

Chapter 14

Nanomedicine and Healthcare Innovation

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1. What is nanomedicine?

Nanomedicine utilizes the principles, tools and techniques of nanotechnology to the prevention, diagnosis, monitoring and treatment of disease, a multidisciplinary field, is the science of a matter that is measured in nanometres (nm), a dimension of 1 to 1,000 nanometres. A nanometre is one billionth of a metre (10^{-9} m): To get an idea of the scale—one human hair is about 80,000–100,000 nm wide and the diameter of a red blood cell is about 7,000–8,000 nm. Proteins, DNA strands, lipid bilayers, and engineered nanoparticles are all on the same size scale as the basic cellular mechanisms of the cell, in the range of 1–200 nm size, and are the molecules structures of interest for nanomedicine. This dimensional overlap is no mere accident of scale, but rather the mechanistic basis of the whole discipline. If a drug or other material can be engineered to match a biological target in size, geometry, and surface chemistry – a receptor, an enzyme, a membrane channel, or even a cancer cell – it can interact with the target with unprecedented precision. Small-molecule drugs are mostly based on chemical affinity. The second dimension of control added to nanomedicine is spatial architecture. Engineering size, shape, surface charge, porosity and the number of ligands at the nanoscale opens up therapeutic approaches that are well beyond the scope of conventional pharmaceutical chemistry.

1.1. The nanometre size

What is special about the nanoscale in biology and medicine? The size hierarchy of biological structures is the key to the answer. Viruses are approximately 20–300 nm, making the engineered NP size window the same. The thicknesses of cell membranes are 5–10 nm. The size of plasma proteins like albumin is 7–8 nm. The width of a double helix of DNA is 2 nm. The protein synthesis machinery of the cell, the ribosomes, have a diameter of about 25 nm. Nanomedicine can be engineered to penetrate biological barriers (cell membrane, endosomal compartment, in some cases, blood–brain barrier), to evade immune surveillance, and to target subcellular targets, that are completely inaccessible to macroscale carriers.

The unique physicochemical properties are also characteristic of nanomaterials as opposed to their bulk counterparts. As the particle size decreases, the surface-area-to-volume ratio also rises, and the surface reactivity and the quantity of drug loaded per volume also increases. The optical and electronic properties of semiconductor nanocrystals (quantum dots) are modified by the quantum confinement effects, allowing the nanocrystals to fluorescently emit light at an exactly tunable wavelength for bioimaging. In diagnostic applications, gold nanoparticles are used due to their ability to absorb and scatter light at wavelengths dependent on their size and shape; in photothermal cancer therapy, the property of gold nanoparticles is used. These size-dependent

phenomena are unique and do not occur in bulk materials and are the value proposition of the nanoscale.

1.2. Scope and subdisciplines

Nanomedicine is a wide and growing variety of activities, often clustered into the three overlapping domains below: Nano-drug delivery: Engineering nanocarriers (liposomes, polymeric nanoparticles, dendrimers, solid lipid nanoparticles, exosomes, inorganic nanoparticles) for encapsulation, protection, transport and controllable release of therapeutic agents at the disease site. Nano-diagnostics: Development of nanoscale contrast agents, biosensors and point-of-care platforms for the ultrasensitive detection of disease biomarkers, pathogens, circulating tumour DNA and metabolites – often at the single molecule level. In theragnostic, it is essential to combine therapeutic and diagnostic capabilities in a single nanoscale device for simultaneous imaging and therapy and for monitoring therapeutic response in real time, for closed-loop personalised medicine. In addition to these, nanomedicine has the potential to play a role in other areas including nano-immunology, nanoparticulate vaccine adjuvants, nanorobots, photodynamic agents, and nano-immunology, immune checkpoint modulation, and nanostructured scaffolds for tissue engineering. The field is truly multi-disciplinary, involving the disciplines of materials science, chemistry, cell biology, pharmacology, engineering and clinical medicine.

1.3. Historical development of nanotechnology in medicine

1.4. The conceptual origins: Feynman's vision

It is believed that the intellectual inspiration for nanotechnology started with the presentation of a single lecture by the Nobel Prize-winning Physicist Richard P. Feynman at the American Physical Society in December 1959. It was a stunning guess that the laws of physics did not obviously bar the direct manipulation of individual atoms and molecules that the lecture, ‘There’s Plenty of Room at the Bottom: An Invitation to Enter a New Field of Physics’, proposed. Feynman imagined miniaturized machines that could be written on the head of a pin, could be used to synthesize new types of molecules one atom at a time, and — most prophetically to medicine — could be swallowed and then “swim around and inject a drug or cut with a knife” at the point of the problem. In 1959, the technology to make these visions come true would not yet have existed, but Feynman’s lecture provided a conceptual framework that would direct two generations of scientists. The word ‘nanotechnology’ was not used until 1974, when the Japanese engineer Norio Taniguchi introduced it to describe the precise machining of materials to nanometre tolerances. The theoretical underpinnings were expanded upon in 1986 by MIT engineer K. Eric Drexler with *Engines of Creation* and again in 1992 with the technical monograph *Nanosystems: Molecular Machinery, Manufacturing, and Computation* which sparked much scientific debate but undoubtedly stimulated the field.

1.5. Enabling technologies

To realize the conceptual frameworks into reality, instruments were needed that could image and manipulate matter at the atomic scale. A landmark discovery was made in 1981 by Gerd Binnig and Heinrich Rohrer at IBM Zurich, the invention of the scanning tunnelling microscope (STM), of which they were awarded the 1986 Nobel Prize for Physics. The individual atoms on a surface could for the first time be imaged with a resolution better than an Ångström. The extension of this capability to non-conductive biological material in 1986 with the advent of the atomic force microscope (AFM), allowed for the image of DNA, proteins, and cell membranes in near physiological conditions to be observed.

The building blocks for nanomedicine came from parallel developments in materials science. In 1985, Kroto, Curl and Smalley discovered buckminsterfullerene, C_{60} , the stable, cage-like nanocarbon, shedding light on the fact that carbon can assume a range of stable nanoscopic geometries with astonishing chemical and physical properties (Nobel Prize, Chemistry, 1996). In 1991, multi-walled carbon nanotubes were discovered by Sumio Iijima, which enabled the development of ultra strong, electrically conducting nanoscale tubes, and research quickly began on new uses for these nanocarbons as drug delivery vehicles and components of biosensors. At the same time, the colloidal chemistry community was working on ways to synthesize monodisperse gold nanoparticles, quantum dots and iron oxide superparamagnetic nanoparticles (SPIONs), all of which were to prove to be central to the field of nanomedicine.

KEY MILESTONE

Gordon Moore predicted in 1965 the number of transistors on an integrated circuit would double about every two years, also known as 'Moore's Law'. The same pattern applies to nanomedicine, with the number of articles published in peer-reviewed journals doubling every five years approximately, from less than 100 articles per year in 1990 to more than 30,000 articles published in 2020.

1.6. From bench to bedside: the first nanomedicines

The first attempts at clinical translation of nanomedicine were with liposomal drug formulations in the early 1990s. Spherical vesicles enclosed by phospholipid bilayers (liposomes) were described by a British haematologist, Alec Bangham, in 1965, but it took another 20 years for their pharmaceutical potential to be fully appreciated. One of the key insights was the ability of liposomes to alter the pharmacokinetic profile of cytotoxic anticancer drugs dramatically, extending the time that the drugs remain in the bloodstream, decreasing the toxicity of the drugs in off-target organs, and using the increased permeability of capillaries in the tumour tissue and the increased retention of nanoparticles in the tumour to preferentially accumulate the nanoparticles in the tumour tissue. The United States Food and Drug Administration (FDA) approved the liposomal form of the chemotherapy drug doxorubicin (Doxil) in 1995

as a treatment for Kaposi's sarcoma in patients with AIDS. It was the first FDA approved nanomedicine and the beginning of a new era of clinical oncology. Pegylated (polyethylene glycol-coated) liposomes of Doxil had remarkably greater half lives than free doxorubicin, mediated by the ability of the pegylated liposomes to avoid mononuclear phagocyte system uptake and to accumulate in tumour vasculature. The cardiotoxicity reduction was clinically significant and was an excellent proof-of-concept for the therapeutic benefits of nanotechnology mediated drug delivery of free doxorubicin.

1.7. Chronological timeline of nanomedicine development

The following Table 1 summarises the major milestones in the historical development of nanomedicine, from foundational conceptual contributions to landmark clinical achievements:

Table 1.

Summary of Historical development of nanomedicine

Period	Milestone	Significance	References
1959	Feynman's Lecture 'There's Plenty of Room at the Bottom'	First conceptual framework for nanoscale manipulation of matter	Feynman RP. There's plenty of room at the bottom. *Engineering and Science*. 1960;23(5):22–36.
1974	Norio Taniguchi coins the term 'Nanotechnology'	Formal recognition of the field and its engineering potential	Taniguchi N. On the basic concept of "nano-technology." *Proc. Int. Conf. Prod. Eng.*; Tokyo, Part II. Japan Society of Precision Engineering; 1974.
1981	Scanning Tunneling Microscope (STM) invented	Enabled direct visualization and manipulation of atoms	Binnig G, Rohrer H, Gerber C, Weibel E. Surface studies by scanning tunneling microscopy. *Phys Rev Lett*. 1982;49:57–61.
1985–1990	Discovery of Fullerenes and Carbon Nanotubes	Novel nanoscale carbon structures with unique biomedical properties	Kroto HW, Heath JR, O'Brien SC, Curl RF, Smalley RE. C60: Buckminsterfullerene. *Nature*. 1985;318:162–163. Iijima S. Helical microtubules of graphitic carbon. *Nature*. 1991;354:56–58.
1995	First FDA-approved nanoparticle drug: Doxil (liposomal doxorubicin)	Landmark in targeted cancer nanotherapy reducing cardiotoxicity	Barenholz Y. Doxil® — the first FDA-approved nano-drug: lessons learned. *J Control Release*. 2012;160:117–134.
Early 2000s	Rapid expansion of nanoparticle drug delivery systems	Hundreds of nanomedicine formulations enter clinical development	Bangham AD, Standish MM, Watkins JC. Diffusion of univalent ions across the lamellae of swollen phospholipids. *J Mol Biol*. 1965;13:238–252.
2010s	Gold nanoparticles in diagnostics; RNA nanostructures	Theranostic platforms combining therapy and imaging emerge	Polack FP et al. *N Engl J Med*. 2020;383:2603–2615. Baden LR et al. *N Engl J Med*. 2021;384:403–416. Hou X et al. Lipid nanoparticles for mRNA delivery. *Nat Rev Mater*. 2021;6:1078–1094.
2020–2021	Lipid nanoparticle (LNP) mRNA COVID-19 vaccines	Nanomedicine delivers first mRNA vaccines at global scale	Bobo D et al. *Pharm Res*. 2016;33:2373–2387. Anselmo AC, Mitragotri S. Nanoparticles in the clinic: an update. *Bioeng Transl Med*. 2019;4\;e10143.

1.8. The mRNA vaccine revolution: nanomedicine at global scale

The COVID-19 pandemic was perhaps the most dramatic example of the potential of nanomedicine to transform. Both BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna) vaccines have been approved for emergency use and given to billions of people globally in December 2020, and are essentially nanomedicines. Both vaccines contain sensitive mRNA molecules that are enclosed in lipid nanoparticles (LNPs), which are ionisable lipid-based delivery vehicles designed to protect the mRNA from degradation by serum ribonucleases, promote cellular uptake by endocytosis and facilitate endosomal escape to release the mRNA payload into the cytoplasm where it is used to direct the production of the SARS-CoV-2 spike protein.

The LNP technology used in these vaccines was inspired by decades of nanomedicine research, particularly the groundbreaking work of lipid nanoparticle formulation pioneers Pieter Cullis and Ian MacLachlan and colleagues at the University of British Columbia and the fundamental mRNA chemistry stabilisation work by Katalin Karikó and Drew Weissman that was shared with the 2023 Nobel Prize in Physiology or Medicine. The global rollout of LNP-mRNA vaccines has confirmed the potential of nanomedicine as a platform technology that can be used at population-level scale and spurred unprecedented investment in new generation nanomedicines for cancer, cardiovascular disease and inherited genetic disorders.

1.9. Importance in modern healthcare

1.10. Addressing the limitations of conventional medicine

Nanomedicine has significant value in modern medicine because it can find solutions to problems that are not properly addressed by traditional medicine and pharmaceuticals. In spite of enormous progress over the last century, there remain four major limitations for pharmacotherapy: inadequate target specificity (drugs can reach unintended tissues, causing toxicity); low bioavailability (many drugs are rapidly broken down, poorly absorbed, or rapidly excreted); multi-drug resistance (pathogens and tumours develop resistance to conventional drugs); and the inability to deliver macromolecular therapeutics (proteins, nucleic acids, gene editing tools) intact across biological barriers.

Each of these challenges can be addressed systematically with nanomedicine. The therapeutic index (effective dose/tolerated dose) can be greatly enhanced by targeted nanoparticles, with surface ligands (such as antibodies, aptamers, peptides, or small molecules) that can bind to receptors expressed on diseased tissue. Labile drugs can be protected from premature degradation and controlled and sustained release can be achieved with nanoencapsulation. Multidrug resistance may be overcome by using nanoparticles that are taken up via endocytic pathways bypassing membrane efflux pumps. And, as the mRNA vaccine age

has proven, lipid nanoparticles could transport a range of different nucleic acid macromolecules that would otherwise be immediately destroyed when injected as free molecules.

1.11. Key healthcare applications and impact areas

To understand the potential role of nanomedicine in contemporary medicine, it is best to appreciate its changing impact in the various therapeutic fields:

Oncology: Nanomedicine has revolutionized cancer drug therapies. Cytotoxic agents (paclitaxel, doxorubicin, irinotecan) formulations using nanoparticles are less toxic and more effective at concentrating in tumours. Probably the fastest growing class of oncology medications are antibody-drug conjugates (ADCs), nanoscale hybrid constructs comprising a cytotoxic agent bound to a tumour-targeting antibody. In the active clinical development phase, tumour-microenvironment-responsive nanoparticles, immunostimulatory nanoparticle cancer vaccines and siRNA nanoparticles silencing oncogenes have been developed.

Infectious Disease: LNP-mRNA vaccines for COVID-19 set the precedent; influenza, RSV, HIV, tuberculosis and malaria vaccines in advanced development. Biofilm-associated infections and resistant pathogens are treated with a nano-antibiotic formulation. Silver and copper nanoparticles have broad-spectrum antimicrobial activity applicable to infection control in hospital settings.

Neurology: The blood-brain barrier (BBB) is one of the most daunting delivery barriers in medicine. Ligands (transferrin, apolipoprotein E, low-density lipoprotein receptor peptides) attached to engineered nanoparticles can be used to open up delivery routes to Alzheimer's disease, Parkinson's disease, brain tumours, and stroke by transcytosing the BBB.

Cardiovascular Disease: Nanoparticles that target atherosclerotic plaques for targeted delivery of anti-inflammatory agents. Myocardial regeneration with cardiac patch nanocomposites containing conductive nanoparticles is currently being studied. The first FDA approved RNAi nanomedicine (outside oncology) is LNP-siRNA therapeutics (inclisiran) targeting PCSK9.

Superparamagnetic iron oxide nanoparticles (SPIONs) are used for MRI contrast agents. In lateral flow assays (LFA), and surface-enhanced Raman spectroscopy (SERS) sensors, use of gold nanoparticles boosts signal. Multiplexed fluorescence imaging of tumour biomarkers is possible with quantum dot probes. Circulating tumour DNA is detected in liquid biopsy platforms with a sensitivity of picomolar by nanosensor arrays.

1.12. Economic and regulatory significance

The global nanomedicine market size reached about USD 177 billion in 2023 and is anticipated to hit an exceeding USD 550 billion by 2032, with the compound annual growth rate (CAGR) being one of the highest in the pharmaceutical industry. Since its formation in 2000, the United

States National Nanotechnology Initiative (NNI) has spent more than USD 30 billion on nanotechnology research and development. The regulatory authorities of the USA (the FDA), Europe (the EMA) and Japan (the PMDA) have established specific regulatory frameworks and guidelines focusing on nanomedicines, recognising the specific physicochemical complexity of nanoscale therapeutics and the requirement for characterisation standards that go beyond those used for small molecule drugs.

2. Fundamentals of nanotechnology

2.1. Nanoscale concepts and properties

2.2. Defining the nanoscale

The nanoscale is generally agreed to be the range of sizes from 1 to 1,000 nanometres (nm), or one billionth of a metre. A human scale for comparison: A hydrogen atom is about 0.1 nm in diameter, a glucose molecule is 0.8 nm, a typical protein is 5-10 nm, a ribosome is 25 nm, a small virus (poliovirus) is 25-30 nm and a large virus (influenza) is 100 nm. The nanoparticles engineered for use in medicine usually fall within the range of 10–200 nm, which was targeted with a conscious choice because it falls in the window of the molecular machinery of human cells.

The overlap in size is a crucial point for mechanisms. The size of the nanoparticles (10-100nm) allows for encapsulating several molecules of a drug as well as for the display of targeting ligands on their surface, which can be taken up into cells by endocytosis and pass through leaky tumour vasculature due to enhanced permeability and retention (EPR) effect, while avoiding rapid clearance by the mononuclear phagocyte system (MPS) with proper surface engineering. Nanoparticles $< \sim 8$ nm are easily filtered out by the kidneys and $> \sim 200$ nm are efficiently filtered in the liver by Kupffer cells and splenic filtration. So the therapeutic window of 10–200 nm is not a random choice, but rather it's a result of the overlap of biological barriers and pharmacokinetic needs.

