Advances in Bioimaging Using the Nanoparticulate Contrast Systems

Chin Ng* and Yashwant Pathak**
*Associate Professor of Radiology and Pharmacology, University of Louisville, School of Medicine, Louisville, KY, 40202, chin.ng@louisville.edu
** Assistant Dean of Academic Affairs, Chair and Professor, Department of Pharmaceutical Sciences, Sullivan University College of Pharmacy, Louisville, KY 40205, ypathak@sullivan.edu

ABSTRACT

Recent developments in the contrast agents and the biosensors being used in bioimaging, especially the development of nanoparticulates, have opened many new vistas in this field. Bioimaging is extensively used to characterize the particle distribution and accumulation in biosystems. The nano-sized systems offer an excellent tool to understand biological processes at molecular levels and to develop nano diagnostic tools and innovative drug delivery systems and its evaluation in biosystems. Several nanoparticulate contrast systems like quantum dots, gold nano particles, and dye doped silica nano particles have offered better photo stability, higher quantum yield, and *in vitro* and *in vivo* stability as compared to the conventional contrast dyes. Multi modality nano particulate systems can be used across multiple *in vivo* imaging platforms with optical, magnetic resonance imaging (MRI), computed tomography (CT), ultrasound, positron emission tomography (PET), and single photon emission computed tomography (SPECT). This presentation will review the recent developments in nanoparticulate contrast imaging agents and biosenors and its potential applications in bioimaging.

Key Words: **bioimaging, biosystems, nanoparticulate**

1 INTRODUCTION

Diagnostic techniques such as CT, nuclear medicine (SPECT and PET), MRI, and ultrasound are widely-used techniques to investigate the distribution of the biomarkers, architecture, and physiologic functionalities of body. Due to relatively low resolution of PET or SPECT, there is a need for combining it with CT scanning techniques for appropriate and accurate interpretation. But there is always a concern regarding the long term exposure of the ionized radiation. MRI is a relatively safer, non-invasive technique used for bioimaging, but it requires a radiofrequency shield for the scanner room and whole body imaging is not practical at this time.

Conventionally molecular fluorophores were used as labels for the bio-molecular detection. With the advent of nanoparticulate materials as labels in bio-molecular detection, improvements have been made in sensitivity, selectivity, and multiplexing capacity. Nevertheless, there is a need for simplifying these technologies for easy applications, handling, and disposal of the materials with special emphasis on nano safety and nano toxicity. There are several recent developments in this area such as bio-affinity sensors for the detection of nucleic acids and proteins [1-2].

Many important technological advances have been made in the use of nanotechnology for bio-molecular detection [3-5]. Complimenting significant developments in the field of optical, electrochemical, and various other techniques and nanotechnology for monitoring bio-recognition events on solid devices and in solution, has led to realizing accurate, sensitive, selective, and practical bio-sensing devices for both laboratory and point-of-care applications.

2 NEW TRENDS IN CONTRAST AGENTS FOR MRI

Many MRI techniques are based on relaxation properties of water protons, the most abundant nuclei in the human body. MRI is used to detect the distribution of water molecules in different types of tissues; the image contrast is dependent on the relaxation characteristics of the protons in the tissues, proteins, and lipids. It is estimated that out of the 35 million MRI procedures done, more than 35% use the contrast agents to enhance the signal to noise ratio. Several new contrast nano particulate agents have been recommended for this purpose. A significant research has been reported in this area and several nano particulate MRI contrast agents have been developed for different applications. The versatility of gadolinium to form chelates with other entities has opened new vistas of MRI agents. Table 1 shows the applications of gadolinium products as contrast agents [6].

