TNFR2 Agonist OD-003 Expands Immunosuppressive Tissue Treg and Has the Potential to Treat Autoimmune and Inflammatory Disease

Lee Kim Swee[1], Rashi Singhal[2], Tomasz Prochnicki[3], Brian Sanchez[2], Elizabeth McMillan[3], Alissa Telling[2], Hanbin Lu[3], Ferdinand Huber[1], Annegrit Seifried[1], Laura Preiß[1], Karsten Thierbach[1], Nigel Waters[3], Kimberly Aardalen[3], Casey Landry[3], Taylor O'Donnell[3], Anthony W Opipari[2], Tobias Stuwe[1], Elaine Pinheiro[3], Dennis Dean[3], Michael Delacher[4], Stephen M Soisson[3], and Luigi Franchi[2]

Affiliations: [1] Odyssey Therapeutics GmbH, Frankfurt am Main, Hessen, Germany; [2] Odyssey Therapeutics, Inc., Ann Arbor, MI; [3] Odyssey Therapeutics, Inc., Boston, MA; [4] University Medical Center Mainz, Rheinland-Pfalz, Germany

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Background / Purpose

Regulatory T cells (Treg) are necessary for immune homeostasis, and their dysregulation has been implicated in inflammatory disease. While the use of IL-2 to expand Treg has shown some benefit in atopic dermatitis and alopecia areata, IL-2-expanded Treg have several drawbacks: they have limited immunosuppressive function ("quality") and tissue migration capacity, and can transdifferentiate into pro-inflammatory effector cells in the presence of inflammatory cytokines ("stability"). Tumor necrosis factor receptor 2 (TNFR2) is a surface receptor expressed at high levels on Treg, and its activation induces a potent, stable, immunosuppressive phenotype. We developed OD-003, a TNFR2 agonist currently in IND-enabling studies, and a murine surrogate; both are superior to IL-2 in inducing high-quality Treg with improved tissue migration, stability, and in vivo efficacy. Together, these results suggest OD-003 has the potential to provide benefit across autoimmune and inflammatory diseases with unmet need.

Methods

OD-003 was engineered as a VHH-Fc fusion molecule designed to induce selective activation of Treg vs. other TNFR2-expressing cell types such as endothelial cells or effector T cells. A murine surrogate of OD-003 was used to generate gene-expression profiles in naive mice by scRNA-seq, and efficacy was evaluated with therapeutic dosing in the experimental autoimmune encephalomyelitis (EAE) model. TNFR2 agonism was assessed on Treg from human PBMCs by evaluating expansion, tissue-homing markers, gene expression, suppressive function, and stability under pro-inflammatory conditions. To assess the potential activation of non-Treg cells, OD-003 selectivity was evaluated using PBMCs, and repeat dosing was assessed in nonhuman primates (NHPs).

Results

TNFR2 expression was highest on BATF+ Treg, a subset of stable immunosuppressive Treg that home to and repair tissue. In mice, the murine surrogate drove brain Treg expansion upon therapeutic dosing and reduced disease severity, whereas IL-2 did not increase Treg in the brain or reduce disease severity. In human PBMCs, TNFR2 agonism expanded Treg, increased suppressive markers and function, improved Treg stability under pro-inflammatory challenge, and upregulated a tissue-repair gene signature. In PBMCs from healthy donors and patients with SLE, TNFR2 agonism selectively expanded Treg and upregulated FOXP3 and BATF. The Treg-selective activity of OD-003 was further confirmed in NHPs.

Conclusions

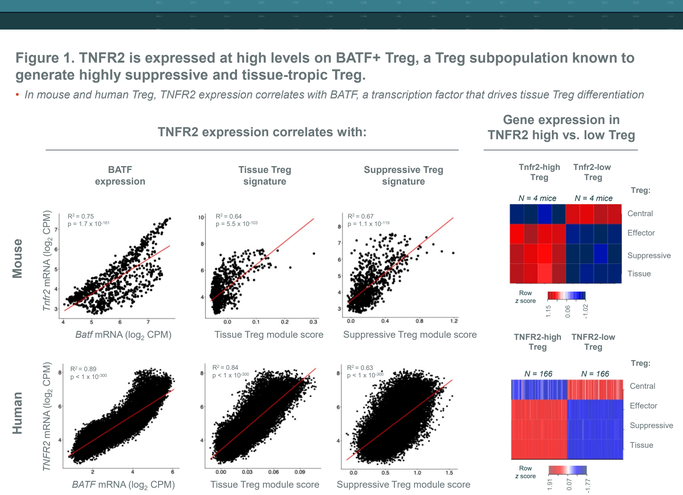
OD-003 selectively expands stable Treg that can migrate into diseased tissue. This activity could improve upon the results observed with IL-2-based therapeutic approaches and broaden the number of indications addressed by Treg-directed therapies.

