Designing Optimized Biologics Through Our Expanded Genetic Alphabet Platform

November 2019

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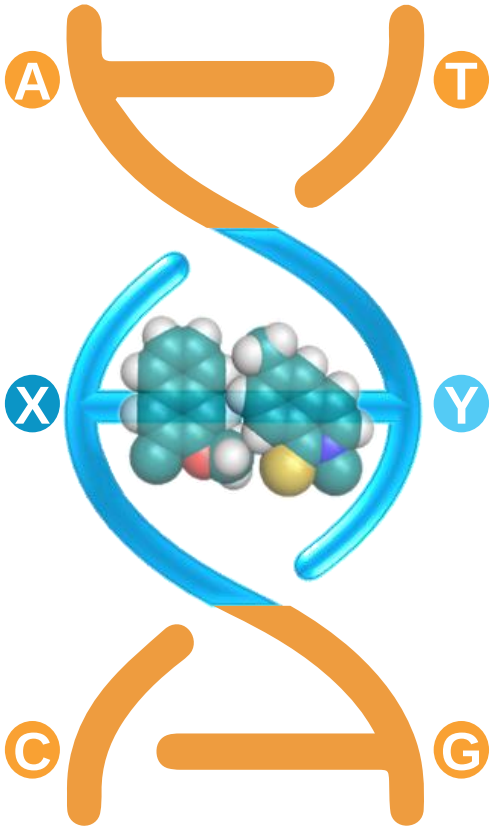
Leveraging our first-of-its-kind Expanded Genetic Alphabet platform to meet today's challenges for people suffering from cancer and auto-immune disorders

- Initial focus is on creating optimized cytokines that target validated mechanisms of action in immuno-oncology and autoimmune disorders where existing therapies have significant drawbacks
- Lead oncology product candidate, THOR-707, is a "not-alpha" interleukin-2 (IL-2) in early clinical phase development for solid tumors
- Lead autoimmune product candidate, THOR-809, is an IL-2 variant that preferentially expands T regulatory cells ("Tregs"), without expanding conventional T effector and helper cells ("Tcons") and is in preclinical development
- Advancing preclinical IL-15 and IL-10 Synthorins for cancer
- Company well-positioned for success with experienced management team and robust financial position

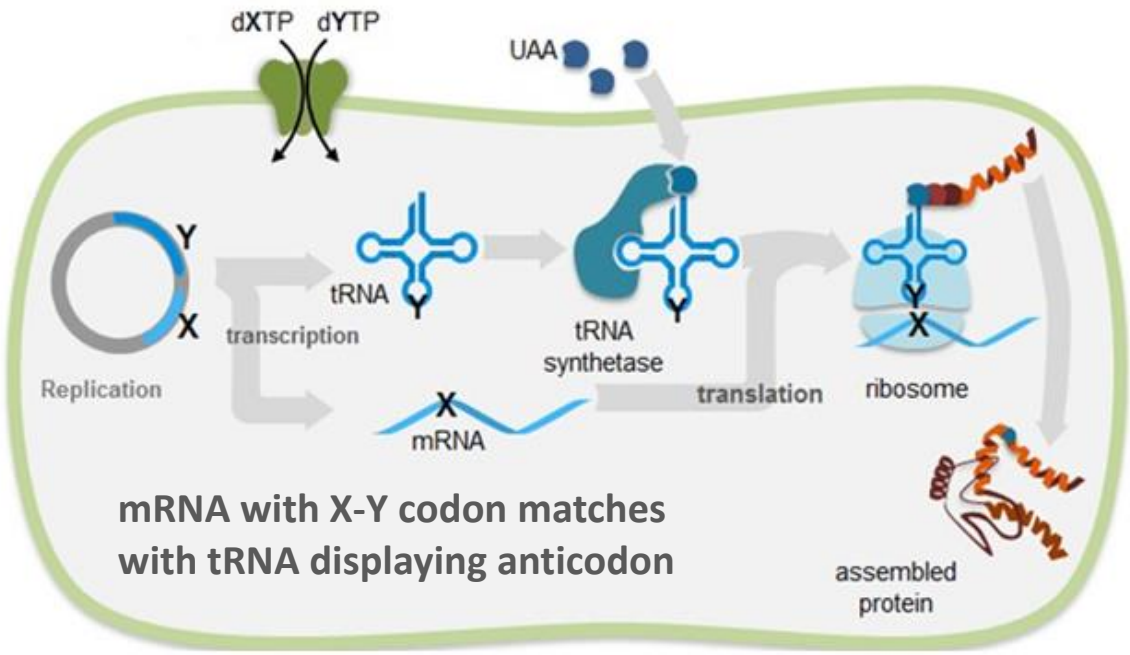
Our goal is to bring multiple Synthorins™ to market to positively impact millions of patients worldwide

X-Y Base Pair Enables Installation of a Novel Amino Acid Utilizing and Engineered Strain to Produce Therapeutic Proteins with Optimized Properties



X and YTPs enter via transporter

Novel Amino Acid diffuses into cells; used by aminoacyl tRNA synthetase to charge X-Y tRNAs



Translation machinery decodes X-Y codons to introduce nAA into Synthorin proteins

