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

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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

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Design and Discovery of NKTR-358

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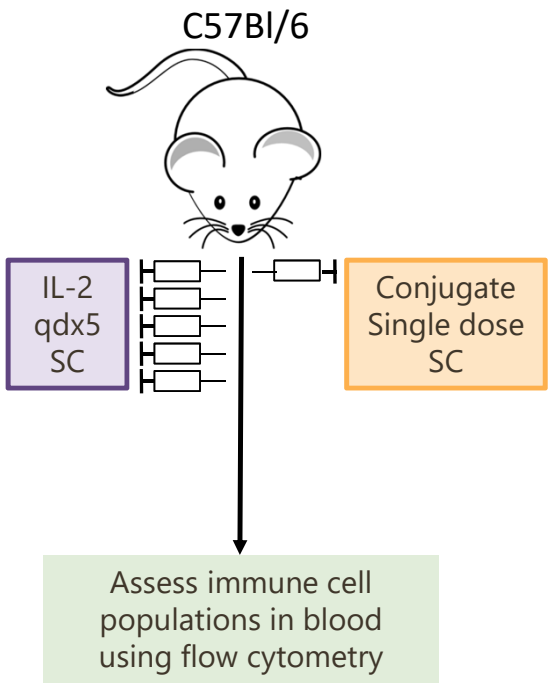
NKTR-358 was Discovered by In Vivo Screening



- 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

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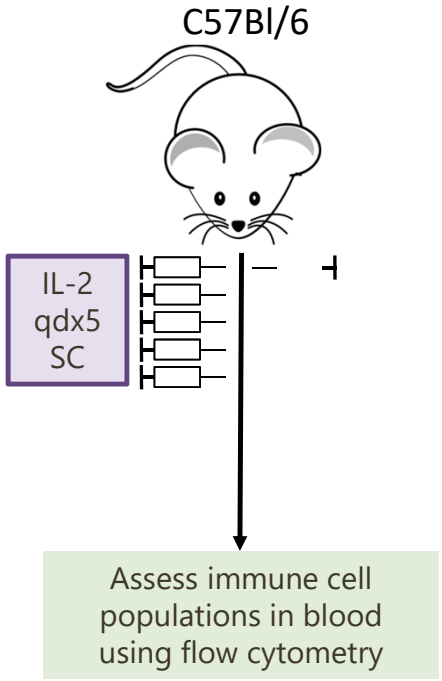
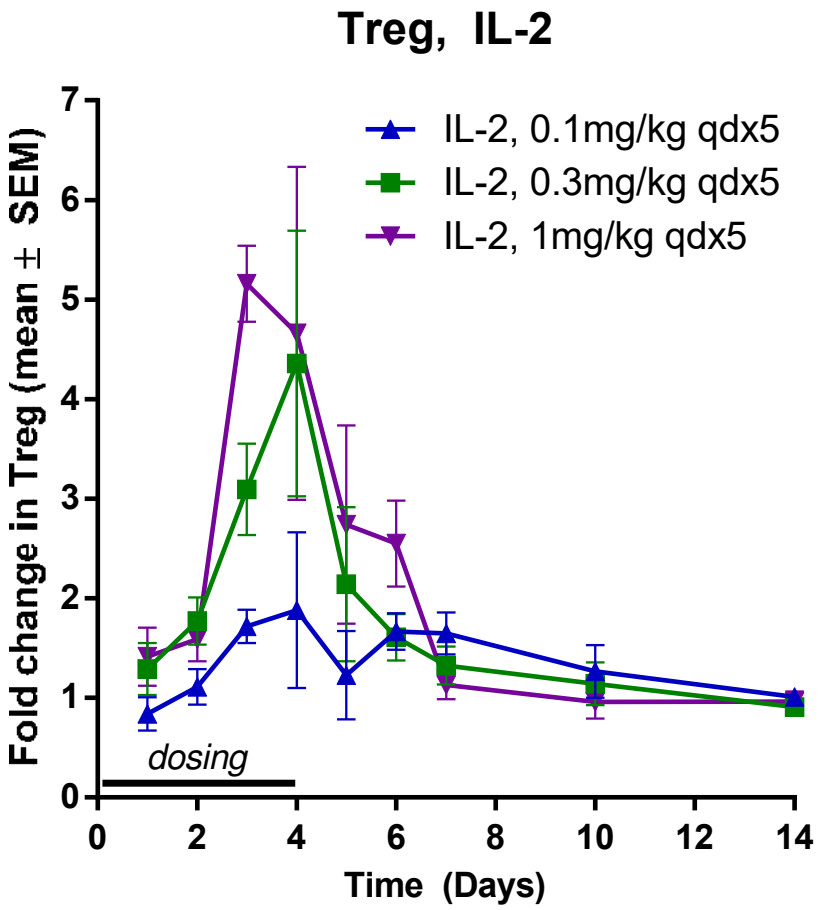
Calibrating the System with Native IL-2





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

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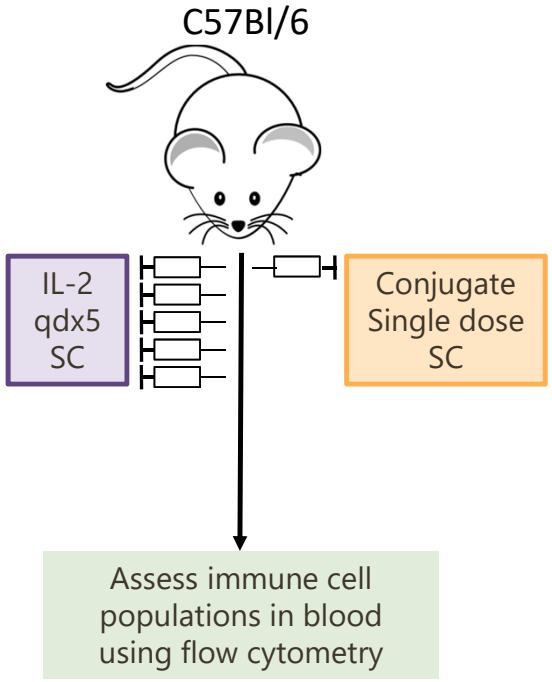
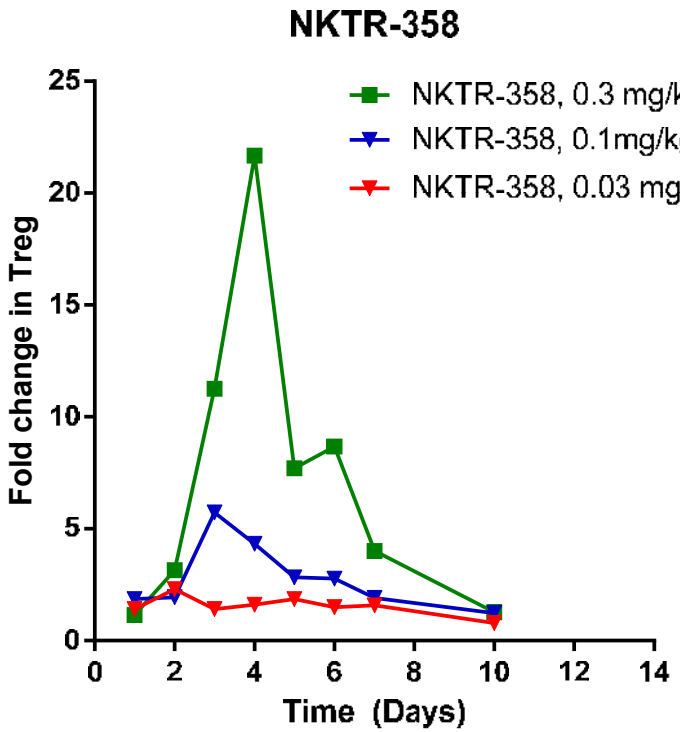
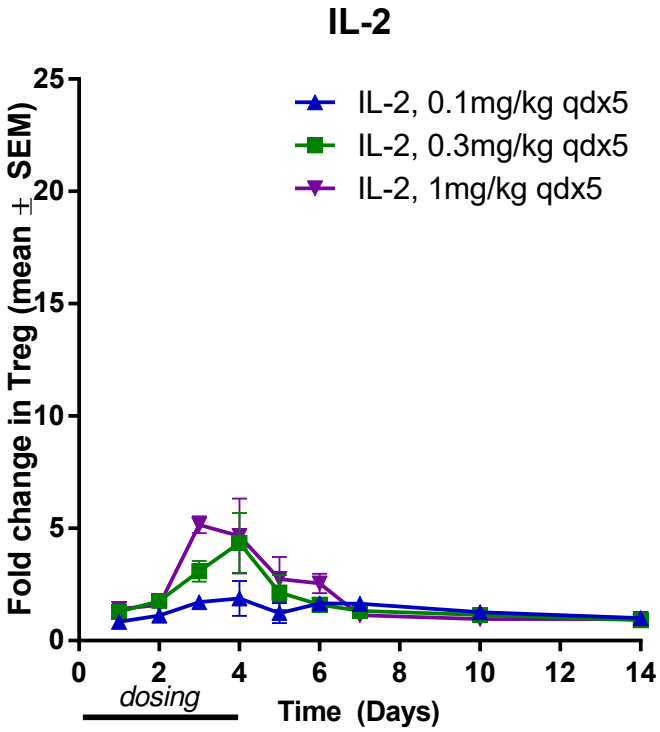
Comparison of NKTR-358 and IL-2 by In Vivo Screening







