B-9

CXCR4 as Radio-Theranostic Target for High Grade Lung NETS and NECS

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BACKGROUND: High grade lung neuroendocrine tumors (NETs) and neuroendocrine carcinomas (NECs) are currently incurable. CXCR4 has been closely involved in tumor proliferation and)metastases indicating poor prognosis. Preliminary data has demonstrated: 1) high CXCR4 expression in poorly-differentiated NETs and NECs as compared to well-differentiated low-grade NETs in patients' specimens; 2) and specific targeting of 68Ga-Pentixafor (CXCR4 antagonist) to CXCR4 positive tumor xenografts in mice by PET/CT imaging and biodistribution. In this study, we investigated the radio-theranostics of CXCR4 antagonists targeting CXCR4 in high-grade atypical lung NET carcinoid and lung NECs.

METHODS: The expression of SSTR2 and CXCR4 was assessed in a panel of typical, atypical lung neuroendocrine carcinoid and NECs cell lines by qPCR and flow cytometry. Mice tumor xenografts and patient tissue microarray were evaluated for CXCR4 expression by immunohistochemistry and graded for staging by Ki-67. PET/CT imaging and biodistribution profile of 68Ga-Pentixafor was acquired in mice bearing CXCR4-positive tumor xenografts. In vitro cytotoxicity of 90Y-, 177Lu- and 212Pb-Pentixather was evaluated by alarma blue test. Toxicity of 177Lu-Pentixather was assessed in mice to determine the maximum tolerated dose(ongoing).

RESULTS: qPCR and flow cytometry demonstrated that 1/3 of the typical, 1/1 atypical bronchial/lung neuroendocrine carcinoid, and 5/5 lung NEC cell lines expressed CXCR4, while the SSTR2 expression was relatively low in all the NEC cell lines. PET imaging using 68Ga-pentixafor in mouse xenograft models verified

that the radionuclide was targeted to the tumors. 90Y-, 177Lu- and 212Pb-Pentixather demonstrated time- and dose- dependent in vitro cytotoxicity. Mice treated with 9.25, 17.5 and 25.9 MBq of 177Lu-pentixather did not demonstrate weight loss or a change in body conditioning indicating the treatment was well-tolerated.

CONCLUSION: CXCR4-targeted theranostics can be used in mouse models to identify high grade lung NETs and NECs. And further radionuclide therapy targeting CXCR4 will be conducted in tumor-bearing mice.