J. Mat. NanoSci. 2016, 3(2), 50-56 Viewpoint

Journal of
Materials NanoScience

Integrated Science

Prospects of applied nanomedicine: potential clinical and (bio)medical interventions via nanoscale research advances

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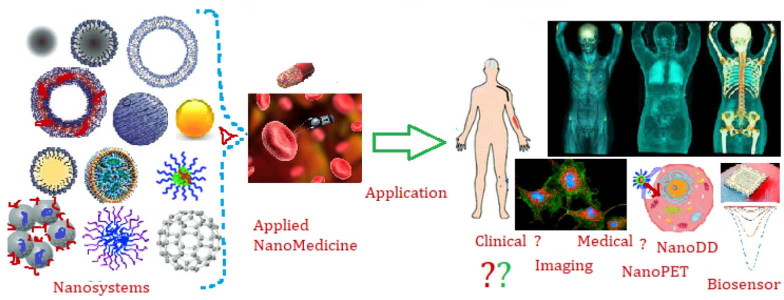
Abstract



The nanoscale research advances meant for application in medical sciences has seen a prominent participation of experts from different fields. The leading explorations have brought about new methods, techniques, technologies and drug formulations that find applications in different specialties of medical science. The new materials for clinical applications (the drug formulations and systems under evaluation with possible application in therapeutics) and medical fields (the techniques and drug formulations available for use in treatment of different diseases) have been possible with advances in development of nanomedicinal and nanobiotechnological research. Various systems and pharmaceuticals made possible include biosensors, nanorobotics, nanoradippharmaceuticals, nanoPET, nanodrug delivery systems, nanosurgery, and other biomedical applications. This article provides a discussion about the different fields of clinical sciences and medical specialties where nanomedicine research has potential application with translational possibilities.

Keywords: NanoDrug Delivery, Nanotherapeutics, Nanodiagnosis, Nanopharmaceuticals, Nanobiotechnology, Nanobiosensor, Nanoscience

INTRODUCTION

Scaling down the biomedical research to nanomolecular level provide advantage of utilization of properties of nanoscale biomaterials for efficient and improved development of drugs and drug delivery systems. Understanding of the molecular properties at nanometer level has provided a new vista in development of new remedies to incurable diseases through new drugs and delivery vehicles besides the robust developments in materials sciences.

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Cite as: J. Mat. NanoSci., 2016, 3(1), 50-56.

 ISSN 2394-0867 http://pubs.iscience.in/jmns

Nanomedicine research has grown potentially in last decade and has established itself as a new field of scientific research for development of better therapeutics and diagnostics. Based on utilization of nanoscale material, many new drugs and delivery systems has been approved by FDA and other appellate approving authorities in different countries for clinical applications. Having understood the fundamental aspects of nanoscale designing and nanomolecular properties, the research has oriented more towards development of translational medicine with emphasis on development of applicable biomaterials through nanoscale study. The fundamental nanomedicine maturation has moved the field to applied nanomedicine now.

The scope of applied nanomedicine research is very wide and covers nearly all fields of biomedical and medical research including nanochemistry of drugs design, nanoinformatics, nano-biosensors, nanopeptides, nano drug delivery systems including nanoparticulates, carbon nanomaterials, nanoassembled natural products (nanopeptides, nanoglycans, nanolipids liposomes), toxicity of nanobiomaterials, nanotools and techniques (nanobiotechnology, biomedical nanotechnology), nanorobotics, nanomedicine for molecular imaging (nanoimaging), green nanoscience (environment friendly develoment of nanomedicine techniques), nanotoxicology, nanobiotherapeutics, nanobiopharmaceutics, nanophytopharmaceuticals, clinical nanomedicine, and all other research advances leading to translational biomedical applications development.

