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Current trends in nanomedicine and nanobiotechnology research

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ABSTRACT

Applications of Nanoparticles and nanopharmulations in drug development and drug delivery have been an extensive field of research to find out the alternative better therapeutics. The past research in nanomedicine and nanobiotechnology mostly emphasized on improving the profile of existing drugs, however, a recent pattern has seen in variation of field and aspects studied using nanomedicine. The current nanomedicine research has oriented in developing new drugs based on the interaction of nanoparticles on targets like cancer therapeutics, development of new biosensors, bioimaging (cellular and in vivo), new vistas of anti-viral drugs, besides the most researched field of nano delivery of drugs for cancer, diabetes, anti-bacterial, and other ailments. An overview of current research trends is presented based on the literature published at different platforms in recent time.

Keywords: Nanodrug delivery, Nanoimaging, Nanobiosensor, Nanopharmaceuticals, Nano-anti-viral drugs.

INTRODUCTION

The biomedical application of nanoscience and nanotechnology has huge potential in development of new therapeutics and promises better cure for various diseases. The nanomedicine and nanobiotechnology makes use of chemistry, biology, technology, medical science and clinical sciences at nanomolecular level towards development of new therapeutic possibilities. The proposition of miniaturized robotics in medical application in 1980s gave the boost to research in development of new drugs, delivery methods and newer therapeutics using nanometer scale properties of molecules and conjugates. Since then the field of nanomedicine has grown potentially and many new drugs or drug conjugates have come to market with better therapeutic potential. The nanomedicine research has progressed and spread to all sub-fields of medical sciences with wide spread applications.[1]

The nanomedicine research is development of new medicines using nanoscale properties of molecules. The nanobiotechnology is study of technological developments for biomedical applications using biomolecules at nanometer scale, and development of new tools using nanoscale properties. The nanomedicine and nanobiotechnology fields are interwoven and are indistinguishable from one another. Both cover the study of each other and generally terms are used interchangeably to represent study of either field.

The research in field of nanomedicine and nanobiotechnolgy has shown a pattern of growth over the world in past and many dedicated research institutes has been set up by different countries owing to potential shown by nanomedicine in translational medicine. As the field has grown exponentially in past 30 years with the participation of chemists, biologists, biotechnologists, biomedical scientists, doctors, clinicians; so is the application areas, particularly the spread of research to hard to find treatment of difficult to treat diseases. In the starting phase, the main emphasis of research activities oriented towards the drug delivery using various nanosystems including nanopolymeric systems, metal nanoparticles, liposome, lipid micelles etc. As the field was growing, the research on the design of these delivery vehicles remained active area of exploration. The development of synthetic methodologies for construction of single layered and multilayered delivery vehicles to meet the desired requirements of delivery of drugs and biomolecules, particularly the targeted delivery remained main focus of development of field. However, with passage of time and newer developments in the field, the research has seen the diversity in exploration of unexplored areas and also the orientation of development of sophisticated tools towards the

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translation medical science research development. The changing pattern in research in nanomedicine in recent past and status of current fields of exploration could be analyzed from the literature published in different journals and platforms. Herein, the journals related to nanomedicine and nanobiotechnology were browsed from nearly all publication platforms and summarized view of published research was evaluated. A brief of application fields of nanomedicine and nanobiotechnology is described here to get a quick of the research ongoing with possible future direction, however, no claim is made for comprehensive and detailed coverage of respective sub-fields. The google scholar database along with individual journal sites were browsed for recent years publications for compilation of overview.

Nanodrug delivery

Drug delivery using nanoscale particles and conjugates (Nano drug delivery systems NDDs) has been the major field of research in nanomedicine. The preferential ability of nanoparticles to cross the cell membrane and transport the drugs at the target sites generated the interest in this field. This Enhanced Permiability Rate (EPR) of nanoscale conjugates across the cell membrane along with increased life of conjugates in blood has potential to develop the nanosystems for enhanced delivery and better pharmacological profile of the drugs. Delivery of a large number of drugs have been evaluated using different set of nanoassemblies (metal nanoparticles – gold nanoparticles, silver nanoparticles, CdS nanoparticles; liposomes, micelles, polymers, hydrogel, Dendrimers, silica nanoparticles, fullerenes, carbon nanotubes, chitosan etc.)[2] to tune the parent drugs to desired properties for delivery at target. Owing to extensive exploration and application, many drug delivery conjugates have reached to clinical applications particularly in field of cancer therapy.

The recent development of Multifunctional nanoparticles having more than one end application or properties (like diagnosis as well as therapy with single conjugate) has added potential in translational application of nanomedicine. Though synthesis of multifunctional nanoconjugates was multistep tedious task, a number of design and construct developed have provided impetus in their studies for end drug delivery applications. Another development has been in workable pH responsive nanoconstructs for applications in which the target tissue differ in pH with that of surroundings (blood and serum). The pH responsive nanoconstruct based on Aptamers for targeted cancer therapy and hydrogel based tropical delivery systems got emphasis in exploration. The magnetic nanoparticles or nanoconstructs for magnetic field guided drug delivery including the biodegradable magnetic nanosystems have shown the desired potential for application.

