# Assignment - 1

## Nanotechnology in Cancer Treatment and Detection

BT6031 Cancer Biology

Fall / Odd Semester 2025

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# 1 Abstract

This report presents an overview of nanotechnology's role in cancer diagnosis and therapy, emphasizing the development of key nanocarriers such as liposomes, polymeric micelles, and inorganic nanoparticles. It outlines advances in targeted drug delivery, imaging, and hyperthermia-based treatments, while briefly addressing regulatory considerations for clinical application of this technology.

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# 2 Introduction

Throughout the 1960s and 1970s, as both low and high-molecular-weight therapeutics emerged, the challenge of achieving specific and efficient drug delivery became increasingly apparent. Once administered, drugs interact with multiple physiological systems that influence their concentration, distribution, and metabolism. Because most drug molecules circulate systemically (binding to plasma proteins, undergoing biotransformation as shown in Figure 2.B) or accumulate nonspecifically in tissues, maintaining therapeutic levels often requires high doses, leading to undesirable side effects and inefficiencies. Thus, there was a need for targeted, cell-specific delivery strategies that maximized efficacy while minimizing toxicity.

The concept of nanocarrier-based delivery emerged in 1965, when Alec D. Bangham discovered that phospholipids could self-assemble into bilayer vesicles (now referred to as multilamellar vesicles), giving rise to liposomes [1].

A decade later, Helmut Ringsdorf (1975) introduced a modular framework for pharmacologically active polymers, in which drugs, solubilizing agents, and targeting ligands could be covalently bound to a modifiable polymer backbone- allowing greater design flexibility than with small molecules. This concept laid the foundation for polymer–drug conjugates, such as antibody–drug conjugates (ADCs), and polymeric micelles, which have since become central to modern targeted drug delivery [2].

Building on these foundations in 1986, Hiroshi Maeda developed SMANCS (Styrene–Maleic Acid Neocarzinostatin), the first clinically applied chemotherapeutic polymer–drug conjugate, which demonstrated tumour-selective accumulation through what would later be termed the Enhanced Permeability and Retention (EPR) Effect [3,4].

Since then, nanomedicine has rapidly evolved to exploit the EPR effect and ligand-mediated targeting for precision cancer therapy. Beyond treatment, these principles have also been extensively applied in cancer detection and imaging, where nanoparticles serve as contrast agents, biosensors, and molecular probes, enabling early diagnosis and real-time monitoring of therapeutic response. Thus, developments in understanding the molecular basis of cancer and advancements in nanoscale engineering have transformed both the therapeutic and diagnostic landscapes of modern oncology. The following sections of the report detail the improved detection and treatment of cancer in modern day.

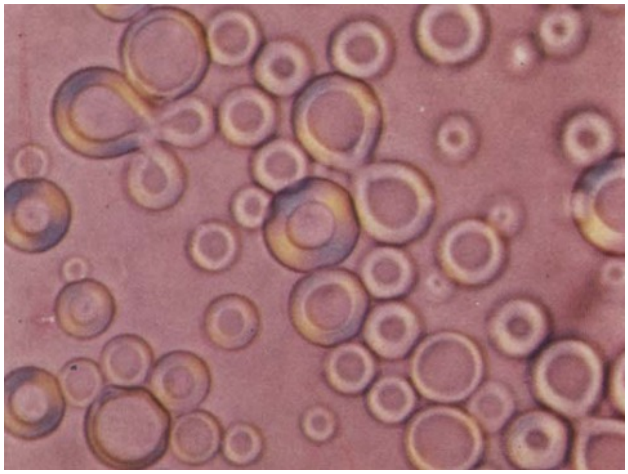

Figure 2.A - Bilayered Liposome [1]

