Cancer Theranostics With High-Z Loaded Nanoparticles

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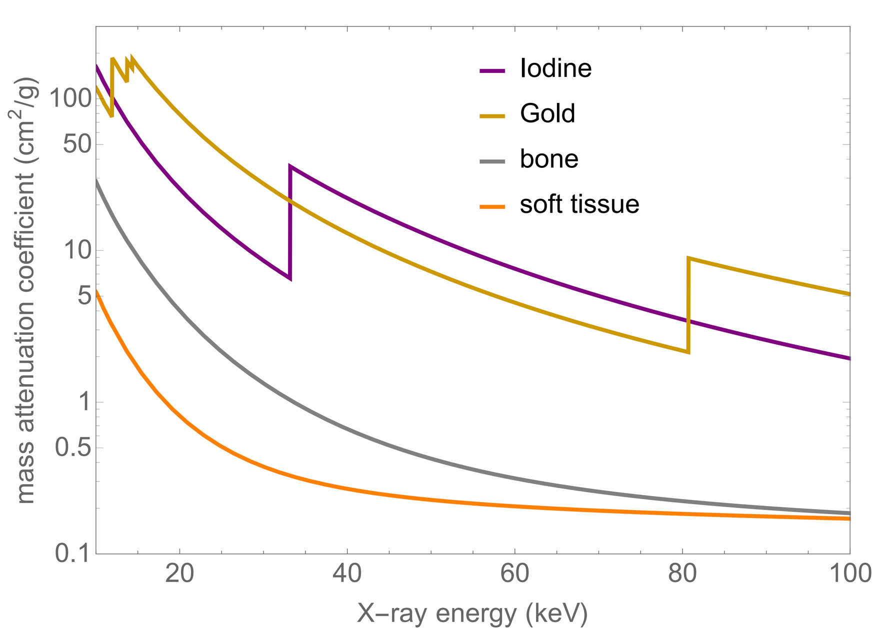
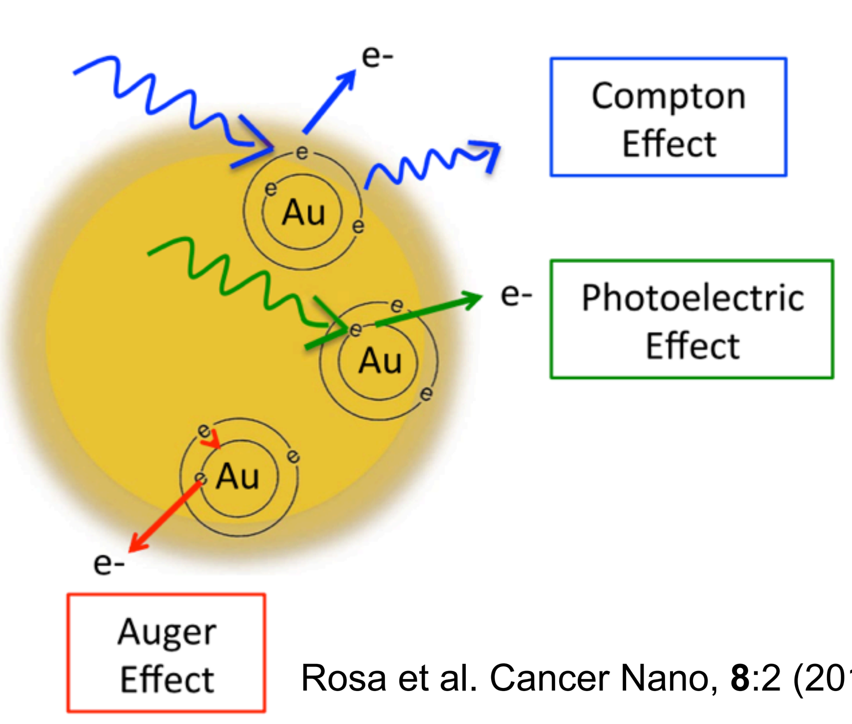
Abstract