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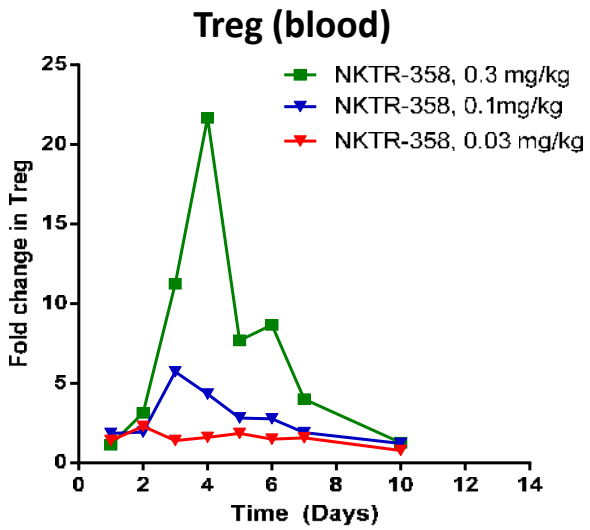
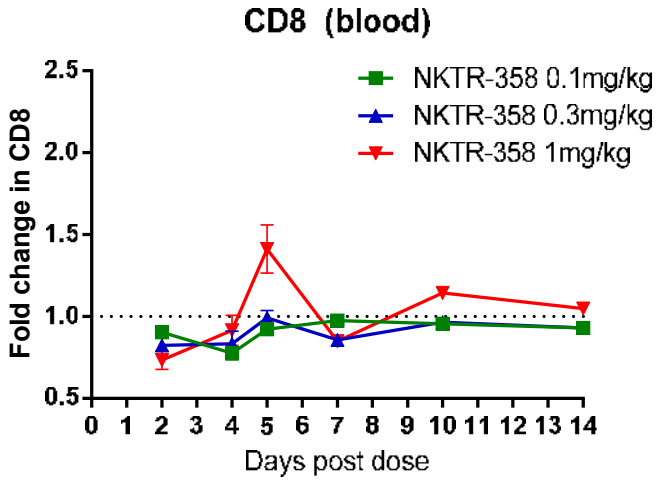
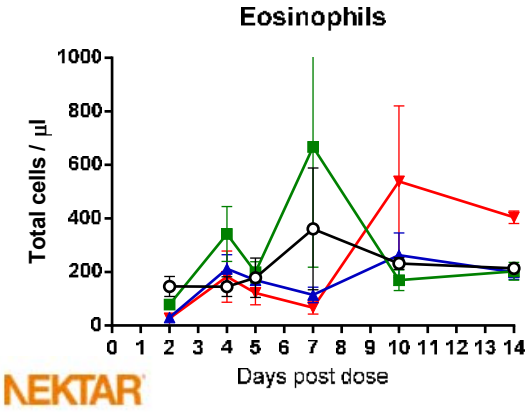
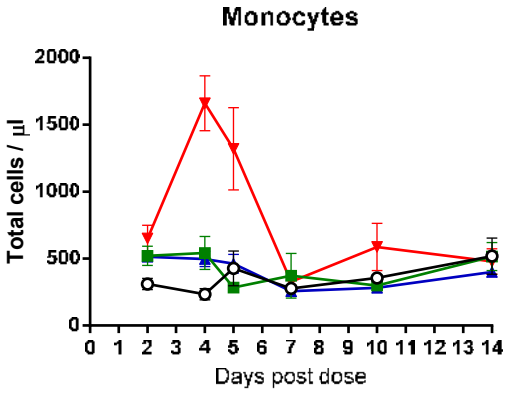
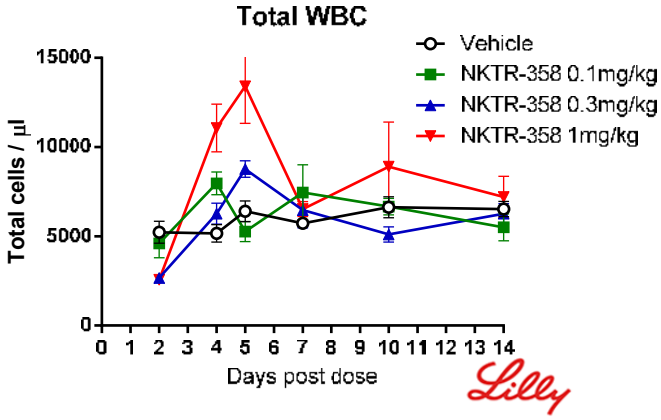
NKTR-358 is Selective for Treg Populations











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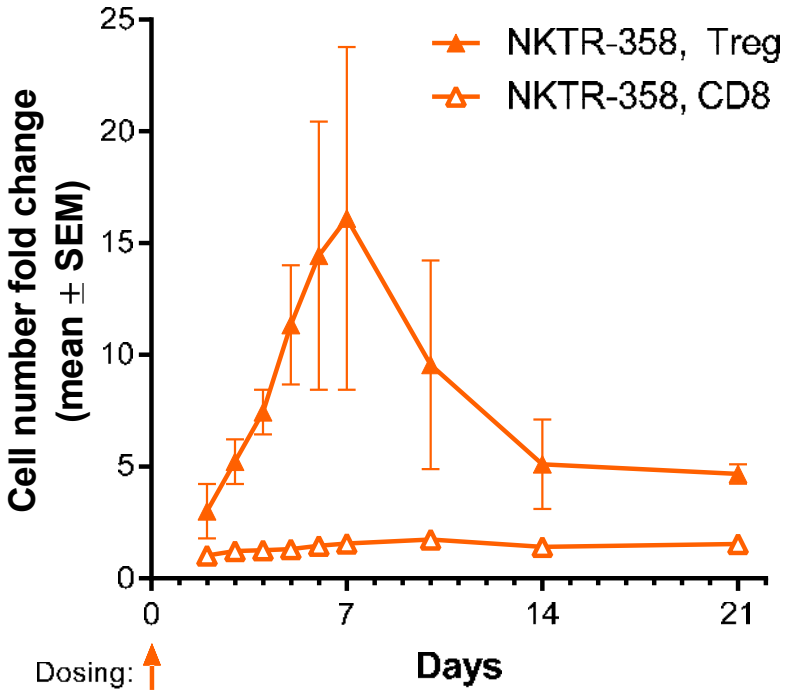
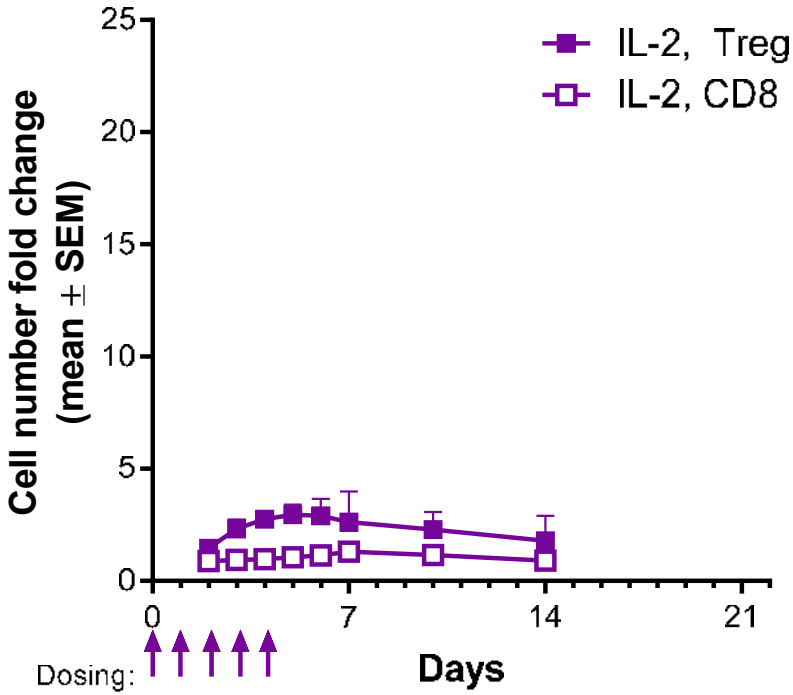
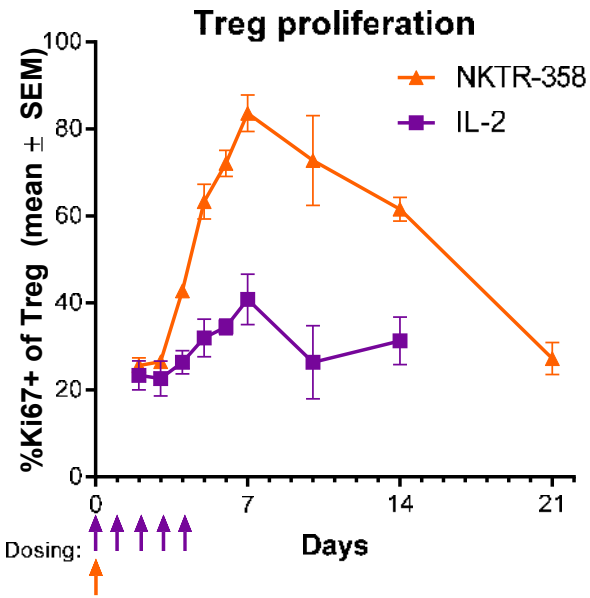
NKTR-358 Preferentially Expands Tregs in Monkeys

