Evaluation of Engineered Antibody Fragments Directed to Prostate Stem Cell Antigen (PSCA) in Moderate and Low PSCA Expressing Pancreatic Tumor Xenografts Using PET Imaging

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Background: PSCA is a highly glycosylated GPI linked protein that is frequently overexpressed in prostate, bladder and pancreatic cancers. We evaluated engineered antibody fragments comprised of scFv-C_H3 dimer (Minibody; Mb; 80 kDa) and scFv dimer (Cys-diabody; Cys-Db; 55 kDa) for imaging pancreatic tumors that expressed moderate or low levels of PSCA. These engineered fragments retain equivalent binding affinity and specificity compared with the parental monoclonal antibody (MAb) but have the advantage of improved pharmacokinetics properties.

Methods: The parental MAb and corresponding Mb and Cys-Db were radioiodinated with I-124 ($t_{1/2}$ 4.2 days) using the Iodogen method. Mice bearing low (Capan-1), moderate (HPAC) and negative (MIA-PaCa-2) PSCA expressing pancreatic tumors were injected i.v. with [124]I-Cys-Db, [124]I-Mb or [124]I-mAb and serially imaged by PET/CT. After the last scan, mice were sacrificed and tumor, blood and organs harvested to determine the percent injected dose per gram (%ID/g). Regions of interest (ROIs) were drawn over the heart and tumors to calculate blood clearances and tumor uptakes.

Results: The radiochemical purities of the MAb and fragments ranged from 90-99%, the specific activities from 4-6 µCi/µg and cell-based immunoreactivities from 34-83%. In the low PSCA expressing Capan-1 tumor model, the Cys-Db exhibited a positive tumor to blood ratio of 9.5 at 24 hrs which was 7-fold greater than that of the Mb and 15-fold greater than that of the parental MAb as determined by ROIs. Biodistribution analyses revealed positive to negative tumor ratios of 5.7 for the Cys-Db at 24 hrs and 5.8 for the Mb and at 48 hrs and tumor to blood ratios of 4.9 and 3.1 respectively. In the moderate PSCA expressing HPAC tumor model, the Mb exhibited a more favorable PK profile resulting in better overall ratios and image contrast. Biodistribution analysis showed an increased positive tumor to blood ratio of 9.7 for the Mb at 48 hrs with a similar for the Cys-Db (5.2) at 24 hrs. The positive tumor uptakes were 1.20±0.13% ID/g at 24 hrs for the Cys-Db and 4.06±0.62% ID/g at 48 hrs for the Mb corresponding to a 3- and 6-fold increase respectively above that of Capan-1. The elimination phase ($t_{1/2\beta}$) was determined to be 3.63, 8.66, and 80.45 hrs for the Cys-Db, Mb and parental MAb respectively.

Conclusion: Specific targeting and high contrast images were obtained with [124]I-Cys-Db and [124]I-Mb fragments in pancreatic tumor models that express varying levels of PSCA. Different kinetics and overall results were obtained with these two imaging agents in the Capan-1 and HPAC tumor models highlighting the importance of evaluating more than one model before selecting a lead imaging candidate for clinical development.

Capan-1

Mb (48h)   Cys-Db (24h)

High

Low

HPAC

Mb (48h)   Cys-Db (24h)