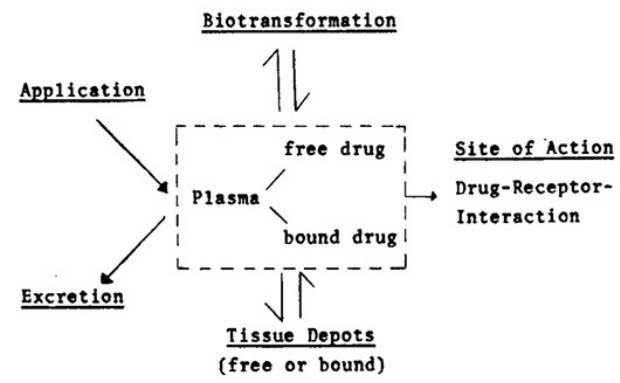


Figure 2.B - Drug Pathways [2]

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# 3 Nanotechnology in Cancer Detection and Diagnosis

## 3.1 Enhanced Imaging and Identification Techniques

### Magnetic Resonance Imaging (MRI)

MRI is a non-invasive imaging technique widely used to visualize anatomical structures and physiological processes within the body. Clinically, positive (bright) contrast,as produced by gadolinium-based contrast agents (GBCAs), is preferred for diagnostic clarity, and such agents have therefore been the conventional standard in MRI. However, GBCAs are small-molecule chelates, not nanoparticles, with molecular sizes typically below 1 nm. While they offer strong $T_1$ (bright) contrast, their use is limited by several drawbacks, including gadolinium deposition in the brain, the risk of nephrogenic systemic fibrosis (NSF) in patients with renal impairment, short circulation time, and non-specific tissue distribution, all of which reduce imaging precision and raise long-term safety concerns.

In recent decades, superparamagnetic iron oxide nanoparticles (SPIONs) have emerged as promising alternatives owing to their biodegradability, low toxicity, and strong magnetic responsiveness. These nanoparticles offer superior sensitivity and extended blood circulation, enabling molecular-level visualization of tissues. However, they traditionally produce negative (dark) $T_2$ or $T_2$* contrast, which clinicians find less desirable because dark signals are difficult to distinguish from natural hypointensities [5].

To address this limitation, recent advances such as Susceptibility Gradient Mapping (SGM) have been introduced to convert dark SPION signals into bright, interpretable images. Furthermore, PEG-coated SPIONs (PEG-SPIONs) enhance biocompatibility, circulation stability, and vascular targeting, allowing for improved tumour visualization even across an intact blood–brain barrier. In glioblastoma imaging studies, PEG-SPIONs combined with SGM successfully revealed angiogenic vasculature that conventional gadolinium agents failed to detect [6,7].

These developments suggest that PEG-SPIONs and related nanoparticle systems, integrated with SGM, with more research offer a gadolinium-free, non-invasive, high-resolution imaging strategy for brain tumour angiogenesis and vascular mapping [6,7].

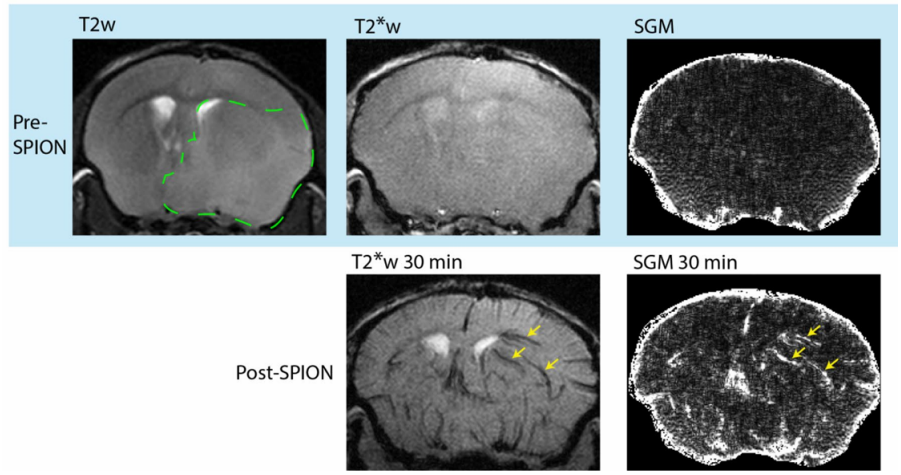


Figure 3.1.A - MRI imaging before and post-SPION injection. Patient with glioblastoma, abnormal blood vessels are visible in the right hemisphere post-SPION (yellow arrows) [7]

