THOR-707, an engineered not-alpha IL-2, for the treatment of solid tumors induces strong immunological responses *in vivo*

Gilles Dufour, PhD
Director, Corporate Development and Clinical Strategy

CSCO Immunotherapy Seminar, Endorsed by AACR
March 22-23, 2019 • Shanghai, China

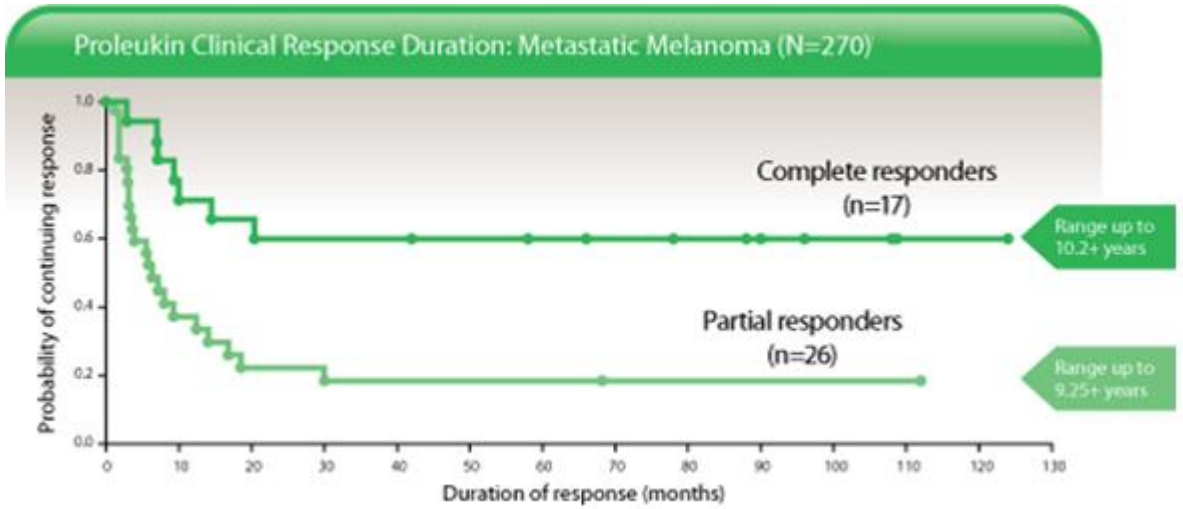
Forward-Looking Statements

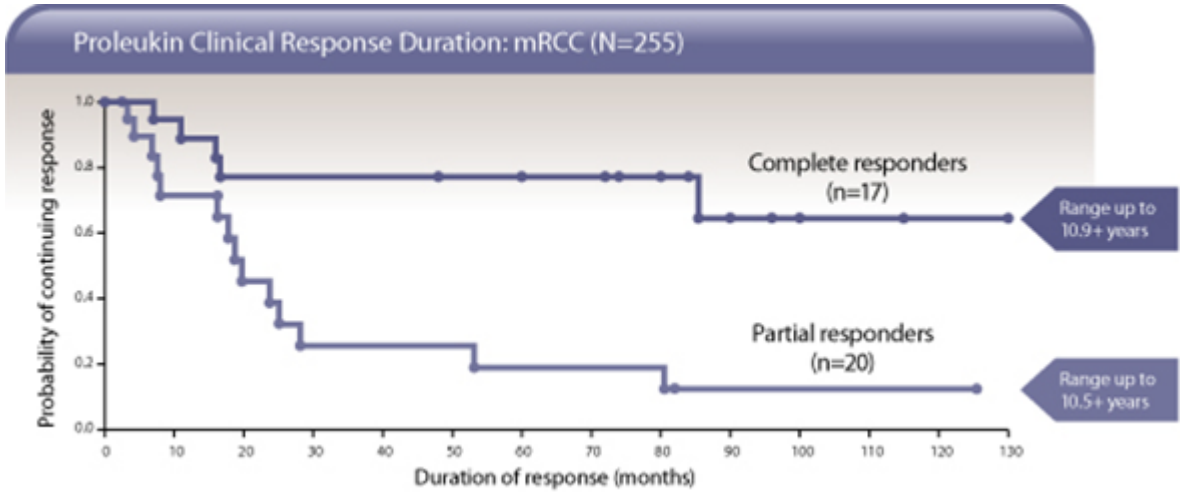
Statements contained in this presentation regarding matters that are not historical facts are "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995, including statements associated with the expected ability of Synthorx, Inc. (the “Company”) to undertake certain activities and accomplish certain goals and objectives. These statements include but are not limited to statements regarding the Company’s business strategy, the Company’s plans to develop and commercialize its product candidates, the safety and efficacy of the Company’s product candidates, the Company’s plans and expected timing with respect to regulatory filings and approvals, and the size and growth potential of the markets for the Company’s product candidates. Because such statements are subject to risks and uncertainties, actual results may differ materially from those expressed or implied by such forward-looking statements. Words such as "believes," "anticipates," "plans," "expects," "intends," "will," "goal," "potential" and similar expressions are intended to identify forward-looking statements. These forward-looking statements are based upon the Company’s current expectations and involve assumptions that may never materialize or may prove to be incorrect. Actual results and the timing of events could differ materially from those anticipated in such forward-looking statements as a result of various risks and uncertainties, which include, without limitation, risks associated with the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such drugs. These and other risks concerning the Company’s development programs and financial position are described in additional detail in the Company’s filings with the Securities and Exchange Commission. All forward-looking statements contained in this presentation speak only as of the date on which they were made. The Company undertakes no obligation to update such statements to reflect events that occur or circumstances that exist after the date on which they were made.