Nanoparticles have gained much interest in cancer diagnosis and therapy due to its natural cancer-seeking traits. High-Z nanoparticles can be both used for imaging the tumor and for enhancing the dose delivered to tumor. However, the exact mechanism of radiosensitization effect not yet fully explained and experiments often report much higher dose enhancement than predictions based on physical models. Therefore, it is important to quantify the dose enhancement effect with respect to various parameters such as material type, concentration and irradiating energy. Such an experiment will not only provide database for future modeling and experiments but also find the optimal setup for treatment. We propose to use mesoporous silica nanoparticles (MSNs) which can be loaded with multiple types of cargo in order to study the effect of different heavy elements widely used in medicine, namely silver, iodine, gadolinium and gold. A monochromatic source of X-rays is crucial for the study of energy dependence; we plan to use a 20-100 keV beamline at SPring-8 synchrotron light source. Cancer diagnosis using nanoparticles and K-edge subtraction method is also presented.

Nanoparticles for radiotherapy

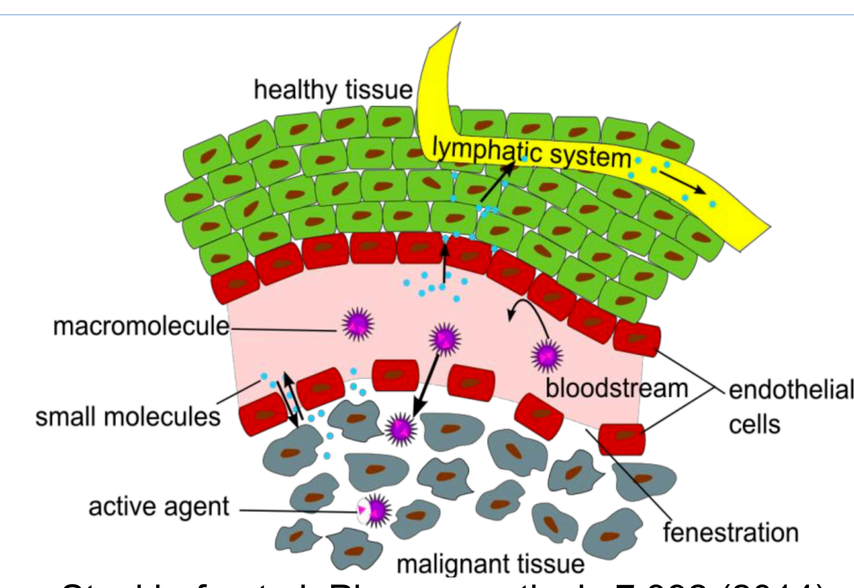




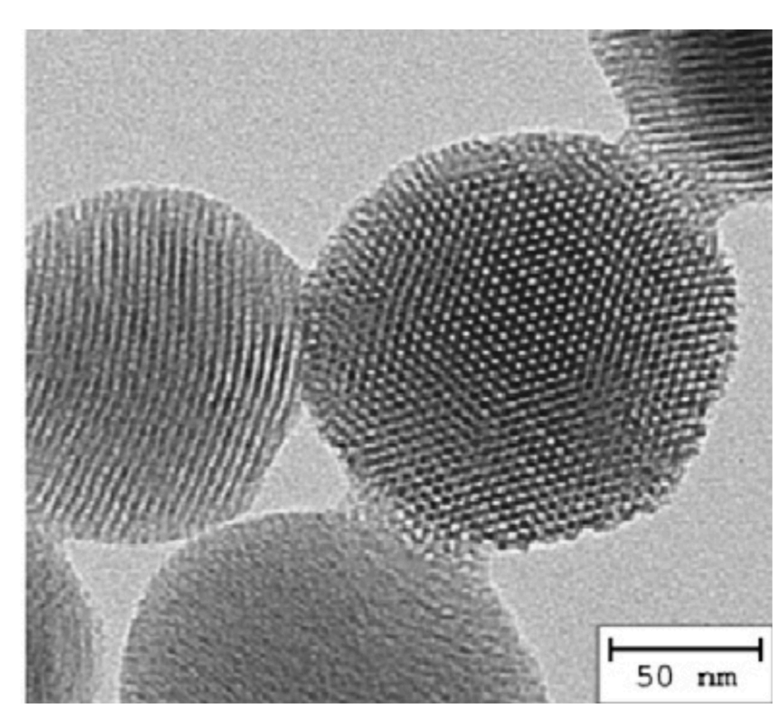
Rosa et al. Cancer Nano, **8**:2 (2017)

Heavy elements have much higher photoelectric cross section than body tissues, and the energy absorbed by them can be re-emitted to nearby tissue through Auger effect and fluorescence.