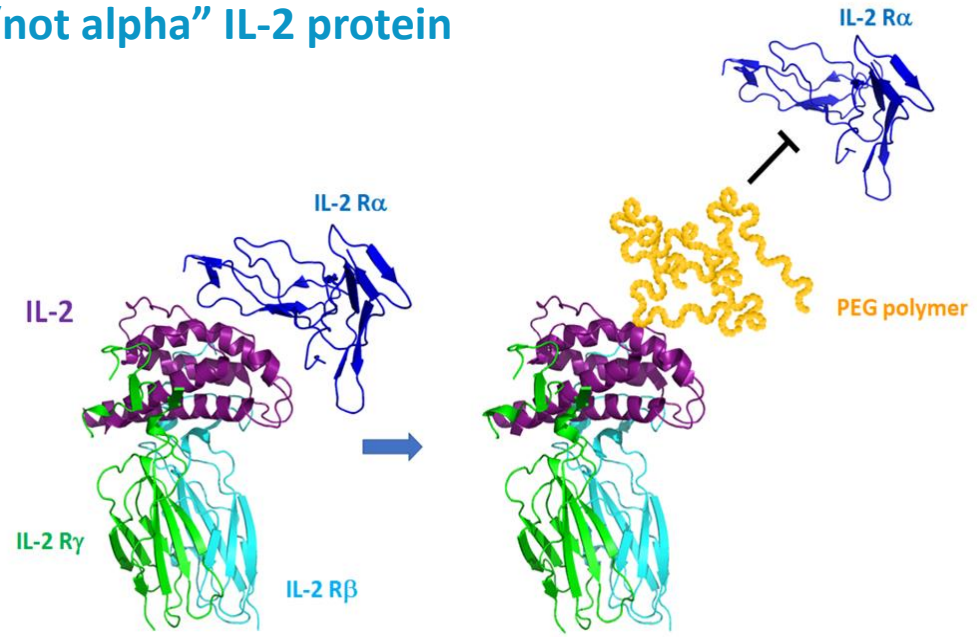
- Novel amino acid provides versatility and diversity to optimize proteins (e.g. chemical hook for bioconjugation)
- Covalent attachment (e.g. PEG) improves drug properties (increased half-life; altered receptor binding)
- Shields potentially immunogenic epitopes from immunosurveillance

1. doi:10.1038/nature13314. 2. doi:10.1038/nature24659

THOR-707, a "not alpha" IL-2 Retains Efficacy of Aldesleukin without Signs of VLS in Preclinical Studies

PEG-IL-2 Synthorin Properties

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



IL-2 binds to the IL-2 receptor αβγ complex at high affinity because of the α chain

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

THOR-707's Activity and Safety

Improved Selectivity

Reduced CD4+ Treg bias with retained stimulatory activity of CD8+ T cells and NK cells in preclinical studies

Strong Preclinical Anti-Tumor Activity Alone and in Combination with Anti-PD-1

- THOR-707, as a single agent, elicits CD8+ T cell tumor infiltration, activation of effector and memory T cells, and improved survival
- In combination with anti-PD-1, THOR-707 leads to durable anti-tumor responses and rejection upon re-challenge

Increased Therapeutic Index for VLS

At least 10 in preclinical non-human primate (NHP) studies

HAMMER: First-In-Human Study of THOR-707

Part 1 & 2 Dose Escalation

THOR-707 Q3W

MTD/OBD/RP2D (TBD)

*

Dose Level N (TBD)

*

16 µg/kg (Enrolling)

*

8 µg/kg ** (Starting Dose, Completed)

THOR-707 Q2W

MTD/OBD/RP2D (TBD)

*

Dose Level N (TBD)

*

8 µg/kg (Starting Dose, Enrolling)

THOR-707 + Pembrolizumab Q3W **

MTD/OBD/RP2D (TBD)

*

Dose Level N (TBD)

*

THOR-707 X µg/kg (Starting Dose, TBD)

Part 3 Dose Expansion

THOR-707 Single Agent and Combination (PD-1i/PD-L1i, Other Established and Emerging Therapies) Cohorts at RP2Ds

End of Line Acceleration Approval Opportunities

Signal Finding Tumor-Specific; Signal Finding Biomarker "Baskets"

