PhD Thesis title: 'Molecular imaging methodologies with radiolabeled nanoparticles for the quantitative evaluation of angiogenesis spatial distribution in malignant tumors'

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ABSTRACT:

The aim of the present project is the *in vivo* evaluation of quantitative monitoring of angiogenesis making use of the molecular imaging methodology. A new cyclic RGDfK (Arg-Gly-Asp-D-Phe–Lys) derivative, namely the cRGDfK-Orn_3-CGG, was evaluated as eventually promising in early tumor detection through specifically targeting integrin $\alpha_v\beta_3$ receptors, overexpressed in angiogenesis. This new peptide, availing the ^{99m}Tc-chelating moiety CGG (Cys-Gly-Gly), is appropriately designed for ^{99m}Tc-labeling, as well as consequent conjugation onto nanoparticles. Specifically, RGD-conjugated iron oxide nanoparticles (10±2 nm) have been developed appropriately for SPECT/MRI imaging and hyperthermia treatment. Particularly, they were evaluated as tumor imaging agents: ^{99m}Tc-RGD (cRGDfK-Orn_3-CGG), ^{99m}Tc-NPs and ^{99m}Tc-NPs-RGD. The new derivatives were examined with regard to their radiochemical, radiobiological and imaging characteristics. It has been demonstrated that they were obtained in high radiochemical yield and presented high *in vitro* stability being examined: a) at different time-points, b) in the presence of an excess of antagonist moites for ^{99m}Tc, c) in human plasma or serum. The *in vivo* study and the biodistribution evaluation of radiolabeled products were assessed in normal mice and in pathological models (scid mice) bearing experimental U87MG glioblastoma tumors. The quantitative evaluation of angiogenesis spatial distribution confirmed high specific binding of the ^{99m}Tc-RGD peptides to $\alpha_v\beta_3$ integrins, with significantly high tumor uptake 11.60±3.06 % ID/g, while targeting with ^{99m}Tc-NPs-RGD demonstrates high tumor uptake 9.01±0.19 ID/g. The ^{99m}Tc-RGD was appropriately designed to have urine excretion due to the ornithine (Orn_3) linker, while the ^{99m}Tc-NPs exhibits hepatobiliary excretion, compared to ^{99m}Tc-NPs-RGD, which exhibit lower values of liver uptake with a significantly higher kidney uptake, which can be attributed to the attachment of the RGD derivative on the surface of NPs. Satisfactory tumor images were obtained with the radiolabeled derivatives ^{99m}Tc-RGD and ^{99m}Tc-NPs. Finally, the *in vivo* heating efficiency experiment showed that hyperthermia induction with the aid of iron oxide NPs was feasible, resulting to anti-tumor effect in a U87MG tumor-bearing mouse. The above preliminary results indicate that targeted iron oxide NPs are promising candidates for the quantitative monitoring of angiogenesis for molecular imaging and potential cancer therapy.

References to author publications that relate specifically to the dissertation:

- Tsiapa I., Loudos G., Varvarigou A., Fragogeorgi E., Psimadas D., Tsotakos T., Xanthopoulos S., Mihailidis D., Bouziotis P., Nikiforidis C.G., Kagadis C.G., 'Biological evaluation of an ornithine-modified ^{99m}Tc-labeled RGD peptide as an angiogenesis imaging agent', Nuclear Medicine and Biology 40, 262-272, 2013.