# Nanoparticles Used in X-Ray Photodynamic Therapy

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Photodynamic therapy (PDT) has long been known as an effective method for treating surface cancer tissues. Deeper penetration of X-rays into tissues has been implemented, which is now known as X-ray photodynamic therapy (XPDT). The two methods differ in the photon energy used, thus requiring the use of different types of scintillating nanoparticles. These nanoparticles are known to convert the incident energy into the activation energy of a photosensitizer, which leads to the generation of reactive oxygen species.

Keywords: X-ray photodynamic therapy ; photodynamic therapy ; nanophosphor ; scintillating nanoparticles ; photosensitizer

# 1. Nanoparticles as Photosensitizers

Cu–Cy. Copper–cysteamine Cu–Cy nanoparticles were used as a photosensitizer  $^{[\underline{1}]\underline{2}]}$ .

TiO<sub>2</sub>:Ce. Single TiO<sub>2</sub> is not effective enough in the generation of ROS. For example, Chun-Chen Yang and his colleagues <sup>[3]</sup> doped the anatase lattice of TiO<sub>2</sub> with Ce, which was more effective than a single TiO<sub>2</sub> for better photosensitivity and ROS generation results.

Cerium was used to dope the  $TiO_2$  anatase structures to increase photochemical reactions owing to its strong catalytic potential and light response extension. Furthermore, it could suppress the recombination of electron–hole pairs and increase their lifetime. Additionally, Ce has a greater X-ray photon interaction cross-section than that of biological tissues, which leads to the intense X-ray interaction with control materials and ROS generation <sup>[4]</sup>. The X-ray radiation dose was approximately 0.133 Gy for 100 s.

TiO<sub>2</sub>:C. Chun-Chen Young and his co-authors <sup>[4]</sup> investigated nanoparticles with a narrow bandgap and ROS generation under the influence of soft X-ray radiation to destroy tumor cells with less damage to healthy tissues. In this experiment, anatase lattice was doped with C, and then it was activated by X-rays to produce more reactive oxygen species and destroy tumor cells. After X-ray radiation and the introduction of TiO<sub>2</sub>:C to tumor cells, the size of the tumor gradually reduced. The X-ray radiation dose was approximately 0.133 Gy for 100 s.

 $(n-Bu4N)_2(Mo_6I_8(OCOCF_3)_6)$ . Kaplan Kirakci et al. <sup>[5]</sup> studied the nanoparticles made of the octahedral molybdenum cluster compound or  $(n-Bu_4N)_2(Mo_6I_8(OCOCF_3)_6)$ . These nanoparticles generate singlet oxygen  $O_2(^1\Delta_g)$  from blood under X-ray irradiation. The  $(n-Bu_4N)_2(Mo_6I_8(OCOCF_3)_6)$  nanoparticles were prepared by nanoprecipitation.

 $(n-Bu_4N)_2(Mo_6I_8(OCOCF_3)_6)$  nanoparticles efficiently absorbed X-rays because they consist of heavy elements, which in turn leads to the generation of the excited triplet states of photosensitizer interacting with molecular oxygen to produce singlet oxygen  $O_2(^{1}\Delta_g)$ .

Some specific concentrations of the obtained nanoparticles are non-toxic and quite stable in water. The simple structure of nanoparticles leads to their significantly higher activity at lower concentrations. This fact is mainly based on the energy transfer between scintillating nanoparticles and photosensitizers. In addition, the small size of the nanoparticles provides a large energy transfer. The smaller the particles are, the closer they can approach the target. This means that the value of the transferred energy from the nanoparticle to the molecular oxygen is higher. As a result, it leads to the formation of a higher number of ROS. Thus, the enhancement effectiveness of  $(n-Bu_4N)_2(Mo_6I_8(OCOCF_3)_6)$  nanoparticles could be achieved by their size. The X-ray dose reported as 1 Gy and 2 Gy for 100 s.

Pollen-structured gold cluster. The pollen-structured gold cluster (PSGC) were designed for mediating X-ray-induced PDT for radiotherapy enhancement <sup>[6]</sup>. PSGCs were made of mesoporous silica and then their core was passivated by a rich

layer of gold nanoparticles (**Figure 1**). PSGCs were synthesized with a deposition–precipitation process. The architecture of PSGCs provides a large surface area, which in turn leads to the generation of ROS under X-ray irradiation.

# Mesoporous silica nanoparticle (MSN) Gold nanoparticle



**Figure 1.** Schematic illustration of the pollen-structured gold cluster. The cluster consists of a mesoporous silica core and a gold active shell [I].