Group of the Contrast Agent	Products	Applications
Gadolinium Chelate Based	Magnevist	Neuro. Whole body
	Multihans	CNS, Liver
	Eovist	Liver
	Gadovist	CNS, Whole body
	Gadolinium Silica Nano particles	Whole body
	Gadolinium Liposomes	Whole body
	Gadolinium Dendrimers	Whole body
Fullerenes based	C_{60},C_{72},C_{74}, C_{76},C_{84}	Experimental for whole body
Gadofullerenes	Gd@C_{60}, Gd@C_{84}	Reticular endothelial systems
Trimetaspheres	Sc_3@C_{80}	Liver, Spleen, and Kidney
Gadolinium Trimetaspheres	$ScGd_2N$@C_{80}	Liver, Spleen
Hydrochalarones (water soluble)	Gd_3N@C_{80}	Tissue specific targets

Table 1: Applications of Gadolinium Products as Contrast Agents

3 THE USE OF NANOPARTICLES IN CT, PET, AND OPTICAL IMAGING

A new x-ray contrast agent using gold nanoparticles has been developed by Nanoprobes (Yaphank, NY) for *in vivo* imaging using standard microCT. This new agent has a longer blood residence time than the iodine agents commonly used in the clinic and the contrast has improved close to 10 fold. Its low toxicity may potentially propel this new contrast agent to be used in the clinic in the future. The combined modality of PET and CT has made a significant impact on patient care in the diagnosis and the staging of cancer. Thus, efforts have been focused on the development of a new combined modality of PET and MRI in order to provide a capability of performing functional and anatomical imaging in one study [7]. It has demonstrated the proof of concept in mice xenografted with U87MG human gliobastoma cell line by attaching a Cu-64 labeled RGD peptide to an iron oxide nanoparticle core. Likewise, a nanoparticle probe can also be developed for the combined use of PET and optical imaging [8]. It used a quantum dot made of cadmium telluride to have a Cu-64 labeled RGD peptide attached to it. Preliminary images obtained in mice xenografted with U87MG human gliobastoma cell line have demonstrated the feasibility of such a concept.

4 NUCLEIC ACID AND PROTEIN DETECTION

In the area of developing biosensors for bioimaging applications, major advances have been made in detecting nucleic acids and proteins. Two techniques are widely used for DNA assay, a combination of amplification by polymerase chain reaction (PCR) and detection using molecular fluorophores as labels. Detection is in the pico molar range. There are several major drawbacks in these techniques. The accuracy is reduced due to broad absorption and emission bands and non uniform rates of fluorophore photo bleaching. Immunoassays are usually used to detect proteins. Enzyme-linked immuno-sorbent assay (ELISA) remains the gold standard in protein detection, with detection limits in the pico molar range. There is a need for improving the sensitivity of these techniques of protein detection. Nanoparticles, in particular, have been used extensively in bio-affinity sensors for nucleic acids and proteins [9-10]. These particles are unique because their nanometer size gives rise to a high reactivity and beneficial physical properties (electrical, electrochemical, optical, and magnetic) that can be chemically tailor made. Their usage can potentially translate into new assays that improve on current methods of DNA and protein detection. Table 2 shows various nanoparticulate materials used for the detection of DNA and proteins [11-13].

Nanoparticles Used	Analytical Techniques Used	Applications
Au (Gold) Nanoparticles	Optical detection	Oligonuckleotides / DNA
Ag (Silver) nano particles	Scanomatric detection	DNA
Au-Ag nano particles	Highlight scattering power	Nucleic acid and Proteins
Au nano particles	Raman Spectroscopy	Proteins and DNA
Latex nano particles	Surface Plasmon Resonance (SPR)	Proteins and DNA
Au Nanoparticles	Scanning electro-chemical microscopy	Proteins and DNA
Magnetic nanoparticles	Electromagne tic detection	Oligonucleotides/ DNA
Silica nano particles	Optical detection	Proteins and DNA
Metal and semiconductor nanoparticles	Organic fluorescence	Oligonucleotides /DNA
Quantum dots		Proteins and DNA

Table 2: Demonstrating various nanoparticulate materials used for the detection of DNA and proteins [11-13].

5 CONCLUSIONS

Many recent research reports are discussing and showing the tremendous potential of nanoparticulate contrast systems for biosensors as well as imaging systems. It appears to be most versatile and to have lots of uses in this area. New and newer novel nano systems are being developed and this is an exciting time for the development of bio-imaging contrast agents. These Nanoparticles have shown interesting applications as bio-molecular detection markers with electrochemical tags and with Dendrimer polymer systems. The new systems will have to give better results and applications than the presently used systems to be accepted as main stream techniques.

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