Intratumoral delivery of mPH-804 (TIGIT targeting INTASYL compound) inhibits tumor growth and confers an inflammatory tumor microenvironment

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AACR American Association for Cancer Research
VIRTUAL ANNUAL MEETING II
June 22-24, 2020
Abstract: 5745

Introduction

Blocking PD-1 or CTLA-4 inhibitory immune checkpoints has shown remarkable clinical benefit. However, limited response indicates the need for attacking additional checkpoint molecules such as T-cell immune receptor with Ig and ITIM domains (TIGIT).

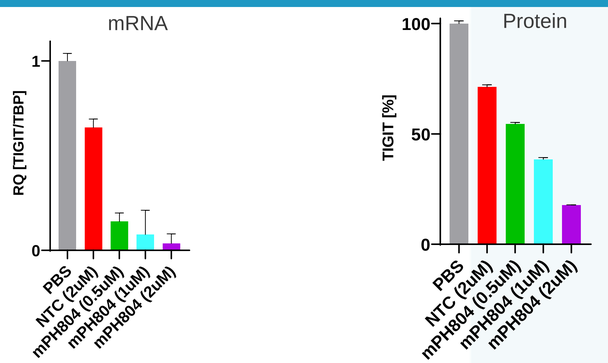
TIGIT is an inhibitory receptor expressed by activated T-cells, Tregs and NK cells. Its expression has shown to be highly elevated in tumor infiltrating lymphocytes (TILs), which ultimately limits their anti-tumor activity.

Several companies are investigating anti-TIGIT antibodies in clinical trials including Roche, Merck, Bristol-Meyers-Squibb, Astellas Pharma, Arcus Biosciences, Beigene, and Mereo Biopharma. Recently the anti-TIGIT antibody Tiragolumab (Roche) in combination with Tecentriq showed positive results against PD-L1-positive metastatic non-small cell lung cancer (NSCLC).

Previously, we have shown the ability of INTASYL™ RNAi technology to reprogram immune cells both *in vivo* (“*in situ*”) and *ex vivo* (adoptive cell therapy) improving their efficacy. INTASYL comprises an asymmetric duplex structure, a small duplex region (≤ 15 base pairs), a single-stranded phosphorothioate tail and chemical modifications to confer stability resulting in optimized tissue distribution and efficient cellular uptake without the need for delivery vehicles or special formulations.

Here we show how a TIGIT targeting INTASYL compound can be a viable alternative to anti-TIGIT antibodies.

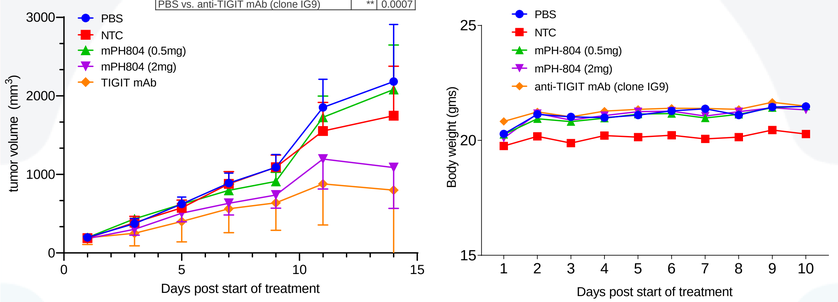
mPH-804 silences TIGIT in tumor cells *in vitro*



A cell-based screen identified a potent INTASYL compound able to knock down both mRNA (≥90%) and protein (≥80%) in the Hepa1-6 TIGIT expressing murine cell line. Hepa1-6 cells were incubated with mPH-804 for 72 hours, mRNA assayed by RT-qPCR and protein by flow cytometry.