Historically, the field of nanomedicine is as old as beginging of nanotechnology or nanoscience. The study of nanomedicine began almost half a century ago when the first lipid vesicles were described and Nanomedicine has been considered a possibility ever since the concept of nanotechnology was first articulated in 1959 by Richard Feynman, in his famous Caltech talk, “There’s Plenty of Room at the Bottom”.[1]

Lateron, in 1986, field of nanoscale research was propagated by Eric Drexler who proposed and popularized the notion of cell repair machines, the nanosized vehicles to repair damaged DNA, organelles and other cellular structures with great precision, as explained in his visionary book, *Engines of Creation*.[2]

First generation nanomedical capabilities emerged in early 1990’s with the development of different organic and inorganic nanosystems as functionalized nanoparticles having novel chemical, physical and biological characterstics. Since then the nanoscale research has undergone rapid expansion dramatically.[3]

In 1996, Robert Freitas Jr. composed concepts of biomedical nanotechnology in his ‘Nanomedicine’ books which contained detailed array of nanomedical possibilities.[4–6] H.S. Nalwa has comprehended the wide and detailed information on nanoscale advances in different encylopedia[7–9] and through serial publications. Addressed as ‘NanoMan from India’,[10] H.S. Nalwa has large compilation to his credit with wide range of literature in field of nanoscience and nanotechnology.[11,12] The overall literature of nanomedicine research has grown exponentially in last 15 years including journals and patents.

It is the novel properties and characteristic functionalities of different nanoscale materials that led to development of potential overwhelming interest of research fraternity. The small size of nanoparticles endows them with properties that can be very useful in different biomedical applications including oncology, imaging, biosensing, tissue engineering. The gold nanoparticles, silver nanoparticles, CdS, CdSe, carbon nanotubes, fullerenes, magnetic nanoparticles and other nanoparticles has characterstic properties that makes them suitable for specific applications. 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. Exploration of cheristic nanophenomenon has provided many drugs formulations for therapeutic applications in clinical settings. Some nanotechnology-based drugs that are commercially available or in human clinical trials include: Abraxane, the nanoparticle albumin bound paclitaxel has been approved by FDA to treat breast cancer, non-small- cell lung cancer (NSCLC) and pancreatic cancer.[13,14] Doxil, the Doxorubicin encapsulated in liposomes, originally approved for the HIV-related Kaposi's sarcoma, is now being used to treat ovarian cancer and multiple myeloma.[15,16] Onivyde is liposome encapsulated irinotecan for treatment of metastatic pancreatic cancer. C-dots (Cornell dots), the smallest silica-based nanoparticles has potential to use as diagnostic tool for location of tumours. Similarly, many other drug nanoformulations has been approved for clinical applications or are under final clinical trials.

Besides cancer and tumour therapy, diagnosis and therapy of many other dreaded disease like tuberculosis, malaria would be possible with better results by use of different nanoconjugates. The exciting field of nanorobotics has potential for targeted repairing of molecular and cellular components. Furthermore, advanced modular nanosensors would lead to exciting changes in medical diagnostics.

There is ongoing growing scope of nanomedical capabilities made possible by evermore and evenmore clever combinations of unique nanomaterials and targeting agents. The nanoconjugates with possible dual functions show promise of diagnosis as well as therapy without generating the burden of drug overdoses to patients. The systematically devloped and advanced layered structure of many nanoconjugates have capacity to combine different functionalities in a single system with capability of performing different tasks simultaneously. The multifunctional and multitasking nanosytems have introduced new challenges and changes in arena of medicinal research.

Biocompatibity wise, there are myriad subtle electronic, chemical, thermal and mechanical interactions between nanomaterials and the particular environments (inside the human body, tissue, fluid, cell and cell organelles) within which they might be immersed or present. These interactions need to be fully understood for compatible nanomaterial design and development. These interactions will, of necessity, have to be methodically and thoroughly elucidated as a prerequisite to the widespread implementation of specific nanomaterials, intended for use as commercialized nanotechnology based enhancements or nanomedical diagnostic and therapeutic tools.

Nanomedicine Applications

With diversity of nanoconjugates and nanoformulations, the nanomedicine has been a promising tool for viablity of use in different specialities of medical sciences. The key features of the nanomedical applications are included as follows: nanobiosensor, nanoradiopharmaceuticals, molecular imaging, nanodrug delivery, nanosurgery, nano orthopaedics, biomedical engineering, nanodentistry, role of nanotechnology in tissue engineering, stem cells and regenrative therapies, cognitive sciences, and nanorobotics (Figure1).

