IR Laser Triggered Chemo-Photothermal Therapy of Doxorubicin Resistant Breast Cancer Cells

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INTRODUCTION

Photothermal Therapy of MGNs

- MGNs: Multibranched Gold Nanoantennaes
- Spherical core and sharp protrusions which captures tissue penetrating near-infrared (IR) light
- MGNs are able to efficiently converts light to heat (photothermal effect)
- Heat can induce mild hyperthermia and ablate cancer cells → cell death
- Hyperthermia – condition in which cells are more susceptible to drugs

Thermosensitive Liposomes (TSLs)

- Self-assemble and transport drugs that are normally cardiotoxic, like Doxorubicin
- At the transition temperature (42°C), liposome will disassemble, releasing drug

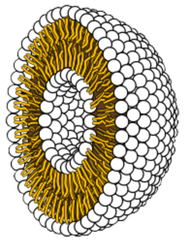


Figure 1: Liposomes have a hydrophilic head and hydrophobic tails.

Source: http://www.nextadvance.com/public/image/media/images/liposome.png

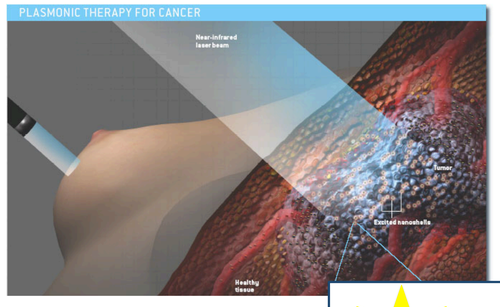


Figure 2: Figure adapted from Phil Saunders[2].

Why Light-Triggered Therapy

- Highly noninvasive, no surgery needed, safe, and controllable without complete patient discomfort
- MGNs enable photothermal hyperthermia, releasing drug from TSLs, and photothermal ablation which results in cancer cell death
- Hyperthermia also enhances drug uptake in chemotherapy resistant highly aggressive breast cancer cells

OBJECTIVE

Our goal is to demonstrate multimodal chemophotothermal therapy in highly aggressive drug resistant triple negative breast cancer cells. We will show that the photothermal ability of MGNs can simultaneously induce hyperthermia and release drugs from TSLs and result in photothermal ablation of cancer cells resulting in cell death.

METHODS

Synthesis of MGNs

- MGNs were mixed with water and HEPES, a biological buffer, at various concentrations to achieve a desired resonance

Liposomes by Reverse Phase Method

- Composition of different lipids in a 90:10:4 mole ratio (DPPC : MSPC : DSPE-PEG-2000)
- Extrusion of Liposomes to achieve a size of 100 nm
- Dox-loading by pH gradient method
- Purification by size-exclusion chromatography

Photothermal Therapy

- MDA-MB-231 breast cancer cells are incubated with MGNs for 24 hours
- Drug concentration at 2 ug/ml → incubation for 12 hours → additional 30 hours of drug-free media incubation before imaging

RESULTS

MGNs Synthesis

- HEPES-mediated MGNs synthesis results in MGNs with sharp protrusions
- Peak spectrum of MGNs are at 793 nm

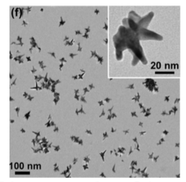


Figure 3: Sharp protrusions of MGNs.[1]

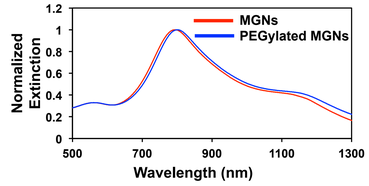


Figure 4: UV-vis spectroscopy of MGNs

Drug Release

- Liposomes loaded with Dox were set at either 37, 42, or 45°C and reactions were halted at certain time points
- At 42°C, 90% of drug is released within the first ten minutes

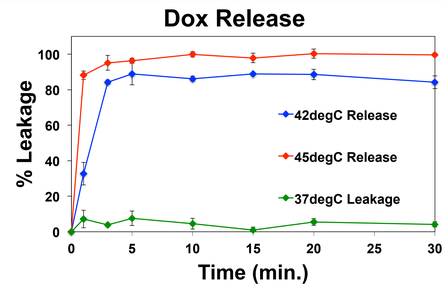


Figure 5: The percent of Dox that is released from liposomes after certain time points.

