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NB002, a novel therapeutic antibody targeting unique epitope on TIM-3, presents potent antitumor activity

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Abstract

Antibody-based immune checkpoint inhibitors (ICI) targeting cytotoxic T lymphocyte antigen-4 (CTLA-4) or programmed death receptor-1 (PD-1) have significantly improved clinical outcomes in cancer treatment. T-cell immunoglobulin and mucin domain containing-3 (TIM-3) has been proposed as a target for cancer immunotherapy. Besides negatively modulating T cell status, TIM-3 is also expressed on natural killer (NK) cells, dendritic cells (DCs), macrophages and regulates immune responses bridging innate immunity and adaptive immunity. NB002 is a novel humanized Fc-engineered IgG1κ antibody, developed via NeologicsBio's integrated target validation & antibody screening Tier-A platform. NB002 bound to human TIM3 with high affinity in the low nanomolar range and antagonized the TIM-3 pathway effectively in reporter cell and primary cell assays. NB002 increased the secretion of IFN-γ by activated PBMC cells and enhanced activation and killing activity of NK cells. Moreover, it exhibited a distinctive activity of restoring immune cell functions, including antigen presentation and processing during anti-tumor immune responses, and exhibited superior efficacy in multiple humanized mouse models of cancer as monotherapy regimen. Importantly, X-ray crystallography demonstrated that NB002 recognized a unique epitope on TIM-3 and was confirmed by epitope binning assay and structural alignment. These data potentially explain novel features of NB002, restoring both acquired and innate immunity which could lead cold tumor to hot tumor. In summary, these data show that NB002 is a potent anti-TIM-3 antibody with pre-clinical properties. A phase 1 study is planned and patients with advanced metastatic solid tumors will be recruited.

Introduction

TIM-3 is a promising target for cancer immunotherapy.

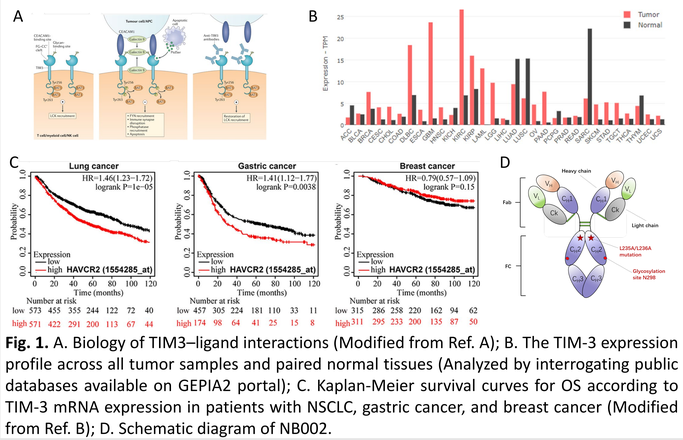

Fig. 1. A. Biology of TIM3–ligand interactions (Modified from Ref. A); B. The TIM-3 expression profile across all tumor samples and paired normal tissues (Analyzed by interrogating public databases available on GEPIA2 portal); C. Kaplan-Meier survival curves for OS according to TIM-3 mRNA expression in patients with NSCLC, gastric cancer, and breast cancer (Modified from Ref. B); D. Schematic diagram of NB002.

Results

NB002 binds to human TIM-3 only with high affinity in the low nanomolar range.

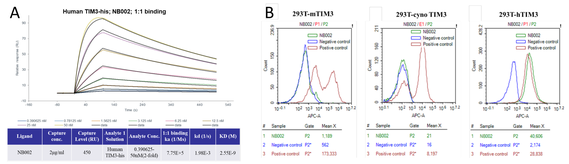

Fig. 2. A. Biacore SPR analysis of human TIM-3-his to captured NB002; B. Binding capacity of NB002 to 293T cells stably expressing mouse TIM-3, cynomolgus TIM-3, or human TIM-3 examined by FACS.

NB002 binds TIM-3 expressing cells specifically.

