PINPOINT KEV/MEV X-RAY SOURCES FOR X-RAY DRUG DELIVERY SYSTEM

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Abstract

X-ray Drug Delivery System (DDS) is the most advanced radiation therapy coming after IMRT (Intensity Modulated Radiation Therapy) and IGRT (Image Guided). DDS uses advanced nano-scaled polymers which contain and deliver drug or contrast agent to cancers without side effects. Several X-ray DDS poses high-Z atoms like Pt and Au to absorb X-rays effectively and used as contrast agent for inspection. Moreover, they have radiation enhancement effect by emission of Auger electron and successive characteristic X-rays. The enhancement factor of Pt and Au is more than five. This can be used for therapy. This new modality must be very important for inspection and therapy of deep cancers. We are making use of our Compton scattering monochromatic keV X-ray source and MeV linac aspinpoint keV/MeV X-ray sources for the purpose. Physical analysis and evaluation of the contrast efficiency and radiation enhancement of the X-ray DDS are under way. Furthermore, a new compact X-band linac with a multi-beam klystron for a pinpoint X-ray source is proposed and designed. Updated research status and result are presented.

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]. 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. They are also developing the PDT (PhotoDynamic Therapy)-DDS such as dendrimer with visible laser [2]. PDT has a great success in clinical application, of course, but its drawback is a limitation to deep tumors. 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 this year. 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 sweetbread 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 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 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.

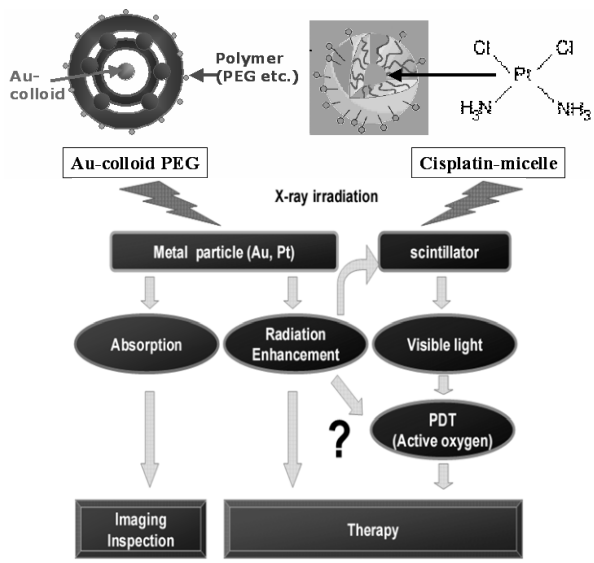

Figure 1: X-ray DDS (Drug Delivery System) containing Pt and Au and its mechanism.

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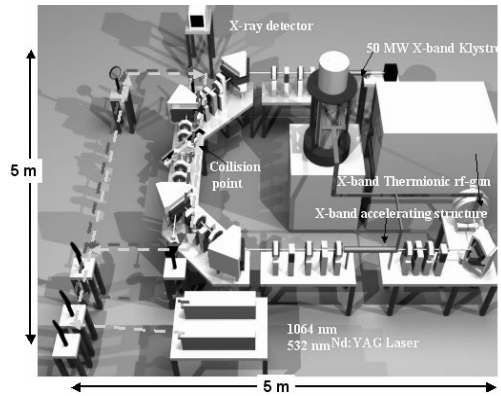

Figure 2: X-band (11.424 GHz) linac and monochromatic keV X-ray source.

Now, we are performing the fundamental study for the DDS and pinpoint X-ray sources mainly. In this paper, we present the review of the X-ray DDS development, current status of advanced compact X-ray sources and our strategy for a new X-ray DDS.

PINPOINT X-RAY SOURCE DEVELOPMENT

Here we explain Compton scattering monochromatic tunable keV X-ray source by X-band (11.424GHz) linac and YAG laser and propose 10 MeV X-band linac with multi-beam klystron as for pinpoint MeV X-ray source.

