ImmunoPET of urokinase plasminogen activator (uPA) system: broad applicability in cancer imaging

Yang, Dongzhi; Severin, Gregory; Dougherty, Casey A.; Chen, Daiqin; Mazar, Andrew P.; Hong, Hao

Published in:
Journal of Nuclear Medicine

Publication date:
2016

Document Version
Peer reviewed version

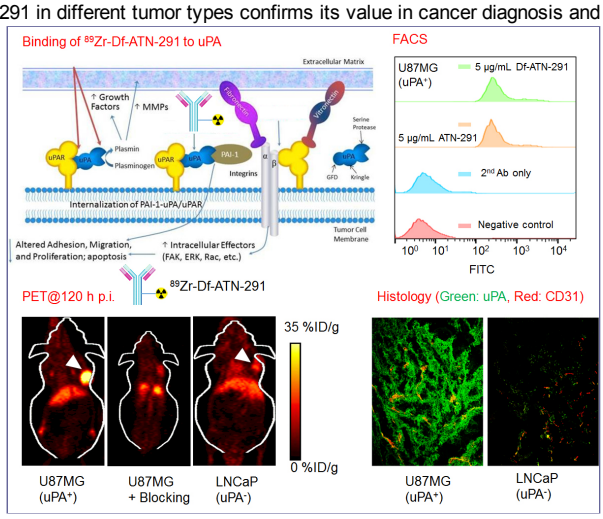
Print this Page for Your Records Close Window

Control/Tracking Number: SNMMI-A-781-2016
Activity: Annual Meeting - Physician/Scientist/Pharmacist
Current Date/Time: 1/6/2016 9:22:16 AM

ImmunoPET of urokinase plasminogen activator (uPA) system: broad applicability in cancer imaging

Author Block: Dongzhi Yang[1], Gregory W. Severin[2], Casey A. Dougherty[1], Daiqin Chen[1], Andrew P. Mazar[3], Hao Hong[1], [1]University of Michigan, Radiology, Ann Arbor, MI, [2]Technical University of Denmark, Center for Nuclear Technologies, Roskilde, DENMARK, [3]Northwestern University, Chemistry of Life Processes Institute, Evanston, IL.

Abstract:
OBJECTIVES: The urokinase plasminogen activator (uPA) system is a proteolytic system comprised of a serine protease (uPA), its cell surface receptor (uPAR), and an inhibitor for uPA (PAI-1). Mounting evidence has demonstrated that over-expression of uPA/uPAR can be found in a variety of cancer cells along with tumor-associated stromal cells, and their expression is closely associated with cancer progression and metastasis. The uPA system is almost undetectable in healthy, quiescent tissue making it an attractive target for cancer imaging/therapy. Our goal is to utilize the uPA system as a universal cancer detection marker and develop a positron emission tomography (PET) tracer for imaging of uPA/uPAR in various cancer types.
METHODS: A monoclonal antibody for uPA (named ATN-291) was produced, conjugated to p-isothiocyanatobenzyl-desferrioxamine (p-SCN-Bn-Df), and subsequently labeled with ^{89}Zr. Competitive binding assay, flow cytometry and confocal microscopic studies were performed in cancer cell lines with different uPA expression levels (high: U87MG, low: LNCaP). PET imaging, biodistribution, histological examination and Western Blot were performed in mouse xenografts bearing different types of tumors (glioma, breast, prostate, pancreatic, and ovarian) to evaluate the capacity and specificity of ^{89}Zr-Df-ATN-291 to target uPA in vivo.
RESULTS: Binding assay and FACS analyses in U87MG and LNCaP cells revealed similar uPA binding affinity/specificity (in the nanomolar range) between ATN-291 and Df-ATN-291, which was further validated by fluorescence microscopy. ^{89}Zr-labeling was achieved with high yield and specific activity. PET imaging revealed that uptake of ^{89}Zr-Df-ATN-291 could delineate U87MG tumors (high uPA) as early as 2 h post-injection, and the tumor accumulation was very persistent (34.1±2.3%ID/g at 120 h p.i. with a tumor-to-muscle ratio of 45.2±9.0, n = 4) while its uptake in LNCaP (low uPA) was significantly lower (<8%ID/g at each time point, n = 3). Accumulation of ^{89}Zr-Df-ATN-291 in MDA-MB-231, PC-3, BXPC-3, and SKOV-3 tumors was also detected by PET and validated by organ distribution via gamma counting. Interestingly, both Western Blot and histology studies showed strong correlations between uPA+uPAR expression (rather than sole uPA expression) in these tumor tissues and tumor uptake of ^{89}Zr-Df-ATN-291.
CONCLUSION: Successful PET imaging of the uPA system with ^{89}Zr-Df-ATN-291 in different tumor types confirms its value in cancer diagnosis and envisages the potential of this novel antibody for targeted radiotherapy and detection of cancer.
:



Presentation Preference (Complete): Oral or Poster
Category Selection (Complete): Preclinical Probes for Oncology
FDA Disclosure/Additional Information (Complete):
: No

Awards (Complete):
Cardiovascular YIA Symposium: No
Brain Imaging Council (Neurosciences) YIA Symposium: No
Computer and Instrumentation Council YIA Symposium: No
Radiopharmaceutical Sciences Council (RPSC) YIA Symposium: Yes

Center for Molecular Imaging Innovation & Translation (CMIIT) YIA Symposium: Yes
Nuclear Oncology YIA Symposium: No
Berson-Yalow Award: Yes
Correlative Imaging Council Walter Wolf YIA: Yes
Young Professional Committee (YPC) Award: Yes

Awards Cont. (Complete):
Pediatrics Council YIA: No
Art Weis Award: No
Masahiro Iio, MD Award: No

Payment (Complete): Your credit card order has been processed on Wednesday 6 January 2016 at 9:18 AM.
Attached Files:
No Files Attached
Status: Complete

Leave OASIS Feedback