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NANOMEDICINES: MODERN SYSTEM OF DRUG DELIVERY

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ABSTRACT

A nanoparticle or ultrafine particle is usually defined as a particle of matter that is between 1 and 100 nanometres (nm) in diameter. The term is sometimes used for larger particles, up to 500 nm, or fibers and tubes that are less than 100 nm in only two directions. At the lowest range, metal particles smaller than 1 nm are usually called atom clusters instead. Nanoparticles are usually distinguished from microparticles (1-1000 µm), "fine particles" (sized between 100 and 2500 nm), and "coarse particles" (ranging from 2500 to 10,000 nm), because their smaller size drives very different physical or chemical properties, like colloidal properties and ultrafast optical effects or electric properties. Being more subject to the Brownian motion, they usually do not sediment, like colloidal particles that conversely are usually understood to range from 1 to 1000 nm. Being much smaller than the wavelengths of visible light (400-700 nm), nanoparticles cannot be seen with ordinary optical microscopes, requiring the use of electron microscopes or microscopes with laser. For the same reason, dispersions of nanoparticles in transparent media can be transparent, whereas suspensions of larger particles usually scatter some or all visible light incident on them. Nanoparticles also easily pass through common filters, such as common ceramic candles so that separation from liquids requires special nanofiltration techniques. Nanomedicine is the medical application of nanotechnology. Nanomedicine ranges from the medical applications of nanomaterials and biological devices, to nanoelectronic biosensors, and even possible future applications of molecular nanotechnology such as biological machines. Current problems for nanomedicine involve understanding the issues related to toxicity and environmental impact of nanoscale materials (materials whose structure is on the scale of nanometers, i.e. billionths of a meter). Functionalities can be added to nanomaterials by interfacing them with biological molecules or structures. The size of nanomaterials is similar to that of most biological molecules and structures; therefore, nanomaterials can be useful for both in vivo and in vitro biomedical research and applications. Thus far, the integration of nanomaterials with biology has led to the development of diagnostic devices, contrast agents, analytical tools, physical therapy applications, and drug delivery vehicles.

Nanoparticle drug delivery systems are engineered technologies that use nanoparticles for the targeted delivery and controlled release of therapeutic agents. The modern form of a drug delivery system should minimize side-effects and reduce both dosage and dosage frequency. Recently, nanoparticles have aroused attention due to their potential application for effective drug delivery. Nanomaterials exhibit different chemical and physical properties or biological effects compared to larger-scale counterparts that can be beneficial for drug delivery systems. Some important advantages of nanoparticles are their high surface-area-to-volume ratio, chemical and geometric tenability, and their ability to interact with biomolecules to facilitate uptake across the cell membrane. The large surface area also has a large affinity for drugs and small molecules, like ligands or antibodies, for targeting and controlled release purposes.

KEYWORDS: Nanoparticle, Nanomedicine, Drug Delivery, Medications.

INTRODUCTION

Nanomedicine seeks to deliver a valuable set of research tools and clinically useful devices in the near future. The National Nanotechnology Initiative expects new commercial applications in the pharmaceutical industry that may include advanced drug delivery systems, new therapies, and *in-vivo* imaging. Nanomedicine research is receiving funding from the US National Institutes of Health Common Fund program, supporting four nanomedicine development centers. Nanomedicine sales reached $16 billion in 2015, with a minimum of $3.8 billion in nanotechnology R&D being invested every year. Global funding for emerging nanotechnology increased by 45% per year in recent years, with product sales exceeding $1 trillion in 2013. As the nanomedicine industry continues to grow, it is expected to have a significant impact on the economy. Nanoparticles refer to a large family of materials both organic and inorganic. Each material has uniquely tunable properties and thus can be selectively designed for specific applications. Despite the many advantages of nanoparticles, there are also many challenges, including but not exclusive to: nanotoxicity, biodistribution and accumulation, and the clearance of nanoparticles by human body.[1]

The National Institute of Biomedical Imaging and Bioengineering has issued the following prospects for future research in nanoparticle drug delivery systems:

1. Crossing the blood-brain barrier (BBB) in brain diseases and disorders;
2. Enhancing targeted intracellular delivery to ensure the treatments reach the correct structures inside cells;
3. Combining diagnosis and treatment.

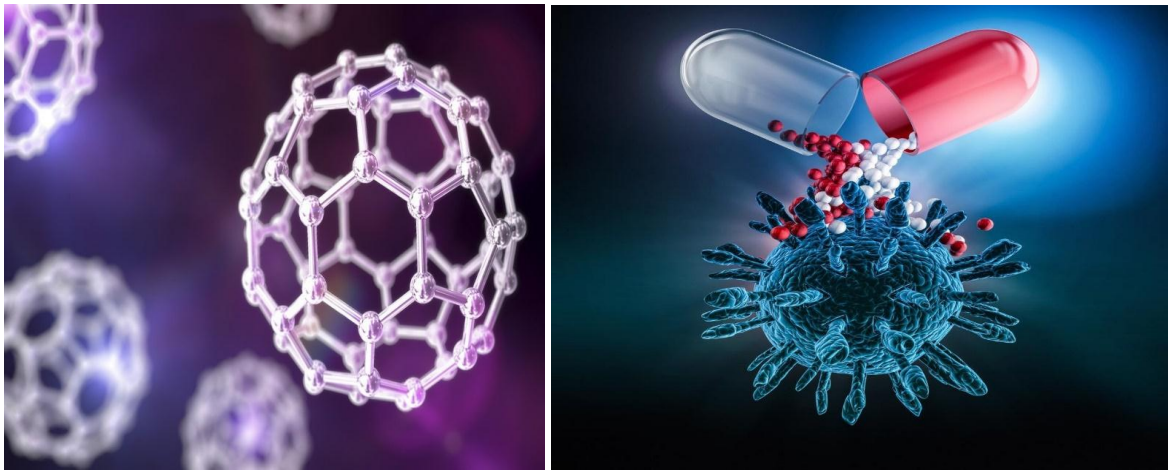
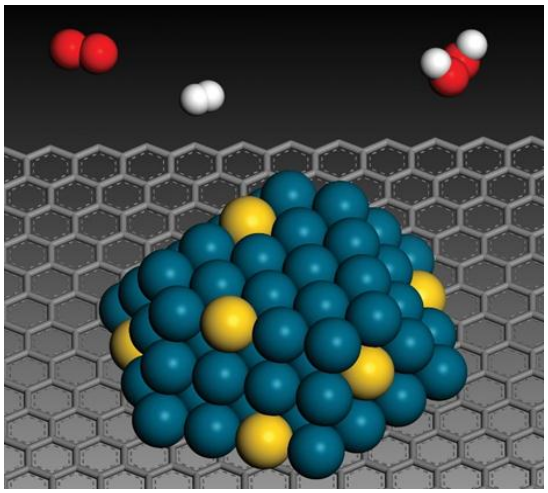
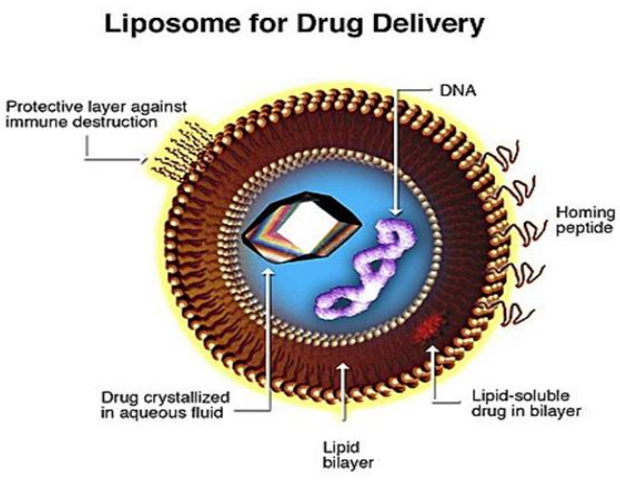


Figure-1: Nanoparticles.