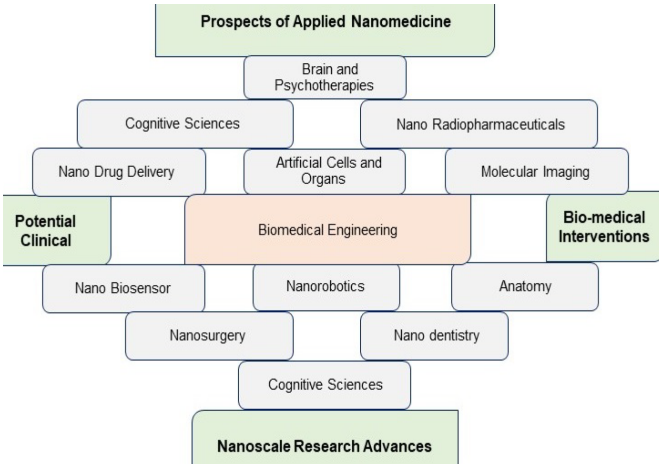

Figure 1. Different applied nanomedicine fields

NanoBiosensor

For very accurate and sensitive detection, there is a need for a sophisticated tool that is capable of detecting accurately with required sensitivity and meets the desired parameters.[17] The various physical and chemical parameters of the specific molecules are interlinked and other features depend on them. The use of nanotechnology enhanced the capacity and capabilities of these desired tools. The main base of such features and expectations are multifunctional nanomaterials. These new nanomaterial tools adopted for biosensors (simple, robust, and sensitive) have transformed in enhanced, robust, miniaturized as nanobiosensors. These highly precise diagnostic tools are capable of detection of the diseases through routine tests that were employed for diagnosis. These nanobiosensors consist of biological molecules capable of recognition and has a transducer that can detect the signal at the surface. The interaction between the biorecognition molecule and diseased surface generate the possibilities and act as a deciding factor to judge the performance of nanobiosensor. Therefore, these tools inbuilt with nanomaterial achieve their performance based on the mechanism of molecular detection. These tools are employed with biomarkers for the detetction of any diseased cell/tissue with greater sensitivity in minimum time duration. The nanobiosensor are applied for detection of proteins and nucleic acids, and generally biomarkers were employed for it. The technique of nanofabrication is applied for the designing of nanoplasmonic biosensors to obtain the nanoplasmonic features. These plasmonic characteristics and diagnostic tools are influenced by the size, shape, and orientation of the nanomaterials used in the designing. Several changes were detected to varify the various interfaces during the probe at target destination and nanostructured surfaces. Nanobiosensors are utlized for clinical diagnosis, environmental monitoring, and biosecurity. These are four types i.e. electrochemical, optical, microgravimetric, and thermometric. The nanobiosensor has recognition elements, antibodies, aptamers, and microRNAs to enhance the possibilities of analysis for early diagnosis. Nowadays, these tools are employed for monitoring in several pathologies. For the initial diagnosis of the diseases, these nanobiosensor play the key role before a suitable treatment can be recommended. An accurate diagnosis help in a low percentage of the drug to treat the infection and in monitoring of progress of therapy. The output of nanobiosensor analysis depends on specific elements of structure, nanobioconjugates and cellular interactions involved. The diverse mechanisms involved in multi-step enzyme reactions generate the specific accurate detection.[17]

NanoRadiopharmaceuticals

The assembly of nanoparticles with radioactive materials or elements is a breakthrough in the discovery of radioactives and nuclear medicine.[18] These remedies and nanoscale tools are quite helpful in the treatment and diagnosis of cancer and other ailments. Among different radiolabelled nanoscale materials, for example, the hydroxyapatite labelled with ^{99m}Tc have come as nanotheranostics for bone cancer imaging.[19] The nano-radiopharmaceuticals for oncology constitute a major portion in nuclear medicine, and these also been used to cure inflammation. The use of nanomaterials in designing and development of nano-radiopharmaceuticals help to enhance their suitability with the biological system *in vitro* and *in vivo*, improves the imaging contrast (radiodiagnosis), reduces the dosage of radioactive material for equivalent outcomes (diagnosis or therapy). For example, the liposomes and micelles labeled with radionuclides can effectively imrprove the delivery and accumulation of radioactivity in target organs for the improved imaging or therapeutics purpose in a quantitative fashion. The thrust area in the field of radiopharmaceuticals is to design novel specific tumor-targeting radiopharmaceuticals, and here, the nanotechnology opens new avenues. The nano-radiopharmaceuticals has brought paradigm improvement in SPECT. The radionuclides with nanoformulations has played a crucial role in enhancing the performance of PET/CT (positron emission tomography/computed tomography) with high sensitivity to provide the best anatomical resolution.[20]

