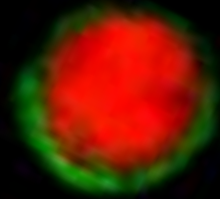


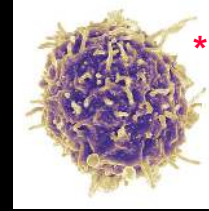
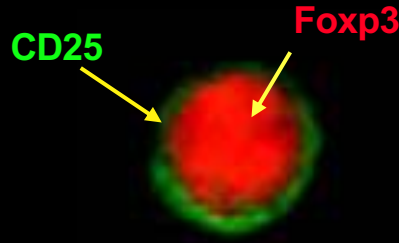
Regulatory T Cells for Immunotherapy of Neurological Autoimmunity



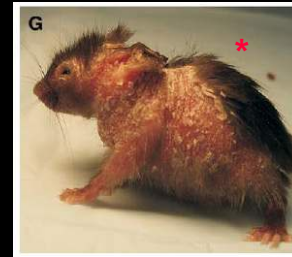
WanJun Chen M.D.
Chief, Mucosal Immunology Section, NIDCR, NIH
Email: wchen@mail.nih.gov

Regulatory T cells (Treg)

CD4⁺
CD25⁺
Foxp3⁺



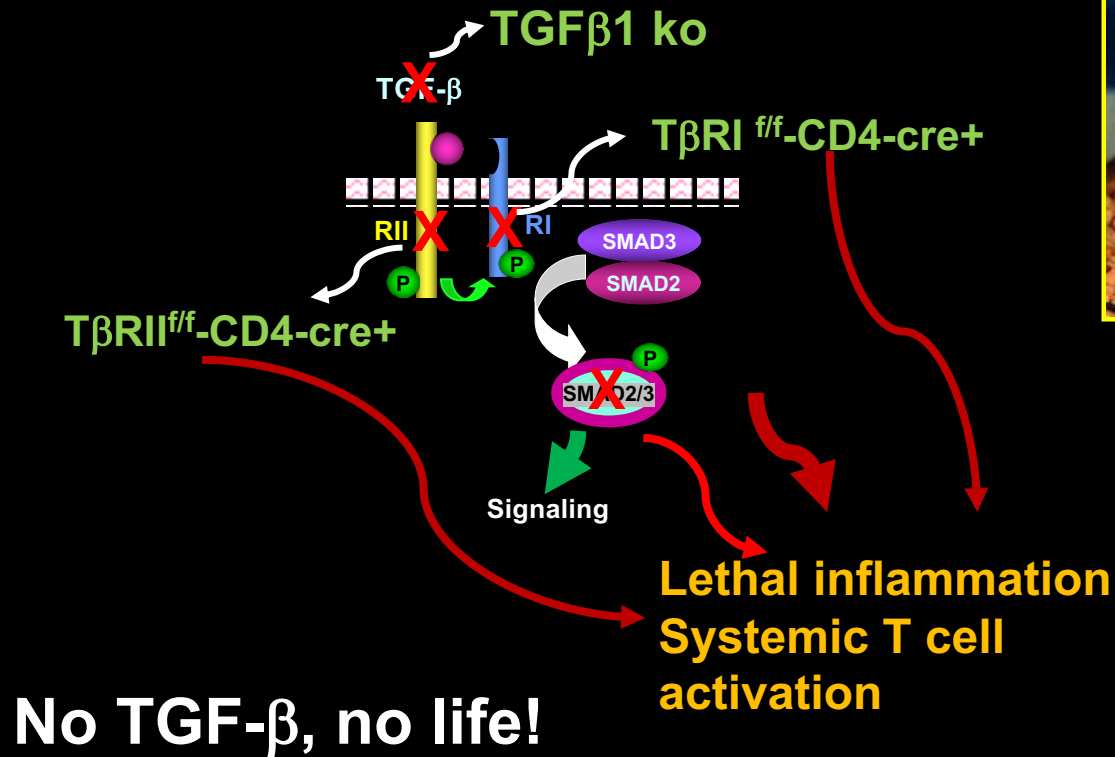
- In both human and mouse
- Essential in immune tolerance
- Prevent transplant rejection
- Regulation of autoimmunity & inflammation
- Weakening anti-tumor immunity
- HIV infection
- Regenerative medicine



IPEX (human)

*
Fehervari & Sakaguchi
Scientific American (2006)
Fortenot et al, *Nat Immunol* (2003)