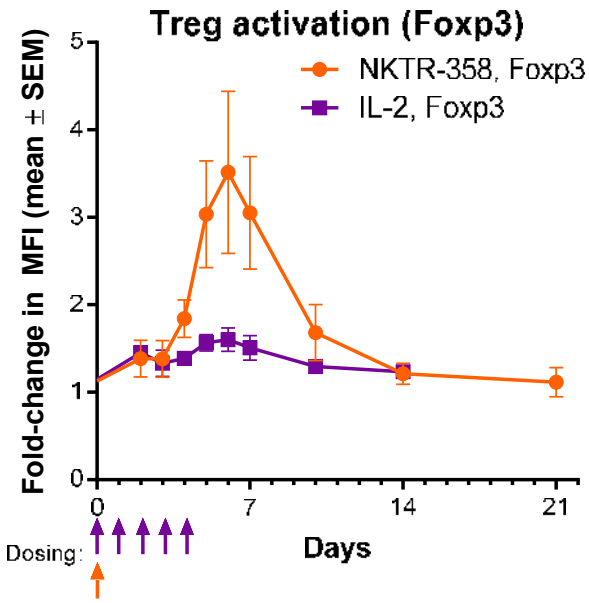


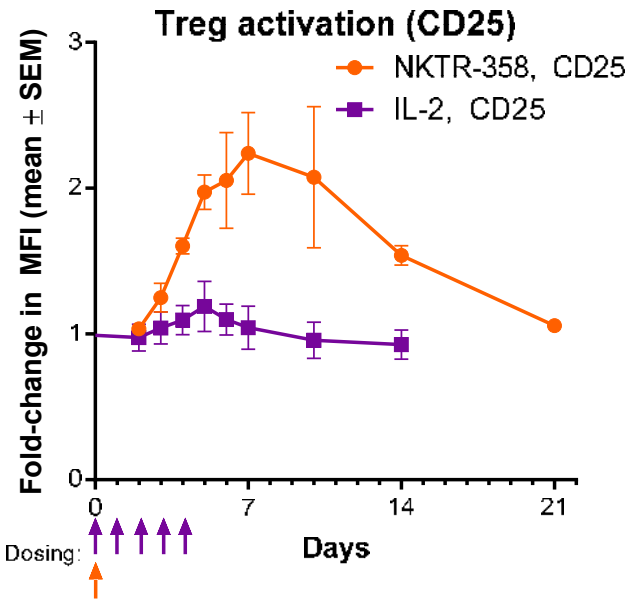


Cynomolgus monkey : 1M + 1F
25µg/kg : NKTR-358 single dose *vs.* qdx5 for IL-2

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

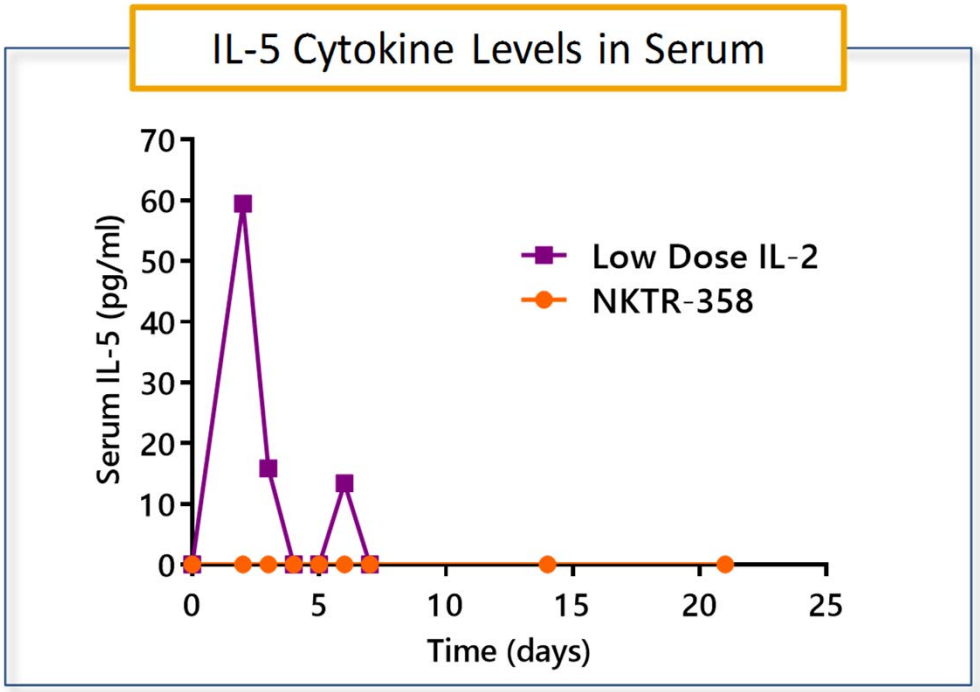


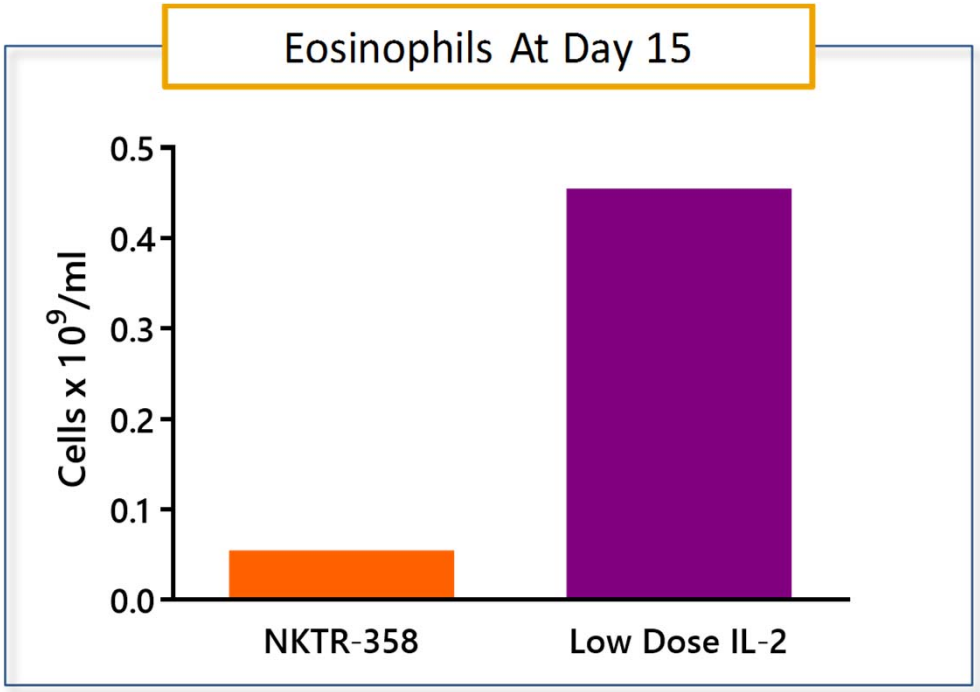




Cynomolgus monkey : 1M + 1F
25µg/kg : NKTR-358 single dose *vs.* qdx5 for IL-2

NKTR-358 Does Not Increase Eosinophil Levels in Monkeys





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

Molecular Pharmacology Characterization of NKTR-358

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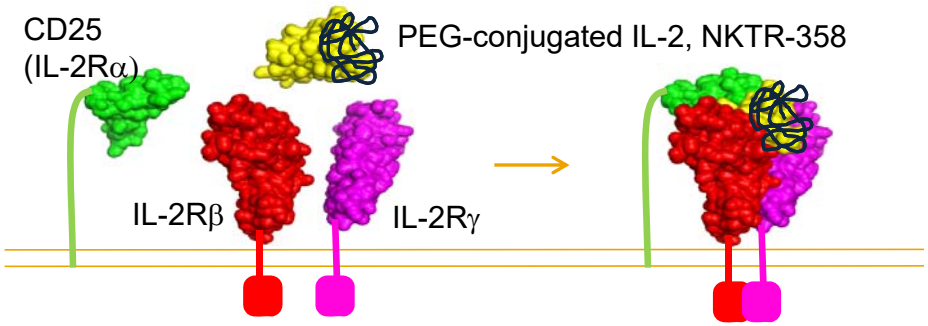
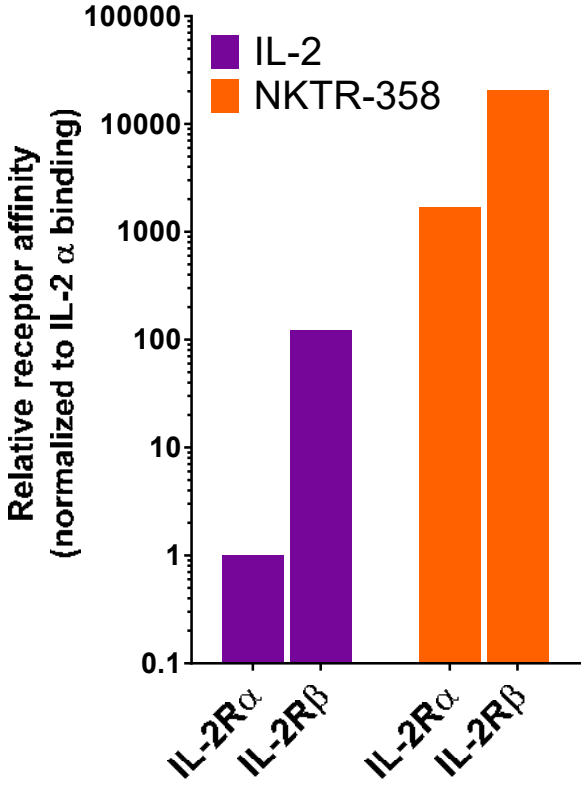
NKTR-358 has Attenuated Affinity to IL-2 Receptors



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

Receptor Binding



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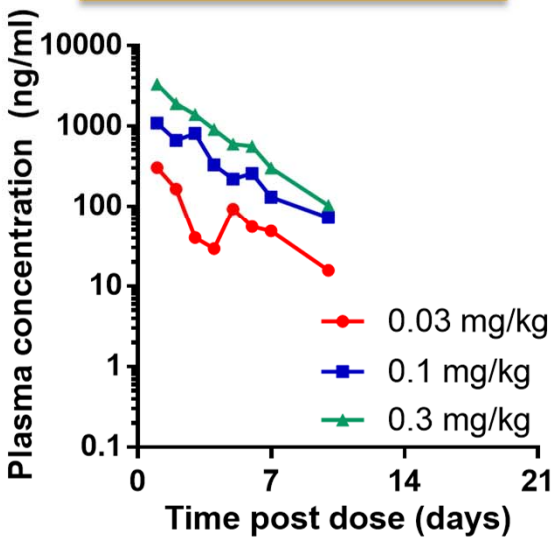
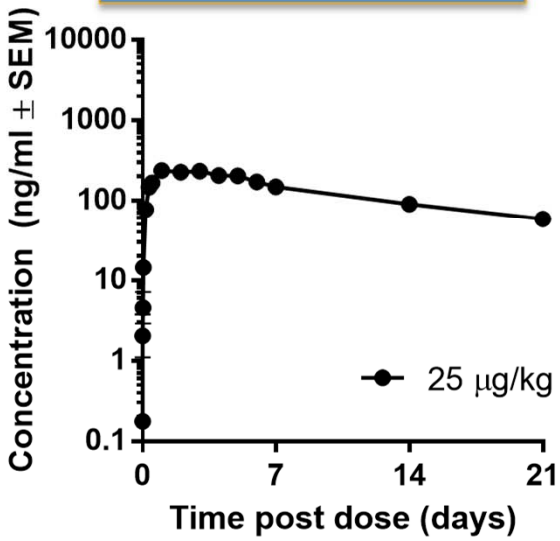
NKTR-358 PK After Subcutaneous Administration to Mouse and Monkey

