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Lectura recomendada

Kit for preparation of multimeric receptor-specific ^{99m}Tc -radiopharmaceuticals based on gold nanoparticles

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Abstract

Background: Multivalency is a design principle by which organized arrays amplify the strength of a binding process, such as the binding of multimeric peptides to specific receptors located on cell surfaces. The conjugation of peptides to gold nanoparticles (AuNPs) produces biocompatible and stable multimeric systems with target-specific molecular recognition.

Aim: The aim of this research was to develop a kit for technetium-99m (^{99m}Tc) labelling of AuNPs that are conjugated to Lys³-bombesin, cyclo[Arg–Gly–Asp–D–Phe–Lys–(Cys)] or thiol-mannose to produce receptor-specific multimeric systems.

Methods: A freeze-dried kit formulation for the instant preparation of ^{99m}Tc -ethylenediamine-*N,N'*-diacetic acid (EDDA)/hydrazinonicotinyl (HYNIC)-Tyr³-octreotide (^{99m}Tc -EDDA/HYNIC-TOC) (vial 1) and a second vial containing 1.5 ml of AuNP solution (1 nM, 20 nm diameter, surface area=1260 nm², 37 000 surface Au atoms, 1.05×10^{12} particles) plus 10 μl of Lys³-bombesin, cyclo[Arg–Gly–Asp–D–Phe–Lys–(Cys)] or mannose (50 μM , approximately 285 molecules per AuNP) (vial 2) were prepared. Multimeric radiopharmaceuticals were prepared by adding 1 ml of 0.2 mol/l phosphate buffer, pH 7.0, and 1 ml of $^{99m}\text{TcO}_4^-$ (4 GBq) to vial 1, and the mixture was incubated at 92°C for 20 min in a dry block heater. A total of 100 μl (200 MBq) of ^{99m}Tc -EDDA/HYNIC-TOC solution (122 HYNIC-TOC molecules per AuNP) was added to vial 2. No further



purification was carried out. Radiochemical purity was determined by instant thin-layer chromatography-silica gel/2-butanone (R_f values for the radiolabelled AuNP and $^{99m}\text{TcO}_4^-$ were 0.0 and 1.0, respectively), ultrafiltration, size-exclusion high-pressure liquid chromatography and a PD-10 column. The conjugates were characterized by ultraviolet-visible, far-infrared and X-ray photoelectron spectroscopy. In-vitro binding studies were carried out in $\alpha_v\beta_3$ receptor-positive C6 glioma cancer cells, gastrin-releasing peptide receptor-positive PC3 cancer cells or mannose receptor-positive rat liver cells. Biodistribution studies were carried out in athymic mice with induced tumours (PC-3 or C6 cancer cells) or in Wistar rats (^{99m}Tc -AuNP-mannose for sentinel lymph node detection). Images were obtained using a micro-single-photon emission computed tomography/computed tomography system.

Results: Radiochemical purity was $96\pm 2\%$ for all of the multimeric radiopharmaceuticals. Far-infrared showed a characteristic band at $279\pm 1\text{ cm}^{-1}$, which was assigned to the Au-S bond. ultraviolet-visible and X-ray photoelectron spectroscopy also indicated that the AuNPs were functionalized with peptides or mannose. Radiopharmaceuticals showed specific recognition for receptors expressed in cancer cells or rat liver cells. Micro-single-photon emission computed tomography/computed tomography images showed clear tumour uptake and lymph node accumulation. The kit (i.e. vial 1 and vial 2) demonstrated excellent stability during storage at 4°C for 6 months.

Conclusion: Multimeric systems of ^{99m}Tc -AuNP-peptide/mannose prepared from kits exhibited properties suitable for use as target-specific agents for molecular imaging of tumours and sentinel lymph node detection



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