Molecular Imaging

The nanotechnology-based imaging probes are employed for quantitative detection in the living cells and tissues. The use of nanoscale materials in the process enhanced contrast of the interface as compared to the traditional contrast agents. The unique properties of nanodevices combined with contrast agents perform better in molecular imaging of cells, cellular components, and physio-chemical changes at the nanometer size scale. Besides it, these agents can be applied for a proper investigation of pharmacokinetics (distribution and half-life time of the drug molecules). During the identification of the diseases, (optical, photoacoustic, and nuclear medical imaging), the received outputs have a high accuracy with sensitivity and high predictive results. An accurate molecular imagining depends on the assembling of the contrast agents and it has observed that nanoparticles can enhance this process. The second, the tissue barriers hindered the delivery distribution of contrast agents and thus impact imaging process,[21] therefore, the use of nanoscale materials with well known property of enhanced transfer across barriers helps to to overcome it. The nanoparticles inbuilt tools are required to enhance the process of signal amplification for perfect molecular imaging. These nanodevices are further capable of target recognition, binding, monitoring of biodistribution,to detect therapeutic events concurrently. In the near future, very small sizes, components of cellular environment such as ribosomes, and transport vesicles may be covered by the molecular imaging. These emerging imaging techniques are employed for stem cell tracking and to get functional and molecular information. Therefore, the multifunctional nanomaterials enhanced the possibilities for accurate diagnosis of the disease and concerned microenvironment. The most important aspects of these molecular imaging techniques are their diagnostic performance with accuracy and sensitivity. The immunocytochemistry and complex behaviors of the disease can be monitored using nanosize molecular imaging tools, that bring as good results in vivo characterization. Therefore, these nanotechnological fields find potential place among recent innovations, and helping to bring revolutionary improvements.

NanoDrug Delivery

Nanodrug delivery is one of the most explored field in nanomedicine. Because of enahnced permeability rate (EPR) of the nanoscale materials across the cell membranes, all short of nanomaterials including metal nanoparticles, QDots, Carbon nanomaterials (fullerene, carbon nanotubes,[22,23] graphene), liposomes, micelle, and other nanomaterials has been evaluated in various formulations for the better therapeutic drug delivery. The multifunctional conjugates at the nanoscale have been constructed for more than one simultaneous applications such as devices for diagnostic tools and therapeutic agents to target the specific diseased cells and tissues. The targeted enhanced delivery of therapeutic drug molecules, therefore, make these nanoconjugates as the precise medicines delivery vehicles. The variety of chemotherapeutic[24,25] and immunotherapeutic agents have been evaluated towards implied improvement in therpay using concept of nanomedicine and nano delivery systems. The discovery of these NanoDrug Delivery technologies is also enhancing the efficacy of existing novel and old drugs[26–29] and improved applications as versatile molecular imaging tools, cancer gene therapies, and potential stimulus agents. These nanosystems have been able to address the issues of required enhanced delivery, reduced side effects, higher therapeutic impact compared to the conventional delivery systems.[30] The addition of microfluidics and biomimetic processes to the nanosystems for drug delivery have displayed the much-awaited characteristics that are leading to clinical translation processes, a boost for the field of nano-drug, nanomedicine, and pharmaceutical nanotechnology, as concept illstrated in the figure 2.

The most notable advantage of these nanodevices include their capacity to cross over the biological barriers (like blood brain barrier BBB) and therefore have potential of application in hard to reach targets. The delivery system have also been used in Regenerative medicine using nanoscale materials and combination has shown better tissue regeneration capabilities. The use of the nanoscale delivery tools for stem cell survival, differentiation, and engraftment have been reported along with development as nanorobots capable of the brain and cardiac repair. Their pharmacological clinical performance using atomic and molecular level properties have brought high capacity and ability to control any degradation that may occur during transport leading to efficient and controlled or sustained release.[31]

