Breast Cancer Vaccines: Antibody Recombinant Proteins, and Peptides

Breast cancer is a type of cancer originating from breast tissue of humans and other mammals. Worldwide, breast cancer comprises 23% of all cancers in women. In 2008, breast cancer caused 458,503 deaths worldwide (13.7% of cancer deaths in women). Breast cancer is more than 100 times more common in women than in men. Prognosis and survival rates for breast cancer vary greatly depending on the cancer type, stage, treatment, and geographical location of the patient. Self-examination, mammography and clinical breast exam can indicate an approximate likelihood that a lump is cancer. Breast cancers are classified by several grading systems (histopathology, Grade, Stage, Receptor status such as ER/PR/Her2 positive). Each of these influences the prognosis and can affect treatment response. Breast cancer is usually treated with surgery and then possibly with chemotherapy or radiation, or both. A multidisciplinary approach is preferable. For the purpose of 'Breast Cancer Vaccine', we will review ‘Her2 positive’ cancers that comprise about 30% of breast cancer.

HER2 (Human Epidermal Growth Factor Receptor 2) also known as Neu, ErbB-2, CD340 (cluster of differentiation 340) or p185 is a protein that is encoded in humans by the ERBB2 gene. HER2 is a member EGFR/ErbB family. The HER proteins, including Her2, regulate cell growth, survival, adhesion, migration, and differentiation—functions that are amplified or weakened in cancer cells. Since breast cancer cell overexpress and need Her2 protein for their proliferation, target or induce neutralization of Her2 would impair the ability of breast cancer to spread and grow. Herceptin (trastuzumab made by Genentech and approved in 1998) is a humanized monoclonal antibody that binds to Her2 protein and interferes with its functions. Herceptin is made by recombinant DNA technology in then injected into patient. It increases the survival of people with cancer by 20-25 months in late stages. However, cancers usually develop resistance to trastuzumab. Approx. 70% of HER2+ patients do not respond to treatment. In fact resistance is developed rapidly by treatment, in virtually all patients. The antibody treatment is also expensive ($100,000 per year). Another monoclonal antibody, Pertuzumab, which inhibits dimerization of HER2 and HER3 receptors, was approved by the FDA in 2012.

Breast cancer vaccines mimic the success of Herceptin by immunizing with either large recombinant Her2 protein fragments or various antigenic peptides (single or mixture). The objective is to induce the production of antibodies in the patients. This will reduce the cost of producing and injecting Herceptin and also reduce Her2 resistance. NeuVax, developed by Galena Biopharma, is a peptide-based vaccine aimed at preventing or delaying the recurrence of breast cancer in cancer survivors who achieve remission after standard of care treatment (e.g., surgery, radiation chemotherapy). It consists of the E75 synthetic peptide (Her2 369-377) initially isolated from HER2/neu proto-oncogene combined with the immune adjuvant, granulocyte macrophage colony stimulating factor (rGM-CSF from yeast).

GP2 peptide (654-662) is a 9 aa HLA-A2-restricted peptide derived from the transmembrane domain of HER2. It is as effective as E75 at inducing a CTL response, suggesting that it might be more immunogenic than E75. A phase I clinical study using GP2 in combination with GM-CSF is ongoing. AE37 peptide (776-790 aa) is a HER2/Neu-derived epitope linked to I-Key peptide (I-Key/HER2/neu hybrid peptide or AE37). A Phase I clinical trial administering AE37, a HER2/neu Class II epitope to disease-free, NN breast cancer patients showed that the Li-Key moiety, a 4-amino acid (LRMK) epitope from the MHC class II-associated invariant chain (Li protein), increases T-helper cell stimulation. QIAGM5SYL is a peptide, derived from the ECD of Her2. It is naturally presented by various HER2 positive cell lines.

**Multi peptide vaccines**: These are peptides derived from the ICD and ECD of Her2. ECD-derived peptides (p42 (aa 42–56), p98 (aa 98–114) and p328 (aa 328–345); ICD-derived peptides (p776 (aa 776–790), p927 (aa 927–941) and p1166 (aa 1166–1180); Derived from both domains: p369 (aa 369–386), p688 (aa 688–703) and p971 (aa971–984). Peptides derived from the HER2/trastuzumab interface Peptides derived from the HER2/trastuzumab interface (563CYC is a cyclic peptide containing the sequences 563-598; 585CYC is a cyclic peptide containing sequences 585-598. 597ACY is a cyclic peptide containing sequences 597-626. The last a.a cyan is mutated to Leu so as to prevent interference with natural disulphide formation. pE2A is a peptide containing sequences 613-626.

Her2 Protein Vaccines: HER2 ICD (aa 676-1255): phase I clinical trial showed T cell response specific for HER2 ICD in 89% of immunized patients and 82% developed anti-Her2 IgGs. dHER2 is a recombinant anti-Her2 protein-based vaccine, made of the HER2 ECD and a portion of the transmembrane domain, was effective in inhibiting carcinogenesis in a transgenic mouse model; Herre2/neu peptide vaccine comprising measles virus epitope MVF-HER-2 (266-296) and MVF-HER-2 (597-626) emulsified with non-MDP in ISA 720.

Her2 DNA Vaccines: DNA vaccines encode a modified human Her2 protein without tyrosine kinase activity. All of them induced both cellular and humoral immune responses leading to in vivo tumor protection. pE2A which encodes a full length HER2 in which Lys753 has been substituted by Arg to remove the ATP-binding Lys residue; pE2TM encodes the HER2 signal peptide, extracellular and transmembrane domains but not the intracellular; psecE2 encodes the 1–505 of ECD as a secreted protein. pcyrE2 (i.e., HER2 without signal peptide) elicited only a CD8+ TL response; p1B5 encodes Her2 ECD and the TM domain, was effective in inhibiting carcinogenesis in a transgenic mouse model; MAVA-BN-Her2 formed by a non-replicating viral vector encoding a truncated form of HER2 protein (without its ICD) and two universal T epitopes of the tetanus toxin used to boost the immune system.

All of the above vaccines (her2 peptides, protein or DNA) must be able to induce robust antibodies to Her2 protein. It will also be important to identify subtype of her2-antibody as a result of vaccine. ADI has developed antibody ELISA kits for animals and humans to determine the efficacy of various existing Her2 vaccines and test new vaccines. ADI is further expanding the antibody ELISAs to measure IgG (and IgG1, IgG2a, IgG3, IgG4) and IgM classes. ELISA kits are also available to measure the her2 in animals and humans, and if patients are producing antibodies to HER2 in response to Herceptin immunotherapy. We have also developed ELISA kits to detect if cancer patients or animals already have autoantibodies to Herceptin immunotherapy. We have also developed ELISA kits to detect if cancer patients or animals already have autoantibodies to Herceptin immunotherapy.