### Surface-Enhanced Raman Spectroscopy (SERS)

SERS is an optical imaging technique that enhances the Raman scattering of biomolecules adsorbed onto metallic nanostructures (gold or silver nanoparticles). This effect, driven by localized surface

plasmon resonance, amplifies molecular signals by up to $10^6 - 10^{14}$ times, enabling single-molecule detection.

In cancer diagnostics, SERS has been employed for ultrasensitive and label-free detection of circulating biomarkers such as exosomes, miRNAs, and proteins in liquid biopsy samples. It utilizes nanostructured gold and silver SERS substrates that were capable of detecting breast cancer biomarkers with an accuracy exceeding 90%, utilizing machine-learning algorithms for spectral classification. This technique provides a non-invasive and highly specific diagnostic approach, surpassing conventional fluorescence- and ELISA-based assays in both precision and sensitivity [8].

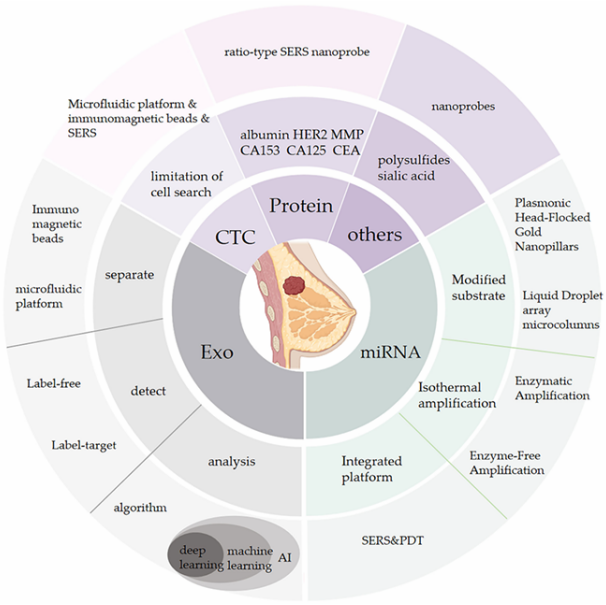


Figure 3.1.B -Schematic representation of the novel SERS-based biosensor platform for breast cancer detection [8]

## 3.2 Circulating Tumour Cell Detection

Circulating Tumour Cells (CTCs) are cancer cells that detach from the primary tumour and enter the bloodstream, acting as seeds for metastasis. They are scarce (often just a few cells among billions of blood cells), yet they carry critical information about tumour genetics, invasiveness, and treatment response. Detecting CTCs offers a non-invasive method for monitoring cancer progression, assessing therapeutic efficacy, and predicting relapse by utilizing samples obtained from liquid biopsies.

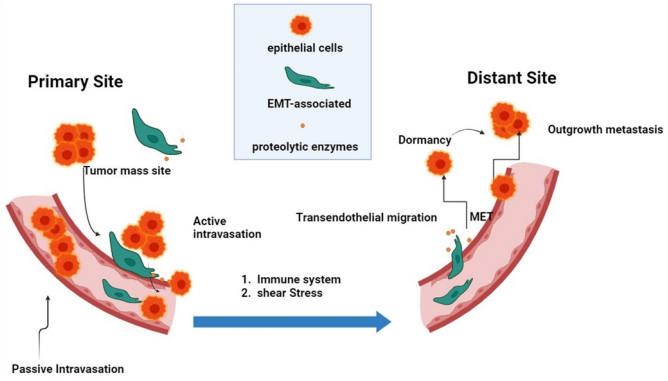


Figure 3.2.A - Tumour Cell Metastasis [9]