Mouse



Monkey



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

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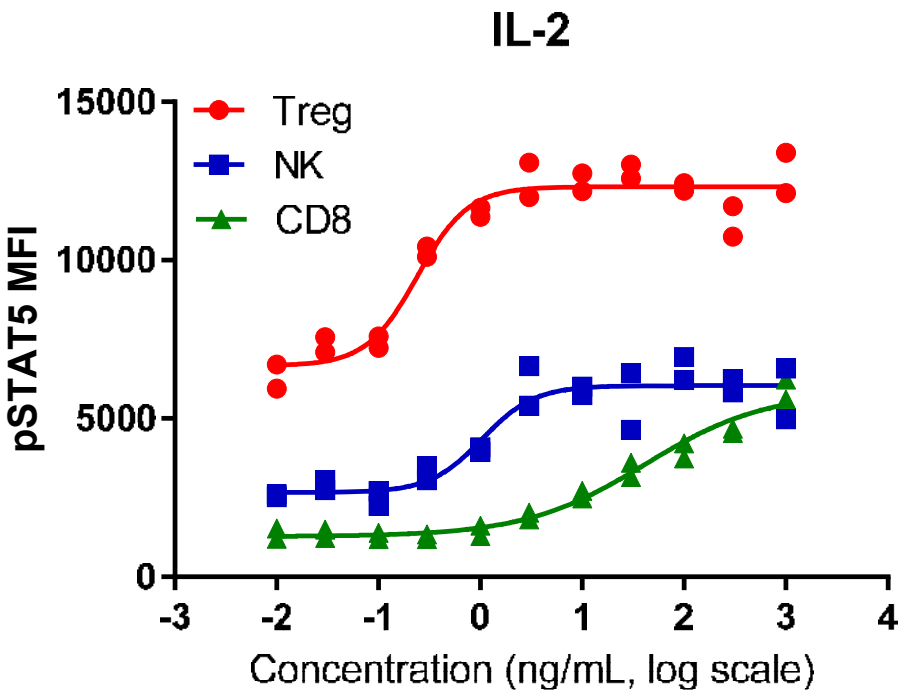
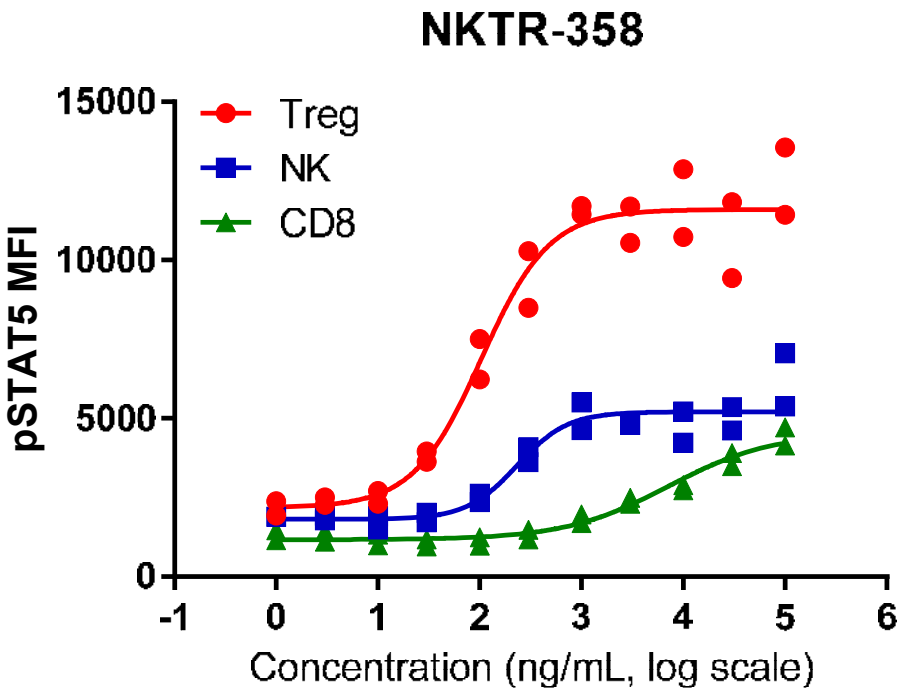
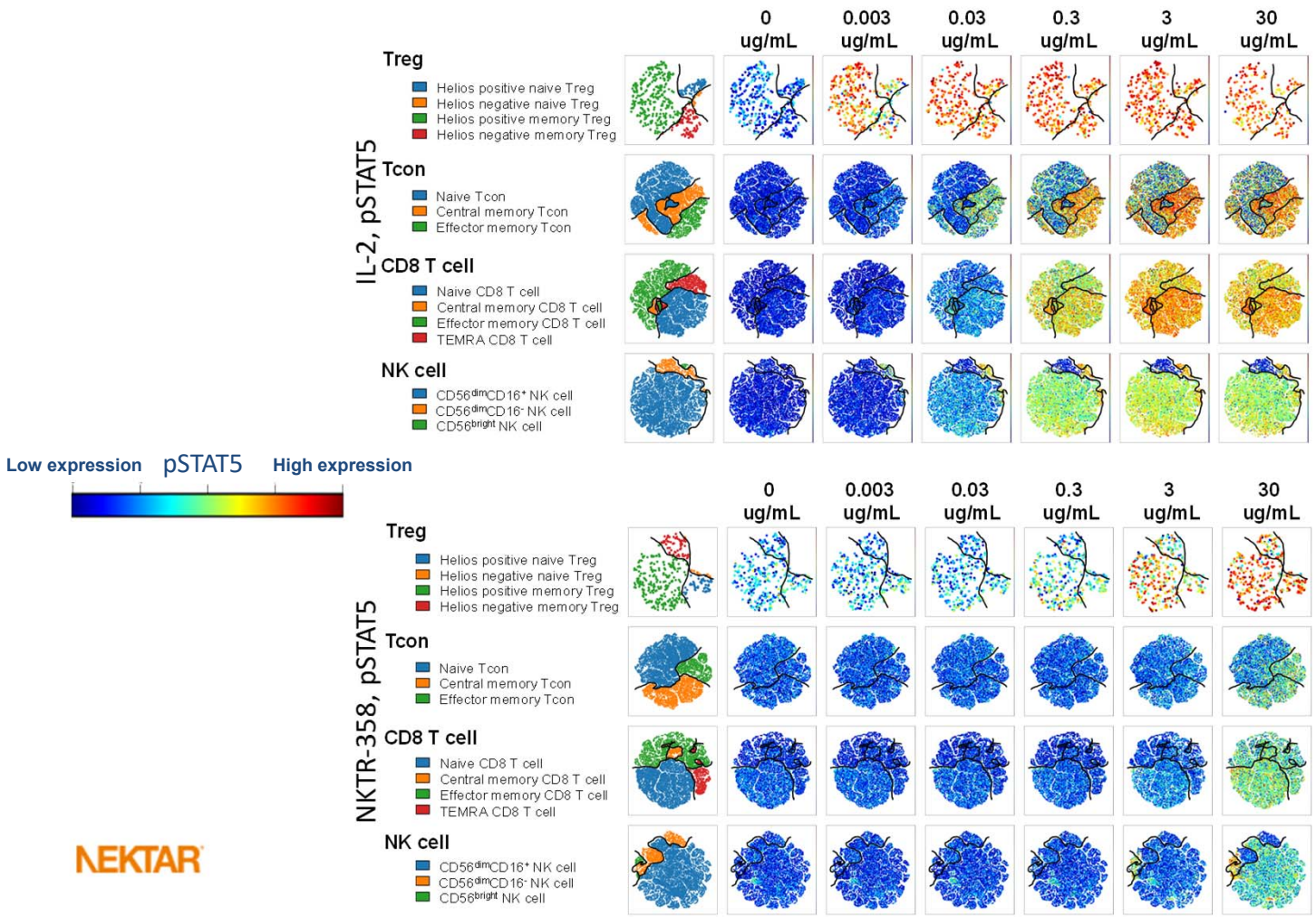
NKTR-358 Favors Activation of Treg Over Tcon





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)

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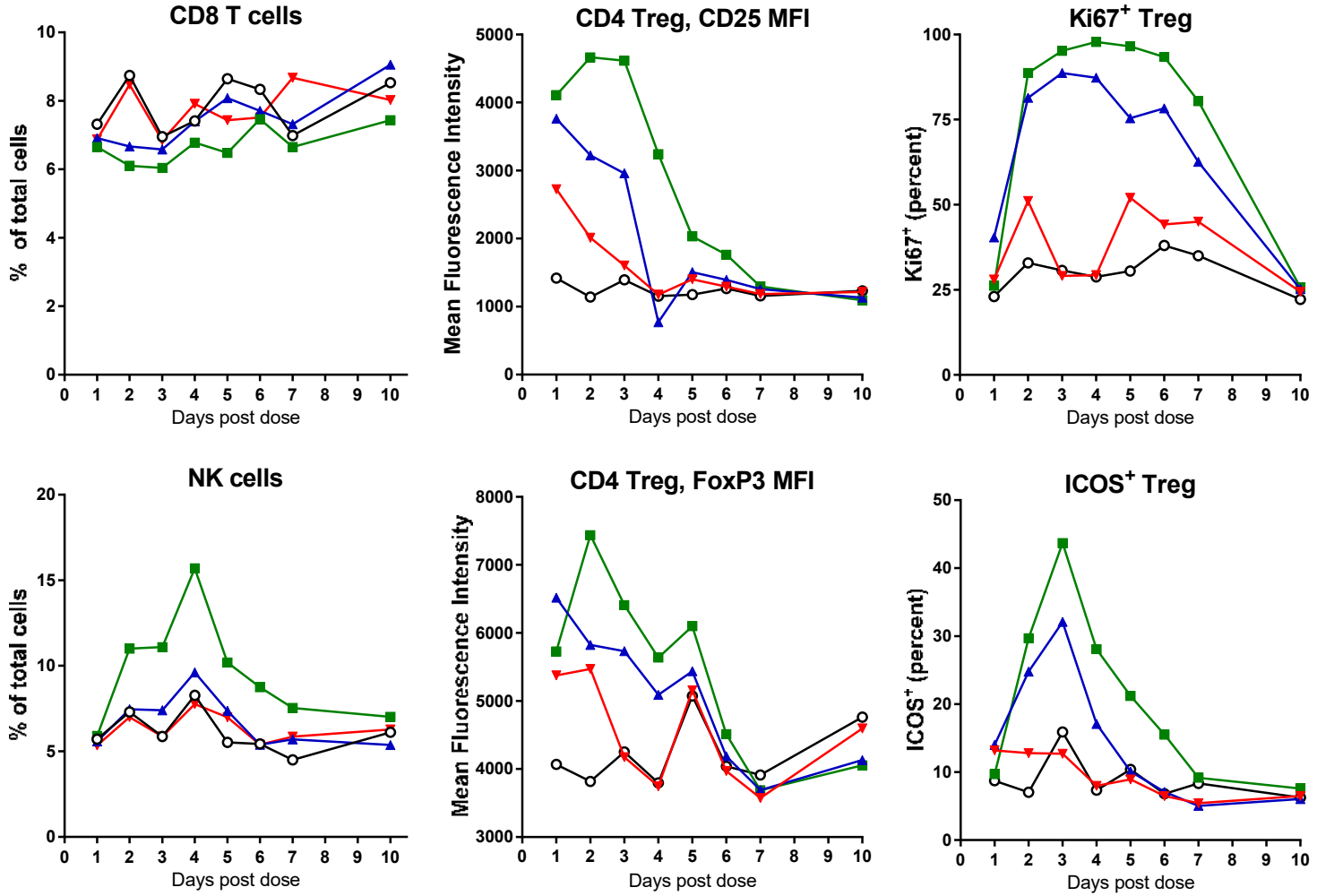
NKTR-358 Promotes Selective Treg Activation In Vivo



