

NKTR-358: A Selective Regulatory T Cell Inducing Agent for the Treatment of Autoimmune and Inflammatory Diseases

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NEKTAR

Lilly

Introduction

- A progressive imbalance of regulatory T cells (Tregs) relative to conventional T cells (Tcon) is shared by many autoimmune diseases
- Enhanced sensitivity of Tregs to IL-2 supports use of low-dose IL-2 therapy
 - Low-dose IL-2 therapy hampered by poor pharmacokinetics, AEs, short-lived effects
 - Magnitude of Treg mobilization ultimately limited by elicitation of Tcon
 - Clinical benefit demonstrated in GVHD, psoriasis, SLE and other indications

NKTR-358

- Preferential increase in number and activity of Tregs, minimal action on non-Tregs
 - Potential first-in-class therapeutic for direct manipulation of Tregs
- Biotherapeutic born from Nektar's extensive development experience with IL-2 and polymer conjugation
- Utilizes the FDA-approved aldesleukin sequence
- Monthly or twice monthly self-administered subcutaneous product for the treatment of autoimmune, chronic inflammatory, and allergy indications

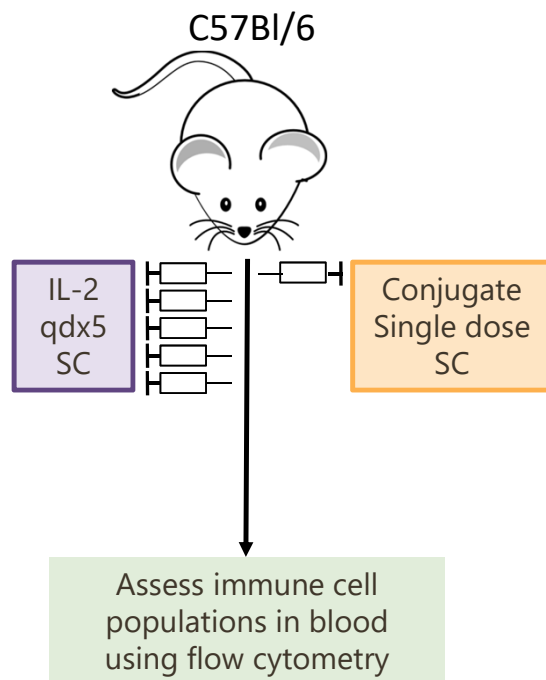
Nektar and Eli Lilly entered into a co-development agreement for NKTR-358 in August 2017

Design and Discovery of NKTR-358

NEKTAR

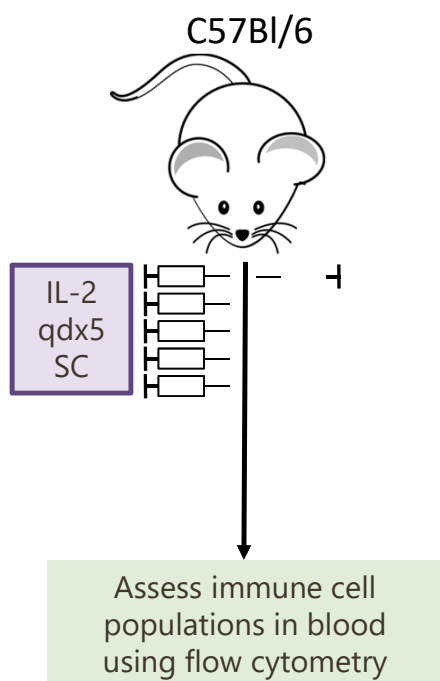
Lilly

NKTR-358 was Discovered by In Vivo Screening

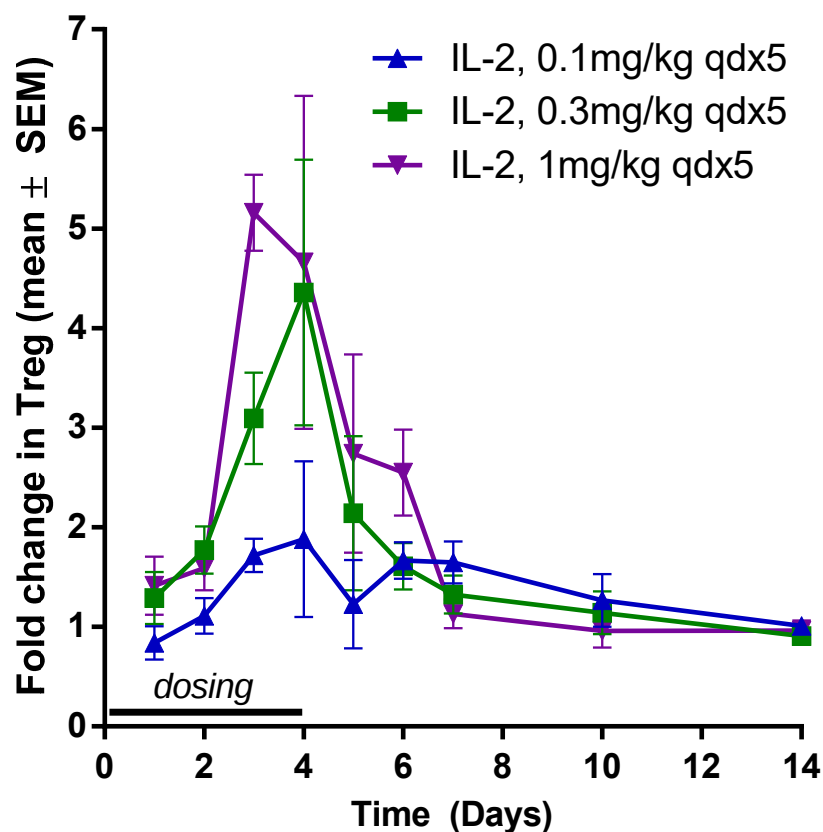


- NKTR-358 discovered through an *in vivo* testing funnel
 - Subcutaneous injection
 - Blood Treg levels measured
 - Similar results in spleen
 - Assessment of Tconv and Teff to examine potential for broad-scale immune activation
- Design goals
 - Optimize IL-2 pathway activation for Treg specificity
 - Biological activity on both nTreg and iTreg populations
 - Improve margin of Treg/Tcon responses seen with IL-2
 - Reversible pharmacological effect to increase both Treg number and function
 - Utilize FDA approved aldesleukin amino acid sequence
 - Subcutaneous route of administration
 - Q2wk or Q4wk dosing

Calibrating the System with Native IL-2

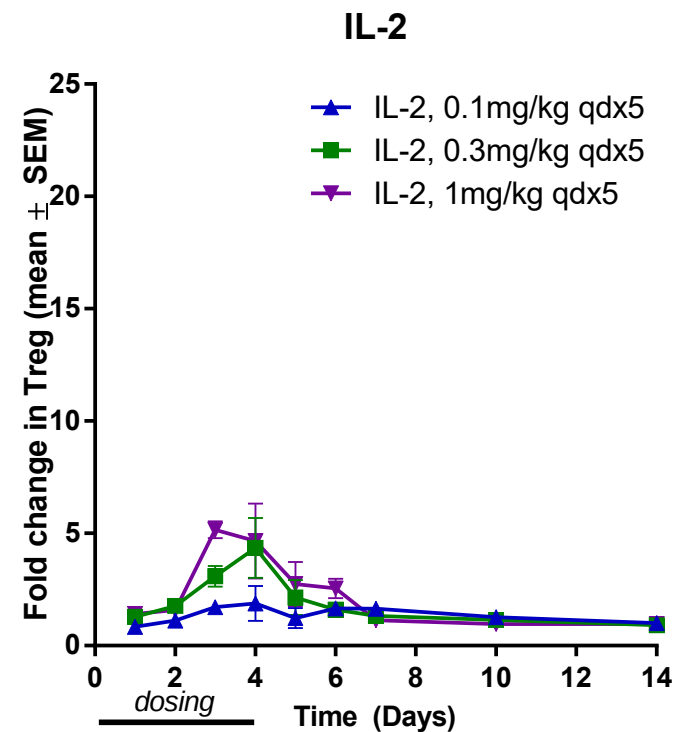
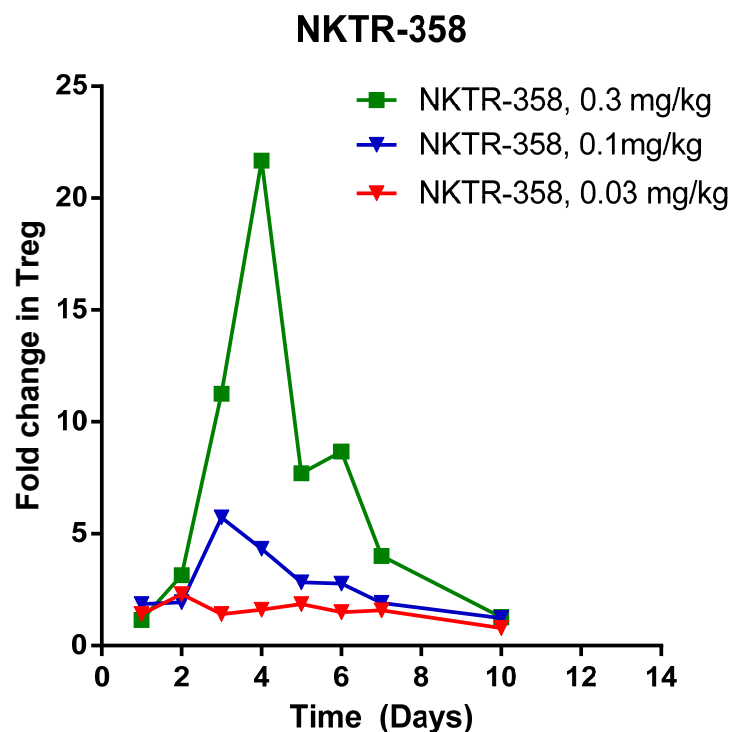
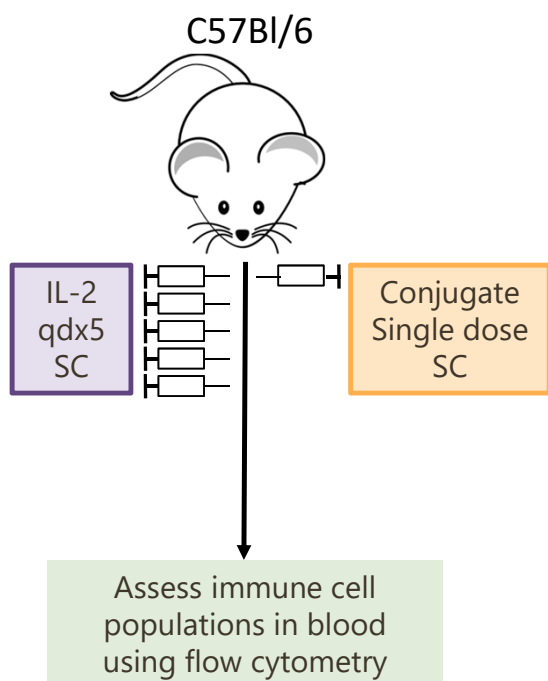


