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Rare Earth Doped Nanoparticles in Cancer Therapy

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ABSTRACT

Bosom malignant growth is the second driving reason for disease passing among ladies and speaks to 14% of death in ladies around the globe. The standard conclusion technique for bosom tumor is mammography, which is regularly related with false-negative outcomes prompting helpful postponements and contributing in a roundabout way to the advancement of metastasis. Nanoparticles in cancer studies are commonly used in photodynamic therapy (PDT) and son dynamic therapy (SDT) as a sensitizing agent, in computed tomography imaging (CT) and radiation therapy as an enhancement agent, in dual-mode image contrast and enhancement therapy as an image contrast agent. Titanium dioxide nanoparticles (TiO_2 NPs) are known as a commonly used nanoparticles in medical applications and hence in cancer studies .Along these lines, the advancement of new apparatuses that can identify bosom malignant growth is a pressing need to diminish mortality in ladies. Here, we have created Ti2O3:Eu3+ nanoparticles functionalized with folic corrosive (FA), for bosom malignancy recognition.

Keywords **：** ***Nanoparticles, cancer, photodynamic therapy (PDT) , chemotherapy ,SDT***

I.Introduction

Nanoparticles have developed as potential instruments for the finding and treatment of malignant growth because of their particular amassing in disease tissue by means of upgraded permeation and maintenance (EPR) impact [1]. Because of the potential advantages of nanoparticles in malignancy, different multimodality nanoparticle stages have been created for cancer imaging utilizing registered tomography (CT), positron outflow tomography (PET), and single-photon emission processed tomography (SPECT) [2–4]. In any case, because of the absence of spatial goals and low affect ability, a large portion of these imaging strategies neglect to identify malignancy at a beginning time [5, 6]. Along these lines, an increasingly touchy double imaging test is required for early disease analysis that can supplement clinically affirmed methodology, for example, CT. Then again, fluorescent imaging is rising as an amazing strategy to distinguish malignancy at a beginning period of the sickness because of its high goals (0.5–3 μm) and affectability [7, 8].

Regardless of having these properties, nanoparticles have likewise inconveniences, for example, molecule collection and troublesome taking care of as a result of their little size . In any case, nanoparticles are utilized in numerous applications in medication and beautifying agents. Tumor focusing on utilizing nanoparticle conveyance frameworks, nanoparticles for oral conveyance of peptides/proteins, nanoparticles for quality

conveyance, nanoparticles for medication conveyance and focusing on the nanoparticles to epithelial cells in the GI (gastrointestinal) tract utilizing legends are only a couple of instances of the investigations on nanoparticles.

Synthesis of various Eu^{3+}:RE_2O_3 luminescent nanoma- terials using Y, La or Gd as RE element has been reported [15–17]. Among them nanoparticles with Ti2O3 are of great interest due to its low phonon energy [18], proton relaxation [19] and scintillation [20] properties making it an excellent candidate for fluorescence imaging, MRI and X-ray CT, respectively. These Eu^{3+} doped Ti2O3 nano- particles with different sizes and morphologies have been utilized in a variety of applications such as in optical dis- plays, solar cells and in vivo imaging .

Physicochemical properties such as size and shape of the nanoparticles are very important for passive target- ing of tumor vasculature through EPR effect. Studies elucidating the behavior of nanoparticle size, shape and surface charge on bio-distribution and biocompatibility in vivo are present in the literature [24, 25]. There are now various evidence that specificity and efficiency of passively targeted nanoparticle can be enhanced by surface modification with a specific targeting legend. Therefore, introduction of surface modification is preferable for improving the dispersion properties and targeting potential .

Folate receptor alpha (FR) is highly expressed in some forms of cancers such as ovarian cancer and in up to 80% of breast cancer tumors . Therefore, the addi- tion of folic acid molecule has been used to increase the specificity of nanoparticles or drugs for cancer cells. The strong affinity of FR for its ligand folate, permit the internalization via receptor-mediated endocytosis and specific uptake FA-functionalized nanoparticles . Hence, folic acid represents an important ligand that could be used clinically for specific targeting of breast cancer. A variety of RE-doped nanoparticles has been proposed for targeted cancer cell imaging. For instance, Setua et al. reported higher cellular uptake of FA.

conjugated fluorescent magnetic RE nanocrystals on FR positive human nasopharyngeal carcinoma cells (KB) compared to FR depressed KB and FR negative lung can- cer cells A549 control cells. Stefanakis and Ghanotakis demonstrated specific targeting of HeLa cells using $Tb_2(OH)_5NO_3$-FA nanoparticles doped with Europium.