Early approaches for CTC detection were divided into biological and physical methods. Biological techniques relied on surface biomarkers such as EpCAM (Epithelial Cell Adhesion Molecule) and cytokeratins for immunomagnetic separation. Physical methods, including microfiltration and dielectrophoresis, leveraged differences in size, charge, or density to separate CTCs from normal blood cells. However, these approaches suffered from low recovery rates and poor reproducibility.

Nanotechnology has transformed CTC detection, offering ultra-sensitive, selective, and reproducible tools for cell capture and characterization. Gold nanoparticles (AuNPs) utilize surface plasmon resonance for optical biosensing; when conjugated with anti-EpCAM antibodies, they achieve a capture efficiency of over 90% on nanostructured substrates, significantly outperforming prior systems [9].

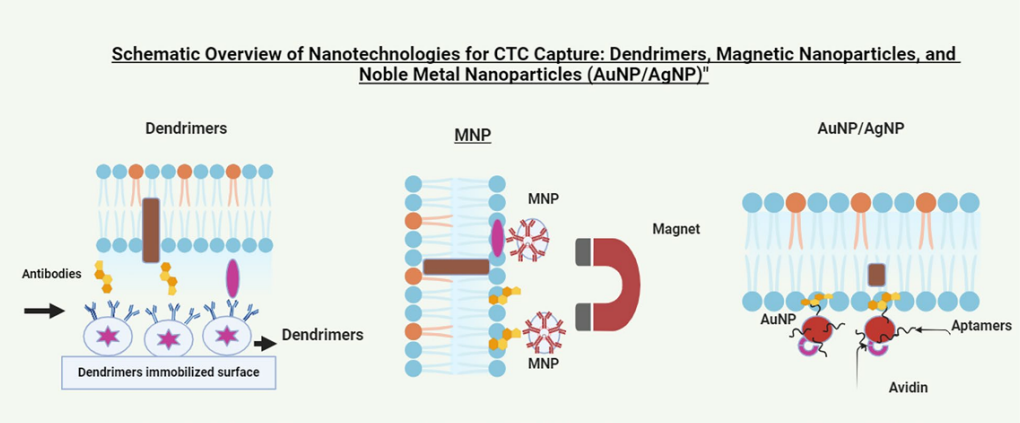


Figure 3.2.B - Schematic Overview of CTC capture and isolation [9]

Magnetic nanoparticles ($Fe_3O_4$ or $Fe_3O_4$/Au core–shell) enable immunomagnetic isolation under an external magnetic field, with the potential to be integrated into microfluidic devices for rapid, high-throughput, and high-purity separation. Further, graphene oxide and quantum dot–based 3D biosensors combine electrical and optical signal amplification for real-time, label-free detection of single CTCs. Such hybrid nanosystems integrate nickel micropillar scaffolds, PEG nanofibers, and quantum dot–linked antibodies, enabling high-sensitivity electrochemical readouts of captured cells [9].

## 3.3 Nanoprobes for Cancer Detection

Traditional diagnostic modalities, such as PET and ELISA assays, although effective for structural or biochemical analysis, are often limited by their low molecular sensitivity and inability to detect early-stage disease [10].

To overcome these limitations, nanoprobes have emerged as highly sensitive, multifunctional tools that integrate biorecognition, amplification, and imaging into a single nanosystem. These nanoscale probes, typically synthesised as gold nanoclusters (AuNCs) or carbon nanotubes (CNTs), are engineered with antibodies, ligands, or peptide substrates that selectively bind to tumour-associated biomarkers [10].