Treg, IL-2



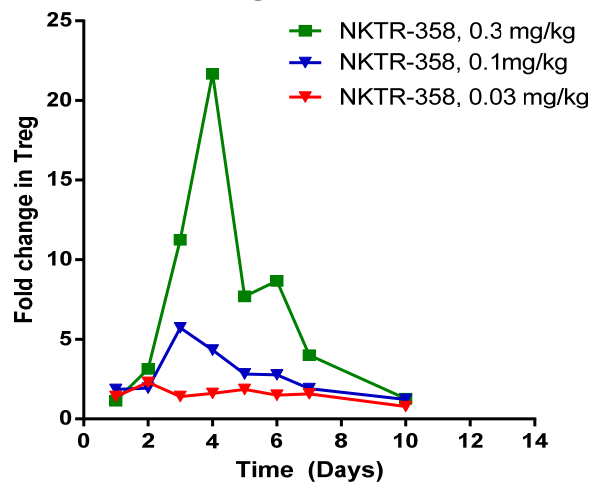
- 1mg/kg qdx5 is near MTD and anti-tumor efficacious dose
- 0.1mg/kg qdx5 is an appropriate comparison to low-dose IL-2

Comparison of NKTR-358 and IL-2 by In Vivo Screening

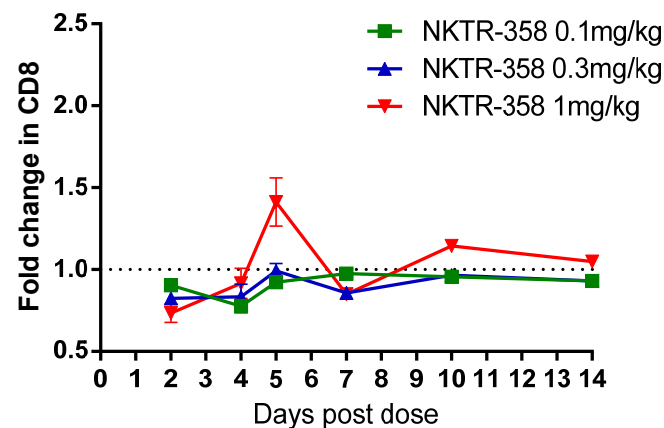


NKTR-358 is Selective for Treg Populations

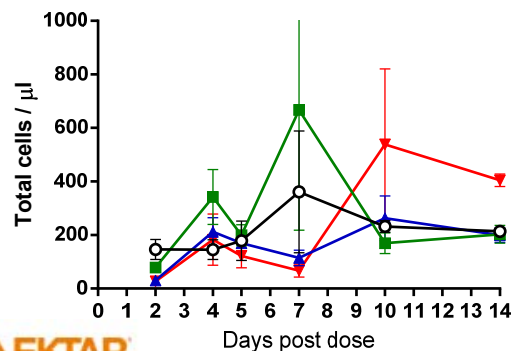
Treg (blood)



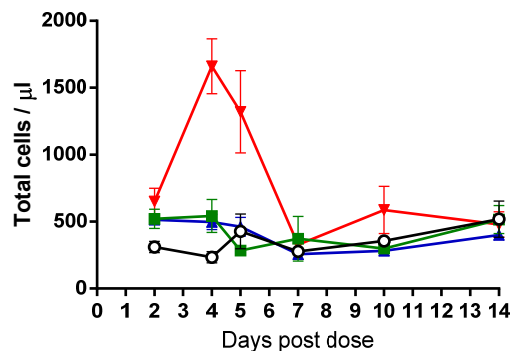
CD8 (blood)



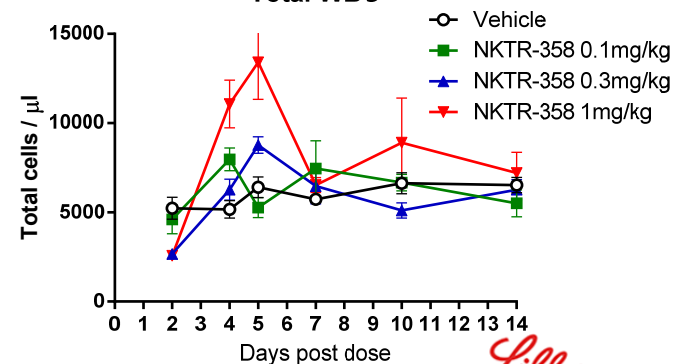
Eosinophils



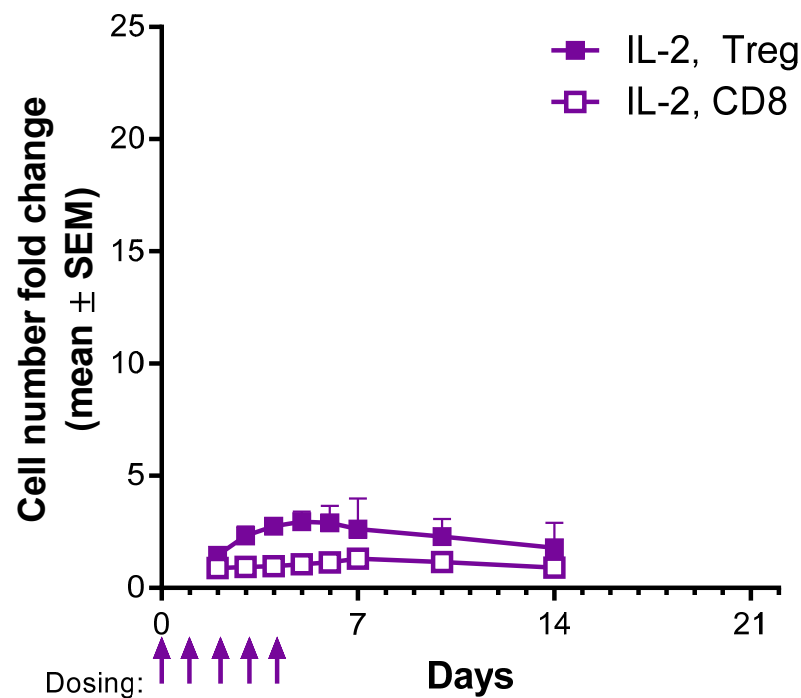
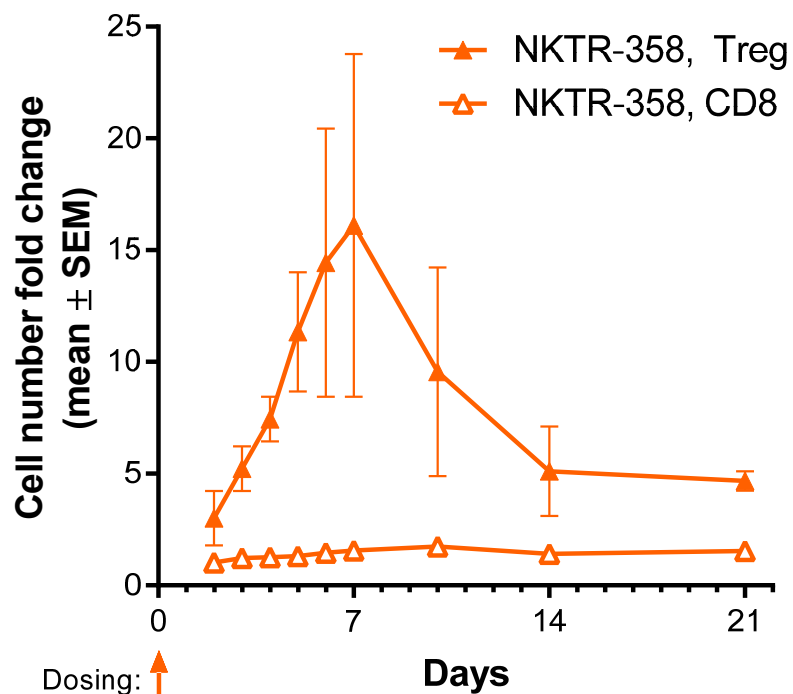
Monocytes



