

# Nanotechnology Driven Non-Invasive Cancer Diagnosis Management and Perspectives

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## Description

The vascularity of tumors is highly heterogeneous, ranging from areas of vascular necrosis to areas which are densely vascularized in order to sustain the adequate supply of oxygen and nutrients to the growing tumor. Tumor blood vessels have several abnormalities compared to normal blood vessels, including a high proportion of proliferating endothelial cells with aberrant underlying basement membrane, increased tortuosity of blood vessels, and a deficiency in pericytes. Tumor microvessels demonstrate enhanced permeability, which is regulated in part by abnormal secretion of vascular endothelium growth factor, bradykinin, nitric oxide, prostaglandins, and matrix metalloproteinases. The transport of macromolecules across tumor microvasculature may occur through open interendothelial junctions or transendothelial channels. The pore cutoff size of these transport pathways in various models has been estimated to be in the 1  $\mu$ m range, and in vivo measurement of extravasation of liposomes into tumor xenografts suggests a cutoff size in the 400 nm range. In general, particle extravasation is inversely proportional to size, and smaller particles (200 nm size) would be most effective for extravasating the tumor microvasculature. The tumor lymphatic system is also abnormal, resulting in fluid retention in tumors and high interstitial pressure with an outward convective interstitial fluid flow. This property is thought to promote tumor cell intravasation, resulting in tumor metastasis and blockage of nanocarrier extravasation from microvasculature into the tumor interstitium. However, the lack of an intact lymphatic system also results in retention of the nanocarriers in the tumor interstitium since these particles are not readily cleared from the interstitium. When taken together, the leaky microvasculature and the lack of intact lymphatic system results in enhanced permeation and retention (EPR) effect and "passive" cancer targeting through the accumulation of nanocarriers in the tumor at a higher concentration that is present in the plasma and in other tissues.

The release of drugs from nanocarriers in this case results in a relatively higher intratumoral drug concentration translating into enhanced tumor cytotoxicity. These nanocarriers may be further modified for "active" cancer targeting by functionalizing the surface of nanocarriers with ligands such as antibodies,

aptamers, peptides, or small molecules that recognize tumor-specific or tumor-associated antigens in the tumor microenvironment. When nanocarriers are targeted to the extracellular portion of transmembrane tumor antigens, they may be specifically taken up by cancer cells through receptor mediated endocytosis. The specific targeting, intracellular uptake, and regulated therapeutic delivery of a payload are properties that are derived through a rational design of nanocarriers. The application of nanotechnology to cancer therapy, including the development of "smart" nanoparticles, is indeed an exciting and promising area of investigation. In the following sections, we review some of the most important breakthrough nanotechnology platforms for cancer therapeutic applications.

## Biodegradable Polymeric Nanoparticles

Two modalities have been used to target nanoparticles to tumor sites, active and passive targeting. Active targeting involves linking ligands to nanoparticles that are tumor-specific. Several groups have reported the use of antibody-conjugated nanoparticles to localize cell surface proteins epidermal growth factor receptor (EGFR). Akermann et al. used quantum dots conjugated to peptides that were specific for either blood or lymphatic vessels to demonstrate specific targeting of vessels. Passive targeting of nanoparticles takes advantage of the inherent size of nanoparticles and the unique properties of tumor vasculature. In contrast to normal endothelium, tumor vessels are lined by a simple layer of endothelium with few pericytes and smooth muscle cells. Tumor blood vessels are distinct from normal vessels, in that the endothelial cells in tumors possess wide fenestrations, ranging from 200 nm to 1.2  $\mu$ m. The large pore sizes allow the passage of nanoparticles into the extravascular spaces and accumulation of nanoparticles inside tumors. Gao et al. demonstrated this property in a murine prostate cancer model by successfully localizing and visualizing unlabeled quantum dots at the tumor site. Nanoscale objects with hydrophobic surfaces administered in vivo are taken up primarily by the reticuloendothelial system (RES). This property limits the circulation time of systemically administered nanoscale objects and may hinder their intended application. Coating nanoparticles with hydrophilic molecules, such as poly (ethylene) glycol (PEG), is a commonly employed strategy to

overcome rapid reticuloendothelial system uptake. PEG modification does not appear to hinder other biologic properties.

## Nano Technology Detection

As mentioned before, nanoparticles (NP) are of a few of nm and the cells are of the size of few microns. So NP can enter inside the cells and can access the DNA molecules/Genes and, there is a possibility that the defect in the genes can be detected. DNA molecules can be detected in their incipient stage. This could be possible in vivo or in vitro. It will be shown latter that NP does show potential of cancer detection in its incipient stage.

These are another recent invention. NS are miniscule beads coated with gold. By manipulating the thickness of the layers making up the NS, the beads can be designed that absorb specific wavelength of light. The most useful nanoshells are those that absorb nearinfrared light that can easily penetrate several centimeters in human tissues. Absorption of light by nanoshells creates an intense heat that is lethal to cells.

Nanoshells can be linked to antibodies that recognize cancer cells. In laboratory cultures, the heat generated by the light-absorbing nanoshells has successfully killed tumor cells while leaving neighbouring cells intact.

A number of nanoparticles that will facilitate drug delivery are being developed. One such molecule that has potential to link treatment with detection and diagnostic is known as dendrimer. These have branching shape which gives them vast amounts of surface area to which therapeutic agents or other biologically active molecules can be attached. A molecule that recognizes cancer cells, a therapeutic agent to kill those cells and a molecule that recognizes the signals of cell death. It is hoped that dendrimers can be manipulated to release their contents only in the presence of certain trigger molecules associated with cancer. Following drug releases, the dendrimers may also report back whether they are successfully killing their targets. The technologies mentioned above are in the various stages of discovery and development. Some of the technologies like quantum dots, nano pores and other devices may be available for detection and diagnosis and for clinical use within next ten years.