Nano-IRT : Indirect radiation therapy development with target Nanoparticles

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Abstract:

Indirect radiation therapy inactivates cancer cells by secondary radiation products evolving from incorporated target material upon specific absorption of a therapy beam. The power of the method depends on the absorption cross section, the physiological acceptable concentration of the target material and the intracellular location after incorporation. We have developed heavy metal chelate entrapped nanoparticles for indirect radiation therapy with synchrotron radiation, neutrons and gamma-photons.

Nanoparticles are suitable for local deposition and uptake of absorption material at high concentration level, i.e. > 10 mM in tissue. As nanoparticles systems we use a modular combination of liposomes for water soluble and lipid-bound metal complexes, solid lipoid particles for hydrophobic drugs, and Ferrofluids for magnetic manipulation. The metals Lutetium, Erbium, Gadolinium and cis-Platinum were entrapped, and tested with cell cultures and some animal tests.

Target liposomes entrapping Gd-, Er-, Lu-DTPA, cis-Platinum and a cis-Pt-lipid were characterized by anomalous X-ray small angle scattering ASAXS, X-ray absorption spectroscopy, time resolved neutron scattering TR-SANS, dynamic light scattering DLS and electron microscopy. The particle properties were optimised for maximal absorption of the therapy beam, avoiding the embolic risk limit of 500 nm, and local deposition. The optimal particles, e.g. unilamellar liposomes SUV at high ionic strength, depicted a size of 100-200 nm. The entrapped lumen contained up to 300 mM Lanthanide chelate at an entrapping rate of 10%, enough for a localization by K-edge absorption imaging. A typical target nanoparticle concentrates 1,000,000 target atoms. A part of the nanoparticles was prepared in a formulation braking the blood-brain barrier, as required for treatment of brain tumors.

For the cell culture tests we have developed an irradiation setup and protocol for a late apoptosis test. In the setup a multiple collection of submerse cells is irradiated in multiwell plates. The protocol provides the proliferation rate, which is the equivalent of tumor growth and inactivation. Thus we follow up complete growth curves rather than cell inactivation, which is the equivalent to unfavorate early tumor disruption (necrosis). The study is done in parallel with synchrotron radiation (PAT, photon activation therapy), neutrons (Gd-NCT, Gadolinium neutron capture therapy) and gamma photons from a clinics accelerator (E-PT, enhanced photon therapy).

For synchrotron photon activation therapy PAT some animal tests were done with rats bearing brain tumor tumors from 9L- and F98-cancer cells. The untreated animals showed no demage by the target liposome material, or the blood brain barrier braking formulation. Application of Lutetium-liposomes before the radiation treatment resulted in a prolonged survival. The healing effect is now optimized by parallel cell culture tests, especially for improved cellular uptake.

Nano-IRT is a promising method for improved radiotherapy of cancer. With nanoparticles a sufficient amount of a heavy metal target can be introduced at the tumor area locally. The metal specific beam absorption of a treated 1 cm tumor-target area is ~10% for synchrotron radiation (63 keV, Lu) and 100% for neutrons (Gd – cold neutrons), and visible in K-edge imaging. With synchrotron radiation at ESRF-ID17 the therapy effect was demonstrated with cell cultures and early animal tests.

References

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Specific WEB-site: www.mpsd.de/irt/