F040 STUDIES OF THE ADDUCT FORMED ON INTERACTING CISPLATIN WITH HUMAN APOTRANSFERRIN: SYNTHESIS, IN VITRO BINDING KINETICS, IN VIVO PHARMACOKINETICS AND BIODISTRIBUTION IN THE RAT.

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Transferrins are glycoproteins which are important in the cellular transport and storage of iron and other metal ions into cells [1]. Since many tumor cells overproduce transferrin receptors, an attractive concept is to consider using transferrin as a delivery system to target cancer drugs specifically to tumor cells. We have undertaken a test of this concept using a cisplatin(cisPt)-apotrans- ferrin(aTf) adduct which was (1) synthesized, isolated (via dialysis), and analyzed via ^{195m}Pt radioactivity, (2) tested in vivo for antitumor activity *vs* implanted M5076 ovarian sarcoma tumors in the mouse, and (3) used to study the pharmacokinetic and biodistribution properties in vivo for comparison with those of cisplatin.

The results and conclusions are as follows: (1) CisPt reacts with human aTf with an apparent first-order rate constant of $\sim 2 \times 10^{-5}$ sec^{-1}. Since this rate constant is comparable to that for the aquation reaction of cisPt, it is likely that the reaction proceeds via an aquation intermediate. (2) The isolated adduct is non-stoichiometric with an approximate empirical formula of $Pt_{0.41-0.75}Tf$. (A Pt/Tf ratio of 1.8-2.0 would be expected if the cisPt-aTf reaction went to completion and cisPt occupied both available Fe(III) binding sites.) (3) The cisPt-aTf adduct is inactive against murine M5076 ovarian sarcoma over a wide range of dose levels (799-3318 mg as Tf/Kg body weight), indicating that active cisPt is not being delivered via the adduct. (4) The cisPt-aTf adduct is a unique entity which exhibits pharmacokinetic and biodistribution properties distinctly different from those of cisPt.

1. Crichton, Robert R., "The Chemistry and Biology of the Transferrins" in Inorganic Biochemistry of Iron Metabolism, Ch. 6., Ellis Horwood, N. Y., **1991.**