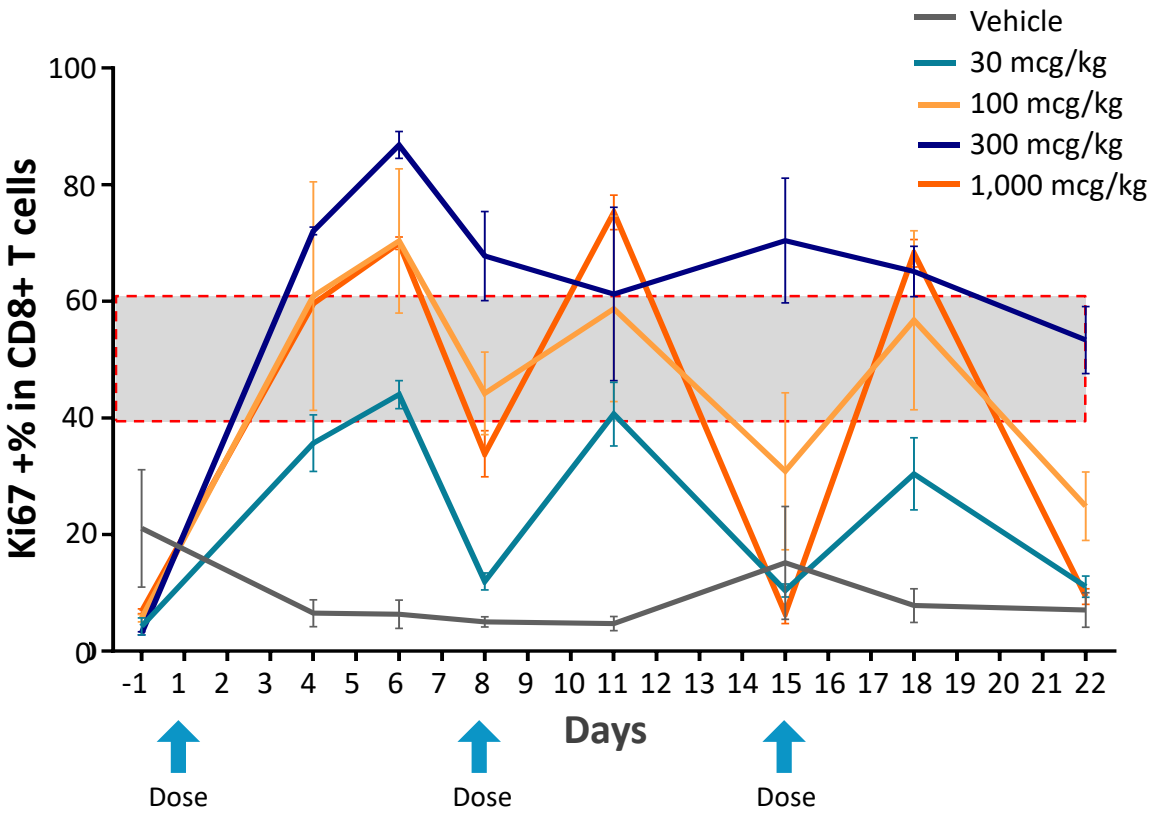
- **Design:**
  - **Part 1 & 2:** Dose Escalation (3+3)
  - **Part 1 & 2:** Safety Expansion (up to 10 subjects at established highest tolerated dose)
  - **Part 3:** Dose Expansion (10-20 subjects at RP2D)
- **Eligibility:**
  - **Part 1:** Solid tumors, advanced stage, late-line only
  - **Part 2:** Solid tumors, all lines; refractory or naïve to PD-1i's
  - **Part 3:** Solid tumors, all lines; refractory or naïve to PD-1i's
- **Objectives:**
  - **Primary:** Safety and tolerability
  - **Secondary:** PK/PD, anti-tumor activity
- **Biomarkers (Pre- and Post-THOR-707 Dose):**
  - **CD8+ T cell** and **NK cell counts** in blood and tumor
  - **Ki67 expression** on CD8+ T cells
  - **Cytokine** levels pre- and post-dose

*Dose escalation and expansion decisions made by a Safety Review Committee (SRC) comprising study investigators and company representatives

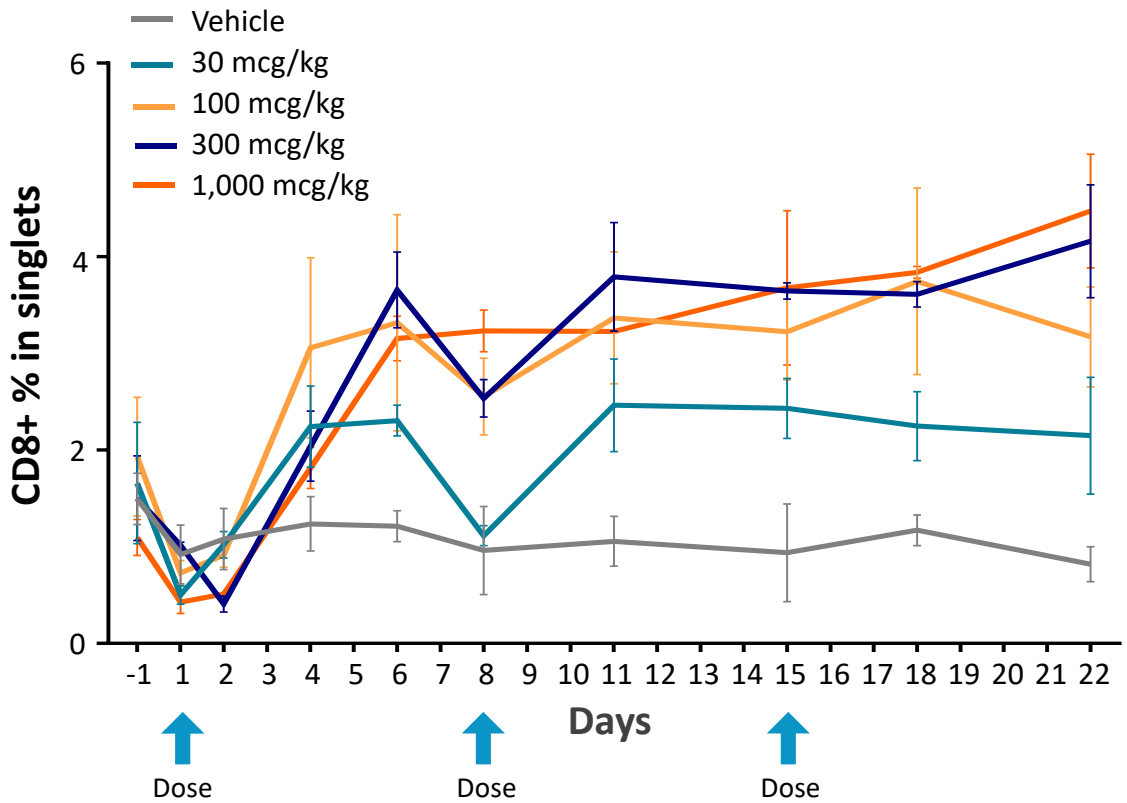
**Threshold for initiation of THOR-707 plus PD-1 inhibitor cohorts is a single agent dose that elicits a CD8+ T cell expansion of 1.5x above pre-treatment baseline and a Ki67 expression level of 40%-60%

In Preclinical studies, Ki67 Levels at or Above the 60% Level Correlated with a Maximum Peripheral Expansion of CD8+ T Cells (2.5x to 4.0x from Baseline)

