

Potent Adjuvant Activities of Novel NKT-stimulatory Glycolipids

Alice L. Yu

The Genomics Research Center, Academia Sinica, Taipei, Taiwan

Dr. Alice L. Yu

Dr. Yu is a Distinguished Research Fellow and Associate Director of the Genomics Research Center at the Academia Sinica in Taiwan. Prior to her return to Taiwan at the end of 2003, she was the Professor and Chief of the Division of Pediatric Hematology/Oncology at the University of California in San Diego. After obtaining her MD from National Taiwan University, Dr. Yu received her PhD in Microbiology & Immunology from the University of Chicago. After completing her pediatric residency training, she received Immunology Fellowship trainings at the Boston Children's Hospital, Harvard School of Medicine. She then joined UCSD as a tenured faculty in 1978. Dr. Yu has been pursuing translational medicine throughout her career. Her research focus lies in the immunotherapy of cancer and molecular biology of cancer and glycomics of breast cancer stem cells. As a pioneer of anti-GD2 immunotherapy in neuroblastoma, Dr. Yu has taken a chimeric anti-GD2 from initial IND filing all the way to an international phase III randomized study of the chimeric anti-GD2 in high-risk neuroblastoma, which has recently demonstrated the efficacy of this immunotherapy.

We have evaluated more than 40 glycolipid analogs of α -Galactosylceramide (α -GalCer) synthesized by Wong's group for their immune-enhancing activities and shown that several novel glycolipids containing an aromatic ring in their acyl tail or sphingosine tail to be more potent than α -GalCer in activating / expanding NKT cells, and inducing Th1, Th2 cytokines and chemokines. We assessed the adjuvant effects of α -GalCer and its analogs for vaccines containing protein, DNA or carbohydrate antigens. Mice immunized with tetanus toxoid (TT) + glycolipid developed significantly greater antibody production than tetanus toxoid + alum. Among the 4 glycolipids tested, C11 and C16 induced the highest antibody levels, followed by C9 and α -GalCer. Upon boosting with TT at 24 weeks, glycolipids treated groups showed greater antibody production and T cell proliferation than alum group. Similarly, α -GalCer and its analogs also displayed significant adjuvant activities for DNA vaccine expressing hemagglutinin antigen of avian influenza virus, H5N1. At suboptimal DNA dose, several glycolipids containing aromatic ring were more potent than α -GalCer in enhancing anti-H5 titer and increase the number of H5-specific interferon- γ secreting CD8⁺ T cells. More importantly, it conferred significantly better protection from lethal challenge of H5N1 viruses than low dose DNA vaccine alone or with alum as adjuvant. Lastly, the adjuvant activities of these glycolipids were evaluated for carbohydrate-based antigens, which are well known to be poor immunogens. Mice were immunized with a hexasaccharide antigen overexpressed in breast cancer, Globo H conjugated to KLH, with / without NKT stimulatory glycolipids as adjuvants. As expected, Globo H-KLH was barely immunogenic. The addition of glycolipids

induced significant titers of antibody reactive with not only Globo H but also Gb5. The latter was also highly expressed in breast cancer and breast cancer stem cells. These findings suggest that NKT stimulatory glycolipids may be useful as vaccine adjuvant for a variety of antigens including poorly immunogenic glycans which are potential targets for cancer immunotherapy.