Pre-clinical characterization of anti-CEACAM1 antibody

Jinyu Dong[1], Yu Zhang[1], Baiyang Wang[1], Tingting Pu[1], Liegang Shao[1], Binbin Wang[1], Dong Wang[1], Jie Ni[1], Sunan Li[1], Haojie.Wang[1], Bishnu Nayak[2], Xin Dong[1,2]

[1]NeoLogics Bioscience Co. Ltd., Suzhou, China; [2]NeoLogics Early Discovery Center, San Diego, CA.

Jinyu.dong@neologicsbio.com; http://en.neologicsbio.com/

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Biologics for immune modulation

Abstract

Targeting checkpoint molecules cytotoxic T lymphocyte antigen-4 (CTLA-4) or programmed death receptor-1 (PD-1) expressed on immune cells has shown promising outcomes in the treatment of cancer patients. Nevertheless, only a small portion of patients benefited from current ICI treatments, so there should be other mechanisms potential immune evasion. The carcinoembryonic antigen cell adhesion molecule 1 (CEACAM1) is an activation-induced inhibitory molecule on T and NK cells. In a wide range of cancer types, CEACAM1 is also expressed on tumor cells and other immune cells including macrophages and neutrophils. Homophilic interaction between CEACAM1 or heterophilic binding between CEACAM1 and other ligands dampens NK and T cell function, mediates tumor migration, and promotes tumor angiogenesis, which implies that CEACAM1 is an important molecule for tumor progression.

Here, we describe the identification and characterization of a novel humanized anti-human CEACAM1 therapeutic antibody NB003, which was developed via Neologics' novel target validation and antibody screening Tier-A platform. NB003 specifically binds to recombinant human CEACAM1 with nM level affinity, significantly enhances T cell activities and NK killing on CEACAM1 or CEACAM5 expressing tumor cells, and inhibits tumor cell migration and polyploidy in vitro as well. NB003 evidently reduces melanoma and pancreatic tumor growth in humanized mouse models.

Taken together, we have demonstrated NB003 specifically enhance NK cell cytotoxicity, modulate T cell immune activation and inhibit tumor migration, which support further clinical investigation for various indications.

Background

CEACAM-1 is widely expressed on tumor cells and tumor infiltrating lymphocytes, and the elevation of CEACAM1 correlates with tumor progression.

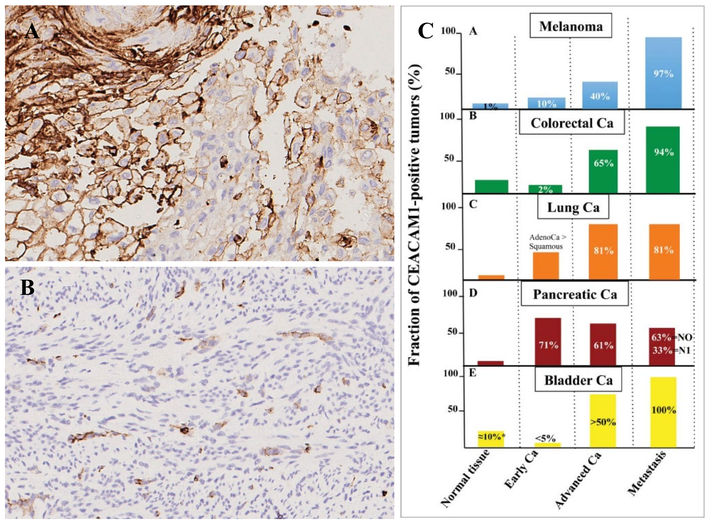

Figure 1. **(A)** CEACAM1 is expressed on Uterine corpus endometrial tumor cells (UCEC). **(B)** CEACAM1 is expressed on immune cells in UCEC. **(C)** The expression level of CEACAM1 increases as the disease progress in relevant tumors (referred to ONCOIMMUNOLOGY 2017, VOL. 6, NO. 7, e1328336)

Result

NB003 restores T cell activation.

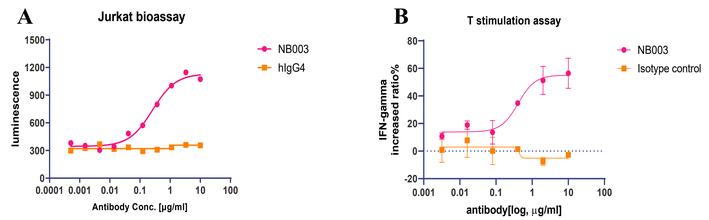

Figure 2. **(A)** NB003 enhances NFAT activity in CEACAM1-NFAT-luci-Jurkat cell line in the present of anti-CD3 and anti-CD28 antibodies. **(B)** NB003 increases IFN-gamma secretion in activated T cells when it co-cultured with CEACAM1 and anti-CD3 overexpressing 293T stable cell line.

NB003 enhances cytotoxic cells killing efficacy to CEACAM1 expressing tumor cells.

