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Emerging Opportunities at the Interface of Photonics, Nanotechnology and Biotechnology

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Emerging Opportunities at the Interface of Photonics, Nanotechnology and Biotechnology

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Today major breakthroughs are more likely to occur in interdisciplinary areas. This paper discusses opportunities created by interfacing photonics with nanotechnology and biotechnology. Examples are provided from our work at the Institute for Lasers, Photonics and Biophotonics. Specifically discussed are applications of nanophotonics to nanomedicine, which is an emerging field utilizing nanostructures for bioimaging, biosensing and targeted therapy. Applications of quantum dots for bioimaging and of fluorescence labeled magnetic nanoparticles for multimodal imaging are presented. Use of nanoparticles for light-activated therapy, the photodynamic therapy, is discussed. Examples of nanophotonics to optically track and monitor nanoparticle delivery genes of and subsequent transfection is given. Finally, some examples of future opportunities are presented.

Keywords: bioimaging; gene delivery; photodynamic therapy; quantum dots

INTRODUCTION

This is the era of interdisciplinary science and technology where major breakthroughs are more likely to occur at the interface of disciplines. This paper discusses the interface of photonics with nanotechnology and biotechnology. The new frontiers created by these interfaces are represented in Figure 1. Fusion of photonics with nanotechnology has produced the field of "Nanophotonics" which is defined by

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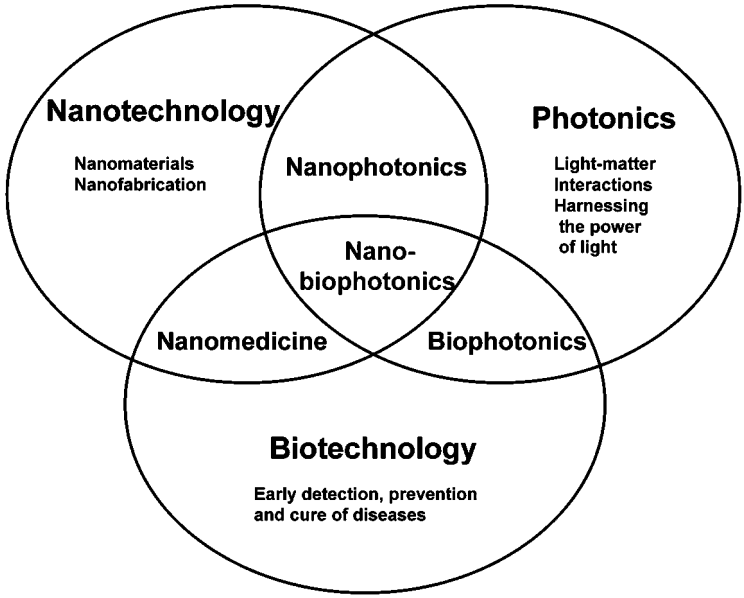

FIGURE 1 Interfaces created by fusion of Photonics, Nanotechnology and Biotechnology.

interaction between light and matter at nanoscale [1]. Nanophotonics creates new opportunities which includes those for information technology, power generation and biomedical applications. Combination of photonics with biotechnology has created the field of "Biophotonics" which deals with interaction of light with biological or biologically relevant matter [2]. The field of biophotonics holds promise for new forms of optical diagnostics, bioimaging, biosensing, as well as new modalities of light-guided and light-activated therapies. Integration of Nanotechnology into Biotechnology has lead to the emergence of a new frontier, Nanomedicine. Here nanoprobes and nanostructures can be used for multi-modal imaging, effective drug distribution, targeted therapy and real-time monitoring of drug action or therapy.

We have a comprehensive program at our Institute in the area of Nanomedicine. This program is represented by Figure 2. We utilize nanobiophotonics approach for nanomedicine. This paper will focus on this approach. Nanostructured organic, inorganic, polymeric and ceramic materials play vital roles in the development of these interdisciplinary fields. Thus, we have placed a major effort on the development of these nanostructures and nanomaterials.