The trademarks included herein are the property of the owners thereof and are used for reference purposes only. Such use should not be construed as an endorsement of such products. This presentation discusses product candidates that are under clinical study and which have not yet been approved for marketing by the U.S. Food and Drug Administration. No representation is made as to the safety or effectiveness of these product candidates for the therapeutic use for which such product candidates are being studied.

IL-2: Background

- Recombinant IL-2 (rIL-2; aldesleukin) is a well known systemic immunostimulatory cytokine that has consistently shown single agent responses and survival benefits across multiple tumor types[1,2] thanks to its ability to expand CD8 T cell counts both peripherally and intratumorally



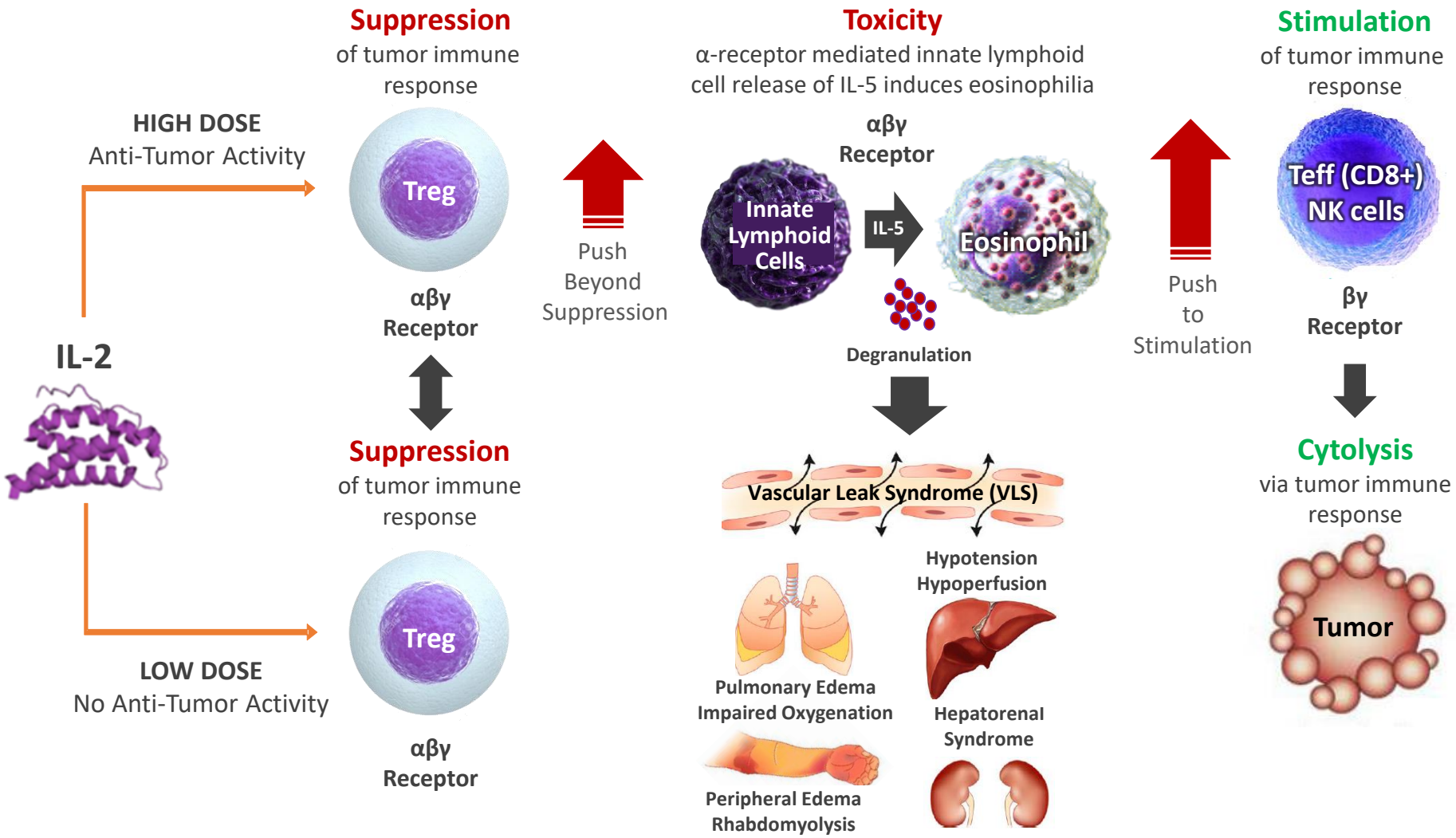


- IL-2's ability to expand CD8 T cell counts makes it a potential agent for combination with checkpoint inhibitors (e.g., anti-PD1 mAbs) to further promote CD8 responses

- **However**, rIL-2 is clearly limited by suboptimal pharmacological properties and dose-limiting AEs (vascular leak syndrome (VLS)) that reduce its therapeutic index

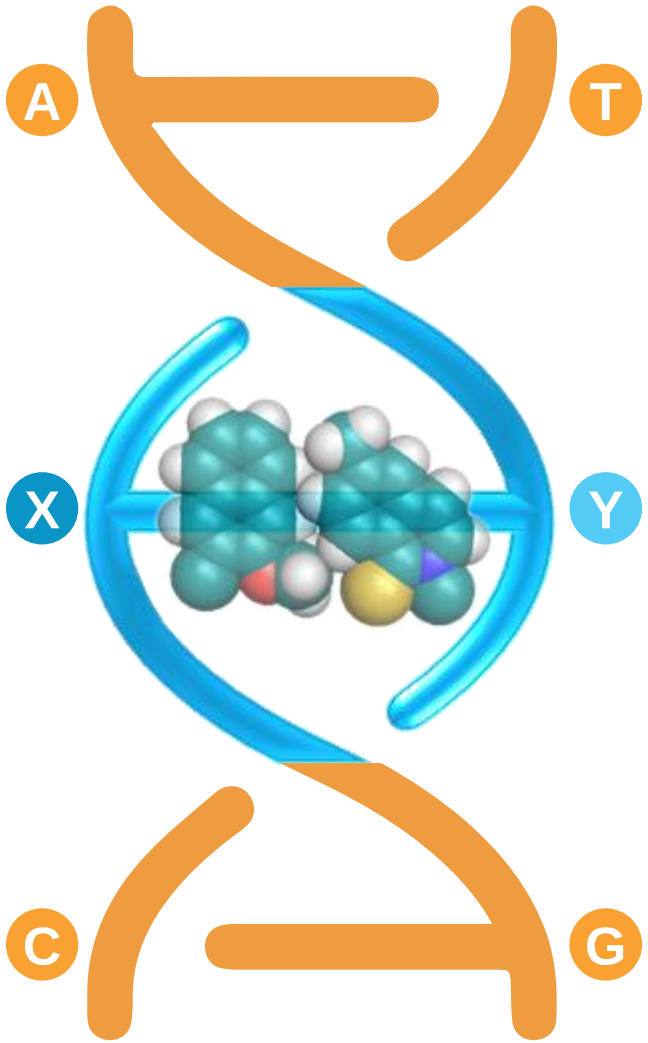
[1]Proleukin Melanoma HCP Website
[2]Proleukin Renal Cell Carcinoma HCP Website

IL-2 Biology: Dual Pharmacology Explains Low Therapeutic Index



Blood 2014 124:3572-3576

Novel Amino-Acid Allows Site-specific Pegylation To Create “Not-Alpha” IL-2



Novel Amino-Acid 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

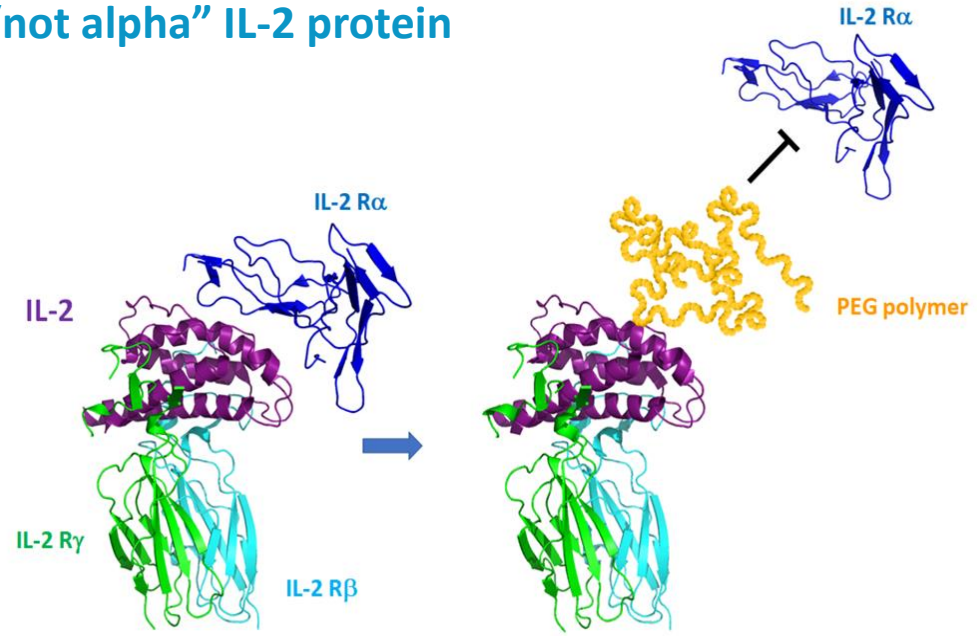
1. doi:10.1038/nature13314. 2. doi:10.1038/nature24659