TGF- β and immune responses



Kulkarni et al, *PNAS* (1993)
Chen et al, *J Exp Med.* (2001)
Chen et al, *J Exp Med* (2003)
Marie et al, *Immunity*, (2006)
Li et al, *Immunity*, (2006)
Liu et al, *Nat Immunol.* (2008)
Takimoto et al, *J Immunol* (2010)

Transforming growth factor-beta (TGF- β) in:

- Development and generation of Tregs
- *In vivo* induction of antigen-specific Tregs for immunotherapy to autoimmunity

Treg development & generation:

Transforming growth factor-beta 1 induces anergic/suppressor CD4⁺CD25⁺CTLA-4⁺ T cells

Author(s): Chen WJ et al

Source: JOURNAL OF LEUKOCYTE BIOLOGY **Pages:** 102-102 **Supplement:** Suppl. S **Meeting Abstract:** 362 **Published:** 2001

Times Cited: 0 **References:** 0

Document Type: Meeting Abstract

Language: English

Addresses: NIH, NIDCR, OIIB, Cellular Immunol Sect, Bethesda, MD 20892 USA

Publisher: FEDERATION AMER SOC EXP BIOL, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3998 USA

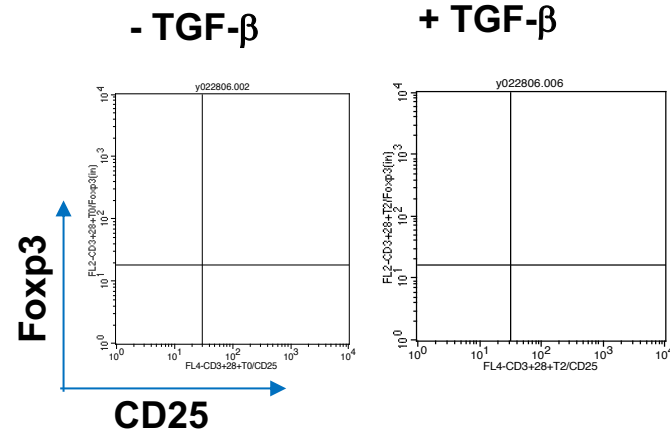
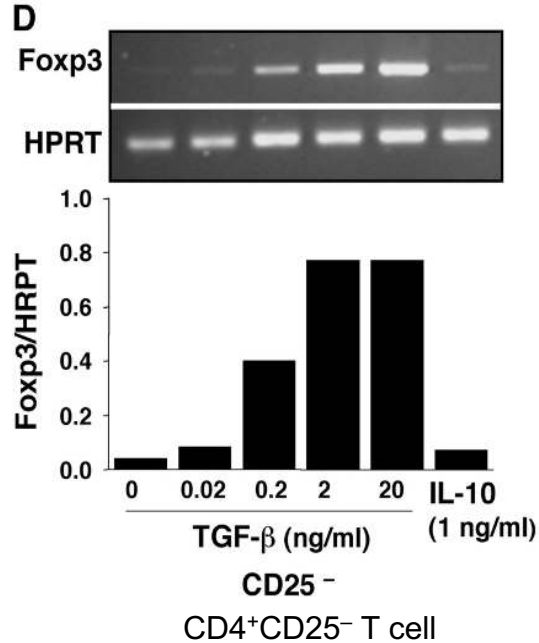
IDS Number: 480UY