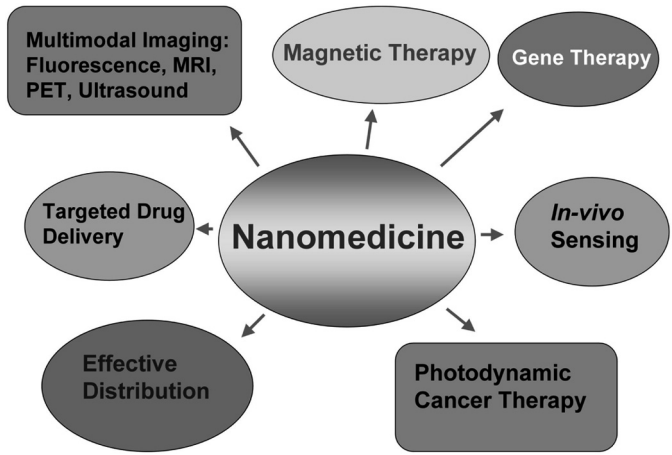

FIGURE 2 A comprehensive overview of Nanomedicine.

This paper will describe our efforts on materials development in relation to nanobiophotonics and nanomedicine. It concludes with a discussion of future opportunities in this exciting field.

BIOIMAGING

Nanobiophotonics provides new approaches for bioimaging. There are inorganic nanoparticle emitters which can be utilized for optical imaging. These inorganic nanoemitters offer several advantages over generally used organic dyes. They are thermally and photochemically more stable than organic dyes and have narrow emission profiles. Thus, one can readily utilize many narrow emission wavelengths for multiplexing or simultaneously imaging different subcellular structures and events. Two types of nanoemitters being developed in our laboratory are quantum dots [3] and up-converting rare-earth nanoparticles [4,5]. Quantum dots are inorganic semiconductor nanoparticles which exhibit size dependent absorption and emission, once their size becomes smaller than a certain characteristic length called Bohr's radius [1]. This size dependence is derived from quantum confinement of carriers (electrons and holes). Most of the work has been conducted with groups II-VI semiconductors such as CdSe [6,7]. To confine the carriers further, as well as to protect the surface, one often coats the quantum dots with a layer (shell) of a wider bandgap material such as ZnS. This core-shell type quantum dot structure is highly luminescent and has been utilized extensively for bioimaging.

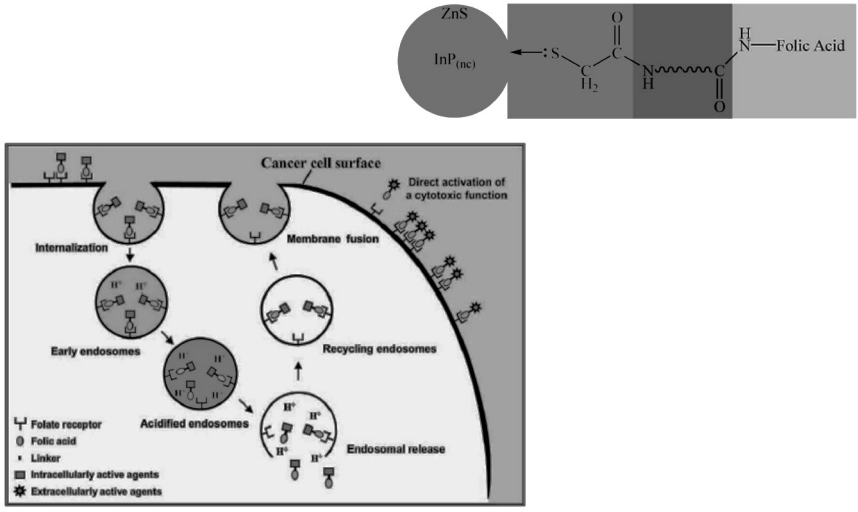

FIGURE 3 Schematic representation of folate receptor mediated nanoparticle delivery. Receptor mediated endocytosis of InP-ZnSe core shell quantum dots with folic acid in KB cells is shown.

Our effort has focused on the development of III-V semiconductor nanoparticles, specifically InP, for two reasons: (i) these semiconductors are expected to be much less toxic than CdSe, and (ii) they cover a longer wavelength region of emission which offers increased penetration in biological specimen to achieve in-depth 3-D imaging. We have developed new precursor colloidal synthesis routes to rapidly produce highly monodispersed InP-ZnSe core-shell quantum dots which can be coupled to folic acid in order to target biological cells which are folate receptor positive [8]. Our scheme is shown in Figure 3. Confocal image of folate receptor positive cells (KB cells) using InP-ZnSe quantum dots with folic acid receptor is shown in Figure 4. Another feature we have noticed is enhanced two-photon activities of these quantum dots. Direct two-photon absorption of $\sim$800 nm femtosecond pulses produce strong visible emission which we have used for two-photon microscopy.

