route	Administration scheme
Autoimmune diseases							
NCT00445913[i]	I	Randomized, single group assignment, double-blind	Completed	T1D	BM-derived DCs treated with antisense oligonucleotides targeting CD80, CD86, CD40	i.d	4 Injections, bi-weekly
NTR5542[ii]	I	Nonrandomized, single arm	Completed	T1D	Proinsuline-loaded VitD3-tolDCs	i.d.	2 Injections with 28-day interval
NCT02354911[iii]	II	Randomized, double blind, placebo-controlled, cross-over study	Unknown	T1D	BM-derived DCs treated with antisense oligonucleotides targeting CD80, CD86, CD40	i.d.	4 Injections, bi-weekly
NCT03895996[iv]	I/II	Randomized, parallel assignment, placebo controlled, double-blind	Recruiting	T1D	Autologous dendritic cell therapy (AVT001)	i.v.	3 Monthly injections
NCT03337165[v] (TolDCfoRA)	I	Single group assignment, open label	Completed	RA	Dex-tolDCs	i.a.	Dose escalation, single injection
Rheumavax	I	Nonrandomized, control group, open label	Completed	RA	NF-κB inhibitor-treated DCs, loaded with citrullinated peptides	i.d.	2 Progressive dose levels
CRiSKCT0000035[vi] (CreaVax-RA)	I	Interventional, single arm, open label	Completed	RA	DCs pulsed with PAD4, HNRNPA2B1, citrullinated filaggrin, and vimentin antigens		5 Injections according to two dose regimens: low and high
NCT01352858[vii] (AutoDECRA)	I	Randomized, parallel assignment, open Label	Completed	RA	Dex/VitD3-tolDC loaded with autologous synovial fluid	i.l.	Dose escalation, single injection
NCT02283671[viii]	I	Single group assignment, open Label	Completed	MS, neuromyelitis-optica	Dex-tolDCs loaded with myelin peptides or aquaporine-4-derived peptide	i.v.	Dose escalation, 3 injections administered bi-weekly
NCT02903537[ix] (TOLERVIT-MS)	I/IIa	Nonrandomized, parallel assignment, open label	Recruiting	MS	VitD3-tolDCs loaded with a pool of myelin peptides	i.n.	Dose escalation, 6 injections: 4 bi-weekly and 2 monthly
NCT02618902[x]	I/IIa	Nonrandomized, parallel assignment, open label	Recruiting	MS	VitD3-tolDCs loaded with a pool of myelin peptides	i.d.	Dose escalation, 6 injections: 4 bi-weekly and 2 monthly
2007-003469-42[xi]	I	Sequential-cohorts, dose-range	Completed	Crohn's disease	Dex/VitA tolDCs	i.p.	Dose escalating, single injection vs 3 injections bi-weekly
NCT02622763[xii]	I	Randomized, parallel assignment, single blind	Terminated (low recruitment)	Crohn's disease	Dex-tolDCs	i.l.	Unknown

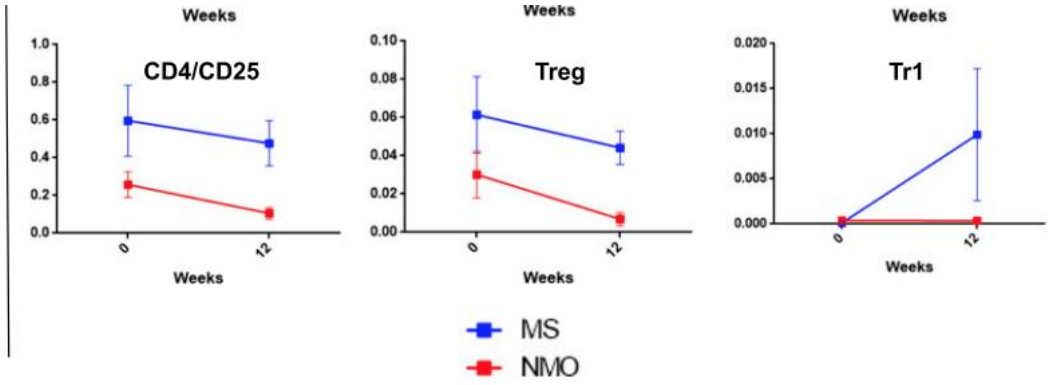
Morante-Palacios O, et al. Trends Immunol. 2021;42(1):59-75

Immune tolerance in multiple sclerosis and neuromyelitis optica with peptide-loaded tolerogenic dendritic cells in a phase 1b trial

12 patients, 8 with MS and 4 with NMOSD
Autologous monocyte-derived DCs (dexamethasone)

