HER2 CANCER VACCINE OPTIMIZATION BY COMBINING DROSOPHILA S2 INSECT CELL MANUFACTURING WITH A NOVEL VLP-DISPLAY TECHNOLOGY

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Breast cancer is a widespread oncology indication affecting more than 1.3 million people worldwide annually, 20%-30% of which are HER2 positive. HER2 is a tyrosine kinase receptor that is frequently overexpressed in several solid-tumor cancers (incl. breast, prostate, gastric, esophageal and osteosarcoma) where it denotes an aggressive phenotype, high metastatic rate, and poor prognosis. In a human context, passive HER2-targeted immunotherapy using monoclonal antibodies (mAb, e.g. Trastuzumab and Pertuzumab) has proven to be an effective treatment modality, which has dramatically improved clinical outcomes. Unfortunately, mAb therapy is very expensive and the repeated injections of high doses can be associated with severe side-effects that reduce efficacy.

Vaccines are highly cost-effective, but overall progress in development of anti-cancer vaccines based on cancer-associated antigens (e.g. HER2) has been hampered by inherent immune-tolerogenic mechanisms rendering the immune system incapable of reacting against the body’s own cells/proteins (i.e. self-antigens). Consequently, many attempts to develop anti-cancer vaccines have failed in clinical trials due to insufficient immunogenicity. To circumvent this central issue, we have developed a proprietary virus-like particle (VLP)-based vaccine delivery platform. Notably, the VLP-platform is currently the only available technology to effectively facilitate multivalent “virus-like” display of large/complex vaccine antigens. This is key to overcome immune-tolerance and enable induction of therapeutically potent antibody responses directed against cancer-associated self-antigens.

In this talk I will discuss the non-viral Drosophila S2 insect cell production system and how it was applied to the production of hHer2/neu antigen, including using advanced production methods such as perfusion for clinical material manufacture. Furthermore, I will present our data from a transgenic mouse model for spontaneous breast cancer development, where high-density display of the HER2 extracellular domain on the surface of virus-like particles (VLPs) enables induction of therapeutically potent anti-HER2 responses. Split-protein tag/catcher conjugation was used to facilitate directional covalent attachment of HER2 to the surface of icosahedral bacteriophage-derived VLPs, thereby harnessing the VLP platform to effectively overcome B-cell tolerance. Vaccine efficacy was demonstrated both in prevention and therapy of mammary carcinomas in HER2 transgenic mice. Thus, the HER2-VLP vaccine shows promise as a new strategy for treatment of HER2-positive cancer. The modular VLP system may also represent an effective tool for development of self-antigen based vaccines against other non-communicable diseases.