

## PINPOINT KEV X-RAY IMAGING FOR X-RAY DRUG DELIVERY SYSTEM

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### Abstract

In X-ray Drug Delivery System, anticancer drugs containing Pt, such as cisplatin and dachplatin, and Au colloid contrast agent are surrounded by polymers (micelle, PEG (polyethylene glycol), etc.). Their sizes are controlled to be 20-100 nm. Since holes of capillary to organ are as large as 100 nm in only cancer, those large particles can be accumulated in cancer effectively. That is called as EPR (Extended Penetration and Retention effect). We have observed the distribution of Pt of dachplatin-micelle in cancer of mouse's pancreas by X-ray fluorescence analysis using 10  $\mu\text{m}$  pinpoint 15 keV X-ray by SPring8. Further, in-vitro- and in-vivo-experiments of Au colloid and Au-PEG are under way. It is expected to be used as contrast agent for dynamic tracking treatment for moving cancer. Imaging properties for polychromatic X-rays from X-ray tube and monochromatic Compton source are numerically analyzed and discussed. We continue to analyze radiation enhancement by Auger electrons and successive characteristic X-rays and its toxic effect to cancer.

### INTRODUCTION

Recently, the drug delivery system (DDS) with advanced nanotechnology is becoming one of the most important technologies in Japan. For example, Prof. Kataoka's group is successfully developing the DDS of cisplatin by nanomicell[1,2]. Not only the DDS itself but also the combination with physical energies such as ultrasonic-wave, microwave and laser are going to have a variety of possibilities. Since a visible laser light cannot penetrate to human body deeply, a catheter with optical fiber is needed for the deep tumors. To overcome this problem, the combination with higher-energy such as keV, MeV X-rays is expected.

Now we have started the feasibility study of the combination of the advanced DDS and physical energies recently[3,4]. The physical energies we have adopted are keV, MeV X-rays for so-called X-ray DDS for deeper digestive system cancers in liver, stomach spleen and so on. It consists of drug- and chemical technology,

advanced compact keV, MeV X-ray source and in-vitro- and in-vivo-evaluation and finally clinical inspection and technology, advanced compact keV, MeV X-ray source and in-vitro- and in-vivo-evaluation and finally clinical inspection and therapy. The mechanism of the X-ray DDS is depicted in Fig.1. Cisplatin which is an anti-cancer drug and contain Pt is expected to have the synergy effect of chemical and radiation therapy. It absorbs keV X-ray effectively and this aspect is good for imaging. Moreover, Auger electron and characteristic X-rays are emitted successively. The cisplatin, which original scale is about 20 nm, is surrounded by micelle polymer to be about 100 nm in size. Since the hole size of blood capillary to cancer is abnormally more than 100nm, such DDS can enter only the cancer cells. This is called EPR (Enhanced Penetration and Retention) effect. The second promising

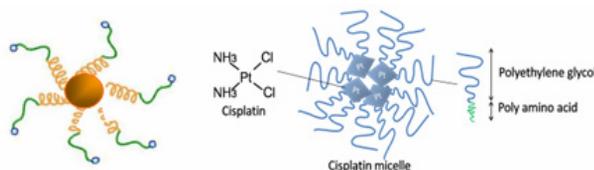
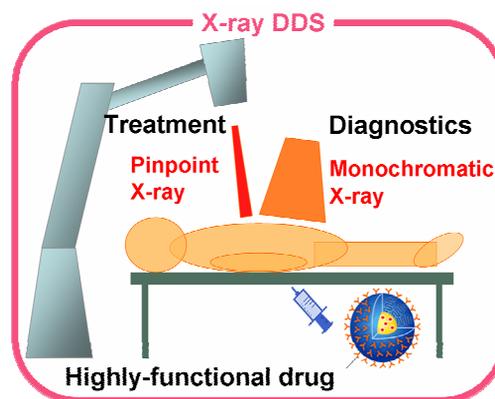


Figure 1: X-ray DDS (Drug Delivery System) containing Pt and Au and its mechanism.

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X-ray DDS is Au-colloid surrounded by PEG (polyethylene glycol) or liposome or dextran. Au density of tens nm sized Au-colloids is so high that the strong absorption and remarkable imaging effect is expected.

Now, we are performing the fundamental study for the DDS and pinpoint X-ray sources mainly. In this paper, we present our strategy for a new X-ray DDS via MCNP simulation, in-vitro and in-vivo experiments using gold nanoparticles and cisplatin micelle.