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

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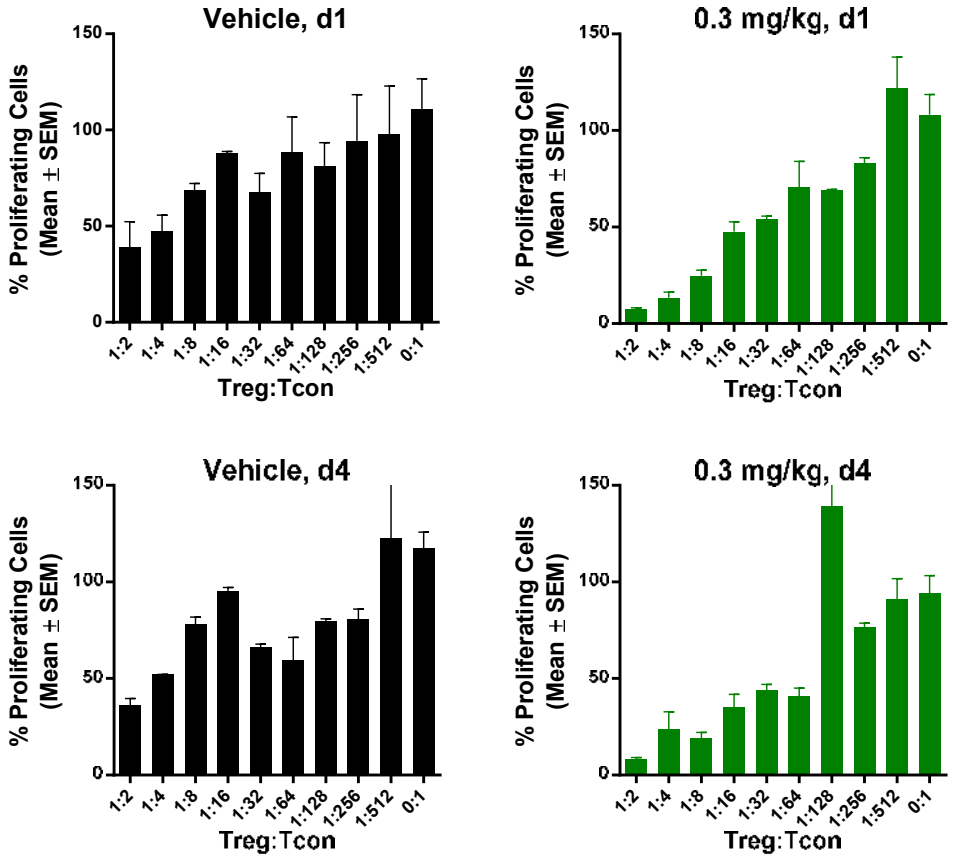
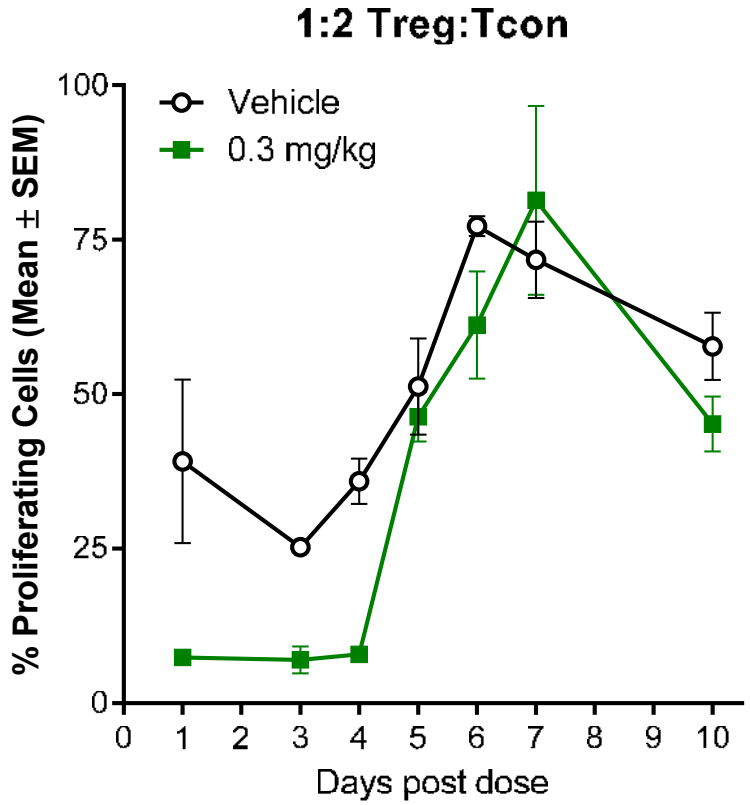
NKTR-358 Promotes Treg Suppressive Function In Vivo