The development of new drug systems is time-consuming; it takes approximately seven years to complete fundamental research and development before advancing to preclinical animal studies.

Drug delivery: Nanotechnology has provided the possibility of delivering drugs to specific cells using the nanoparticles. The overall drug consumption and side-effects may be lowered significantly by depositing the active pharmaceutical agent in the morbid region only and in no higher dose than needed. Targeted drug delivery is intended to reduce the side effects of drugs with concomitant decreases in consumption and treatment expenses.[2]





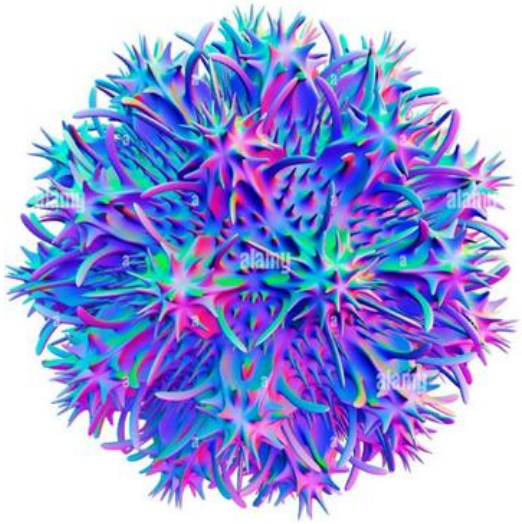


Figure-2: Nanoparticles, liposomes, and dendrimers are some nanomaterials being investigated for use in nanomedicine.

Additionally, targeted drug delivery reduces the side effect possessed by crude drug via minimizing undesired exposure to the healthy cells. Drug delivery focuses on maximizing bioavailability both at specific places in the body and over a period of time. This can potentially be achieved by molecular targeting by nanoengineered devices. A benefit of using nanoscale for medical technologies is that smaller devices are less invasive and can possibly be implanted inside the body, plus biochemical reaction times are much shorter. These devices are faster and more sensitive than typical drug delivery. The efficacy of drug delivery through nanomedicine is largely based upon: a) efficient encapsulation of the drugs, b) successful delivery of drug to the targeted region of the body, and c) successful release of the drug. Several nano-delivery drugs were on the market by 2019.[3]

Drug delivery systems, lipid- or polymer-based nanoparticles, can be designed to improve the pharmacokinetics and biodistribution of the drug. However, the pharmacokinetics and pharmacodynamics of nanomedicine is highly variable among different patients. When designed to avoid the body's defence mechanisms, nanoparticles have beneficial properties that can be used to improve drug delivery. Complex drug delivery mechanisms are being developed, including the ability to get drugs through cell membranes and into cell cytoplasm. Triggered response is one way for drug molecules to be used more efficiently. Drugs are placed in the body and only activate on encountering a particular signal. For example, a drug with poor solubility will be replaced by a drug delivery system where both hydrophilic and hydrophobic environments exist, improving the solubility. Drug delivery systems may also be able to prevent tissue damage through regulated drug release; reduce drug clearance rates; or lower the volume of distribution and reduce the effect on non-target tissue. However, the biodistribution of these nanoparticles is still imperfect due to the complex host's reactions to nano- and microsized materials and the difficulty in targeting specific organs in the body. Nevertheless, a lot of work is still ongoing to optimize and better understand the potential and limitations of nanoparticulate systems. While advancement of research proves that targeting and distribution can be augmented by nanoparticles, the dangers of nanotoxicity become an important next step in further understanding of their medical uses. The toxicity of nanoparticles varies, depending on size, shape, and material. These factors also affect the build-up and organ damage that may occur. Nanoparticles are made to be long-lasting, but this causes them to be trapped within organs, specifically the liver and spleen, as they cannot be broken down or excreted. This build-up of non-biodegradable material has been observed to cause organ damage and inflammation in mice. Magnetic targeted delivery of magnetic nanoparticles to the tumor site under the influence of inhomogeneous stationary magnetic fields may lead to enhanced tumor growth. In order to circumvent the pro-tumorigenic effects, alternating electromagnetic fields should be used. Nanoparticles are under research for their potential to decrease antibiotic resistance or for various antimicrobial uses. Nanoparticles might also be used to circumvent multidrug resistance (MDR) mechanisms.[4]

Characterization: Nanoparticle drug delivery focuses on maximizing drug efficacy and minimizing cytotoxicity. Fine-tuning nanoparticle properties for effective drug delivery involves addressing the following factors. The surface-area-to-volume ratio of nanoparticles can be altered to allow for more ligand binding to the surface. Increasing ligand binding efficiency can decrease dosage and minimize nanoparticle toxicity. Minimizing dosage or dosage frequency also lowers the mass of nanoparticle per mass of drug, thus achieving greater efficiency. Metal nanoparticles, such as gold nanoparticles, have optical qualities (also described in nanomaterials) that allow for

less invasive imaging techniques. Furthermore, the photothermal response of nanoparticles to optical stimulation can be directly utilized for tumor therapy.

Platforms: Current nanoparticle drug delivery systems can be catalogued based on their platform composition into several groups: polymeric nanoparticles, inorganic nanoparticles, viral nanoparticles, lipid-based nanoparticles, and nanoparticle albumin-bound (nab) technology. Each family has its unique characteristics.

Polymeric nanoparticles: Polymeric nanoparticles are synthetic polymers with a size ranging from 10 to 100 nm. Common synthetic polymeric nanoparticles include polyacrylamide, polyacrylate, and chitosan. Drug molecules can be incorporated either during or after polymerization. Depending on the polymerization chemistry, the drug can be covalently bonded, encapsulated in a hydrophobic core, or conjugated electrostatically. Common synthetic strategies for polymeric nanoparticles include microfluidic approaches, electro dropping, high pressure homogenization, and emulsion-based interfacial polymerization. Polymer biodegradability is an important aspect to consider when choosing the appropriate nanoparticle chemistry. Nano carriers composed of biodegradable polymers undergo hydrolysis in the body, producing biocompatible small molecules such as lactic acid and glycolic acid. Polymeric nanoparticles can be created via self-assembly or other methods such as particle replication in no wetting templates (PRINT) which allows customization of composition, size, and shape of the nanoparticle using tiny molds.[5]

Dendrimers: Dendrimers are unique hyper-branched synthetic polymers with monodispersed size, well-defined structure, and a highly functionalized terminal surface. They are typically composed of synthetic or natural amino acid, nucleic acids, and carbohydrates. Therapeutics can be loaded with relative ease onto the interior of the dendrimers or the terminal surface of the branches via electrostatic interaction, hydrophobic interactions, hydrogen bonds, chemical linkages, or covalent conjugation. Drug-dendrimer conjugation can elongate the half-life of drugs. Currently, dendrimer use in biological systems is limited due to dendrimer toxicity and limitations in their synthesis methods. Dendrimers are also confined within a narrow size range (<15 nm) and current synthesis methods are subject to low yield. The surface groups will reach the de Gennes dense packing limit at high generation level, which seals the interior from the bulk solution – this can be useful for encapsulation of hydrophobic, poorly soluble drug molecules. The seal can be tuned by intramolecular interactions between adjacent surface groups, which can be varied by the condition of the solution, such as pH, polarity, and temperature, a property which can be utilized to tailor encapsulation and controlled release properties.[6]