ISSN: 074



Rockefeller
University
Press

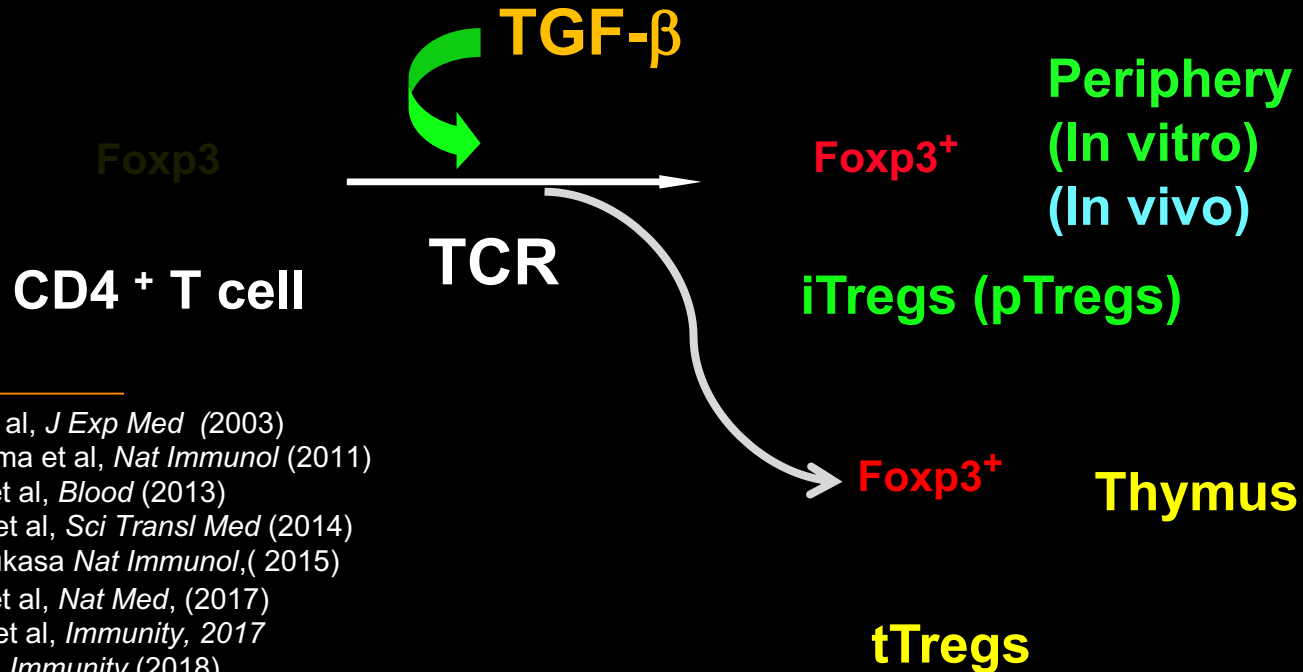
From: Conversion of Peripheral CD4⁺CD25⁻ Naive T Cells to CD4⁺CD25⁺ Regulatory T Cells by TGF- β Induction of Transcription Factor Foxp3
Chen W et al, J Exp Med (2003) 198 (12) 1875-1886



Cited >5600 times

Liu et al, 2006, Transplantation

TGF- β signaling is essential for generation of Tregs



Chen et al, *J Exp Med* (2003)
Maruyama et al, *Nat Immunol* (2011)
Zhang et al, *Blood* (2013)
Kasagi et al, *Sci Transl Med* (2014)
Nakatsukasa *Nat Immunol*, (2015)
Zhang et al, *Nat Med*, (2017)
Konkel et al, *Immunity*, 2017
Tu et al, *Immunity* (2018)
Zhang et al, *Immunity* (2019)
Liu et al, *Nat Immunol* (2008)
Konkel et al, *PNAS* (2014)
Chen & Konkel, *EJI*, (2015)

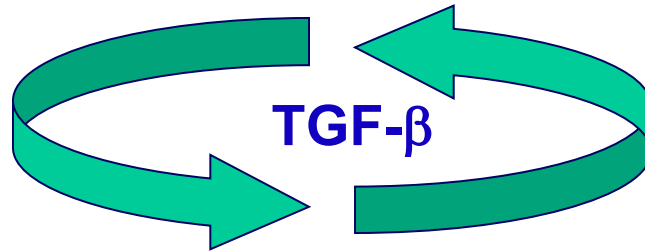
Manipulation of TGF- β and Tregs for immunotherapy

Autoimmunity
Transplantation
Cancer

T cell immune tolerance

Apoptosis

Anergy



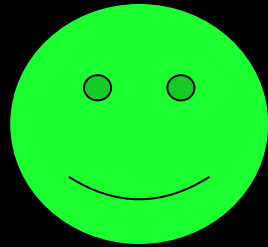
Active suppression

Suppressive cytokines

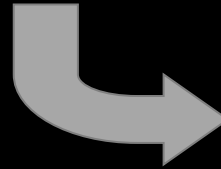
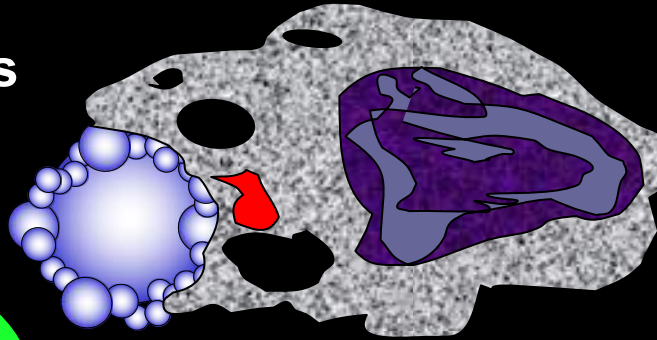
Regulatory T cells