Peripheral CD8+ T Cells Ki67 Expression in NHP

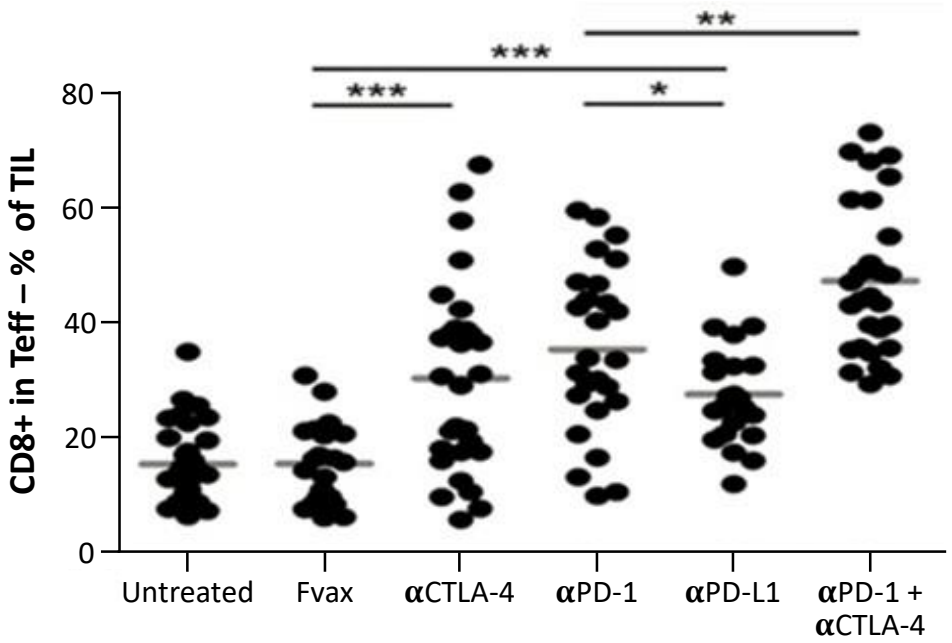


Peripheral CD8+ T Cell Proliferation in NHP



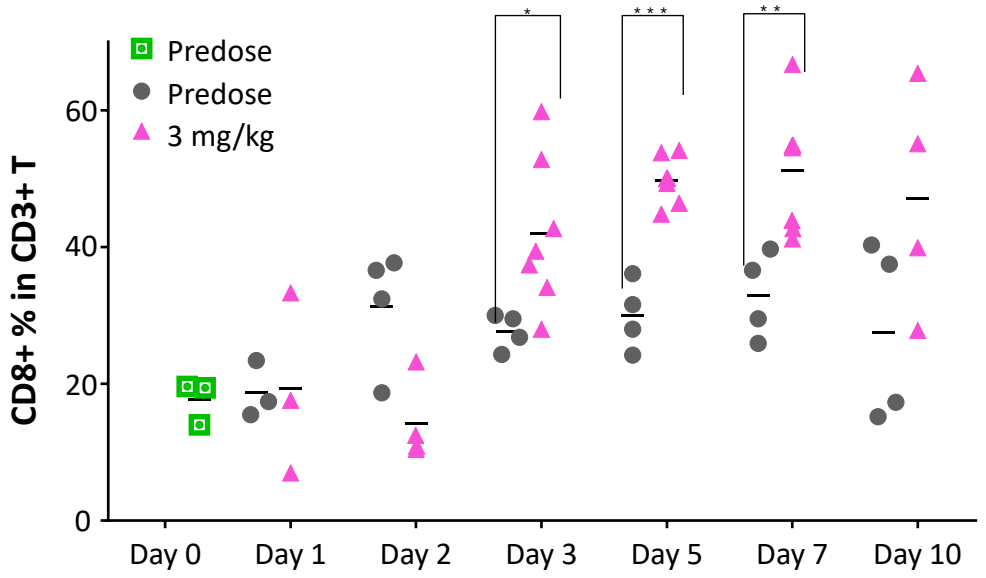
In Preclinical studies, THOR-707 Drives CD8+ T Cell Expansion and Tumor Infiltration at Levels Comparable to Immune Checkpoint Inhibitors

Select Immune Checkpoint Inhibitors



Following 3 Doses IV of CPIs B16F10 model[1]