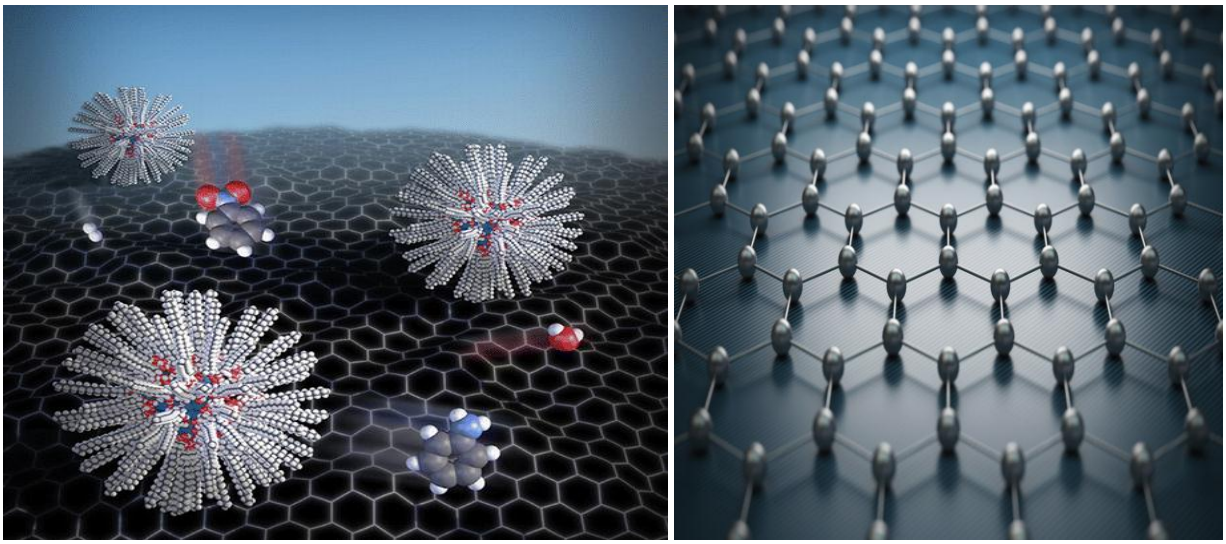


Figure-3: Platinum Nanoparticle.

Inorganic Nanoparticles and Nano crystals: Inorganic nanoparticles have emerged as highly valuable functional building blocks for drug delivery systems due to their well-defined and highly tunable properties such as size, shape, and surface functionalization. Inorganic nanoparticles have been largely adopted to biological and medical applications ranging from imaging and diagnoses to drug delivery. Inorganic nanoparticles are usually composed of inert metals such as gold and titanium that form Nano spheres, however, iron oxide nanoparticles have also become an option.

Quantum dots (QDs), or inorganic semiconductor Nano crystals, have also emerged as valuable tools in the field of bio nanotechnology because of their unique size-dependent optical properties and versatile surface chemistry. Their diameters (2 - 10 nm) are on the order of the exciton Bohr radius, resulting in quantum confinement effects analogous to the "particle-in-a-box"

model. As a result, optical and electronic properties of quantum dots vary with their size: nanocrystals of larger sizes will emit lower energy light upon fluorescence excitation.[7]

Surface engineering of QDs is crucial for creating nanoparticle–biomolecule hybrids capable of participating in biological processes. Manipulation of nanocrystal core composition, size, and structure changes QD photo-physical properties designing coating materials which encapsulate the QD core in an organic shell make nanocrystals biocompatible, and QDs can be further decorated with biomolecules to enable more specific interaction with biological targets. The design of inorganic nanocrystal core coupled with biologically compatible organic shell and surface ligands can combine useful properties of both materials, i.e. optical properties of the QDs and biological functions of ligands attached.

Toxicity: While application of inorganic nanoparticles in bionanotechnology shows encouraging advancements from a materials science perspective, the use of such materials *in-vivo* is limited by issues related with toxicity, biodistribution and bioaccumulation. Because metal inorganic nanoparticle systems degrade into their constituent metal atoms, challenges may arise from the interactions of these materials with biosystems, and a considerable amount of the particles may remain in the body after treatment, leading to buildup of metal particles potentially resulting in toxicity.

Recently, however, some studies have shown that certain nanoparticle environmental toxicity effects aren't apparent until nanoparticles undergo transformations to release free metal ions. Under aerobic and anaerobic conditions, it was found that copper, silver, and titanium nanoparticles released low or insignificant levels of metal ions. This is evidence that copper, silver, and titanium NP are slow to release metal ions, and may therefore appear at low levels in the environment. Additionally, nanoshell coatings significantly protect against degradation in the cellular environment and also reduce QDs toxicity by reducing metal ion leakage from the core.[8]

Organic Nanocrystals: Organic nanocrystals consist of pure drugs and surface active agents required for stabilization. They are defined as carrier-free submicron colloidal drug delivery systems with a mean particle size in the nanometre range. The primary importance of the formulation of drugs into nanocrystals is the increase in particle surface area in contact with the dissolution medium, therefore increasing bioavailability. A number of drug products formulated in this way are on the market.[9]

Solubility: One of the issues faced by drug delivery is the solubility of the drug in the body; around 40% of newly detected chemicals found in drug discovery are poorly soluble in water. This low solubility affects the bioavailability of the drug, meaning the rate at which the drug reaches the circulatory system and thus the target site. Low bioavailability is most commonly seen in oral administration, which is the preferred choice for drug administration due to its convenience, low costs, and good patient practice. A measure to improve poor bioavailability is to inject the drugs in a solvent mixture with a solubilizing agent. However, results show this solution is ineffective, with the solubilizing agent demonstrating side-effects and/or toxicity. Nanocrystals used for drug delivery can increase saturation solubility and dispersion velocity. Generally, saturation solubility is thought to be a function of temperature, but it is also based on other factors, such as crystalline structure and particle size, in regards to nanocrystals. The Ostwald-Freundlich equation below shows this relationship:

$$\log\left(\frac{C_s}{C_\alpha}\right) = \frac{2\sigma V}{2.303RT\rho r}$$

Where $\mathbf{C_s}$ is the saturation solubility of the nanocrystal, $\mathbf{C_\alpha}$ is the solubility of the drug at a non-nano scale, $\boldsymbol{\sigma}$ is the interfacial tension of the substance, **V** is the molar volume of the particle, **R** is the gas constant, **T** is the absolute temperature, $\boldsymbol{\rho}$ is the density of the solid, and **r** is the radius. The advantage of nanocrystals is that they can improve oral adsorption, bioavailability, and action onset and reduces intersubject variability. Consequently, nanocrystals are now being produced and are on the market for a variety of purposes ranging from antidepressants to appetite stimulants. Nanocrystals can be produced using two different ways: the top-down method or the bottom-up method. Bottom-up technologies are also known as nanoprecipitation. This technique involves dissolving a drug in a suitable solvent and then precipitating it with a non-solvent. On the other hand, top-down technologies use force to reduce the size of a particle to nanometers, usually done by milling a drug. Top-down methods are preferred when working with poorly soluble drugs.[10]