Examples of rare-earth nanoemitters being developed are Er_{3+} doped yttria (Y_2O_3) nanoparticles which absorb CW radiation at $\sim$980 nm and produce up-converted red and green emission. Again $\sim$980 nm penetrates deeper in biological samples. We have developed formulations which allow us to make stable aqueous dispersions of these nanoparticles that are $\leq$50 nm in size and exhibit strong up-converted emissions.

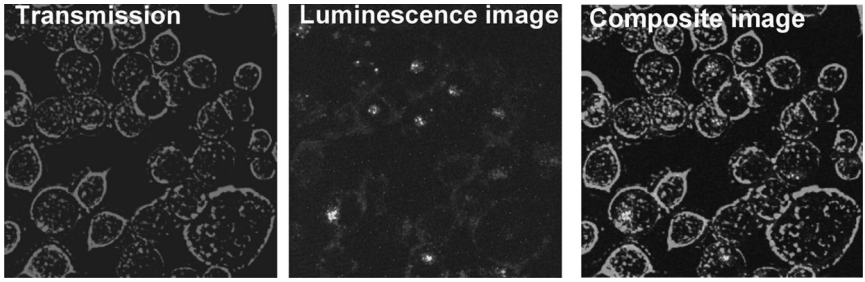

FIGURE 4 Bioimaging of KB cells using the folic acid coupled InP-ZnSe quantum dot-core shell structure. KB cells are known to be folate receptor positive.

MULTIMODAL IMAGING

A nanomedicine approach using nanoparticles also offers opportunities to combine different bioimaging techniques. An example is designing nanoparticles for both MRI and optical imaging. For this purpose we have utilized MRI contrast enhancer magnetic nanoparticles such as Fe_3O_4. The surfaces of these nanoparticles are functionalized to contain −OH and −COOH groups which have been used to

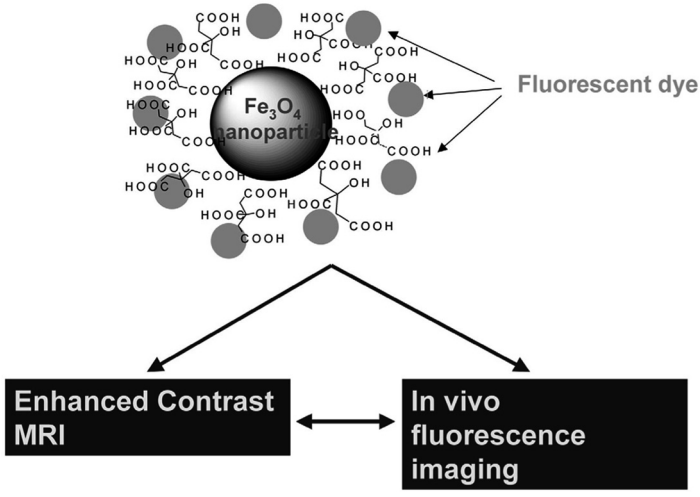

FIGURE 5 Schematic representation of fluorescence labeled magnetic nanoparticles used for enhanced contrast MRI and *in vivo* fluorescence imaging.

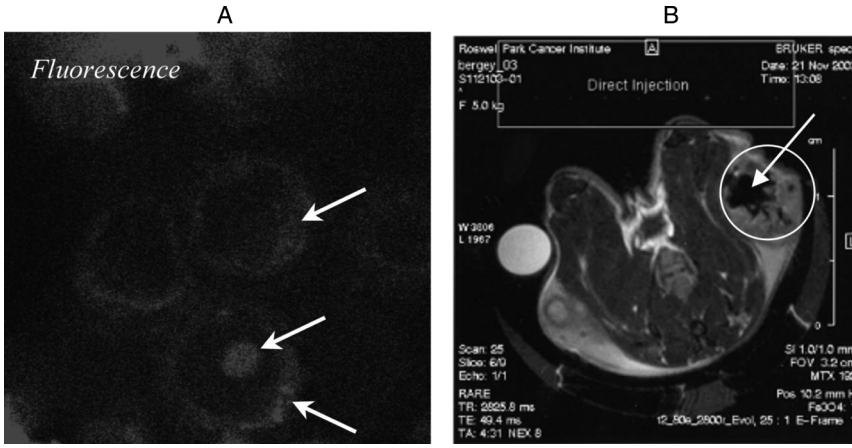

FIGURE 6 *In vitro* and *in vivo* images generated by magnetic nanoparticles; A. Fluorescent image of magnetic nanoparticles in cells; B. MRI image of magnetic nanoparticles in tumor tissue.

couple fluorescent dyes for fluorescence imaging [9]. This scheme is shown in Figure 5. As an illustration, Figure 6 shows a fluorescence confocal image of cells using these fluorescent magnetic nanoparticles. It also shows enhanced contrast MRI of a tumor tissue, in which these magnetic nanoparticles have accumulated.