Why does matter behave differently at the nanoscale?

As size goes on shrinking to the atomic scale, two fundamental physical properties of materials dominate, giving rise to the special properties of nanomaterials: the large surface-area-to-volume ratio and the appearance of quantum mechanical properties.

2.3. Surface-Area-to-Volume Ratio

The surface area of a sphere is proportional to r^2 and its volume is proportional to r^3 . The surface-area-to-volume ratio rises with a decrease in r as $1/r$. About 1 of every 10 million gold atoms is on the surface of a 1cm cube of gold. About 30% of the atoms in a 10-nm gold

nanoparticle are atoms at the surface. The implications of this explosion in surface atom fraction are enormous: surface atoms are in incomplete coordination spheres with higher free energy and chemical reactivity than interior atoms. That is why gold nanoparticles are very reactive catalysts and bulk gold is as chemically inert as it gets — this is all due to size.

In medicine, this ratio has been used to measure the drug-loading capacity (more surface area per unit mass = more drug adsorbed or conjugated), the dissolution rate (dissolution is a surface phenomenon), the catalytic activity relevant to the formation of reactive oxygen species (ROS) in the process of photodynamic therapy (PDT) and to increase the sensitivity of biosensors. The surface-to-volume argument is also at the heart of the issue of predicting nanomaterial toxicity from bulk material safety data, which is important for regulatory purposes.

2.4. Quantum mechanical effects

The electronic and optical properties of a material at the macroscale are given by the bulk band structure of the material and are essentially independent of the size of the material. When particle sizes get into the range of 1 - 20 nm, quantum confinement effects appear as the particle dimensions approach the de Broglie wavelength of the electrons. In the bulk material, the energy bands are continuous, but when electrons and holes are spatially confined, the energy bands split up into quantised energy bands in all three dimensions. Energy (and consequently wavelength) of absorbed and emitted photons becomes directly proportional to particle size between the spacing of these levels.

Semiconductor quantum dots take full advantage of this quantum size effect, as it is clearly demonstrated here. The same quantum dot — CdSe — yields blue (2-nm) and red (5-nm) light, an entire range of fluorescence spectra possible depending on the size of the dot. The quantum dot is 10-100 times more fluorescent than an organic dye, it does not photobleach, and it can be modified to target a specific type of cell. Due to these properties, they are great multiplexed bioimaging, single-molecule tracking and in vivo tumour imaging tools, although concerns over the potential toxicity of the heavy metals in the dots have spurred the development of less toxic alternatives such as indium phosphide (InP) and carbon dots (Cdots).

SCALE PERSPECTIVE

A human cell would be the size of a city (30 km), a human body would be able to span the distance from the earth to the moon (384,000 km) and a nanoparticle would be the size of a football (30 cm). This view provides a glimpse of the fact that although nanoparticles are invisible, they are functioning at the same architectural scale as the molecular machinery with which they interact.

2.5. Surface plasmon resonance in metal nanoparticles

Noble metal nanoparticles – mainly gold and silver – have a property called localised surface plasmon resonance (LSPR). The incident light of a certain frequency causes the collective oscillation of conduction electrons at the surface of the metal nanoparticle, in resonance with

the oscillating electromagnetic field. This resonance condition gives rise to strong absorption and scattering of light at a characteristic wavelength which is sensitive to the size, shape, composition and the dielectric properties of the medium contiguous to the particle.

The LSPR peak is about 520 nm (visible green) for gold nanospheres of 20 nm diameter, resulting in the ruby-red colour typical of the colloid. The LSPR is shifted in the nanorods to the near-infrared (NIR) range (650–900nm), a spectral region in which the tissue is relatively transparent to light. The NIR light is absorbed by gold nanorods, which generate heat very efficiently, allowing for the destruction of tumours without damaging the surrounding tissue. Also, the gold nanoparticles have the ability to induce a significant enhancement of Raman scattering signals (surface-enhanced Raman scattering, SERS), which can detect biomolecules at concentration levels as low as one molecule.

2.6. Key nanoscale properties summary

The following Table 2 summarises the principal nanoscale properties and their biological and medical implications:

Table 2.

Nanoscale properties and their biological and medical implications

Property	Nanoscale Behaviour	Biological Consequence	Medical Relevance	References
Surface-area-to-volume ratio	Increases exponentially as size decreases	Higher drug loading, faster dissolution	Improved bioavailability and dose efficiency	Nel AE et al. Understanding biophysicochemical interactions at the nano–bio interface. <i>*Nat Mater*</i> . 2009;8:543–557.
Quantum confinement	Discrete electronic energy levels emerge	Fluorescence at size-dependent wavelengths	Quantum dot bioimaging, diagnostics	Murray CB, Norris DJ, Bawendi MG. <i>*J Am Chem Soc*</i> . 1993;115:8706–8715. Michalet X et al. Quantum dots for live cells, in vivo imaging, and diagnostics. <i>*Science*</i> . 2005;307:538–544.
Surface plasmon resonance	Collective electron oscillations in metal NPs	Strong light absorption and scattering	Gold NP photothermal therapy, SERS sensing	Eustis S, El-Sayed MA. <i>*Chem Soc Rev*</i> . 2006;35:209–217. Hirsch LR et al. Nanoshell-mediated NIR thermal therapy of tumors. <i>*PNAS*</i> . 2003;100:13549–13554.
Superparamagnetism	No magnetic hysteresis below critical size	Controllable by external magnetic field	MRI contrast, magnetic hyperthermia	Lu AH, Salabas EL, Schüth F. Magnetic nanoparticles. <i>*Angew Chem Int Ed*</i> . 2007;46:1222–1244.
Enhanced permeability	Nano size bypasses tight junctions, enters cells	Transcytosis across biological barriers	BBB penetration, intracellular delivery	Matsumura Y, Maeda H. <i>*Cancer Res*</i> . 1986;46:6387–6392.
EPR effect	Long-circulating NPs accumulate in leaky tumour vasculature	Passive tumour targeting	Reduced chemo toxicity, improved efficacy	Matsumura Y, Maeda H. <i>*Cancer Res*</i> . 1986;46:6387–6392.

2.7. Types of nanomaterials

2.8. Classification framework

Medically used nanomaterials can be classified in several orthogonal ways: by composition (organic, inorganic, carbon, composite), by dimensionality (0D: nanoparticles; 1D: nanotubes and nanowires; 2D: nanosheets; 3D: nanostructured scaffolds), by source (synthetic, biological, natural) and by surface architecture (bare, coated, functionalized, stimuli-responsive). From the clinical perspective, the most useful primary classification is between the lipid-based, polymeric nanoparticles and inorganic nanoparticles, carbon nanomaterials, and biologically derived nanostructures. The synthesis pathways, surface chemistry, biocompatibility characteristics, as well as regulatory precedents vary from class to class (Table 3).

Table 3.

Organic and inorganic NPs

ORGANIC NPs	Lipid-Based • Liposomes (phospholipid bilayer vesicles) • Solid lipid nanoparticles (SLNs) • Nanostructured lipid carriers (NLCs) • Lipid nanoparticles (LNPs) for mRNA delivery • Self-emulsifying drug delivery systems	Polymer-Based • PLGA, PLA, PCL biodegradable particles • Chitosan nanoparticles (mucoadhesive) • Polyamidoamine (PAMAM) dendrimers • Polymeric micelles from amphiphilic block copolymers • Hydrogel nanoparticles for sustained release	Barenholz 2012 (above). Wang-Gillam A et al. NAPOLI-1. <i>*Lancet*</i> . 2016;387:545–557. Davis ME, Chen Z, Shin DM. Nanoparticle therapeutics. <i>*Nat Rev Drug Discov*</i> . 2008;7:771–782.
INORGANIC NPs	Metal & Metal Oxide • Gold nanoparticles (nanospheres, nanorods, nanoshells) • Superparamagnetic iron oxide NPs (SPIONs) • Silver nanoparticles (antimicrobial) • Zinc oxide and titanium dioxide NPs • Copper nanoparticles (antibacterial)	Silica & Quantum • Mesoporous silica nanoparticles (MSNs) • Quantum dots (CdSe/ZnS, InP/ZnS, carbon dots) • Calcium phosphate nanoparticles • Hydroxyapatite nanoparticles (bone regeneration) • Cerium oxide NPs (antioxidant nanoenzymes)	Kam NWS et al. <i>*PNAS*</i> . 2005;102:11600–11605. Poland CA et al. Carbon nanotubes introduced into the abdominal cavity of mice show asbestos-like pathogenicity. <i>*Nat Nanotechnol*</i> . 2008;3:423–428

2.9. Nanoparticles (0-Dimensional nanomaterials)

The most prevalent class of nanomaterials used in medicine is termed nanoparticles (NPs) and is defined as three-dimensionally constrained materials with all three dimensions in the 1–1000 nm range. They are the bulk of approved and investigational nanomedicines. Their clinical applications result from their ability to encapsulate, adsorb, or conjugate therapeutic and diagnostic agents, shield their payloads from degradation, and display engineered surfaces for immune evasion and targeted delivery.

2.10. Liposomes

Liposomes are spherical vesicles containing a single or multiple phospholipid bilayers enclosing an aqueous compartment, and have diameters of 50–1000 nm. They are structurally similar to cell membranes, making them naturally biocompatible and biodegradable. The hydrophilic drugs are encapsulated in the aqueous interior, the hydrophobic drugs are intercalated in the lipid bilayer and amphiphilic drugs are at the interface. PEGylation (coating with polyethylene glycol chains) significantly decreases opsonisation and increases the plasma half-life from minutes to days, as in the case of Doxil, the first FDA approved nanomedicine (1995), which reached tumour tissue by utilising the EPR effect. Examples of modern liposomal platforms are thermosensitive liposomes that deplete their payload in response to the mild hyperthermia present in tumour tissue, pH-sensitive liposomes that break at the pH found in tumour tissue and antibody-decorated immunoliposomes for active targeting to the tumour.

2.11. Polymeric Nanoparticles

Polymeric nanoparticles are made using biocompatible, biodegradable synthetic polymers, particularly poly(lactic-co-glycolic acid) (PLGA) and poly(lactic acid) (PLA) and poly(caprolactone) (PCL) or natural polymers, such as chitosan. The degradation products of PLGA nanocapsules (lactic acid and glycolic acid) are natural metabolites, and the rate of degradation of PLGA – and thus the release of the drug – can be controlled by changing the ratio of lactide:glycolide and the molecular weight. Drug release from PLGA matrices is predictable and biphasic with an initial burst from surface-adsorbed drug and sustained release due to hydrolytic degradation of the polymer matrix over days to weeks. This controlled release is especially useful in the case of chemotherapy, because the steady concentration of the drug within the tumour is more effective than peaks.

2.12. Dendrimers

Dendrimers, which are synthetic macromolecules from the Greek dendron (tree) are perfectly branched, three-dimensional macromolecules radiating from a central core. A dendrimer is also monodisperse, having a well-defined number of surface functional groups, size (usually 1-10nm), and molecular weight, in contrast to conventional polymers, which have polydisperse molecular weight. The most studied medical dendrimers are the polyamidoamine (PAMAM) dendrimers, in which the number of amine groups on the surface doubles with each generation. The multivalent surface of dendrimers can be targeted with targeting ligands, loaded with drug molecules, equipped with imaging agents and furnished with stealth polymers, thus yielding true nanoplatforms for multifunctional drug delivery. Also, as a property of dendrimers, there is an intrinsic gene-transfection ability of the cationic amine groups on the surface of the dendrimer forming electrostatic complexes with anionic nucleic acids (dendriplexes) which enable the dendrimer to enter the cells and release the gene in the endosomes.

2.13. Nanotubes (1-Dimensional nanomaterials)

Nanotubes are one dimensional cylindrical nanomaterials which are hollow and have a diameter of nanometres and lengths of micrometres or even millimetres. The most prominent example is carbon nanotubes, which are a single graphene sheet rolled into a seamless cylinder of 0.4-2nm diameter or concentric cylinders with outer diameters of 2-100nm known as multi-walled carbon nanotubes (MWCNTs). Depending on the exact rolling angle (chirality), the electronic properties of SWCNTs vary: armchair CNTs are metallic conductors, zigzag and chiral CNTs are semiconductors. The mechanical properties of CNTs are extremely high, with Young's modulus reaching up to 1 TPa (approximately 100 times higher than steel, with a 1/6th density), and their thermal and electrical conductivity also being very high.

In medicine, CNTs have been explored as drug delivery vehicles (due to their hollow interior, which can encapsulate small molecules, and due to the external surface that can be functionalized with peptides, antibodies, and nucleic acids), as photothermal agents (absorb strongly in the NIR and convert light to heat with high efficiency), as biosensor transducers (exquisitely sensitive to events on the surface upon adsorption), and as scaffold materials for neural and cardiac tissue engineering (conductivity that supports the propagation of electrical signals in engineered tissues). Biocompatibility issues have been the major obstacle to the clinical translation of CNTs: pristine hydrophobic CNTs will aggregate in physiological environments, are not biodegradable, and for longer MWCNTs will induce asbestos-like inflammatory responses. These concerns are greatly reduced by surface functionalisation with hydrophilic groups (carboxylation, PEGylation and amine-coating), and biodegradable CNTs have been shown in vivo.

2.14. Nanofibers (1-Dimensional extended structures)

Nanofibers are solid or hollow fibrous nanostructures that have diameters less than 1,000 nm and aspect ratio (L/D) is usually more than 100:1. Nanofibers are not necessarily hollow and are normally produced using a technique that involves a high voltage electric field that pulls a polymer solution from a needle tip into a continuous nanoscale fibre which is deposited on a grounded collector. Nanofibres can be created from a diverse array of synthetic polymers (PLGA, PLA, polyurethane, polycaprolactone), natural biopolymers (collagen, gelatin, silk fibroin, hyaluronic acid, chitosan) and composite blends, with diameters of the fibres controlled by varying polymer concentration, solvent system, applied voltage and needle-to-collector distance.

The main medical virtue of nanofibers is that they mimic the structure of the extracellular matrix (ECM) — the fibrillar collagen and elastin structure that form the physical scaffolding and biochemical environment for all mammalian cells. ECM fibre diameter is in the range of 50-500nm, which dictates cell adherence, migration, proliferation and differentiation. This architecture is replicated with incredible fidelity in electrospun nanofiber scaffolds, and is the most widely used material platform for tissue engineering in nearly all organ systems: skin wound dressings (re-epithelialisation and angiogenesis), vascular grafts (endothelial cell seeding and smooth muscle alignment), bone and cartilage regeneration (hydroxyapatite-polymer composites with mineralised nanofibers), cardiac patches, neural conduits, and corneal replacement. Drug-loaded electrospun membranes deliver both structural scaffold and pharmacological activity at the site of a wound, in the same material.

2.15. Unique physical, chemical, and biological characteristics

2.16. Physical Characteristics

The physical properties of nanomaterials are significantly different from the bulk materials, and the differences are not only quantitative but also qualitative.

Melting point depression: Gold nanoparticles with a diameter of 2 nm melt at around 300°C, whereas bulk gold melts at 1,064°C. This size-dependent melting point depression is due to the fact that there is a high percentage of surface atoms that have fewer neighbors with which to interact, thus having a lower cohesive energy. The property has implications in medicine on the stability of nanoparticles during sterilisation and storage.

Magnetic behaviour: below ~20 nm magnetic nanoparticles are superparamagnetic, meaning that the remanence is negligible in the absence of an external field but is high when an external field is applied (causing them to aggregate in biological fluids). This property allows

magnetic imaging with MRI, magnetic separation of labelled cells and magnetic hyperthermia (oscillating fields heat up magnetically responsive tumour-targeted nanoparticles).

Optical properties: As discussed in Section 2.1, the optical properties of metal nanoparticles (due to LSPR) and semiconductor quantum dots (due to quantum confinement) are size and shape dependent as opposed to bulk materials. These properties underlie the medical applications of nanoscale photonics.

2.17. Chemical Characteristics

High surface area to volume ratio and the surface defects, edge atoms, coordinatively unsaturated sites make nanomaterials far more chemically reactive than bulk materials. In contrast to bulk CeO_2 , cerium oxide nanoparticles (nanoceria) have enzyme-mimetic antioxidant activity, meaning they can act as catalytic scavengers of reactive oxygen species.

Surface functionalisation capacity: Nanomaterial surfaces have an unprecedented number of functional groups that can be chemically modified. Thiol-gold chemistry allows covalent coupling of targeting peptides, PEG chains and drug molecules to a gold nanoparticles surface with great precision. The attachment of pH-dependent gatekeeping molecules that control release of the drug from drug loaded pores whose opening is triggered by the pH decrease in the tumour microenvironment is a stimuli-responsive controlled release mechanism that is enabled by silanol chemistry on mesoporous silica nanoparticles.

P1: Protein corona formation: As soon as the nanoparticles enter into a biological fluid (blood, cerebrospinal fluid, interstitial fluid), plasma proteins start to adhere to their surface within seconds creating a ‘protein corona’. This corona changes the biological identity of the nanoparticle in fundamental ways, covering up engineered surface ligands, altering cell uptake pathways, and whether the particle is recognised as ‘self’ or ‘foreign’ by immune cells. Comprehending and controlling the composition of protein corona is now recognized as being essential to rational nanomedicine design and not simply ignored.

2.18. Biological Characteristics

The interactions between nanomaterials and cells, tissues, and the immune system are fundamentally different from small molecules, and thus influence the biological behaviour of nanomaterials.

