PRECLINICAL SAFETY STUDIES OF $^{213}$Bi LABELED PAI2 FOR TARGETED ALPHA THERAPY OF CANCER

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The urokinase plasminogen activator (uPA) system is involved in cancer growth and metastasis. The plasminogen activator inhibitor type 2 (PAI2) and uPA can form a stable complex, which is bound to the cell surface uPA receptor (uPAR). We labeled PAI2 with $^{213}$Bi to form the alpha conjugate. This conjugate targets uPA/uPAR and has been found to have promising therapeutic properties for breast, prostate and pancreatic cancer. This paper reports studies of the acute and delayed toxicity in mice; the effect of lysine renal protection; pharmacokinetics; a comparison of CHX-A$^*$-DTPA and cDTPA chelators, and in vivo $^{213}$Bi-PAI2 stability by Ca-DTPA challenge.

Pharmacokinetics of $^{213}$Bi-PAI2 in nude mice demonstrated that the kidneys were the critical organs for retention of Bismuth in the chelate complex. The CHX-A$^*$-DTPA and cDTPA immunoconjugates were found to have similar %ID/kg in the kidney, with no significant retention of $^{213}$Bi evident in other organs such as liver, heart, lung, and spleen. Ca-DTPA chelators significantly reduced the renal $^{213}$Bi accumulation at 15 minutes, not for 30 and 120 minutes, indicating high in vivo stability of $^{213}$Bi-PAI2 and the need for pre-injection purification of conjugates.

The acute toxicity limit by weight loss was more than 450 MBq/kg. Mild to moderate, patchy tubular necrosis was observed accompanied by slight urea increase. Radiation nephritis was the source of lethal delayed toxicity arising at 20 - 30 weeks post-treatment, for which the maximum tolerance dose was 110 MBq/kg. Kidney uptake was not significantly decreased by lysine at 185 MBq/kg, nor was there any change in delayed toxicity.