Abstract #364 | Oral or Poster presentation

Ga-68-Trivehexin enables PET/CT imaging of carcinomas in humans by targeting the "cancer integrin" αvβ6

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Introduction

Expression of the TGF-β activating cell adhesion receptor αvβ6-integrin is closely related to cancer malignancy, since it drives invasion and metastasis. αvβ6-integrin is found in high density on tumor cells especially of pancreatic ductal adenocarcinoma (PDAC) [1], but also squamous cell-, cervical-, lung adeno-, and other carcinomas as well as fibrotic diseases (idiopathic pulmonary fibrosis, IPF). Sensitive probes for clinical imaging of αvβ6-integrin are thus highly desirable.

Methods

Trimerization of the αvβ6-integrin selective peptide cyclo[YRGDLAYp(NMe)K] on the TRAP chelator scaffold [2], followed by automated Ga-68 labeling, yielded Ga-68-Trivehexin. Affinities for the integrin subtypes αvβ6, αvβ8, αvβ3, and α5β1 were determined by ELISA [3]. H2009 (αvβ6-positive) and MDA-MB-231 (αvβ6-negative) cells were used for cell binding assays and to generate subcutaneous xenografts in SCID mice, which were used for biodistribution (90 min p.i.), and for dynamic (90 min) and static (75 min p.i.) µPET imaging. A in-vivo comparison with the predecessor compound Ga-68-TRAP(AvB6)$_3$ [4] elucidated structure-activity-relationships. Ga-68-Trivehexin was tested for PET/CT imaging of HNSCC, metastatic salivary duct carcinoma, and PDAC in 4 patients (2 female, 2 male, ages 37–80y).

Results/Discussion

Ga-68-Trivehexin combines a high αvβ6-integrin affinity (IC_{50} = 0.033 nM) with a pronounced selectivity over other RGD-recognizing integrins (selectivity factors calcd. from IC_{50} are 188 for αvβ8; 82 for αvβ3; 667 for α5β1). Uptake in H2009 cells was specific (i.e., blockable) and insignificant in MDA-MB-231 cells. A high target-specific uptake in tumor and a low non-specific uptake in other organs and tissues (except the excretory organs, kidneys and urinary bladder) was confirmed by preclinical PET imaging and ex-vivo biodistribution. In cancer patients, a similar biodistribution pattern was observed. Ga-68-Trivehexin showed high and persistent uptake in metastatic PDAC and HNSCC (SUV_{max} = 10–13) and in kidneys/urine. Even small liver metastases of PDAC could be visualized by Ga-68-Trivehexin PET. A comparison with [^{18}F]FGD PET revealed that ^{68}Ga-Trivehexin accumulates in HNSCC lesions but not in adjacent inflammation sites and tumor-negative lymph nodes.

Conclusions

^{68}Ga-Trivehexin is a promising PET probe for all indications and conditions known to be frequently associated with elevated αvβ6-integrin expression, such as various carcinomas (e.g. pancreatic adeno, HNSCC, colorectal, cervical, lung adeno) [5], and fibrosis. We envisage a clinical value for identification of PDAC primaries and metastases, chemotherapy follow-up, improved delineation of HNSCC for radiation therapy planning, and other purposes.

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Disclosure

N.G. Quigley, K. Steiger, and J. Notni are co-inventors of patents related to Trivehexin. J. Notni is co-founder and shareholder of TRIMT GmbH, which is active in the field of radiopharmaceutical development. No conflicts of interest were disclosed by the other authors.

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