



Meeting Report | Oncology: Basic, Translational & Therapy

[¹³¹I]MIP-1466, a small molecule prostate-specific membrane antigen (PSMA) inhibitor for targeted radiotherapy of prostate cancer (PCa)

Shawn Hillier, Kimberley Rubino, Kevin Maresca, John Marquis, Mathias Tesson, Craig Zimmerman, William Eckelman, Rob Mairs, John Joyal and John Babich

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Abstract

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Objectives [¹²³I]MIP-1095, (S)-2-(3-((S)-1-carboxy-5-(3-(4-iodophenyl)ureido)pentyl)ureido)pentanedioic acid, a high affinity ligand for PSMA (*Can Res* 2009), has been shown to localize to radiologically-confirmed metastatic PCa in man. The high expression of PSMA in PCa has led us to evaluate the ¹³¹I analog of MIP-1095 (MIP-1466) for therapeutic efficacy in a mouse tumor model of human PCa.

Methods High specific activity MIP-1466 was prepared with Na¹³¹I via iododestannylation. PSMA(+) LNCaP spheroids were treated with 0-3.7 MBq/mL MIP-1466 for 2 hr. Mice with LNCaP xenografts were administered 0.4 MBq for tissue distribution studies, or 1.9, 5.6 or 16.7 MBq for radiotherapy. To determine whether PSMA binding

was specific, a cohort of mice was co-injected with 10 mg/kg PMPA to block PSMA binding. Radiotherapy was initiated when tumors reached 300 mm³. Tumor growth and body weight were monitored twice per week.

Results MIP-1466 was synthesized at 40% radiochemical yield, >95% radiochemical purity and >75 GBq/μmol specific activity. In tissue distribution studies, MIP-1466 displayed a high absorbed radiation dose to the tumor and a favorable tumor:kidney ratio. The growth of LNCaP spheroids and xenografts was inhibited in a dose dependent manner by MIP-1466, with tumor doubling times of 55, 89, and >130 days for the 1.9, 5.6, and 16.7 MBq groups, respectively, compared to 16 days in vehicle treated mice. Spheroids incubated with PMPA and tumors in mice co-injected with PMPA grew at a rate equivalent to the controls indicating PSMA dependent efficacy. Non-radioactive [¹²⁷I]MIP-1466 did not inhibit tumor growth. No significant change in body weight was observed in any group.

Conclusions MIP-1466 inhibited the growth of tumor xenografts in a PSMA specific manner at ¹³¹I doses that are clinically relevant. These data support clinical investigation of MIP-1466 as a targeted radiotherapeutic for treatment of PCa in man

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