References

1. Immunity 2020;52:295-312
2. Immunity 2021;54:702-720
3. Cell Mol Immunol 2021;18(2):398-414
4. Nat Immunol 2015;16(3):276-285
5. Immunity 2019;50(2):493-504
6. Immunity 2023;56(12):2836-2854
7. TNF mutein from US20250122256A1 (variant 5)

Figure 1. TNFR2 is expressed at high levels on BATF+ Treg, a Treg subpopulation known to generate highly suppressive and tissue-tropic Treg.

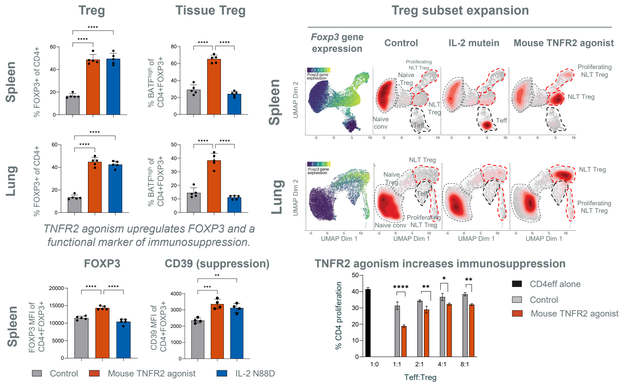
- *In mouse and human Treg, TNFR2 expression correlates with BATF, a transcription factor that drives tissue Treg differentiation*



Correlation of TNFR2 (Tnfrsf1b/TNFRSF1B) expression with BATF expression and with tissue[1,2], effector[3–5], suppressive[5], and central[3,4] Treg gene signatures in mouse and human Treg assessed from single-cell gene expression data[6]. CPM = counts per million.

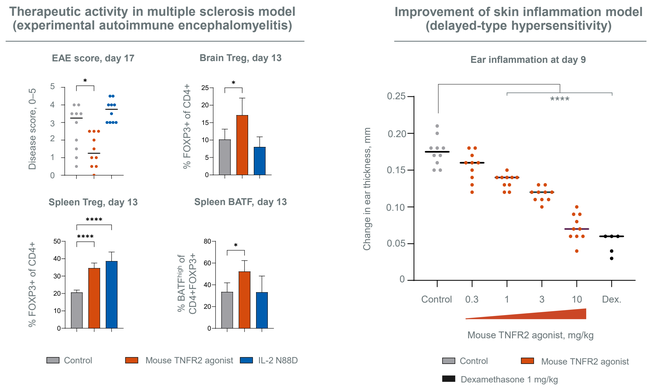
Figure 2. In vivo TNFR2 agonism promotes expansion of highly suppressive Treg with tissue tropism.

- *Total Treg can be expanded in spleen and lung by both TNFR2 agonist and IL-2 mutein*
- *BATF+ non-lymphoid tissue (NLT) Treg were expanded only by the TNFR2 agonist*
- *The IL-2 mutein, but not the TNFR2 agonist, expands effector T cells (Teff)*



*Treg subset expansion, and FOXP3 and CD39 expression were determined by flow cytometry or single-cell RNA sequencing, and suppressive function was assessed ex vivo, 5 days after injection of mouse TNFR2 agonist (3 mg/kg) or IL-2 N88D (1 mg/kg) in WT C57BL/6 mice; n = 4–5 per group, one-way ANOVA or t-test (for immunosuppression); * = p < 0.05, ** = p < 0.01, *** = p < 0.001, **** = p < 0.0001.*

Figure 3. TNFR2 agonist induces tissue Treg increase and improves dermatitis and experimental autoimmune encephalomyelitis.

