APPLICATION of PLASMONIC NANOMATERIALS IN NANOMEDICINE

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ABSTRACT

Plasmonic nanoparticles are being researched as a noninvasive tool for ultrasensitive diagnostic, spectroscopic and, recently, therapeutic technologies. With particular antibody coatings on nanoparticles, they attach to the abnormal cells of interest (cancer or otherwise). Once attached, nanoparticles can be activated/heated with UV/visible/IR, RF or X-ray pulses, damaging the surrounding area of the abnormal cell to the point of death. Here, we describe an integrated approach to improved plasmonic therapy composed of nanomaterial optimization and the development of a theory for selective radiation nanophotothermolysis of abnormal biological cells with gold nanoparticles and self-assembled nanoclusters. The theory takes into account radiation-induced linear and nonlinear synergistic effects in biological cells containing nanostructures, with focus on optical, thermal, bubble formation and nanoparticle explosion phenomena. On the basis of the developed models, we discuss new ideas and new dynamic modes for cancer treatment by radiation activated nanoheaters, which involve nanocluster aggregation in living cells, microbubbles overlapping around laser-heated intracellular nanoparticles/clusters, and laser thermal explosion mode of single nanoparticles ('*nanobombs*') delivered to the cells.

INTRODUCTION

In recent years, there has been a tremendous increase in research at the nanoscale for materials (for example, [1] and references in this book). One particular area is the application of plasmonic nanoparticles to enhance the diagnostic and treatment methods available for cancer [2-8]. The application of nanotechnology for laser thermal-based killing of abnormal cells (e.g., cancer cells) targeted with absorbing nanoparticles (e.g., gold solid nanospheres, nanoshells or nanorods) is becoming an extensive area of research. Studies have shown that by coating the surface of nanoparticles with a specific protein (a 'targeting agent,' normally an antibody), the nanoparticles will bind to a complementary protein such as found on a cancer cell [3,7-12], as shown in *Figure 1a*. After the nanoparticles are bound to the cancerous cells, they can be heated with electromagnetic radiation (UV/visible/IR, RF or X-ray pulses), inducing a variety of effects around the particles [7,9,11,12], as shown in *Figure 1b*.

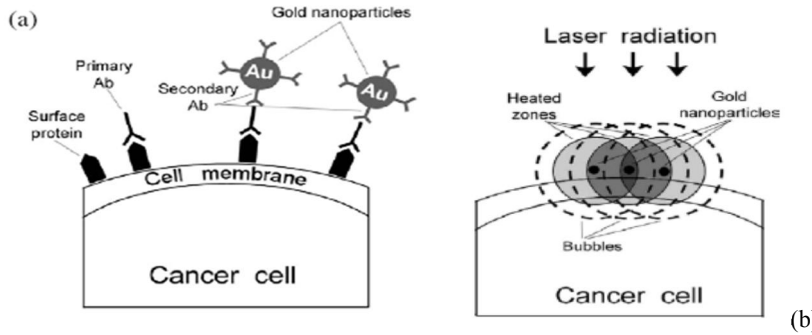

Fig 1 – Principle of selective nanophotothermolysis of cancer cells: (a) cancer cell targeted with primary antibodies (Ab) which are selectively attached to secondary antibodies conjugated with gold nanoparticles; (b) schematic of laser-induced heating effects around the particles

The heated particle can cause the cell to experience hyperthermia, resulting in surface-protein denaturing [13] and changing membrane permeability [14]. Alternatively, the nanoparticle itself can heat to the point of melting, evaporation or explosion [5,6], causing further damage to cells. These effects can be used to increase the sensitivity of photoacoustic diagnosis or aid in therapy, such as selective photothermolysis, by selective thermal killing of tumor cells into which absorbing nanoparticles have been incorporated. The potential advantages of these new photothermal sensitizers heated with short laser pulses may include:

- selective cancer-cell targeting by means of conjugation of absorbing particles (e.g., gold nanospheres, nanoshells or nanorods) with specific antibodies;
- localized tumor damage without harmful effects on surrounding healthy tissue;
- absorption at longer wavelengths in the transparency window of most biotissues;
- no undesired side effects (e.g., cytotoxicity or cutaneous photosensitivity); and
- relatively fast treatment involving potentially just one or several laser pulses.

Progress towards the development of selective nanophotothermolysis technology requires the investigation of new physical concepts and new approaches to the study of short/ultrashort laser pulse interactions with biological systems containing nanostructures. In this paper, we present a theory for laser-induced linear and nonlinear synergistic effects in biological cells containing nanostructures with focus on cluster aggregation, bubble formation and nano-

particle explosion phenomena. The theory is based on our experience in theoretical studies relevant to the nanoparticles [1,5,5,6,12,15-25].

Our presentation consists of two parts. In part I we discuss the new dynamic modes in selective nanophotothermolysis for nanomedicine applications. The second part of the presentation is devoted to the education and workforce development in nanomedicine and medical physics in general.

NEW DYNAMIC MODES IN SELECTIVE CANCER NANOMEDICINE

Microbubble overlapping mode. Bioconjugated nanoparticles are selectively attached to chosen cellular targets, in particular to membrane receptors activated by other antibodies as shown in *Fig. 1a*. When nanoparticles are irradiated by short laser pulses, they absorb the laser radiation, and their temperature rises very quickly, reaching the threshold of microbubble formation in the surrounding liquid medium. We proposed and studied theoretically a new dynamic mode for selective cancer treatment that involves the overlapping of bubbles inside the cell volume (shown in *Fig. 1b* and *Fig.2b*). The microbubble overlapping mode around intracellular structures induced by short laser pulses can dramatically increase the efficiency of the cancer treatment as a result of the larger damage range and higher expenditure rate in comparison to a thermal damage mode.