Nanoparticles are ideal for delivering the heavy elements to the tumor site, since particles of size about 100 nm more readily accumulate in tumor sites due to the abnormal vascular structure in tumors, known as enhanced permeability and retention (EPR) effect. In a tumor, blood vessels formed inside have wide leaky openings and lymphatic drainage tends to be poor, causing large molecules and nanoparticles to accumulate inside. Active cancer-seeking molecules can also be attached to nanoparticles, increasing the selectivity.

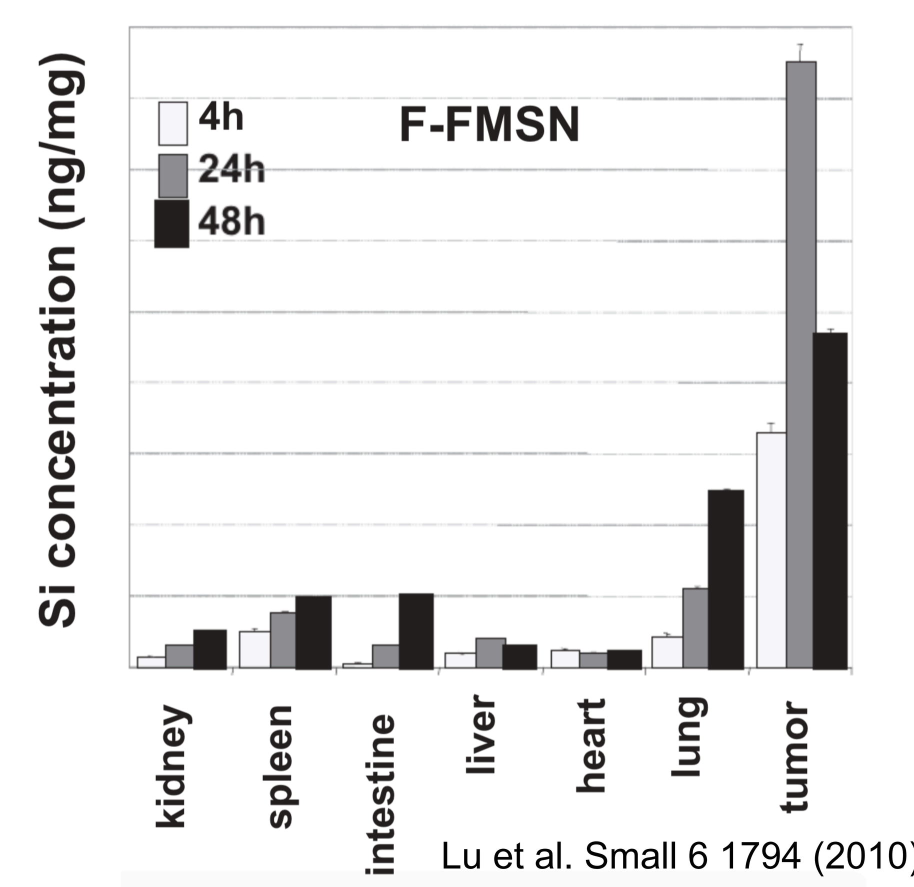


Stockhofe et al. Pharmaceuticals 7 392 (2014)



Lu et al. Nanomedicine 8 212 (2012)