Total WBC

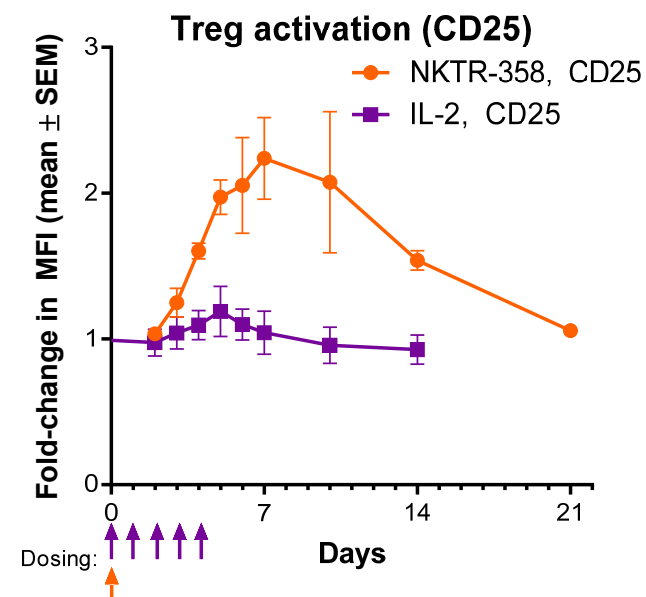
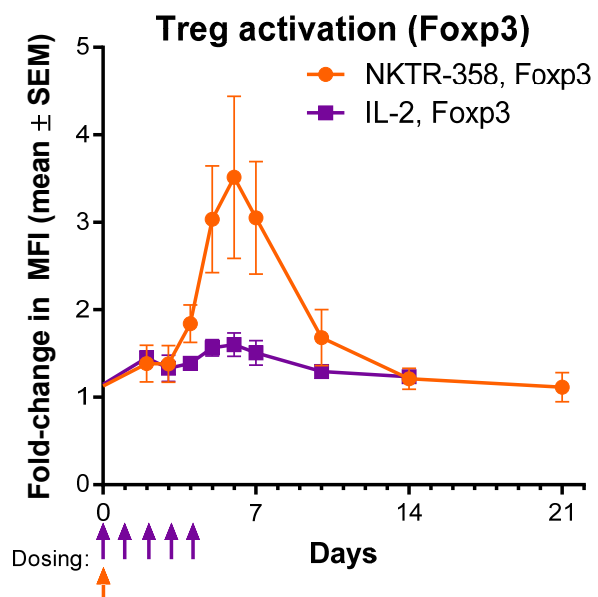
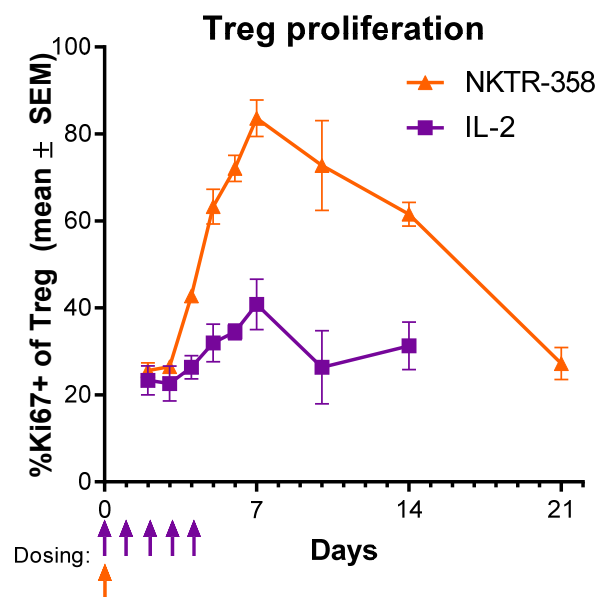


NKTR-358 Preferentially Expands Tregs in Monkeys



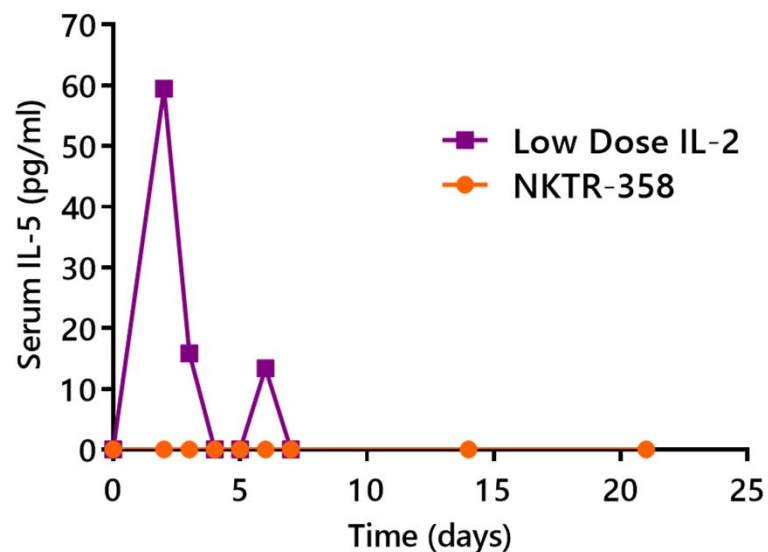
Cynomolgus monkey : 1M + 1F
25 μ g/kg : NKTR-358 single dose vs. qdx5 for IL-2

NKTR-358 Promotes Greater Treg Proliferation and Activation than IL-2

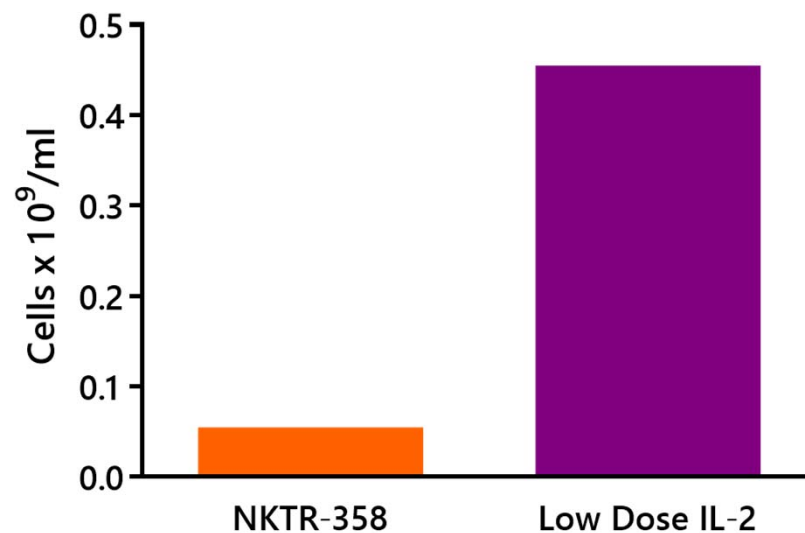


NKTR-358 Does Not Increase Eosinophil Levels in Monkeys

IL-5 Cytokine Levels in Serum

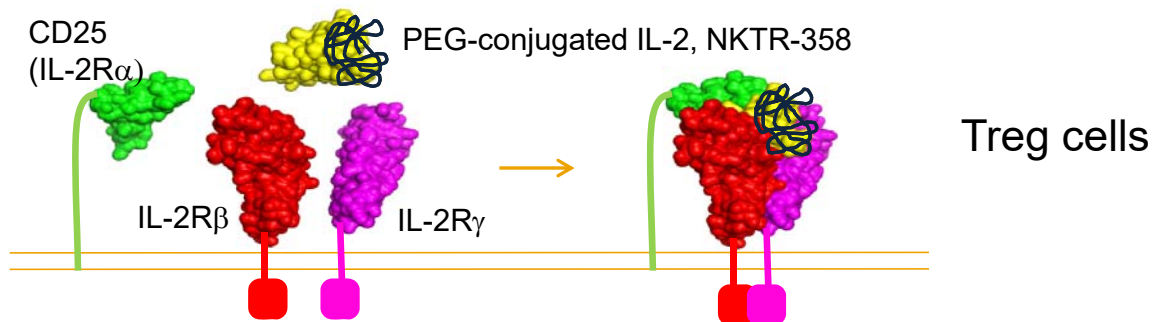


Eosinophils At Day 15



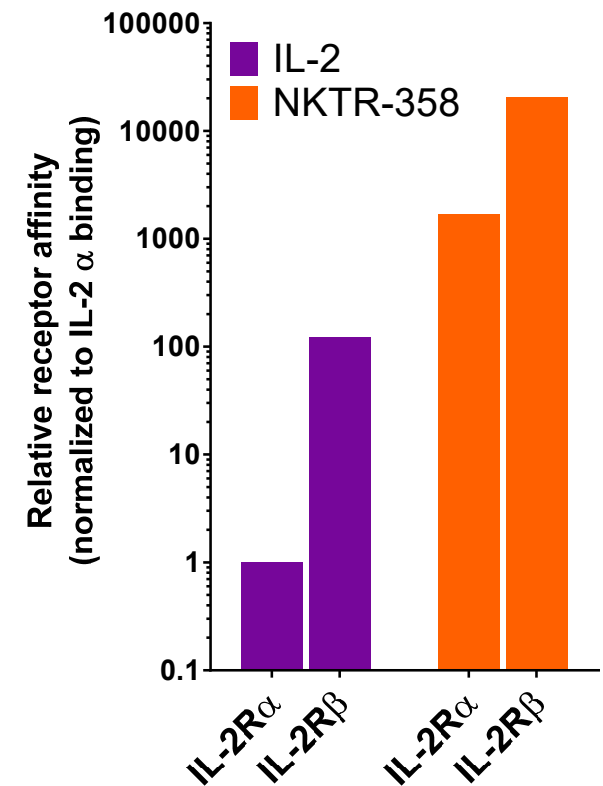
Molecular Pharmacology Characterization of NKTR-358

NKTR-358 has Attenuated Affinity to IL-2 Receptors

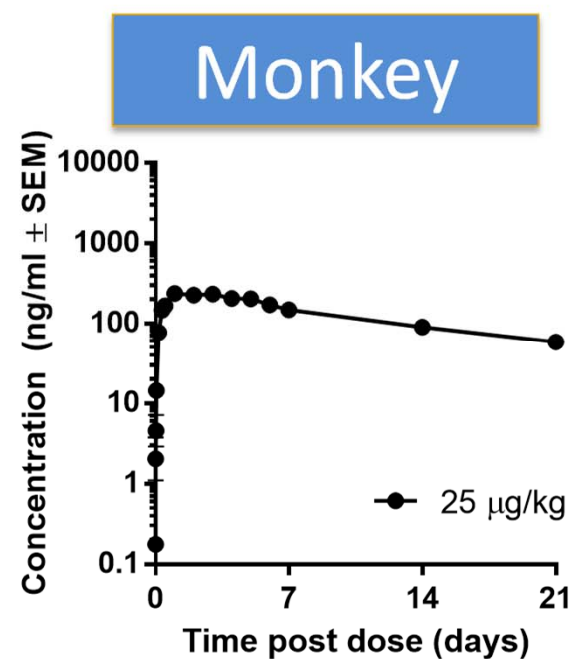
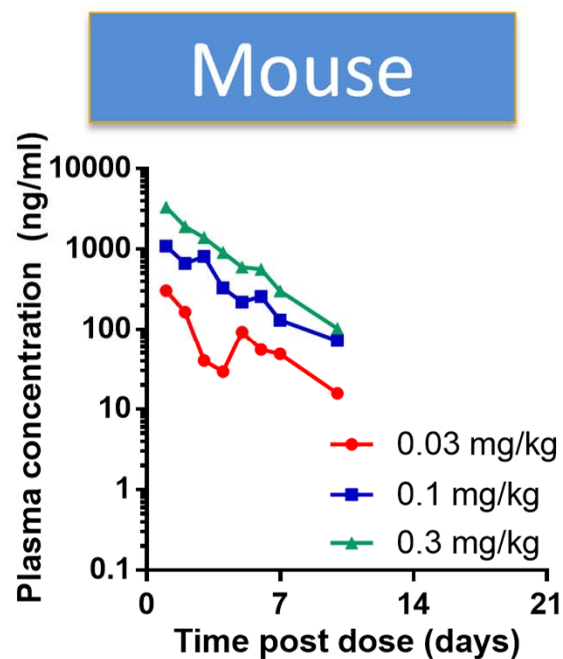


