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SPECT imaging and biodistribution studies of 111In-EGF-Au-PEG nanoparticles in vivo

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Introduction: Radiolabelled antibodies and peptides hold promise for molecular radiotherapy but are often limited by low payload resulting in delivery of inadequate amounts of radioactivity to tumour tissue and, therefore, modest therapeutic effect. We have developed PEGylated epidermal growth factor (EGF)-gold nanoparticles (NP) with a high indium-111 (^{111}In) payload (^{111}In-EGF-Au-PEG NPs) as a prototypic NP-based theranostic radiopharmaceutical.
Materials and methods: EGF-Au-PEG NPs were prepared via an interaction between gold and the disulphide bonds of EGF followed by PEGylation by mPEG-thiol (MW: 800, 2000, 6000) and characterised by SEC-HPLC, DLS and zeta potential. The targeting property of NPs with various PEG MWs was investigated by confocal imaging following exposure of MDA-MB-468 (1.3 x 10^6 EGFR/cell) and MDA-MB-231/H2N (10^5 EGFR/cell) cells to Cy3-EGF-Au-PEG NPs. ^{111}In-EGF-Au-PEG (MW: 6000) and ^{111}In-EGF-Au NPs were chosen for SPECT imaging and biodistribution studies using MDA-MB-468 xenograft-bearing mice.
Results: Successful PEGylation was confirmed by DLS and zeta potential measurements, showing the hydrodynamic sizes of NPs were 18.5, 19.4, 24.8 and 32.5 nm; the zeta potentials in water were -24, -15, -14 and -9 mV for EGF-Au and EGF-Au-PEG with MWs of 800, 2000 and 6000, respectively. SEC-HPLC showed that the retention time of EGF-Au-PEG NPs was shorter than EGF-Au NPs as PEGylation resulted in larger NPs. Confocal imaging demonstrated that both EGF-Au and EGF-Au-PEG NPs were efficiently bound and internalised by MDA-MB-468 cells. In vivo SPECT studies in mice bearing MDA-MB-468 xenografts revealed high tumour uptake in animals that received ^{111}In-EGF-Au-PEG (MW: 6000) compared to ^{111}In-EGF-Au. The tumour/muscle radioactivity ratios for ^{111}In-EGF-Au-PEG and ^{111}In-EGF-Au were 7.2 and 2.5.
Conclusion: An ^{111}In-labelled EGF-Au-PEG nanosystem was developed. It enabled targeted delivery of a high ^{111}In payload to an EGFR-positive cancer model that can be potentially exploited for molecularly targeted radiotherapy.

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Melanoma targeting with [99mTc(N)(PNP3)]-labeled NAPamide derivatives: preliminary pharmacological studies

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Introduction: Malignant melanoma is the most lethal form of skin cancer and the most commonly diagnosed malignancy among young adults with an increasing incidence. Hence, the development of new melanoma-specific pharmaceutical for diagnosis and/or therapy is a subject of great interest and intense research. The purpose of this study was to examine the effect of cyclization on the biological profile of [^{99m}Tc(N)(PNP3)]-labeled α-MSH peptide analogs (PNP3 = N,N-bis(dimethoxypropylphosphinoethyl)methoxyethylamine).
Method: A lactam bridge-cyclized H-Cys-Ahx-βAla^3-c[Lys^4-Glu-His-D-Phe-Arg-Trp-Glu^{10}]-Arg^{11}-Pro-Val-NH_2 (NAP—NS2) and the corresponding linear H-Cys-Ahx-βAla-Nle-Asp-His-D-Phe-Arg-Trp-Gly-NH_2 (NAP-NS1) peptide were synthetized, characterized by ESI-MS spectroscopy and their MC1R binding affinity were determined in B16/F10 melanoma cells. In vitro stability and pharmacological parameters of [^{99m}Tc(N)(NAP—NS1)(PNP3)]$^+$ (**1**) and [^{99m}Tc(N)(NAP—NS2)(PNP3)]$^+$ (**2**) were assessed. Challenges with an excess of glutathione and cysteine and Log P values were also investigated. Furthermore, **1** and **2** were applied to study in vivo stability and the pharmacokinetic profiles on healthy rats.
Results: **1** and **2** were obtained in high yield (RCY > 90%). Log P values demonstrate the hydrophilic nature of the radiolabelled peptides: -1.43 for **1**; - 2.087 for **2**. No significant variations in RCPs of both the complexes were observed in challenge experiments with an excess (10 mM) of glutathione and cysteine. A high in vitro stability was observed for both complexes after incubation in human and rat sera as well as in rat liver homogenate; a fast degradation of **2** was detected in kidneys homogenate. **1** retains a high receptor affinity (K_d=7.1 ± 0.5 nM). Biodistribution data of **1** display a favorable pharmacokinetic profiles characterized by a fast blood clearance and elimination from normal tissues. A rapid excretion via the renal pathway was observed according to the high hydrophilic character of the radio-conjugate. The effect of the cyclization on the pharmacokinetic profile of **2** was reflected in a reduction of the blood clearance and of the elimination from the other organs, in particular, from excretory organs such as liver and kidneys.
Conclusion: Compared with the linear peptide, cyclization negatively affects the biological properties of NAP-NS2 peptide by reducing its binding affinity for MCR1R (Ki: 0.9±0.3 nM for NAP_NS1; 7.1±2.4 nM for NAP_NS2) and decreasing the overall excretion rate of the corresponding [^{99m}Tc(N)(PNP3)]-labeled peptide from the body as well as its stability. Thus only the linear [^{99m}Tc(N)(PNP3)-labeled peptide is suitable for further investigations in tumor bearing animals. This research was supported by MIUR through PRIN 20097FJHPZ-004 and FIRB "RINAME"2010-RBAP114AMK.

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[^{68}Ga]NODAGA-RGD: cGMP synthesis and data from a phase I clinical study

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Introduction: Preclinical studies demonstrated that [^{68}Ga]NODAGA-RGD allows imaging of integrin $\alpha_v\beta_3$ expression using PET. Here we present all data (quality control, toxicological study, and dosimetry estimation) necessary to initialize clinical studies, the establishment of the remote controlled synthesis, and data from the phase I clinical study.
Methods: Labelling was carried out in a remote controlled synthesis unit under clean room conditions. Quality control included TLC, HPLC, GC, pH control, Ge-breakthrough, half-life, endotoxin content, and control of sterility. Storage stability after 4 h was studied and dose estimations based on animal data were carried out using OLINDA. Sprague-Dawley rats were used for an extended single dose toxicity study. The phase I clinical study included 9 patients with hepatocellular carcinoma (HCC). Static scans at 5, 30, and 60 min p.i. including 5 bed positions each were performed using the Discovery 690 PET/CT. Blood was sampled 30 and 60 min p.i. and urine 60 min p.i. and used for stability studies via HPLC.
Results: [^{68}Ga]NODAGA-RGD could be produced in high radiochemical yield and radiochemical purity (HPLC and TLC >99%). The pH in the final isotonic saline formulation was approx. 6. Ethanol content was between 2.5 and 3.0% v/v. No detectable ^{68}Ge-germanium was found. LAL test revealed 0.7 EU/ml. Sterility tests showed that all samples met the specifications according to Ph. Eur.. No radiolysis of