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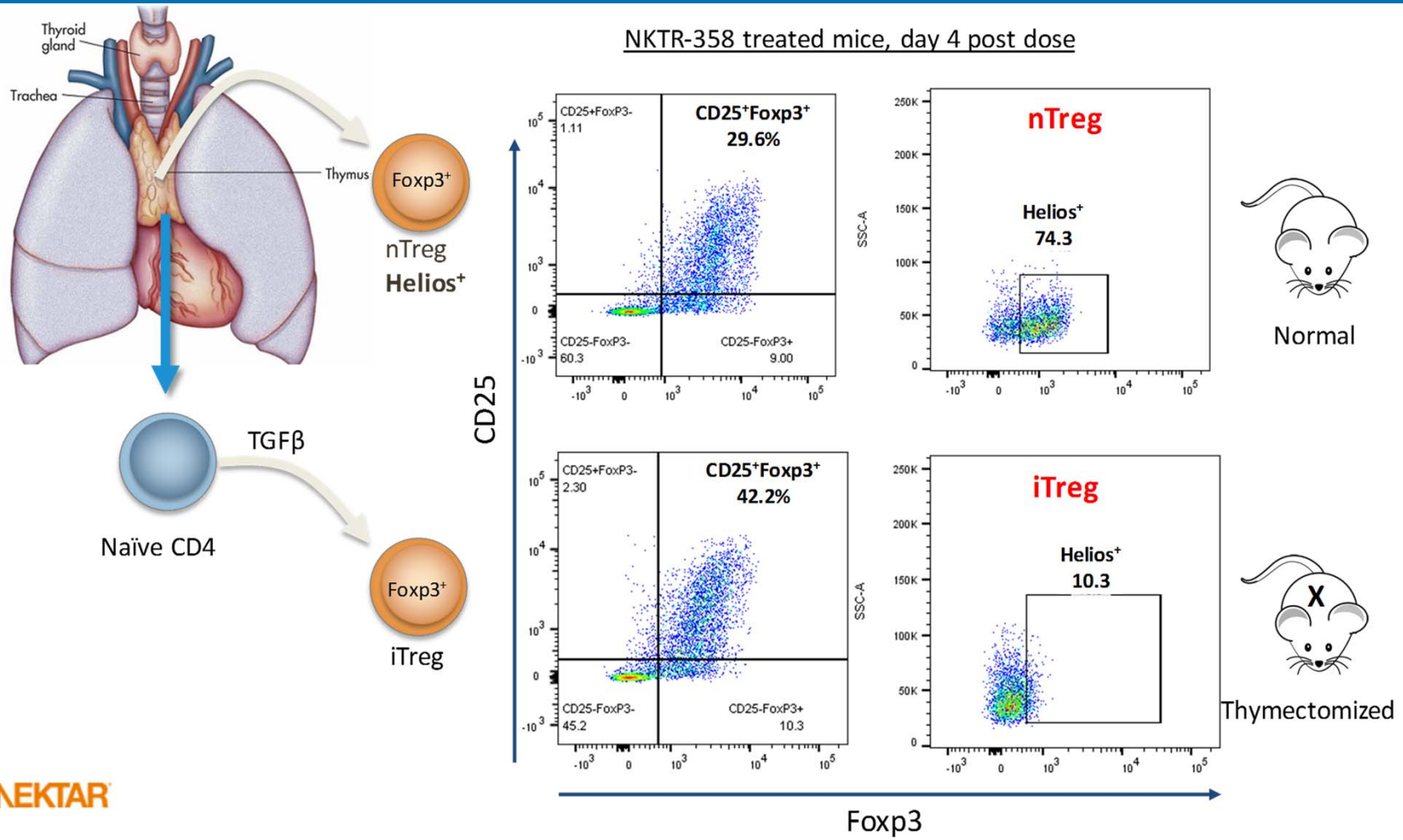
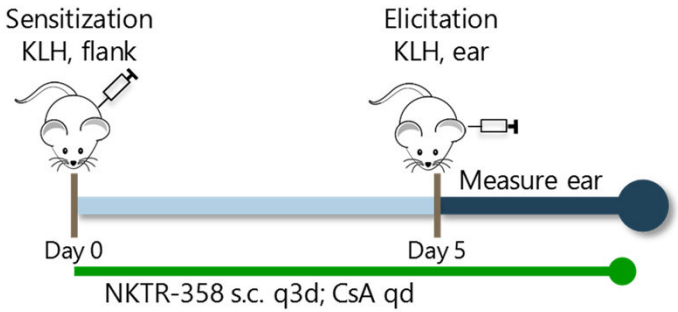
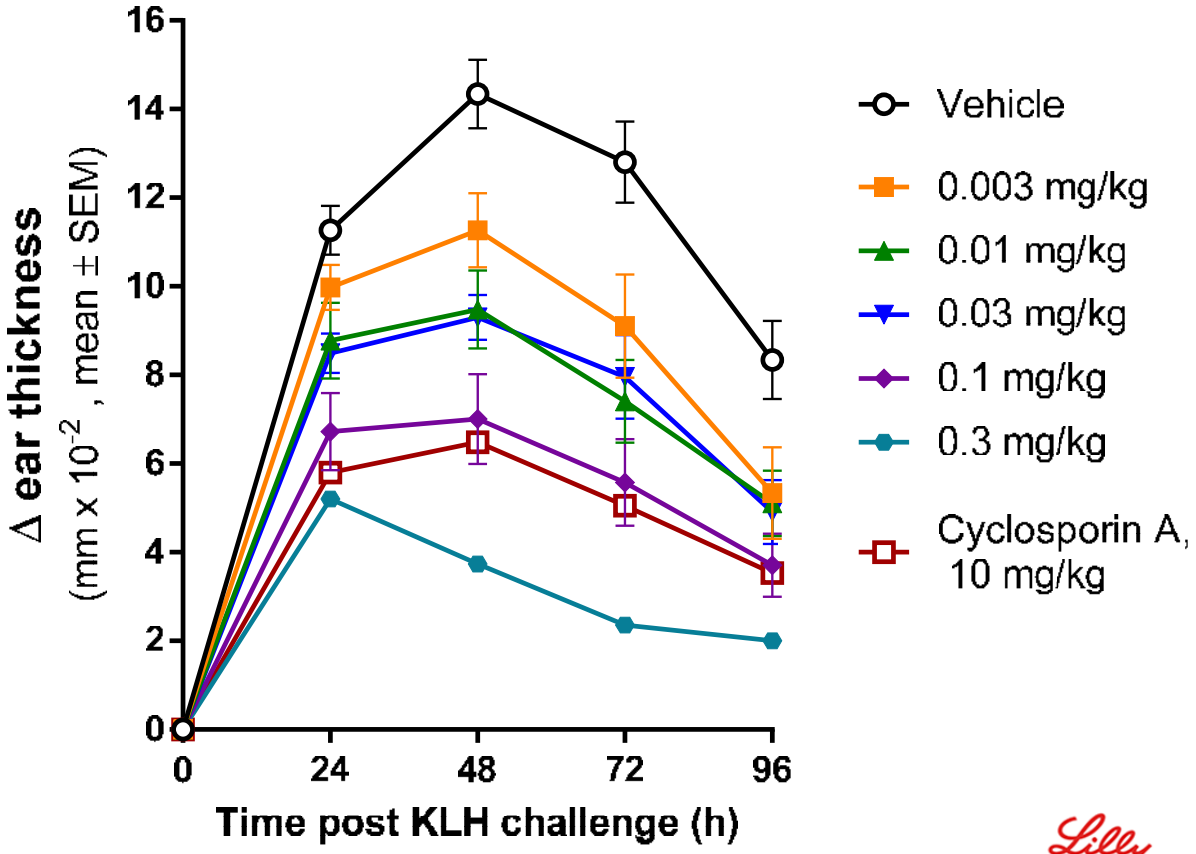
NKTR-358 Expands Both nTreg and iTreg Populations In Vivo



NKTR-358 Suppresses Inflammation in Mouse DTH





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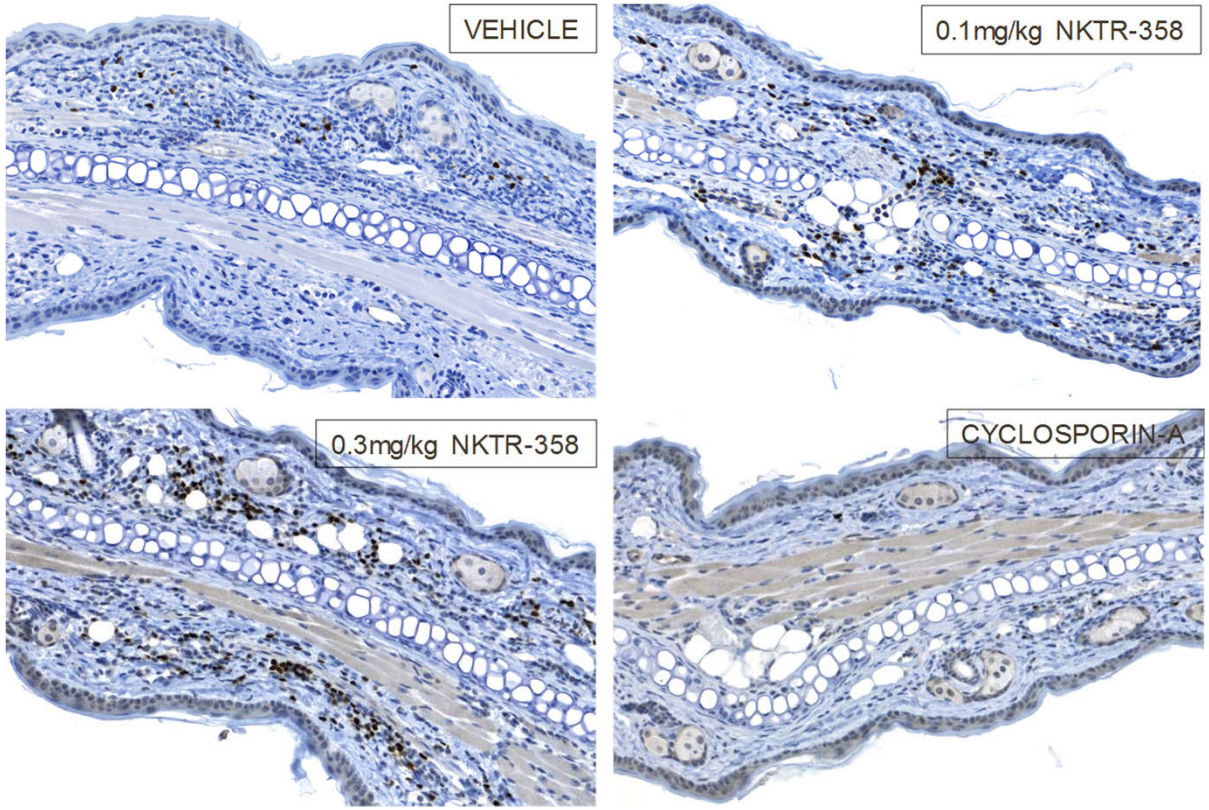
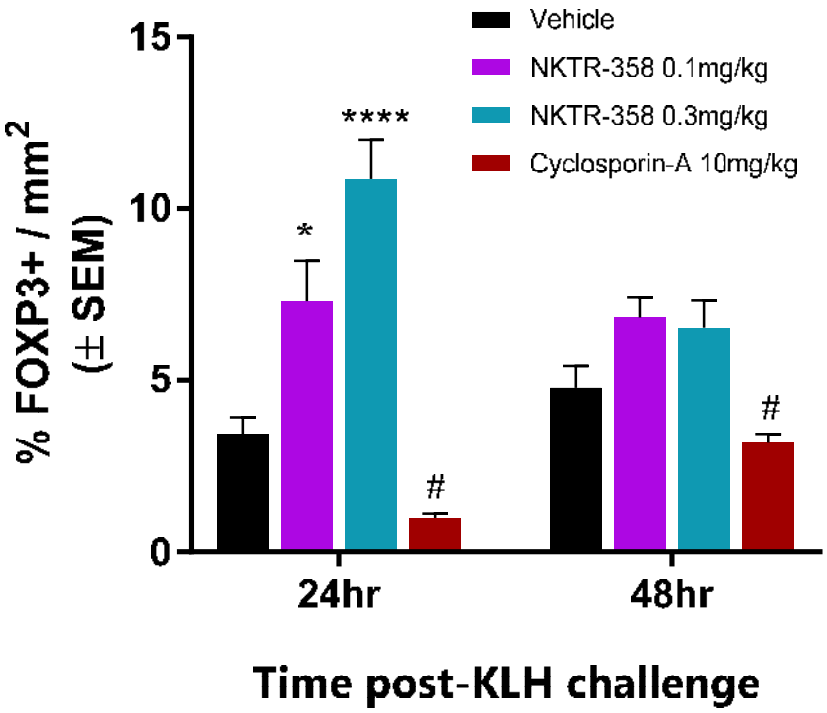
NKTR-358 Promotes Treg Infiltration in Mouse DTH