Apoptosis

**Phagocytes
(Macrophages,
Immature DCs)**



Healthy cell



TGF- β

(IL-10, PGE2)

We would utilize this mechanism to develop immunotherapy for autoimmune diseases by induction of antigen-specific Tregs in vivo

Fadok et al, *JCI* (1998)
Chen et al, *Immunity* (2001)
Perruche et al, *Nat Med* (2008)

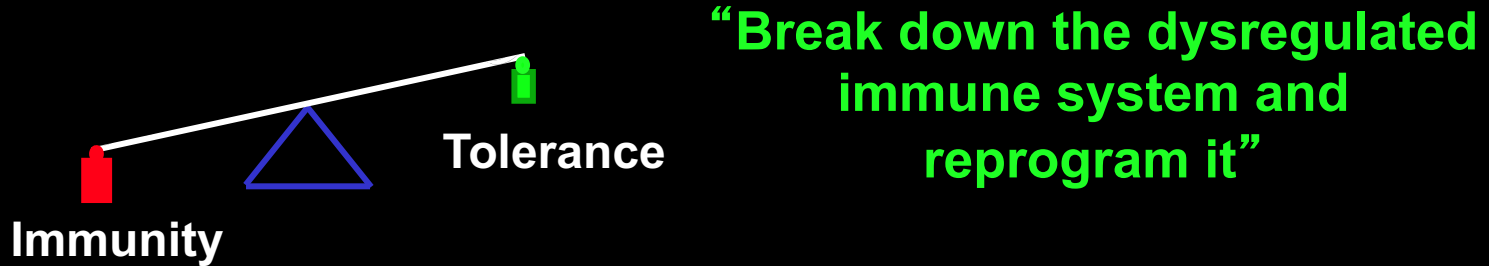
How to develop Treg-immunotherapy in autoimmune diseases?

- Adoptive transfer of polyclonal Treg pool? **NO**
- Adoptive transfer of *in vitro* generated antigen-specific Tregs? **Maybe**
- *In vivo* generation of antigen-specific Tregs by e.g. administration of low-doses of peptides (work only in naïve mice)? **NO**
- *In vivo* expansion of Tregs (e.g. by IL-2)? **Maybe**
- Engineered Treg? Car-Treg? **unknown**

Challenges:

- how to generate autoantigen-specific Tregs in the animals and ultimately in patients with **established autoimmune diseases** to specifically suppress the inflammation in the organs/tissues affected (treat/cure the disease), ..**without compromising the overall immunity (e.g. to infections and cancer)?**

In vivo generation of autoantigen-specific Tregs for treatment of autoimmune diseases



Step I: Induction of apoptosis of immune cells *in vivo* (*transient*)
“good meal” for phagocytes

Step II: Creation of an immunoregulatory milieu (*transient*)
phagocytes produce TGF- β

Step III: Generation and maintenance of autoantigen-specific Tregs (*long-term*)
Introduction of specific peptide

“Apoptosis-phagocytes-peptides”

In vivo-generated antigen-specific regulatory T cells treat autoimmunity without compromising antibacterial immune response.