Carbon nanotube matrix biosensors were developed to detect the pancreatic cancer biomarker CA19-9, achieving femtomolar-level sensitivity through detection of changes in electrical impedance. The CNT network, functionalized with anti-CA19-9 antibodies, formed a high-surface-area conductive scaffold that significantly amplified the biosensing response [11].

Similarly, ultrasmall gold nanocluster (AuNC) probes ($< 2$ nm) have been engineered as renal-clearable catalytic nanoprobes for non-invasive, in vivo cancer detection. Functionalized with protease-cleavable peptide substrates, these AuNCs activate upon encountering tumour-specific proteases (e.g., MMP-9), releasing a colorimetric urinary signal that enables rapid and quantitative diagnosis within an hour [12].

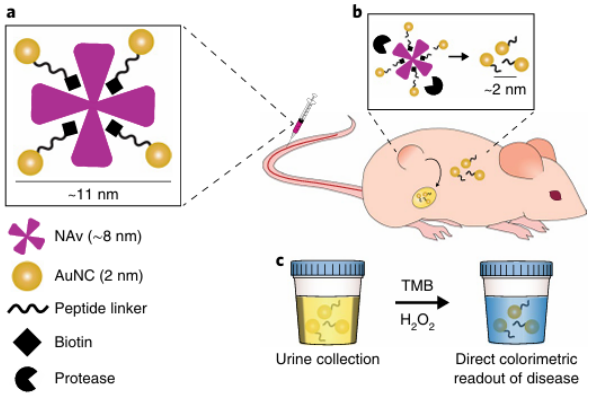


Figure 3.3.A - Gold nanoclusters used for protease-triggered colorimetric detection of disease biomarkers [12]

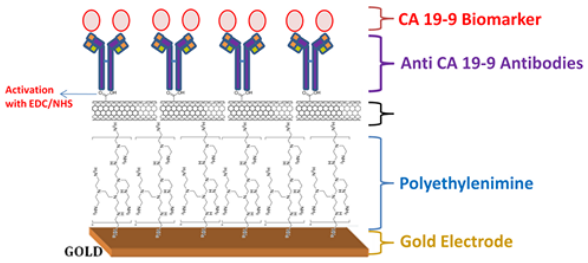


Figure 3.3.B - Carbon nanotube–based gold electrode biosensor for impedance detection of the pancreatic cancer biomarker CA19-9 [11]

Figure 3.3.A shows Protease-sensitive AuNC–NAv complexes disassemble upon protease activity, releasing gold nanoclusters filtered into urine. Liberated AuNCs catalyze a colorimetric reaction, enabling direct visual detection of disease biomarkers.

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# 4 Nanotechnology in Cancer Treatment

The Enhanced Permeability and Retention (EPR) effect, first demonstrated by Hiroshi Maeda, describes the preferential accumulation of macromolecular drugs and nanoparticles within tumour tissues due to their leaky vasculature and defective lymphatic drainage [13].

This phenomenon forms the fundamental basis for modern nanoparticle-based chemotherapeutic delivery, enabling selective localization of therapeutic agents in tumour microenvironments. Subsequent advancements have built upon this foundational principle, resulting in enhanced and controlled versions of EPR.

## 4.1 Enhanced Permeability and Retention (EPR)

The EPR effect, as stated earlier, describes the preferential accumulation of macromolecular drugs and nanoparticles within tumour tissues. Rapid angiogenesis in tumours leads to abnormal endothelial gaps (100 nm–2 µm), elevated vascular mediators such as bradykinin, nitric oxide, and VEGF, and impaired lymphatic clearance. These factors allow large drug–carrier complexes (>40 kDa) to extravasate and remain concentrated within tumours while being excluded from normal tissues. This passive mechanism became the foundation of tumour-targeted nanotherapy, exemplified by SMANCS (styrene–maleic acid–neocarzinostatin), the first clinically approved polymer–drug conjugate for hepatocellular carcinoma [13].