In this study, Ti2O3:Eu^{3+} nanoparticles were produced using sucrose combustion synthesis. Ti2O3:Eu^{3+} nanoparticles (N1-Bare) were then coated with amino- silane coupling agent APTMS to introduce amine groups (N2-APTMS). Finally, these amine groups were conju- gated to the carboxyl groups of FA molecule using EDC- NHS coupling mechanism to produce FA-functionalized Ti2O3:Eu^{3+} nanoparticles (N3-FA). We examined the biocompatibility and potential of folic acid-function- alized Ti2O3:Eu^{3+} nanoparticles to target breast can- cer cells in vitro and in vivo using a xenograft model by dual-modal fluorescence and CT imaging. The target-

ing ability and toxicity of these folic acid-functionalized Ti2O3:Eu^{3+} nanoparticles is compared with N1-Bare and/or N2-APTMS. Our findings suggest that folic acid- functionalized Ti2O3:Eu^{3+} nanoparticles are promising candidates for the detection of breast cancer.

II. Titanium Dioxide Nanoparticles

Titanium dioxide occurs in nature as the minerals retile and anatine, and additionally as two high pressure forms. One of these is a monoclinic baddeleyite-like form known as akaogiite, and the other is an orthorhombic α-PbO_2-like form known as brookite, both of which can be found at the Ries crater in Bavaria.[8][9][10] It is mainly sourced from limonite ore. This is the most widespread form of titanium dioxide-bearing ore around the world. Retile is the next most abundant and contains around 98% titanium dioxide in the ore. The metastable anatine and bookie phases convert irreversibly to the equilibrium rutile phase upon heating above temperatures in the range 600–800 °C (1,112–1,472 °F).[11]

Titanium dioxide has eight modifications – in addition to retile, anatine, akaogiite, and brookite, three metastable phases can be produced synthetically (monoclinic, tetragonal and orthorhombic), and five high-pressure forms (α-PbO_2-like, baddeleyite-like, cotunnite like, orthorhombic OI, and cubic phases) also exist.

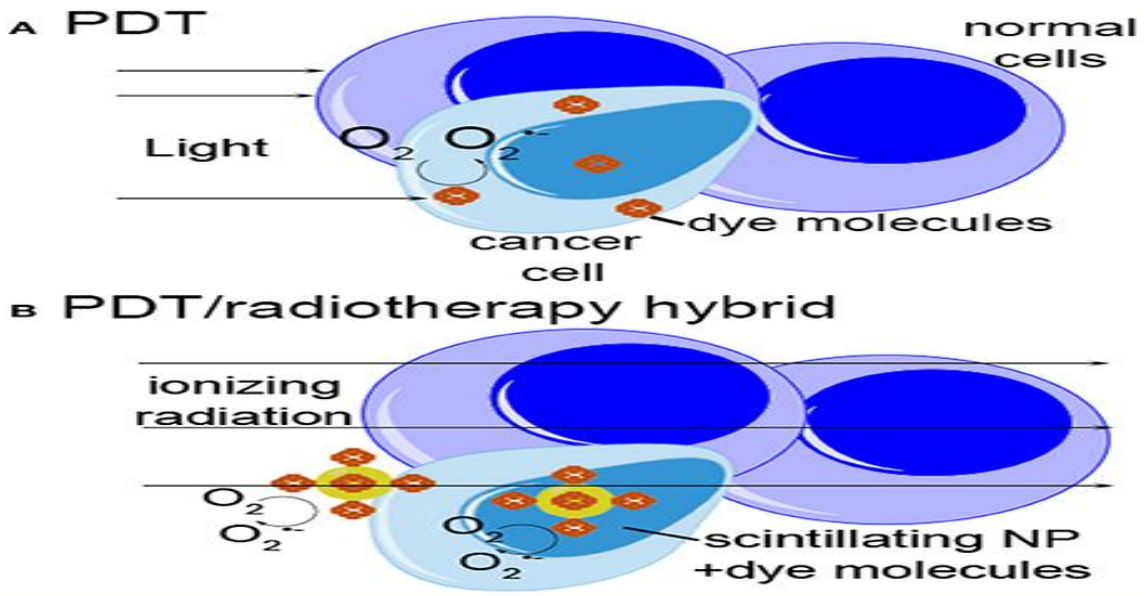
III. Photodynamic Therapy

Photodynamic therapy (PDT) is a treatment that uses a drug, called a photo sensitizer or photosensitizing agent, and a particular type of light. When photo sensitizers are exposed to a specific wavelength of light, they produce a form of oxygen that kills nearby cells (1–3).

Each photo sensitizer is activated by light of a specific wavelength (3, 4). This wavelength determines how far the light can travel into the body (3, 5). Thus, doctors use specific photosensitizes and wavelengths of light to treat different areas of the body with PDT.

