Modulation of Cell Proliferation by Hybrid Photo-Magnetic Stimulation in Presence of Multifunctional Nanocarriers

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PURPOSE

In the survey of current cancer treatment approaches, recent research efforts have been focused on combining Photodynamic Therapy (PDT) and Photothermal Therapy (PTT) especially for the second line and third-line therapy recipients. The results pointed out a synergistic effect of PDT/PTT superior to that of any single modality treatment applied solely. Efficacy of magnetic hyperthermia (MHT) is well documented, however, thus far no research is available combining the effects of MHT, PTT, and PDT, despite carrying strong treatment potential. In this study, an innovative multimodal hyperthermia strategy that has been unexplored thus far – "hybrid photo-magnetic (PMA) stimulation"- has successfully been implemented on rapidly proliferating cells in culture, which demonstrated complete ablation. The ultimate combined tumor cell destruction approach was performed by coupling MHT, PTT, and PDT simultaneously.

OBJECTIVES

1) Explore whether the hybrid photo-magnetic actuation can enhance the efficacy of nano-scale temperature regulation compared to the currently available approaches.

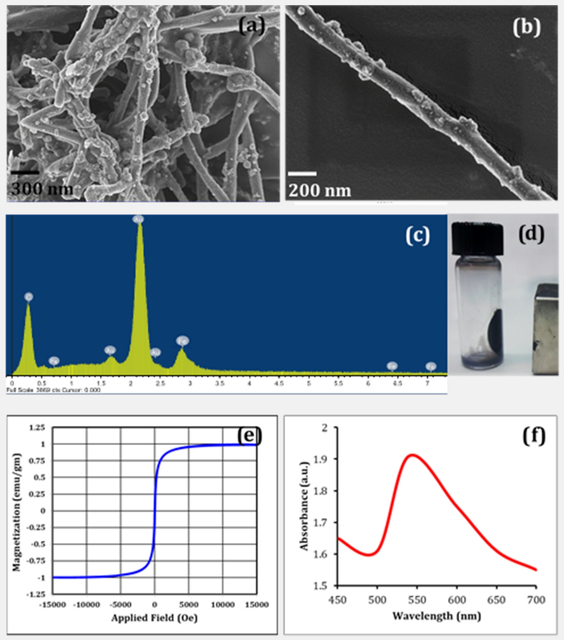
2) Investigate if the induced coupled hyperthermia launch acute apoptotic machinery of the cells in culture.