The obtained nanoparticles were exposed to a variety of irradiation doses: 0.5, 1, 2, and 5 Gy. A single dose of X-ray irradiation was provided with the voltage of the tube equal to 160 kV.

PSGCs have a significantly higher ability to generate ROS and they offer a better treatment of breast cancer cells <sup>[6]</sup>, demonstrating the potential clinical application in the treatment of deep tumors.

# 2. Scintillating Nanoparticles

 $Y_2O_3$ :Eu and  $Y_3A_{15}O_{12}$ :Eu. Yang C. et al. in <sup>[8]</sup> investigated the luminescent properties of  $Y_2O_3$ :Eu and  $Y_3A_{15}O_{12}$ :Eu particles as scintillating nanoparticles irradiated with X-rays in PDT. The nanoparticles can be used for cancer treatment in combination with some kind of photosensitizers that selectively accumulate in tumor cells. Two sets of finely dispersed  $Y_2O_3$ :Eu and  $Y_3A_{15}O_{12}$ :Eu phosphors were synthesized by the Pechini method and self-propagating high-temperature

synthesis. The data in <sup>[B]</sup> show that the use of this X-ray activated phosphor in combination with the photosensitizers results in the destruction of tumor cells under irradiation thus confirming a high efficiency of the suggested approach.

 $Y_2O_3$ . Jonathan P. Scaffidi et al. in <sup>[9]</sup> investigated the combination of yttrium oxide ( $Y_2O_3$ ) scintillating nanoparticles, a part of the HIV-1 TAT (Human immunodeficiency viruses – 1 trans-activator of transcription) peptide, and psoralen was investigated by X-ray radiation. The X-ray radiation is absorbed by the  $Y_2O_3$  nanoparticles, which then emit UV light. The absorption of UV photons by the nanoparticles connected with psoralen has the potential to cross-link adenine and thymine residues in DNA.

NaGdF<sub>4</sub>: Gd<sup>3+</sup>, Eu<sup>3+</sup>. Some lanthanide-doped nanoparticles can absorb X-ray radiation. There was a series of Gd<sup>3+</sup> and Eu<sup>3+</sup> compositions in lanthanide fluorides for optimizing the emission from Eu<sup>3+</sup> under X-ray excitation <sup>[10]</sup>. In addition, the optimum concentration of Eu<sup>3+</sup> that produced the most intense emission in NaGdF<sub>4</sub> was 15% molar concentration. Moreover, an attempt to include a sensitizer (Ce<sup>3+</sup>) in NaGdF<sub>4</sub>:Eu<sup>3+</sup> resulted in a reduction in the emission following X-ray excitation.

 $LiGa_5O_8$ :Cr. Hongmin Chen in <sup>[11]</sup> used nanoscintillators based on  $LiGa_5O_8$ :Cr, which emit persistent near-infrared luminescence. This allows to obtain optical images of deep tissues that can be used to control exposure. In particular,  $LiGa_5O_8$ :Cr nanoparticles and a 2,3-naphthalocyanine photosensitizer were encapsulated in mesoporous silica nanoparticles. Nanoconjugates can be efficiently accumulated in lung tumors, as evidenced by monitoring X-ray luminescence from  $LiGa_5O_8$ :Cr. It should be noted that  $LiGa_5O_8$ :Cr nanoparticles were prepared by a polystyrene sphere-assisted sol–gel method.

## 3. Nanocomposites: Photosensitizers and Scintillating Nanoparticles

AIE-Au. Wenjing Sun et al. in their work <sup>[12]</sup> investigated such conjugates of photosensitizers as aggregation-induced emission heterogeneous Au clustoluminogens (AIE-Au) which consist of glutathione-protected gold clusters (GCs) to achieve efficient low-dose XPDT.

When irradiated, AIE-Au strongly absorbed X-rays to generate hydroxyl radicals, which increased the radiotherapy effect by damaging DNA. Furthermore, the aggregates of glutathione-protected GCs increased the X-ray excited luminescence. The AIE-Au transformed X-rays into optical luminescence and excited the rose bengal (RB) photosensitizers, which oxidizes lipid membranes. In other words, AIE-Au clustoluminogens triggered the generation of reactive oxygen species. X-ray doses used in this investigation were 1 Gy.

 $LiYF_4@SiO_2@ZnO.$  Qien et al. in <sup>[13]</sup> reported herein on the integration of a scintillator and a semiconductor as an XPDT agent. These conjugates are core-shell Ce<sup>III</sup>-doped LiYF<sub>4</sub>@SiO<sub>2</sub>@ZnO nanoparticles (LSZNPs).