- PEG-conjugation reduces binding affinity of NKTR-358 relative to IL-2
- Relative to IL-2, NKTR-358 has:
 - Lower binding affinity to IL-2R β
 - Different binding bias for IL-2R α & IL-2R β

Receptor Binding

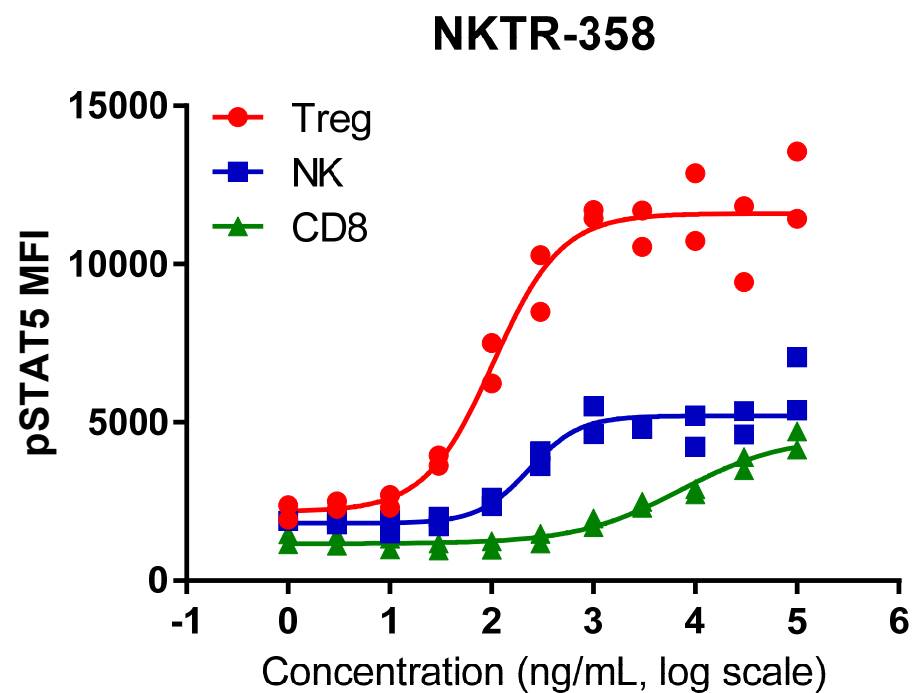
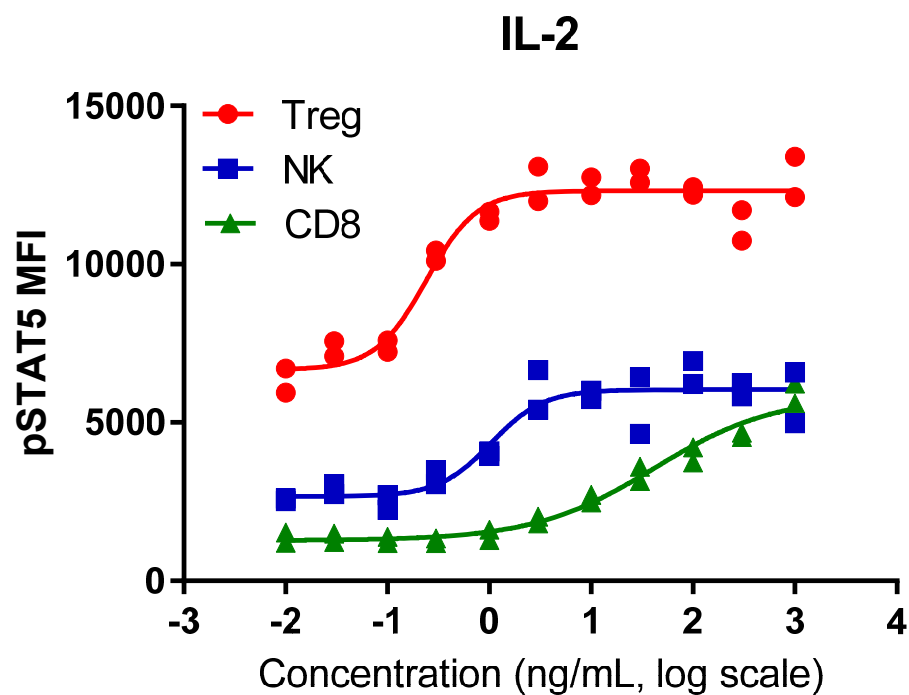


NKTR-358 PK After Subcutaneous Administration to Mouse and Monkey

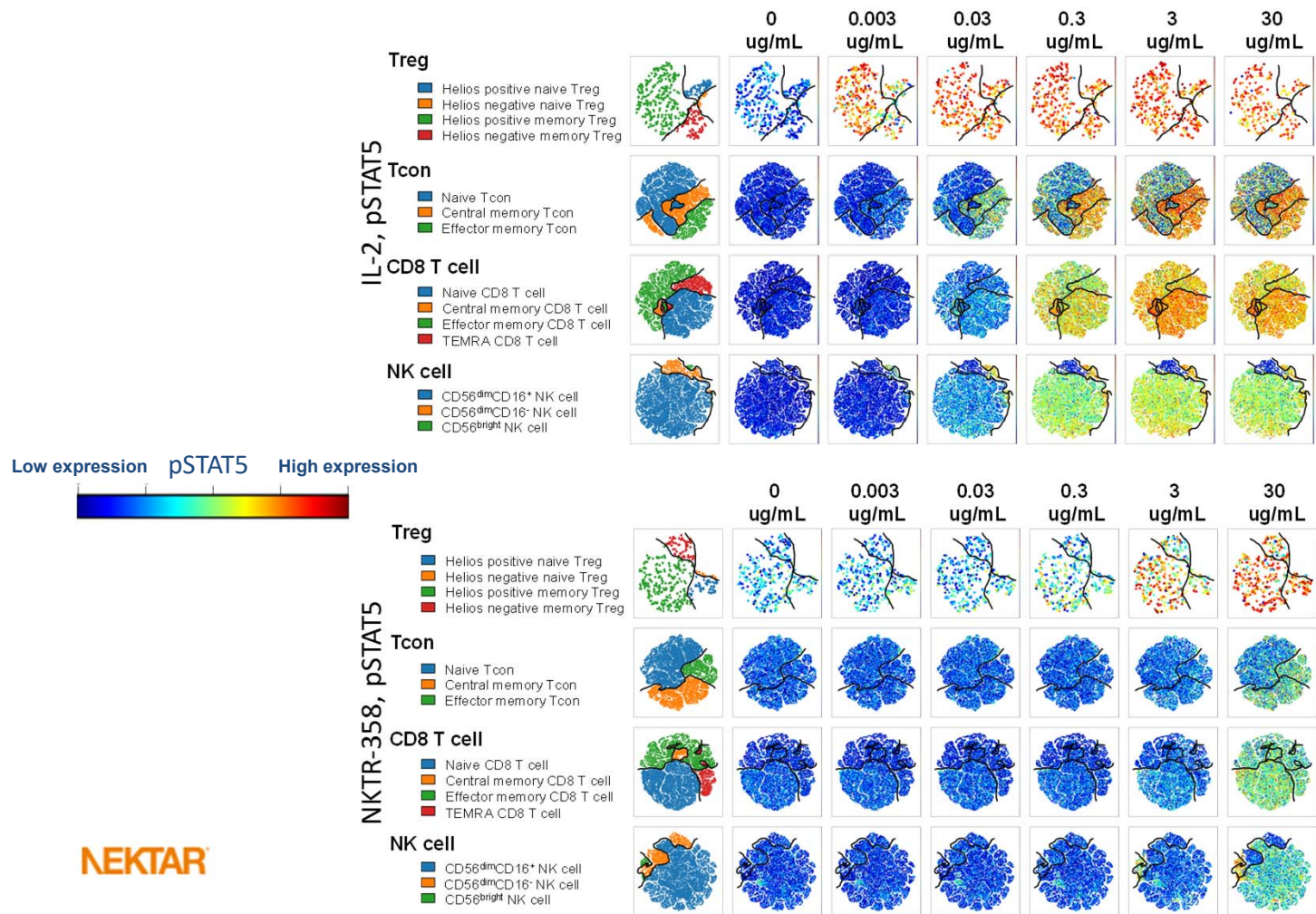


- Half-life values are:
 - ~2 days in mouse and rat
 - ~10 days in monkey

NKTR-358 Favors Activation of Treg Over Tcon

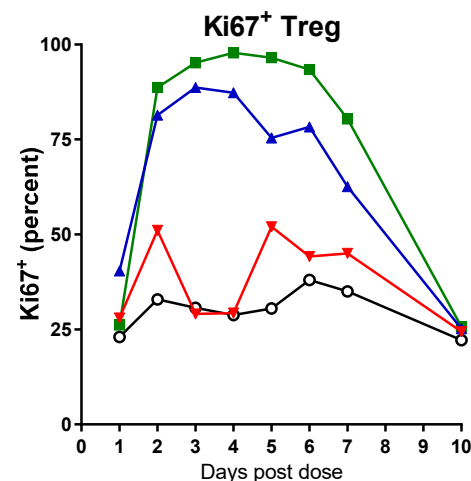
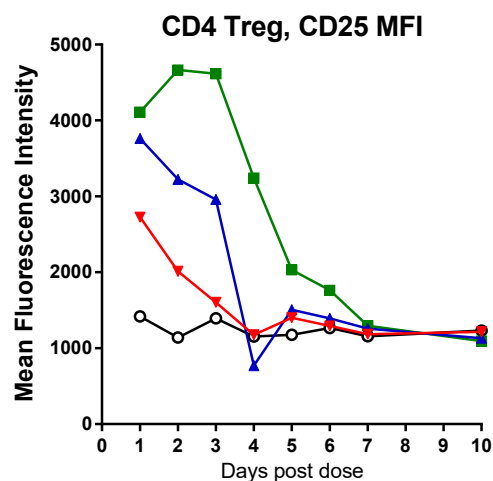
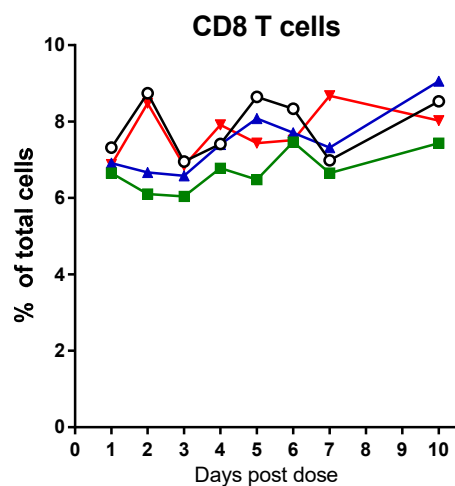


