THOR-707, A Novel Not-alpha IL-2, Elicits Durable Pharmacodynamic Responses in Non-human Primates and, Efficacy as Single Agent and in Combination with Anti PD-1 in Multiple Syngeneic Mouse Models

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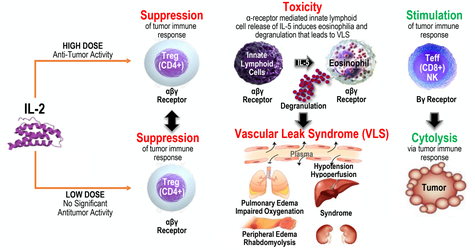
BACKGROUND

IL-2 Has A Low Therapeutic Index Due to Its Dual Pharmacology at the High Affinity αβγ and Intermediate Affinity βγ Receptor Forms



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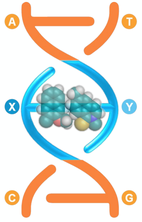
Novel Amino Acids Encoded By Our New DNA Base Pair Enable Optimization of Biologics



X-Y Enables

Site-Specific Bioconjugation

- Installation of a novel amino acid containing a dedicated chemical hook at a specific site
- Designed to bioconjugate moieties such as PEG for improved properties

Specificity

Improved selectivity through altered receptor binding

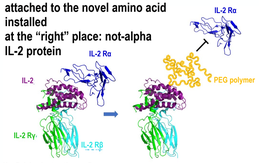
Polymer-Conjugates

- Increased half-life
- Epitope shielding through covalent PEG attachment via bio-orthogonal chemistry

THOR-707: IL-2 IO Synthorin

PEG-IL-2 Synthorin Properties

Single, stable PEG covalently attached to the novel amino acid installed at the "right" place: not-alpha IL-2 protein



IL-2 binds to the αβγ receptor form with high affinity because of α chain

Targeted pegylation of THOR-707 at the novel amino acid blocks α chain engagement

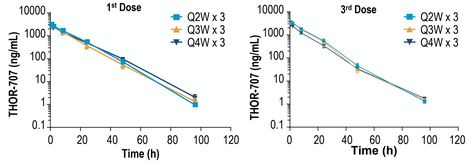
THOR-707's Key Differentiations

- **Improved Selectivity** - Reduced CD4+ Treg bias with retained activity at CD8+ T and NK cells
- **Increased Therapeutic Index** - At least 10 in preclinical non-human primate (NHP) studies
- **Ease of Use** - Expected Q2W dosing or less frequent
- **Reduced Risk of Immunogenicity** - Covalent attachment of stable PEG shields new amino acid; pegylation site devoid of MHC-II anchors

RESULTS

THOR-707 Plasma Exposure Is Sustained Upon Re-dosing in NHP

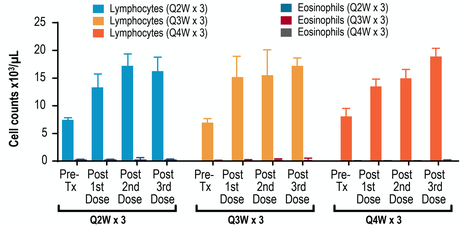
After three 0.1 mg/kg IV doses, THOR-707 PK parameters were similar between the 1st and 3rd dose



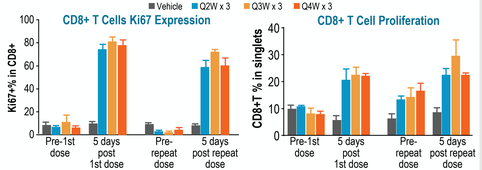
THOR-707 dosing schedule (N=3)	First Dose			Third Dose		
	C_{max}	AUC_{0-t} (ng*h/mL)	$t_{1/2}$ (h)	C_{max}	AUC_{0-t} (ng*h/mL)	$t_{1/2}$ (h)
Q2W	3190	46,300	7.88	3710	49,700	8.39
Q3W	3130	39,900	8.95	3870	46,500	14.3
Q4W	2890	42,300	8.94	2640	33,400	15.3