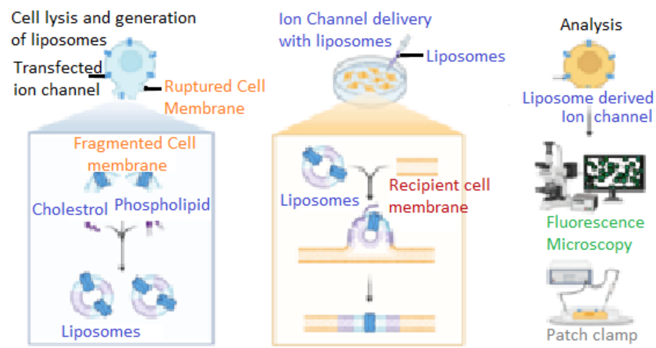

Figure 2. Illustration of nanodrug delivery functioning along with the analysis methodology.

NanoSurgery

The surgical repair of tissue and cells using the nanomaterials based nanotools is bringing revolution in the field of minisculized therapy of damaged tissues. Comfortably addressed as Nanosurgery includes a diverse kind of tools and procedures used for tissues repair at miniscule scale. The starting stages included the in vitro culture techniques for cell and tissue growth manipulations, with further advancing of nanosurgery as safe and reliable biological procedure for in vivo operations. This technique is suitable for gene therapy and nerve regeneration with a high degree of specificity. Several biological segments and subcellular components of the cellular environment have the same scale similar to the equipment employed in the nanosurgery. The nanosurgery involve various scaffolds that are implemented towards enhanced material-cell interaction. These scaffolds can be used to deliver stem cells to replace the defective cells. The nanosurgery is applied for operation of pigmented epithelial cells in age-related macular degeneration. The nanosurgery may be employed to replace weakened collagen fibers. The various applications of nanosurgery include nanotechnology in cardiac therapy, nanoneurosurgery, medical nanobots, laser nanosurgery,[32] biological nanomotor, and intracellular nanosurgery; all that making nanosurgery as an effective technique that can be employed for the treatment of degraded/damaged tissues and cells.[33]

Biomedical Engineering

The nanobiomaterials have been extensively explored using Biomedical Engineering expertise for the development of advanced tools and techniques for the therapy of various ailments. The different specialities discussed in this article, in one way, constitute the fragments for biomedical engineering. The nanomaterials has characterstic magnetic and optical properties (distinct from bulk materials) that have been utilized for the development of medical devices. The nanomaterials have utilized in many different ways in the field of biomedical engineering. For example, (1) the multifunctional nanomaterials are known for their application to inhibit infection and enhance tissue growth, (2) the nanomaterials have been used in the regeneration of cardiovascular and bladder (3) They enhanced the stem cells biological parameters (4) These special materials employed during transplantation (5) The nanodevices and materials are also employed during organ implanatation necessarily in immunosuppression, and very easily deals with the persistent complications (6) they are utilized in the area of genomic, and proteomic profiling (7) The foremost application of this technology is in earlier detection and curing of disease.

There is a further need for the refined implementation with innovation of new nanotools and devices in biomedical engineering, so that these application tools define the healthcare technology. Still there is need for a applicable tool/system for controlled release of diverse therapeutic agents. The nanotools development in biomedical engineering would emerge as integrator technology in medicine as these have also displayed potential for the regulation of the biological processes. The recent need is to redefine these cutting-edge technologies for the precise medical application along with proper assessment of health risks.[34]

Nano Orthopaedics

The musculoskeletal systems related ailments require distinct therapies, generally abled with replacement or stronger adhesion of tissues and organs. This requirement of orthopedic replacement materials for clinical application has led to search orientation to the field of nanomedicine. The nanomaterials for orthopaedics based on nanomedicine can be developed using pharmacological agents and further introduction of surface modifications through to regulation and toxicology. The functioality and reliability of existing implantable medical devices for orthopaetics have been engineered using unique chemical, physical, and biological properties of nanostructures (Figure 3). In orthopaedic therapy using nanomedicine, there is still need and challenge of development of techniques for mimicking living bone tissue.[35]