However, clinical application of EPR has shown considerable inter-tumour and inter-patient variability, with many solid tumours exhibiting weak or inconsistent EPR responses. To address these limitations, Maeda and colleagues introduced "EPR 2.0", an evolved framework emphasizing active modulation of the tumour microenvironment to improve drug accumulation and retention [14].

EPR 2.0 incorporates vascular modulation (using nitric oxide donors, ACE inhibitors, or prostaglandin analogues) to temporarily enhance perfusion; tumour-stroma conditioning to reduce interstitial fluid pressure; and external triggers, such as mild hyperthermia, ultrasound, or localized radiation, to transiently increase vascular permeability [14]. Through these combined strategies, EPR 2.0 enhances the passive concept into a controllable and reproducible drug-delivery paradigm, minimizing tumour- and patient-dependent variability and ensuring more uniform therapeutic outcomes.

## 4.2 Organic Nanoparticles for Chemotherapeutic Delivery

Organic nanoparticles are primarily composed of biocompatible polymers or lipids, allowing for high drug-loading efficiency, controlled release, and biodegradability. They are broadly classified into liposomes, polymeric micelles, dendrimers, and polymer–drug conjugates, based on structural organization and assembly mechanisms.

Liposomes are spherical, bilayered vesicles made of phospholipids. These amphiphilic molecules enable encapsulation of both hydrophilic and hydrophobic drugs, improving solubility, bioavailability, and circulation time.

Liposomes are classified (as shown in Figure 4.2) based on their size and lamellarity into:

- Small unilamellar vesicles (SUVs): 20–100 nm, single bilayer:- ideal for intravenous delivery of chemotherapeutics.
- Large unilamellar vesicles (LUVs): $>$ 100 nm, single bilayer:- used for sustained release of hydrophilic agents.
- Multilamellar vesicles (MLVs): $>$ 500 nm, multiple bilayers:- suitable for depot formulations.
- Multivesicular vesicles (MVVs): $>$ 1 µm, multiple internal vesicles:- used for high drug load and controlled release systems.

Liposomes have been successfully commercialized across diverse therapeutic areas, including liposomal doxorubicin for cancer treatment [15].

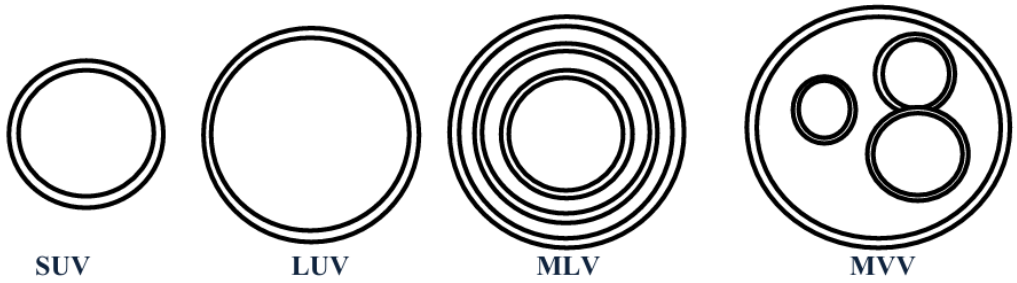


Figure 4.2 -Classification of Liposomes [15]

Polymeric micelles self-assemble from amphiphilic block copolymers such as PEG–PLA or PEG–PCL, localizing hydrophobic drugs in their cores while their hydrophilic coronas confer steric stabilization in plasma. Polymeric micelles have been utilized in cancer therapy to solubilize and deliver paclitaxel, cisplatin, and doxorubicin.

Dendrimers (such as PAMAM) possess branched nanostructures enabling multivalent drug conjugation and surface functionalization for targeted delivery.

Mechanistically, these systems utilize Enhanced Permeability and Retention (EPR)-mediated passive targeting and may also employ ligand-based active targeting (e.g., folate, antibodies). However, side effects include immunogenicity and hepatic accumulation from slow degradation [16].