TARGETTED DRUG DELIVERY

Nanoparticles of dimensions <50 nm or smaller offer a number of advantages for targeted therapy from within the cell. Nanoparticles offer a number of advantages, some of which are:

- Nanoparticles are non-immunogenic, not eliciting any immune response when introduced in the body's circulatory system.
- The nanoparticles can be tailored with compositions so that they do not undergo enzymatic degradation and can effectively protect the encapsulated probes or drugs.
- Nanoparticles provide three different structural platforms, as shown in Figure 7, for diagnostics and therapy. These are:
  - A) An interior volume in which various imaging contrast and/or therapeutic agents can be encapsulated.
  - B) The surface which can be functionalized to introduce a hydrophilic (polar), hydrophobic (non-polar) or amphiphilic character to enable dispersibility of therapeutic agents in biological media.

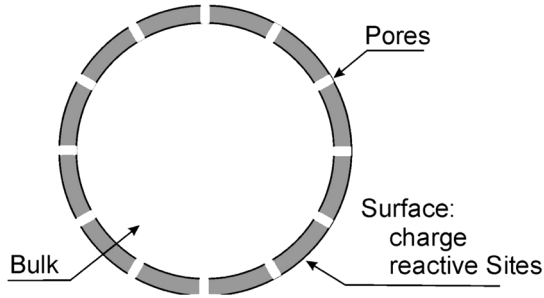

FIGURE 7 Schematic of nanoparticle platform for Nanomedicine.

C) The surface which can be functionalized for attachment of ligands to effect selective targeting by nanoparticles.
D) Porosity of nanoparticles which can be tailored to specific sizes for selective intake or release of biologically active molecules.

Two specific examples discussed here are photodynamic therapy and gene delivery.

Nanoparticle-based Photodynamic Therapy

Photodynamic therapy (PDT) is a rapidly growing treatment method in the arsenal of cancer therapies [10]. When exposed to light at appropriate wavelengths, a photo-sensitizer is activated and energy is transferred to molecular oxygen in the triplet state, producing an activated oxygen specie, singlet oxygen which oxidizes critical elements of the cells [2]. This photosensitization process provides a powerful approach to photomedicine which can be useful for many oncological applications, macular degeneration, dermatological infections/conditions and dental diseases (prevention of caries and treatment of periodontal disease) [10].

Nanomedicine can provide a mechanism to manipulate many of the current limitations in the delivery, biodistribution and efficacy of newer photosensitizing agents. An appropriately tailored nanoparticle with the control of bulk, surface, and porosity can provide the following benefits for photodynamic therapies:

- Bulk encapsulation and/or surface attachment of the hydrophobic near-IR absorbing photosensitizer to a nanoparticle with grafted lyophilic character will enhance dispersion and transport in biological systems.

- *In situ* of photosensitizer co-localized in tissue with upconverting rare-earth doped nanoparticles which, by a step-wise two-photon absorption of 970 nm light (deeper tissue penetration), produces up-converted emission in green or red region.
- Colocalization of two-photon absorbing (TPA) molecules along with the photosensitizer, where an effective fluorescence resonance energy transfer (FRET) from many TPA centers acting as photon harvesting antennas to the photosensitizer, will produce a very effective two-photon excitation using a near IR (~800 nm) pulse laser source.
- Nanoparticles with heavy atom (e.g. iodine) to control the dynamics of excited state of the photosensitizer leads to enhanced singlet oxygen generation for PDT.
- Nanoparticle containing targeting groups based on recognition of biomarkers of a specific cancer enhances localization in tumor and increase the efficacy.

