

AbstractID: 1392 Title: Estimation of Area under the Curve (AUC), Mean Residence Time (MRT) and Associated Errors for Cognate Monoclonal Antibodies in the Blood

Cognate antibodies to a tumor antigen can be produced by recombinant DNA engineering. To evaluate their relative effectiveness in tumor targeting, it is important to determine pharmacokinetic results for each protein. Fundamental variables are blood area under the curve (AUC) and mean residence time (MRT). Two cognate cT84.66 antibodies to Carcinoembryonic Antigen (CEA) were engineered, radioiodinated and evaluated in experiments using human colon tumor LS174T xenografts in nude mice. Cognates included the single chain (scFv) and minibody with respective molecular weights (MW) of 28 and 80 kDa. A two-exponential model was fitted to the blood uptake curve in units of percent-injected dose per gram (%ID/g) and integrated to produce AUC and MRT values. Standard deviations were estimated using a Taylor's series approach with the covariance matrix generated via the fitting procedure. It was found that the AUC (%ID/g h) values varied by approximately one order of magnitude between these two cognates: 21.1 %ID/g h vs. 247 %ID/g h for the scFv and minibody respectively. Corresponding Taylor's series sigmas were 0.75 and 20.9 %ID/g h showing that the estimates did not overlap. A similar result held for the MRT: 4.1 +/- 0.45 h (scFv) vs. 7.1 +/- 2.6 h (minibody). We conclude that lowest MW anti-CEA cognate (scFv) exhibited significantly reduced blood AUC and lowered MRT compared to the intermediate MW protein, the minibody. Correspondingly, tumor uptakes were approximately 4X higher for the minibody in the nude mouse model.