THOR-707

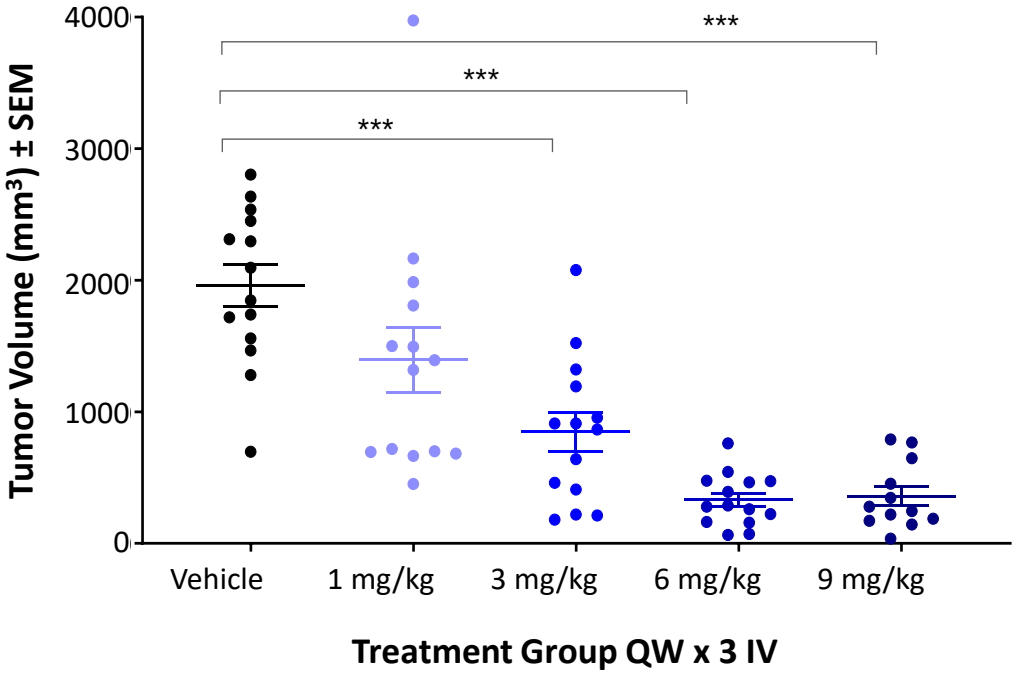


Following Single Dose of THOR-707 B16F10 model

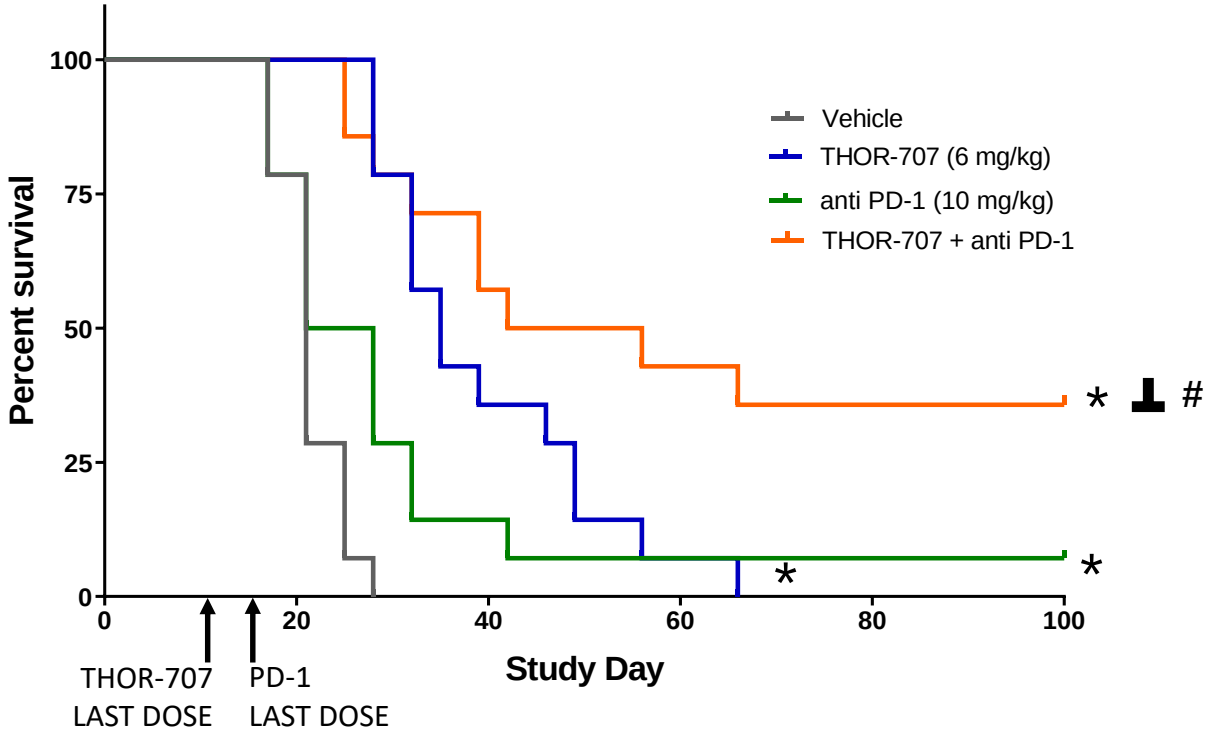
1. *PNAS* Vol 107 No. 9, pages 4275-4280 (02 Mar 2010)

THOR-707 Is Efficacious as a Single Agent and when Combined With a PD-1 Inhibitor in the CT-26 Mouse Tumor Model

THOR-707 Single Agent Study, Day 17



Combination Study Overall Survival (n=14)