Stability: A disadvantage of using nanocrystals for drug delivery is nanocrystal stability. Instability problems of nanocrystalline structures derive from thermodynamic processes such as particle aggregation, amorphization, and bulk crystallization. Particles at the nanoscopic scale

feature a relative excess of Gibbs free energy, due to their higher surface area to volume ratio. To reduce this excess energy, it is generally favorable for aggregation to occur. Thus, individual nanocrystals are relatively unstable by themselves and will generally aggregate. This is particularly problematic in top-down production of nanocrystals. Methods such as high-pressure homogenization and bead milling, tend to increase instabilities by increasing surface areas; to compensate, or as a response to high pressure, individual particles may aggregate or turn amorphous in structure. Such methods can also lead to the reprecipitation of the drug by surpassing the solubility beyond the saturation point (Ostwald ripening). One method to overcome aggregation and retain or increase nanocrystal stability is by use of stabilizer molecules. These molecules, which interact with the surface of the nanocrystals and prevent aggregation via ionic repulsion or steric barriers between the individual nanocrystals, include surfactants and are generally useful for stabilizing suspensions of nanocrystals. Concentrations of surfactants that are too high, however, may inhibit nanocrystal stability and enhance crystal growth or aggregation. It has been shown that certain surfactants, upon reaching a critical concentration, begin to self-assemble into micelles, which then compete with nanocrystal surfaces for other surfactant molecules. With fewer surface molecules interacting with the nanocrystal surface, crystal growth and aggregation is reported to occur at increased amounts. Use of surfactant at optimal concentrations reportedly allows for higher stability, larger drug capacity as a carrier, and sustained drug release. In a study using PEG as a stabilizer was found that nanocrystals treated with PEG enhanced accumulation at tumor sites and had greater blood circulation, than those not treated with PEG. Amorphization can occur in top-down methods of production. With different intramolecular arrangements, amorphization of nanocrystals leads to different thermodynamic and kinetic properties that affect drug delivery and kinetics. Transition to amorphous structures is reported to occur through production practices such as spray drying, lyophilization, and mechanical mechanisms, such as milling. This amorphization has been reportedly observed with or without the presence of stabilizer in a dry milling process. Using a wet milling process with surfactant, however significantly reduced amorphization, suggesting that solvent, in this case water, and surfactant could inhibit amorphization for some top-down production methods that otherwise reportedly facilitate amorphization.[11]

Liposome delivery: Liposomes are spherical vesicles composed of synthetic or natural phospholipids that self-assemble in aqueous solution in sizes ranging from tens of nanometers to micrometers. The resulting vesicle, which has an aqueous core surrounded by a hydrophobic membrane, can be loaded with a wide variety of hydrophobic or hydrophilic molecules for therapeutic purposes.[12]

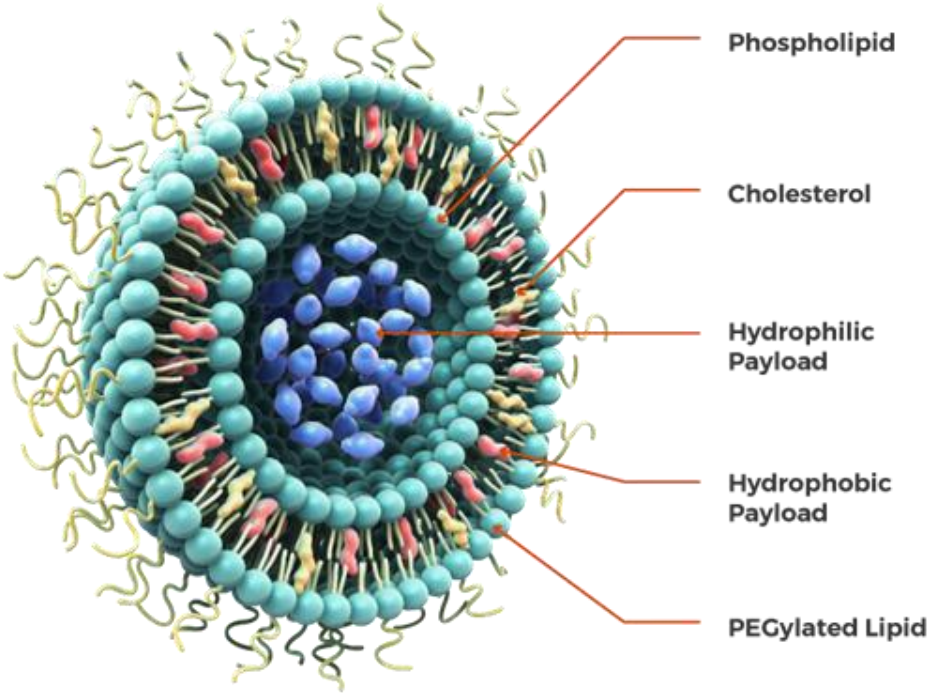


Figure-4: Basic Liposome Structure.

Liposomes are typically synthesized with naturally occurring phospholipids, mainly phosphatidylcholine. Cholesterol is often included in the formulation to adjust the rigidity of the membrane and to increase stability. The molecular cargo is loaded through liposome formation in aqueous solution, solvent exchange mechanisms, or pH gradients methods. Various molecules can also be chemically conjugated to the

surface of the liposome to alter recognition properties. One typical modification is conjugating polyethyleneglycol (PEG) to the vesicle surface. The hydrophilic polymer prevents recognition by macrophages and decreases clearance. The size, surface charge, and bilayer fluidity also alter liposome delivery kinetics. Liposomes diffuse from the bloodstream into the interstitial space near the target site. As the cell membrane itself is composed of phospholipids, liposomes can directly fuse with the membrane and release the cargo into the cytosol, or may enter the cell through phagocytosis or other active transport pathways. Liposomal delivery has various advantages. Liposomes increase the solubility, stability, and uptake of drug molecules. Peptides, polymers, and other molecules can be conjugated to the surface of a liposome for targeted delivery. Conjugating various ligands can facilitate binding to target cells based on the receptor-ligand interaction. Altering vesicle size and surface chemistry can also be tuned to increase circulation time. Various FDA-approved liposomal drugs are in clinical use in the US. The anthracycline drug doxorubicin is delivered with phospholipid-cholesterol liposomes to treat AIDS-related Kaposi sarcoma and multiple myeloma with high efficacy and low toxicity. Many others are undergoing clinical trials, and liposomal drug delivery remains an active field of research today, with potential applications including nucleic acid therapy, brain targeting, and tumor therapy.[13]