Nanodentistry

The nanodentistry, a field aligned with nano-orthopaedics, have additional challenges due to buccal cavity environment. A nanomaterial that carries antiquaries potential can be used in dentistry. The advances in nanodentistry have brought incredible materials and devices that have been implemented in clinics as biocompatible dental materials. The development of new nanomaterials opened new avenues in advancement of clinical devices for oral health care and dental practice. The biophysical and biochemical features of nanoscale dental materials transformed them into novel topology. These nanomaterials displayed potential to stop dental caries and tooth hypersensitivity. These characteristics are a good source for the designing of the antimicrobial dental implants and personalized dental health care. The nanomedicine is possibly a superior approach for the designing of biocompatible dental materials with high anticaries potential. The nano-devices find use in oral health-related problems and these minute machinery can do manipulations at the nanoscale to repair oral lesions. By employing the technologies of the nanodentistry, desired antimicrobial dental implants, long-lasting, corrosion-resistant dentures and crowns, nano-impressions, nanoceramics, molecular disease imaging materials, tools therapeutic intervention, and nanocomposites can be designed and prepared. The nanodentistry can improve oral health by monitoring, constructing, repairing, enhancing defense, and removing the persistent complications.[36]

Role of Nanotechnology in Tissue Engineering, Stem Cells and Regenerative Therapies

The impact of nanotechnology in tissue engineering and nanomedicine therapies is huge and recently it successfully achieved several milstones. The main focus in field of tissue engineering is regeneration of the engineered tissue constructs capable of performing the desired tasks, along with other aspects related to control of cell survival, functioning, recapitulate the functional and structural properties. The nanomedicine help in developing biomimetic scaffolds and concerned tissue engineering materials. The nano-devices, so developed, contribute as a therapy to repair and regenerate the cells and the tissues of the cardiovascular, neural, and bone segments. The most desired aspects of these therapies are to generate the muscle tissue at the interface of the stem cell and nanomaterials, to easy govern the stem cell parameters of the cell growth, migration, proliferation, and differentiation, to develop the biomimetic material by mimicking the concerning nature of tissue.[37]

The nano-advances generate the possibility of extending tissue engineering into genome-editing technology, which will be much efficient to draw therapies based on a disease model and as per the need of the immune response. The efforts are to achieve organ transplantation, and therapeutic cloning to get the bioartificial liver, cartilage and other tissues. These features will help to overcome the damage by replacing the old cell or tissue. One of the major hurdles of the main components of the tissue engineering is, how to deal with the physiology and the mechanism of the chemokines, inhibitors, cytokines, the biochemical and mechanical microenvironment of the cellular environment, i.e. the most complicated task is the deal with the cell-matrix interactions and cellular signaling processes. However, the nanotechnology-based approaches are playing the key role in designing of scafolds for aforementioned needs, development of nano-tools for tissue engineering, artificial cells and artificial organs.[38]

Nanorobotics

Nanorobots are nanomolecular sized machines meant to perform a particular physiological function in the body. Specific machines possible through construct made of nanomaterials are capable of controlled movement, scissoring, tweezers, surgery and other potential physiological actions.[6,39]

Cognitive Sciences

The cognition and cognitive behaviour of human are complex phenomenon involving different interacting fields including physiochemicals, nervous system biology, pheromones,