THOR-707: “Not alpha” IL-2

Structural Design and Receptor Binding Properties

PEG-IL-2 Synthorin Properties

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

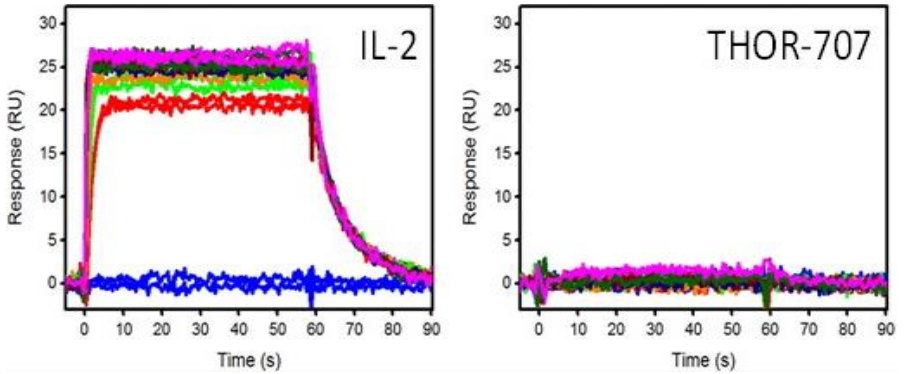


IL-2 binds to the IL-2 receptor αβγ complex at high affinity because of the α chain

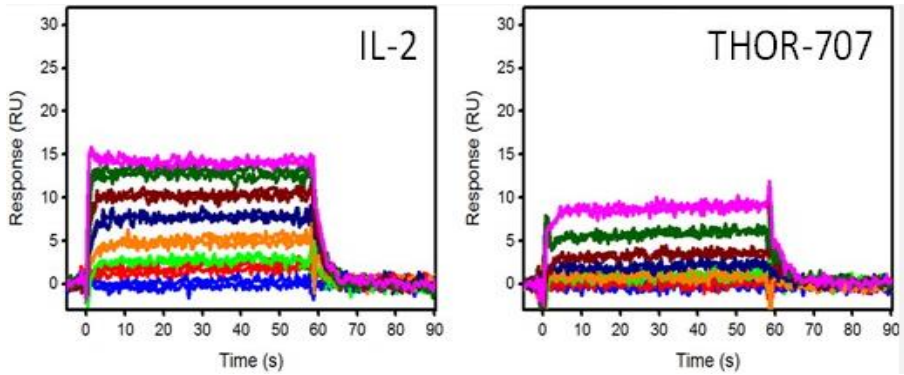
Targeted pegylation of THOR-707 at the novel amino acid blocks α chain binding

