

**Purpose:** X-irradiation induces the expression of novel receptors on the surface of cancer cells. Peptide ligands that bind specifically to these receptors are now used to retarget liposomes and nanoparticles containing chemotherapy for cancer. Here we show that radiolabeling of nanoparticles will be used to image the spatial and temporal distribution of nanoparticles targeted to radiation inducible receptors during planned clinical trials.

**Methods:** Biodegradable nanoparticles were manufactured by use of cross linking reagents with nanoparticle albumin. Peptide ligands that target radiation inducible receptors, HVGGSSV and GIRLRG were conjugated to nanoparticles using bifunctional PEG linkers. Radiolabeling with radioiodine was conjugated to nanoparticles by use of iodigen while Zr86 was conjugated by use of DFO as a chelator. Near infrared imaging was also used when Alexafluor750 fluorophore was conjugated to nanoparticles. Radiolabeled nanoparticles were injected by tail vein into mice bearing irradiated cancers. The biodistribution was imaged by PET, SPECT and NIR imaging.

**Results:** Cancer specific binding of targeted nanoparticle was achieved by both the HVGGSSV and GIRLRG peptide ligands that bind to radiation inducible TIP-1 and GRP-78 receptors respectively. PEGylated nanoparticles have a circulation time greater than 24 hours which necessitated internal emitters with long half lives. Radiolabeled nanoparticles imaged by PET and gamma camera maintained cancer specific binding in mouse models of cancer. Nanoparticles and liposomes that were targeted to radiation inducible proteins bind selectively and for 7 to 9 days respectively. Anti-cancer drugs including doxorubicin in liposomes and paclitaxel in nanoparticle enhanced radiation-induced tumor control in mouse models of cancer.

**Conclusions:** Radiation inducible receptors on cancer are suitable for targeted drug delivery. Long half lived radionuclides are needed to monitor the biodistribution in these PEGylated nanoparticles. PET and SPECT imaging are planned for upcoming clinical trials.

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