Small molecules normally enter cells via passive diffusion of lipids across the cell membrane. Since the size of the nanoparticles is not suitable for direct diffusion through the membrane, they enter the cells by the endocytosis process, which depends on size, shape and surface chemistry and is mediated by clathrin (50-200 nm), caveolae (~60 nm), macropinocytosis (>500 nm) and phagocytosis (>1 μm). Knowledge of the endocytic pathway is vital, because it governs the intracellular trafficking of the nanoparticle — to the lysosome (the

acidic, degradative compartment) or out of the compartment to the cytoplasm (where it must be to deliver the gene).

Immune system interactions: Nanoparticles 100-1000 nm are internalized by macrophages and dendritic cells efficiently; this ability is used in the design of vaccine adjuvants (nanoparticle-antigen conjugates are more effective than soluble antigen at activating innate and adaptive immunity). PEGylated nanoparticles on the other hand, resist MPS uptake and consequently have prolonged circulation time, although repeated administration may lead to the induction of anti-PEG antibodies in some patients (accelerated blood clearance phenomenon).

Biodistribution and clearance: Organ biodistribution is controlled by nanoparticle size: <8 nm are excreted by the kidneys, 8-100 nm are systemic and can be filtered by the spleen, >200 nm are filtered in the spleen. Biodistribution is further modulated by surface charge (zeta potential) - anionic surface more tolerated, cationic more rapidly cleared by the liver and toxic to red blood cells. In clinical practice, biodegradable nanoparticles (PLGA, lipid based) are preferred as they are not permanently retained in organs, but rather are removed by the metabolic pathways (Table 4).

COMPREHENSIVE COMPARISON: Types of Nanomaterials

The following table is a structured comparison of the ten major types of nanomaterials used in medicine, and shows the size range, major examples, main clinical applications, and the specific physicochemical property that makes each nanomaterial type useful for medicine:

Table 4.

Types and Unique Features of Nanoparticles

Type	Size Range	Key Examples	Primary Applications	Unique Feature	References
Liposomes	50–500 nm	Doxil, Onivyde	Drug delivery, vaccines	Bilayer encapsulation, EPR effect	Barenholz 2012 (above). Wang-Gillam A et al. NAPOLI-1. *Lancet*. 2016;387:545–557
Polymeric NPs	10–1000 nm	PLGA, PLA, chitosan particles	Controlled drug release, gene delivery	Biodegradable, surface tuneable	Davis ME, Chen Z, Shin DM. Nanoparticle therapeutics. *Nat Rev Drug Discov*. 2008;7:771–782.
Gold NPs	2–150 nm	Citrate-capped Au, nanorods	Photothermal therapy, diagnostics	Surface plasmon resonance (SPR)	Eustis & El-Sayed 2006 (above).
Iron Oxide NPs	5–200 nm	SPION, Feraheme	MRI contrast, hyperthermia	Superparamagnetism	Lu et al. 2007 (above).
Carbon NTs	0.4–100 nm	SWCNT, MWCNT	Drug delivery, biosensors	Extraordinary tensile strength	Kam NWS et al. *PNAS*. 2005;102:11600–11605. Poland CA et al. Carbon nanotubes introduced into the abdominal cavity of mice show asbestos-like pathogenicity. *Nat Nanotechnol*. 2008;3:423–428.

Quantum Dots	2–20 nm	CdSe/ZnS, InP/ZnS	Bioimaging, diagnostics	Size-tuneable fluorescence	Michalet et al. 2005 (above).
Dendrimers	1–10 nm	PAMAM, PPI dendrimers	Gene/drug delivery, diagnostics	Precise molecular weight, branching	Tomalia DA et al. *Polym J*. 1985;17:117–132. Dufès C et al. *Adv Drug Deliv Rev*. 2005;57:2177–2202.
Nanofibers	1–1000 nm	Electrospun PLA, collagen NFs	Tissue engineering, wound healing	High surface area, ECM mimicry	Reneker DH, Chun I. Nanometre diameter fibres of polymer, produced by electrospinning. *Nanotechnology*. 1996;7:216–223.
Nanoshells	100–200 nm	Silica-gold nanoshells	Cancer photothermal therapy	Tuneable NIR absorption	Hirsch et al. 2003 (above).
Exosomes	30–150 nm	Cell-derived EVs	Drug delivery, biomarker detection	Natural cell-derived origin	Kalluri R, LeBleu VS. The biology, function, and biomedical applications of exosomes. *Science*. 2020;367\;:eaau6977.

3. Nanomedicine: concepts and principles

3.1. How nanomedicine works

3.2. The core operating principle

Essentially, nanomedicine functions through the design of a nanosized carrier system that accomplishes one or more of the following tasks: (1) encapsulates, adsorbs or conjugates a therapeutic or diagnostic payload; (2) protects the payload from premature degradation or clearance by the immune system during systemic circulation; (3) transports the payload to the desired anatomical site with spatial precision; and (4) releases the payload in a controlled fashion, optimised for therapeutic effects, at the desired site. The beauty of nanomedicine is that all four functions can be performed in one single engineered particle, something the traditional molecular pharmacology is unable to achieve.

To appreciate this, it is necessary to trace a nanoparticle from its point of production to its administration, its biodistribution, its binding to its target, its uptake into cells, and its further internalisation, until it releases its payload and the carrier is removed. There are distinct physicochemical and biological principles for each of these stages of the journey, and each stage has opportunities for engineering control and challenges that can adversely affect the therapeutic performance.

THE NANOPARTICLE JOURNEY: From Administration to Therapeutic Effect**STEP 1 Formulation and Surface Engineering**

Drug is encapsulated, conjugated to/adsorbed on/into the nanocarrier. Surface is designed to contain PEG (stealth coating), targeting ligands (antibodies, peptides, aptamers) and stimuli-responsive elements. The size, shape, charge and surface chemistry are specified.

STEP 2 Administration and Bloodstream Entry

Nanomedicines are mostly used intravenously (IV) to avoid intestinal barriers for absorption. Once injected, the nanoparticles come into contact with plasma proteins, red blood cells, platelets, and immune sentinels. In seconds, proteins in the serum start to adsorb to the surface of the nanoparticles (protein corona formation — see Section 3.2).

STEP 3 Circulation and Immune Evasion

PEGylated or zwitterionic nanoparticles are not opsonised or taken up by the MPS and have circulation half-lives of hours to days. Non-stealth particles are removed in minutes by liver Kupffer cells and splenic macrophages. Circulation time is a measure of probability of encounter and accumulation at the target site..

STEP 4 Passive Targeting via EPR Effect

Tumours and inflamed tissues develop leaky fenestrated blood vessels that have poor lymphatic drainage. The Enhanced Permeability and Retention (EPR) effect allows long circulating nanoparticles (usually 10-200 nm) to leak into these tissues and to remain longer in the tissues as the lymphatic clearance is impaired. This passive accumulation is the pharmacological mechanism of action of the first generation of nanomedicines.

STEP 5 Active Targeting and Surface Receptor Engagement

These are '2nd generation' nanoparticles that have targeting ligands (antibodies, folate, transferrin, RGD peptides, aptamers) attached to their surface which bind to receptors that are over-expressed on diseased cells. Active targeting alone does not lead to an increased tumour accumulation, but significantly increases the cellular internalisation of the nanoparticles after they enter the target tissue.

STEP 6 Cellular Internalisation by Endocytosis

Targeted or non-targeted nanoparticles are engulfed by the cells through endocytosis. The type of endocytosis (clathrin mediated, caveolae mediated, macropinocytosis) is determined by the size, surface charge and type of ligands of the nanoparticles. Internalized nanoparticles become trapped in endosomes, which develop into lysosomes (acidic, enzyme rich).

STEP 7 Endosomal Escape and Intracellular Trafficking

In gene therapy, CRISPR and siRNA, the nanoparticles must reach the cytoplasm or nucleus before they are degraded in the lysosomes. pH-responsive nanoparticles (ionisable lipids, poly-histidine polymers) swell or disrupt at endosomal pH (~5.5) to release payload to cytoplasm. Particles that do not need to escape from the endosome (most chemotherapeutics) release the drug in the lysosome.

STEP 8 Payload Release and Therapeutic Action

Payload Release and Therapeutic Action

It is released through (1) biodegradation of the carrier matrix (PLGA), (2) pH triggered disruption, (3) enzymatic cleavage, (4) redox activation (glutathione-sensitive disulfide bonds), or (5) photothermal/magnetic stimulation. The drug is released and binds to a molecular target, such as a receptor, enzyme, DNA strand or a protein, which results in a therapeutic effect.

3.3. Passive Targeting: The EPR Effect

The principle of tumour targeted nanomedicine is still the Enhanced Permeability and Retention (EPR) effect, which was first discovered by Hiroshi Maeda and Yasuhiro Matsumura in 1986. To facilitate rapid growth, solid tumours cause the development of new blood vessels by a

process called angiogenesis. The architecture of these tumour associated vessels is abnormal; the endothelial cells are not normally arranged and the intercellular junctions are widened, and there are fenestrations (pores) 200-2,000 nm in diameter, which is much larger than the 5-10 nm fenestrations in normal vessels. This hyperpermeability gives the ability for nanoparticles, which would not be able to penetrate healthy tissues, to extravasate within the interstitial space of the tumour.

At the same time, tumours have no functioning lymphatics in the core of the tumour to remove the macromolecules that have extravasated into the interstitium. This is because the combination of leaky vessels and impaired lymphatic drainage means that the nanoparticles can permeate into the tumour tissue while the drainage into the lymph nodes is impaired, leading to the net accumulation of nanoparticles in tumour tissue over time. The EPR effect is most pronounced from 30-200nm as particles below 8nm are renally cleared before they can accumulate, and particles above 400nm can't extravasate even through tumour vasculature.

CRITICAL PERSPECTIVE ON EPR

For 30 years the EPR effect has been the basis of passive tumour targeting. But it has been subjected to growing doubt over its clinical significance. A recent meta-analysis of 117 published nanoparticle research studies (Wilhelm et al., Nature Reviews Materials, 2016) indicated that in animal models, a median of just 0.7% of the administered dose of nanoparticles actually reach tumour tissues. Human tumours are more heterogeneous than murine models, and have different activity of EPR. This has led to a transition to active targeting, tumour microenvironment-responsiveness release and mixed strategies that pre-condition tumour vasculature to improve EPR.

3.4. Active Targeting Strategies

In active targeting, molecular specificity is added on to the spatial localisation provided by the EPR. It functions based on the display of targeting ligands on the surface of the particle with high affinity and selectivity for receptors that are often over-expressed on target cells, such as cancer cells, activated endothelium, macrophages or certain neurons. The principle is that active targeting does not necessarily lead to the delivery of more nanoparticle into the tumour (this is where EPR comes in), but much more of the tumour-localised nanoparticle is internalised by tumour cells and not by tumour-associated stromal cells in the interstitial space.

3.5. Antibody-Based Targeting

Monoclonal antibodies (mAbs) and antibody fragments (Fab, scFv, nanobodies) are the gold standard targeting ligands for their unrivalled binding specificity and affinity. Anti-HER2 antibodies and trastuzumab conjugates (nanoparticles) selectively target the breast cancer cells that have the HER2 receptor over-expressed. The antibody-drug conjugate (ADC) ado-trastuzumab emtansine (T-DM1, Kadcyla) is a mechanistically single molecule ADC — an antibody that binds to the HER2 receptor followed by lysosomal uptake and release of the cytotoxic agent after linker degradation. Oncology is the fastest-growing drug class, with ADCs.

3.6. Folate Receptor Targeting

Folate receptor alpha (FRa) is a receptor that is overexpressed on many epithelial cancers (ovarian, lung, breast, endometrial) but is not widely expressed in normal tissues. Folic acid, or vitamin B9 is a small molecule that binds to FRa with picomolar affinity, and can be attached to the surface of nanoparticles without appreciable changes in pharmacokinetics. Liposomes, dendrimers and polymeric nanoparticles can be modified with folate to target and enter the cells specifically, in the case of FRa+ tumour cells, a targeting approach that is now in clinical trials for ovarian cancer.

3.7. Transferrin and Glucose Transporter Targeting

Cancer cells and neurons that rapidly divide have significantly increased demands for iron (through the transferrin receptor, TfR1) and glucose (through the GLUT transporters). The TfR1-mediated transcytosis is also used for tumour targeting as well as for crossing the blood–brain barrier, where the expression of TfR1 is very high on brain capillary endothelial cells. Glucose coated nanoparticles take advantage of the Warburg effect: preferential uptake of aerobic glycolysis by cancer cells, which can be achieved by binding to the GLUT1 transporters – which is also a method used for imaging (18F-FDG PET scanning) and drug delivery.

3.8. Stimuli-Responsive Drug Release

The ability to engineer nanocarriers to deliver their payload at targeted disease sites in response to specific disease-related physicochemical signals—with maximal local drug concentration and minimal systemic—is one of nanomedicine’s most promising features. The precision nanotherapy conceptual edge of these stimulatable systems is referred to as ‘smart’ nanoparticles (Table 5).

3.9. Interaction of nanomaterials with biological systems

3.10. The Nano-bio interface: a dynamic and evolving boundary

Once an engineered nanoparticle is introduced into a biological system, it isn’t a known chemical compound. Rather, it immediately initiates a complicated and dynamic set of interactions with the outside biological environment (plasma proteins, immune cells, extracellular matrix, cell surface receptors, intracellular organelles, and finally with the systemic organs of elimination). These interactions together impart the biological identity of a nanoparticle, which can be very different from its engineered physicochemical identity. As the interface between the nanoparticle surface and the biological molecules surrounding the particle continuously evolves, it is crucial

to understand the behaviour of the nano-bio interface to predict in vivo behaviour and design nanomedicines that behave as desired in the complex human body.

Table 5.

Endogenous vs exogenous stimuli

Endogenous Stimuli (Disease-Driven Signals) • pH response: Tumour interstitium pH ~6.5-7.0; endosomal pH ~5.0-5.5 trigger protonation/swelling of pH-labile nanocarriers • Glutathione (GSH): Cytoplasmic GSH concentration 1,000x higher than extracellular — cleaves disulfide bonds in redox-sensitive NPs • Enzyme response: Matrix metalloproteinases (MMPs) overexpressed in tumour stroma cleave peptide linkers releasing drug locally • Hypoxia: Nitroreductases in hypoxic tumour cores reduce azo-bonds, triggering drug release • Temperature: Mild hyperthermia (40-42 C) in tumour melts thermosensitive liposomes (ThermoDox clinical stage)	Exogenous Stimuli (Physician-Controlled Signals) • Near-infrared (NIR) light: Photothermal conversion in gold nanorods/nanoshells disrupts thermosensitive carrier shells on laser irradiation • Ultrasound: Acoustic cavitation disrupts microbubble-drug conjugates, releasing drug in insonated tissue • Magnetic field: Alternating magnetic fields generate local heat in SPION-loaded nanoparticles (magnetic hyperthermia) • X-ray / Ionising radiation: Radiation-responsive polymer linkers cleave in irradiated tumour fields • Near-field electric stimulation: Conductive nanoparticles in implantable scaffolds release drug on electrical pulse
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3.11. The Protein corona: biological identity of nanoparticles

Once a nanoparticle comes into contact with blood or any biological fluid, proteins quickly cover the surface of the nanoparticle. This protein adsorption process creates the protein corona, which significantly alters the surface chemistry, hydrodynamic size and colloidal stability of the nanoparticles. The protein corona is not a static flat layer, but rather a layer that changes with time consisting of a hard corona of proteins that are tightly bound which exchange with the surface slowly and a soft corona of proteins that are loosely bound and exchange with free proteins in solution quickly.

The nature of the protein corona will vary with size and shape of the particle, its surface chemistry, and the type of biological fluid involved. The major plasma proteins in human plasma are the corona proteins albumin, the most abundant plasma protein, fibrinogen, complement proteins (C3, C4, Factor H), immunoglobulins, and apolipoproteins (e.g., ApoE, ApoA-I, ApoA-IV). Each of these proteins has a biological significance: complement proteins are involved in the phagocytic destruction of the nanoparticle; the adsorption of ApoE may have a paradoxical effect on brain uptake, because it elicits the LDL receptor-mediated transcytosis; the adsorption of fibrinogen activates platelets and starts the coagulation cascades.

The protein corona is of great importance in the design of nanomedicine. The active targeting may be lost due to steric occlusion and/or conformational changes of ligands (antibodies, peptides) displayed on the surface of the nanoparticle by the corona. On the other

hand, proteins that have been adsorbed from the corona (especially ApoE) can be an unwanted targeting ligand, directing nanoparticles to tissues not targeted by design. Therefore, engineering of surfaces that resist non-specific protein adsorption, such as via PEGylation, zwitterionic coatings, biomimetic lipid coatings, or cell membrane cloaking, is a key challenge of current nanomedicine formulation science.

PROTEIN CORONA AND CLINICAL TRANSLATION

One of the main challenges in moving to animal models and human trials with nanoparticles that are impressive in cell culture is that protein corona effects are not taken into consideration. The corona phenomenon is completely missing in in vitro experiments carried out in serum-free media or in simplified buffers. The field now realises that such nanoparticles need to be characterized in the appropriate biological medium (plasma, lining fluid from the lungs, cerebrospinal fluid) to produce preclinically relevant data. The deliberate recruitment of beneficial coronas or minimisation of the deleterious ones is an active research frontier, known as corona-informed design of nanoparticles.