Receptor Binding Properties

IL-2 Receptor α Chain



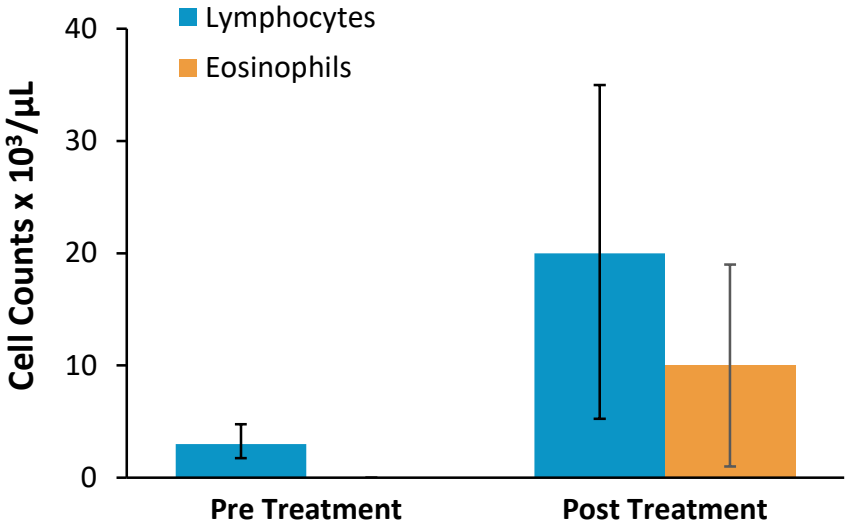
IL-2 Receptor ß Chain



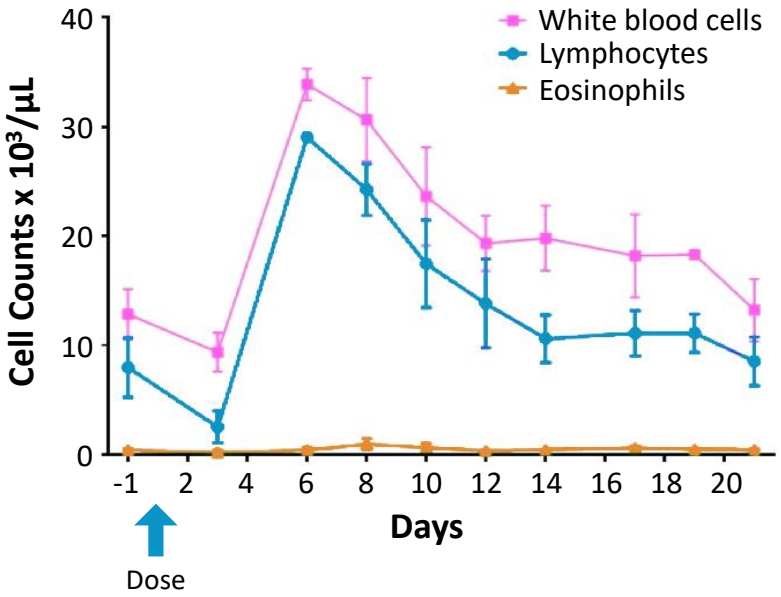
THOR-707

THOR-707 Increases Lymphocyte Expansion in Non Human Primates (NHP) without Increasing Eosinophils

Pre and Post Aldesleukin Induced Lymphocyte Expansion[1]



THOR-707 Single Dose Leukocyte Subpopulations
High Lymphocytes, No Eosinophils



- Aldesleukin dosing limited in people (37 mcg/kg) and NHP by VLS (25 mcg/kg and higher)
- No signs of VLS in NHP with THOR-707 up to 1,000 mcg/kg

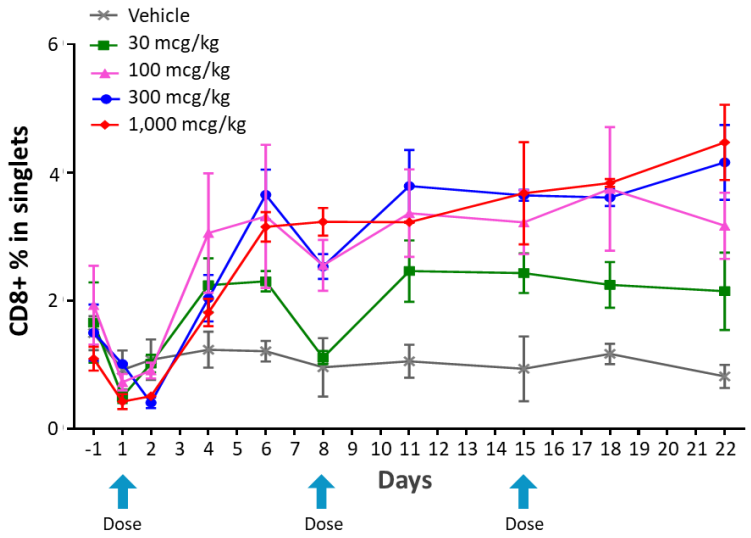
Compared to aldesleukin, THOR-707 shows a strong preference for expanding tumor-fighting lymphocytes vs. eosinophils responsible for VLS