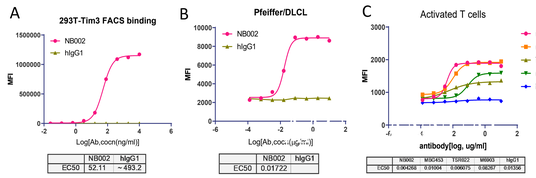

Fig. 3. A. NB002 bound to TIM-3 in 293T-hTIM-3 cell, but did not bind to 293T cells (Data no shown); B. Binding capacity of NB002 to naturally expressed TIM-3 on Pfeiffer cells; C. Binding capacity of NB002 and reference antibody analog to activated human T cells.

NB002 has its Fc-mediated antibody effector functions nullified.

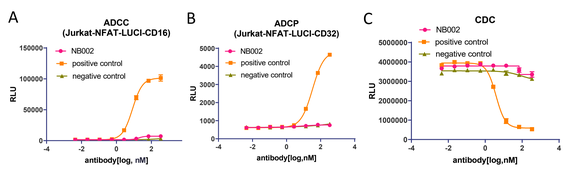

Fig. 4. A. NB002 had no detectable antibody dependent cellular cytotoxicity (ADCC); and B. antibody dependent cellular phagocytosis (ADCP) activities by Jurkat reporter system; C. NB002 had no detectable complement-dependent cytotoxicity (CDC) effect.

NB002 exhibits an unique epitope binding of TIM3 antigen.

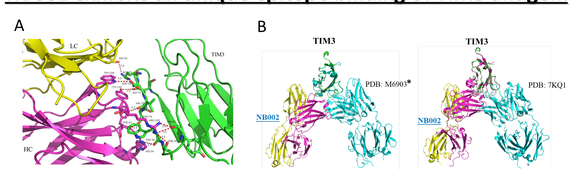

Fig. 5. A. Crystallography analysis revealed the binding epitope of NB002 on TIM-3; B. Docking simulation of NB002 and reference antibody analog available on Protein Data Bank (PDB) .

NB002 binds to TIM-3 in a distinctive pattern.

A

	% Inhibition	Analyte: NB002	MBG453*	M6903*	TSR022*
Solid phase	NB002	100.00%	24.51%	54.21%	9.59%
	MBG453	19.25%	100.00%	99.52%	90.44%
	M6903	55.50%	96.97%	100.00%	81.45%
	TSR022	43.22%	98.87%	101.23%	100.00%

B

Fig. 6. A. The binding of NB002 and reference antibody analog to TIM-3 were characterized through epitope binning; B. Schematic diagram of relevant epitopes between NB002 and other reference antibody analog.

NB002 remarkably enhances T and NK cells functions.

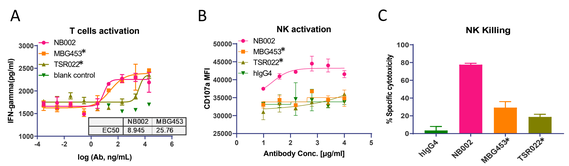

Fig. 7. NB002 and reference antibody analog promoted T cells and NK cells activation by measuring IFN-gamma release (A), CD107a expression (B), and direct NK cell killing (C).

NB002 restores DCs activation suppressed by tumor cells.

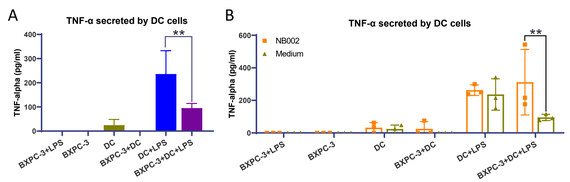

Fig. 8. A. Monocyte derived DC cells were suppressed by BxPC-3 human pancreatic cancer cells under LPS stimulus; B. NB002 restored DC activation from the inhibition by BxPC-3 cells.

NB002 up-regulates genes associated with IFN-γ and antigen presentation.