3.12. Cellular Interactions: Uptake, Trafficking, and Intracellular Fate

3.13. Endocytic Uptake Pathways

Nanoparticles have to cross a selective barrier in order to enter cells. Compared with small molecules, which can pass through the lipid bilayer, the entry of nanoparticles into the cell occurs almost exclusively through endocytosis, which is a cell active and energy-consuming process involving the deformation of the cell membrane to engulf the extracellular material. The primary route of endocytosis is size, surface charge, ligand type, and cell type of the nanoparticles:

Clathrin-mediated endocytosis (CME): Most frequent pathway for 50-200 nm sized nanoparticles that are targeted to cell surface receptors (such as transferrin, folate, LDL). Clathrin-coated pits are formed at the membrane, invaginate and pinch-off to become clathrin-coated vesicles which mature to early endosomes > late endosomes > lysosomes. Most chemotherapeutics escape the lysosome and can be released, while nucleic acids need to escape.

Caveolae-mediated endocytosis: Flask-shaped, cholesterol-rich invaginations (~60 nm) that are abundant in endothelial cells and smooth muscle cells. Caveolar uptake is not in the lysosomal compartment (non-acidic, non-degradative caveosomes), hence it is attractive for the transfer of pH-sensitive payloads. Targeted by albumin-bound nanoparticles (nab-paclitaxel, Abraxane) through caveolae transcytosis via SPARC.

Macropinocytosis: Ruffling of the membrane, forming large irregular vacuoles (0.2-5 μ m); it is a non-selective bulk uptake process that is stimulated by growth factors. Prominent in macrophages and in some cancer cells that have a constitutively active Ras signalling pathway. Permits the absorption of large nanoparticles and nanoparticle aggregates.

Phagocytosis: Opsonised particles $>0.5 \mu\text{m}$ are taken up by specialised cells, called professional phagocytes, phagocytes (macrophages, neutrophils, dendritic cells). Phagocytosis is a clearance mechanism for most therapeutic nanoparticles, but is intentionally utilized for vaccine delivery (antigen loaded nanoparticles taken up by macrophages and dendritic cells activate adaptive immunity).

3.14. Endosomal Escape: The Intracellular Bottleneck

The most important intracellular target for nucleic acid nanomedicines (siRNA, mRNA, CRISPR/Cas9) is the cytoplasm. Once the clathrin-mediated endocytosis is completed, the nanoparticles are contained in endosomes, which will gradually reduce the pH (down from 6.5 to 5.0), and subsequently fuse with lysosomes where the exposed nucleic acids would be degraded by nucleases. To escape from the endosome to the cytoplasm prior to endosome to lysosome fusion is essential. Current strategies include:

Ionisable lipids (for COVID-19 LNP vaccines): When protonated at endosomal pH, ionisable lipids cause non-bilayer lipid phases (inverted hexagonal phase) which leads to the release of the cargo into the cytoplasm.

Poly-L-histidine (PEI): These polymers have a high buffering capacity and bind protons that are pumped to the endosome, thus inhibiting the acidification of the endosome, which causes a continued influx of protons leading to the osmotic swelling and rupture of the membrane.

Fusogenic peptides: pH activated peptides (GALA, influenza HA2) change to alpha-helical structures at low pH and directly perforate endosomal membranes.

Light activation of photosensitisers in the endosomal membrane (photochemical internalisation, PCI): Localised ROS formation in the endosome after laser activation selectively disrupts the endosome, allowing co-encapsulated nucleic acids to be released.

3.15. Tissue-Level and Systemic Interactions

At the tissue and organ level, the interaction between nanoparticles and biological systems will affect the therapeutic efficacy and safety of the nanoparticles. The knowledge of these systemic interactions is crucial to move nanomedicine from cell culture and animal models to clinical application.

Mononuclear phagocyte system (MPS): The primary system of clearance of nanoparticles from the body is the mononuclear phagocyte system (MPS) including liver (Kupffer cells), spleen (marginal zone macrophages), bone marrow and lymph nodes. In non-targeted IV administration, the Kupffer cells take up up to 80-90% of the nanoparticles. In order to prevent the uptake of MPS, the strategies have been introduced such as PEGylation, CD47 ('don't eat

me' signal) coating and biomimetic cell membrane camouflage (erythrocyte membrane cloaked nanoparticles).

Blood-brain barrier (BBB): BBB is composed of tight junction connected brain capillary endothelial cells, astrocyte endfeet and pericytes, and prevents the passage of >98% of all therapeutic molecules. Nanoparticles can be designed to enter the BBB through receptor-mediated transcytosis (transferrin receptor, LRP1, P selectin) or cell-mediated transport (macrophage Trojan horse). This provides opportunities for delivery of drugs that are not available in the mainstream of pharmacotherapy to reach brain tumours, Alzheimer's disease, Parkinson's disease and stroke.

Complement activation and hypersensitivity: Activation of the complement pathway; Intravenously introduced nanoparticles activate complement pathway via the classical (antibody mediated), the alternative or the lectin pathway. The occurrence of acute cardiopulmonary distress reactions as a result of complement activation-related pseudoallergy (CARPA) is clinically seen with liposomal doxorubicin, Cremophor EL-based paclitaxel, and PEGylated nanoparticles. There are treatments available to reduce CARPA risk: pre-medication with corticosteroids and antihistamines, as well as rate-controlled infusion protocols.

The following Table 6 summarises the principal nano-bio interaction types, mechanisms, and clinical implications:

Table 6.

Principle nano-bio interaction types, mechanisms and clinical implications

Interaction Type	Biological Level	Mechanism	Outcome / Implication	References
Protein corona	Molecular / plasma	Rapid adsorption of serum proteins (albumin, fibrinogen, ApoE) onto NP surface	Altered cell uptake, immune evasion, targeting ligand masking	Monopoli MP et al. Biomolecular coronas provide the biological identity of nanosized materials. <i>*Nat Nanotechnol*</i> . 2012;7:779–786. Walkey CD, Chan WCW. <i>*Chem Soc Rev*</i> . 2012;41:2780–2799.
Opsonisation	Immune system	Complement proteins and immunoglobulins coat NP surface marking for destruction	Accelerated clearance by macrophages (MPS)	Rodriguez PL et al. Minimal “self” peptides that inhibit phagocytic clearance. <i>*Science*</i> . 2013;339:971–975. Suk JS et al. PEGylation as a strategy for improving nanoparticle-based drug delivery. <i>*Adv Drug Deliv Rev*</i> . 2016;99:28–51.
Endocytosis	Cellular	Clathrin/caveolae-mediated internalisation; size- and charge-dependent pathway	Controls intracellular delivery efficiency and fate	Conner SD, Schmid SL. <i>*Nature*</i> . 2003;422:37–44. Rejman J et al. <i>*Biochem J*</i> . 2004;377:159–169. Chithrani BD et al. <i>*Nano Lett*</i> . 2006;6:662–668.

Endosomal escape	Subcellular	pH-responsive or membrane-disruptive NPs rupture endosomal membrane	Required for cytoplasmic/nuclear delivery of nucleic acids	Hou et al. 2021 (above). Cullis PR, Hope MJ. <i>*Mol Ther*</i> . 2017;25:1467–1475.
ROS generation	Cellular / tissue	Metal NPs (TiO ₂ , ZnO) generate reactive oxygen species under stimulation	Oxidative stress in target cells — exploited in PDT	Pante N, Kann M. <i>*Mol Biol Cell*</i> . 2002;13:425–434.
Cytoskeletal interaction	Cytoplasmic	NPs interact with actin, tubulin networks affecting intracellular transport	Affects trafficking to nucleus/organelles	Palomäki J et al. <i>*ACS Nano*</i> . 2011;5:6861–6870.
Nuclear entry	Nuclear	NPs < ~40 nm can passively enter nucleus through nuclear pores	Enables direct nuclear drug delivery, epigenetic modulation	Szebeni J. Complement activation-related pseudoallergy. <i>*Toxicology*</i> . 2005;216:106–121.
Inflammation induction	Tissue / systemic	NLRP3 inflammasome activation by long MWCNTs; complement activation	Pulmonary inflammation; systemic cytokine release	Choi HS et al. <i>*Nat Biotechnol*</i> . 2007;25:1165–1170.

3.16. Targeted vs. conventional therapies

3.17. The Limitations of Conventional Pharmacotherapy

Small molecule drugs, that are prepared by conventional organic chemistry, have been a cornerstone of clinical medicine for more than one hundred years. It has done amazing things: antibiotics revolutionised infectious diseases, statins have revolutionised cardiovascular prevention and kinase inhibitors have dramatically lengthened survival in many cancers. However, there are fundamental limitations that are intrinsic to conventional pharmacotherapy that are ideally suited to the capabilities of nanotechnology.

The therapeutic index, defined as the ratio of the dose that is toxic to the dose that is effective, is the main pharmacological problem of traditional medicine. In the case of very active agents against cells that are rapidly dividing (chemotherapy), the therapeutic window may be very small; that is, the dose used to kill cancer cells is close to the dose that also damages healthy bone marrow, gastrointestinal epithelium and cardiac muscle cells. Both harmful effects cause dose reduction and thus a reduction in effectiveness, necessitate hospitalisation, depress quality of life, and restrict therapeutic benefit. Conventional drugs are also not “spatial smart”: Once they are absorbed into the bloodstream, a drug will spread throughout the body based on its physical chemistry, reaching all of a person’s tissues, whether diseased or not. A small percentage of the dose actually gets to the target, the rest causes collateral damage.

3.18. How Targeted Nanomedicine Overcomes These Limitations

The spatio-temporal and biological control features that small molecules lack are added into the pharmacological equation through targeted nanomedicine. Instead of evenly distributed throughout the body, a targeted nanoparticle is directed to a specific site in the body, binds a specific cell-surface receptor, enters a specific cell by a specific endocytic pathway and releases its payload within the cell, while maintaining a surface chemistry that limits detection and clearance by the immune system. This is not just a step up from the old therapies; it's a whole new paradigm in the relationship pharmacology has with biology.

The differences between conventional therapy and targeted nanomedicine are multidimensional and are evaluated by the following comparison of their clinical and pharmacological parameters (Table 7):

Table 7.

Conventional therapy and targeted nanomedicine

Parameter	Conventional Therapy	Nanomedicine / Targeted Therapy	References
Drug specificity	Low — systemic distribution to all tissues	High — ligand-directed accumulation at disease site	
Therapeutic index	Narrow — effective and toxic doses are close	Wide — reduced off-target toxicity, higher safe dose	Davis et al. 2008 (above). Mitchell MJ et al. Engineering precision nanoparticles for drug delivery. <i>*Nat Rev Drug Discov*</i> . 2021;20:101–124
Route of administration	Oral or IV; absorption-dependent	IV nanoparticles bypass absorption barriers	Davis et al. 2008 (above). Mitchell MJ et al. Engineering precision nanoparticles for drug delivery. <i>*Nat Rev Drug Discov*</i> . 2021;20:101–124
Drug payload protection	Unprotected; rapid plasma degradation	Nanoencapsulation shields from enzymatic degradation	Davis et al. 2008 (above). Mitchell MJ et al. Engineering precision nanoparticles for drug delivery. <i>*Nat Rev Drug Discov*</i> . 2021;20:101–124
Release profile	Immediate; high peak — rapid clearance	Controlled / sustained / stimuli-responsive release	Davis et al. 2008 (above). Mitchell MJ et al. Engineering precision nanoparticles for drug delivery. <i>*Nat Rev Drug Discov*</i> . 2021;20:101–124
Drug resistance (cancer)	Significant; membrane efflux pumps active	Endocytic uptake bypasses P-glycoprotein pumps	Davis et al. 2008 (above). Mitchell MJ et al. Engineering precision nanoparticles for drug delivery. <i>*Nat Rev Drug Discov*</i> . 2021;20:101–124.
Imaging capability	Separate diagnostic agent required	Theranostic nanoplateforms combine therapy + imaging	Wilhelm S et al. Analysis of nanoparticle delivery to tumours. <i>*Nat Rev Mater*</i> . 2016;1:16014. Lammers T et al. <i>*J Control Release*</i> . 2012;161:175–187.
Blood-brain barrier	Most drugs excluded; very few CNS agents	Engineered NPs with BBB-targeting ligands can cross	Gradishar WJ et al. <i>*J Clin Oncol*</i> . 2005;23:7794–7803. Von Hoff DD et al. <i>*N Engl J Med*</i> . 2013;369:1691–1703.

Dose frequency	High — short half-life requires frequent dosing	Reduced — long-circulating NPs extend dosing intervals	Adams D et al. *N Engl J Med*. 2018;379:11–21.
Gene/nucleic acid delivery	Not applicable — nucleic acids degraded in plasma	LNPs and polymeric carriers protect and deliver siRNA, mRNA, CRISPR	Ray KK et al. (ORION-10/11). *N Engl J Med*. 2020;382:1507–1519.
Manufacturing complexity	Established chemical synthesis	Complex multi-step formulation; quality control challenges	Verma S et al. (EMILIA). *N Engl J Med*. 2012;367:1783–1791.
Regulatory pathway	Well-defined small molecule framework	Evolving nanotechnology-specific guidance (FDA, EMA)	FDA. *Drug Products, Including Biological Products, that Contain Nanomaterials: Guidance for Industry*. 2022

Clinical Evidence: Where Has Targeted Nanomedicine Delivered?

The clinical evidence base for targeted nanomedicine is still developing and some of the most significant approvals have shown that people benefit in the real world:

Nab-paclitaxel (Abraxane, FDA 2005): Albumin-bound paclitaxel nanoparticles (130 nm) results in dramatically higher intratumoural drug concentrations compared to the Cremophor EL formulations, eliminate hypersensitivity reactions associated with paclitaxel, and improve survival in metastatic pancreatic, breast and NSCLC; the first broad oncological approval of an active-targeting (SPARC/albumin receptor) nanomedicine.

Inclisiran (Leqvio, FDA/EMA 2021): Leqvio (inclisiran) is the first approved cardio-therapeutic RNAi agent targeted to PCSK9 mRNA in hepatocytes through the asialoglycoprotein receptor (ASGR). Targeted nucleic acid nanomedicine can be given twice a year subcutaneously and brings down LDL-C by ~50%, showing that in some patients, it is possible to replace day-to-day oral statin treatment.

Patisiran (Onpattro, FDA 2018): LNP-siRNA targeting transthyretin (TTR) mRNA in hepatocytes — First FDA-approved RNAi medicine. Produces >80% knockdown of pathological TTR protein, stopping and reversing the development of polyneuropathy in hereditary transthyretin amyloidosis, a fatal disease without previously known curative therapy. Validates new platform for delivery of nucleic acids to the clinic.

mRNA-LNP COVID-19 vaccines (Comirnaty, Spikevax, 2020-2021): LNP-mRNA vaccines proved to be 90-95% effective against severe COVID-19, a scale never tested before, and have introduced LNP nanomedicine as a platform technology for COVID-19 vaccines, gene therapy, and cancer vaccines. No previous vaccine development was as fast or effective as conventional vaccine technology.

3.19. Limitations and Challenges of Targeted Nanomedicine

To be honest about targeted nanomedicine, one must admit that it has only a few accomplishments as well as its shortcomings. In oncology, the promise of precision molecular

targeting has only partially been met, in the sense that it has not automatically translated to clinical superiority over traditional treatments:

Heterogeneity of the EPR effect: EPR effect varies from one tumour type to another, between patients, and between different tumour vascularisation states. The modest, variable improvement over systemic distribution seen in the clinic is due to passive EPR-mediated accumulation.

Nanomedicines offer a longer and more complex manufacturing process than small molecules, and have tight size distribution, reproducible surface chemistry, and reproducible drug loading requirements at clinical scale. Clinical translation has encountered many difficulties, including scale-up failures and batch to batch variability.

- Regulatory uncertainty: Nanomedicines do not have any known pharmacokinetic frameworks like small molecules, and therefore need extensive physicochemical characterization at various scales. The regulatory science for nanomedicines is still in its infancy, and uncertainty exists for sponsors.

Cost and access: approved nanomedicines are often significantly more expensive than conventional medicines, leading to difficulties in accessing and reimbursing them in resource-constrained health care systems.

Active targeting does not necessarily mean better: Several Phase III trials on nanoparticles with active targeting compared with non-targeted nanoparticles have shown no benefit in terms of survival, because the targeting ligands are masked by the protein corona in vivo.

THE ROAD AHEAD

Targeted nanomedicine is on a turning point. First generation nanomedicines based on EPR have proven to be successful in specific conditions and have been proof-of-concept in the clinic. Active, targeted platforms are getting incremental but significant enhancements in the second generation. Future directions are third-generation stimuli-responsive, biomimetic, and computationally designed nanoplatforms – incorporating artificial intelligence-guided formulation optimisation, patient-specific protein corona profiling, and immune-engineered surfaces. The future of nanomedicine will be shaped by the integration of synthetic biology, precision oncology, and digital health.

4. Diagnostic Applications

The healthcare sector is witnessing rapid growth in the adoption of lab-on-a-chip (LOC) and nanosensor technologies because of their ability to transform diagnostics and drug delivery. The global LOC market is expected to expand at a fast pace owing to the increasing applications in drug development and healthcare, such as point-of-care (POC) devices, drug discovery, and in vitro diagnostic (IVD) tools including pregnancy kit and glucometer kits. POC diagnostics are the largest segment of the global microfluidics market, which was estimated at \$762 million in 2018.