THOR-707 Dosed Q2, 3 and 4W Elicited Similar Expansion of Lymphocytes in NHP After Each Dose, With No Expansion of Eosinophils

- Cynomolgus monkeys were given three IV 0.1 mg/kg doses of THOR-707 Q2, 3 or 4W
- On all three dosing schedules, THOR-707 induced maximal lymphocyte expansion on day 7 following each dose without expanding eosinophils responsible for VLS



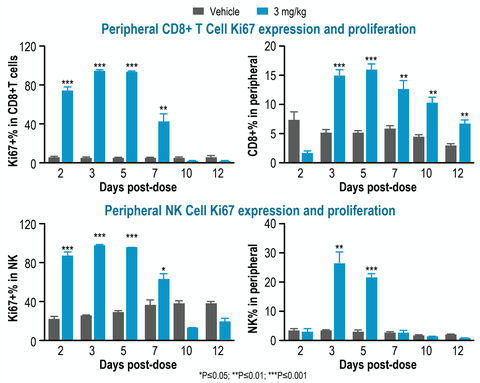
THOR-707 Dosed Q2, 3 & 4W Showed Similar Expansion of Peripheral CD8+ T Cells in NHP. Ki67 Expression Increased ≥60% After Each Dose



- Following each dose, Ki 67 expression reached ≥60% and correlated with expansion of CD8+ T Cells for all dosing schedules
- THOR-707 did not induce the proliferation of peripheral CD4+ regulatory T cells at any schedule utilizing this dose

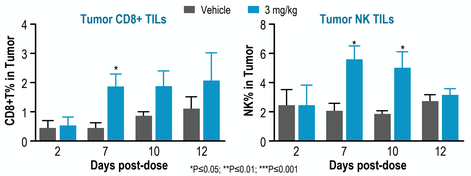
RESULTS

A Single 3 mg/kg IV Dose of THOR-707 Expands Peripheral CD8+ T and NK Cells, Increasing Ki67 Expression in CT-26 Tumor-bearing Mice



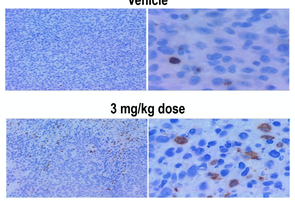
A Single 3 mg/kg IV Dose of THOR-707 Induces Sustained CD8+ T and NK Cell Infiltration in CT-26 Tumors in Mice

- CD8+ TILs continue to elevated by the end of the study on day 12
- THOR707 does not change Treg infiltration over time



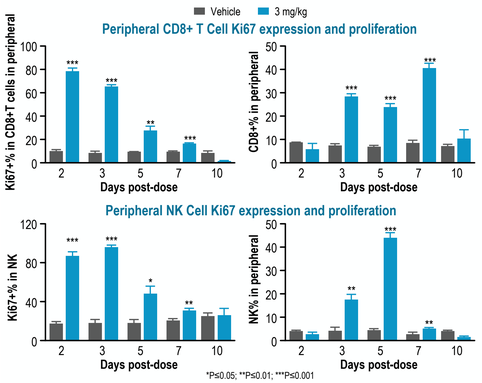
IHC Analysis: CD 8+ TILs Localized to Areas of Tumor Necrosis in THOR-707 Treated CT26 Tumor-bearing Mice

- Tumor samples collected at Day 7 after a single 3 mg/kg IV dose of THOR-707; stained for CD8+ TILs
- CD8+ TILs: More cells observed around the edges of the tumor and at areas of necrosis



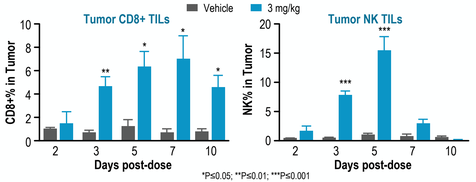
RESULTS

A Single 3 mg/kg IV Dose of THOR-707 Expands Peripheral CD8+ T and NK Cells, Increasing Ki67 Expression in B16F-10 Tumor-bearing Mice

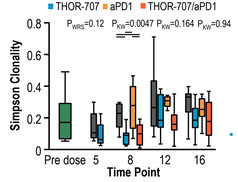


A Single 3 mg/kg IV Dose of THOR-707 Induces Sustained CD8+ T and NK Cell Infiltration in B16F-10 Tumors in Mice