Kasagi S et al, *Sci Transl Med*. 2014 Jun 18;6(241):241ra78



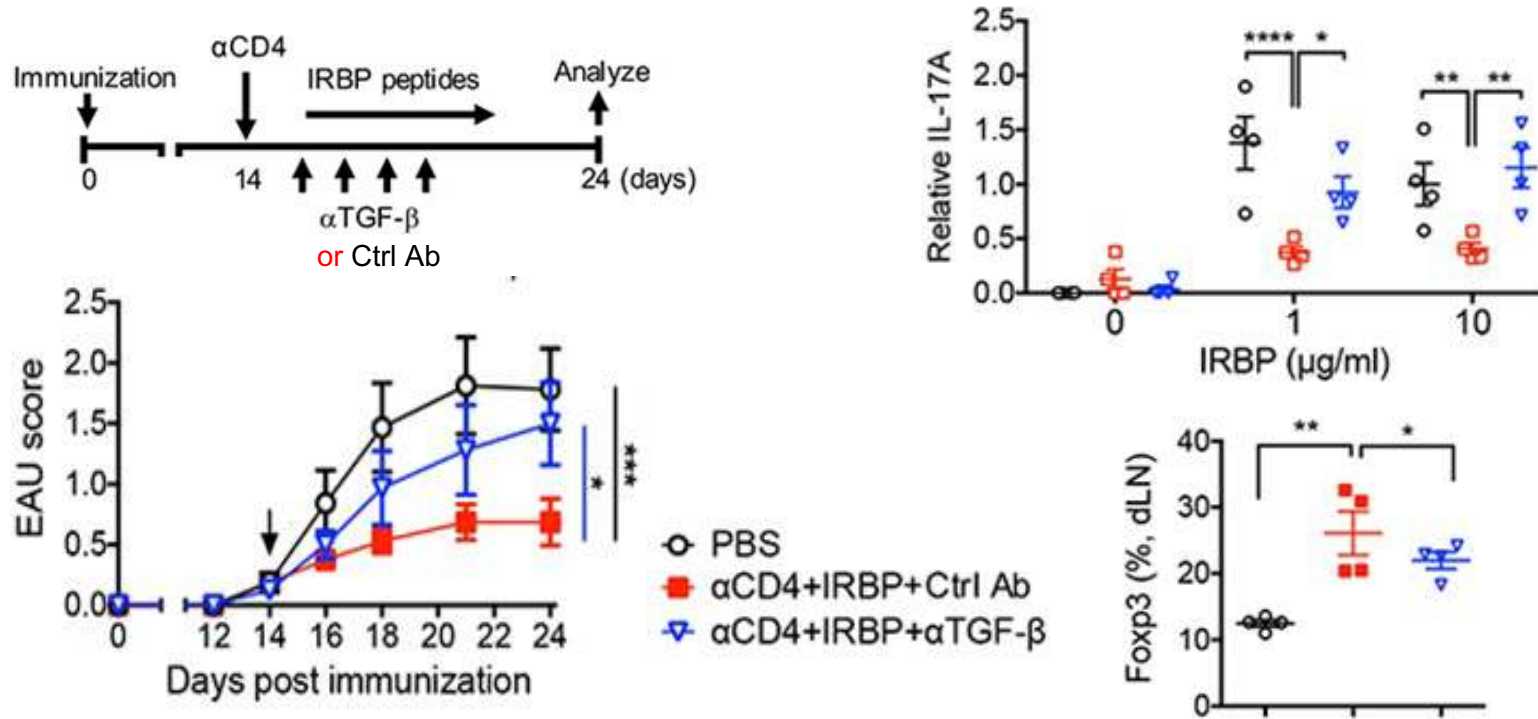
- *Apoptosis of CD4, CD8 T cells or B cells with different auto-antigenic peptides*
- *Long-term suppression of autoimmunity (EAE, Type I Diabetes)*
- *Autoantigen-specific Treg generation dependent on **TGF- β***
- *Therapy does not compromise anti-bacterial and overall immune responses*

Experimental diseases in mice treated or to be tested :

- **EAE**: experimental autoimmune encephalomyelitis (MS) (Yes)
- **EAU**: experimental autoimmune uveitis (Yes)
- **RA**: rheumatoid arthritis(yes)
- **SS**: Sjogren Syndrome(yes)
- **Type I diabetes** (yes)
- Transplantation?