Nanotechnology is really good at helping us find diseases on. We have these things called gold nanocages and immuno-gold nanocages that are very good at showing us where the bad cells are in our body. They help us see the cancer cells. Get rid of them using special light. This makes it easier to find and watch the cancer cells. When we combine these materials with special tiny machines we can make devices that can diagnose diseases very quickly and accurately. These devices are very small. Can fit on a tiny chip. We call them biosensor-on-chip systems. They are good for finding diseases like cancer, infections and problems with our brains. Nanotechnology and these tiny machines work together to make these devices very good, at what they do.

The use of materials, small fluid systems and special recognition methods has made it possible to detect very small amounts of biomarkers with high accuracy. This improves our ability to diagnose diseases early. Wearable sensors that use materials, like graphene, carbon nanotubes and gold particles are helping to track our health continuously. This supports healthcare and allows for early action to be taken.

4.1. Nano-based Imaging Techniques

Nanotechnology has really changed imaging. It has made imaging better by making the pictures clearer and more detailed. This is an improvement over older methods like MRI, CT, PET and optical imaging. Traditional imaging methods often miss diseases when they are just starting. They have trouble seeing what is going on at the level of molecules and cells. When we add special tiny materials like gold nanoparticles, quantum dots, iron oxide nanoparticles and liposomal contrast agents the pictures get even clearer. This helps doctors see what is going on at the level.

Nanotechnology has made it possible to detect diseases early. It has also made it possible to combine diagnosis and treatment into one system. This means that doctors can use the system to figure out what is wrong, with someone and to treat the problem. Nanotechnology and medical imaging are really good together (Figure 1). They help doctors see what is going on and make people better.

Nanotechnology in imaging bridges the gap between anatomical and functional visualization. By targeting specific biomarkers or tissues, nanoparticles improve the accuracy of diagnostic readings, reduce background noise, and allow simultaneous multimodal imaging. Such improvements are particularly valuable for diseases where early detection is critical, including cancers, cardiovascular disorders, and neurodegenerative conditions.

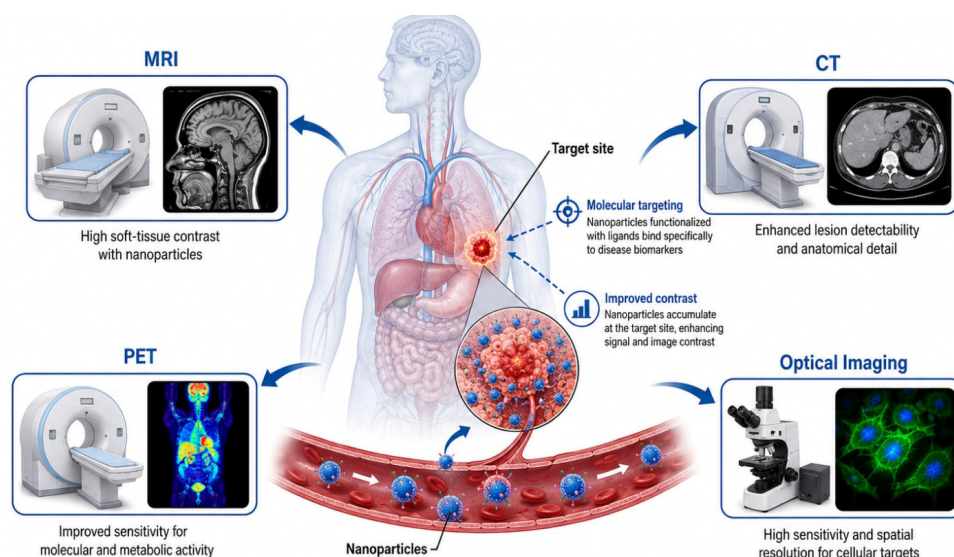


Figure 1. Nano-based imaging techniques

4.2. Enhancement of traditional imaging with nanotechnology

Nanomaterials enhance conventional imaging in multiple ways. Gold nanoparticles provide enhanced contrast in optical imaging through their tunable surface plasmon resonance, which allows highly sensitive detection of biomarkers and enables multiplexed imaging of several molecular targets simultaneously. Quantum dots offer narrow, tunable emission spectra for fluorescent imaging, allowing for precise localization of molecules within tissues. Iron oxide nanoparticles serve as T2-weighted MRI contrast agents, improving sensitivity and enabling visualization of small lesions, vascular structures, and cellular-level abnormalities.

Hybrid nanoparticles combining optical and magnetic properties facilitate multimodal imaging, integrating MRI, CT, PET, and optical imaging into a single platform. This integration allows clinicians to obtain both structural and functional information in a single diagnostic session^{15,16} however fears over long term stability of polymer coated particles have arisen. Gold coating IONPs results in particles of increased stability and robustness. The unique properties of both the iron oxide (magnetic). Furthermore, nanoparticles can be functionalized with antibodies, peptides, or aptamers to target specific tissues or cellular receptors, enabling molecular-level imaging that surpasses the capabilities of traditional contrast agents.

Targeted nanocarriers also enable theranostic applications, where the same nanoparticle serves both as an imaging agent and a therapeutic vehicle. For example, gold-iron oxide core-shell nanoparticles provide optical contrast while simultaneously carrying chemotherapeutic agents, enabling real-time monitoring of drug delivery.

4.3. Applications in early diagnosis

Nano-based imaging plays a crucial role in early detection of cancer, cardiovascular diseases, and neurodegenerative disorders. In oncology, quantum dots and gold nanoparticles allow highly sensitive detection of tumor-associated antigens and low-abundance biomarkers, which may be undetectable using standard imaging techniques. Photoacoustic imaging with gold nanorods offers deep tissue visualization of angiogenesis and tumor microenvironments, enabling clinicians to detect malignancies before they progress to advanced stages.

In cardiovascular medicine, nanoparticles conjugated with targeting ligands can detect early markers of atherosclerosis or myocardial infarction. For example, iron oxide nanoparticles enhance MRI detection of vascular plaques and inflammatory biomarkers, which can improve prognosis by allowing early intervention.

For neurodegenerative disorders, superparamagnetic iron oxide nanoparticles (SPIONs) and fluorescent quantum dots can cross the blood-brain barrier, providing enhanced visualization of amyloid-beta plaques in Alzheimer's disease or Lewy bodies in Parkinson's disease. This enables earlier diagnosis and monitoring of disease progression. Moreover, multimodal imaging platforms allow combination of MRI, PET, and optical imaging, yielding complementary anatomical, functional, and molecular information from a single session.

4.4. Advantages and challenges of nano-based imaging

4.5. Advantages of nano-based imaging

High Sensitivity and Specificity: Nanoparticles amplify signals from low-abundance biomarkers, improving the detection of subtle pathological changes.

Targeted and Molecular Imaging: Ligand-functionalized nanoparticles accumulate specifically in diseased tissues, increasing signal contrast while reducing background noise.

Multimodal Imaging: Integration of multiple imaging modalities in one nanoparticle enables simultaneous structural and functional assessment.

Theranostic Potential: Nanoparticles can combine diagnostic and therapeutic functions, allowing clinicians to track therapy delivery and efficacy in real time.

4.6. Challenges of Nano-based Imaging

Biocompatibility and Toxicity: Some nanoparticles may trigger immune responses, oxidative stress, or off-target accumulation, raising safety concerns.

In Vivo Stability and Clearance: Maintaining nanoparticle integrity in the bloodstream while ensuring efficient excretion remains challenging.

Regulatory Hurdles: Approval for multimodal nanomedicines requires extensive preclinical and clinical validation, slowing clinical translation.

Manufacturing and Scalability: Producing nanoparticles with uniform size, shape, surface chemistry, and functionalization for reproducible imaging results is technically demanding.

4.7. Biosensors and Lab-on-a-Chip Devices

Recent advances in nanotechnology have greatly improved the sensitivity and specificity of biosensors (Figure 3) and lab-on-a-chip (LOC) (Figure 4) platforms, enabling rapid, precise, and miniaturized diagnostic systems. These technologies integrate nanoscale materials with microfluidics and biorecognition elements, allowing the detection of biomarkers at extremely low concentrations in body fluids such as blood, saliva, and interstitial fluid. By combining microfluidics with nanosensors, lab-on-a-chip systems offer point-of-care (POC) diagnostics that are faster, more accurate, and portable compared to traditional laboratory tests.

4.8. Nano-enabled Biosensors: Enhancing Sensitivity

Nanomaterials significantly enhance the performance of biosensors. Graphene, carbon nanotubes, gold nanoparticles, and quantum dots are widely used to increase surface area, improve electron transfer, and enhance signal transduction. Gold nanocages and immuno-gold nanocages offer high optical contrast for fluorescence-based detection, enabling the identification of tumor-associated antigens at picomolar levels.

The incorporation of nanomaterials allows biosensors to detect weak biochemical signals, including enzymatic activity, cytokines, nucleic acids, and low-abundance proteins, making them highly suitable for early-stage disease diagnosis. Additionally, nanomaterials provide multiplexing capabilities, allowing simultaneous detection of multiple biomarkers from a single sample, which is particularly useful for complex diseases such as cancer, cardiovascular disorders, and neurodegenerative diseases.

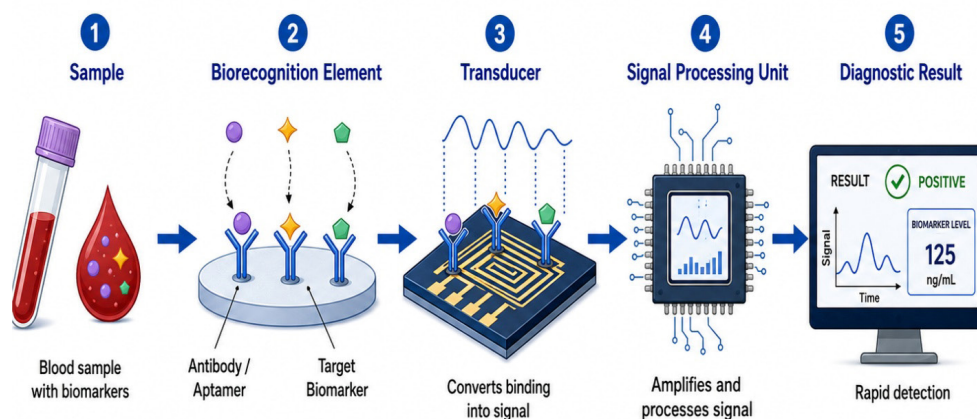


Figure 2. Biosensor working principle.

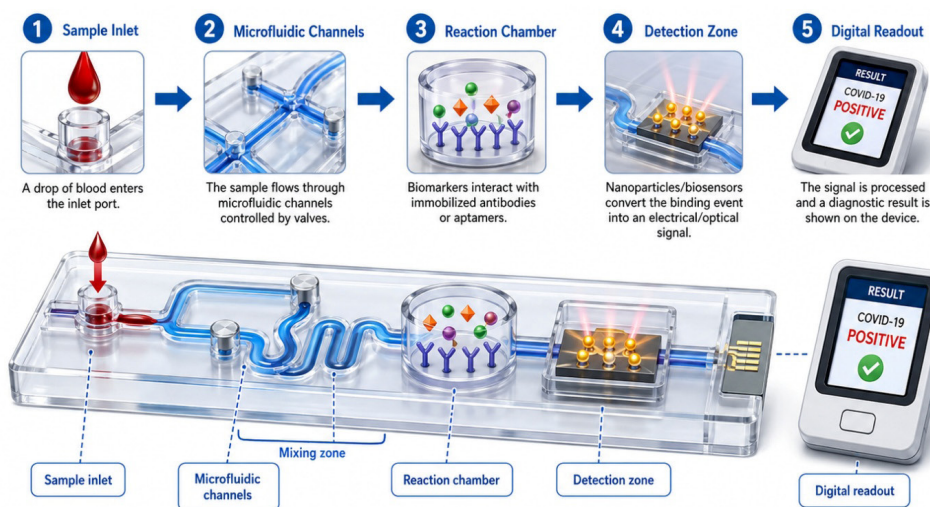


Figure 3. Lab-on-a-chip device.

4.9. The Role of Lab-on-a-Chip Devices

Lab-on-a-chip (LOC) platforms integrate microfluidics, nanosensors, and detection units into compact devices capable of performing complex biochemical assays on a microscale. LOC systems reduce sample and reagent volumes, minimize assay time, and enable automation for high-throughput analysis.

Typically, LOC devices consist of multiple modules: an inlet for sample introduction, a reaction chamber for biomolecular interactions, a detection unit coupled to nanosensors, and a data processing unit for signal conversion. LOC devices may use passive, active, or hybrid fluidic

mechanisms to control sample flow, enabling precise handling of picoliter to microliter volumes (Figure 2).

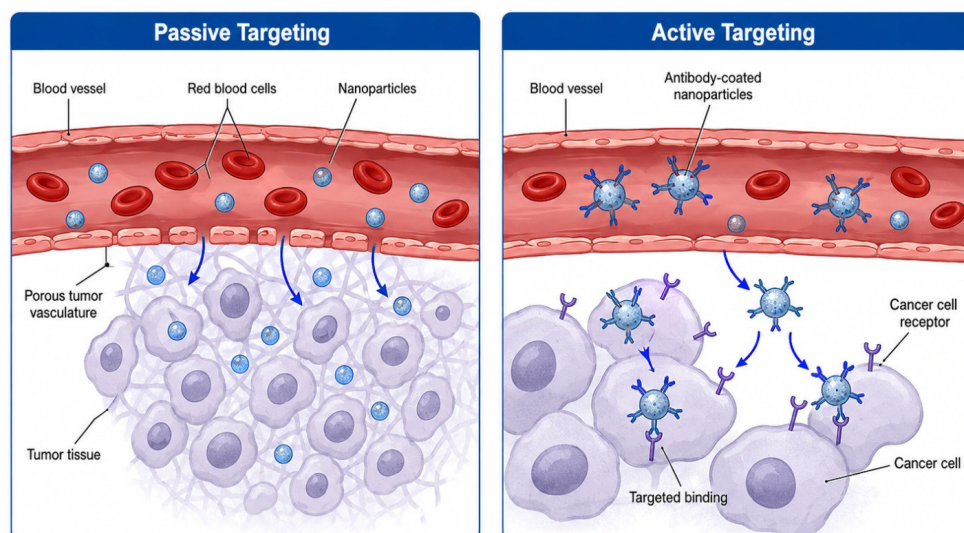


Figure 4. Nanoparticle contrast agents: passive and active targeting.

Integration of nanomaterials within LOC platforms enhances sensitivity and lowers detection limits. For example, microfluidic chips functionalized with gold nanoparticles or graphene sheets improve signal amplification, allowing detection of low-abundance disease biomarkers in POC settings. Additionally, these platforms enable multiplexed detection of multiple targets in a single run, which is crucial for early diagnosis of multifactorial diseases such as cancer and neurodegeneration for actuation of bulk motion of emulsion. The experiments involve immersing two vertical parallel electrodes in an oil-in-water emulsion and applying AC fields (15–40Vp-p; 5–500Hz).

4.10. Clinical Applications of Biosensors and Lab-on-a-Chip Devices

Nano-enabled biosensors and LOC devices have demonstrated significant clinical potential. In oncology, immuno-gold nanocage-based sensors detect tumor antigens with high specificity, enabling early detection and therapy monitoring. In infectious disease diagnostics, quantum-dot-based biosensors allow rapid detection of viral RNA and bacterial DNA, facilitating early intervention in outbreaks such as COVID-19 and influenza.

For neurodegenerative diseases, LOC platforms integrated with SPIONs and quantum dots improve the detection of amyloid-beta plaques and tau proteins, enabling earlier diagnosis of Alzheimer's and Parkinson's diseases. In cardiovascular medicine, graphene-based nanosensors in microfluidic chips detect biomarkers such as troponin and B-type natriuretic peptide (BNP), enabling rapid diagnosis of myocardial infarction and heart failure.

Beyond diagnostics, LOC devices support drug screening and personalized medicine. By incorporating patient-derived cells, microfluidic platforms allow real-time testing of therapeutic responses, optimizing drug dosing and treatment selection. This combination of rapid detection, miniaturization, and multiplexing is expected to bring laboratory-level analysis to bedside diagnostics, particularly in resource-limited settings.

4.11. Early disease detection system

Detecting diseases at their earliest stages is vital for successful management, increasing the chances of survival, and cutting down treatment costs. Unfortunately, traditional diagnostic techniques are unable to detect diseases when they are still at an early stage, thus making treatment difficult. Nanotechnology is one area that has proved very useful in diagnosing diseases at their earliest stages using ultra-sensitive, rapid, and non-invasive diagnostic techniques. Through the combination of nanotechnology with microfluidics, biosensors, and other tools, it is possible to detect any molecular or cellular changes before actual signs of the disease occur (see Figure 5). In recent years, nanodiagnostics, wearable sensors, and lab-on-a-chip technologies have made it possible to diagnose cancers, cardiovascular disorders, infectious diseases, and genetic abnormalities with unprecedented precision.

