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Radiolabeled peptidomimetic inhibitor of the VEGF/NRP-1 complex for the imaging of malignant tumours - preliminary research

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Background: The widest possible range of available molecular targets and their vectors is a crucial key for targeted diagnosis and cancer therapy problems. The presented work concerns a vector –the peptidomimetic inhibitor, the molecular target of which is neuropilin-1 (NRP-1). NRP-1 is a receptor for the vascular endothelial growth factor-165 (VEGF₁₆₅) playing an important role in pathological angiogenesis and in tumor development and progression. It has been observed that NRP-1 overexpression is associated with tumor aggressiveness in several types of cancers. The demonstrated involvement of VEGF₁₆₅/NRP-1 complex in pathological angiogenesis has catalyzed interest in searching for inhibitors of such interaction to combat angiogenesis dependent diseases. It was shown before that a heptapeptide Ala-Thr-Trp-Leu-Pro-Pro-Arg (A7R) is a good inhibitor of the VEGF₁₆₅/NRP-1 interaction.

Aim: The work involved the labeling of the Lys-(hArg)-Dab-(Ahx-DOTA)-Pro-Arg peptide (working name *KM1*) and preliminary physicochemical studies of obtained radiobioconjugate (Figure 1). *KM1* is an analog of the A7R peptide what is stronger inhibitor of VEGF₁₆₅/NRP-1 complex than A7R.

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Figure 1. Structure of ⁶⁸Ga-DOTA-KM1 radiobioconjugate.

Methodology: Peptide *KM1* was synthesized in the Peptides Laboratory of the University of Warsaw using the SPPS method on Wang resin using the Fmoc strategy. The labeling was performed with ⁶⁸Ga (95℃, 10 min) and the obtained radiobioconjugate was purified by HPLC (semi-preparative Jupiter® Proteo column). Lipophilicity (logP value) was determined in a standard biological system (PBS solution and *n*-octanol) and the stability of the compound was tested in human serum.

Results and discussion: The labeling yield was about 72%. The determined logP value equal to -4.16 ± 0,02 indicates that ⁶⁸Ga-DOTA-KM1 radiobioconjugate is a strongly hydrophilic compound. Stability studies in human serum showed that about 85% of the radiobioconjugate remains in the free form in the serum solution (about 15% is combined with the protein present in the serum).

Conclusion: The presented studies are the first step on the new VEGF/NRP-1 radioisotopically labeled peptidomimetic inhibitors for cancer diagnostics and therapy. In the next steps the syntheses of new peptidomimetics are planned as well as the using of a long-lived isotope, e.g. ¹⁷⁷Lu or a ^{43,44}Sc/⁴⁷Sc theragnostic pair.

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