NKTR-358 Favors Activation of Treg Over Other Subsets

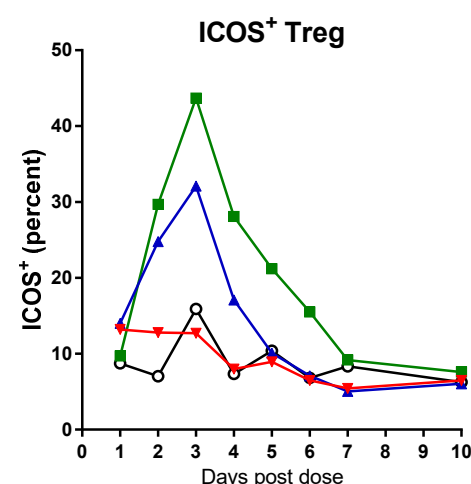
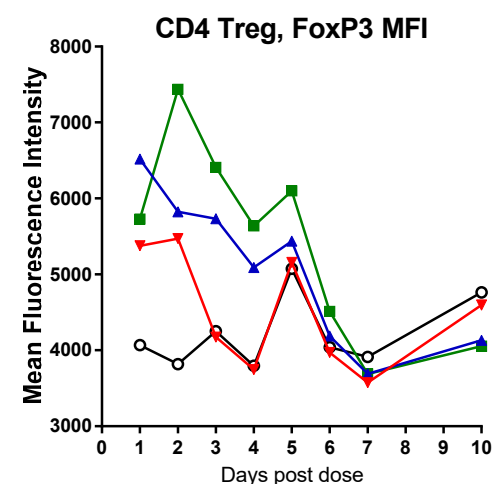
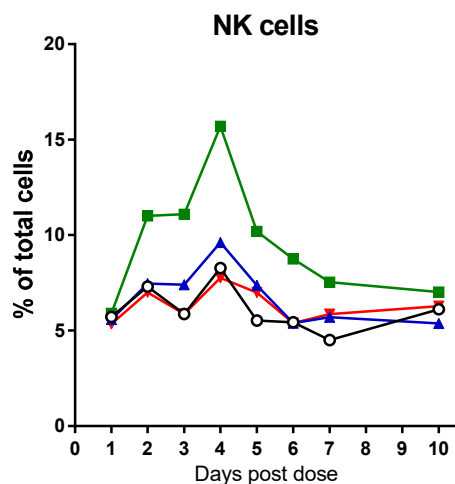


- Healthy human PBMCs
 - IL-2 or NKTR-358 for 15 min
 - Analysis by CyTof
- IL-2 and NKTR-358 had primary effect on pSTAT5
 - No effect on pAKT, pERK, pS6, and pSTAT3 (save IL-2 on CD56+++ NK)

NKTR-358 Promotes Selective Treg Activation In Vivo

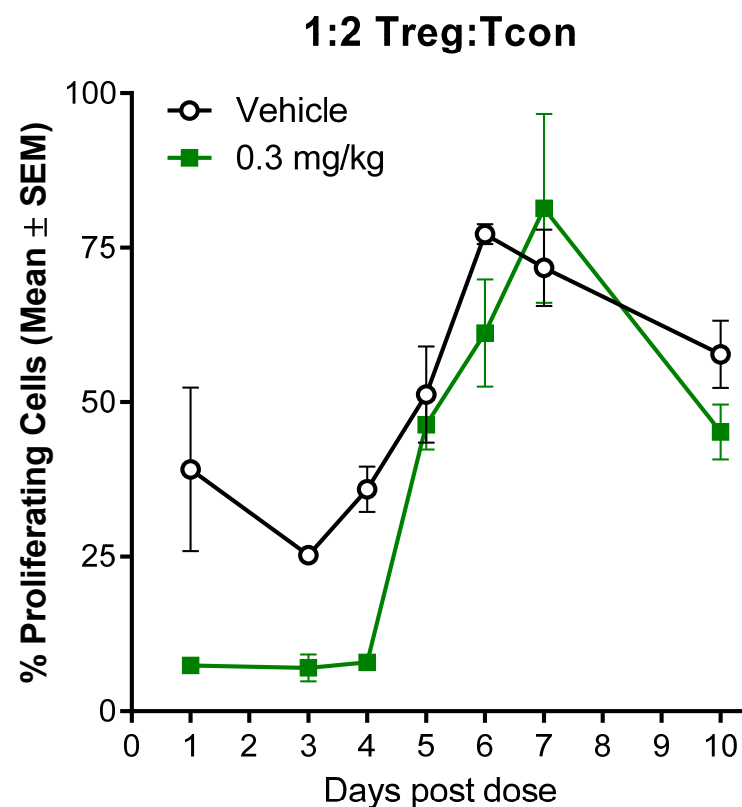
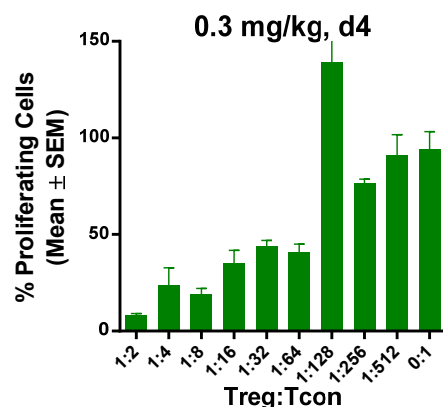
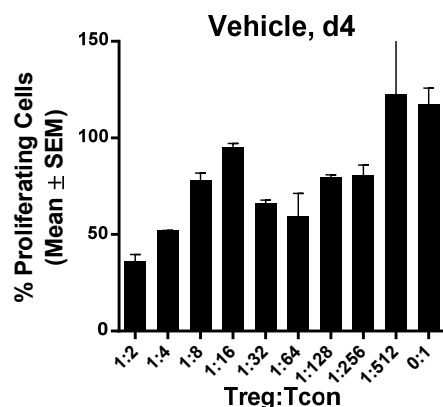
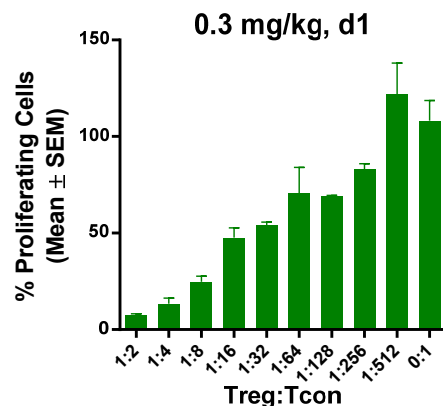
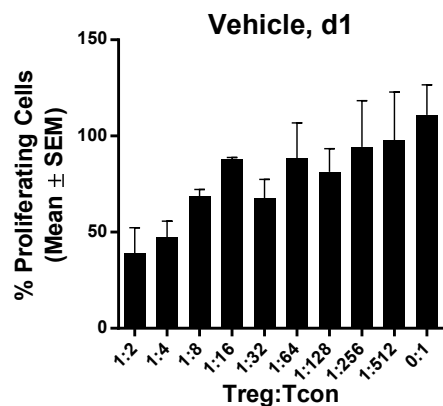


■ 0.3 mg/kg
▲ 0.1 mg/kg
▼ 0.03 mg/kg
○ Vehicle

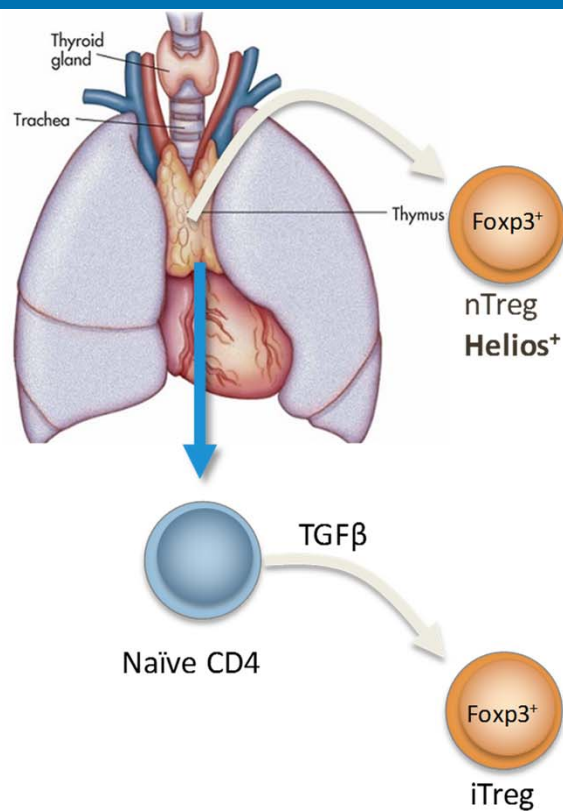


Helios, GITR, CTLA-4,
CD39, CD73, OX40, and
PD-1 (not shown)