The first one is compact X-band (11.424GHz) linac and laser-Compton scattering monochromatic keV X-ray source based on updated RF (Radio-Frequency) technique as shown in Fig. 2 [3]. Here, 35 MeV X-band linac and 10 ns, 2 J YAG laser are used. Monochromatic visible lights of 1064, 532 nm are converted to monochromatic X-rays of 0.055 nm (22 keV), 0.27 nm (44 keV) in the direction of the incident electron, respectively. As we cut widely scattered X-rays by cylindrical collimator, the energy spread of X-rays becomes narrower. Actually, +/- 2.5 mrad collimation gives about 10 % energy spread and 2.5-mm-radius-spot. We have finished construction of the whole system and are going to start the medical application from now on. For example, dual energy CT to evaluate 3D distributions of effective atomic number and electron density [4] is planned.

The second one is 10 MeV X-band linac with 10 MW multi-beam klystron as depicted on Fig. 3. Here, pinpoint Bremstrahlung X-rays with 1 mm ϕ collimator are used

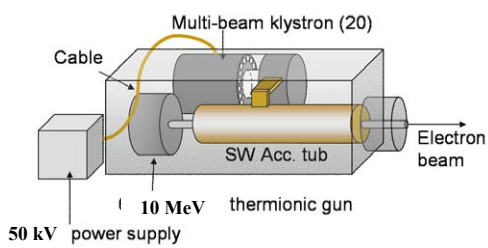

Figure 3: Schematic drawing of 10 MeV X-band linac with multi-beam klystron.

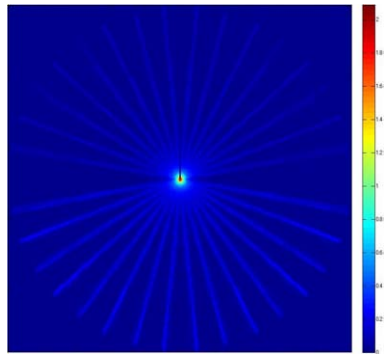

Figure 4: Calculated energy deposition of 1mm collimated X-rays in human body.

for therapy of deep cancers. We are going to realize the performance of S-band therapy machine with more than 10 MeV by the size of 6 MeV X-band cyberknife. The schematic drawing of the system and Monte Carlo simulation result of the energy deposition of 10 MeV collimated X-ray multi-beams in a human body are shown in Fig. 4. The detailed design and result will be presented in the next occasion.

DEVELOPMENT OF INNOVATIVE X-RAY DDS

The first X-ray DDS aiming both imaging and therapy is cisplatin micelle, a platinum contained anticancer drug encapsulated with a polymeric micelle (see Fig. 1). Cisplatin is thought to attach to DNA strands, and prevents their replication [5]. To verify the interaction between X-ray and cisplatin micelle, survival fractions of CHO and BxPc3 (human pancreas cancer cell) were measured by colony assay method. Cells were cultured in flasks, and cisplatin micelle was added in the medium 24 hours before X-ray irradiation (0-6Gy). However, up to now, the synergy effect was not observed in case of BxPc3 as shown in Fig. 5. Now we are conducting further experiments to verify these synergy effects.

Research of gold colloids has been recently investigated in the thermotherapy and radiotherapy to develop new cancer treatment. In order to delivery gold particles to the targeting tumor more efficiently and avoid interaction with immune system cells, invisible to macrophages, PEG-modified gold particles and liposome-transduced gold particles are designed. Effectiveness of

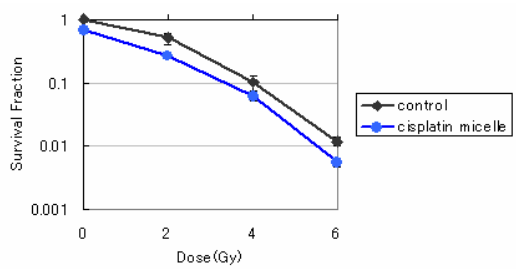

Figure 5: Survival fraction of BxPc3 cells with the exposure to 50μM of cisplatin and 0, 2, 4, and 6 Gy of X-ray irradiation.