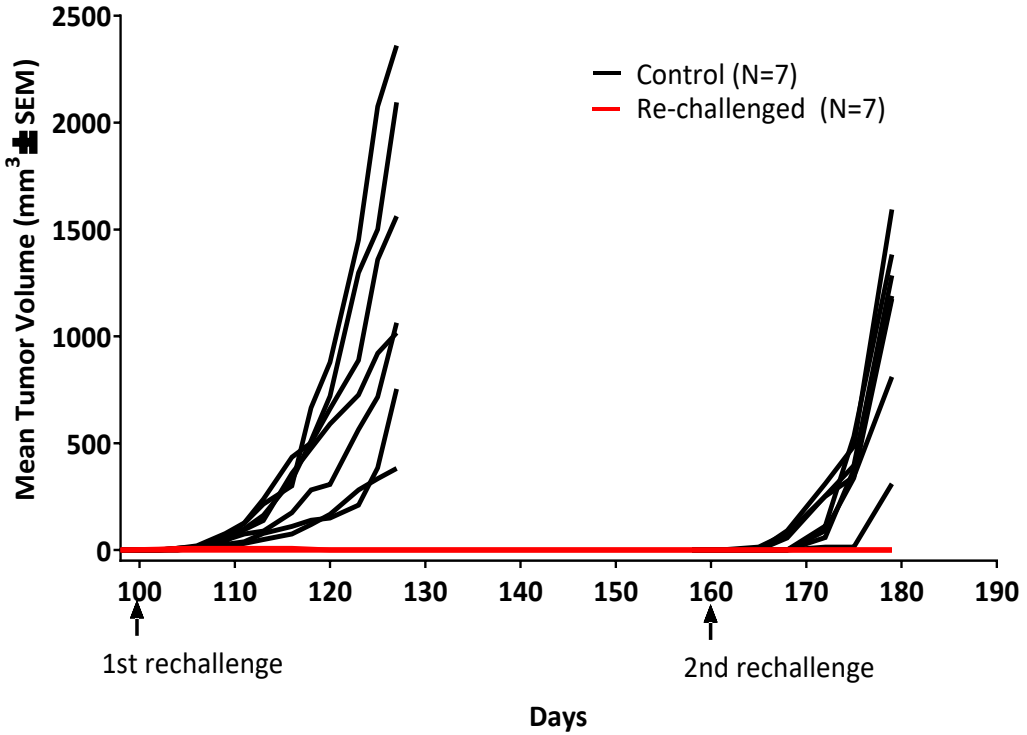


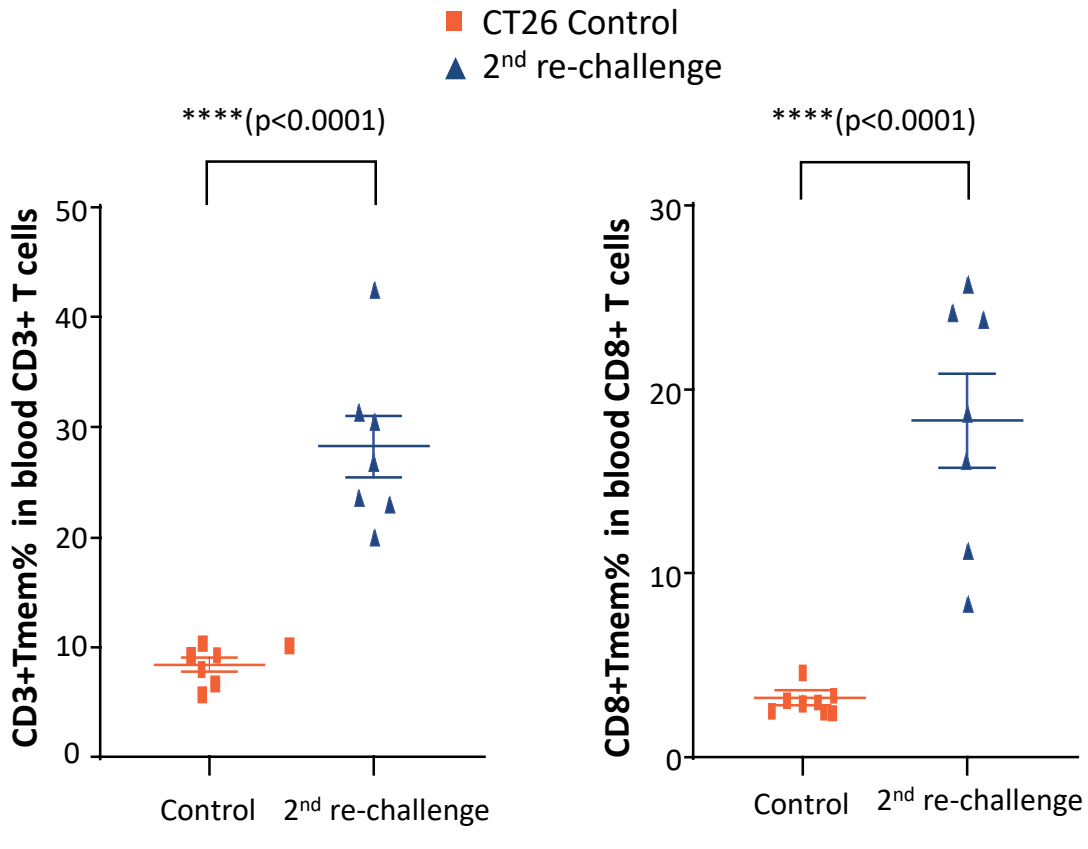
- **5/14:** complete regression (last THOR-707 dose Day 14)
- All 5 mice remained tumor-free by Day 100 (36%)

Across two studies, 9 mice treated with THOR-707 (QW x 3) and anti-PD-1 (Q3D x 6) showed complete tumor regression beyond 100 days

*P ≤ 0.05; **P ≤ 0.01; ***P ≤ 0.001

The Mice Showing Complete Regression were Re-challenged with Tumor cells and Remained Tumor-free with no Additional Treatment





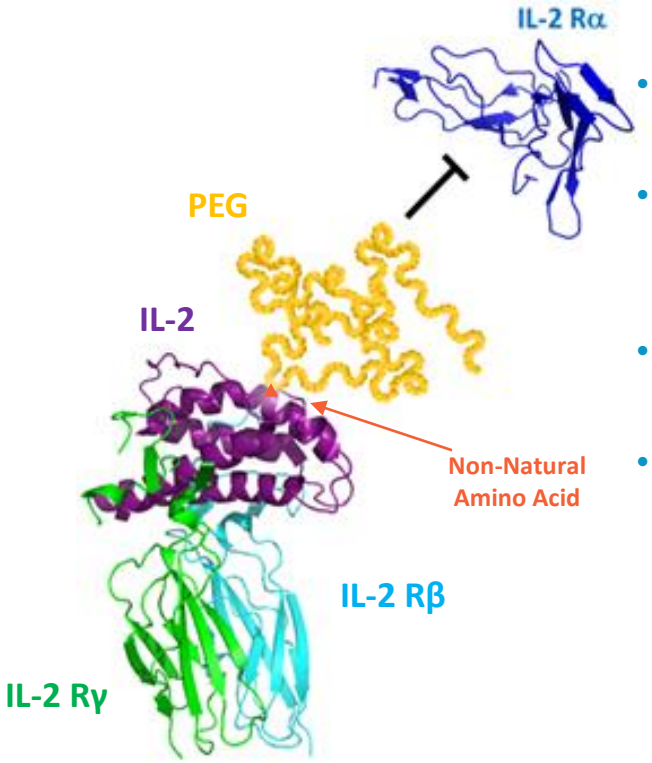
These data demonstrate activation of memory T cells leading to durable anti-tumor responses, which was observable in the blood of re-challenged animals