1. Meyers FJ, et al. *Clin Pharmacol Ther*. 1991;49:307.

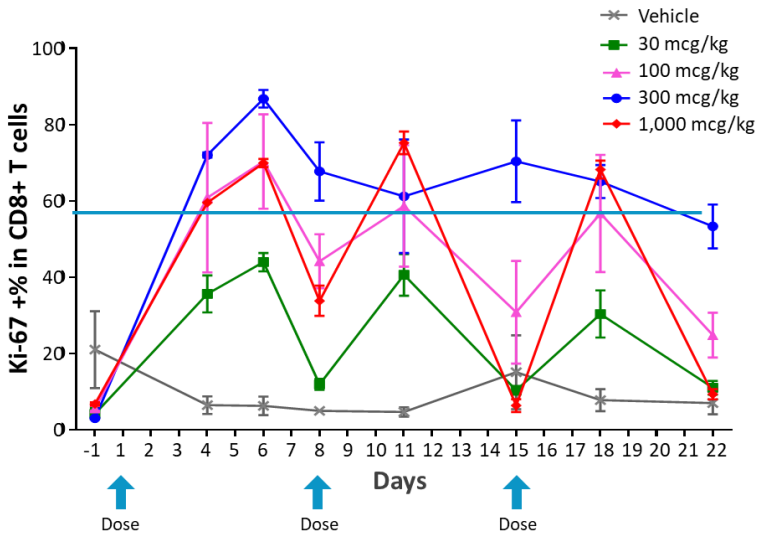
THOR-707

60% Ki-67 in CD8+ Teff Cells Is Associated With Maximal Expansion and Can Be Achieved With THOR-707 Without VLS in NHPs

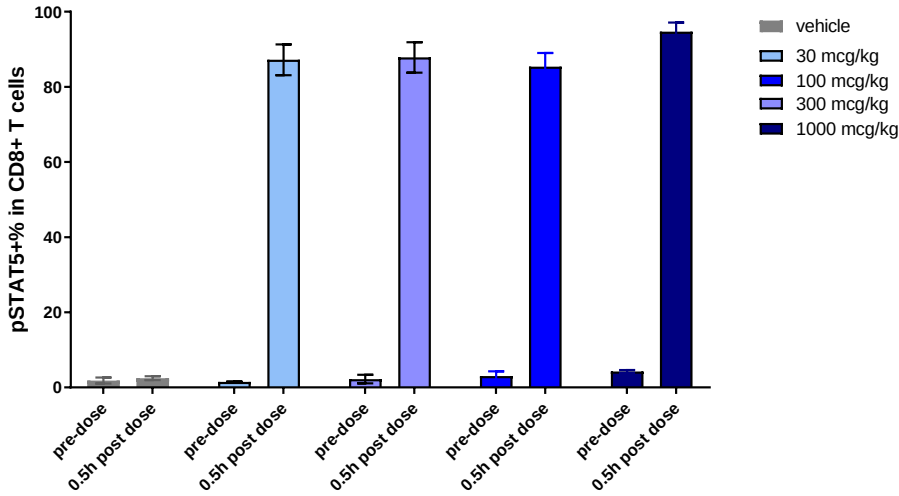
Peripheral CD8+ T Cells Activation and Proliferation



Peripheral CD8+ T Cells Ki67 Expression



Peripheral CD8+ T Cells pSTAT5 Expression

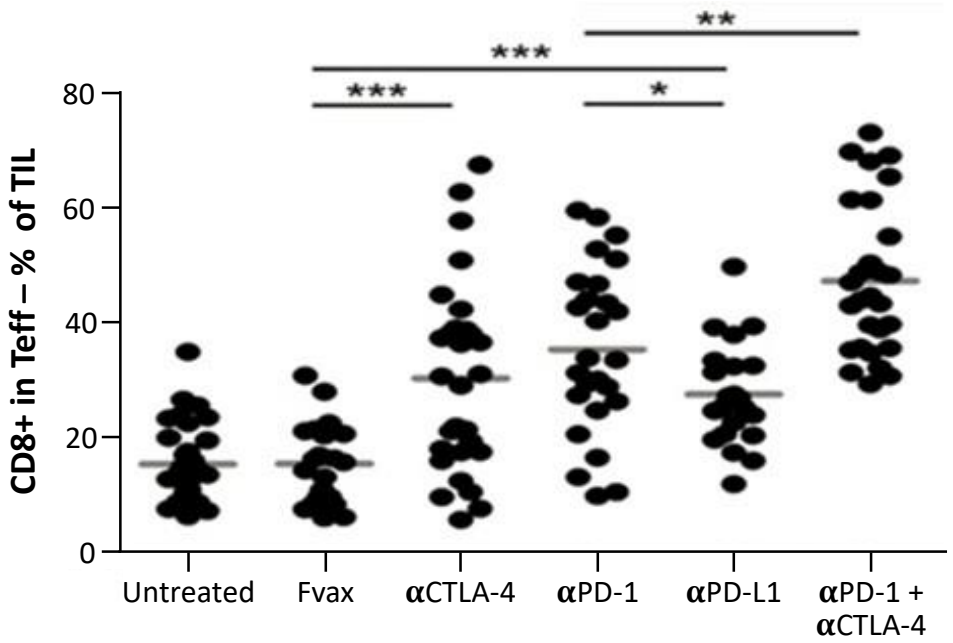


Ki67 is a closer PD marker to monitor cell proliferation compared to pSTAT5 in CD8+ T cells.