(a)What are the limitations of PDT?

The light needed to activate most photosensitizes cannot pass through more than about one-third of an inch of tissue (1 centimetre). For this reason, PDT is usually used to treat tumours on or just under the skin or on the lining of internal organs or cavities (3). PDT is also less effective in treating large tumours, because the light cannot pass far into these tumours (2, 3, 6). PDT is a local treatment and generally cannot be used to treat cancer that has spread (metastasized) (6).



(b) How to Overcome

By the synthesis of Ti2O3 with Europium Doped Nano particles we can pass light into tumours.

IV. Methods -Materials

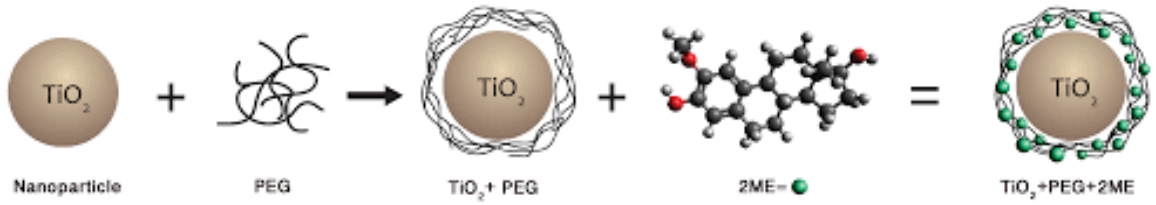
Gadolinium nitrate (Ti $(NO_3)_2 \cdot 6H_2O$, 99.9%) and europium nitrate (Eu $(NO_3)_2 \cdot 6H_2O$, 99.9%) were purchased from Aldrich and Alfa Aesar, respectively. Sucrose ($C_{12}H_{22}O_{11}$, 99.5%), 3-aminopropyltrimethoxysilane (APTMS, 97%), toluene (ACS grade, ≥ 99.5%), folic acid (≥ 97%), N-(2-dimethylaminopropyl)-N-ethyl carbodiimide hydrochloride (EDC), N-hydroxyl succinimide (NHS, 98%), dimethyl -sulfoxide (DMSO, ≥ 99.5%), KBr (FTIR grade, 99%) were purchased from Sigma-Aldrich.

V (a) Synthesis of Ti2O3:Eu^{3+} nanoparticles (Gd/Eu = 0.95/0.05) (N1‑Bare)

Ti2O3:Eu^{3+} nanoparticles were synthesized by sucrose combustion synthesis as previously reported [35]. Stoichiometric amounts of the metal precursors and fuels were weighed and mixed with 30 ml of distilled water under magnetic stirring for 25 min at room temperature. The obtained transparent solution was transferred to a preheated muffle furnace maintained at 380 °C. The solution was kept inside the furnace for 25 min for the complete decomposition of fuel. The synthesis was completed with the ignition of the fuel. The obtained highly porous black powder was gently crushed with a pestle and mortar. Finally, the powder was annealed at 1000 °C for 3 h to obtain a white nano crystalline Ti2O3:Eu^{3+} powder.

V (b) Synthesis of Ti2O3:Eu^{3+}@ APTMS nanoparticles (N2-APTMS)

Freshly prepared Ti2O3:Eu^{3+} nanoparticles were dispersed in 80 ml of toluene with the help of probe sonication. After 30 min, APTMS was introduced in an equimolar ratio with Ti2O3:Eu^{3+} nanoparticles and placed under magnetic stirring, during 20 h, for efficient grafting of silane layer. The temperature of the reaction was then increased to 80 °C for 4 h for the formation of solid bonds between nanoparticle surface and silane groups. The nanoparticles were washed 4 times with ethanol and centrifuged at 6000 rpm for 15 min and dried at 65 °C overnight.



V(c) Synthesis of folic acid-functionalized Ti2O3:Eu^{3+} nanoparticles (N3-FA)

For the surface fictionalization with FA, 0.05 M folic acid was prepared in DMSO under magnetic stirring. For the activation of carboxyl groups present in FA mol- ecule, freshly prepared 1 ml EDC (75 mM) and 1 ml NHS (150 mM) in DMSO were added to 30 ml the mix- ture. The reaction was allowed to continue for 4 h under an N_2 atmosphere in the dark. Then, APTMS coated Ti2O3:Eu^{3+} nanoparticles (N2-APTMS) dispersed in PBS (pH 7.4) were introduced into the activated folic acid solution. The reaction was stirred for another 24 h under similar condition. Lastly, the nanoparticles were washed several times with DI water and ethanol and centrifuged at 6000 rpm for 15 min and dried at 65 °C overnight.