Viral vectors, viral-like particles, and biological nanocarriers: Viruses can be used to deliver genes for genetic engineering or gene therapy. Commonly used viruses include adenoviruses, retroviruses, and various bacteriophages. The surface of the viral particle can also be modified with ligands to increase targeting capabilities. While viral vectors can be used to great efficacy, one concern is that may cause off-target effects due to its natural tropism. This usually requires replacing the proteins causing virus-cell interactions with chimeric proteins. In addition to using viruses, drug molecules can also be encapsulated in protein particles derived from the viral capsid, or virus-like particles (VLPs). VLPs are easier to manufacture than viruses, and their structural uniformity allows VLPs to be produced precisely in large amounts. VLPs also have easy-to-modify surfaces, allowing the possibility for targeted delivery. There are various methods of packaging the molecule into the capsid; most take advantage of the capsid's ability to self-assemble. One strategy is to alter the pH gradient outside the capsid to create pores on the capsid surface and trap the desired molecule. Other methods use aggregators such as leucine zippers or polymer-DNA amphiphiles to induce capsid formation and capture drug molecules. It is also possible to chemically conjugate of drugs directly onto the reactive sites on the capsid surface, often involving the formation of amide bonds. After being introduced to the organism, VLPs often have broad tissue distribution, rapid clearance, and are generally non-toxic. It may, however, like viruses, invoke an immune response, so immune-masking agents may be necessary.[14]

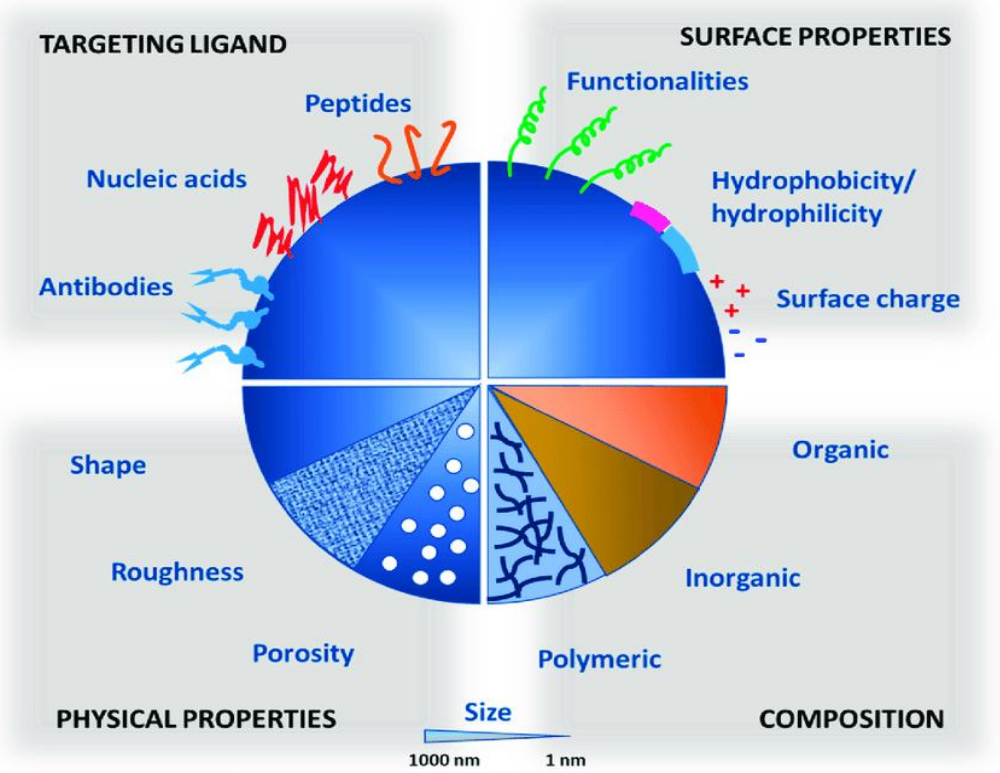


Figure-5: Biological Nanocarriers.

Nanoparticle Albumin-bound (nab) Technology: Nanoparticle albumin-bound technology utilizes the protein albumin as a carrier for hydrophobic chemotherapy drugs through noncovalent binding. Because albumin is already a natural carrier of hydrophobic particles and is able to transcytose molecules bound to itself, albumin composed nanoparticles have become an effective strategy for the treatment of many diseases in clinical research.[15]

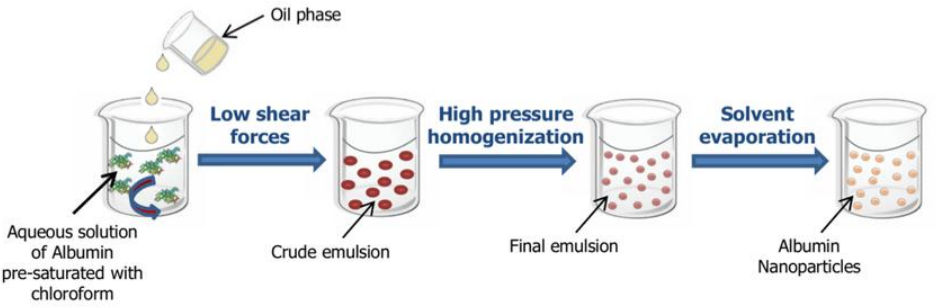


Figure-6: NAB Technology.

Delivery and release mechanisms: An ideal drug delivery system should have effective targeting and controlled release. The two main targeting strategies are passive targeting and active targeting. Passive targeting depends on the fact that tumors have abnormally structured blood vessels that favor accumulation of relatively large macromolecules and nanoparticles. This so-called enhanced permeability and retention effect (EPR) allows the drug-carrier be transported specifically to the tumor cells. Active targeting is, as the name suggests, much more specific and is achieved by taking advantage of receptor-ligand interactions at the surface of the cell membrane. Controlled drug release systems can be achieved through several methods. Rate-programmed drug delivery systems are tuned to the diffusivity of active agents across the membrane. Another delivery-release mechanism is activation-modulated drug delivery, where the release is triggered by environmental stimuli. The stimuli can be external, such as the introduction of a chemical activators or activation by light or electromagnetic fields, or biological - such as pH, temperature, and osmotic pressure which can vary widely throughout the body.[16]

Polymeric nanoparticles: For polymeric nanoparticles, the induction of stimuli-responsiveness has usually relied heavily upon well-known polymers that possess an inherent stimuli-responsiveness. Certain polymers that can undergo reversible phase transitions due to changes in temperature or pH have aroused interest. Arguably the most utilized polymer for activation-modulated delivery is the thermo-responsive polymer poly (N-isopropylacrylamide). It is readily soluble in water at room temperature but precipitates reversibly from when the temperature is raised above its lower critical solution temperature (LCST), changing from an extended chain conformation to a collapsed chain. This feature presents a way to change the hydrophilicity of a polymer via temperature. Efforts also focus on dual stimuli-responsive drug delivery systems, which can be harnessed to control the release of the encapsulated drug. For example, the triblock copolymer of poly (ethylene glycol)-b-poly (3-aminopropyl-methacrylamide)-b-poly (N-isopropylacrylamide) (PEG-b-PAPMA-b-PNIPAm) can self-assemble to form micelles, possessing a core–shell–corona architecture above the lower critical solution temperature. It is also pH responsive. Therefore, drug release can be tuned by changing either temperature or pH conditions.[17]

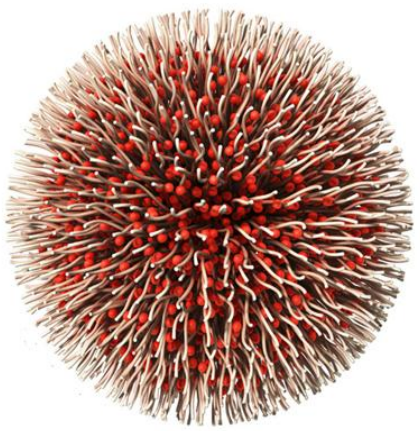


Figure-7: Polymeric Nanoparticle.

