Recent and future applications of ultrasound-induced piezomagnetic nanoparticles for anticancer treatment

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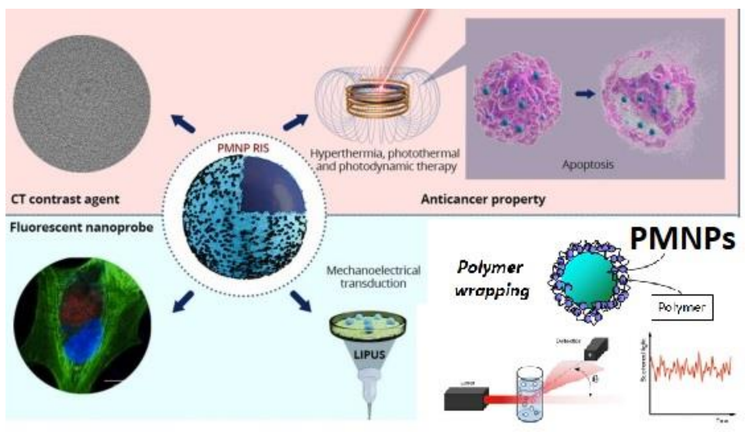
Introduction

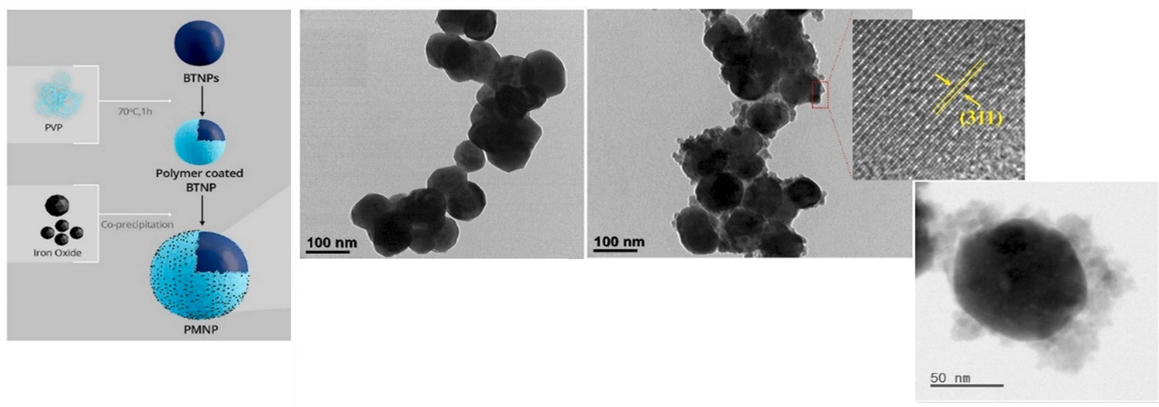
The field of nanomedicine utilizes nanomaterials to improve diagnosis, prevention and treatment of many diseases and cancer [1]. Classical anticancer approaches and therapeutic strategies are associated with different limitations and side effects. Therefore, innovative methodologies are being investigated, and several researchers propose the use of remotely activated nanoparticles to trigger cancer cell death. Noninvasive treatment approaches are gaining more attention in recent times due to the potential improvement in treatment efficiency. The innovative solutions consist in a platform based on biocompatible piezoelectric and magnetic nanoparticles able to target and remotely inhibit cancer cells. The anti-proliferative effects of the ultrasound-driven piezoelectric nanoparticle-assisted stimulation significantly can reduce the proliferation by inducing the cell cycle arrest. The ultrasound-induced piezoelectric nanoparticles paradigm would constitute a promising tool to solve undesired effects.