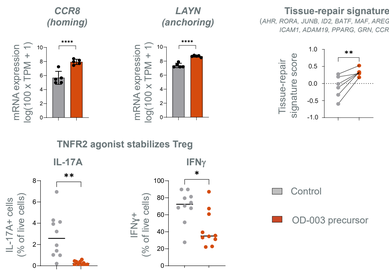


*Disease score was assessed on day 17; Treg in brain and spleen, and tissue Treg in spleen, were measured on day 13. Disease was induced on day 0 (MOG peptide/pertussis toxin) and day 1 (pertussis toxin) in C57BL/6 mice. Mice were injected with mouse TNFR2 agonist (30 mg/kg) or IL-2 N88D (1 mg/kg) on day 8; n = 4-10 per group; one-way ANOVA; * = p < 0.05, **** = p < 0.0001.*

*C57BL/6 mice were injected subcutaneously with KLH in complete Freund's adjuvant on day 0 and challenged with KLH in the ear on day 8. Mouse TNFR2 agonist was given on day 6; dexamethasone was given daily on days 6–8; n = 5-10 per group; one-way ANOVA; **** = p < 0.0001.*

Figure 4. Human TNFR2 agonist upregulates markers of tissue homing and repair and increases Treg stability.

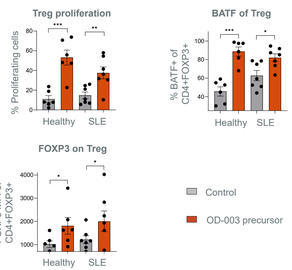
*CCR8, layilin (LAYN), and tissue-repair gene signature expression was measured in isolated human Treg stimulated with anti-CD3 and IL-2 with 1 nM control or OD-003 precursor for 5 days; t-test; ** = p < 0.01; **** = p < 0.0001; n = 5–6.*



*IL-17A and IFNγ expression were measured in human Treg stimulated with 1 nM OD-003 precursor or control in the presence of anti-CD3 and IL-2 for 5 days and then challenged for 11 days with IL-1β, IL-23, IL-21, and TGF-β (left) or IL-1β, IL-23, and IL-21 (right); t-test; * = p < 0.05, ** = p < 0.01; n = 10.*

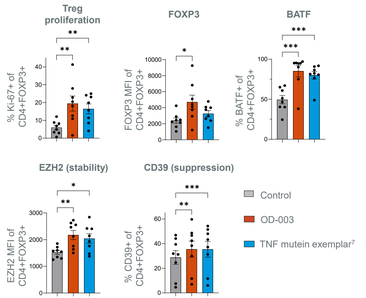
Figure 5. Activity of TNFR2 agonism is preserved in SLE patient samples.

The TNFR2 agonist expands Treg and upregulates markers of tissue homing and stability in PBMCs from healthy donors and patients with SLE.



*The percentage of proliferating Treg (CD4+FOXP3+), and BATF and FOXP3 expression were measured after 5 days anti-CD3 stimulation of PBMCs from healthy donors or SLE patients, with 1 nM control or OD-003 precursor; n = 6 or 7 per group; mean ± SEM; t-test; * = p < 0.05, ** = p < 0.01, *** = p < 0.001, **** = p < 0.0001.*

Figure 6. In vitro activity of OD-003 compared with a TNF mutein exemplar.



*The percentage of Ki-67+, BATF+, and CD39+ cells and FOXP3 and EZH2 expression (MFI) were measured in Treg (CD4+FOXP3+) after 5 days of stimulation of human PBMCs with anti-CD3 plus 1 nM control, OD-003, or TNF mutein exemplar; n = 8 per group; mean ± SEM; one-way ANOVA; * = p < 0.05; ** = p < 0.01; *** = p < 0.001.*

Figure 7. OD-003 is a potent TNFR2 agonist that selectively expands, activates, and stabilizes Treg after repeat dosing.

Summary of human TNFR2 agonist activity in preclinical studies

Category	Effect
Selectivity	Selectively expands Treg over conventional T cells
Tissue homing	Upregulates tissue Treg markers BATF and CCR8
Stability	Upregulates the markers of stability, FOXP3 and EZH2, and prevents conversion into IL-17- and IFNγ-producing cells in vitro
In vivo Treg expansion	Expands Treg in spleen and tissue in human TNFR2 knock-in mice
In vitro cytokine release	Does not induce pro-inflammatory cytokine release in whole blood from healthy donors or patients with SLE

OD-003 selectively expands Treg in nonhuman primates without inducing proinflammatory cytokine release

	Treg (maximum fold change)		CD4+ / CD8+ Teff (maximum fold change)	
Group	1st dose	2nd dose	1st dose	2nd dose
Low dose	2.0x	1.7x	1.0x / 1.0x	1.0x / 1.1x
Mid dose	2.3x	1.3x	0.7x / 1.1x	0.8x / 1.0x
High dose	2.7x	2.0x	0.9x / 1.0x	0.8x / 0.8x

No increase in TNF, IL-6, IFNγ, or IL-1β was observed across doses.