Inorganic nanoparticles: Drug delivery strategies of inorganic nanoparticles are dependent on material properties. The active targeting of inorganic nanoparticle drug carriers is often achieved by surface functionalization with specific ligands of nanoparticles. For example, the inorganic multifunctional nanovehicle (5-FU/Fe3O4/αZrP@CHI-FA-R6G) is able to accomplish tumor optical imaging and therapy simultaneously. It can be directed to the location of cancer cells with sustained release behavior. Studies have also been done on gold nanoparticle responses to local near-infrared (NIR) light as a stimuli for drug release. In one study, gold nanoparticles functionalized with double-stranded DNA encapsulated with drug molecules, were irradiated with NIR light. The particles generated heat and denatured the double-stranded DNA, which triggered the release of drugs at the target site. Studies also suggest that a porous structure is beneficial to attain a sustained or pulsatile release. Porous inorganic materials demonstrate high mechanical and chemical stability within a range of physiological conditions. The well-defined surface properties, such as high pore volume, narrow pore diameter distribution, and high surface area allow the entrapment of drugs, proteins and other biogenic molecules with predictable and reproducible release patterns.[18]

Systems under research: Advances in lipid nanotechnology were instrumental in engineering medical nanodevices and novel drug delivery systems, as well as in developing sensing applications. Another system for microRNA delivery under preliminary research is nanoparticles formed by the self-assembly of two different microRNAs deregulated in cancer. One potential application is based on small electromechanical systems, such as nanoelectromechanical systems being investigated for the active release of drugs and sensors for possible cancer treatment with iron nanoparticles or gold shells.[19]

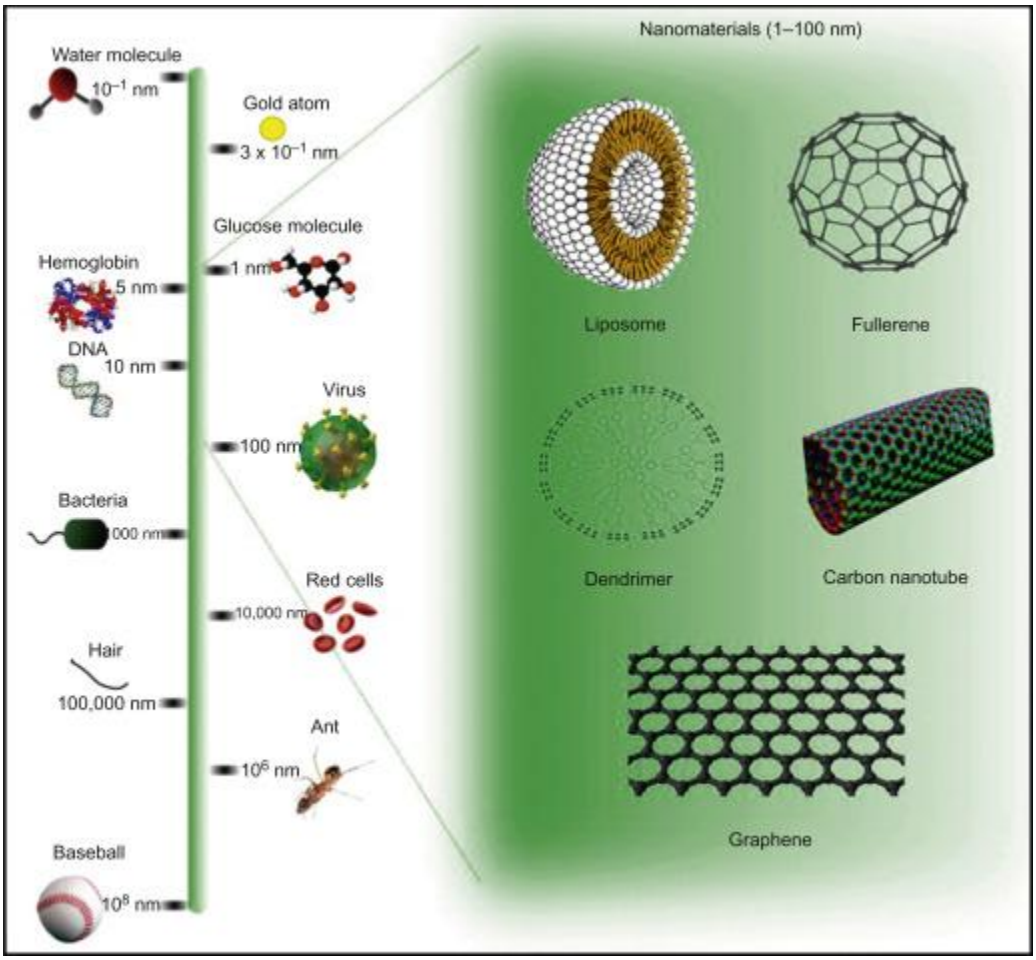


Figure-8: Nanomedicines.

Applications: Some nanotechnology-based drugs that are commercially available or in human clinical trials include:

1. Abraxane, approved by the U.S. Food and Drug Administration (FDA) to treat breast cancer, non-small-cell lung cancer (NSCLC) and pancreatic cancer, is the nanoparticle albumin bound paclitaxel.
2. Doxil was originally approved by the FDA for the use on HIV-related Kaposi's sarcoma. It is now being used to also treat ovarian cancer and multiple myeloma. The drug is encased in liposomes, which helps to extend the

life of the drug that is being distributed. Liposomes are self-assembling, spherical, closed colloidal structures that are composed of lipid bilayers that surround an aqueous space. The liposomes also help to increase the functionality and it helps to decrease the damage that the drug does to the heart muscles specifically.

3. Onivyde, liposome encapsulated irinotecan to treat metastatic pancreatic cancer, was approved by FDA in October 2015.

4. Rapamune is a nanocrystal-based drug that was approved by the FDA in 2000 to prevent organ rejection after transplantation. The nanocrystal components allow for increased drug solubility and dissolution rate, leading to improved absorption and high bioavailability.[20]

5. Cabenuva is approved by FDA as cabotegravir extended-release injectable nano-suspension, plus rilpivirine extended-release injectable nano-suspension. It is indicated as a complete regimen for the treatment of HIV-1 infection in adults to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine. This is the first FDA-approved injectable, complete regimen for HIV-1 infected adults that is administered once a month.[21]

Imaging: *In vivo* imaging is another area where tools and devices are being developed. Using nanoparticle contrast agents, images such as ultrasound and MRI have a favorable distribution and improved contrast. In cardiovascular imaging, nanoparticles have potential to aid visualization of blood pooling, ischemia, angiogenesis, atherosclerosis, and focal areas where inflammation is present. The small size of nanoparticles endows them with properties that can be very useful in oncology, particularly in imaging. Quantum dots (nanoparticles with quantum confinement properties, such as size-tunable light emission), when used in conjunction with MRI (magnetic resonance imaging), can produce exceptional images of tumor sites. Nanoparticles of cadmium selenide (quantum dots) glow when exposed to ultraviolet light. When injected, they seep into cancer tumors. The surgeon can see the glowing tumor, and use it as a guide for more accurate tumor removal. These nanoparticles are much brighter than organic dyes and only need one light source for excitation. This means that the use of fluorescent quantum dots could produce a higher contrast image and at a lower cost than today's organic dyes used as contrast media. The downside, however, is that quantum dots are usually made of quite toxic elements, but this concern may be addressed by use of fluorescent dopants. Tracking movement can help determine how well drugs are being distributed or how substances are metabolized. It is difficult to track a small group of cells throughout the body, so scientists used to dye the cells. These dyes needed to be excited by light of a certain wavelength in order for them to light up.[22]