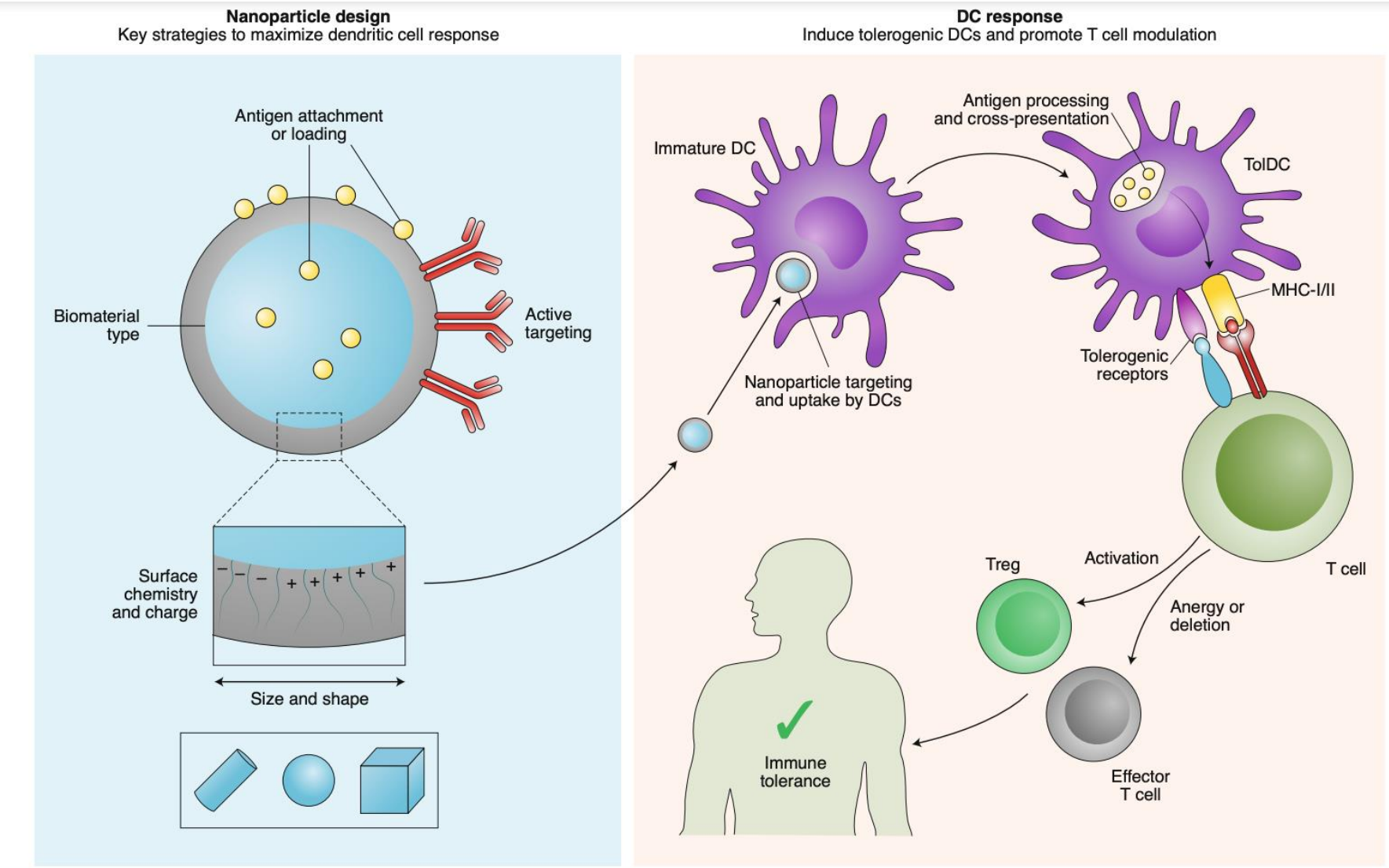


Significant increase in the production of IL-10 levels in PBMCs stimulated with the peptides as well as an increase in the frequency of a regulatory T cell, known as Tr1, by week 12 of follow-up.



Zubizarreta I, et al. PNAS 2019;116(17):8463-70

Inducing immune tolerance with dendritic cell-targeting nanomedicines



In situ induction of tolDC via nanoparticles

Cifuentes-Rius A, et al. Nat Nanotechnol. 2021;16(1):37-46

Conclusions

- Achieving immune tolerance has been one of the most elusive goals in immunology, but:
- Recent years have witnessed tremendous progress in the understanding of both pathogenesis of autoimmune disease, but also Treg and DC cell biology
- Additional progress in receptor engineering (CAR), genome editing (CRISPR-Cas9) of native immune cells, as well as delivery of antigens (nanoparticles)
- Vivid interest by the industry!
- Multiple trials ongoing, both with Tregs and with tolDC

Dr House to a scientist:

“So, basically, you’re an underpaid nerd…”