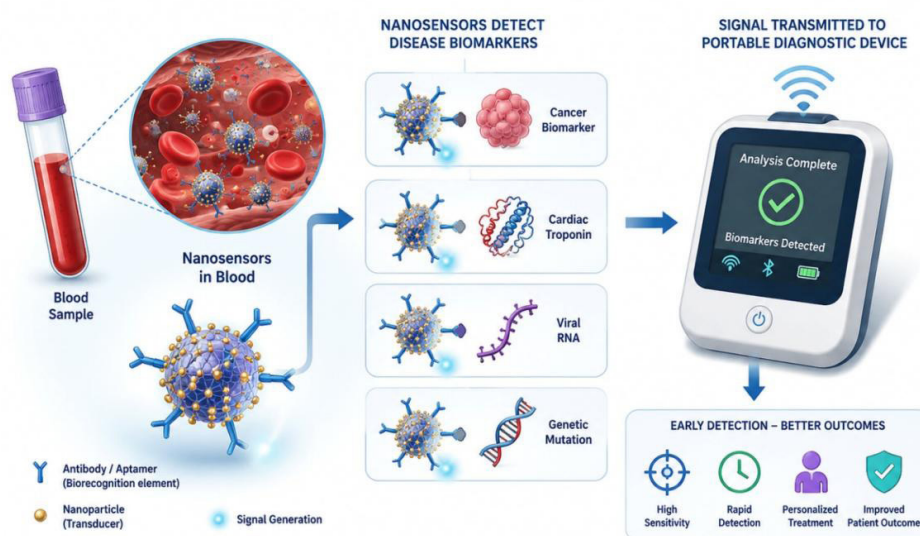


Figure 5. Early disease detection using nanosensors.

4.12. Nanotechnology in Early Disease Detection

Nanotechnology enhances early detection by exploiting the unique physicochemical properties of nanoparticles, including their high surface-area-to-volume ratio, tunable optical and magnetic properties, and functionalizability with biomolecules. Functionalized gold nanoparticles, quantum dots, and magnetic nanoparticles act as highly specific probes for biomarkers such as

proteins, nucleic acids, and metabolites, enabling detection at picomolar or even femtomolar concentrations.

The combination of nanomaterials with lab-on-a-chip platforms allows for miniaturized, high-throughput, and multiplexed assays. For instance, microfluidic devices integrated with nanosensors can detect multiple disease biomarkers from microliter volumes of blood or saliva in real time. These systems are particularly advantageous for point-of-care diagnostics in resource-limited settings, bringing laboratory-level analysis directly to the patient bedside.

4.13. Nanodiagnostics in Cancer and Cardiovascular Disease

In oncology, nanodiagnostics have revolutionized early detection. Gold nanoparticles conjugated with antibodies can identify tumor-associated antigens and circulating tumor cells with high specificity and sensitivity. Quantum dot-based nanosensors enable simultaneous detection of multiple cancer biomarkers, providing comprehensive molecular profiling of tumors. Photoacoustic imaging using gold nanorods allows visualization of angiogenesis and tumor vasculature, supporting both early diagnosis and monitoring of therapeutic response.

For cardiovascular diseases, graphene-based nanosensors integrated into microfluidic chips detect early biomarkers such as troponin, B-type natriuretic peptide (BNP), and C-reactive protein, facilitating timely intervention in myocardial infarction and heart failure. Magnetic nanoparticles further enhance MRI-based imaging of vascular plaques and inflammation, allowing non-invasive assessment of atherosclerotic progression.

4.14. Detection of Infectious Diseases and Genetic Disorders

Nanotechnology has also advanced the detection of infectious diseases. Quantum dot-based and gold nanoparticle-based nanosensors can rapidly identify viral RNA or bacterial DNA, enabling early diagnosis of infections such as COVID-19, influenza, and HIV. These nano-biosensors offer high sensitivity, real-time monitoring, and the ability to multiplex several pathogens in a single assay, which is crucial during outbreaks.

In genetic disorders, lab-on-a-chip devices integrated with nanosensors facilitate the detection of gene mutations, single nucleotide polymorphisms, and chromosomal abnormalities. This technology allows non-invasive prenatal testing, rapid genotyping, and early identification of inherited diseases, enabling prompt clinical management.

4.15. The Future of Early Disease Detection with Nanotechnology

The future of early disease detection is poised for a paradigm shift with the integration of advanced nanotechnology, microfluidics, and artificial intelligence. Emerging nanosensors and lab-on-a-chip platforms are expected to become increasingly sophisticated, combining high-

throughput multiplexed detection with real-time data analysis, allowing clinicians to identify disease at pre-symptomatic stages. Nanomaterials will continue to enhance imaging and biosensing capabilities.

Hybrid nanoparticles combining optical, magnetic, and radioactive properties enable multimodal imaging for simultaneous structural, functional, and molecular insights, which can detect tumors, cardiovascular lesions, and neurodegenerative changes far earlier than conventional methods. Moreover, functionalized nanoparticles with tissue-specific ligands or antibodies allow precise targeting, minimizing off-target signals and improving both diagnostic accuracy and therapeutic monitoring.

Integration with artificial intelligence and machine learning is another transformative trend. AI can analyze massive datasets from nanosensors, wearable devices, and lab-on-a-chip systems, identifying subtle patterns indicative of disease progression or therapeutic response⁵³. Predictive algorithms will enable clinicians to stratify patients, tailor interventions, and anticipate disease outbreaks, thus achieving truly personalized and proactive medicine (Figure 6).

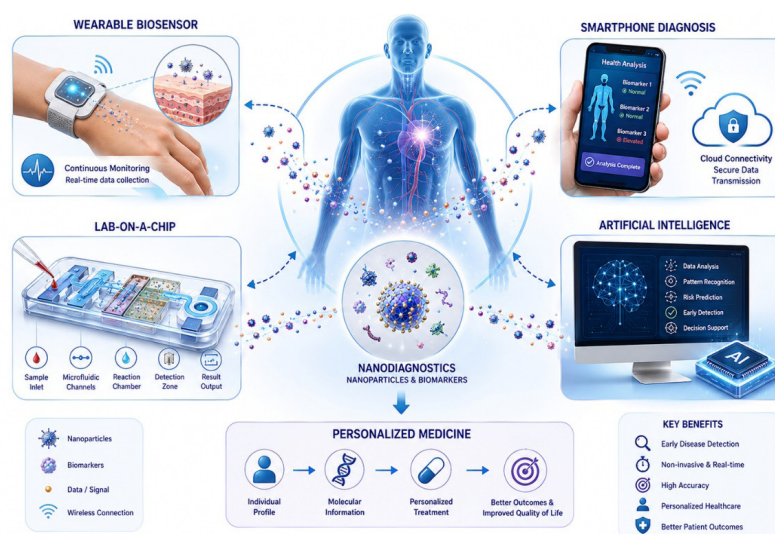


Figure 6. Future of nanodiagnostics with AI and wearables.

Future directions also include implantable nanosensors capable of continuous monitoring of physiological and biochemical parameters *in vivo*, coupled with remote data transmission for real-time clinical interpretation. Nanorobots and responsive nanocarriers may further enable theranostic applications, combining precise imaging, targeted drug delivery, and feedback-controlled therapy. These systems have the potential to transform disease management, enabling early detection, monitoring, and intervention in a single integrated platform.

Challenges remain, including biocompatibility, long-term stability, regulatory approval, ethical considerations, and integration into existing healthcare infrastructure. Addressing these hurdles will be essential to realizing the full potential of nanotechnology in early disease detection.

With continued innovation, cross-disciplinary collaboration, and AI-assisted analytics, the next generation of nanodiagnostic tools promises to redefine preventive and personalized medicine.

5. Nanotechnology-based approaches for cancer treatment

Cancer remains one of the leading causes of morbidity and mortality worldwide despite significant advances in diagnostics and therapeutics. Conventional treatment modalities such as chemotherapy, radiotherapy, and surgery have improved patient survival; however, their effectiveness is often limited by systemic toxicity, poor selectivity, the development of multidrug resistance, and tumor recurrence. In response to these limitations, nanomedicine has emerged as a transformative approach in oncology by enabling targeted drug delivery, improving therapeutic efficacy, and reducing off-target toxicity. Nanoparticles can be engineered to selectively accumulate in tumor tissues through enhanced permeability and retention (EPR)-based passive targeting or ligand-mediated active targeting, enabling controlled and site-specific drug release. Furthermore, nanotechnology facilitates theranostic platforms that integrate diagnostic imaging with therapy for real-time monitoring of treatment response. Among the most promising applications of nanomedicine in cancer treatment are targeted drug delivery systems, nanoparticle-mediated chemotherapy, photothermal therapy (PTT), and photodynamic therapy (PDT), which enhance tumor selectivity and therapeutic outcomes through synergistic mechanisms.

5.1. Targeted Cancer Therapy

The goal of targeted cancer therapy is to kill or inhibit cancer cells with minimum damage to healthy cells. The advent of nanoparticles has greatly improved this method by targeted delivery of therapeutic agents to tumor locations. The enhanced permeability and retention (EPR) effect, which occurs due to the abnormal and highly permeable vasculature in solid tumors, can be used to enhance the localization of drugs to the tumor, thus minimizing systemic toxicity.

Nanoparticles can be also functionalized with antibodies, peptides, aptamers, folic acid, transferrin, and other ligands that are able to bind to receptors that are overexpressed on cancer cells, which will improve the cellular uptake and hence active targeting. The common molecular targets are human epidermal growth factor receptor 2 (HER2), epidermal growth factor receptor (EGFR), transferrin receptors, and folate receptors, which are often over-expressed in breast, lung, ovarian, and other cancers.

Recent advances in smart and stimuli-responsive nanocarriers have further improved the precision of targeted cancer therapy. These nanocarriers are designed to respond to specific features of the tumor microenvironment, including acidic pH, elevated glutathione concentrations, hypoxia, reactive oxygen species, and aberrant enzyme expression, enabling controlled and site-specific drug release. Such responsive systems improve therapeutic efficacy while minimizing off-target effects. For example, pH-sensitive polymeric nanoparticles have

demonstrated enhanced intracellular drug release within acidic tumor microenvironments, resulting in increased cytotoxicity toward cancer cells while reducing systemic exposure to chemotherapeutic agents.

Lipid-based nanocarriers have also demonstrated considerable clinical potential due to their excellent biocompatibility, biodegradability, and ability to encapsulate both hydrophilic and hydrophobic drugs. Surface modifications such as polyethylene glycol (PEG) coating and ligand conjugation can prolong circulation time, reduce immune recognition, and enhance tumor accumulation. These properties have made lipid nanoparticles one of the most extensively investigated platforms for cancer-targeted drug delivery.

Collectively, these advances highlight the transformative role of nanotechnology in precision oncology, enabling highly selective drug delivery, improved therapeutic efficacy, and reduced treatment-related toxicity.

5.2. Nanoparticles in Chemotherapy

Chemotherapy remains a cornerstone of cancer treatment; however, conventional chemotherapeutic agents are often limited by poor aqueous solubility, rapid systemic clearance, nonspecific biodistribution, dose-limiting toxicity, and the development of multidrug resistance. Nanoparticle-based drug delivery systems have emerged as an effective strategy to overcome these challenges by improving drug stability, enhancing pharmacokinetic profiles, prolonging circulation time, promoting tumor-specific accumulation, and enabling controlled drug release.

Liposomes, polymeric nanoparticles, dendrimers, polymeric micelles, and mesoporous silica nanoparticles are among the most extensively investigated nanocarriers for chemotherapeutic drug delivery due to their ability to improve drug solubility, stability, bioavailability, and tumor accumulation.

Liposomal formulations such as PEGylated liposomal doxorubicin (Doxil®/Caelyx®) have demonstrated prolonged circulation time, improved tumor targeting, and significantly reduced cardiotoxicity compared with conventional doxorubicin formulations.

Polymeric nanoparticles, particularly those based on poly(lactic-co-glycolic acid) (PLGA) and PEG-PLA systems, provide controlled and sustained drug release while protecting encapsulated therapeutics from premature degradation and clearance. Mesoporous silica nanoparticles have attracted considerable attention because of their high surface area, tunable pore structure, large drug-loading capacity, and versatile surface chemistry, making them suitable for the co-delivery of chemotherapeutic drugs and nucleic acids in combination therapies.

Recent research has focused on nanocarrier-mediated reversal of multidrug resistance (MDR). Nanoparticles can bypass membrane-associated drug efflux pumps such as P-glycoprotein through endocytosis-mediated cellular uptake, thereby increasing intracellular drug accumulation in resistant cancer cells. Furthermore, co-delivery systems combining

chemotherapeutic agents with gene-silencing molecules such as siRNA and miRNA have demonstrated potential for suppressing resistance-associated signaling pathways and restoring drug sensitivity.

Prodrug-based nanomedicine has also emerged as a promising strategy, in which inactive drug precursors are selectively activated within the tumor microenvironment through enzymatic, pH-responsive, or redox-triggered mechanisms, thereby enhancing therapeutic selectivity while minimizing systemic toxicity.

5.3. Photothermal therapy (PTT)

Photothermal therapy (PTT) is a minimally invasive treatment modality that utilizes photothermal agents to convert near-infrared (NIR) light into localized heat, resulting in selective tumor ablation. Near-infrared light is particularly suitable for cancer treatment because of its relatively deep tissue penetration and low absorption by endogenous biological chromophores, allowing efficient energy delivery to tumor tissues.

Upon NIR irradiation, photothermal agents generate localized hyperthermia that induces protein denaturation, membrane disruption, mitochondrial dysfunction, and apoptosis or necrosis of cancer cells. Common photothermal nanomaterials include gold nanoparticles, gold nanorods, graphene oxide, carbon nanotubes, transition metal sulfides, and iron oxide nanoparticles, all of which exhibit strong light-to-heat conversion capabilities.

Gold nanoparticles remain among the most extensively investigated photothermal agents owing to their tunable surface plasmon resonance, excellent biocompatibility, and high photothermal conversion efficiency. Recent developments have focused on multifunctional hybrid nanostructures, including gold–polydopamine and gold–silica composites, which offer improved stability, enhanced photothermal performance, and the potential for combined therapeutic and diagnostic applications.

Emerging evidence suggests that photothermal therapy can stimulate anti-tumor immune responses through the release of tumor-associated antigens and damage-associated molecular patterns (DAMPs) following thermal ablation, thereby promoting immunogenic cell death and enhancing systemic anti-cancer immunity. Consequently, increasing attention has been directed toward combining PTT with immunotherapeutic strategies such as immune checkpoint blockade to improve therapeutic outcomes.

Furthermore, multifunctional theranostic nanoparticles enable simultaneous imaging and therapy, integrating modalities such as magnetic resonance imaging (MRI), computed tomography (CT), photoacoustic imaging, and fluorescence imaging with photothermal treatment. These platforms facilitate real-time monitoring of nanoparticle biodistribution and

treatment response. Preclinical studies have demonstrated promising therapeutic efficacy of PTT in breast cancer, melanoma, prostate cancer, and hepatocellular carcinoma models.

5.4. Photodynamic therapy (PDT)

Photodynamic therapy (PDT) is a clinically approved, light-activated cancer treatment that relies on photosensitizers which are activated by specific wavelengths of light to generate reactive oxygen species (ROS), leading to oxidative damage and apoptosis in cancer cells. The therapeutic mechanism of PDT involves three essential components: a photosensitizer, a light source, and molecular oxygen. Upon light activation, the photosensitizer transfers energy to molecular oxygen, generating singlet oxygen and other ROS that damage cellular membranes, proteins, and nucleic acids, ultimately inducing cell death.

Despite its clinical potential, conventional PDT is limited by poor solubility of photosensitizers, low tumor selectivity, limited tissue penetration of light, and tumor hypoxia, which reduces ROS generation efficiency. Nanotechnology-based delivery systems have been developed to overcome these limitations by improving photosensitizer stability, enhancing tumor accumulation, and enabling controlled release in the tumor microenvironment.

Nanocarriers such as liposomes, polymeric nanoparticles, and silica-based systems are widely used to improve the pharmacokinetics and tumor targeting of photosensitizers. In addition, up conversion nanoparticles (UCNPs) have emerged as promising platforms that convert deeply penetrating near-infrared (NIR) light into visible light, enabling activation of photosensitizers in deep-seated tumors.

A major advancement in PDT is the development of oxygen-generating nanoplatforms, such as catalase-loaded nanoparticles and manganese dioxide (MnO_2)-based systems, which alleviate tumor hypoxia and enhance ROS production efficiency. Furthermore, combination nanoplatforms integrating photothermal therapy (PTT) and PDT have demonstrated synergistic effects, leading to improved tumor ablation and reduced recurrence rates.

5.5. Nanotechnology in cancer immunotherapy and mRNA vaccines

Nanotechnology has emerged as a foundational platform in the advancement of mRNA-based cancer vaccines. In particular, lipid nanoparticles (LNPs) represent the most clinically established delivery vehicles, owing to their capacity to protect mRNA from ribonuclease-mediated degradation and to promote efficient cytosolic delivery to antigen-presenting cells (APCs). Following cellular uptake, the delivered mRNA is translated into tumor-associated antigens, which are subsequently processed and presented via major histocompatibility complex (MHC) pathways, thereby initiating coordinated innate and adaptive immune activation (Table 8).

Beyond vaccine development, nanotechnology-enabled systems are increasingly being leveraged to enhance cancer immunotherapy through improved immune modulation, adjuvant

functionality, and targeted delivery of immune checkpoint inhibitors, including anti-PD-1 and anti-CTLA-4 antibodies. By optimizing pharmacokinetics, enhancing tumor accumulation, and facilitating immune cell-specific delivery, these nanocarrier platforms improve therapeutic index while simultaneously reducing off-target toxicity and systemic immune-related adverse effects.

One of the major advantages of mRNA-based nano-vaccines is their rapid and scalable design. Once the antigen sequence is known, mRNA constructs can be synthesized and formulated into lipid nanoparticles within days, enabling rapid vaccine development platforms, as demonstrated during recent infectious disease vaccine development. Additionally, mRNA vaccines are considered relatively safe because they do not integrate into the host genome and are transiently expressed in the cytoplasm.

