30PE-01

AFFINITY OF THERAPEUTIC MONOCLONAL ANTIBODIES AND FUSION PROTEINS TO NEONATAL FC RECEPTOR (FCRn)

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The neonatal Fc receptor (FcRn) plays a critical role in regulating IgG homeostasis, in addition to the role in the transfer of IgG from the mother to the fetus or newborn. FcRn binds Fc domain of IgG at acidic pH of the endosome and protects IgG from degradation. The number of approved Fc domain-containing protein drugs (i.e. antibodies or Fc fusion proteins) has been rapidly increasing over the last several years, and several are recognized to be essential drugs for the treatment of serious diseases such as cancer and rheumatoid arthritis at present. Since these drugs contain Fc domain of IgG, FcRn may affect their pharmacokinetics. In order to elucidate the role of FcRn in pharmacokinetics of Fc domain-containing protein drugs in human, we firstly evaluated the affinity of the drugs to FcRn with Surface Plasmon Resonance (SPR). The soluble portion of human FcRn produced in CHO cells was purified and immobilized to flow cells on CM5 biosensor chip. A BIACORE 2000 biosensor system was used to assay the interaction of FcRn with the analytes. The analytes used were human antibody (Adalimumab), humanized antibodies (Dacituzumab and Omalizumab), chimeric antibody (Infliximab), and Fc fusion proteins (Etanercept and Alefacept). The affinity of Fc domain-containing protein drugs to FcRn was almost correlated with the serum half-lives in humans, suggesting the importance of FcRn in regulating serum half-life of these drugs.

30PE-02

ANTIGEN-DEPENDENT INTERNALIZATION IS RELATED TO RAPID ELIMINATION FROM PLASMA OF HUMANIZED ANTI-HM1.24 MONOCLONAL ANTIBODY (AHM)

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AHM is a humanized anti-HM1.24 monoclonal antibody that binds to the antigen HM1.24. The antigen was over-expressed on multiple myeloma cells. The pharmacokinetic studies of AHM in cynomolgus monkeys were conducted, and HM1.24 antigen-dependent internalization mechanism was investigated to estimate the contribution on the pharmacokinetics of AHM using KPMM2 cells which is expressed HM1.24 antigen on cell surface. The elimination of AHM from plasma after single intravenous doses of 0.2–20 mg/kg in monkeys was rapid compared with that in other therapeutic antibodies. Non-linear pharmacokinetics was observed, and total clearance decreased with increasing doses. The elimination of AHM from plasma was accelerated when AHM was given intravenously once a week for 4 weeks. The internalization of 125I-AHM bound on the surface of KPMM2 cells was rapid. AHM and degradation products were detected within cells. The occupancy ratio of HM1.24 antigen by AHM rose with increasing in AHM concentration, the ratio showed about 90% at the concentration corresponding to 10-fold of Kd value.

Conclusion: The rapid elimination of AHM from plasma in monkey would be due to HM1.24 antigen-dependent internalization processes. The saturation of the binding of AHM to the antigen may be consistent with the non-linear pharmacokinetics of AHM in monkey. The repeated dose pharmacokinetic study indicates that HM1.24 antigen may be up-regulated by continuous stimulation of AHM.