*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

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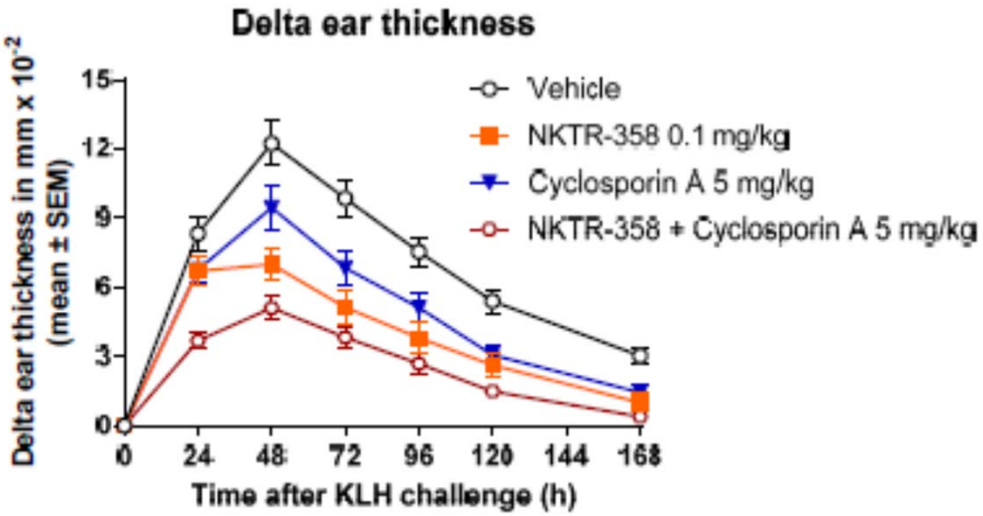
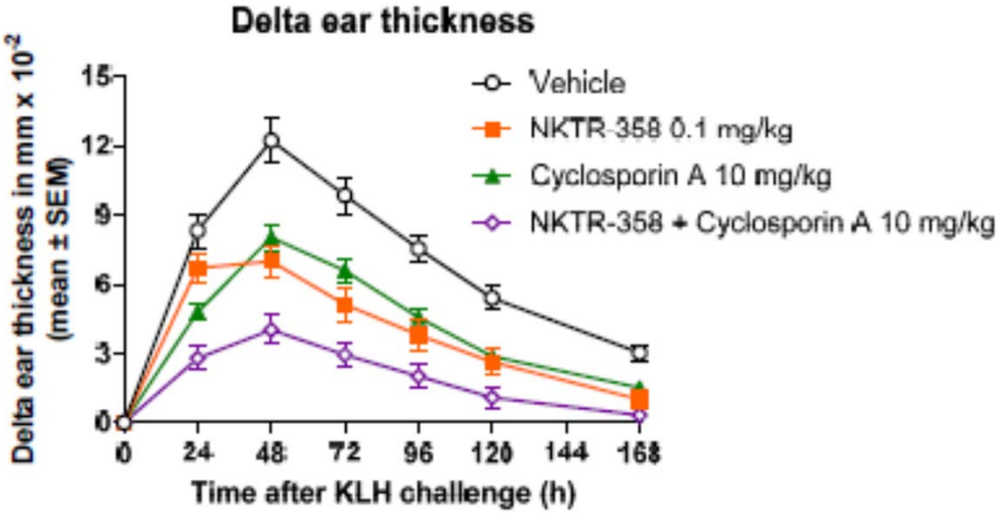
Combination of NKTR-358 + Anti-Inflammatory: Synergy of Non-Overlapping MOAs





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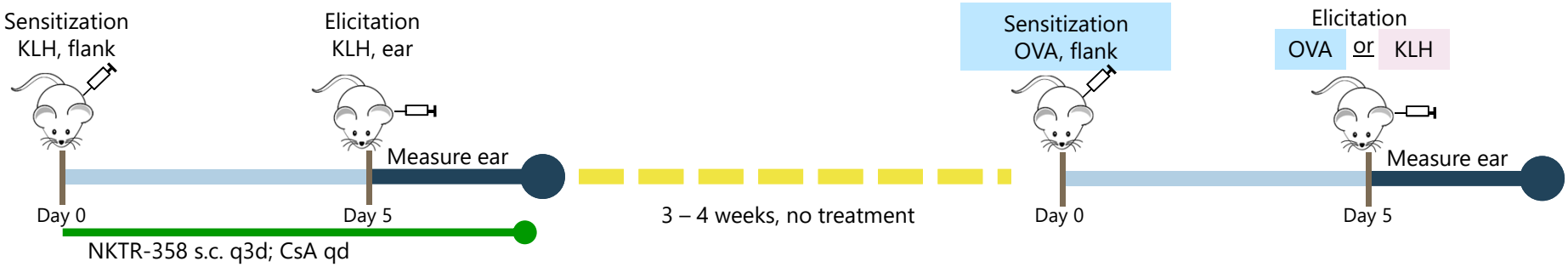
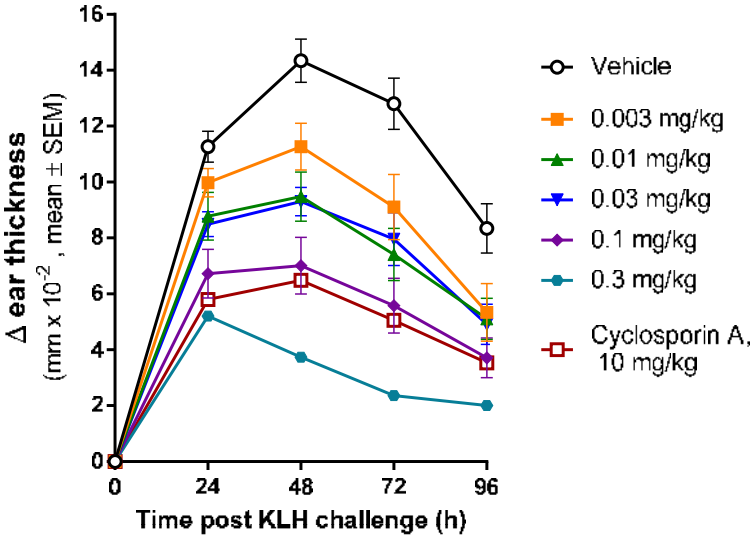
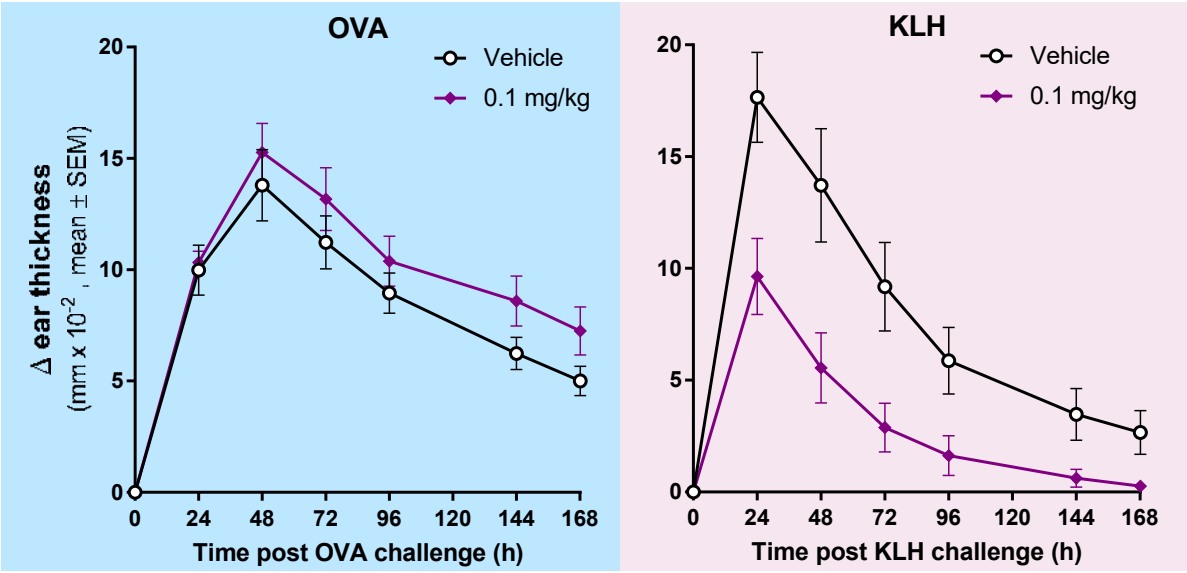
NKTR-358 Promotes Antigen-Specific Treg Memory



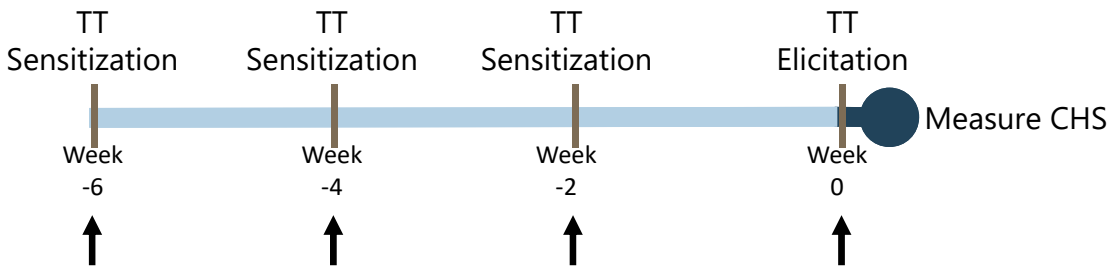
Primary efficacy



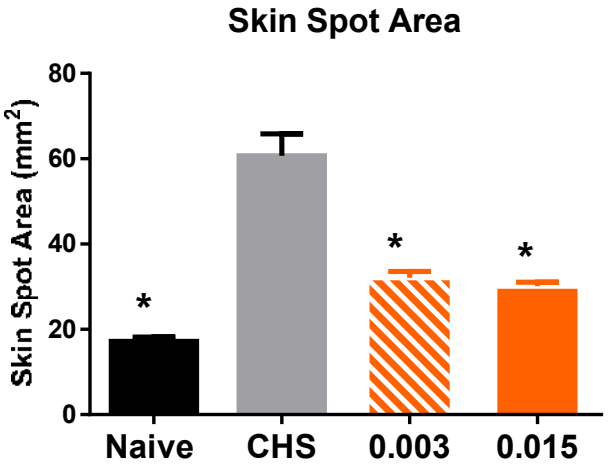
Rechallenge : Antigen-specific Treg memory