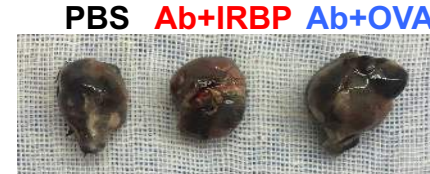
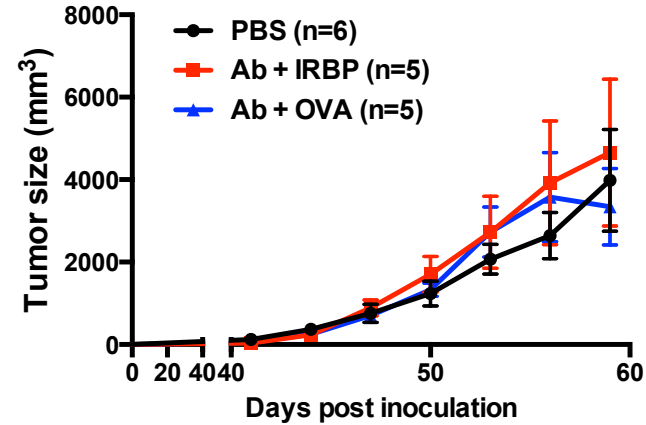
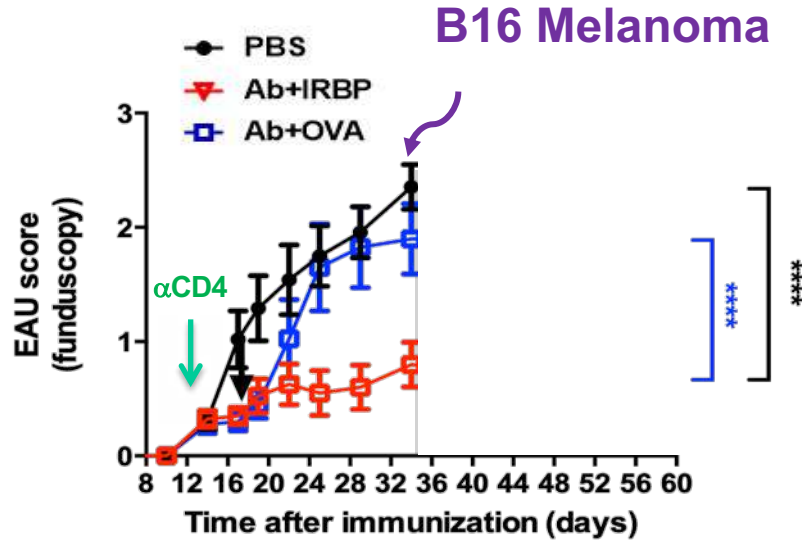
Kasagi et al, Sci Transl Med, 2014
Kasagi et al, EBioMedicine, 2019
Chen H. et al, Sci Rep. 2019
Chen X. et al, Sci Transl Med, 2021
Chen J et al, Ebiomedine,2021
Liu O et al, iScience, 2021
Xu, et al, In revision, 2021

TGF- β is required for the generation of antigen-specific Treg and suppression of EAU



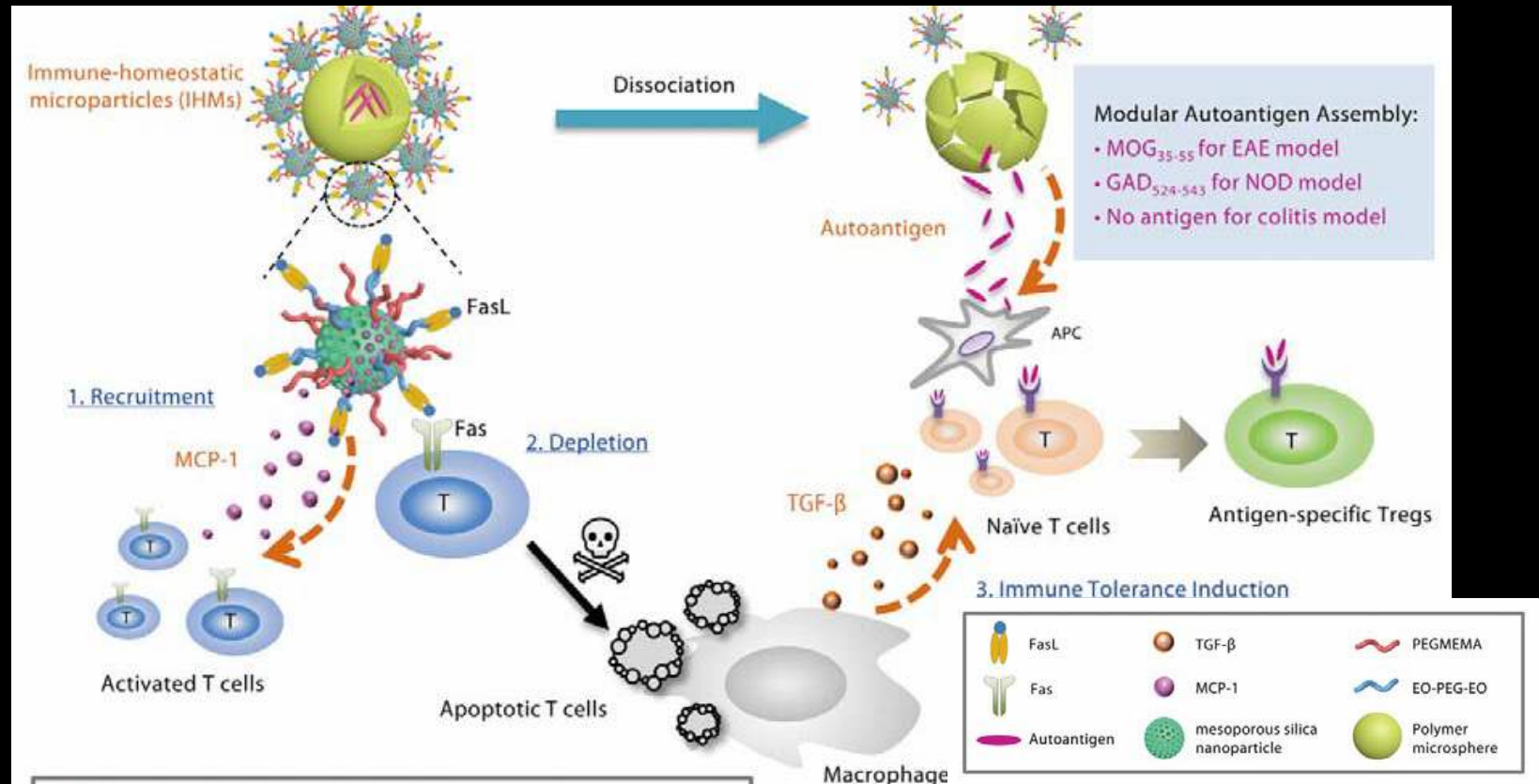
Does suppression of EAU affect anti-tumor immunity?

