**HER3 as a potential cancer target**

**A Novel Anti-HER3 Monoclonal Antibody**

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| **Project Number:** | 1773 |
| **Principal Investigator:** | Prof. Yosef Yarden |
| **Patent Status:** | Pending |

**Overview**

**A novel high affinity monoclonal antibody against the HER3 receptor.**

**Background and Unmet Need**

The ErbB/HER family of receptor tyrosine kinases includes epidermal growth factor receptor (EGFR, also termed ErbB-1, HER1), HER2 (ErbB-2), HER3 (ErbB-3) and HER4 (ErbB-4). These receptors regulate cellular proliferation and migration during both embryogenesis and oncogenesis. Kinase activation of the HER family members is generally considered to involve ligand-induced active dimer formation. HER3, has an influence on signaling pathways, via its preferential dimerization with EGFR or HER2, and its subsequent phosphorylation by these active tyrosine kinases. Similar to EGFR and HER2, the identification of somatic mutations in HER3 was recently reported in colon and in gastric cancer, reflecting the potential importance of this receptor for tumor progression.

Targeted therapies against HER family members using monoclonal antibodies (mAbs) and/or chemotherapeutic agents are widely used in cancer therapy. However, some cancers become resistant to anti-HER targeted therapy after prolonged treatment. Several studies reported that these resistant tumors show strong expression of HER3.

Drugs targeting HER3 that are currently developed or in clinical trials show promising results, but their efficacy can be viewed as modest. **It is therefore imperative to develop new strategies to improve the benefit of HER3 targeting.**

**The Solution**

The group of Prof. Yosef Yarden have developed a novel high affinity (KD <10nM) anti-HER3 antibody capable of intercepting stroma–tumor interactions, accelerate HER3 degradation, and possibly inhibit tumor growth better than other antibodies presently available. These anti-HER3 mAbs can act either as an individual anti-cancer treatment or in combination with other therapies.

**Technology Essence:**

The team of Prof. Yarden created an anti-HER3 mAb, named NG33, using a fusion protein combining the extracellular domain of HER3 and human Fc (IgB3) to immunize mice. The purified mAb bound the native receptor with a KD value of 2.6 nM as measured using FACS.

**Applications and Advantages**

* A novel treatment targeting the HER3 receptor.
* Can be used to augment the efficacy of other anti HER receptor drugs.

**Development Status**

The research team of Prof. Yosef Yarden tested verified the binding affinity of NG33 using FACS and NIH/3T3-R2R3 cells, which co-overexpress ectopic HER2 and HER3. NG33 capacity to down-regulate HER3 was determined by Western blotting using various cancer cell lines and was shown to induce faster and more extensive receptor degradation than neuregulin (NRG), HER3 native ligand. In direct competition assay NG33 successfully blocked NRG binding to HER3, preventing NRG-induced HER3 phosphorylation and subsequent downstream activation. NG33 treatment also reduced NRG-induced migration in ovarian cancer cells.

Using MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay, NG33 was shown to inhibit (20–50%) NRG-induced cell survival in several cancer cell lines (breast, MCF7 and SKBR-3; lung, NCI-H322M; ovarian, OVCAR-5; pancreatic, BXPC3; and gastric, N87). NG33 was also shown to be as effective as a clinically approved therapeutic mAb directed against HER2 in its ability to decrease cancer cell growth, as tested using N87, a gastric cancer cell line overexpressing HER2 and co-expressing EGFR and HER3. The same efficacy was shown both *in vitro* by using a colorimetric assay on NRG-stimulated N87 cells, and *in vivo* by using N87 cell xenografts.

In other *in vivo* testing the team used xenografted mice and a series of tumor cell lines (gastric, N87; lung, A549; pancreatic, BXPC3; ovarian, OVCAR-5; and head and neck, CAL-27) in two separate experiments. NG33 demonstrated effective cell survival inhibition, specifically in the pancreatic BXPC3 cell line which is known to over express NRG and HER3.

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