In this structure, the ultraviolet fluorescence from the  $Ce^{III}$ -doped LiYF<sub>4</sub> nanoscintillator under irradiation gives rise to the formation of electron–hole pairs in ZnO nanoparticles leading to the formation of biotoxic hydroxyl radicals.

This method demonstrates a reduced dependence on the intracellular oxygen levels by integrating the scintillator and semiconductor as a photosensitizer. These nanoparticles have been used as the scintillation nanoparticles in the down-conversion of X-rays to match the energy gap of a semiconductor to produce ROS from water molecules for an effective explosion.

The volume of the tumor (the HeLa cell line was used) with the introduced LSZNPs and exposed to an X-ray radiation of 8 Gy was almost completely inhibited in 15 days. In addition, late-stage apoptosis featuring karyopyknosis, karyorrhexis and the significant formation of apoptotic bodies was observed after the irradiation of these tissues. The application of these nanoparticles demonstrates antitumor therapeutic effectiveness. X-ray irradiation was used at 3 Gy.

RGD-ZSM-RB. Zn- and Mn-incorporated silica (ZSM) nanoscintillators were conjugated with photosensitizer rose bengal and arginylglycylaspartic acid (RGD) peptide, due to the fact that they are intrinsically dual modal targeted imaging probes as it was shown in <sup>[14]</sup>. The proposed RGD-ZSM-RB nanosensitizer shows excellent deep-tumor therapy with low dose X-ray irradiation (1 Gy). After the conjugation of RGD peptides with silicate scintillators, the nanosensitizer could show effective accumulation in cancer cells and local inhibition. Moreover, Zn and Mn dopants are significant elements in the human body. XPDT treatment therefore minimizes the potential adverse effects of local radiotherapy due to the application of low radiation doses like 1 Gy, while the typical dose for a solid epithelial tumor varies from 60 to 80 Gy.

LaF<sub>3</sub>. Lanthanum fluoride is a transparent material that could allow radioluminescence at a set of wavelengths through the simple substitution of lanthanum ions with other luminescent lanthanides. For example, in <sup>[15]</sup> Kudinov K. et al. prepared lanthanum fluoride nanoparticles doped with cerium, terbium, or both, which had good spectral overlap with Rose Bengal photosensitizer molecules.

LaF<sub>3</sub>:Tb. Lanthanum fluoride nanoparticles have been improved and doped with rare-earth element Tb<sup>3+</sup> in <sup>[16]</sup>. They were Tb<sup>3+</sup>-doped LaF<sub>3</sub> scintillating nanoparticles (LaF<sub>3</sub>:Tb) combined with meso-tetra(4-carboxyphenyl)porphyrin photosensitizer, followed by activation with soft X-rays. Scintillating LaF<sub>3</sub>:Tb nanoparticles were obtained, sized approximately 25 nm. They had good dispersibility in aqueous solutions and demonstrated great biocompatibility.

CeF<sub>3</sub>:Tb<sup>3+</sup>. In the studies of K. Popovich et al. <sup>[16]</sup> CeF<sub>3</sub>:Tb<sup>3+</sup>-based nanoparticles modified with SiO<sub>2</sub> and protoporphyrin IX (PpIX) were investigated. Nanopowder CeF<sub>3</sub>:Tb<sup>3+</sup> was prepared via the sol–gel method, with further surface coating by SiO<sub>2</sub> layer and the conjugation with photosensitizer PpIX. Radioluminescence spectra showed an energy transfer from Ce<sup>3+</sup> to Tb<sup>3+</sup> ions and from Tb<sup>3+</sup> to the molecules of PpIX photosensitizer. The samples were exposed with X-rays using a tube with a Cu anode (voltage 40 kV, current 30 mA, average wavelength K<sub>a1.2</sub> = 0.15418 nm).

Emission bands of  $Tb^{3+}$  overlap well with the absorption lines of protoporphyrin PpIX. Therefore, the efficient energy transfer from donor to acceptor and the production of singlet oxygen were expected. This combination of nanoparticles generated ROS. Nanocomposites under investigation may be quite good candidates for the application in XPDT.

