Novel pretargeted radionuclide therapy for HER2-expressing cancers shows promise

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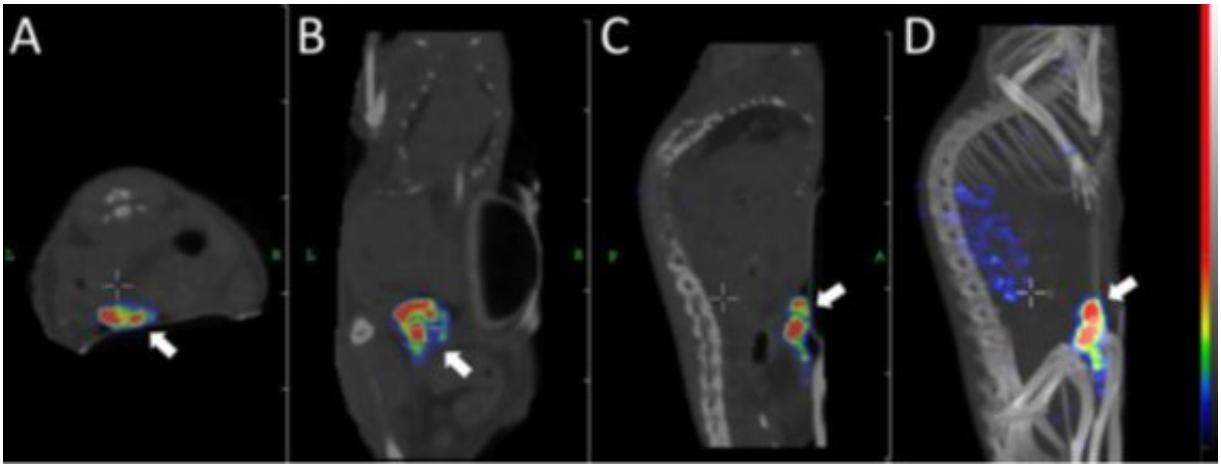

Transversal (A), coronal (B), sagittal (C) nanoSPECT/CT images and maximum intensity projection (D) obtained 30 h after injection of pretargeted ^{177}Lu-HP2. Tumor (indicated by arrow) was located on the abdomen. Credit: Uppsala University, Uppsala, Sweden

In a mouse model, researchers have demonstrated that a novel, affibody-based pretargeted radionuclide therapy for HER2 (human epidermal growth factor receptor 2)-expressing cancers is non-toxic to the kidneys and improves survival. The study is reported in *The Journal of Nuclear Medicine*'s July featured article of the month.

"Affibody molecules, small proteins engineered to bind to specific

tumor-associated target proteins, have demonstrated excellent features for targeted molecular imaging, but their application for radionuclide therapy has so far been prevented by high renal reabsorption," explains Vladimir Tolmachev, DMSc, professor at Uppsala University in Uppsala, Sweden. "We have now shown that the use of peptide nucleic acid (PNA)-mediated pretargeting enables a safe application of affibody molecules for radionuclide therapy."

For the study, affibody-pretargeted lutetium-177 (^{177}Lu)-labeled PNA was tested and evaluated in mice bearing HER2-expressing xenografts. Experimental radionuclide therapy of the mice was performed in six cycles separated by 7 days.

The data showed very rapid clearance of ^{177}Lu-PNA from most tissues. The only tissues with prominent uptake were the kidneys and tumor, however, tumor uptake was four-fold higher than renal uptake at one hour post-injection. In addition, 84 percent of the renal uptake cleared with a 15-minute half-life, whereas the tumor clearance half-life was 63 hours.

Results demonstrate that this pretargeting system can deliver an absorbed dose to tumors that appreciably exceeds the dose to critical organs, making affibody-based PNA-mediated pretargeted radionuclide therapy highly attractive.

Marion de Jong, Ph.D., professor at Erasmus MC in Rotterdam, The Netherlands, states, "The safe application of radiolabeled affibody molecules for radionuclide therapy in patients will open up a whole new world of therapeutic options, as affibody molecules are excellent targeting moieties and can be generated for a wide range of targets."

de Jong adds, "More specifically regarding anti-HER2 applications, the pretargeted affibody-based anti-HER2 might be used for treatment of

patients who developed resistance to trastuzumab or other HER2-targeting therapies. Such resistance might be accompanied by preserved high expression of HER2."

Amelie Eriksson Karlström, Ph.D., professor at KTH Royal Institute of Technology in Stockholm, Sweden, points out additional advantages to using an affibody molecule as the pretargeting vector, explaining, "Production of affibody molecules is much cheaper than the production of antibodies. This might make our constructs more affordable and available."

She adds, "Another important feature of our approach is the modular design of the construct. The Sortase A-mediated coupling can easily be used for the conjugation of an affibody molecule with specificity to a different target or even another class of targeting scaffold protein. Labelsare not limited to ^{177}Lu; probes could also be labeled with the alpha-emitting nuclides actinium-225 (^{225}Ac) or thorium-227 (^{227}Th), or a positron-emitting nuclide such as gallium-68 (^{68}Ga) for theranostics (both diagnosis and therapy). We anticipate that this study is a first step in the validation of a versatile pretargeting platform."

More information: Kristina Westerlund et al, Radionuclide Therapy of HER2-Expressing Human Xenografts Using Affibody-Based Peptide Nucleic Acid–Mediated Pretargeting: In Vivo Proof of Principle, *Journal of Nuclear Medicine* (2018). DOI: 10.2967/jnumed.118.208348

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