Immunotherapy of EAU by autoantigen-specific Tregs without compromising anti-tumor immunity

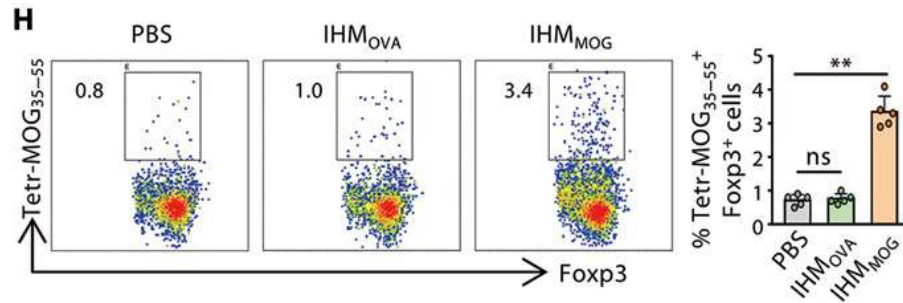
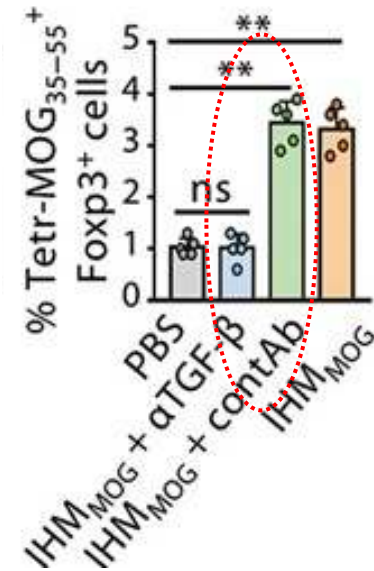
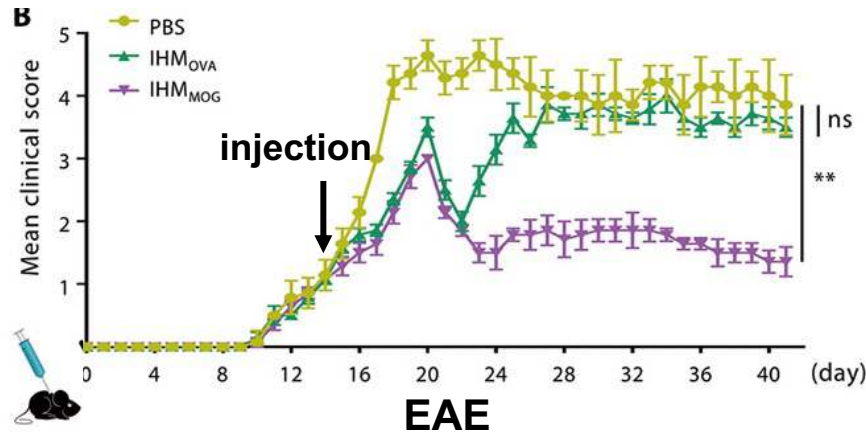


Can we selectively induce apoptosis of active/effector/inflammatory immune cells together with autoantigenic peptide to induce antigen-specific Tregs *in vivo* to treat autoimmunity?