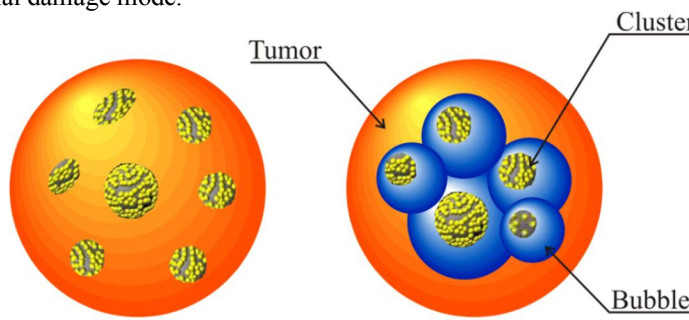

Fig. 2 – Principle of the nanocluster aggregation mode (a), and microbubble overlapping mode around gold nanoparticles (b) in selective nanophotothermolysis

Nanoclusters aggregation mode. We also proposed a new mechanism for selective laser killing of abnormal cells by nanoclusters aggregated in the cell volume, as shown in Fig. 2a). A cluster is a group of closely-located nanoparticles separated by the thickness of antibodies (10-30 nm), which has a typical size of 200-400 nm. Here, the effective therapeutic effect for cancer cell killing is achieved due to a large damage area at the relatively-low energy density of the incident laser pulse.

Thermal explosion mode – nanobombs. We have proposed another new mechanism for selective laser killing of abnormal cells by laser thermal explo-

sion of single nanoparticles – *nanobombs* – delivered to the cells, as shown in *Fig. 3*.

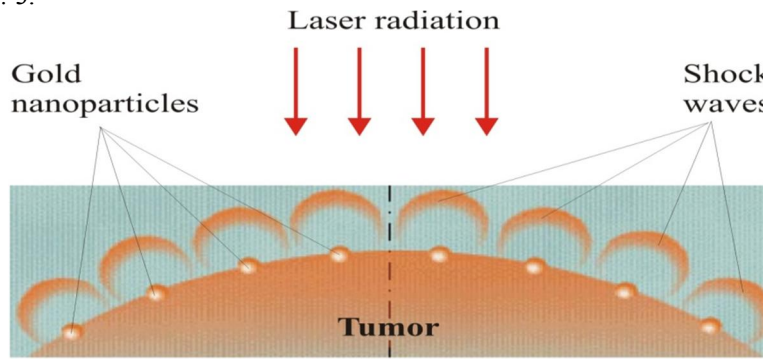

Fig. 3 – Principle of the thermal explosion mode of nanoparticles –"nano-bombs", in selective nanophotothermolysis of the cancer

Thermal explosion of nanoparticles is realized when heat is generated within the strongly-absorbing target more rapidly than the heat can diffuse away. Here, the effective therapeutic effect for cancer cell killing is achieved due to nonlinear phenomena, which accompany the thermal explosion of the nanoparticles: generation of a strong shock wave with supersonic expansion of a dense vapor in the cell volume, producing sound waves and optical plasma as shown in *Fig. 4*.

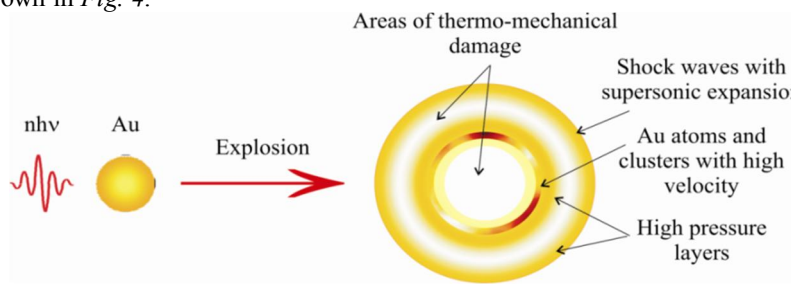

Fig. 4 – Laser-induced thermal explosion of a gold nanoparticle

NANOMEDICINE EDUCATION AND WORKFORCE DEVOPMENT IN MEDICAL PHYSICS

The coming ability to carry out targeted medical procedures by means of nanotechnology at the molecular level will bring unprecedented power to the practice of medicine. Within a few short decades, we can expect a major revolution in how the human body is healed. Nanomedicine lays the foundations for understanding this revolution. Nanomedicine demands expertise from a wide variety of disciplines, and scientists will often have physics, engineering,

and optics backgrounds, but at the same time possess knowledge about laser-tissue interactions and good general knowledge of biology, anatomy, and physiology. Training of professionals and contributing to this rapidly growing technological field requires multidisciplinary education.

Nanomedicine is a part of the Medical Physics science. A huge demand for competent Medical Physicists and Medical Dosimetrists exists in the country. Also, there is a challenge in training of qualified professions in these arenas. Today's challenges in Medical Physics (MP) education and workforce development are to:

- Train the next generation of scientists and clinicians in a multidisciplinary environment.
- Invent and train to use novel MP products to fight life-threatening diseases.
- Expand the talent pool for translation and commercialization of novel MP treatment/diagnostic technologies.
- Bring relevant information to the public regarding new developments in MP.

Acknowledgements

This presentation is supported by the Radiological Technologies University in South Bend IN, USA.

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