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

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

**HIGH DOSE**
- Anti-Tumor Activity
- Treg
  - \(\alpha\beta\gamma\) Receptor
  - Suppression
    - of tumor immune response
- \(\alpha\beta\gamma\) Receptor
- Push Beyond Suppression

**LOW DOSE**
- No Anti-Tumor Activity
- Treg
  - \(\alpha\beta\gamma\) Receptor

**Toxicity**
- \(\alpha\)-receptor mediated innate lymphoid cell release of IL-5 induces eosinophilia
- Eosinophil
  - \(\alpha\beta\gamma\) Receptor
  - Push to Stimulation
  - Degranulation
  - Vascular Leak Syndrome (VLS)
  - Hypotension
  - Hypoperfusion
  - Pulmonary Edema
  - Impaired Oxygenation
  - Renal Impairment
  - Peripheral Edema
  - Rhabdomyolysis

**Stimulation**
- Teff (CD8+), NK cells
  - \(\beta\gamma\) Receptor
  - Cytolysis
    - via tumor immune response
  - Tumor

Blood 2014 124:3572-3576
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
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.

PEG-IL-2 Synthorin Properties

Receptor Binding Properties

IL-2 Receptor α Chain

IL-2 Receptor β Chain

IL-2

THOR-707

IL-2

THOR-707
THOR-707

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

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

• 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

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

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 model1

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
• 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

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