Immune-homeostatic microparticles treat autoimmunity by induction of antigen-specific Tregs



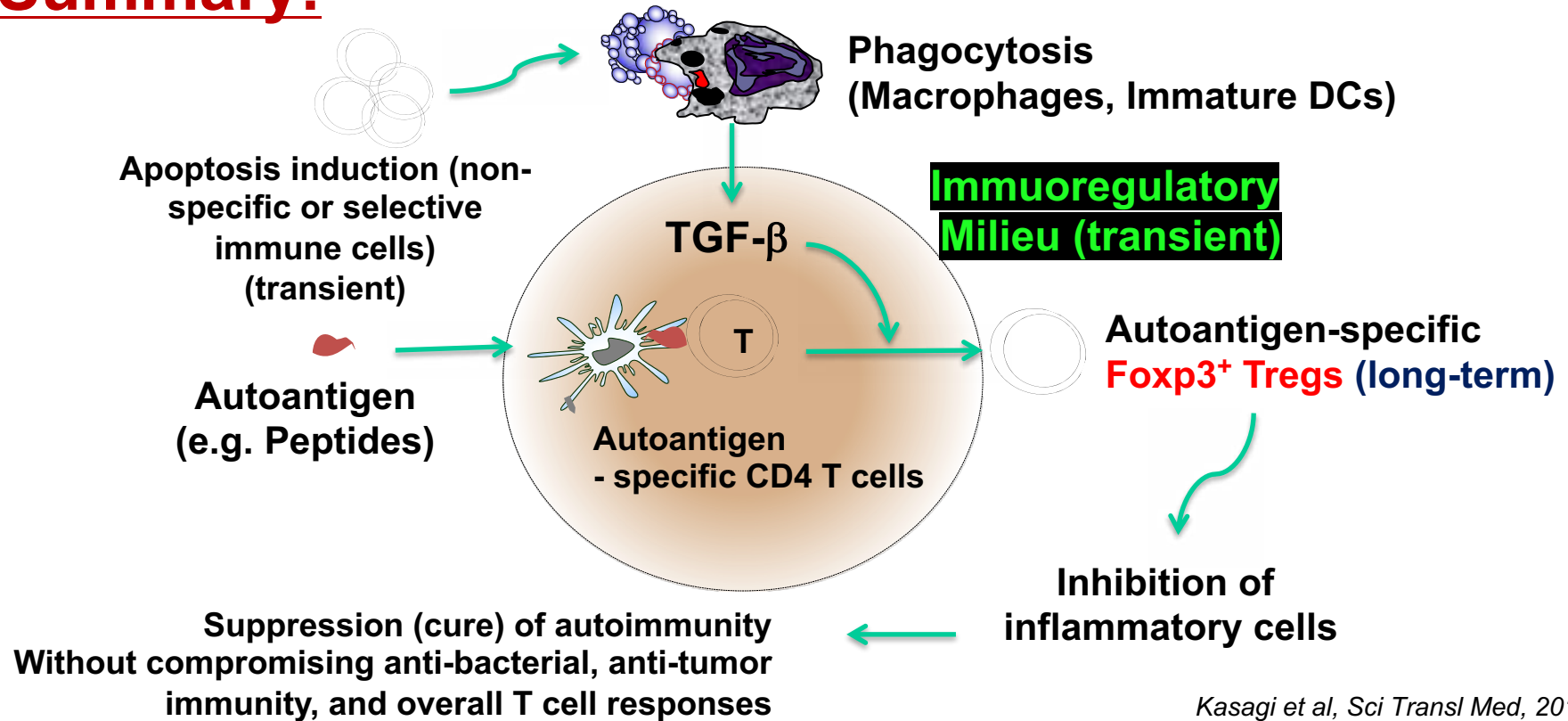
IHMs treat EAE by induction of antigen-specific Tregs



Brain & Spinal cords

Similar therapeutic effect was obtained in type 1 diabetes model

Summary:



Opposite approach: induction of anti-tumor neoantigen-specific T effector cells?

Kasagi et al, Sci Transl Med, 2014
Kasagi et al, EBioMedicine, 2019
Chen H. et al, Sci Rep. 2019
Liu S et al, Sci Transl Med, 2021
Xu et al, In revision, 2021
Chen Z. et al, EBioMedicine, 2021



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