- CD8+ TILs continue to elevated by the end of the study on day 10
- THOR-707 does not change Treg infiltration over time



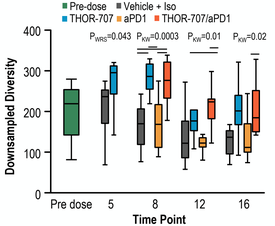
Treatment with THOR-707 Results in Lower TCR Repertoire Clonality in CT-26 Tumors



- TIL TCR sequencing was performed via immunoSEQ™ (Adaptive Biotechnologies). By Day 8, tumors from mice dosed with THOR-707 (6 mg/kg) or in combination with mouse anti-PD-1 (10 mg/kg) showed significantly lower TCR repertoire clonality within treatment groups. Wilcox rank sum test was used for 2-sample comparisons, Kruskal Wallis test for groups 3 or more
  - Anti-PD-1 dosed BIW, the first dose concurrent with THOR-707
- Post-hoc Dunn's test at Day8 demonstrates that the THOR-707 and THOR-707 + anti-PD-1 treatment groups have significantly lower clonality compared to either vehicle or anti-PD-1 alone

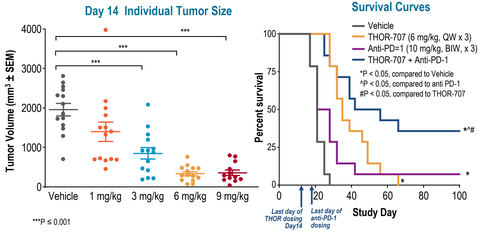
RESULTS

Treatment with THOR-707 Results in Greater TCR Repertoire Diversity in CT-26 Tumors



- TCR sequencing also revealed that tumors from mice dosed with THOR-707 (6 mg/kg) or in combination with mouse anti-PD-1 (10 mg/kg) showed a significant increase in TCR repertoire diversity at all time points. Wilcox rank sum test used for 2-sample comparisons, Kruskal Wallis test for groups 3 or more
  - Determined by counting unique clones after down-sampling to the lowest common template count (339)
- Consistent with clonality data, repertoire diversity is higher in groups treated with THOR-707 at all time points relative to vehicle and anti-PD-1 monotherapy

THOR-707 Shows Dose-dependent Efficacy as Single Agent and in Combination With Anti-PD-1, Eliciting Durable Anti-tumor Responses in CT-26 Tumor-bearing Mice



- CT-26 colon tumor-bearing Balb/c mice were treated with THOR-707 (1, 3 or 6 mg/kg QWx3) alone, anti-PD-1 (10 mg/kg, BIW x 3) alone or the combination of THOR-707 at 6 mg/kg with anti-PD-1
- THOR-707 showed dose-dependent single agent antitumor activity. In combination with anti-PD1, 5/14 animals showed tumor regression and no detectable tumors for 100 days

CONCLUSIONS

- THOR-707 does not show signs of inducing T-cell exhaustion
  - Peripheral CD8+ T cell proliferation was comparable across dose schedules and correlated with CD8+ T cell expression of Ki67 ≥60%
- In NHP, after repeat dosing at 0.1 mg/kg, THOR-707 showed similar PK profiles after the first and the third dose when dosed Q2, 3 and 4W
  - No decrease in exposure with re-dosing
- THOR-707 expands T-cells in the periphery and in tumors in mouse models
  - In both CT-26 and B16F-10 tumor-bearing mice, THOR-707 induced Ki67 in peripheral CD8+ T and NK cells ≥60%, resulting in the expansion of those populations in peripheral blood
  - Within the tumor, THOR-707 drove CD8+ T and NK cell infiltration with no CD4+ Treg recruitment. CD8+TILs localized to areas of tumor necrosis
  - THOR-707 significantly increased the TIL TCR repertoire diversity in CT-26 tumors
- THOR-707 demonstrated efficacy as single agent and in combination with Anti PD-1 in CT-26 syngeneic tumors, eliciting durable anti-tumor responses