## 4.3 Inorganic Nanoparticles

Inorganic nanoparticles comprise a broad class of nanoparticles engineered from metallic, semiconducting, or ceramic materials, including gold, iron oxide, mesoporous silica, and carbon nanotubes.

They can be classified into chemotherapeutic delivery agents and photothermal or magnetic hyperthermia nanoparticles, depending on their primary mechanism of therapeutic action.

### 4.3.1 Chemotherapeutic Delivery Agents

Among inorganic nanocarriers, gold nanoparticles (AuNPs) and mesoporous silica nanoparticles (MSNs) are the most investigated for drug delivery.

AuNPs are preferred for their chemical inertness, ease of functionalization (via thiol chemistry), and surface plasmon resonance, which enables optical tracking. They can be synthesized through physical (laser ablation), chemical, or biogenic routes and tailored into structures such as nanorods, nanoshells, and nanocages to control biodistribution and absorption [17].

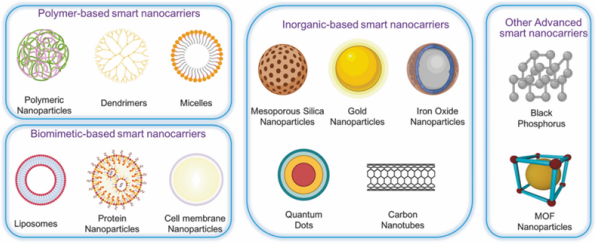


Figure 4.3.A - Different Types of Nanocarriers [17]

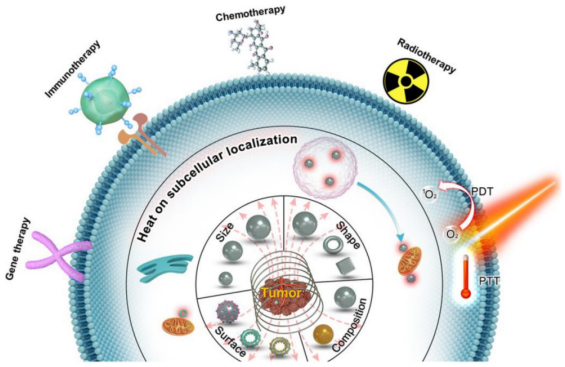


Figure 4.3.B - Synergistic combination of MNPs-MH with other therapeutic strategies [20]

MSNs, in contrast, offer ordered porous networks with controllable pore sizes (2–50 nm) and large surface areas, resulting in a high drug loading capacity. Surface grafting with pH or enzyme-sensitive polymers allows controlled drug release at acidic tumour sites [17].

Drug-loaded nanoparticles accumulate in tumour tissue via the EPR effect. Upon internalization of the nanocarrier, acidic endosomal conditions or specific enzymatic activity (depending on how the drug is conjugated to the carrier) trigger drug release from the carrier into the target cancer cells [17]. Despite their therapeutic efficacy, metal-based nanoparticles may induce ROS-mediated oxidative stress and hepatic or renal accumulation [18].

### 4.3.2 Photothermal and Magnetic Hyperthermia Nanoparticles

Photothermal nanoparticles, principally gold nanostructures (nanorods, nanoshells, and nanocages), convert near-infrared (NIR) light into heat via surface plasmon resonance. When irradiated with NIR lasers (650–900 nm), localized temperatures rise to 42–46 °C, inducing thermolysis of cancer cells while sparing surrounding tissue. Functionalization with tumour-specific ligands improves selectivity and minimizes off-target effects. However, current validation of these systems has been confined to in vivo mouse models, and in vitro human studies. Extensive preclinical and clinical research is still required before these photothermal platforms can be translated into routine clinical oncology applications [18,19].