VI Analysis and benefits of Study

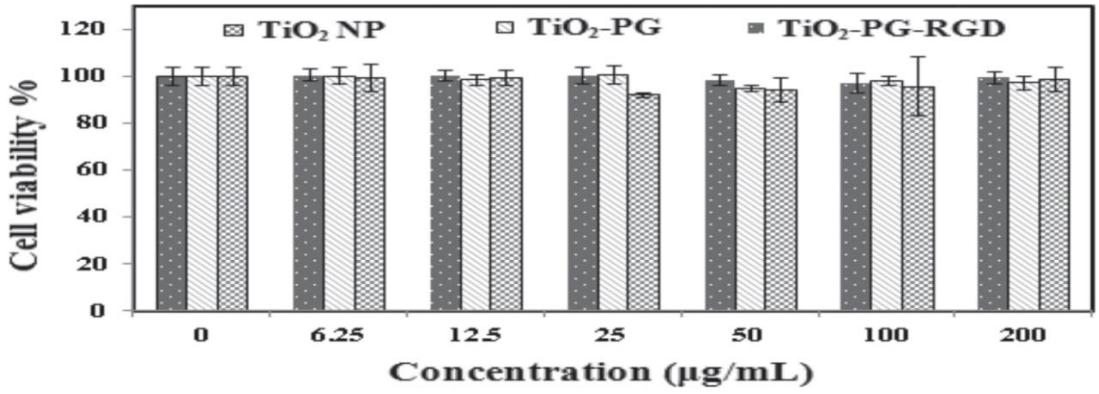
(a) Bio-distribution analysis of nanoparticles in tumor bearing mice

Breast cancer tumor xenografts were established by subcutaneous injection of either T-47D cells (5×10^6, n = 9) or MDA-MB-231 cells (2×10^6, n = 3) to each flank of female nude mice (female, 6–8 weeks old). All the mice were fed autoclaved food and water. For the mice receiving T-47D cells, in addition to normal food, they were fed with 2 g/kg of chocolate spread contain- ing 5 µl of β-estradiol (10 nM) every day. Tumor growth was monitored using a vernier caliper, and their volume was calculated using the following formula: Volume=[length×$(width)^2$]/2. Three and 7 weeks after the inoculation of MDA-MB-231 and T-47D cells, respectively, mice received an

intravenous inoculation of PBS, APTMS coated (N2-APTMS, 200 mg/kg) and FA-conjugated (N3-FA, 200 mg/kg) Ti2O3:Eu^{3+} nanoparticles (n = 3 per group). Organ extraction was performed 2 h after i.v. of nanoparticles and were prepared for cryo sectioning. Bio distribution was analyzed using CLSM as described before and by CT imaging.

(b) µCT and image processing

The scanning of the tumors was done with a SkyScan 2211 nano-CT (Bruker micro-CT, Belgium). The samples were scanned using voltage of 40–50 kV, target current of 70 µA (0.1 µm Tungsten source), and exposure time of 300–350 ms, with resolution from 2.2 to 3.0 µm, depending on sample geometry, resulting in 1536 × 1920 pixels on a flat panel detector, rotation step of 0.200°, frame averaging of 4, and 360° scan to minimize artifacts produced by the combination of high-density Ti2O3:Eu^{3+} nanoparticles and low-density tissue. The reconstructed slices were obtained with NRecon v1.7.1.0 and each time histograms were forced to stay within − 750 to 5000 HU (Hounsfield Units). No staining was required. To obtain the ratio of the volume of nanoparticles/volume of the tumor, image-processing scripts were created and run with the native software of the nano-CT (CT Analyzer v1.17.7.1; Bruker micro-CT, 2017). The processed volume for each tumor was fixed to ~ 0.99 mm^3 (for comparison purpose) consisting of cylindrical sections with a diameter and height of 1.5 and 0.56 mm, respectively.



(c) Statistical analysis

Statistical analyses were performed using GraphPad Prism v5.0 software (GraphPad Software, Inc). Comparisons of three or more groups were conducted with a 1-way ANOVA test, followed by a Bonferronis post-test. For responses that were affected by two variables, a 2-way ANOVA with a Bonferronis or Tukey post-test was used. Results are expressed as mean ± SEM and a $P \leq 0.05$ was considered significant.

VII Conclusion

In summary i have described synthesis of Ti2O3 with Doped Eu3+ ,nano particles ,which are having low toxicity so they can be used as a fluorescent probe for the detection of Folr1 breast cancer in vivo. This study provides major evidence that justify future research focused towards the clinical application of FA-conjugated $Ti_2O_3:Eu^{3+}$ for detection of breast cancer using optical imaging. In combination with CT scans, it would be possible to achieve high-resolution imaging and detection of deeply located tumors.

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