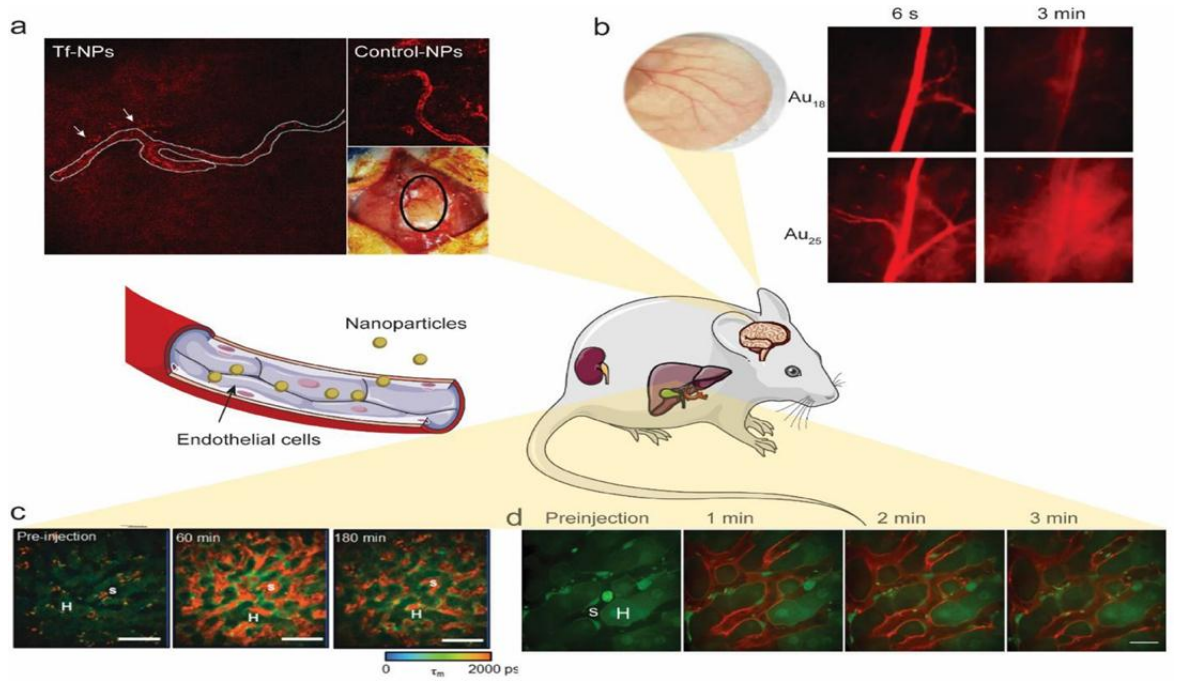


Figure-9: Scanning through Nanoparticles.

While different color dyes absorb different frequencies of light, there was a need for as many light sources as cells. A way around this problem is with luminescent tags. These tags are quantum dots attached to proteins that penetrate cell membranes. The dots can be random in size, can be made of bio-inert material, and they demonstrate the nanoscale property that color is size-dependent. As a result, sizes are selected so that the frequency of light used to make a group of quantum dots fluoresce is an even multiple of the frequency required to

make another group incandesce. Then both groups can be lit with a single light source. They have also found a way to insert nanoparticles into the affected parts of the body so that those parts of the body will glow showing the tumor growth or shrinkage or also organ trouble.[23]

Sensing: Nanotechnology-on-a-chip is one more dimension of lab-on-a-chip technology. Magnetic nanoparticles, bound to a suitable antibody, are used to label specific molecules, structures or microorganisms. In particular silica nanoparticles are inert from the photophysical point of view and might accumulate a large number of dye(s) within the nanoparticle shell. Gold nanoparticles tagged with short segments of DNA can be used for detection of genetic sequence in a sample. Multicolor optical coding for biological assays has been achieved by embedding different-sized quantum dots into polymeric microbeads. Nanopore technology for analysis of nucleic acids converts strings of nucleotides directly into electronic signatures. Sensor test chips containing thousands of nanowires, able to detect proteins and other biomarkers left behind by cancer cells, could enable the detection and diagnosis of cancer in the early stages from a few drops of a patient's blood. Nanotechnology is helping to advance the use of arthroscopes, which are pencil-sized devices that are used in surgeries with lights and cameras so surgeons can do the surgeries with smaller incisions. The smaller the incisions the faster the healing time which is better for the patients. It is also helping to find a way to make an arthroscope smaller than a strand of hair.[24]

Research on nanoelectronics-based cancer diagnostics could lead to tests that can be done in pharmacies. The results promise to be highly accurate and the product promises to be inexpensive. They could take a very small amount of blood and detect cancer anywhere in the body in about five minutes, with a sensitivity that is a thousand times better a conventional laboratory test. These devices are built with nanowires to detect cancer proteins; each nanowire detector is primed to be sensitive to a different cancer marker. The biggest advantage of the nanowire detectors is that they could test for anywhere from ten to one hundred similar medical conditions without adding cost to the testing device. Nanotechnology has also helped to personalize oncology for the detection, diagnosis, and treatment of cancer. It is now able to be tailored to each individual's tumor for better performance. They have found ways that they will be able to target a specific part of the body that is being affected by cancer.[25]

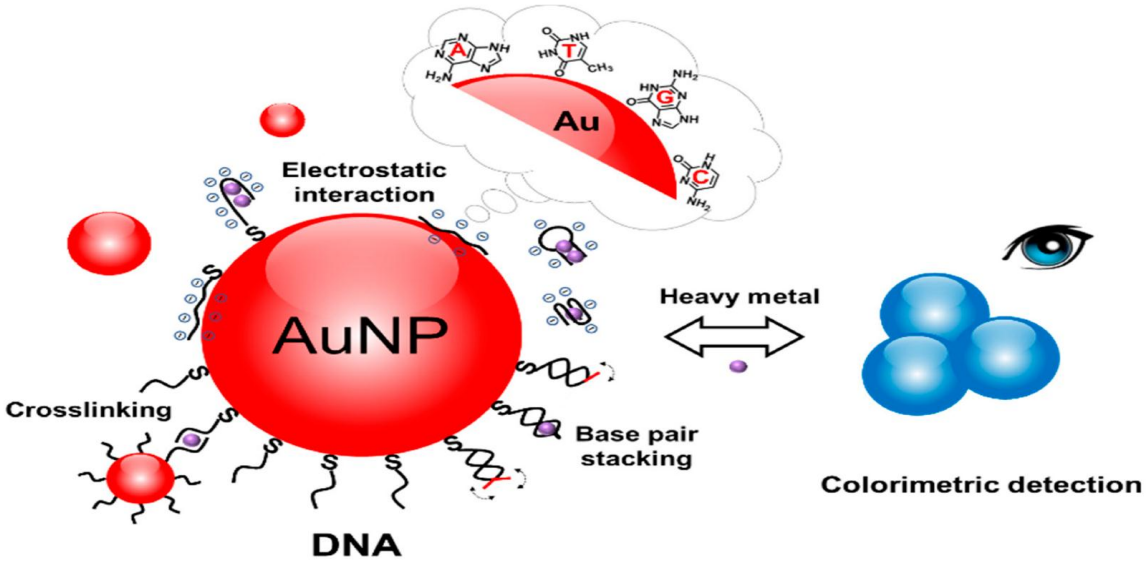


Figure-10: Biosensors.