CeF<sub>3</sub>:Tb<sup>3+</sup>, Gd<sup>3+</sup>. Another promising nanoparticle is CeF<sub>3</sub> doped with Gd<sup>3+</sup> and Tb<sup>3+</sup> (CGT) investigated in [17]. CGT nanoparticles were synthesized with a hydrothermal process. Co-doped CeF<sub>3</sub>:Gd<sup>3+</sup>, Tb<sup>3+</sup> scintillating nanoparticles were then coated with mesoporous silica. Such doping with Gd and Tb boosted the scintillation properties of the CeF<sub>3</sub> nanoparticles.

The enhancement of the X-ray-excited optical luminescence was due to the fact that the energy levels of  $Gd^{3+}$  lie between the activator ( $Ce^{3+}$ ) and the luminescent center ( $Tb^{3+}$ ), giving rise to efficient energy transfer. The irradiation of nanoparticles was carried out with single X-ray dose 3 Gy.

ZnGa<sub>2</sub>O<sub>4</sub>:Cr (ZGO:Cr/W). Song L. and others reported in <sup>[18]</sup> on a low-dose X-ray-activated persistent luminescence nanoparticle (PLNP)-mediated PDT nanoplatform for treating deep cancer tumors. The high persistent luminescence and long persistent luminescence time were the key points for effective cancer treatment. In order to achieve this goal, W<sup>VI</sup>doped ZnGa<sub>2</sub>O<sub>4</sub>:Cr (ZGO:Cr/W) PLNPs were synthesized. In comparison with the traditional ZnGa<sub>2</sub>O<sub>4</sub>:Cr PLNPs, ZGO:Cr/W PLNPs show a higher persistent luminescence intensity and a longer persistent luminescence time after the same irradiation dose. Then, by coupling with PS Zn(II) phthalocyanine tetrasulfonic acid (ZnPcS<sub>4</sub>), the PDT nanoplatform (ZGO:Cr/W–ZnPcS<sub>4</sub>) was constructed. The constant luminescence could continue exciting the coupled PS after the X-ray irradiation was removed, leading to the reduced X-ray dose (~0.18 Gy for 2 min) to minimize the side effects of XPDT.

ZnS:Cu,Co. Like Lun Ma et al. in <sup>[19]</sup> synthesized copper- and cobalt-doped ZnS (ZnS:Cu,Co) scintillating nanoparticles which were then used in combination with tetrabromorhodamine-123 (TBrRh123) photosensitizer. It was determined that in the conjugates there was an efficient energy transfer from nanoparticles to photosensitizers. As a result, singlet oxygen was generated for the treatment of cancer cells.

Furthermore, ZnS:Cu, Co nanoparticles have a long X-ray excited afterglow used as a continuous light source to activate XPDT. ZnS: Cu, Co-TBrRh123 X-ray conjugates are very effective for the destruction of cancer cells. Besides ZnS:Cu, Co nanoparticles irradiated by X-rays (2 Gy) can also be used to visualize cells. All this indicates that ZnS:Cu, Co nanoparticles are promising for biomedical applications.

 $GdEuC_{12}$  micelles. It should be mentioned that sometimes lanthanide micelles are used as nanoparticles in XPDT. For instance, Slávka Kaščáková et al. designed a liponanoparticle based on  $GdEuC_{12}$  micelles including hypericin as a photosensitizer in their hydrophobic core, which provides singlet oxygen production upon X-ray irradiation <sup>[20]</sup>. The micelles were composed of amphiphilic lanthanide chelates and incorporated hypericin as photosensitizer in the hydrophobic core.

 $Tb_2O_3$ .  $Tb_2O_3$  has recently become the center of attention. Anne-Laure Bulin et al. in <sup>[21]</sup> used  $Tb_2O_3$  coated with a polysiloxane layer. This nanosystem was combined with porphyrin molecules that were able to generate singlet oxygen, which is a major cytotoxic agent in X-ray photodynamic therapy. This combination was suitable for singlet oxygen formation under X-ray irradiation.

The BaGdF<sub>5</sub> nanophosphors doped with different Eu:Gd ratios in the range from 0.01 to 0.50 were synthesized by new microwave route <sup>[22]</sup> in <sup>[23]</sup>. Different coatings with amorphous SiO<sub>2</sub> and citrates were studied. Micro-CT imaging demonstrate supe-rior X-ray attenuation and sufficient contrast in liver and spleen after intravenous injection of citric coated nanoparticles. Nitrogen adsorption/desorption analysis revealed mesoporous SiO<sub>2</sub> formation characterized by the slit-shaped type of pores, that should be accessible for Methylene Blue photosensitizer molecules. It was shown that SiO<sub>2</sub> coating subsequently facilitate Methylene Blue conjugation and result to the formation of BaGdF<sub>5</sub>:10%Eu<sup>3+</sup>@SiO<sub>2</sub>@MB nanocomposite (**Figure 2**) as a promising candidate for appli-cation in XPDT.



