Molecular Dynamics for Antibody Drug Development against Cancer Recurence and Metastasis : An Introduction to Japanese Government Project

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Antibody therapeutics are widely accepted as molecular targeting drugs with less adverse effect, and the clinical use grows rapidly to nearly 40 billion USD/year. Traditional 1st generation antibody kills cancer cells by immune mechanisms such as ADCC (antibody-dependent cell cytotoxicity) or CDC (complement dependent cytotoxicity), which requires high density of target proteins on cancer cell surface as well as binding of higher number of antibodies. Response rates of 1st generation antibody drugs may be relatively low (30-40%). In order to enhance cytotoxic activities, 2nd generation antibody drugs are modified by conjugating isotopes or toxins, or by reducing fucose contents. Conjugation of isotopes or toxins may be very effective, but, however, adverse effects such as bone marrow suppression may deteriorate. These adverse effects may be improved by shortening of exposure tile using pre-targeting strategy. Initially, cancer cells are marked by a binding domain of antibody protein,single chain variable fragment (scFv), conjugated with streptoavidin (SA). It takes nearly 3 days for the binding of antibody to cancer cells, and additional several days will be needed to wash out remaining antibodies. After completion of wash out, the marked cancer cells are recognized biotin conjugated with either diagnostic probes or therapeutic reagents. As compared with binding affinities of antigen-antibody, biotin-streptoavidin has highest binding affinity. This enables isotopes or toxins conjugated with biotin can reach cancer cells fairly quickly and remaining isotopes or toxins are rapidly cleared out from the human body. The aim of current project is developing this pre-targeting drugs within 5 year.