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Abstract #4467: Targeting tumor microenvironment with radiolabeled inhibitors of seprase (FAP\#945;)

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Abstract

Seprase, also know as fibroblast activating protein alpha (FAP\#945;) is a key component of the tumor microenvironment. Its expression is normally restricted to fetal mesenchymal tissue and sites of wound healing, but is selectively over expressed in the tumor stroma. It is expressed in cancer-associated fibroblasts of greater than 90% of human primary epithelial tumors including breast, lung, colorectal, gastric, cervical and ovarian cancers, making it an attractive target to exploit for noninvasive radioimaging, as well as targeted radiotherapy of cancer. Seprase is an 88 kDa, type II, intregral membrane peptidase in the dipeptidyl peptidase-4 (DPP-IV) family of prolyl peptidases. We designed, synthesized and evaluated a series of iodine substituted benzamido-glycine-boronoproline analogs as seprase antagonists, with the potential to be radiolabeled with either ^{123}I or ^{131}I for radiodiagnostic or radiotherapeutic use, respectively. Iodine was substituted at the three positions of the benzene ring, and compounds were assessed for their ability to inhibit the enzymatic activity of recombinant human seprase in a fluorescence based assay. Among the most active compounds, an *ortho*-iodine analog (MIP-1231) displayed an IC_{50} of 6 nM, whereas even more potent *para*- (MIP-1232) and *meta*-substituted (MIP-1233) analogs both had IC_{50} values of 0.6 nM. To examine the selectivity for seprase over other prolyl peptidases, compounds were tested for their ability to inhibit the enzymatic activity of prolyl oligopeptidase (POP), the only other endopeptidase in this family of peptidases. The IC_{50} values of MIP-1231, MIP-1232, and MIP-1233 for POP were 58, 19, and 7 nM, respectively, with POP/FAP ratios of 10, 32, and 12, respectively. These data demonstrate that although the *para*- and *meta*- substituted compounds have similar ability to inhibit seprase activity, the *para*- substituted analog displayed better selectivity. To examine binding to seprase *in vivo*, human embryonic kidney (HEK-293) cells were stably transfected with the human seprase gene, and highly expressing clones were selected and verified by Western blotting. MIP-

cells. The K_d of MIP-1232 for seprase was determined to be 30 nM, whereas there was no specific binding to a non-expressing clone. The B_{max} of the seprase expressing cells was determined to be approximately 8 pmol/10^6 cells. In addition, MIP-1232 was shown to inhibit the seprase enzymatic activity of the stable seprase expressing cells. These radiolabeled seprase inhibitors are currently being evaluated for tumor uptake and tissue distribution in mice bearing seprase expressing HEK-293 xenografts, as well as tumors that promote seprase expression in the tumor associated stroma. Radiolabeled seprase inhibitors could be exploited for the diagnosis, staging, prognosis, and potential treatment of solid tumors.

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