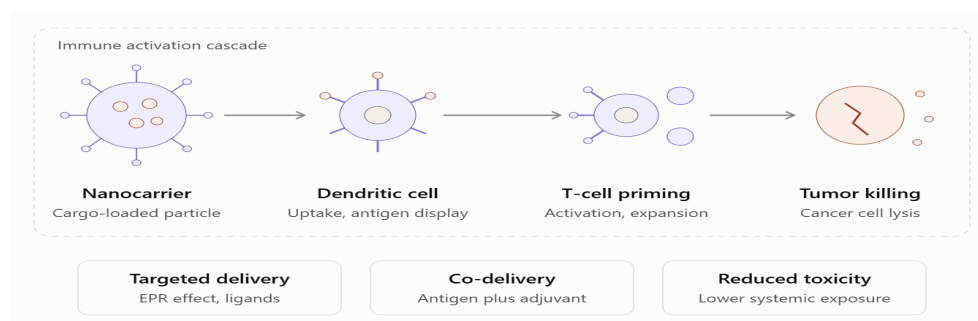


Figure 7. Pictorial representation of nanotechnology in cancer treatment

Table 8.

Different types of nanoparticles and therapeutic systems used in cancer treatment

Nanoparticle Type	Therapeutic System	Cancer Type	Therapeutic Approach	References
Liposomes	PEGylated liposomal doxorubicin	Breast cancer, ovarian cancer	Reduced toxicity chemotherapy delivery	(Barenholz, 2012)
Lipid nanoparticles (LNPs)	siRNA/mRNA-loaded lipid NPs	Liver cancer, breast cancer	Gene silencing & nucleic acid delivery	(Akinc et al., 2019)
Polymeric nanoparticles (PLGA/PEG)	Doxorubicin-loaded PLGA-PEG NPs	Breast cancer (T47D, MCF-7)	Controlled chemo + apoptosis induction	(Danhier et al., 2012)
Dendrimers (PAMAM)	PAMAM–drug conjugates	Breast cancer, melanoma	Targeted drug/gene delivery	(Tekade et al., 2021)
Gold nanoparticles (AuNPs)	Gold nanorods + antibody conjugates	Breast cancer, melanoma, Triple negative breast cancer (TNBC)	Photothermal therapy + imaging	(Jiang et al., 2024)

Iron oxide nanoparticles (SPIONs)	DOX-conjugated SPIONs	Breast cancer, brain tumors	MRI imaging + hyperthermia + drug delivery	(Catalano, Geisler, & Kristensen, 2019)
Silver nanoparticles (AgNPs)	Biosynthesized AgNPs (plant-based)	Breast, cervical cancer	ROS-mediated cytotoxicity	(Rupa et al., 2024)
Carbon-based nanoparticles	Graphene oxide / CNTs	Lung, breast cancer	Photothermal ablation + drug delivery	(Cantu et al., 2017)
Gold-polymer hybrid nanoparticles	Au-PLGA nanocapsules	Triple negative breast cancer	Combined chemo + PTT + imaging	(Jiang et al., 2024)
Polymeric micelles	PEG-PLA micelles	Ovarian, prostate cancer	Solubilization of hydrophobic drugs	(Kabanov et al., 2020)

6. Healthcare Innovation through Nanotechnology

Nanotechnology supports healthcare innovation by using nanoscale materials whose properties differ from bulk materials. These properties include altered solubility, reactivity, electrical behaviour, magnetic response, optical activity, and membrane transport. In healthcare, these features are used for diagnosis, imaging, drug delivery, tissue engineering, antimicrobial systems, and medical devices.

Nanoparticles are used to improve early diagnosis, treatment monitoring, wound healing, regenerative medicine, and targeted therapy. Their high surface-area-to-volume ratio and adjustable physicochemical properties allow them to carry drugs, interact with biological targets, and improve therapeutic delivery while limiting unnecessary exposure to healthy tissue.

Smart drug delivery systems can be designed to respond to internal or external stimuli such as pH, temperature, enzymes, magnetic fields, light, ultrasound, or disease-specific microenvironments. These systems support controlled release and targeted treatment.

This chapter focuses on three fact-specific areas of healthcare innovation: smart medical devices, wearable nano-enabled sensors, and the integration of nanotechnology with artificial intelligence and digital health. The main clinical requirements for translation are safety, reproducibility, scalability, regulation, affordability, and data protection.

6.1. Smart medical devices

Smart medical devices are healthcare tools that sense, monitor, diagnose, deliver therapy, or support clinical decision-making through built-in sensing, automated control, communication, or data-processing functions. Nano-enabled smart devices include biosensors, diagnostic chips, implantable devices, smart wound dressings, drug delivery systems, nanogenerators, and connected monitoring systems.

Nanotechnology improves smart devices because nanoscale materials can interact with cells, tissues, proteins, genes, and biomarkers. Their small size, high surface area, optical and magnetic properties, conductivity, and adjustable surface chemistry improve sensitivity, targeting, and miniaturisation.

6.2. Nano-enabled smart devices: revolutionizing healthcare

Nano-enabled smart devices combine nanoscale materials with diagnostic, sensing, imaging, and therapeutic functions. Their main healthcare roles are early biomarker detection, targeted drug delivery, treatment monitoring, antimicrobial activity, and support for regenerative medicine^{12,15,16}.

Targeted drug delivery is a central application. Nanoparticles can carry therapeutic agents to selected tissues and release them in a controlled way. Stimuli-responsive delivery systems may react to pH, enzymes, oxidative stress, tumour microenvironments, light, ultrasound, magnetic fields, or temperature.

Nano-enabled diagnostic systems include nanosensors, nanoparticle imaging agents, nanoparticle-based PCR assays, and lab-on-a-chip devices. These systems can detect low biomarker levels in blood, urine, tissues, and other body fluids, supporting earlier diagnosis and treatment monitoring.

In regenerative medicine, nanomaterials are used in scaffolds, coatings, dressings, and implants to support tissue repair, bone regeneration, skin healing, and antimicrobial protection. Plant-derived nanoparticles are also being studied for drug delivery, antimicrobial therapy, wound healing, cancer treatment, diagnostic assays, and tissue regeneration (Figure 8).

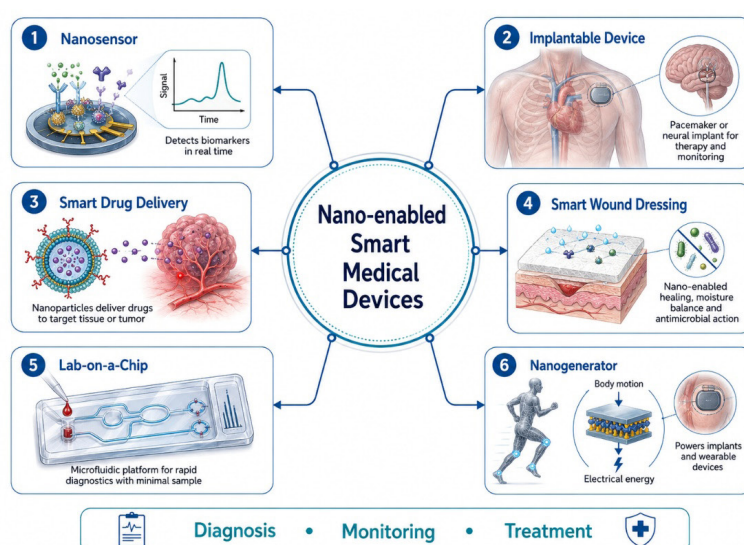


Figure 8. Nano-enabled smart medical devices used for diagnosis, monitoring, and treatment.

6.3. Applications of Smart Devices in Monitoring and Treatment

In monitoring, nano-enabled biosensors and diagnostic devices measure biological markers with high sensitivity. They are useful for early disease detection, disease progression tracking, and assessment of treatment response.

In treatment, nano-enabled devices support targeted drug delivery for cancer therapy, infectious disease management, gene therapy, and chronic disease care. Their value lies in directing treatment to diseased tissues while reducing unnecessary effects on healthy cells.

Implantable nanogenerators can convert mechanical energy from body movement into electrical energy. They may power devices such as pacemakers, neurostimulators, and drug delivery systems, reducing dependence on battery replacement.

6.4. Challenges and Future of Smart Medical Devices

Clinical translation is limited by safety, biocompatibility, toxicity, biodistribution, clearance, and environmental risk. Nanomaterial size, shape, surface charge, chemical composition, and degradation behaviour affect biological response. Manufacturing is another limitation. Smart nano-enabled systems require controlled particle size, surface chemistry, drug loading, release behaviour, and targeting specificity. Variation during production can change safety and performance. Regulation is complex because some smart devices combine nanomaterials, drugs, biological components, sensors, and digital functions. They may be reviewed as medical devices, medicines, biologics, or combination products. Wider clinical use requires standardised testing, quality control, clinical validation, and cost-effective production.

6.5. Wearable Nano-enabled Sensors

Wearable nano-enabled sensors move healthcare from occasional hospital testing toward continuous patient monitoring. These devices combine nanomaterials, flexible electronics, wireless communication, and signal processing to collect physiological or biochemical data in real time. Wearable systems can be integrated into watches, wristbands, patches, tattoos, bandages, contact lenses, clothing, jewellery, or other flexible platforms. Their purpose is to monitor health indicators while maintaining comfort and body compatibility (Figure 9).

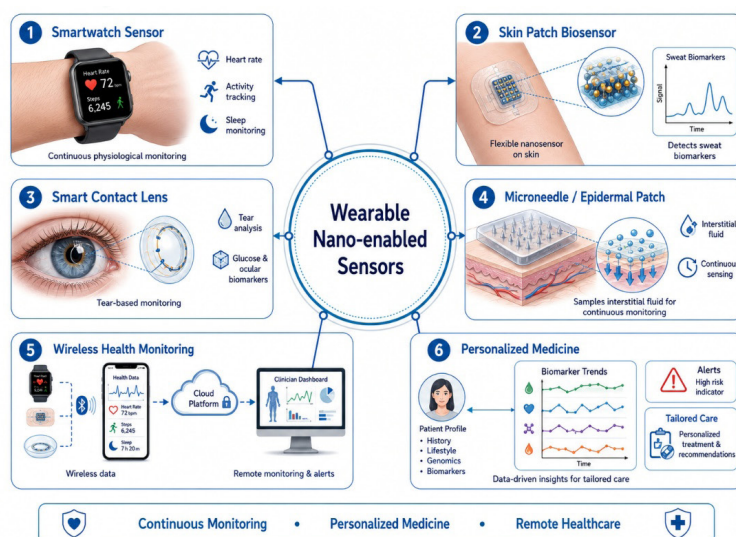


Figure 9. Wearable nano-enabled sensors for personalized medicine.

6.6. How Nanotechnology Enhances Wearable Sensors

Nanotechnology enhances wearable sensors by improving their sensitivity, selectivity, flexibility, and ability to detect low concentrations of biomarkers. Nanomaterials have a very high surface-to-volume ratio, which strengthens their interaction with biological analytes and allows the detection of small concentrations of biomarkers in body fluids such as sweat, blood, and saliva. This is important because slight biomarker changes may indicate the early development of disease before major symptoms appear.

The use of nanomaterials also supports the miniaturisation of wearable devices. Because sensors can be produced at micro- or nanometre scale, they can be integrated into clothing, skin patches, contact lenses, tattoos, smart watches, and other everyday materials. This improves comfort, long-term use, and body compatibility. The reference material states that nanomaterials allow wearable sensors to fit the contours of the human body, improving contact precision and signal transmission.

Different nanomaterials contribute specific advantages. Graphene offers high conductivity, flexibility, biocompatibility, and a high surface-to-volume ratio, making it useful for biosensors, wearable sensors, and neural interfaces. Carbon nanotubes provide high conductivity, mechanical strength, and large surface area, while gold nanoparticles are valuable because of their biocompatibility, chemical stability, conductivity, and low toxicity. Silver nanoparticles and quantum dots also support biosensing, antimicrobial coatings, wound disinfection, wearable displays, and biological sensing platforms.

Nanotechnology also improves fabrication methods for wearable sensors. Electrospinning can produce continuous nanoscale fibres with high surface area, flexibility, and elasticity, making it attractive for wearable sensing. Inkjet printing is also useful because it enables high-resolution patterning on flexible substrates and allows nanoparticle inks to print multiple sensors on the same flexible carrier. These fabrication methods support the development of flexible, scalable, and multifunctional wearable sensors.

6.7. Personalized medicine through wearable devices

Wearable nano-enabled sensors support personalised medicine by allowing continuous monitoring of physiological and biochemical information. Instead of depending only on periodic hospital visits, these devices can collect real-time patient data and help clinicians understand individual health changes over time. The reference material describes this as a move toward “continuous and personalized health management” rather than episodic and hospital-centred care.

Personalised medicine depends on accurate and patient-specific data. Wearable nanosensors can monitor biomarkers in sweat, tears, interstitial fluid, saliva, and blood, offering an alternative to invasive blood-based testing. The reviewed material notes that wearable nanosensors can non-invasively measure biomarkers in biofluids such as sweat, tears, and interstitial fluid, making it possible to monitor essential physiological and biochemical parameters continuously.

These devices can measure a wide range of indicators, including glucose, lactate, sodium, potassium, cortisol, heart rate, blood pressure, respiratory rate, body temperature, motion, and sleep patterns. This kind of multi-parameter sensing provides a more complete picture of individual health and supports early detection, disease management, and treatment adjustment.

Wearable devices are also useful in chronic disease management. Continuous glucose monitors can track glucose trends in diabetes, while wearable systems can provide real-time warnings for cardiovascular disorders such as arrhythmia and atrial fibrillation. In neurological conditions such as Parkinson’s disease and epileptic seizures, wearable devices can monitor movement and gait patterns, helping to predict attacks and support timely intervention.

The integration of machine learning further strengthens personalised medicine. The reference material explains that machine learning combined with wearable technology has transformed medical monitoring by using key biosignals such as ECG, EMG, EEG, and PPG. ECG with machine learning can support disease detection, heartbeat classification, and real-time cardiac monitoring, while PPG supports cardiovascular monitoring because of its non-invasive nature and improved signal processing.

6.8. Challenges and opportunities in wearable nano sensors

The main technical and biological challenges are long-term biocompatibility, nanotoxicity, signal noise, motion artefacts, variable skin contact, temperature effects, sweat variation, and low-power signal quality. Power supply is a major design issue. Batteries add weight, require replacement, and may create leakage risk. Piezoelectric and triboelectric materials can harvest energy from movement, friction, or mechanical force, making self-powered wearable sensors a major development direction. Wearable sensors also raise privacy and ethics concerns because they continuously collect personal health data. Secure data transmission, informed consent, ownership rules, encryption, and protection against unauthorised access are required .

Despite these challenges, wearable nano sensors can support preventive healthcare, chronic disease management, remote monitoring, sports performance assessment, and environmental exposure tracking. Future systems are expected to be smaller, more flexible, self-powered, AI-enabled, and integrated with wireless health platforms.

6.9. Integration with AI and Digital Health

The integration of artificial intelligence and digital health with nanomedicine is becoming one of the most important directions in modern healthcare innovation. Artificial intelligence can process large datasets, identify complex biological patterns, support decision-making, and improve the design of nanotechnologies for diagnosis, imaging, drug delivery, and therapy. The reviewed article explains that the convergence of artificial intelligence and nanotechnology has transformed nanomedicine because AI can improve nanotechnology design by analysing large datasets and recognising complex patterns.

This integration is particularly important because nanomedicine involves complex interactions between nanoparticles, drugs, biological fluids, immune responses, blood vessels, and cell membranes. AI can help predict these interactions and optimize nanomaterial properties for improved therapeutic performance. In this way, digital health and AI do not replace

nanomedicine; rather, they strengthen it by improving prediction, personalization, monitoring, and clinical decision-making (Figure 10).



Figure 10. Integration of nanotechnology, artificial intelligence, and digital health to support predictive and personalized healthcare.

6.10. The Role of AI in Nanomedicine

AI supports nanomedicine in diagnosis, drug discovery, nanoparticle design, imaging, targeted drug delivery, and therapy planning. It is especially useful where large biomedical, imaging, chemical, or molecular datasets must be analysed.

In precision cancer medicine, AI-enabled nanotechnology can support molecular profiling, early diagnosis, patient-specific nanomedicine design, targeting optimisation, dose prediction, and toxicity reduction.

AI also contributes to drug discovery by predicting molecular structures, identifying hit and lead compounds, analysing chemical datasets, and supporting virtual screening. These functions can reduce time and uncertainty in therapy development.

For nanoparticle synthesis, AI can support selection of precursor materials, optimisation of reaction conditions, real-time monitoring, and prediction of nanoparticle properties from synthesis parameters. This can reduce trial-and-error experimentation.

Furthermore, AI supports nanoparticle synthesis. It can help select suitable precursor materials, optimize reaction conditions, monitor synthesis reactions in real time, and predict nanoparticle properties based on synthesis parameters. These functions are important because conventional nanoparticle synthesis often depends on trial-and-error experimentation, which can be time-consuming, expensive, and inconsistent.

6.11. Data analytics and predictive modeling in healthcare

Data analytics enables patient-specific decision-making by analysing biomedical, molecular, imaging, pharmacological, and clinical datasets. AI can identify patterns that are difficult to detect manually.

In cancer nanomedicine, predictive models can estimate nanoparticle delivery efficiency to tumours. This is important because poor delivery efficiency remains a major barrier to successful nanotherapy.

AI can also support drug delivery by analysing patient data such as genomics, biomarkers, medical history, drug solubility, release kinetics, stability, biocompatibility, and drug-loading capacity. This can improve formulation choice, route selection, dosage, and treatment monitoring.