Experimental overview

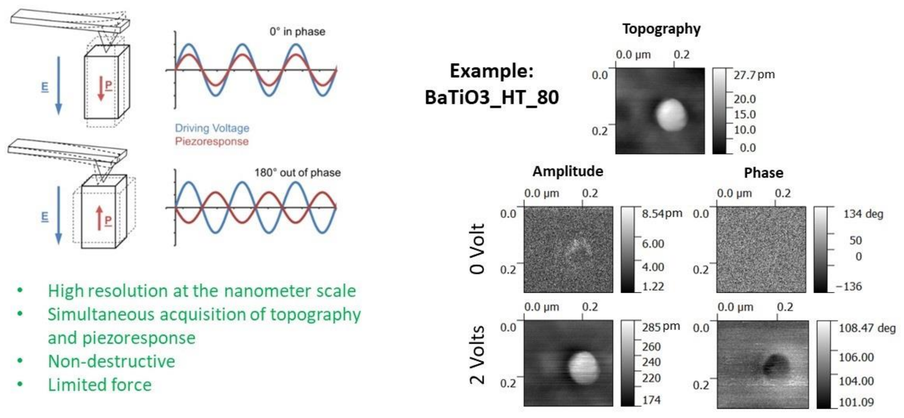
Synthesis method of piezomagnetic nanoparticles (PMNPs)

To synthesis the multiferroic PMNPs, the as prepared tetragonal barium titanate nanoparticles (BTNPs) were added to a Fe_3O_4 precursor solution and made them react directly. Initially, PVP (5 mg) was dissolved in 50 ml DI water in a 250 ml flask followed by the addition of the prepared tetragonal BTNPs (1 g). The mixture was stirred at 75 °C for 1 h. Then carefully add a mixture of $FeCl_3 \cdot 6H_2O$ (1.2 mM) and $FeSO_4 \cdot 7H_2O$ (0.6 mM) to the above aqueous solution under nitrogen bubbling. After 10 min, once the solution was cooled to 65 °C, ammonia solution was added dropwise into the reaction mixture under vigorous stirring to adjust the pH to 11-12. The reaction was kept at the same temperature for 30 min under vigorous stirring and nitrogen atmosphere and then cooled down to room temperature.



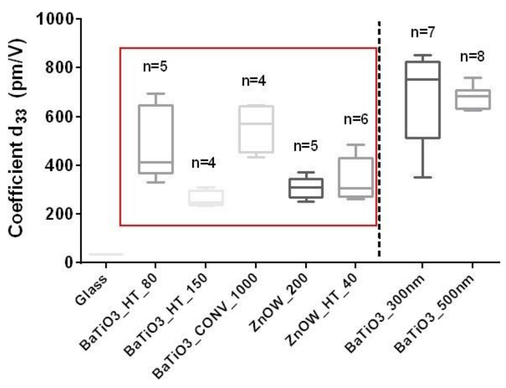
Piezoelectric magnetic properties

Piezoelectric analysis through Piezoforce response microscopy (PFM)



- High resolution at the nanometer scale
- Simultaneous acquisition of topography and piezoresponse
- Non-destructive
- Limited force

PFM: results



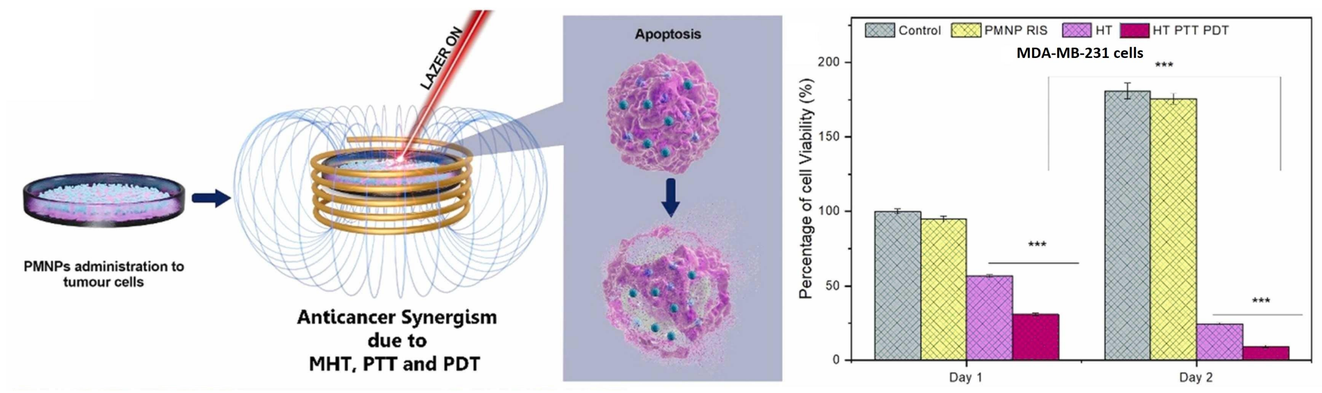
Values above the mimimum target **(40 pm/V)** in all cases