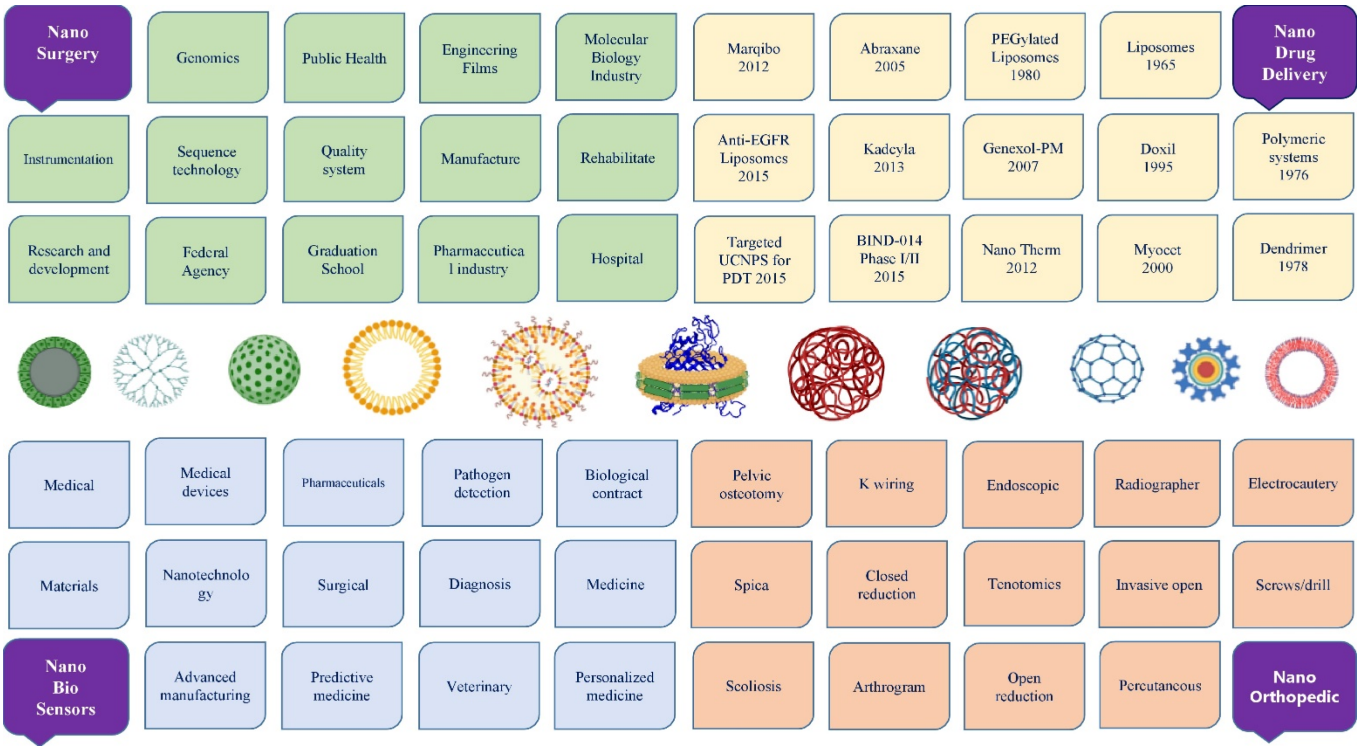

Figure 3. Illustration of the numerous segments, clasification, and application of the nanotechnology.

radiation interaction impact, psychology, mechanization of the mind and act meant towards enhanced human performance.[40] The convergence of the nanotechnology, cognitive science and biotechnology has emerged as interface of knowledge with cognitive science propagating human abilities to do better performance in the field of therapy, augmentation, and intended evolution, transforming the intelligence and behavior of humans, directly influencing the psychology, and a way contributor in emergence of artificial intelligence. The understanding of the behavior of matter at nanoscale is helping in controlled construct of physico-chemical environement and thus, control in cognition and cognitive behaviour.[40]

FUTURE PERSPECTIVE

The future of nanomedicine holds incredibly immense positive potential toward the eradication of practically every known human disease state (inclusive of aging), as well as protection of the human body (via nanomedical immune system augmentation) from any (known or unknown) toxin, microorganism or infectious agent.

The robust and possible development in the nanomedicine field has helped in carving out a standalone subject for education and training of young generation in field of nanomedicine in universities and colleges. The nanomedicine has become an essential components of many curricula at undergraduate as well as at postgraduate level including complete new degree course in many universities.

The multidisciplinary and interdisciplinary nature of nanomedicine brings the collective studies by researchers from different expertise to a merging out common platform for solvation of specific disease condition. The melting out boundries of different disciplines provides more interactive efforts among researchers and better scenario towards new possibilities and possible therapeutics. The nanochemists, nanophysicists, nanobiotechnologists, nanobiologists work together towards development of new nanomedicines. This collaborative research would provide a better future arena where we need to fight the increasing drug resistance and as well as emergence of new unforeseen diseases, however, still lot of fundamental studies need to be conducted to understand intricacies of nanomedicine including interaction of different nanoconjugates with bio-organelles at molecular level.

CONCLUSION

To sum up, the nanomedicine research has been a fantastic voyage, productive present and have an exciting future with potential new unexplored fields and applications mainly translational medicine. The tunable properties and nanoscale size of the nanomaterials provide boost to their possible applications in diverse medical specialities with newly innovated drug conjugates; leading to the carving out a space and indentity for nanomedicine in medical fields and clinical applications.

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