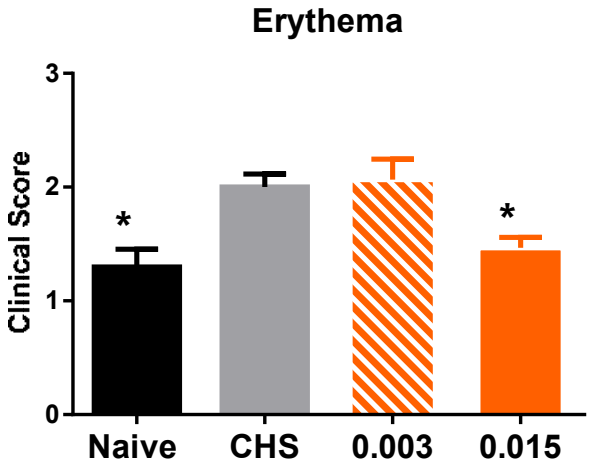


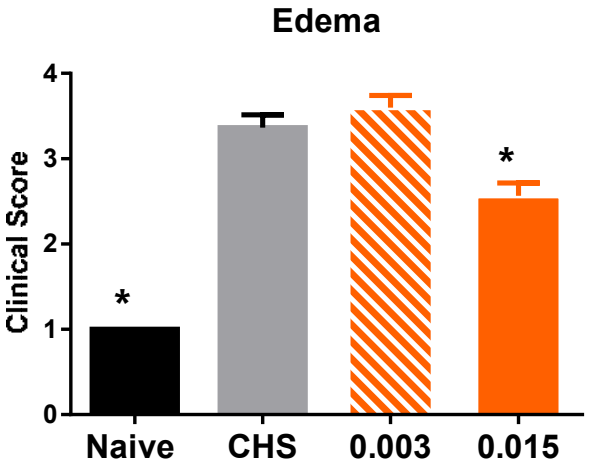
NKTR-358 Suppresses Inflammation in Monkey DTH



CHS: Cutaneous Hypersensitivity
TT: Tetanus Toxoid
Arrows: NKTR-358 s.c., 0.003 & 0.015 mg/kg q2w
*: $p < 0.05$ vs CHS, ANOVA







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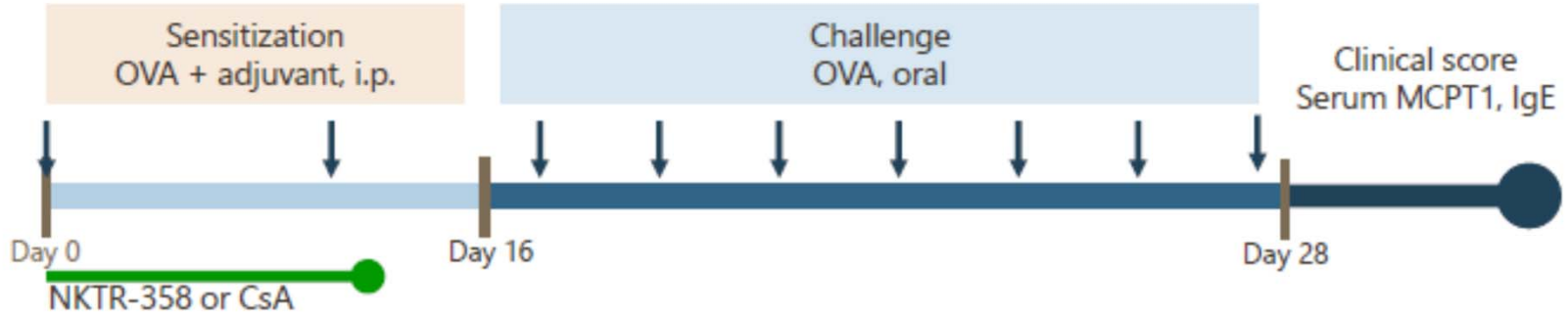
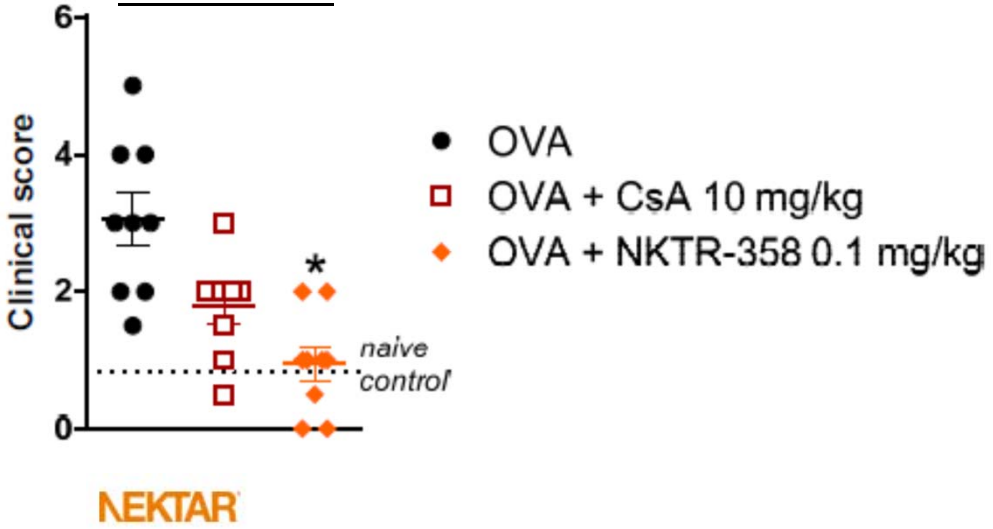
NKTR-358 Efficacy in OVA-Induced Food Allergy in Mice



Clinical Score



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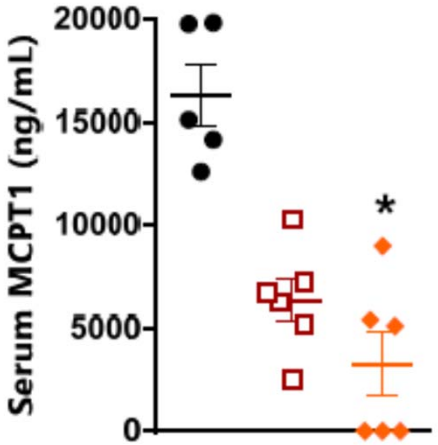
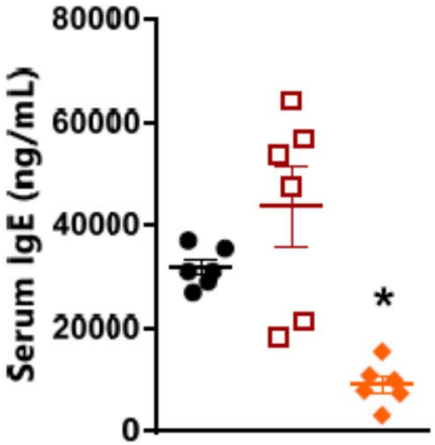
MCPT1



Anti-OVA IgE



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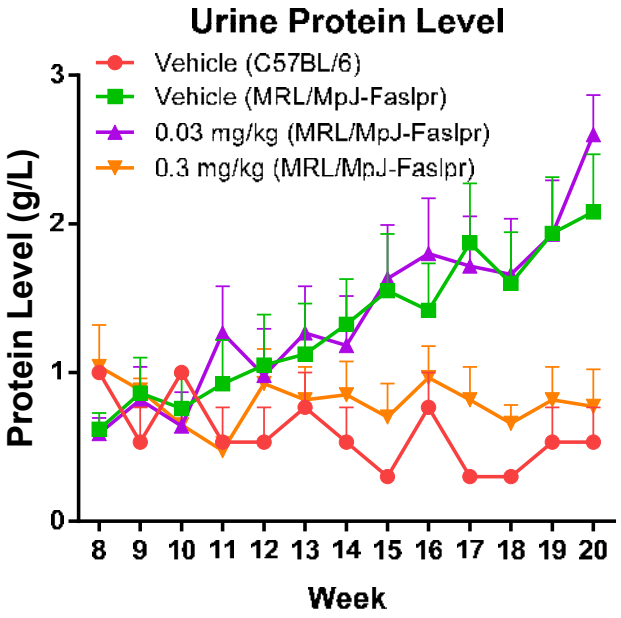
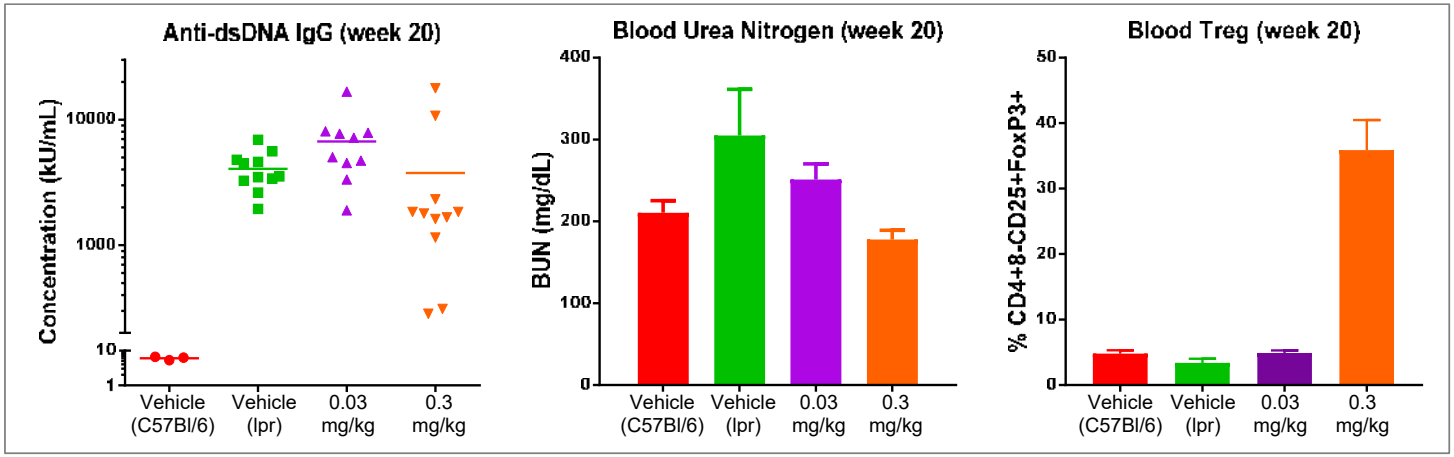
NKTR-358 Efficacy in Mouse SLE





- 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

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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

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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

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