### PINPOINT X-RAY FLUORESENCE ANALYSIS FOR UPTAKE OF PT-TYPE DDS TO CANCER

A section of a human pancreatic tumor planted into mice was used. SR-XRF imaging was conducted at Spring-8, Hyogo, using the beam line BL37XU (15keV,  $10^{12}$ - $10^{13}$  photons/s). The area of  $250\mu\text{m} \times 250\mu\text{m}$  was scanned to obtain the elemental distribution around a tumor nest. The results showed that the micelles could permeate the tumor blood vessel, and could penetrate deep inside the tumor nest. This technique is very useful for the optimization of size, molecular weight, pin<sup>ot</sup> molecules of the micelles against different types of cancer cells.

### IN-VITRO- AND NUMERICAL ANALYSE FOR AU-TYPE DDS

The possibility of using gold nanoparticles was further investigated using MNCP5 [5]. In the set-up (Fig. 2) ball-shaped tumor is irradiated with either 100 or 200ke and the difference in the contrast of the image using iodine and gold nanoparticles was compared. With 100keV Xray energy is used, both gold nanoparticles and iodine is capable of showing contrast. However for high

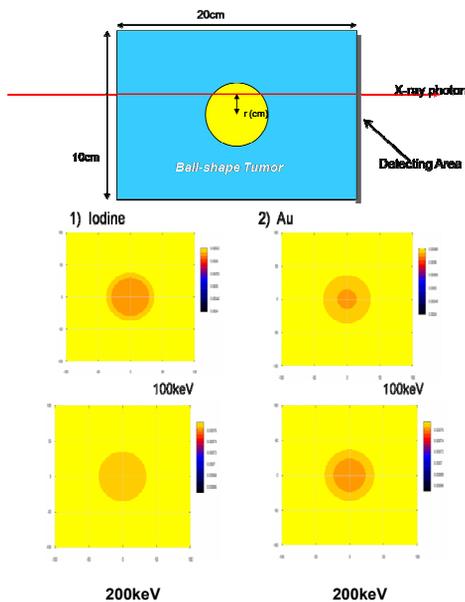
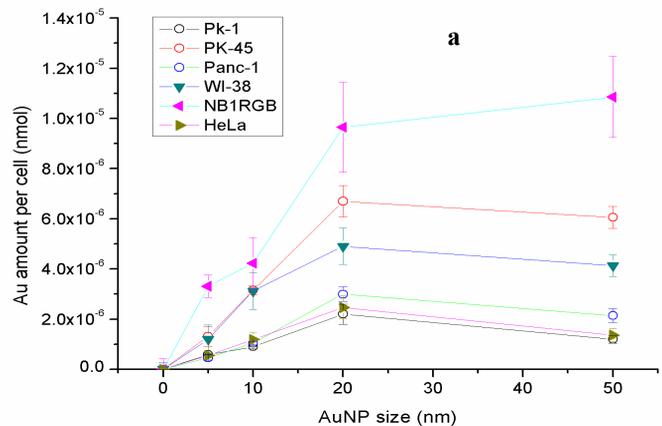


Figure 2: Simulations Results using Gold nanoparticles.

energy, iodine was not able to show contrast in the tumour. High energy x-ray is most preferable as the dose absorbed by the patient is lower compared to lower energies, hence, making the use of gold nanoparticles as an imaging contrast agents far better than iodine.

Intracellular uptake of human cells, both cancer and normal fibroblast were investigated using 5, 10, 20, 50nm gold nanoparticles incubated for 24 hours at 12uM concentration (fig. 3a). It was found that the uptake of 20nm gold nanoparticles is higher compared to other sizes considered, for most of the cell lines used [6]. Further experiments will be conducted to assess toxicity and other parameters that will affect the uptake of gold nanoparticles.

In Figure 3b, the cells were incubated with gold and gold-PEG for 24 hours then cells were exposed to 2,4,8 Gy of gamma-ray. It was found that the cells incubated with gold prior to exposure can decrease the survival fraction as compared to cells without gold. But difference in the survival fraction of gold and gold-peg is not significant for the cell line considered.



### Survival Curve with A549 (lung cancer cell)

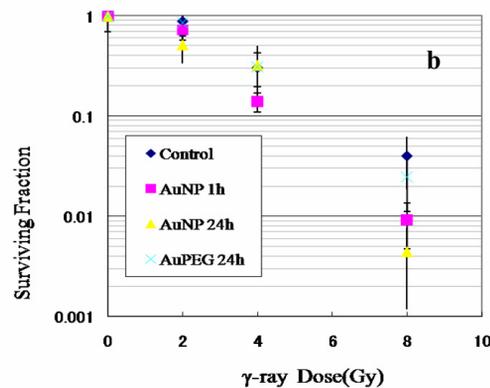


Figure 3: In-vitro results using Gold nanoparticles. a) uptake using different sizes of gold nanoparticles b) survival curve using different doses.