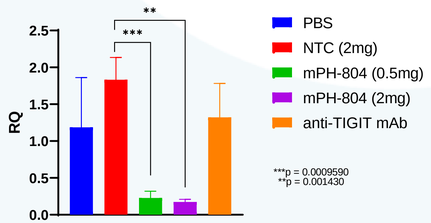
Intratumoral (IT) administration of mPH-804 inhibits tumor growth in a dose dependent manner

PBS vs. NTC	ns	0.57
PBS vs. mPH-804 (0.5mg)	ns	0.9961
PBS vs. mPH804 (2mg)	*	0.0106
PBS vs. anti-TIGIT mAb (clone IG9)	**	0.0007



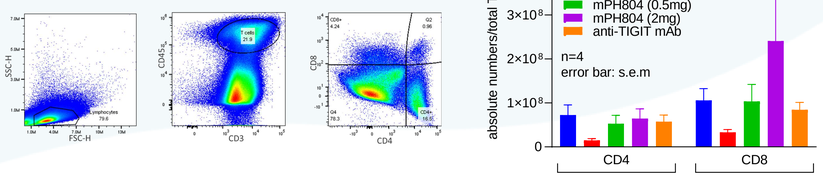
CT26 tumor-bearing mice were treated with INTASYL targeting mouse TIGIT (mPH-804) IT on Days 1, 3, 7 and 10. No overt toxicity or significant differences in body weight were observed.

IT administration of mPH-804 reduced TIGIT mRNA expression in TILs from CT26 tumors

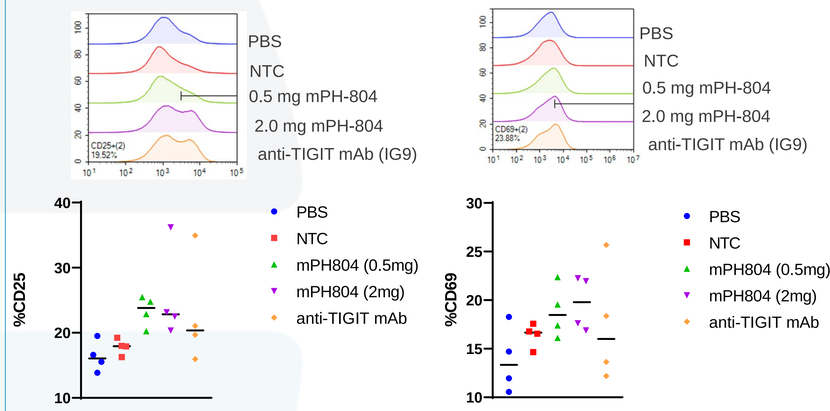


TILs were isolated from CT26 tumors and TIGIT mRNA was assayed by RT-qPCR.

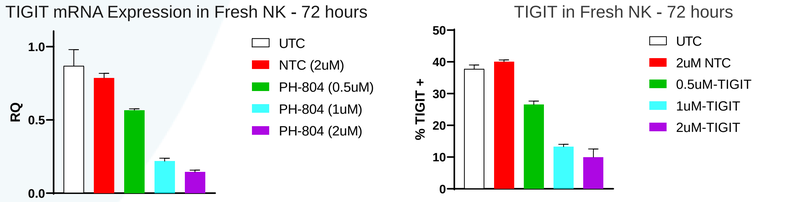
IT administration of mPH-804 increases CD8+ T cells in TME



T cell activation markers CD25 and CD69 are enhanced with mPH-804 treatment



hPH-804 silences TIGIT in primary human NK cells



Conclusion

These data demonstrate the potential of a TIGIT targeting INTASYL compound for suppression of TIGIT in the tumor microenvironment (TME). We show that mPH-804 is efficiently delivered intratumorally to immune cells and this results in a dose dependent inhibition of tumor growth. Analysis of the TME shows enhanced effector T cell function and increased CD8+ T cells. Further data shows the ability of PH-804 to silence TIGIT in other cells such as NK cells. These novel findings support the hypothesis that local TIGIT silencing with INTASYL is a viable alternative to checkpoint inhibiting antibodies and warrants further investigation in patients.

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