6.12. Telemedicine and Remote Healthcare Integration

AI-enabled nanosensors, point-of-care diagnostic systems, imaging platforms, and wearable devices can support remote diagnosis and home-based monitoring. These tools reduce dependence on centralised laboratory testing and allow faster clinical interpretation.

Digital health platforms can receive data from nano-enabled devices, analyse it with AI, and support clinical decisions. This model is relevant to telemedicine, remote patient monitoring, decentralised diagnostics, and long-term chronic disease management.

Integration also increases governance requirements. Privacy, cybersecurity, informed consent, transparency, accountability, algorithmic bias, interoperability, nanotoxicity, and clinical safety must be addressed before large-scale adoption.

6.13. Future Prospects for AI and Nanotechnology in Healthcare

Future healthcare systems may combine nano-enabled detection, wearable monitoring, AI analytics, cloud-based data platforms, and personalised therapy. The expected direction is earlier diagnosis, better patient stratification, adaptive dosing, and more precise treatment delivery.

AI may improve nanoparticle formulation by optimising drug loading, release behaviour, targeting ligands, surface modification, in vivo monitoring, and quality control. Automated synthesis, AI-assisted characterisation, robotic assembly, and real-time feedback can improve reproducibility and manufacturing reliability (Figure 11).

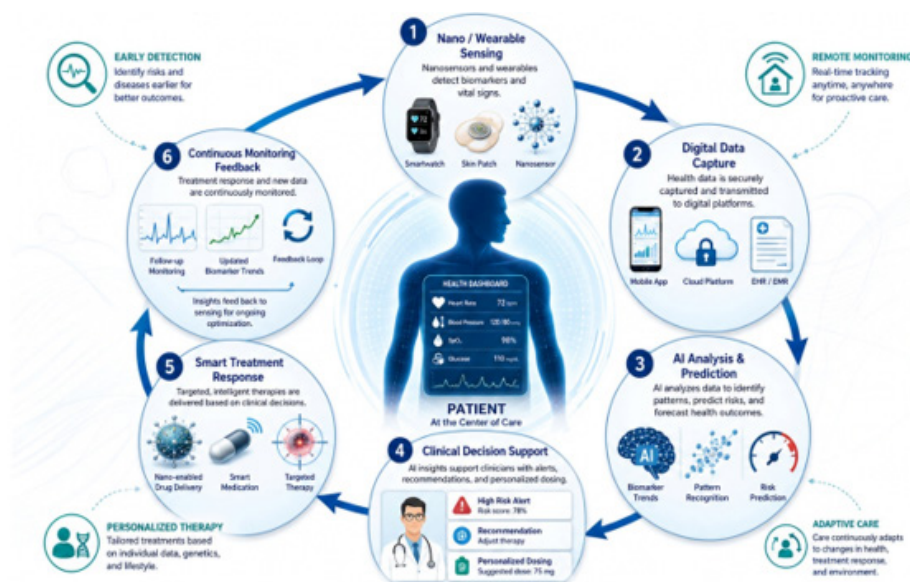


Figure 11. Future closed-loop smart healthcare system.

In addition, AI-driven data analysis will support faster and more cost-efficient healthcare innovation. AI can analyse large-scale omics data, imaging data, clinical trial data, real-world evidence, and biomarker information. This can improve patient stratification, treatment monitoring, disease profiling, and clinical decision-making. Cloud-based collaborative platforms may also allow researchers to share data, AI models, and nanoparticle design strategies more efficiently.

However, future progress will depend on careful management of ethical, safety, and regulatory concerns. Issues such as data privacy, informed consent, algorithmic bias, transparency, accountability, nanotoxicity, patient safety, and global access must be addressed before AI-enabled nanomedicine becomes widely used. Therefore, the future of AI and nanotechnology in healthcare will depend not only on scientific advancement, but also on responsible regulation, clinical validation, affordability, and equitable access.

7. Challenges and Limitations of Nanomedicines

Nanomedicine has the potential to completely change how we diagnose and treat diseases; moving these nanotechnology strategies from the laboratory to the doctor's clinic is a substantial challenge involving scientific, regulatory, and even socioeconomic hurdles.

7.1. Biological Complexity, Toxicity, and Safety Concerns

The unpredictable interaction of nanoparticles with biological systems is one of the most substantial limitation of nanomedicine. In the bloodstream when nanoparticles enter, they come across a complex biological environment made up of lipids, biological enzymes, plasma proteins, and immune cells. As a result, nanomedicine designed for selective and specific targeting sometimes behave differently in vivo studies than expected from in vitro studies. While nanoparticles have incredible potential, they can trigger unintended and harmful reactions within the body, such as inflammatory responses and immune activation, oxidative stress via reactive oxygen species (ROS) generation, and even genotoxicity and mitochondrial dysfunction, where the cell's genetic material is compromised. Although the small size of the nanoparticles enables deep tissue penetration but it causes the concerns related to the long term accumulation of inorganic nanoparticles (e.g., silver, gold, and metal oxides) in the major organs such as brain, lungs, spleen, and liver. It raised unresolved questions about biodegradation and chronic toxicity. Toxicological frameworks of nanoparticles highly dependent on shape, charge on the surface, size, and coating chemistry, causing prediction of safety standard difficult.

7.2. Clinical Translation Gap

Despite all the excitement in research labs and thousands of published articles, few nanomedicines have actually been approved for clinical applications. So far, success stories are limited to specific types like polymeric formulations, liposomal drugs, and few lipid nanoparticles-based systems used in mRNA vaccines.

Most the ideas stuck in what scientist call the “Valley of Death” the difficult transition from lab discovery to real-world medical applications. The major reasons for this includes:

- Lack of standardized evaluation protocols

- Poor reproducibility across laboratories

- Over-reliance on simplified disease models

- Insufficient long term safety data

- Difference between human physiology and animal models

Ultimately, this emphasizes a fundamental gap between clinical applicability and academic innovation of nanomedicines.

7.3. Regulatory Challenges

The regulatory rules for nanomedicine applications for patients are still like trying to navigate a high-tech future with an old map because to evaluate these nanoscale systems most regulatory agencies such as the European Medicines Agency (EMA) and Food and Drug Administration (FDA) still use traditional pharmaceutical guidelines.

The key hurdles include:

Lack of nano-specific toxicity thresholds

complications in assessing complex multifunctional nanocarriers

Absence of standardized definitions of nanomedicine

Inadequate guidance on characterization techniques

Consequently, regulatory challenges increase development costs and delay clinical approval.

7.4. Poor Predictability of In Vivo Performance

The inadequacy of analytical correlation between in vivo and in vitro execution is another hurdle in nanomedicine clinical support. As in a controlled laboratory environment, scientist can control different reaction variable, but human body is a more complex environment.

The major factors affecting this nanomedicine treatments include:

Enzymatic degradation inside the body

Disruption in immune system clearance mechanisms

Shear stress in blood flow

pH alteration in tissues

This changeability makes it incredibly hard for researchers to “rationally design” a nanomedicine that will reliably do work in vivo and in vitro environment.

7.5. Storage, Stability, and Shelf-Life Issues

The storage, stability and shelf-life issues are important yet often unseen challenges in nanomedicine. Over time, these nanoparticles can undergo agglomeration and aggregation, where nanoparticles clump together into ineffective larger masses. They are also susceptible to

hydrolysis and oxidation with exposed to their environment. Their sophisticated surface coatings can be degrade, beyond their internal structure and may even lose their targeting efficiency for the selective ligands. When these physical changes take place, it shifts the drug release profile.

These uncertainties can occur during:

The high-pressure environment of formulation processing

Physical stresses of transport

Long-term storage

Consequently, the physicochemical sustainability for long-term use is a core formulation challenge, particularly for polymer-based and lipid-based nanocarriers.

7.6. Manufacturing and Scale-Up Challenges

In nanomedicine production, one of the biggest roadblocks is the struggle of large scale production of these nanomaterial while keeping their chemical and physical properties perfectly consistent. As nanoparticles are highly sensitive and selective for their target, even small changes between batches can completely alter the medicine pharmacokinetics inside a patient's body. The regulatory approval required consistency but lack of consistency is a major scale-up challenge, as agencies need to be certain that every drug dose will work exactly the same way before the marketing. To fix this problem, research experts are working on the GMP standards optimization precisely for nanotechnology to make it reliable for large-scale production.

7.7. Economic and Accessibility Barriers

Nanomedicine is recently dealing with affordability crisis because designing these treatment methodologies is highly expensive. Contrasting to traditional medicine, synthesizing “smart” nanomaterials involves complex laboratory procedures and also required extremely advanced, high-tech characterization tools such as Dynamic Light Scattering (DLS), Transmission Electron Microscopy (TEM) or Scanning Electron Microscopy (SEM) to identify particle size.

Beyond the lab, the costs continue to increase due to:

Regulatory Red Tape: Agencies like FDA have strict and still-evolving requirements for these specified nanotech organizations, the time and legal framework required to meet these standards adds significantly to the final price.

State of the art Infrastructure: moving from laboratory preparations to industrial production of these nanomedicine is a “manufacturing nightmare” because it is a massive financial burden to building factories for large-scale production of these highly sensitive and selective materials with extreme precision under controlled conditions.

The practical drawbacks of these high costs are an emergent global healthcare gap. Because these drug therapies are expensive to design, synthesize, and, store, they often remain out of reach for middle- and low-income countries. Although nanomedicine has the potential to save lives, it now risks becoming a “luxury” accessible only to the wealthiest nations, potentially broadening the inequality in global healthcare.

To overcome this, researchers are working to explore “paper-based diagnostics” and “green nanomedicine” to find sustainable, more cost-effective ways to bring these novelties to low-resource settings.

7.8. Environmental and Ethical Concerns

With the more practical applications of nanoparticles in different fields, some serious questions arise about how they affect the environment and the people living in it.

Environmental Unknowns: When these nanomaterials synthesized, used, and eventually not disposed of safely, they can leak into the water and soil. The biggest concern related to this is the long-term ecological impact we simply don't understand yet. Because these nanomedicines are modified to be highly reactive, we cannot predict precisely how they will interact with the nature over decades. To solve this problem researchers are now planning to move towards “green nanomedicine” to synthesize materials that are safe for the environment, biodegradable and won't build up in the environment.

Ethical Red Flags: Beyond the natural environment, there are many human concerns that scientists, researchers, and regulators are still trying to navigate:

The Data Gap: We are applying these therapies for treatments even though we lack long-term data on how human body affects over a lifetime being exposed to nanomedicine.

Right to Know: Because nanotechnology is complex and still “in progress” we do not have a legal solid framework for informed consent.

Intergenerational Risks: Unknown intergenerational risks, we do not know how these engineered nanoparticles could impact the future generations.

Potential for Misuse: Finally, there is a worry that this powerful nanotechnology can be misused for non-medical purposes, if could be taken out of the hospitals or laboratories.

Eventually, while these nanomaterials offer a “paradigm shift” in healthcare field, agencies are still working on the rules needed to confirm they are used ethically and safely.

8. Future Perspectives and Emerging Trends in Nanomedicine and Healthcare Innovation

Nanomedicine is moving beyond the experimental “proof-of-concept” stage and entering in a new era focused on synthesizing intelligent, translatable, and digitally connected healthcare systems that precisely works in clinical setup. Rather than just focusing on the development of advanced materials in laboratories, the field is now merging with molecular biology, Artificial Intelligence, and advanced engineering techniques to design treatments that are rapid, and precise. The main goal is to shift from passive tools to adaptive and smart systems that can provide real-time analysis with respect to patients-specific interventions.

RNA therapeutics and next-generation lipid nanoparticles

The clinical validation of mRNA based vaccines has developed lipid nanoparticles (LNPs) as principle drug delivery platform for modern bio-molecular medicine. Recent trajectories in the medical field involve influencing LNPs platforms for various high-impact real-world applications, including mRNA-mediated cancer therapies, systemic delivery of CRISPR/Cas genomic editing components, and RNA-based interferences for rare genetic pathologies. Future research is highly focused on moving towards the integrated healthcare schemes, improving stability, analyte targeting specificity, and immunological compatibility of nucleic acid drug delivery systems.

Precision and personalized nanomedicine

Modern healthcare is enduring a paradigm shift toward precise nanomedication, serving as a core driver for individualized therapeutic approaches. This transition is supported by the application of genomic informed nanocarrier synthesis, biomarker-guided nanoparticle targeting, and the development of individualized patient-specific drug delivery approaches. Furthermore, adaptive nanomedicine integration allows for dynamic therapeutic shifts that responds to physiological alterations of disease progression. By prioritizing the patient's physiological profile, this personalized scheme avoids the shortcoming of conventional, generalized population models and ensuring optimized and highly specific clinical results.

Intelligent and stimuli-responsive nanomedicine

The significant advancement in the nanomedicine field involves the development of stimuli-responsive nanomedicine drug releasing techniques. These smart nanocarrier are programmed to undergo physiochemical shift in response to specific exogenous or endogenous triggers, facilitating controlled drug delivery. The main technological developments include:

Enzymatic and redox responsive nanoparticles for intracellular drug delivery

Light and temperature triggered approaches for externally controlled therapies

Selective pH responsive techniques for tumor targeting in microenvironment

These nanotechnologies aim to reduce the off-target toxicity while increasing therapeutic precision specifically in inflammatory diseases and oncology.

Artificial intelligence-driven nanomedicine design

The integration of Artificial Intelligence (AI) is catalyzing a fundamental shift from trial-and-error methodologies to a data driven design science in nanomedicine. The technical point of care applications include:

In Silico Screening: Rapid computational evaluation of nanocarrier formulations prior to physical synthesis

Kinetic Prediction: AI-assisted drug loading profiles and release efficiencies to ensure precise therapies.

AI driven nanomedicine will ensure precise, specific, efficient, and scalable approach to emerging the next generation of integrated healthcare systems.

Integration of nanomedicine with digital health and wearable systems

Combination of nanotechnology and digitalized healthcare facilities self-sufficient for real time analysis and dynamic therapeutic feedback through closed-loop systems. This integration utilizes wearable bio-nanosensors for different metabolite (e.g., glucose, lactate, and electrolytes) tracking, implantable nanosensors for systemic drug tracking, and theranostic transdermal patches for drug delivery. Coupled with AI-assimilated diagnostic sensors enable a transition toward self-regulating healthcare systems, where diagnostic data and therapeutic involvements are synchronized.

Exosome and biomimetic nanomedicine

In comparison to synthetic nanoparticles, natural and biologically produced nanocarriers are emerging as highly promising alternatives. These biomimetic platforms are progressively applied in regenerative medicine, oncology, and targeted drug delivery system with precision. Consequently, exosome engineering is expected to become as a primary frontier in nanomedicine for the next generation.

Biodegradable, sustainable, and green nanomedicine

In nanomedicine design environmental sustainability and safety are critical priorities. Mostly biodegradable polymeric nanoparticles (e.g., PLGA, chitosan) and green synthesis

approaches mediated by biomolecules and plants are adopted. These techniques aim to reduce ecological impact by minimizing reliance on toxic solvents and heavy metals while preparing environmentally degradable nanocarriers to prevent bioaccumulation and biomagnification. This green nanomedicine shift ensures long term safety, sustainability, and reduces ecological impacts associated with nanomaterials.

Theranostics: Integration of therapy and diagnostics

The theranostic concept is emerging rapidly, where a single nanoparticle based platform can perform diagnosis, drug delivery for therapy, and monitoring response simultaneously.

The key technologies include:

Quantum dots for fluorescence tracking

Gold nanoparticles for photothermal imaging

Multifunctional polymeric nanocarriers for diagnosis

Magnetic nanoparticles for MRI guided therapies

This will enable real-time feedback-controlled therapeutic systems, advancing clinical outcomes.

9. Conclusion

This chapter shows that nanotechnology is an important driver of healthcare innovation. Through smart medical devices, nano-enabled sensors, targeted drug delivery systems, implantable nanogenerators, diagnostic platforms, and regenerative materials, nanotechnology is helping healthcare become more precise, responsive, and patient-centred. Nanomaterials are valuable because of their small size, high surface-area-to-volume ratio, tunable surface properties, and ability to interact with biological systems at cellular and molecular levels .

Smart medical devices are one of the major outcomes of this innovation. Nano-enabled devices can support disease monitoring, controlled drug release, tissue repair, antimicrobial protection, and real-time diagnosis. These devices are especially useful in targeted therapy because they can improve drug delivery, reduce side effects, and support treatment at specific disease sites. Malik et al. (2023) emphasized that nanotechnology is already being applied in diagnostics, lab-on-a-chip devices, nanosensors, drug delivery systems, gene therapy, regenerative medicine, and antimicrobial tools.

The chapter also highlighted the role of wearable nano-enabled sensors in personalized medicine. Wearable devices can continuously monitor physiological and biochemical signals and transmit data for clinical interpretation. When combined with nanomaterials, these sensors

become more sensitive, flexible, portable, and suitable for early detection and chronic disease management. They also support remote healthcare, reducing dependence on hospital-based monitoring.

Finally, the integration of nanotechnology with artificial intelligence and digital health creates new possibilities for predictive, preventive, and personalized healthcare. AI can analyse complex data from nanosensors, imaging systems, wearable devices, and patient records, while nanotechnology provides the tools for sensitive detection and targeted intervention. However, successful clinical translation will depend on addressing safety, toxicity, reproducibility, standardization, regulatory approval, affordability, data privacy, and environmental risks. Plant-derived nanoparticles may contribute to safer and more sustainable healthcare innovation, but they also require further validation and production standardization.

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