THOR-707

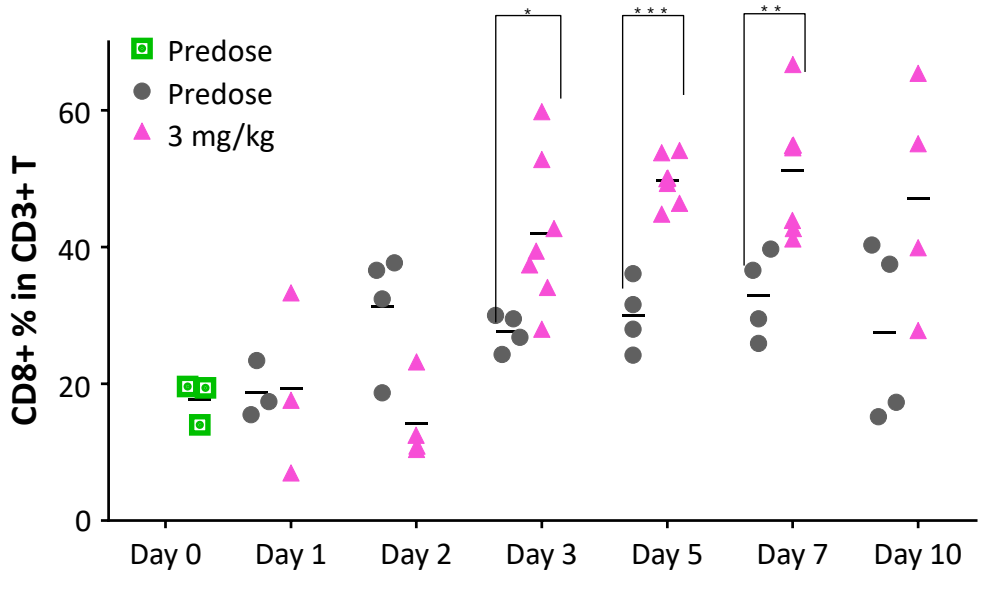
CD8+ Teff Expansion and Proliferation in Tumors Following a Single Dose looks similar to Immune Checkpoint Inhibitors

Select Immune Checkpoint Inhibitors



Following 3 Doses IV of CPIs

THOR-707



Single dose of THOR-707

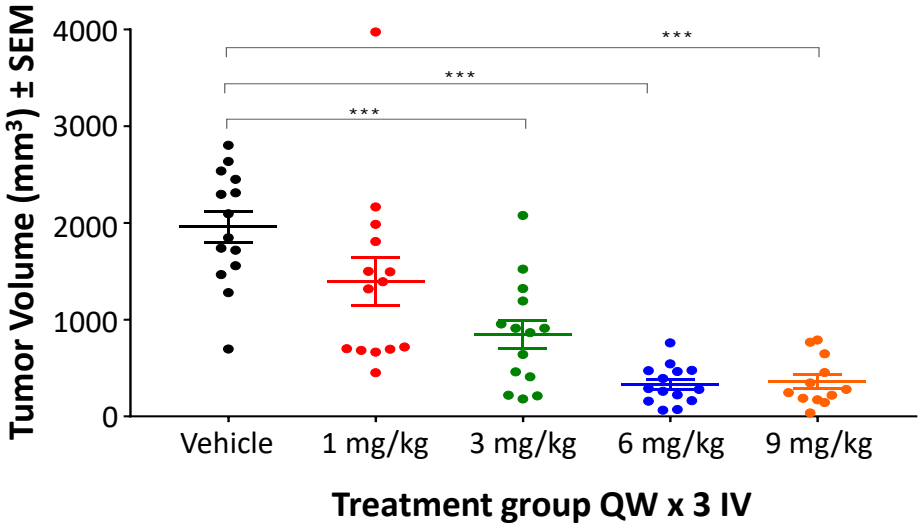
THOR-707 levels of CD8+ tumor infiltration are comparable to those observed for select immune checkpoint inhibitor mAbs (e.g, CTLA-4, PD-1, PD-L1, and combinations of them) in mouse melanoma tumor model[1]

