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Using rare-earth based nanoscintillators for X-ray induced photodynamic therapy

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Pancreatic cancer is associated with a poor prognosis despite multimodal treatments consisting in surgery, chemotherapy and radiotherapy. Photodynamic therapy (PDT) is a promising treatment that aims to activate photosensitizers with light in order to induce local cell damage. However, its use for treating deep tumors, including pancreatic tumors, is limited because of the low penetration depth of light in tissues. To overcome this limitation, it has been proposed to use nanoscintillators (NS) that down-convert ionizing radiation such as X-rays used in radiotherapy, into UV-visible photons. These nanoparticles could improve the efficacy of radiotherapy through at least three effects: the radiation dose-enhancement effect¹ that is a physical effect due to the accumulation of heavy elements in the vicinity of tumors, the emission of UV-C photons that increase direct DNA damage, and the activation of photodynamic therapy by X-rays (X-PDT)². The aim of our project is to conjugate NS with appropriate photosensitizers to achieve PDT during radiotherapy. Here, we present our results obtained with lanthanum fluoride nanoscintillators doped with cerium (LaF₃:Ce) coated with either triphosphate or polyethylene glycol (PEG). The choice of the coating is of major importance because it could modify the NS toxicity and uptake in cells and microtumors, and thus impact their therapeutic efficacy. We studied the properties of NS on both 2D and 3D culture models of pancreatic tumors, grown in suspension or as adherent microtumors. As LaF₃:Ce nanoparticles are only excited by UV photons, they could not be observed with a conventional confocal microscope. Therefore, we used X-ray fluorescence microscopy (ID16, ESRF) and transmission electron microscopy (IBS) to analyze their distribution within the cells, and X-ray fluorescence microtomography (P06, DESY) to study their accumulation in tumor spheroids. We observed that NS functionalized with triphosphate coating formed many aggregates and were present in greater amounts within the cells, compared to those with PEG coating. These experiments also showed a higher concentration of lanthanum – the main constituent of NS – inside the tumor spheroids when a triphosphate coating was used. We obtained similar intrinsic toxicities for both coatings, and promising preliminary results regarding the therapeutic potential of LaF₃:Ce NS.

We are currently investigating the role of the NS coating on treatment efficacy, biodistribution and pharmacokinetics using *in vivo* models of pancreatic tumors. Finally, their conjugation with photosensitizers will be investigated to evaluate X-PDT efficacy.

KEYWORDS: X-ray induced photodynamic therapy, nanoscintillators, pancreatic cancer, radiotherapy, synchrotron radiation

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Photosensitizers as radiosensitizers for metastatic and deep-seated tumors: *in vitro* and *ex-ovo* preclinical studies

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Photodynamic therapy (PDT) is a well-described technique that is primarily used for thin and superficial tumors. Despite the advantages of immune response upregulation, high complete response rates and excellent cosmetics and preservation of tissue structure, the limited light penetration into tissue complicates achieving full-thickness/large-volume treatment of pigmented, thicker, deep-seated or diffuse metastatic tumors¹. Reported *in vitro* studies in melanoma and breast cancer cells show increased expression of major histocompatibility complex I after the combination of psoralen and X-radiation, which is representative of a potential immune response upregulation². The aim here is to investigate the clinical photosensitizer Verteporfin (VP) as a radiosensitizer to achieve deep tissue penetration while retaining immune upregulation, and thereby enhance tumor-specific radiation responses in pancreatic cancer³ and melanoma⁴, which are aggressive tumors with high metastatic potential and low survival rates. *In vitro* studies were carried out with bioluminescent human pancreatic cancer (Panc-1-Luc-2) and murine melanotic melanoma (B16F10) cell lines. The cells were irradiated using 225 kVp (XRAD) or 6 MeV (Linac) X-ray beams, and the treatment response was measured by clonogenicity. In all cases, the presence of VP in the cells reduced survival compared with X-ray only controls: e.g. the group irradiated in the Linac, which includes a contribution from VP activation by X-ray induced Cherenkov light, reached up to 5 Logs of cell death after a single fraction of 10 Gy. In the *ex-ovo* model, duck eggs at 8 days post fertilization were engrafted with 15 μ L ($\sim 5 \times 10^7$) of Panc-1-Luc-2 or B16F10-Luc cells. Treatment was given 3 days later using topical VP administration with irradiation 1.5 h later. Combining a single fraction of 5 Gy with 5 μ g/mL VP gave >2-fold reduction of the bioluminescence compared to <1 fold for radiation alone. After 3 daily fractions, the *in ovo* tumors treated with VP + radiation showed undetectable bioluminescence signal until sacrificed at 2 d after the last fraction. These studies are intended primarily to generate baseline response data for radiodynamic therapy with different nanoparticle formulations, including both lipid-porphyrin porphyrins and metal nanoclusters.

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KEYWORDS: Photosensitizers, verteporfin, radiosensitizer, radiodynamic therapy, radiosensitization