We have demonstrated that nanoparticles can be used as carriers for photosensitizers. Stable aqueous formulations of ultrafine ORMOSIL nanoparticles (average diameter 30 nm), were used to encapsulate the hydrophobic photosensitive drug, HPPH, to improve biodistribution leading to effective localization in tumor tissues [11]. The approach used utilized nanochemistry in the micellar cavity to produce these carriers, spectroscopy to confirm singlet oxygen production and *in vitro* studies using tumor cells to investigate drug-carrier uptake and phototoxicity. Encapsulation prevented aggregation of the drug with no release of the drug from the host matrix, and the particles were dispersed in an aqueous system. An important aspect of ORMOSIL nanoparticles is that their surfaces can be easily modified with various organic functional groups. The functionalized nanoparticles can then be tethered to various probes, targeting ligands and monoclonal antibodies to selectively target specific cells, *in vitro* and *in vivo* and monitor effects in real-time. We have demonstrated targeting of mitochondria using co-encapsulation of mitochondria staining dyes.

Non-Viral Gene Delivery

Nanoparticles can serve as viral vectors for safe and efficient gene delivery [12]. The potential for treatment of genetic disorders has advanced tremendously with the ability to identify specific genes whose defect or absence is responsible for a particular pathological condition.

Viral gene transfer techniques have achieved increasing interest in the treatment of human disorders [12]. However, such systems suffer from inherent difficulties in pharmaceutical processing, scale up, immunogenicity and reversion of an engineered virus. A nanoparticle platform can be used as an effective vehicle for non-viral delivery of genes for gene therapies which lack the significant complications of viral transfection vectors. Recent work by our group has established the feasibility of using amino functionalized organically modified silica (ORMOSIL) nanoparticles as a non-viral vector for *in vitro* gene transfection [13]. Our approach is schematically shown in Figure 8.

Amino-functionalization of the surface of the ORMOSIL nanoparticle enables the formation of nanoparticle/DNA complexes. These nanocomplexes protect the genetic payload from environmental degradation (resistant to DNAase digestion). The release of DNA from surface is pH and time dependent. Using multifunctional nanoplatforms, the transport of the ORMOSIL bound DNA into the cell and subsequent transfection was visualized. The fluorescently labeled DNA was found to be present in both the cytoplasm as well as the nucleus after transfection. Using the plasmid pEGFP-N2 (green fluorescent

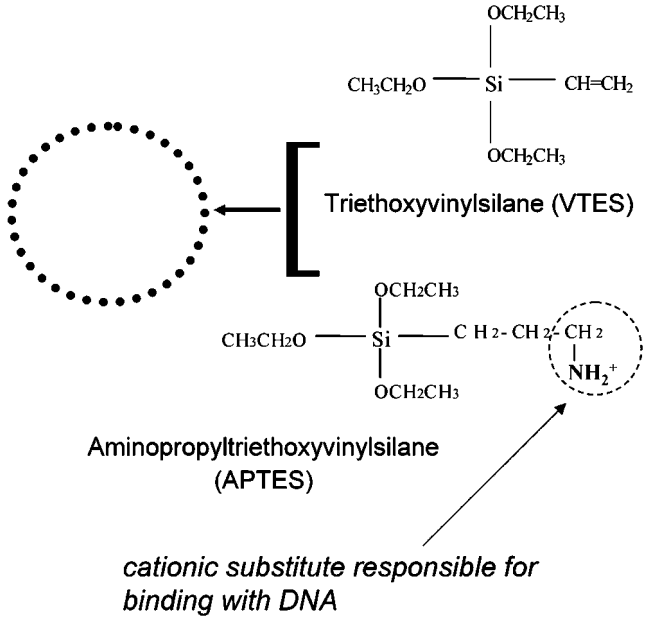

FIGURE 8 Schematic representation of an ORMOSIL nanoparticle structure for binding with the negatively charged DNA.

protein), confocal microscopy visualized the presence of eGFP in the cytoplasm of transfected cells, demonstrating that ORMOSIL is an effective *in vitro* non-viral transfection vector.

More recently, we have also shown successful *in vivo* transfection when ORMOSIL/pEGFP-N2 nanocomplexes were injected into mouse ventral midbrain and into lateral ventricle. *In vivo* fluorescence microscopy was used to visualize the extensive transfection of neuronal-like cells. No general ORMOSIL based toxicity was observed during two weeks after transfection. The efficiency of this transfection equaled or exceeded that obtained in studies using a Herpes Simplex Virus vectors.

FUTURE DIRECTIONS

The development in the field of nanomedicine is a multidisciplinary endeavor that holds considerable challenges and opportunities for nanomaterials development. A crucial aspect is the control of the surface properties of these nanoparticles. Biocompatibility and biodegradability are other features to address.

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