$$Coefficient\ d33\ \left(\frac{pm}{V}\right) = \frac{\left(Amplitude\ (2\ V) - Amplitude\ (0\ V)\right)}{Applied\ voltage}$$

Piezoelectric analysis of PMNPs: Frequency dependent hysteresis polarization (P)-electric filed (E) loops at room temperature, Switching polarity test of PMNPs device up on a shaft load (2 kg) periodically operated with the accelaration of 1 m/s^2 and the inset shows the device located perpendiculaly to the shaft load (2 kg) of a linear motor. The output voltage response of PMNPs device upon the shaft load operated with various accelations (0.1 and 1 m/s^2).

Many in vitro studies with different types of piezoelectric barium titanate NPs and PiezoMagnetic nanoparticles (PMNPs) showed that chronic piezoelectric stimulation arrests cancer cell cycle in G0/G1 phases by interfering with the balance of cancer cell proliferation [1], Ca2+ homeostasis and up-regulating the expression of the gene encoding for Kir3.2 inward rectifier K+ channels, and by affecting the organization of mitotic spindles during mitosis. Moreover, the organization of cytoskeletal elements mediating cell mitosis is affected. Anticancer effects have been proven on osteosarcoma cells, colorectal cancer cells, breast cancer cells [2], and glioblastoma multiforme cells [3].

Schematic illustration represents the synthesis of PMNPs, HR TEM images of BTNPs, PMNPs (Inset shows the lattice spacing of 0.25 nm which is matched well with the (311) planes of Fe_3O_4 NPs formed on the surface of PMNPs, Bright field image of a single PMNPs.



The anticancer efficacy of PMNPs was studied on human breast cancer MDA-MB-231 cell lines. The cells were first incubated for 2 h with PMNPs (100 µg/ml) to taken up by the cells and the anticancer effects were studied under magnetic hyperthermia and magnetophotothermia; the combination of magnetic hyperthermia (HT), photothermal (PT) and photodynamic therapies (PDT).

Conclusions

In summary, this work presented the synthesis and application of brand-new PMNPs as a novel multifunctional therapeutic platform. Due to the strong photo absorption in the NIR region and magnetic properties, the PMNPs simultaneously exhibited the trimodal anticancer effects of PTT/PDT and magnetic hyperthermia, which has been confirmed to realize the excellent antitumour outcome. We also demonstrated the promising results of PMNPs for anticancer effect when stimulated with LIPUS. This is due to the excellent piezoelectric property of PMNPs to generate electric signals when stimulated in vitro using LIPUS. Therefore, this work provided the first example to employ a hybrid nanoparticle for cancer therapy, imaging, and regeneration by exploiting the inherent properties of the nanoparticles itself. As a future perspective, the multifunctionality and ease of functionalisation of PMNPs will allow us to use as an effective therapeutic agent for wide variety of cancers. In conclusion, on the merit of good biocompatibility, anticancer properties, multimodal imaging, and non-invasive stimulation capabilities, PMNPs can be used to control the cell behaviour and fate in order to develop new types of therapies for multiple diseases in remotely controlled approaches.

References
1. Sasikala Kurup, Nano Energy, (2022). 2. Marino Attilio; Scientific reports (2018), 8 (1), 6257.
3. Pucci, C., Acta Biomaterialia (2022).