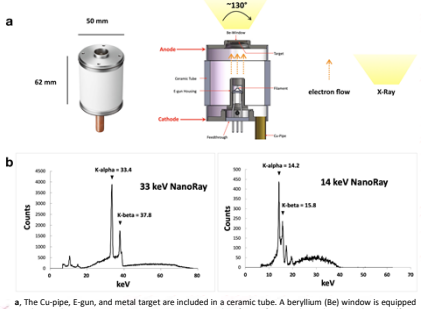
3941

Novel Cancer Therapy Approach based on Auger Effect Mediated by Characteristic X-ray Photons

Erh-Hsuan Lin[1,2], Chi-Chieh Cheng[3], Wen-Wong Kuo[3], Wan-Ting Tseng[3], Shih-Feng Tseng[3], Chien-Hau Chu[4], Wei-Li Chen[3], Chia-Gee Wang[3], Cheng-Wen Wu[1,2*]

Abstract Auger effect is a physical phenomenon that the creation of an initial inner atomic shell vacancy leads to a series of electron transitions, accompanied by emissions of so-called Auger electrons. Most Auger electrons have an energy around 20 - 500 eV and a travel distance from 1 - 10 nm in biological matter. DNA damage caused by Auger effect has been a topic of considerable interest in cancer radiotherapy. Auger effect can be efficiently induced in cells either by radionuclide "Auger emitters", or by monochromatic X-Ray on non-radioactive heavy atoms. However, safety concerns and requirement of a synchrotron accelerator hindered the clinical translation of Auger effect. Here, we show a novel design of transmission type X-Ray tube (denominated as "NanoRay" hereafter), which allows electron beams to pass through the metal target and generates characteristic X-Ray photons. This design substantially minimizes the size of X-Ray generator to be portable, allowing applications in small animal, and foreseeably in clinic. Preclinical studies confirmed a significant and synergistic anti-tumor effect when iododeoxyuridine (IdU) was combined with NanoRay treatment, but not conventional X-Ray irradiator. In vitro assays showed significantly more intense DNA damages within 30 min after NanoRay treatment in cells containing bromodeoxyuridine (BrdU) or IdU, confirming the impact of putative Auger electrons on DNA. NanoRay thus serves as a novel source of medical X-Ray, holding great promise to realize the clinical translation of Auger effect to cancer therapy.

Fig.1, The construct and characteristic spectrum of NanoRay



a, The Cu-pipe, E-gun, and metal target are included in a ceramic tube. A beryllium (Be) window is equipped on the anode as sputtering target. X-Ray is generated in front of Be-window when hot electrons (from filament) hit the target.
b, For biological studies, the "33 keV NanoRay" was equipped with 100 μm La target and 80 kV power, which generate characteristic photons around 33.4 keV (K-alpha of La), close to the K-edge energy of Iodine (33.17 keV). The "14 keV NanoRay" was equipped with 3 μm Molybdenum (Mo) target and 40 kV power (for bremsstrahlung radiation generation), and a Strontium (Sr) filter (1 mm Be + 100 μm Sr + 1mm Be) to generate characteristic photons around 14.2 keV (K-alpha of Sr), close to the K-edge energy of Br (13.47 keV).