## PRELIMINARY EXPERIMENT OF DUAL ENERGY X-RAY CT BY COMPTON SCATTERING SOURCE

Preliminary experiment of the dual energy CT was done by the S-band Compton scattering monochromatic X-ray source of National Institute for Advanced Science and Technology (NIAST). We used the S-band linac tuned to 36 and 43 MeV and Ti-Sapphire laser (100fs, 800 nm, 140mJ) to generate 30.8, 43.8 keV. The experimental set-up and reconstructed CT images, where

we used fan-beams data in one direction assuming the axisymmetry, are shown in Fig.4. Since the machine tuning is not enough for stable X-ray generation, we observe several concentric ghosts. At this moment it is not available to evaluate equivalent atomic number distribution. We will continue to perform the experiment and analysis.

## CONCLUSION

In X-ray Drug Delivery System, anticancer drugs containing Pt, such as cisplatin and dachplatin, and Au colloid contrast agent are surrounded by polymers (micelle, PEG (polyethylene glycol), etc.). Their sizes are controlled to be 20-100 nm. Since holes of capillary to organ are as large as 100 nm in only cancer, those large particles can be accumulated in cancer effectively by the EPR effect. We have observed the distribution of Pt of dachplatin-micelle in cancer of mouse's pancreas by X-ray fluorescence analysis using 10  $\mu$ m pinpoint 15 keV X-ray by SPring8. Further, in-vitro- and in-vivo-experiments of Au colloid and Au-PEG are under way. It is expected to be used as contrast agent for dynamic tracking treatment for moving cancer. Imaging properties for polychromatic X-rays from X-ray tube and monochromatic Compton source are numerically analyzed and discussed. We continue to analyze radiation enhancement by Auger electrons and successive characteristic X-rays and its toxic effect to cancer.

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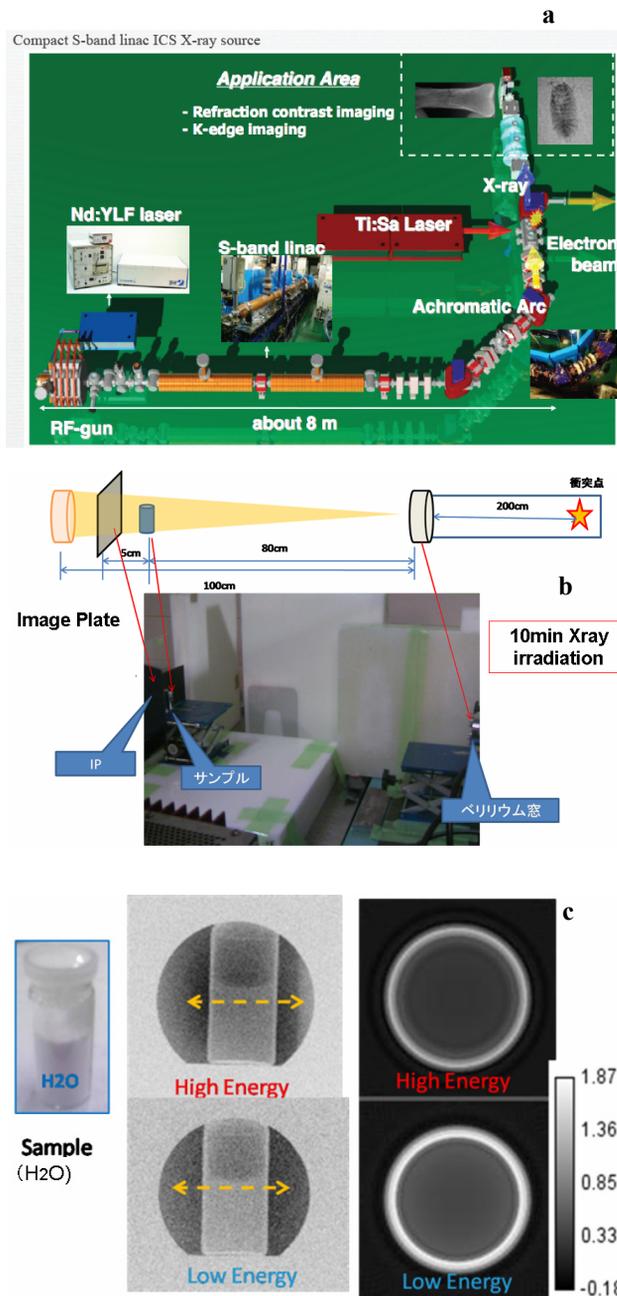


Figure 4: a) S-band Compton scattering source of NIAST, b) CT measurement set-up and c) CT reconstruction images of water-cell for the dual energies (30.8, 43.8 keV).