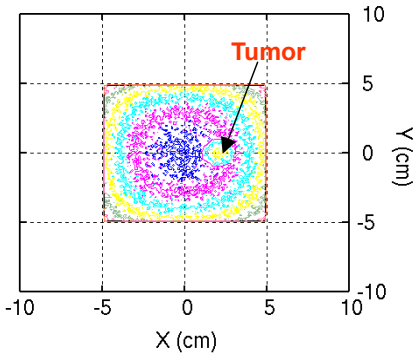

Figure 6: Monte Carlo simulation for imaging of gold colloid DDS concentrated tumor by 100 keV X-rays.

gold colloid DDS for imaging of a tumor is shown in Fig. 6. 100 keV monochromatic X-ray beam irradiates a 200 mm^2-sized human body phantom and then the total deposited energy is calculated by the Monte Carlo simulation. Simulated tumor has a spherical shape (10mm in radius) and concentration of Au equals to 28mg (Au)/g (tumor). This result shows the clear imaging. We especially expect that it can be used to track a moving tumor. To assay intracellular damage caused by radiation, we used the immunostaining method and observed under the optical microscope as shown in Fig. 7. White dots indicate the damaged parts of the DNA.

PULSE RADIOLYSIS EXPERIMENT

In order to demonstrate that the DDS polymer is a hydroxyl radical scavenger to suppress the indirect biological effect, we investigated its absorbance measurement in nano-micro second scale. As the first step, we performed the electron beam pulse radiolysis measurement to simulate X-rays by electrons. The hydroxyl radical is produced from electron beam acting on water. When an electron beam pulse is irradiated on aqueous solution, hydroxyl radicals are produced. HCO_3^- turns to $CO_3\cdot^-$ in the reaction with hydroxyl radicals. The concentration of hydroxyl radicals can be estimated by detecting 600nm light that is absorbed by $CO_3\cdot^-$. It has been demonstrated by the pulse radiolysis experiment that PEG, dextran and liposome are strong radical scavenger. They can be efficiently delivered to the tumor and

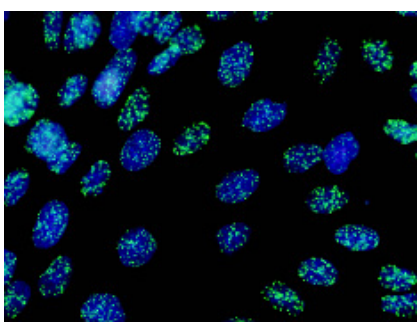

Figure 7: Immunostaining imaging of damaged DNA at 1 hour after 4Gy irradiation in case of gold size 2 nm.

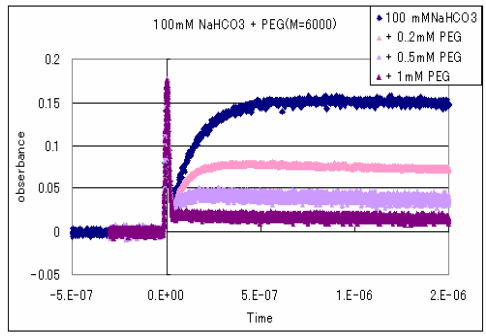

Figure 8: Time-variation of light (600nm) absorbance for different PEG concentration.

perform exposure reduction in the radiography. Figure 8 shows time-variation of the light (600nm) absorbance for different PEG concentrations. The OH radical production is reduced by adding PEG. In the next step, we do the experiment using X-rays instead of electrons to realize more realistic situation. This scavenger effect looks drawback for radiation therapy, but advantage for imaging inspection. Not only further experiment but also overall quantitative analysis of the biological effect should be done.

CONCLUSION

Fundamental study of the X-ray DDS and design and development of the pinpoint keV/MeV X-ray sources are under way by Medicine/Engineering collaboration at University of Tokyo. The synergy effect of chemical and radiation therapies for cisplatin micelle was analyzed by the in vitro test. The imaging effect of gold-colloid-DDS was confirmed by the Monte Carlo simulation. The OH radical scavenger effect was cleared by the pulseradiolysis. More intensive works should be done for this important subject.

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