THOR-707 Summary

- There is a strong preclinical rationale for moving THOR-707, our “not alpha” IL-2 Synthorin, into clinical development
  - Reprogrammed pharmacology of IL-2 by blocking engagement of the alpha chain of the IL-2 receptor; lack of peripheral Treg expansion and greatly reduced risk of vascular leak syndrome while maintaining anti-tumor activity
  - Correlated Ki67 with peripheral CD8+ T and NK cell counts
  - Increases T Cell Receptor-mediated IFN-γ release in combination with PD-1i’s
- HAMMER is a three-part global Phase 1/2 dose escalation and expansion study evaluating the safety and anti-tumor activity of THOR-707, in patients with advanced or metastatic solid tumors:
  - Part 1 of the study will determine the RP2D of THOR-707 as a single agent
  - Part 2 of the study will determine the RP2D of THOR-707 in combination with a PD-1 inhibitor
  - Part 3 of the study will continue to evaluate safety along with anti-tumor activity of THOR-707 alone or in combination with a PD-1 or PD-L1 inhibitor as well as in combination or sequenced with other established and emerging immunooncology therapies via dose expansion
- The starting dose of 8 µg/kg Q3W was well tolerated and changes in biomarkers exceeded the threshold for advancing Part 2 of the study in combination with pembrolizumab
- Enrollment of other cohorts is ongoing

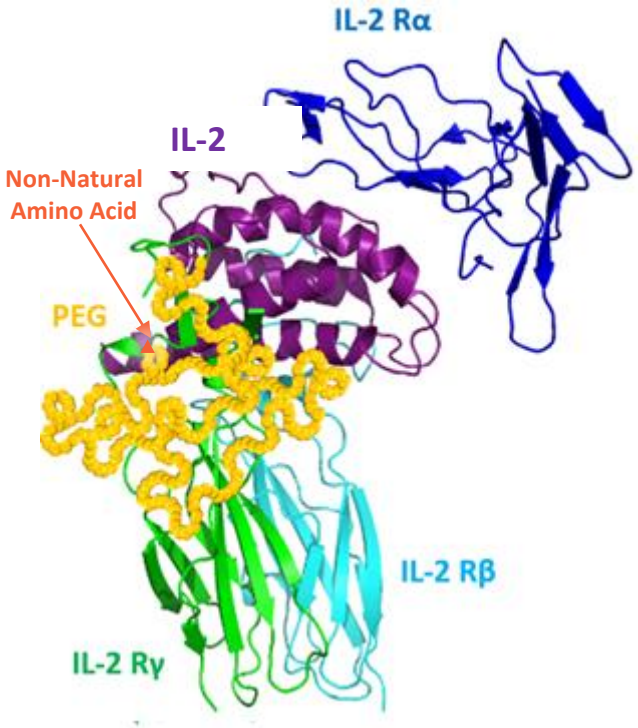
THOR-809 is IL-2 Finetuned to Elicit the Opposite Effect of THOR-707

THOR-707 IL-2 Synthorin for Immuno-Oncology



- PEG blocks engagement of α receptor chain
- Selectively expands anti-tumor CD8+ T cells and NK cells
- No expansion of immune-suppressive CD4+ T cells
- No activation of non-lymphoid cells responsible for vascular leak syndrome

THOR-809 IL-2 Synthorin for Autoimmune Disorders



- PEG blunts engagement of β receptor chains, making potency at IL-2R αβγ contingent on α binding
- Selectively expands CD4+ regulatory T cells
- No expansion of CD8+ T cells and NK Cells

Shared Pharmacological Properties of IL-2 Synthorins

- Pegylation increases IL-2 half-life – no more frequent dosing than Q2W for THOR-707 and THOR-809
- Reduced immunogenicity risk - covalent attachment of stable, “shielding” PEG; amino acid region devoid of MHC-II anchors

THOR-809 Product Profile and Differentiation

- **THOR-809 in non-human primates elicited a 45-fold expansion of the peripheral Treg population without observable expansion of CD8+ T cells or NK cells**

- **THOR-809 in non-human primates demonstrates a lower risk of immunogenicity compared to other IL-2 muteins**
  - Novel amino acid insertion in IL-2 region devoid of MHC-II anchors
  - Covalent, stable PEG bioconjugate acts as a shield for new amino acid

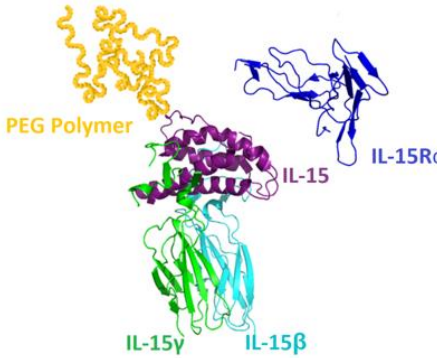
- **THOR-809 will likely be dosed no more frequently than every two weeks; PEG conjugation is an established tool to extend half-life**