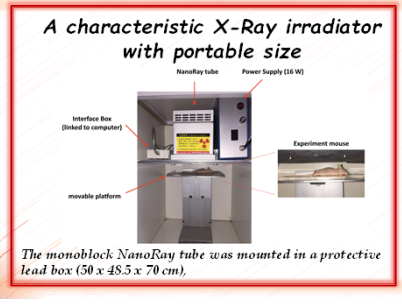
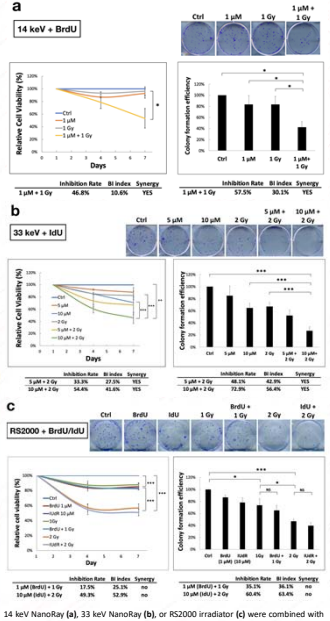
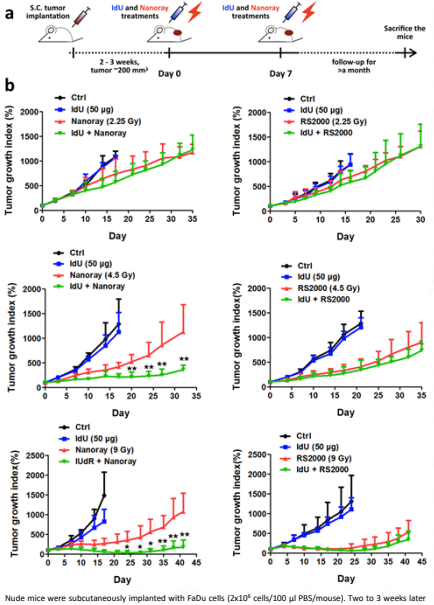


Fig.2, NanoRay synergized with BrdU or IdU to kill cancer cells, while conventional radiotherapy did not



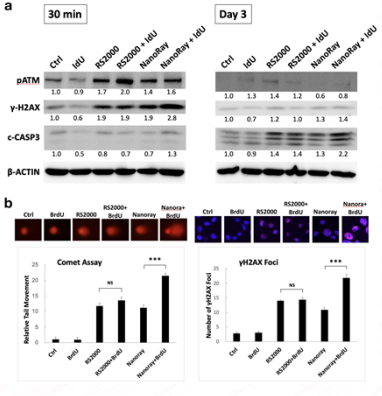
14 keV NanoRay **(a)**, 33 keV NanoRay **(b)**, or RS2000 irradiator **(c)** were combined with BrdU or IdU treatment in FaDu cells. Cell viability and colony forming assays were performed.

Fig.3, NanoRay synergized with IdU to inhibit tumor growth in vivo, while conventional radiotherapy did not

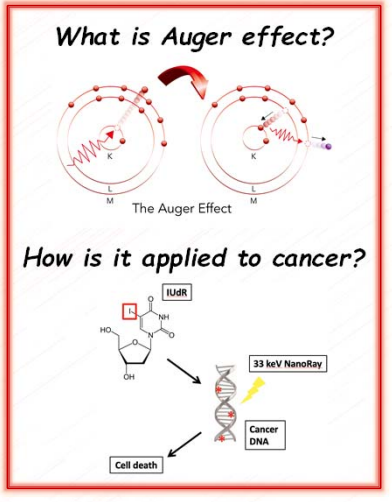


Nude mice were subcutaneously implanted with FaDu cells ($2x10^6$ cells/100 μl PBS/mouse). Two to 3 weeks later when tumors reached a volume of around 200 mm^3, mice were subjected to therapy. On day 0, IdU (50 μg/100 μl PBS/tumor) was intratumorally injected, and tumors were irradiated with X-Ray 4 h later. The same treatment was repeated on day 7.

Fig.3, Auger therapy induced much more intense DNA damage and apoptosis



a, FaDu cells were treated with IdU (0 or 10 μM) and irradiated by RS2000 or 33 keV NanoRay (0 or 2 Gy), and then harvested for Western-Blot analysis 30 min or 3 days after irradiation. **b**, FaDu cells were treated with BrdU (0 or 1 μM) and irradiated by RS2000 or 14 keV NanoRay (0 or 1 Gy), and then harvested for comet assay (left) or γH2AX immunofluorescent staining (right) 30 min after irradiation. More than 100 cells/group were measured in each experiment, and the results were averaged from 3 independent experiments. ***, P<0.001. Ctrl, control group (0 μM+0 Gy).



Affiliation:
1. Institute of BioMedical Sciences, Academia Sinica, Taipei, Taiwan
2. National Yang-Ming University, Taipei, Taiwan
3. Nanoray Biotech Co., Ltd., Taipei, Taiwan
4. Institute of Nuclear Energy Research, Atomic Energy Council, Longtan, Taiwan