**Figure 2.** Schematic illustration of the BaGdF<sub>5</sub>: $Eu^{3+}$ -assisted XPDT concept and possible morphology of the corresponding composite material based on the BaGdF<sub>5</sub>: $Eu^{3+}$  agent coupled with the methylene blue photosensitizer <sup>[23]</sup>.

### 4. Metal–Organic Frameworks as Photosensitizers

Metal–organic frameworks (MOFs) are crystalline porous compounds that consist of organic linkers and metal ions. The demonstrate a great potential in drug delivery applications due to their high surface area and drug-loading capacity, tailorable pore structure as well as their functionality <sup>[24][25][26][27][28][29]</sup>. Many MOFs have already been used as nanoparticles in photodynamic therapy. However, MOFs are also often used as nanoparticles in X-ray photodynamic therapy. Let us consider several structures of MOFs that turned out to be the most successful in various studies.

Hf-DBB-Ru. Recently nanoscale metal–organic frameworks (nMOFs)-Hf-DBB-Ru have been discovered<sup>[30]</sup>. Hf-DBB-Ru is  $(Hf_6(\mu_3-O)_4(\mu_3-OH)_4(DBB-Ru)_6)^{12+}$  where DBB-Ru = bis(2,2'-bipyridine)(5,5'-di(4-benzoato)-2,2'-bipyridine)ruthenium (II) chloride.

Hf-DBB-Ru was synthesized by solvothermal reaction between  $HfCl_4$  and  $H_2DBBRu$  with trifluoroacetic acid as the modulator. Hf-DBB-Ru was irradiated with 1, 2, 3, 5 or 10 Gy X-ray.

This MOF was designed from Ru-based photosensitizers. The cationic framework demonstrated strong targeting to mitochondria. Under X-ray irradiation, Hf-DBB-Ru successfully generated hydroxyl radicals from Hf<sub>6</sub> secondary building units (SBUs) and singlet oxygen from the DBB-Ru photosensitizers. Mitochondria-targeted particles depolarized the mitochondrial membrane to activate the apoptosis of cancer cells, which resulted in the significant regression of colorectal tumor cells. When the volume of the tumor reached 100–150 mm<sup>3</sup>, the tissue was irradiated by light with energy 180 J/cm<sup>2</sup> (650 nm).

 $Hf_6$ -DBA and  $Hf_{12}$ -DBA. Kaiyuan Ni et al. in <sup>[31]</sup> investigated two more nMOF structures based on Hf-Hf<sub>6</sub>-DBA (Hf-Hf<sub>6</sub>-DBA = Hf<sub>6</sub>(µ<sub>3</sub>-O)<sub>4</sub>(µ<sub>3</sub>-OH)<sub>4</sub>(DBA)<sub>6</sub>) and Hf<sub>12</sub>-DBA (Hf<sub>12</sub>-DBA = Hf<sub>12</sub>(µ<sub>3</sub>-O)<sub>8</sub>(µ<sub>3</sub>-OH)<sub>8</sub>(µ<sub>2</sub>-OH)<sub>6</sub>(DBA)<sub>9</sub>), where DBA = 2,5-di(*p*-benzoato) anthracene. These nMOFs were synthesized via solvothermal reactions.

nMOFs were constructed as radio-enhancers by taking advantage of the electron-dense  $Hf_6O_4(OH)_4$  and  $Hf_{12}O_8(OH)_{14}$  SBUs as X-ray absorbers to produce ROS.

Under X-ray irradiation, nMOFs convert energy to anthracene-based bridging ligands, DBA, to emit radioluminescence in the visible spectrum range. For example, in <sup>[31]</sup>  $Hf_{12}$ -DBA and  $Hf_{6}$ -DBA (incubated in CT26 cell line) were irradiated with 2 Gy X-rays dose. It was shown that  $Hf_{12}$ -DBA gave a much brighter radioluminescence signal with respect to  $Hf_{6}$ -DBA.

 $Hf_{12}$ -DBA demonstrated great radio-enhancement over  $Hf_6$ -DBA. It has been suggested that this is due to enhanced X-ray absorption by the electron-dense  $Hf_{12}$  clusters and hydroxyl radical diffusion through the porous nanoplates. It should be noted that under y-rays  $Hf_{12}$ -DBA also exhibited greater radio-sensitization than  $HfO_2$  and  $Hf_6$ -DBA.

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