IL-15 Synthorin

Scientific Rationale

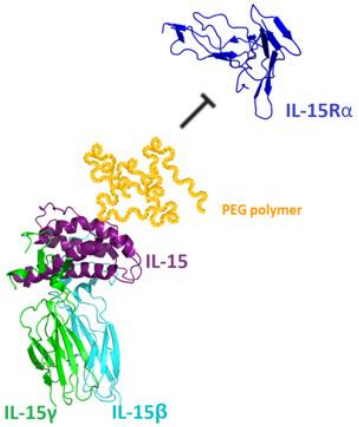
- IL-15 is unique in its ability to sustain activation of antigen-specific memory CD8+ T cells[1]
- Potent activator of NK cells, important for their and proliferation and survival[2]
- Affects all aspects of CD8 T cell biology – development, activation, proliferation, survival and cytotoxicity[3]

IL-15 Synthorin Design



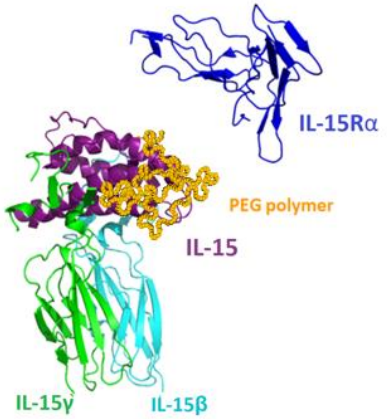
Half-Life Extension Only
THOR-924

Intact IL-15 pharmacology with extended half-life



Not-Alpha, Native Beta
THOR-908

Potential for decreased toxicity due to not-alpha phenotype. Binding at IL-2Rβ is intact



Reduced Alpha and Beta
THOR-918

Decreased binding to IL-2Rα and β; potential for decreased receptor internalization

Status

- ✓ "Not alpha" and "half-life extended" IL-15 Synthorins identified
- ✓ Synthorin IL-15 constructs completed
- ✓ Evaluation of "not alpha" vs "half-life extended" biology
- ✓ *In vivo* evaluation ongoing
- ✓ THOR-924 selected as the lead clinical candidate

Key Areas of Differentiation

- All IL-15 IO Synthorins are designed to have improved pharmacokinetics
- Site-specific placement of the PEG produces three variants with different pharmacological properties

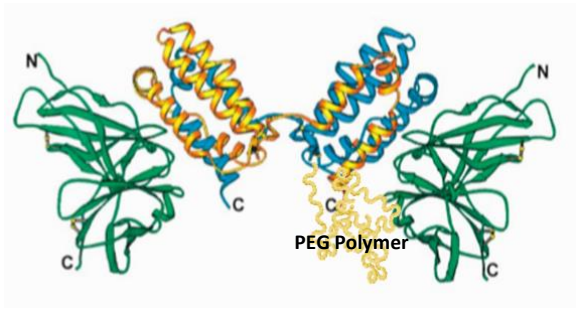
[1]Richer et al. 2015
[2]Nguyen et al. 2002
[3]Weng et al. 2002

IL-10 Synthorin

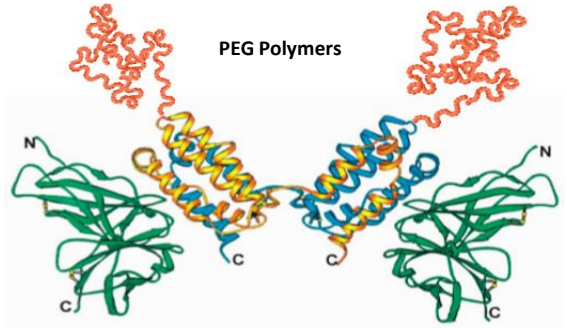
Scientific Rationale

- Critical for the proliferation and cytotoxic activity of CD8+ T cells
- Increases stimulation of T Cell Receptor-activated CD8+ T cells, providing them with anti-apoptotic and proliferative signals[1]
- Reduced levels of IL-10 lower immune surveillance resulting in increase tumor incidence[2]

IL-10 Synthorin Design



Eli Lilly/Armo Pegilodecakin: Pegylation limited to N-Terminus of IL-10 which results in QD dosing



IL-10 Synthorin: Site-specific covalent PEG improves half life and reduces interference at binding sites

Key Areas of Differentiation

- IL-10 IO Synthorin designed to have improved pharmacokinetics
- Sites selected for pegylation avoid interference with IL-10 dimerization and binding to IL-10 receptor

Status

- ✓ Production of dimerized (fully active) IL-10 with high purity
- ✓ Synthorin IL-10 constructs completed or in progress
- ✓ Evaluation of SAR; in vitro, ex vivo and in vivo
- Selection of IND candidate

[1] Naing et al., 2018
[2] Mumm et al., 2011

Synthorin Pipeline

Program	Indication(s)	Discovery	Lead Optimization	IND Enabling	Phase 1	Phase 2	Phase 3	Milestones
THOR-707 Not Alpha IL-2	"All-Comers" Solid Tumors	Single Agent						Biomarker data from the 1st cohort exceeded criteria for opening combo with an anti-PD-1; data to be presented at a scientific conference 1H20
	Documented PD-1 Inhibitor Sensitive Solid Tumors	Combination with Immune Checkpoint Inhibitor(s)						Combo biomarker data to be presented in 2020
IL-2 Autoimmune Synthorin	Autoimmune Disorders							IND candidate selected IND filing 2020
IL-10 Synthorin	Immuno-Oncology							Select IND candidate 2019
IL-15 Synthorin	Immuno-Oncology							THOR-924 selected as the lead clinical candidate

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