Strategies for molecular imaging with inorganic nanoparticles

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Targeted nanoparticles have great potential for application as radionuclide molecular imaging agents but are subject to several limitations, including complex radiolabelling procedures, slow pharmacokinetics, low uptake in target tissue, and potential toxicity. We propose a targeted nanoparticle system comprising biocompatible materials with intrinsic affinity for readily-prepared radiotracers such as [^{18}F]-fluoride and [^{99m}Tc]-technetium bisphosphonate derivatives. Such a system would offer simple labelling, and signal amplification (each particle can deliver many radionuclides). To overcome slow pharmacokinetics we propose to exploit pretargeting whereby the radionuclide-nanoparticle bond can form *in vivo*. Methods: We screened many inorganic nanoparticulate materials for binding to [^{18}F]-fluoride and [^{99m}Tc]-bisphosphonates, and synthesised bifunctional linkers comprising a bisphosphonate group for binding to nanoparticles and a maleimide group for conjugation to biomolecules. Results: Of the materials tested, hydroxyapatite showed the most efficient binding to both [^{18}F]-fluoride and [^{99m}Tc]-bisphophonates. The radiolabel remained associated with nanoparticle in serum, and *in vivo* in mice until taken up in the reticuloendothelial system. Conjugation of the maleimide derivative to thiol groups of proteins and peptides led to efficient binding of the biomolecules to hydroxyapatite particles. Conclusion: hydroxyapatite, bisphosphonate bioconjugates and bone-affine radiopharmaceuticals can be assembled into a targeted nanoparticulate biocompatible system for radionuclide moelcular imaging.