Magnetic hyperthermia, on the other hand, utilizes SPIONs that generate localized heat through Néel and Brownian relaxation when exposed to an alternating magnetic field (typically 100–500 kHz). These particles are administered intra-tumourally, enabling deep-tissue penetration and precise thermal ablation of cancer cells. Additionally, the induced heat enhances the efficacy of chemotherapy and radiotherapy by improving drug diffusion. SPION-based magnetic hyperthermia has progressed to Phase I clinical trials, where it has been evaluated for the treatment of recurrent glioblastoma multiforme and prostate carcinoma, highlighting its potential for combined modality cancer treatment [20].

The major drawback with both techniques is that excessive heating can cause cerebral necrosis, edema, or vascular thrombosis at temperatures above 43 °C. Long-term accumulation and ROS generation also remain a concern, necessitating precise control of dosage and temperature [18-20].

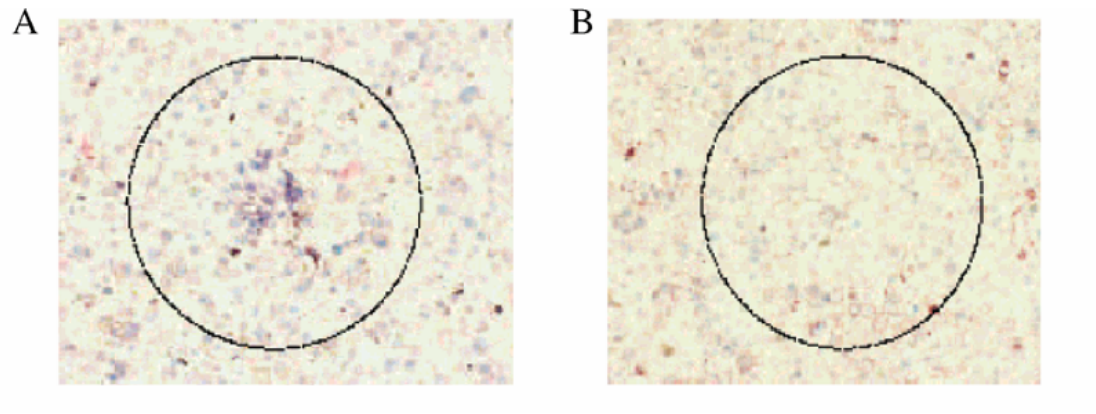


Figure 4.3.C -Gold nanorod–mediated selective photothermal therapy (cancer cells coloured blue in A, Eliminated in B) [19]

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# 5 Patient Safety and Regulatory Considerations

Nanotechnology enables precise and targeted drug delivery but introduces safety and regulatory challenges due to its nanoscale behavior and complex biological interactions. Nanoparticles exhibit size-dependent metabolism and clearance, leading to off-target accumulation, ROS generation, or immune system response. Metallic nanocarriers like gold and iron oxide, though inert, may cause chronic inflammation or hepatic/renal deposition due to slow biodegradation [21].

The U.S. FDA and EMA regulate nanomedicines under existing drug and device laws, emphasizing detailed physicochemical characterization, pharmacokinetic profiling, and bioaccumulation studies. In India, regulation is overseen by CDSCO, ICMR, and DCGI under the 2019 Guidelines for Evaluation of Nanopharmaceuticals, mandating Good Manufacturing Practices (GMPs), toxicological assessment, and post-approval pharmacovigilance to ensure patient safety through standardized manufacturing and long-term monitoring.

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# 6 Conclusion

Nanotechnology has revolutionized oncology by enabling precise, controlled, and multimodal strategies for cancer detection and therapy. Liposomes, polymeric systems, and metal-based nanoparticles offer improved targeting, reduced toxicity, and enhanced imaging capability. The integration of photothermal and magnetic hyperthermia therapies exemplifies the promise of theranostics in clinical practice. Despite remarkable advances, challenges persist in large-scale manufacturing, reproducibility, and long-term safety. Strengthening international regulatory harmonization and predictive nanotoxicology models remains essential for the safe clinical adoption of nanomedicines.

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