Photothermal Therapy

- In the Near Infrared (IR) region, MGNs can absorb light, while body tissue and water cannot, allowing for deep tissue light penetration
- We tested laser intensities of 4, 5, and 7 W/cm^2
- Photothermal ability of MGNs is dependent on the concentration - at 170 ug/ml, MGNs are able to heat up to 55°C from 37°C

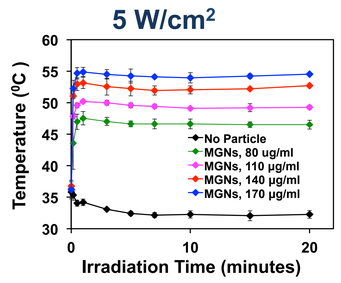


Figure 6: Temperature profile of MGNs with a laser intensity of 5 W/cm^2.

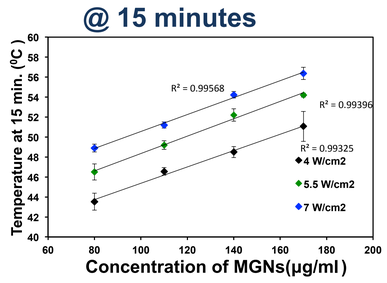
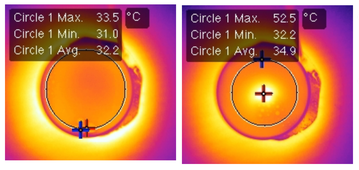
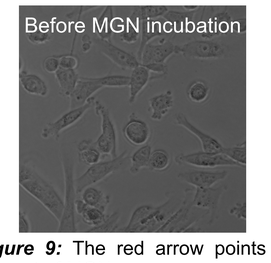


Figure 7: Temperatures at 15 minutes



- Without MGNs, no laser spot is visible
- With MGNs, a white laser spot can be found

Figure 8: At 4 W/cm^2, (left) without MGNs, and (right) with 170ug/ml MGNs present



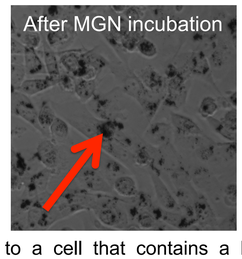
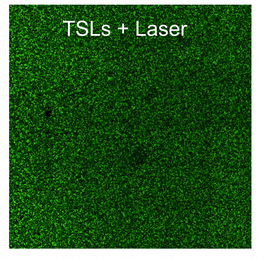


Figure 9: The red arrow points to a cell that contains a large amount of MGNs

- We observe MGNs uptake by cells under phase contrast



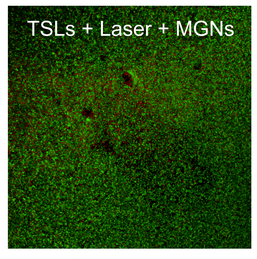


Figure 10: Confocal images with Calcein/PI live/dead cell stain

- The presence of MGNs with IR laser and TSLs causes more breast cancer cell death

Conclusions and Future Directions

- The combination of MGNs, liposomes, and hyperthermia is more effective in cell death than just liposomes alone
- When the transition temperature of liposomes is reached, around 90% of drug is released within the first 10 min.
- Future goals include:
  - MTT assay to obtain cell viability before and after chemophotothermal therapy
  - Conjugate active targeting motif to further improve treatment efficiency

Acknowledgements

- I would like to thank May Ou and Dr. Rizia Bardhan, the Bardhan lab group, and the VINSE REU Program
- This project was supported by **NSF grant DMR-1263182**

1. Webb, J. A.; et.al, Geometry-Dependent Plasmonic Tunability and Photothermal Characteristics of Multibranched Gold Nanoantennas. *The Journal of Physical Chemistry C* **2014,** *118* (7), 3696-3707.
2. Atwater, H.A., The Promise of PLASMONICS. *Scientific American* **2007** sp 17, 56 – 63