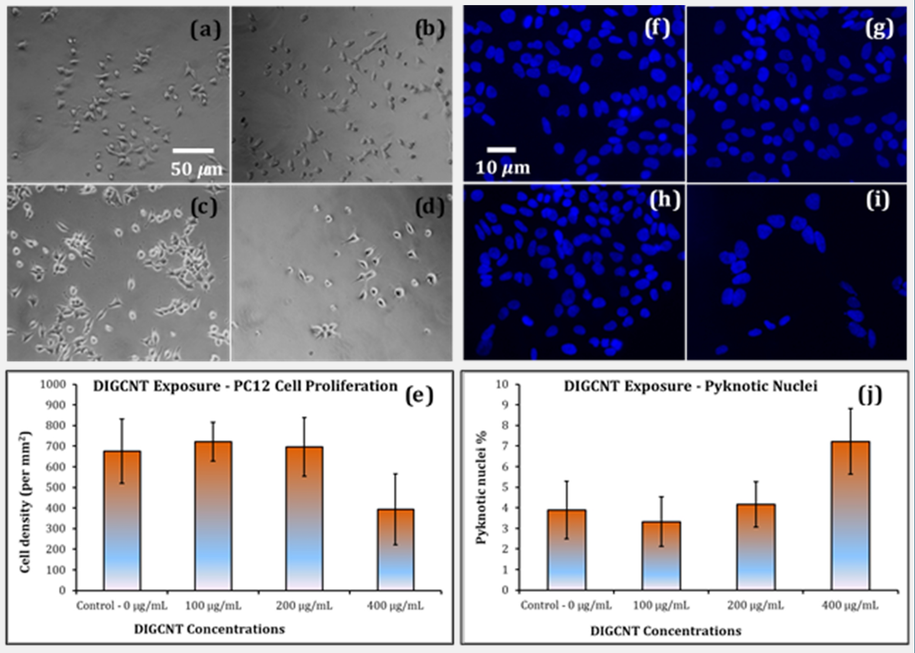
METHODS

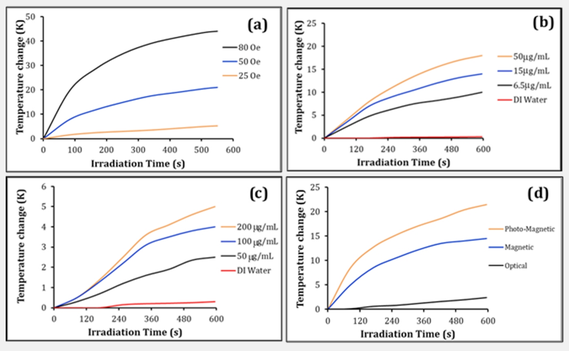
A multifunctional magnetite (Fe3O4)/Gold (Au) nanoparticle (NP) decorated dextran covered carbon nanotube system (NP-CNTs) was synthesized. For cellular hyperthermia, NE-4C cells were routinely cultured at 37°C in 5% CO2 in DMEM containing 10% FBS at 5,000 cells/cm2 in TPP tissue culture tube flasks (10cm2 growth surface area). Following 48h of surface attachment, the cells were washed with serum-free DMEM and were exposed to the colloidally suspended NP-CNTs at final concentrations (0-200 µg/mL). Following NP-CNT addition, the cells were exposed to the PMA stimulation for various durations (15-40 min). After 4h of NP exposure and irradiation, the cells were washed with serum free DMEM and were cultured back into complete DMEM media for 24h. MTT assays were performed per manufacturer's specification to quantify cell viability.

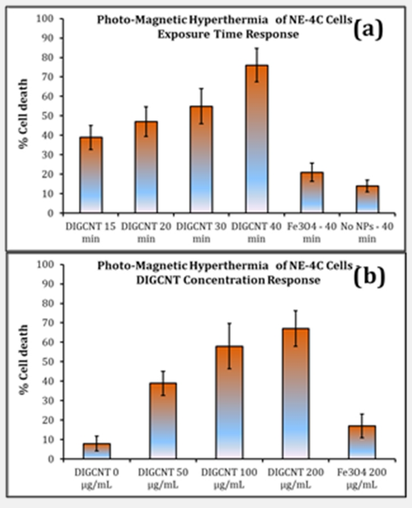
RESULTS

The hybrid photo-magnetic (PMA) stimulation effect was found to be significantly stronger compared to the stand-alone magnetic and photo-thermal responses. The designed nano-structures demonstrated excellent biocompatibility on a PC12 neural cell model; however severely affected the viability of tumor suppressor p53 deficient NE-4C cells when activated by low intensity PMA stimulation [50Oe, 155kHz; 400mW/cm2 - 530nm laser] at a concentration as low as 50µg/mL.









- PC12 cell proliferation in presence of DIGCNTs: (a) control (0 *μ*g/mL); (b) 100 *μ*g/mL; (c) 200 *μ*g/mL; and (d) 400 *μ*g/mL. Scale bar = 50 *μm* in (a), and is also applicable for (b)-(d). (e) Bar chart displaying quantification of average cell densities, indicative of cell proliferation for PC12 cells under all treatment options. Nuclear condensation and fragmentation assessment in presence of DIGCNTs: (f) control (0 *μ*g/mL); (g) 100 *μ*g/mL; (h) 200 *μ*g/mL; and (i) 400 *μ*g/mL. Scale bar = 10 *μm* in (f), and is also applicable for (h)-(i). (j) Bar chart displaying quantification of pyknotic nuclei, indicative of cell death.
- Impact of 50 Oe, 155 kHz, and 400 *m*W/cm² - 530 *nm* laser using DIGCNTs on NE-4C cells in (a) time (15-40 min. at 50*μ*g/mL), and (b) dose dependent manners (0-200*μ*g/mL at 15 min).

CONCLUSIONS

Acute toxicity of this unique hybrid actuation-hybrid material combination, coupled with excellent innate biocompatibility may be extremely relevant to develop in-vivo hyperthermia. Our study suggests that hybrid PMA irradiation is a safer and viable approach for cell destruction, which may be adopted as an efficient technique in clinical management to target rapidly proliferating tumor cells.

WORK IN PROGRESS

- Addressing the concerns regarding CNT Toxicity
- Evaluation of Anti-Cell Proliferation Mechanisms: Synergistic vs. Additive
- Customer Discovery (NSF I-Corps; Award Number 2040086). Performed ~200 interviews.
- Damage Repair of Endothelial Cells (NSF - ERI Award No: 2301688)

SUPPORT / COLLABORATIONS / REFERENCES

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References:
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