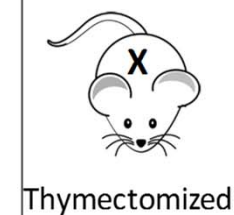
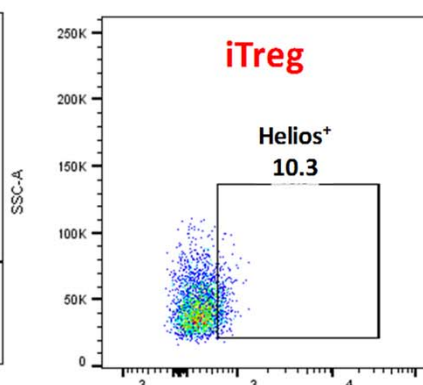
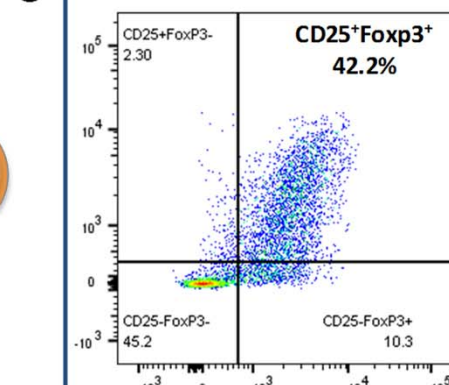
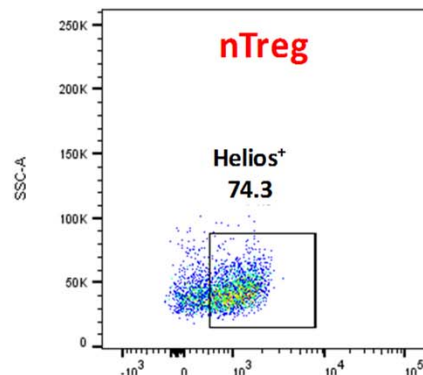
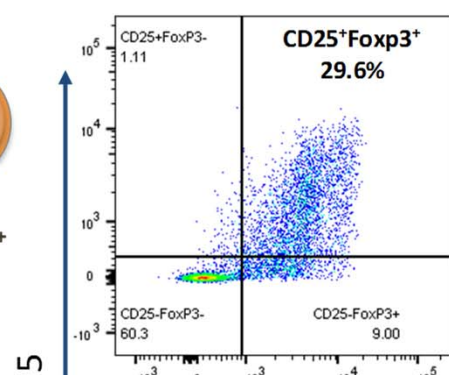
NKTR-358 Promotes Treg Suppressive Function In Vivo



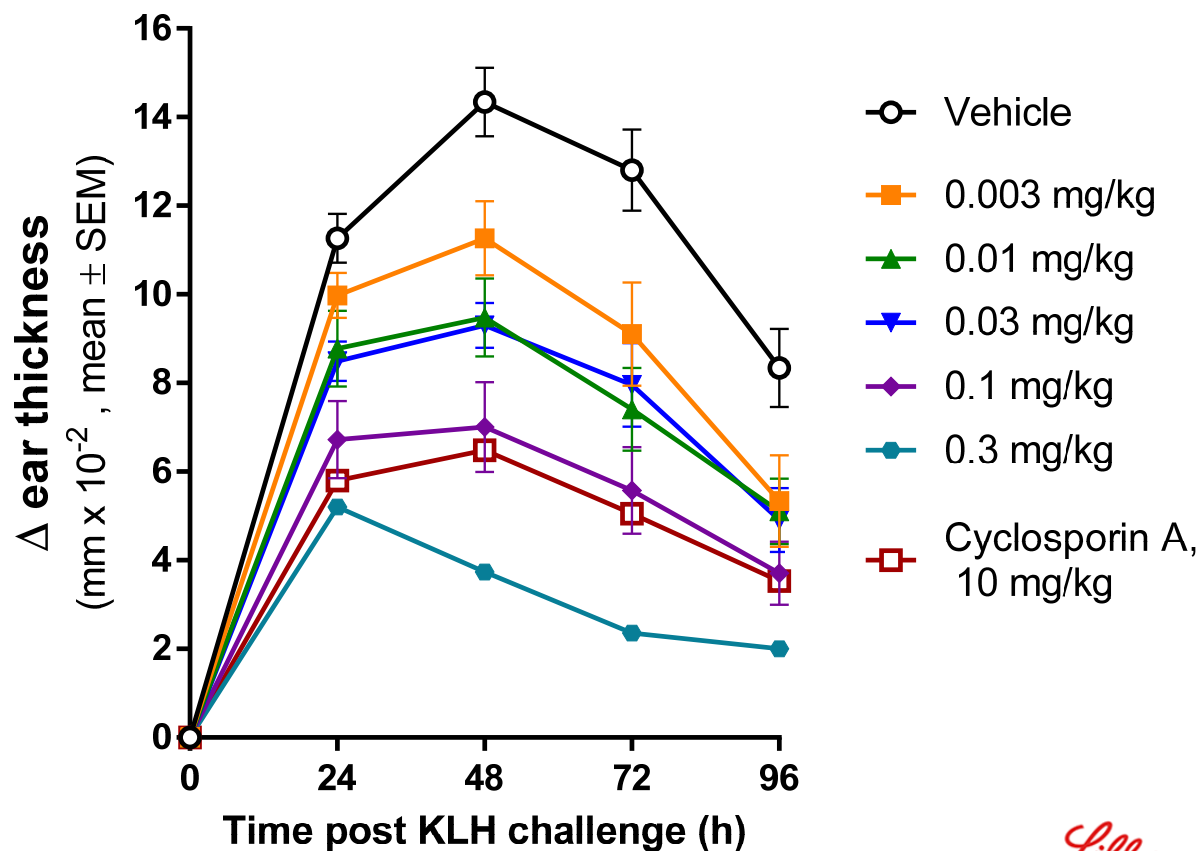
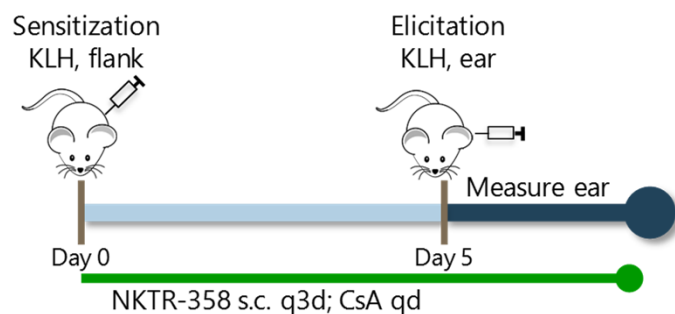
NKTR-358 Expands Both nTreg and iTreg Populations In Vivo



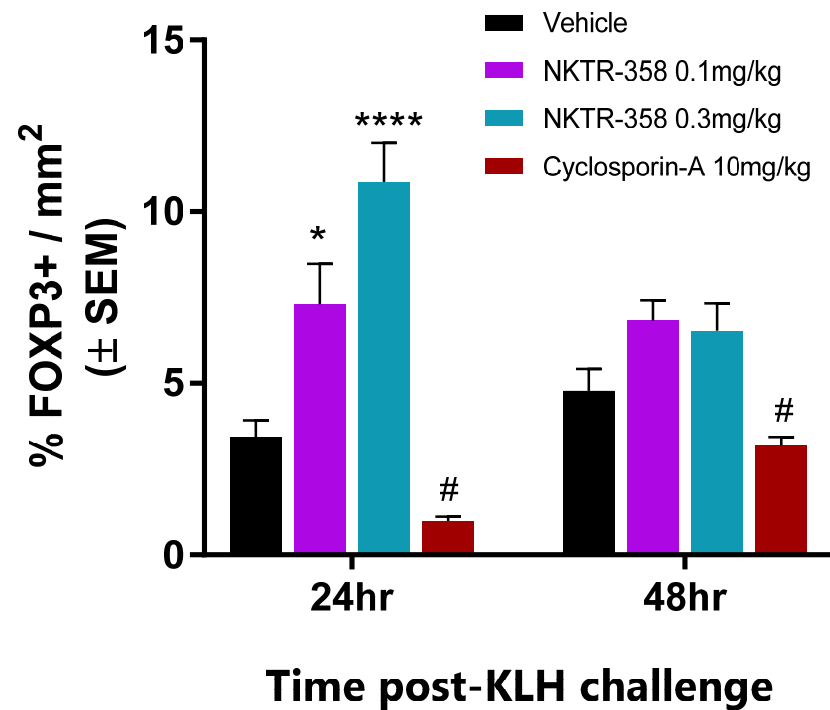
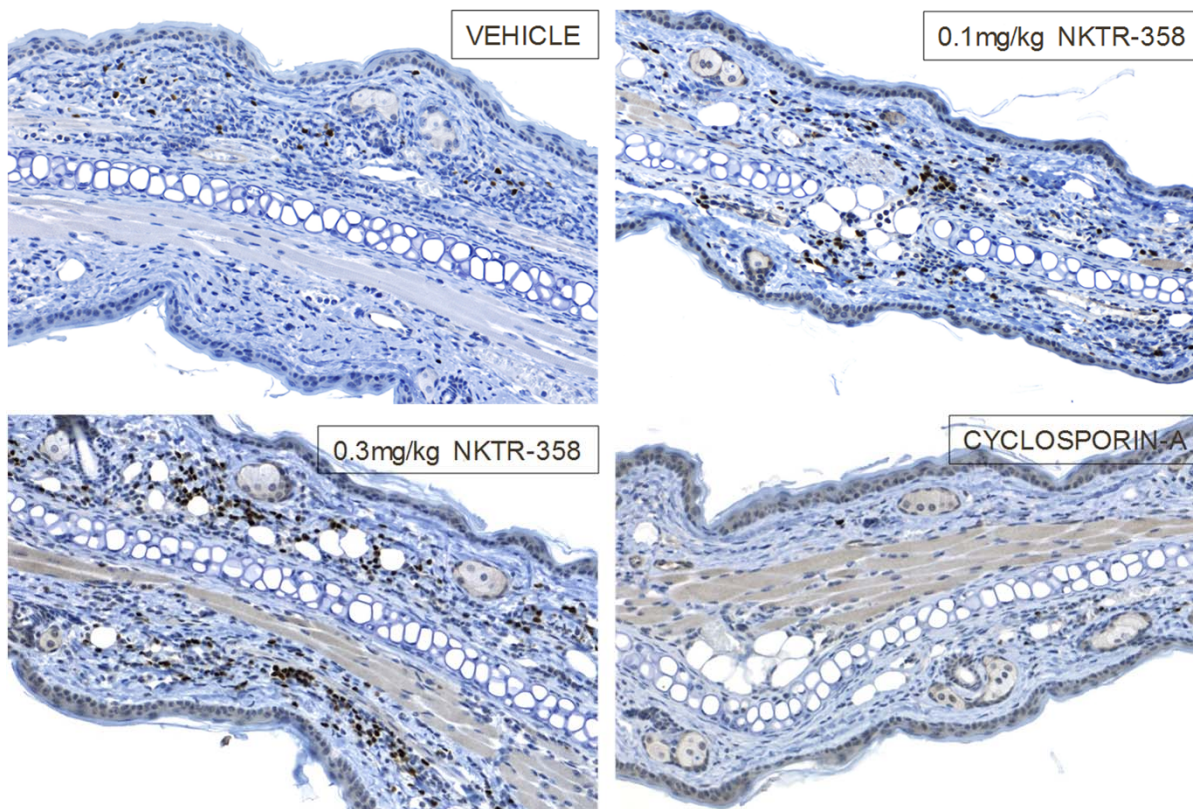
NKTR-358 treated mice, day 4 post dose