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

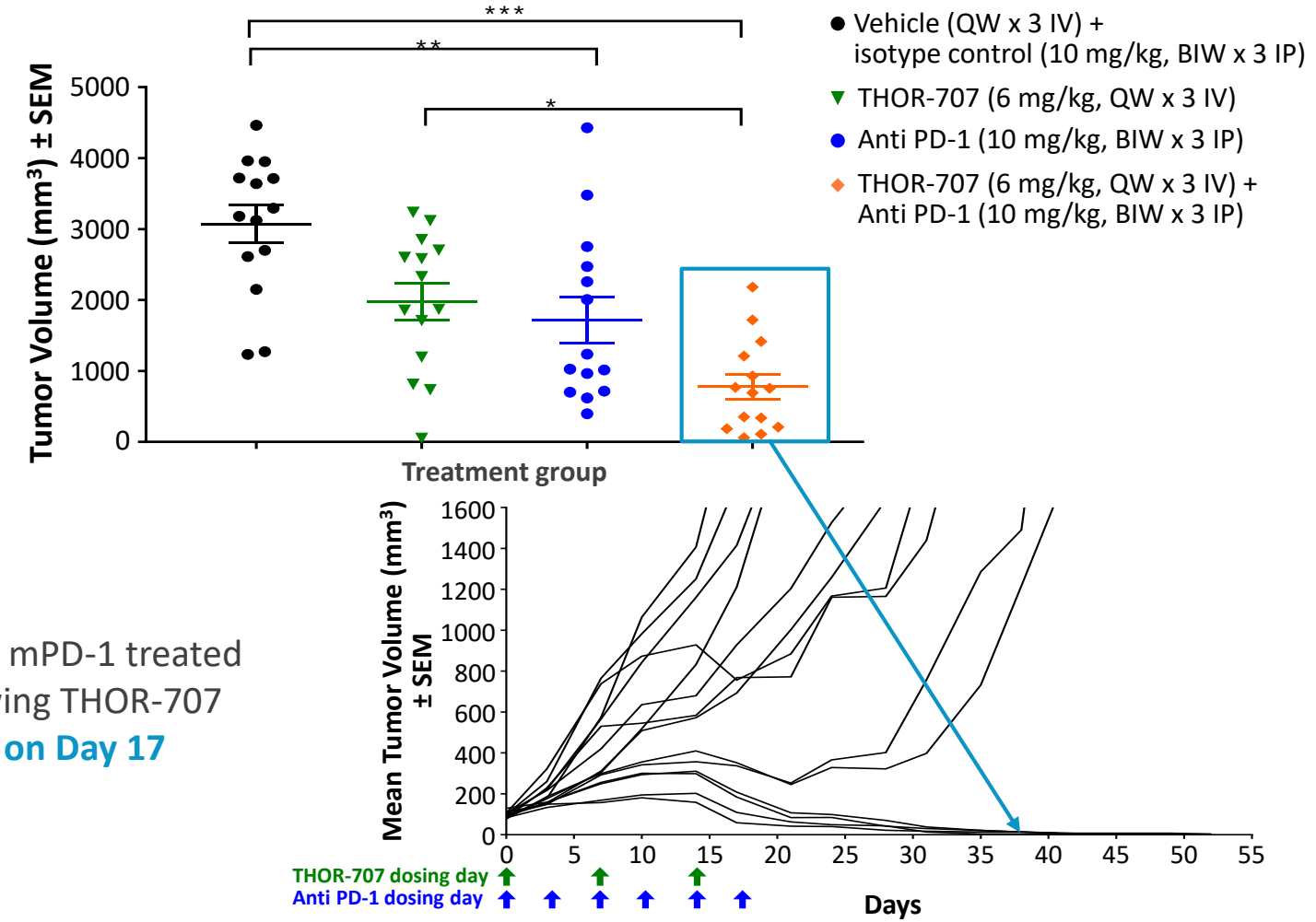
THOR-707

THOR-707 Is Efficacious as Single Agent and When Combined with mPD-1 Antibody

Single Agent, Day 17



Combo, Day 17



Durable regressions observed in THOR-707 + anti mPD-1 treated **mice with four mice tumor free on day 49** following THOR-707 **withdrawal on Day 14** and anti-PD-1 **withdrawal on Day 17**

*P ≤ 0.05; **P ≤ 0.01; ***P ≤ 0.001

Conclusions

- We applied our Expanded Genetic Alphabet platform technology to the design and production of THOR-707, a site-specifically pegylated IL-2 with a not-alpha IL-2R engagement profile
- THOR-707 induces the activation of both pSTAT5 and the molecular marker of proliferation Ki67, which is temporally correlated with the expansion of CD8+ T cells
- In NHP THOR-707 elicits maximal expansion of peripheral CD8+ T at 100 mcg/kg. There are no observations of VLS in those animals up to the maximal tested level of 1,000 mcg/kg
- The ability of THOR-707 to induce the expansion of CD8+ T cells results in anti-tumor effects both as single agent as well as in combination with an anti-PD1 mAb.
- THOR-707 IND submission is planned for 2Q19 with initiation of a Phase I/II clinical studies thereafter

The Synthorx Team

Better medicine is in our
(synthetic) DNA

- Ingrid B. Joseph
- Lina Ma
- Jerod L. Ptacin
- Carolina E. Caffaro
- Hans R. Aerni
- Kristine M. San Jose
- Michael J. Pena
- Robert W. Herman
- Yelena Pavlova
- David B. Chen
- Ken Bragstad
- Shukuan Li
- Jasmine Nguyen
- Laura K. Shawver
- Lilia K. Koriazova
- Marcos E. Milla