Sepsis treatment: In contrast to dialysis, which works on the principle of the size related diffusion of solutes and ultrafiltration of fluid across a semi-permeable membrane, the purification with nanoparticles allows specific targeting of substances. Additionally larger compounds which are commonly not dialyzable can be removed. The purification process is based on functionalized iron oxide or carbon coated metal nanoparticles with ferromagnetic or superparamagnetic properties. Binding agents such as proteins, antibiotics, or synthetic ligands are covalently linked to the particle surface. These binding agents are able to interact with target species forming an agglomerate. Applying an external magnetic field gradient allows exerting a force on the nanoparticles. Hence the particles can be separated from the bulk fluid, thereby cleaning it from the contaminants. The small size (< 100 nm) and large surface area of functionalized nanomagnets leads to advantageous properties compared to hemoperfusion, which is a clinically used technique for the purification of blood and is based on surface adsorption. These advantages are high loading and accessible for binding agents, high selectivity towards the target compound, fast diffusion, small hydrodynamic resistance, and low dosage.[26]

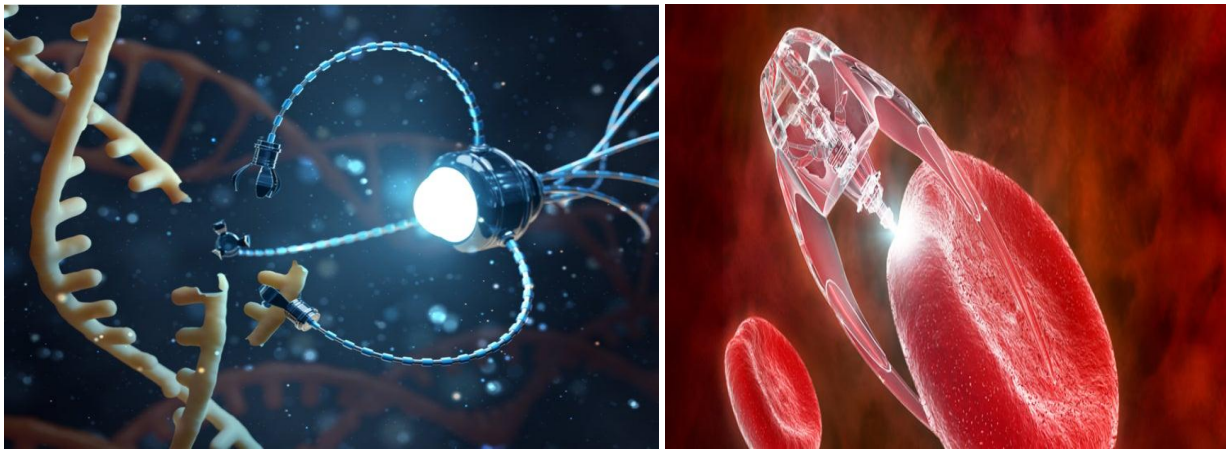


Figure-11: Medical Devices Based On Nano Particle.

Tissue engineering: Nanotechnology may be used as part of tissue engineering to help reproduce or repair or reshape damaged tissue using suitable nanomaterial-based scaffolds and growth factors. Tissue engineering if successful may replace conventional treatments like organ transplants or artificial implants. Nanoparticles such as graphene, carbon nanotubes, molybdenum disulfide and tungsten disulfide are being used as reinforcing agents to fabricate mechanically strong biodegradable polymeric nanocomposites for bone tissue engineering applications. The addition of these nanoparticles in the polymer matrix at low concentrations (~0.2 weight %) leads to significant improvements in the compressive and flexural mechanical properties of polymeric nanocomposites. Potentially, these nanocomposites may be used as a novel, mechanically strong, light weight composite as bone implants. For example, a flesh welder was demonstrated to fuse two pieces of chicken meat into a single piece using a suspension of gold-coated nanoshells activated by an infrared laser. This could be used to weld arteries during surgery. Another example is nanonephrology, the use of nanomedicine on the kidney.[27]

Medical devices: Neuro-electronic interfacing is a visionary goal dealing with the construction of nanodevices that will permit computers to be joined and linked to the nervous system. This idea requires the building of a molecular structure that will permit control and detection of nerve impulses by an external computer. A refuelable strategy implies energy is refilled continuously or periodically with external sonic, chemical, tethered, magnetic, or biological electrical sources, while a non-refuelable strategy implies that all power is drawn from internal energy storage which would stop when all energy is drained. A nanoscale enzymatic biofuel cell for self-powered nanodevices have been developed that uses glucose from biofluids including human blood and watermelons. One limitation to this innovation is the fact that electrical interference or leakage or overheating from power consumption is possible. The wiring of the structure is extremely difficult because they must be positioned precisely in the nervous system. The structures that will provide the interface must also be compatible with the body's immune system.[28]

CONCLUSION

Molecular nanotechnology is a speculative subfield of nanotechnology regarding the possibility of engineering molecular assemblers, machines which could re-order matter at a molecular or atomic scale. Nanomedicine would make use of these nanorobots, introduced into the body, to repair or detect damages and infections. Molecular nanotechnology is highly theoretical, seeking to anticipate what inventions nanotechnology might yield and to propose an agenda for future inquiry. The proposed elements of molecular nanotechnology, such as molecular assemblers and nanorobots are far beyond current capabilities. Future advances in nanomedicine could give rise to life extension through the repair of many processes thought to be responsible for aging. K. Eric Drexler, one of the founders of nanotechnology, postulated cell repair machines, including ones operating within cells and utilizing as yet hypothetical molecular machines, in his 1986 book *Engines of Creation*, with the first technical discussion of medical nanorobots by Robert Freitas appearing in 1999. Raymond Kurzweil, a futurist and transhumanist, stated in his book *The Singularity Is Near* that he believes that advanced medical nanorobotics could completely remedy the effects of aging by 2030. According to Richard Feynman, it was his former graduate student and collaborator Albert Hibbs who originally suggested to him (c. 1959) the idea of a *medical* use for Feynman's theoretical micromachines (see nanotechnology). Hibbs suggested that certain repair machines might one day be reduced in size to the point that it would, in theory, be possible to (as Feynman put it) "swallow the doctor". Some of the same properties that make nanoparticles efficient drug carriers also contribute to their toxicity. For example, gold nanoparticles are known to interact with proteins through surface adsorption, forming a protein corona, which can be utilized for cargo loading and immune shielding. However, this protein-adsorption property can also disrupt normal protein function that is

essential for homeostasis, especially when the protein contains exposed sulfur groups. The photothermal effect, which can be induced to kill tumor cells, may also create reactive oxygen species that impose oxidative stress on surrounding healthy cells. Gold nanoparticles of sizes below 4-5 nm fit in DNA grooves which can interfere with transcription, gene regulation, replication, and other processes that rely on DNA-protein binding. Lack of biodegradability for some nanoparticle chemistries can lead to accumulation in certain tissues, thus interfering with a wide range of biological processes. Currently, there is no regulatory framework in the United States for testing nanoparticles for their general impact on health and on the environment.

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