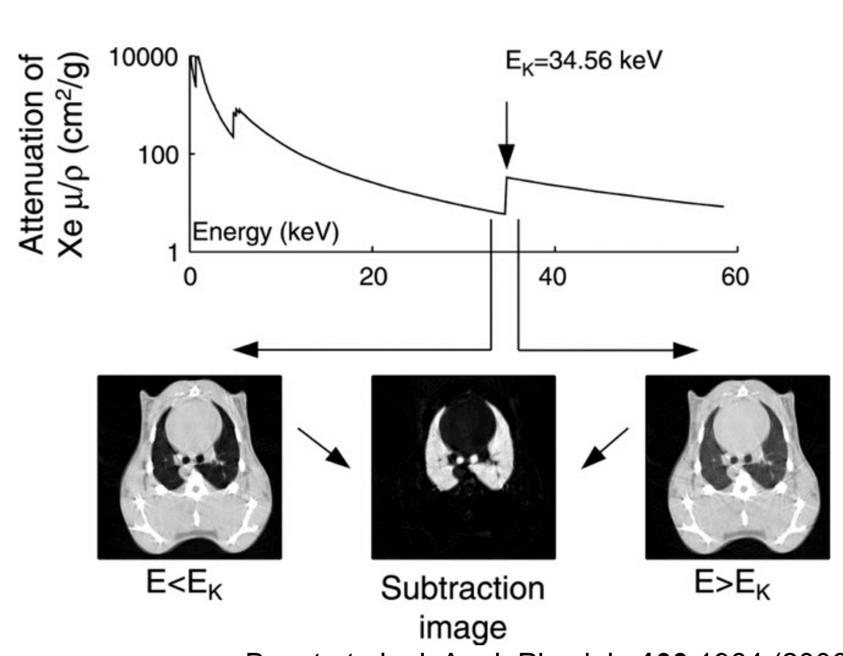
Mesoporous silica nanoparticles (MSNs) are silica nanoparticles with numerous pores, having very large surface area on which cargo can be attached. They have been used for delivering anti-cancer drugs, and can also be used to carry heavy elements for radiotherapy, such as silver, iodine, gadolinium and gold.



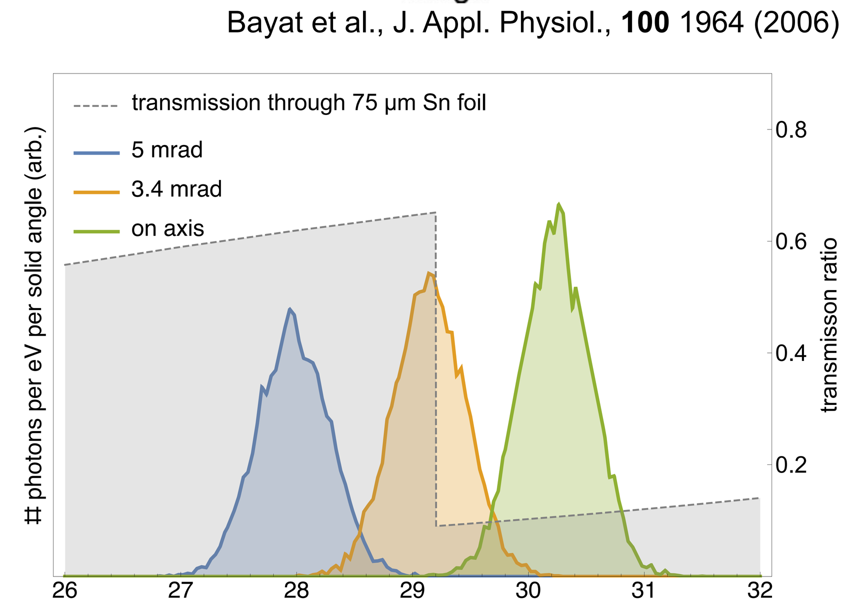
Lu et al. Small 6 1794 (2010)

Theranostics using monochromatic X-rays

The use of high-Z materials as contrast agents in radiology is well-established. The contrast can be dramatically increased by the use of monochromatic X-rays and K-edge subtraction method, where two images using a tunable mono-energetic beam of energies just above and below the K-edge of the contrast agent are taken and digitally subtracted. The background containing no contrast agent is removed, since there is no appreciable difference in the absorption (and thus exposure level) for the images of two slightly different energies. However, since the contrast agent strongly attenuates photons above the K-edge, the difference is accentuated, improving the contrast of the agent location. Cancer-seeking nanoparticles can serve as a dual-purpose drug as contrast agent for precisely locating tumors using the K-edge subtraction, as well as radiosensitizing agent for delivering enhanced dose. Depending on the depth, both could be achieved using the same X-ray beam, where the monochromaticity also helps in reducing unnecessary low-energy dose.