NKTR-358 Suppresses Inflammation in Mouse DTH



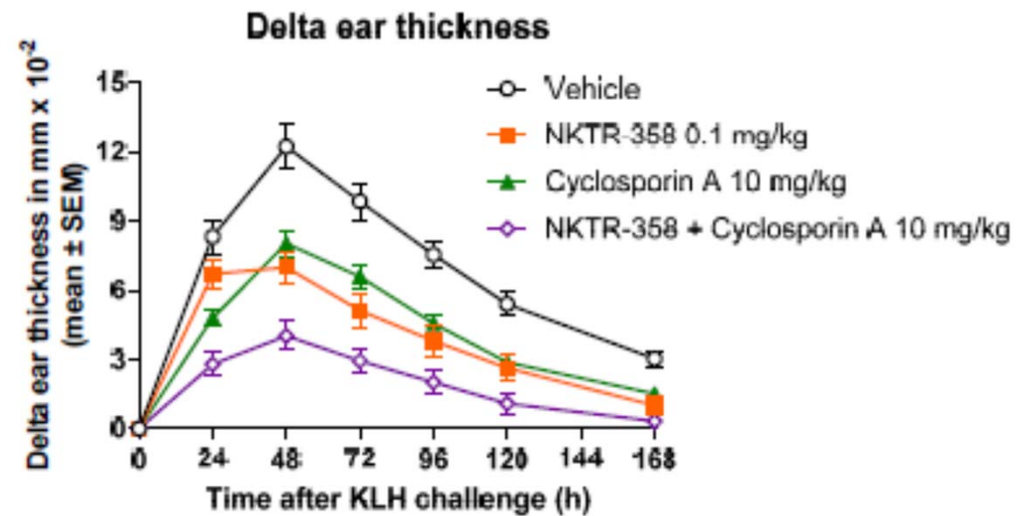
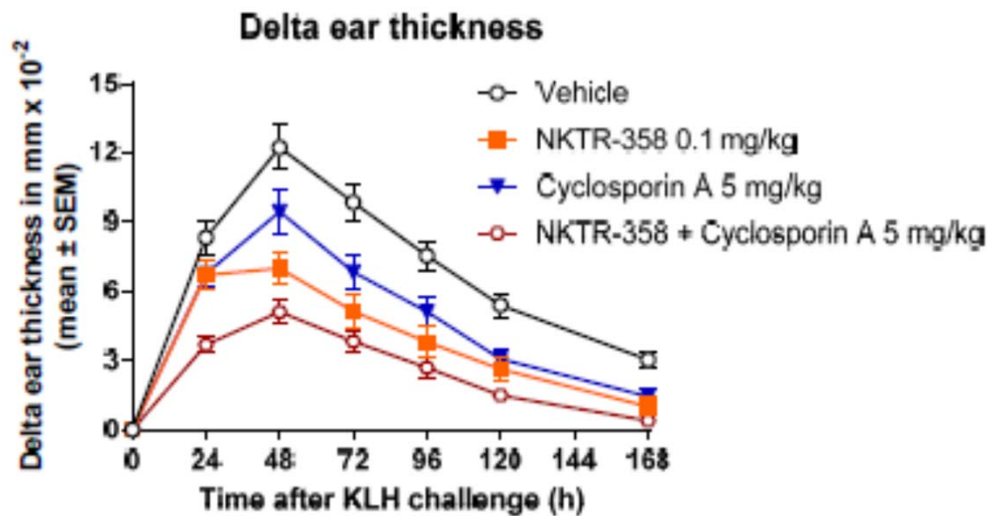
NKTR-358 Promotes Treg Infiltration in Mouse DTH



* $p < 0.05$, **** $p < 0.0001$ vs Vehicle w.r.t. same timepoint
One-way ANOVA (Bonferroni's post-test)

$p < 0.001$, unpaired t-test vs Vehicle w.r.t. same timepoint

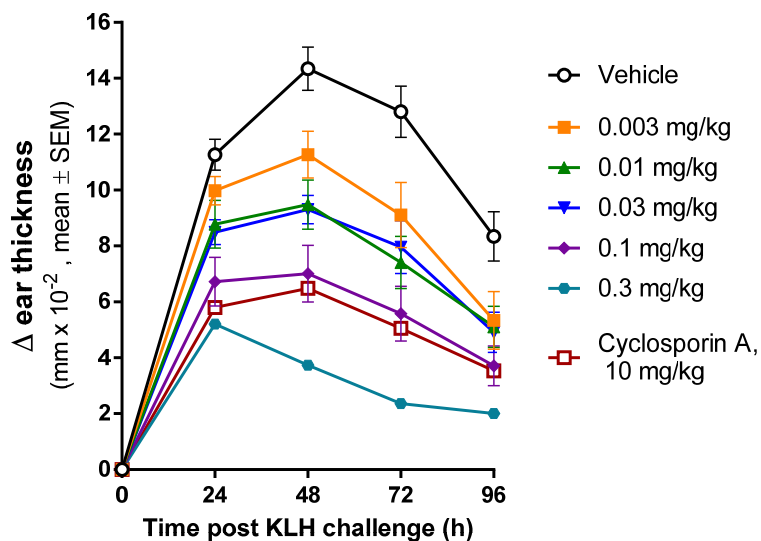
Combination of NKTR-358 + Anti-Inflammatory: Synergy of Non-Overlapping MOAs



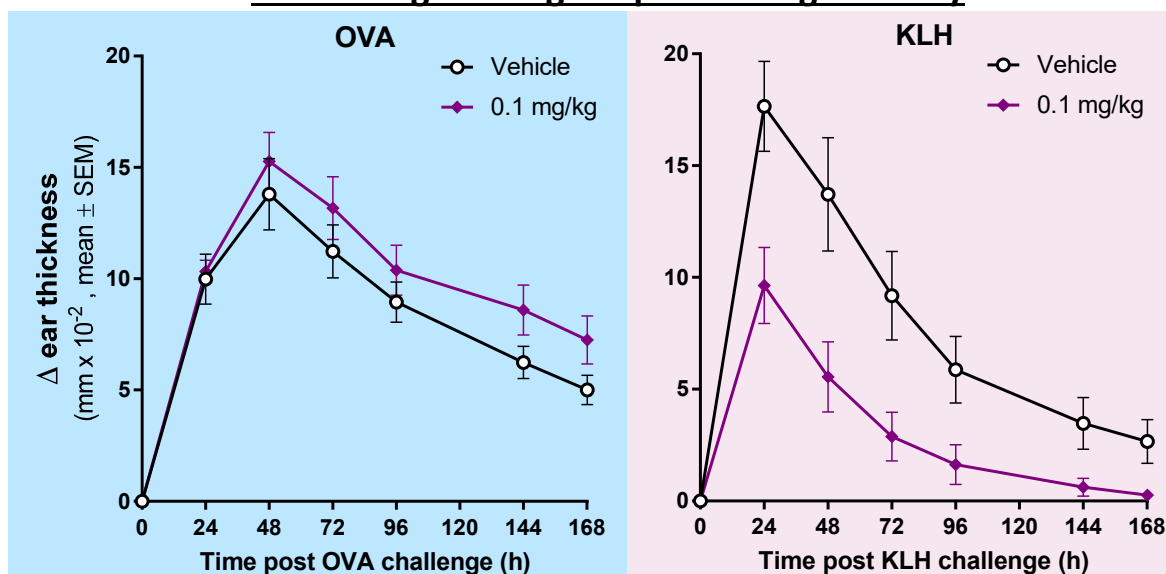
NKTR-358 Promotes Antigen-Specific Treg Memory