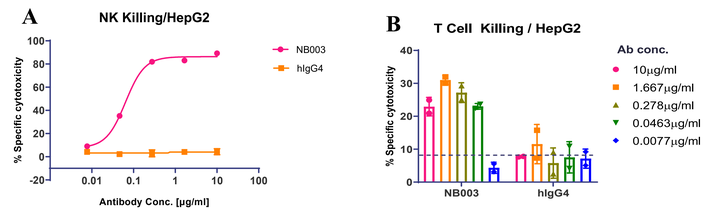

Figure 3. NB003 enhances the killing activity of both NK **(A)** and cytotoxic T cell **(B)** on CEACAM1 expressing tumor cells HepG2, but not to CEACAM1 and CEACAM5 negative tumors (data not shows)

NB003 enhances cytotoxic cells killing effects to CEACAM5 expressing tumor cells may through blocking CEACAM1-CEACAM5 interaction.

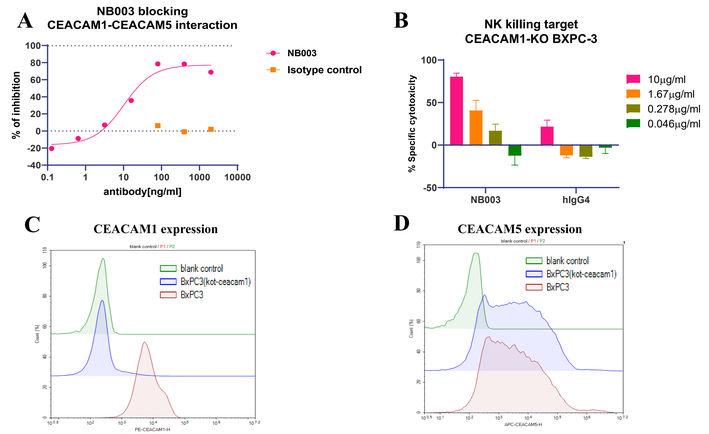

Figure 4. **(A)** NB003 inhibits CEACAM1-CEACAM5 interaction in a dose dependent manner. **(B)** NB003 enhances killing effect of NK cells against CEACAM1-KO BXPC-3 cells. The expression of CEACAM1 **(C)** and CEACAM5 **(D)** on CEACAM1 knockout cells are shown.

NB003 reduces tumor migration and polyploidy mediated by macrophage.

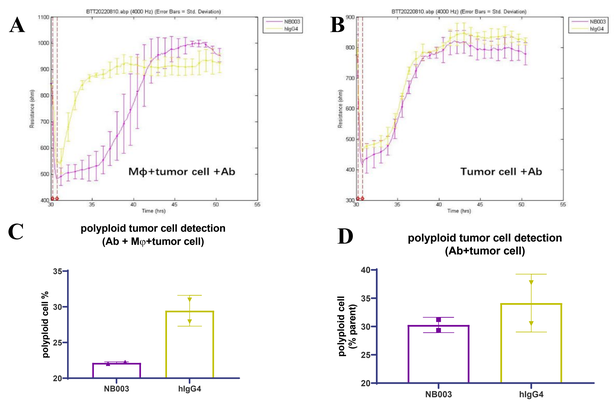

Figure 5. The effect of antibodies on tumor cells migration was examined by Wound Healing assay using an electrical cell-substrate impedance sensing system (ECIS). NB003 significantly extended the migration time of BXPC-3 cells to reach plateau when co-cultured with macrophage **(A)**, but this effect disappeared when macrophage was absent in assay system **(B)**. The percentage of polyploidy of BXPC-3 cells also decreased obviously when co-cultured with macrophage **(C)**, but no difference was observed when macrophage was absent **(D)**.

Anti-tumor effect of NB003 was observed in CEACAM1+ Melanoma and PAAD tumor model.

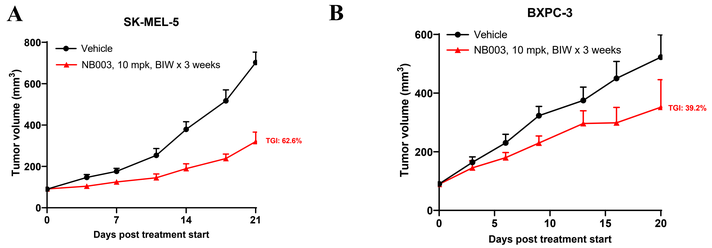

Figure 6. Human melanoma cancer cells SK-MEL-5 **(A)** or human pancreatic tumor cells BxPC-3 **(B)** were subcutaneously implanted into human PBMC humanized nude mice. The mice were treated i.p. with 10 mg/kg of the NB003. NB003 Treatment resulted in maximal tumor growth inhibition.

Conclusions

- **NB003 strengthens T cell response by enhancing NFAT activity in reporter cell line or IFN-gamma secretion in activated T cells**
- **NB003 effectively enhances cytotoxic cells killing efficacy to CEACAM1 or CEACM5 expressing tumor cells**
- **NB003 reduces tumor migration and polyploidy mediated by macrophage.**
- NB003 inhibits tumor growth in humanized mouse model.

Reference:

Sally K. Y. To, Maggie K. S. Tang, Yin Tong, Jiangwen Zhang, Karen K. L. Chan, Philip P. C. Ip, Jue Shi,* and Alice S. T. Wong. Adv. Sci. 2022, 2103230

AACR ANNUAL MEETING 2023,Orlando, Florida