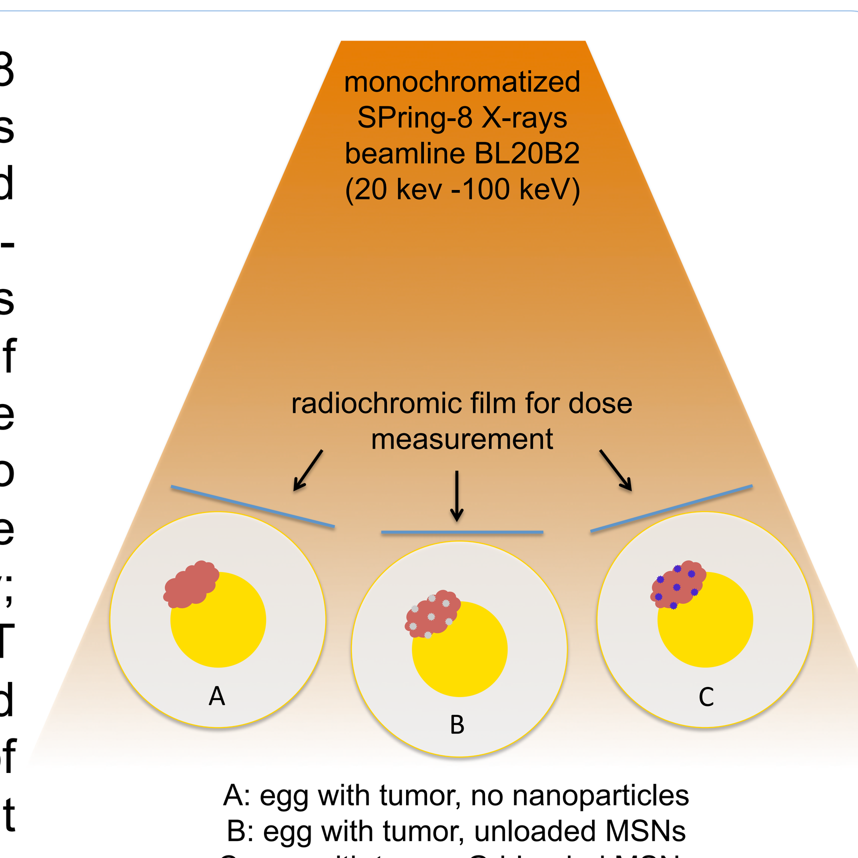
Bayat et al., J. Appl. Physiol., **100** 1964 (2006)



A laser-Compton scattering X-ray source can be used for KES and nanoparticle therapy, utilizing its compactness and angle-dependent monochromaticity.

Experiment planned at SPring-8 SR facility

We have applied for beam time at SPring-8 facility to use monochromatic hard X-rays in 20-100 keV range to irradiate and quantify the dose enhancement with high-Z-loaded MSNs. First, in vitro experiments with cancer cells in the presence of gadolinium-loaded nanoparticles will be done. The X-ray energy will be scanned to find the relationship between the dose enhancement factor and irradiating energy; cell death will be examined using MTT assay. The relationship between increased energy absorption due to the presence of heavy elements and dose enhancement factor will be studied and compared with other factors of cell death previously noted, such as chemical effects. The optimal energy from this first run of experiments will be used in the second in-vivo stage where fertilized chicken eggs with grown tumor are injected with the nanoparticles and irradiated. Confirmation of localization of nanoparticles in tumor and quantitative analysis of decrease in its size will be the primary objectives. The cycle of experiments will be repeated with other elements as beam time permits.



A: egg with tumor, no nanoparticles
B: egg with tumor, unloaded MSNs
C: egg with tumor, Gd-loaded MSNs

Element	K-edge energy	Auger yield
Silver (Ag)	25.5 keV	0.169
Iodine (I)	33.2 keV	0.116
Gadolinium (Gd)	50.2 keV	0.065
Gold (Au)	80.7 keV	0.036