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Development of a new prostate cancer theranostic radiopharmaceutical

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Background: Prostate cancer (PCa) is the second leading cause of cancer deaths for adult men in the Western world. Although radical prostatectomy and local radiotherapy are largely successful for patients with localized cancer, available treatments for metastatic PCa have demonstrated weak curative efficacy. Consequently, new tools to improve the detection of recurrent PCa, and to identify and treat metastases, are imperatively needed. Antibody-based constructs represent a good strategy to develop theranostic agents. Currently, the murine mAb 111In-capromab pendetide (ProstaScint®) is the only product that has been approved by the Food and Drug Administration (FDA) as diagnostic radiopharmaceutical for PCa. ProstaScint® showed promising results in clinical diagnosis, but as a whole antibody exhibits low tumor targeting with a maximum uptake at 6-7 days post-injection and delayed clearance from non-target tissues. These issues limit its use as theranostic agent. Recently, preclinical studies of an anti-PSMA single-chain variable fragment of IgGD2B mAb (scFvD2B) labelled with 123I, showed high tumor affinity, improved antigen-positive tumor uptake, with shorter circulatory half-life, and decreased uptake in non-target tissues. The aim of this work was to develop a new PCa theranostic radiopharmaceutical based on the scFvD2B radiolabel with 177Lu.

Methodology: The scFvD2B was conjugated to the chelating agent DOTA using different stoichiometric molar ratios. The number of DOTA per scFvD2B and the affinity constant (Kd) for each construct was determined to choose the conjugated with the higher specific targeting activity against PSMA receptors. The select DOTA-scFvD2B conjugate was labelled with 177LuCl3. Stability of 177Lu-DOTA-scFvD2B was studied using HPLC analysis after incubation at 37 ℃ with fresh human serum, cysteine, glutathione or EDTA solutions (300-fold excess), at time points ranging from 0.5 to 192 h. *In vitro* cell studies were performed to determine the binding specificity and cellular internalization of 177Lu-DOTA-scFvD2B. Biodistribution studies were performed in both healthy and PCa-bearing mice to evaluate 177Lu-DOTA-scFvD2B pharmacokinetics and assess its tumor-detection potential using SPECT imaging.

Results and discussion: DOTA-scFvD2B Kd values showed that the construct characterized by 1:5 (scFvD2B:DOTA) molar ratio is the one with the greatest number of DOTA per scFvD2B which maintains the high specificity for the PSMA receptor. 177Lu-DOTA-scFvD2B possessed high *in vitro* stability, the radiochemical purity of the radioconjugate accomplished at 192 h after dilution, was higher than 98%. Biodistribution studies performed in healthy mice after intravenous administration of the radioconjugate demonstrated that DOTA did not significantly change the scFvD2B pharmacokinetic properties. Indeed, 177Lu-DOTA-scFvD2B showed a favorable biokinetic profile with a rapid blood clearance. Moreover, SPECT/CT imaging studies carried out in mice bearing PCa tumors in lungs proved good and specific tumor detection properties of 177Lu-DOTA-scFvD2B from 6 to 192 h post-injection.

Conclusion: 177Lu-DOTA-scFvD2B high stability and specific affinity for the PSMA receptors *in vitro* and *in vivo* make this radioconjugate a promising PCa theranostic radiopharmaceutical. However, further dosimetric studies have to be performed to establish its therapeutic potential.

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