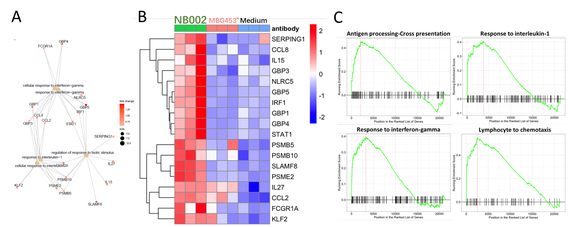

Fig. 9. RNA-seq analysis of human monocytes treated with NB002 and reference antibody analog. A. Gene ontology analysis on upregulated genes of NB002 treatment versus medium control was shown. B. Visualizing the expression of genes enriched in (A) by heatmap. C. Gene sets for response to IFN-γ and antigen presentation were significantly enriched by GSEA analysis.

NB002 preserves activated TIM-3-expressing T cells.

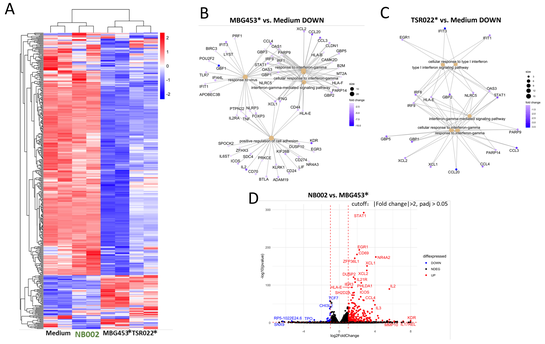

Fig. 10. CD3/CD28 antibody activated Jurkat-TIM3 cells treated with NB002 and reference antibody analog were analyzed by RNA-seq analysis. A. Heatmap showed the differential gene expression by different antibody treatment (fold change >= 2, adjusted p value < 0.05); (B-C) Gene ontology analysis on downregulated genes treated by MBG453 or TSR022 versus medium control respectively; D. The differential genes of NB002 treatment versus MBG453 were visualized with volcano plot.

NB002 monotherapy demonstrates efficacy in multiple preclinical models.

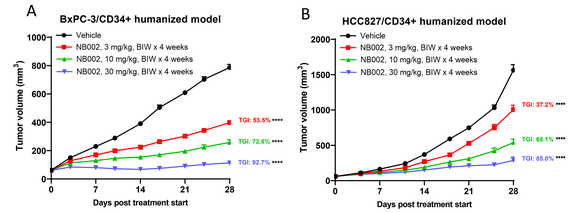

Fig. 11. NB002 as single agent showed a strong anti-tumor activity in BxPC-3 human pancreatic cancer (A) and HCC827 human non-small cell lung cancer (B) hCD34+ humanized mice model.

Summary

1. **NB002 is a novel humanized Fc-engineered IgG1κ antibody specifically binding to an unique epitope on human TIM3 with nM level affinity.**
2. **NB002 enhances T cells activation and killing activity of NK cells, restores DCs function, promotes antigen presentation, and preserves TIM-3 expressing T cells.**
3. **NB002 monotherapy demonstrates potent anti-tumor efficacy in multiple humanized models.**

REFERENCES

A. Wolf Y , Anderson A C , Kuchroo V K . TIM3 comes of age as an inhibitory receptor[J]. Nature Reviews Immunology, 2020, 20(3):173-185.

B. Qin S, Dong B, Yi M, Chu Q and Wu K (2020) Prognostic Values of TIM-3 Expression in Patients With Solid Tumors: A Meta-Analysis and Database Evaluation. Front. Oncol. 10:1288.

Disclaimer:

1. NB002 is an investigational drug candidate that is currently being submitted to the U.S. Food and Drug Administration for Investigational New Drug (IND) Application with. The safety and efficacy of NB002 have not been established.
2. TSR022* and MBG453* were synthesized by Neologics using sequences of TSR022 and MBG453 available on WHO INN list; M6903* was synthesized by Neologics using sequences of M6903 available on PDB (Protein Data Bank) .

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