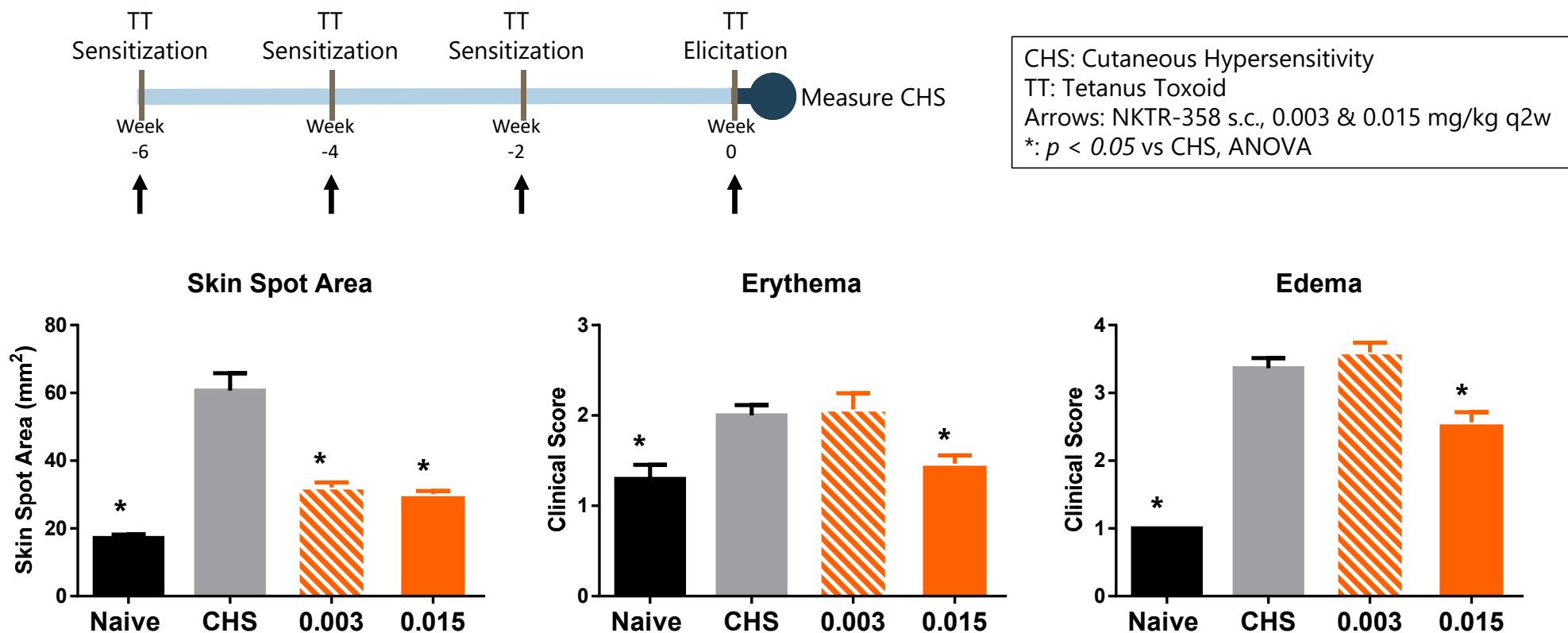
Primary efficacy



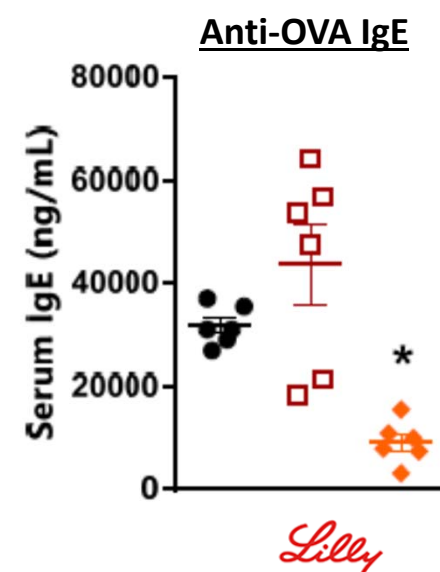
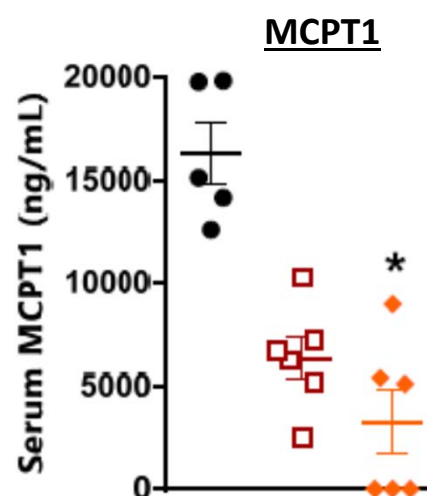
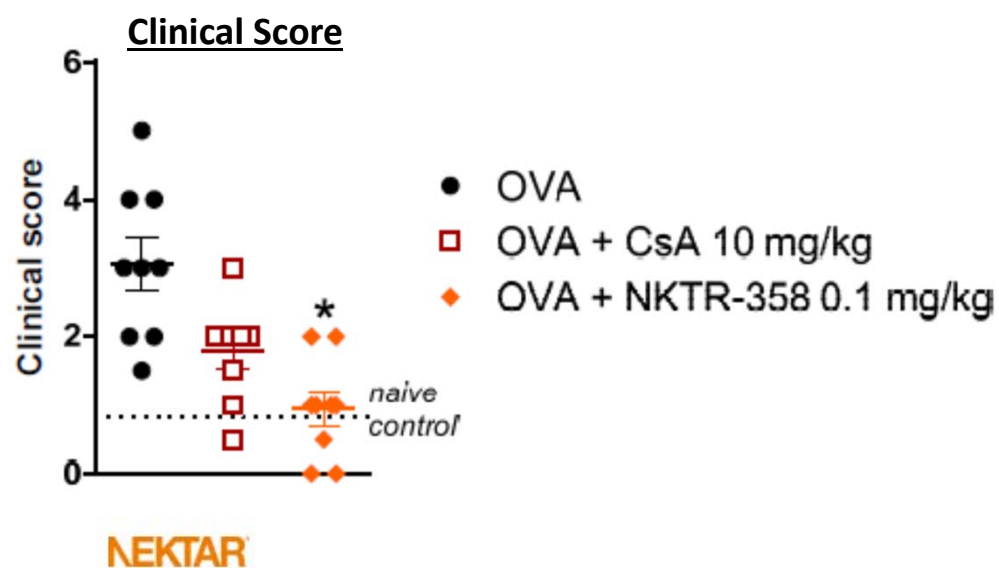
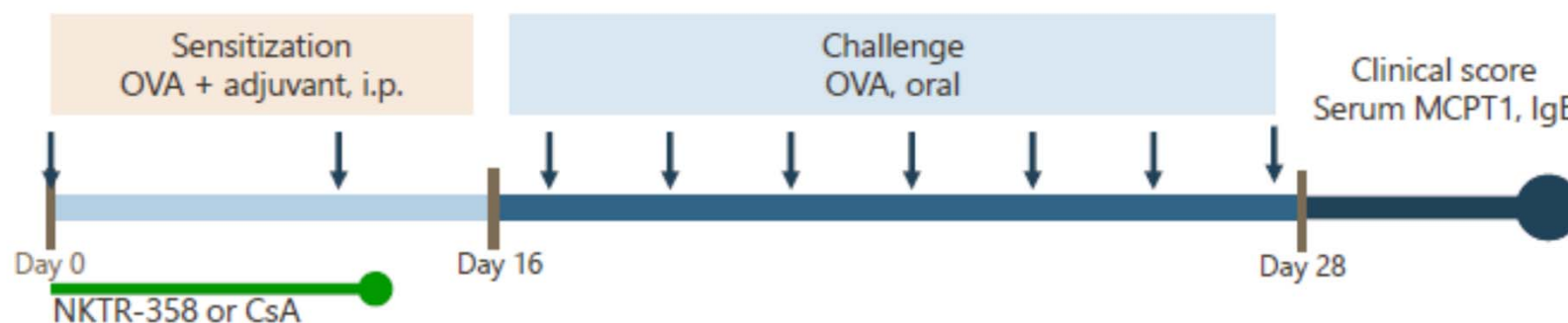
Rechallenge : Antigen-specific Treg memory



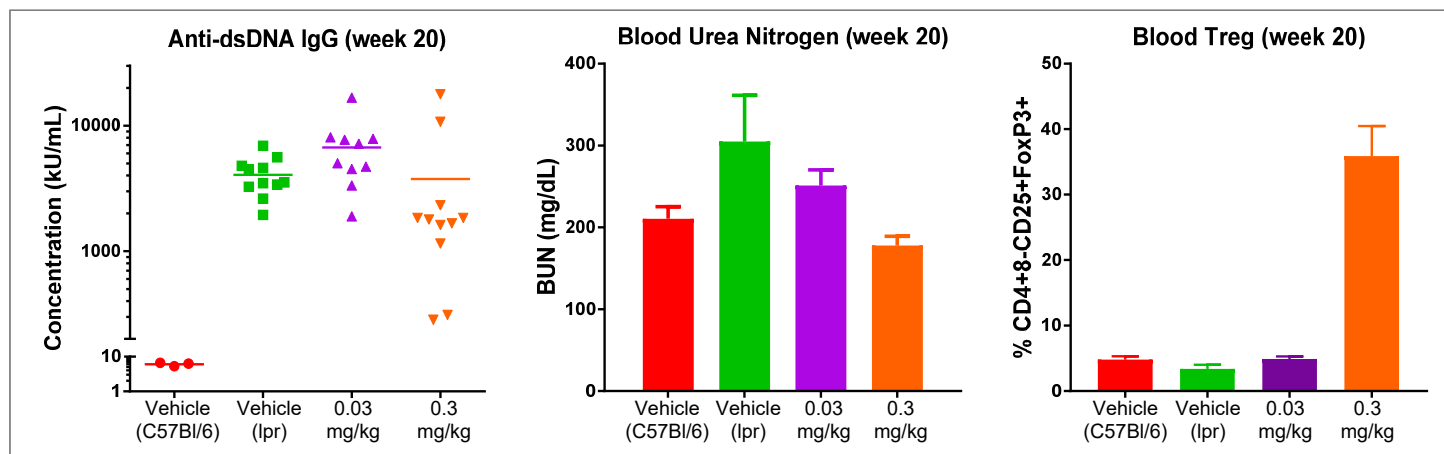
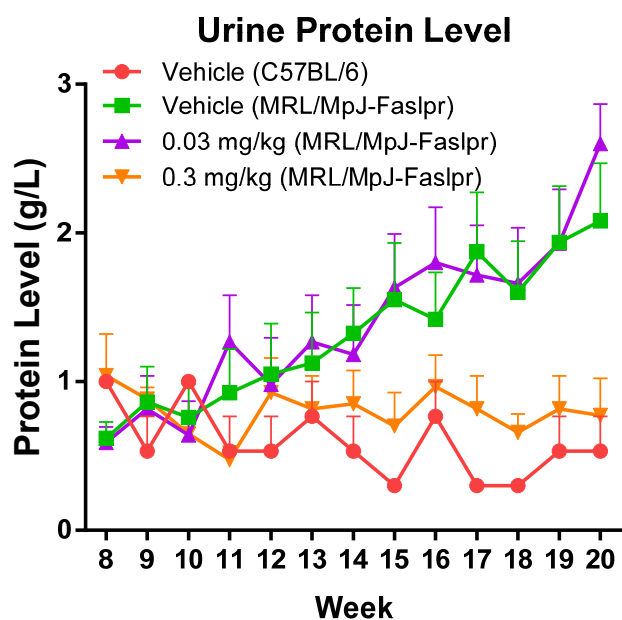
NKTR-358 Suppresses Inflammation in Monkey DTH



NKTR-358 Efficacy in OVA-Induced Food Allergy in Mice



NKTR-358 Efficacy in Mouse SLE



- NKTR-358 demonstrated dose-dependent efficacy on multiple parameters in mouse SLE
- 0.3 mg/kg (q3d, week 8-20) reduces urine protein and blood urea nitrogen to naïve mouse parameters
- Efficacy is consistent with Treg elevation

Development Status of NKTR-358

- Phase I Single Ascending Dose trial initiated March 2017
 - Primary readouts are Treg mobilization and activity, Treg/Tcon selectivity ratio, PK and safety
- Phase I Multiple Ascending Dose trial in SLE Patients initiated May 2018
 - Primary readouts are Treg mobilization, Treg/Th17 ratio, B cell analysis, SLE biomarkers, disease activity
- Nektar and Lilly plan multiple indications in Phase II

Summary of NKTR-358

- NKTR-358 is an immune-regulatory cytokine drug being developed by Nektar and Lilly that induces profound Treg effects
 - Greater magnitude of total Treg cell increase than IL-2
 - Highly selective for Tregs with limited effects on non-Treg cells
 - Increased Treg suppressive capacity and induction of long-lived Treg memory
 - Prolonged activation and proliferation of Treg in higher species
- Clinical development ongoing for the treatment of autoimmune and chronic inflammatory indications