The nanoparticles designing varied according to their mode of delivery. The oral drug delivery using nanosystems such as multicomponent microemulsions is used for delivery of drug resistant anti-cancer drug (the ingestion of drug conjugate) and by slow release of drugs or drug nanoconjugate in mouth cavity for direct uptake (like chewing gum) like the drug release for psychotropic drugs. The NDDs for Nasal and ocular application orients towards the sustained release for longer time. The biocompatibility of nanoconjugates remains a concern for direct application of nanoconjugates to eyes. Ocular nanoconjugates (like that based on Hyaluronan, polymers, hydrogels) have been designed to counterfeit the key barriers in the eyes like static barriers (imposed by the cornea, conjunctiva, and retinal pigment epithelium) and dynamic barriers (tear turnover/wetting of eyes, blood and lymphatic clearance). The intravenous (IV) injected nanoconjugates design with longer availability in blood along with higher permeability in target tissue.

The drug delivery literature indicate a wide exploration of NDDs for Cancer and tumour therapy: The delivery of anti-cancer drugs to drug resistant tumour and alteration of pharmacological profile of anti-cancer drugs to combat the toxicity due to higher doses of drugs has been extensively studied using different types of nanosystesm.[3] Though, most of the drugs studies for anti-cancer treatment using different nanoconjugates (including multifunctional nanoconjugates) have shown more or less expected outcomes (additional problem may also originate), the Antisense oligonucleotide delivery has been challenging research task for nanomedicine researchers. The antisense oligonucleotides could be highly useful in treating the different cancers, but their delivery to target site has been a setback to this therapeutic approach. Various nanoconjugates including liposomes, micelles, nanoparticles, carbon nanotubes, and other nanosystems have been designed for delivery of antisense oligonucleotides (including siRNA) but with little success. The nanoconjugates for Anti-bacterial drug delivery has mainly targeted for drug resistant strains. The nanocojugates for Nervous ailments or drug delivery to brain by overcoming the blood brain barrier (BBB) has been active field of research for better treatment possibilities for nervous system diseases. The drug delivery to brain using nanoemulsions/microemulsions, solid lipid nanoparticles, dendrimers, polymeric micelles, nanoparticles of biodegradable polymers and nanosuspensions has been evaluated still a applicable system need to be further explored.

The Future of nanoconjugates exploration for nanodrug delivery application should orient towards role of nanoparticle size, shape and surface chemistry in drug delivery. The mechanistic aspect with impact of individual nanoconjugate on the target should form the key part of NDDs studies for better understanding of applicability of particular nanosystem in specific application as well as to understand the issues arising in application of particular nanosystem. The Size control (uniformity of nanoconjugate formulation) and mechanism study would provide better drug delivery systems.

Nanobiosensors

Nanoscale biosensors or nanobiosensors have been developed by using nano scale properties of nanomaterials to obtain high level of sensitivity in detection of presence of chemical entity, biomolecules or biomarkers, often to the single molecule level;

or bacteria and virus. The nanobiosensor construct is meant to provide signal in form of color change, electrical current, or fluorescence (FRET) when specific biomarker or biomolecule is present. The use of biomolecule-functionalized (antibody etc.) nanobiosensor surfaces can dramatically boost the specificity of the detection system; however, such biosensors have increased complexity in design and synthesis along with reproducibility problems. Several nanobiosensor architectures based on functionalized nanoparticles surface (like ZnO, CdS, Au nanoparticle), optical resonators (optical fiber), mechanical devices, nanowires, aptamers, carbon nanotubes, graphene, and nanofibers have been designed by researchers and demonstrated in the lab for sensing of specific biomolecule or biomarkars.[4] The easiness of applicability (utility) of nanobiosensors has generated widespread interest among researchers for development of advanced designs of nanobiosensors. As nanobiosensor technology becomes more refined and reliable, it is likely it will eventually make its way from the lab to the clinic, where future lab-on-a-chip devices incorporating an array of nanobiosensors could be used for rapid screening of a wide variety of analytes at low cost using small samples of patient material. This lab-on-chip nanobiosensors would help in rapid detection of diseases or bioanalytes/biomarkar and thus have direct applicability profile.

The research in current time has continued in nanobiosensor designing and development as continuation of development, however, it has expanded in exploration of new designs with the advances in understanding of properties of different nanomaterials and discovery of new nanomaterials. Also the application area of nanobiosensors that are being explored by researcher is expanding to include the selective detection of metal ions (micronutrients), and whole cell detection (virus, bacteria, and cancer cells).

Nanoimaging and therapy

Nanoimaging research is in two fields: development of tools for imaging of nanomaterials itself, and research advances in development and application of nanoconjugates for imaging of biosamples (cellular imaging and diagnostic imaging). The later field covered in nanobiotechnolgy and nanomedicine got delayed attention for robustness of nanoscale application development in the field. The nanoparticle or nanoconjugate designs for application in **cellular imaging** draws parts of concepts from nanobiosensors where mostly nanophosphorescence or nanofluorescence of metal nanoparticle or organic nanoconjugates is used for imaging. This area is emerging field of research and has potential for development of applicable conjugates.

The application of nanoscale properties in **radiodiagnosis** and **radiotherapeutics** research has initiated in recent past and need more efforts in brining the translational biomedical application development in this field. The metal nanoparticle and nanoconjugates have varied biodistribution and higher accumulation (passive or active) in target sites, so development of nanoscale material for radiodiagnosis would provide better contrast images for clear and specific diagnosis. Similar way, the nanoparticle based nanoradiotherapeutics (radiometal based therapy, such as that of tumors) would provide better results as the accumulation of nanoparticle, nanoconjugate or nanoassembly based radiopharmaceutical will be higher in target site, thus would lower the radiotoxicity to normal organs. Particularly, in field of cancer therapy, there has been potential research advances in nanoscale drug development in chemotherapy improvement, similar better results are possible with the nanoscale therapeutics development in radiotherapy.[5] The **magnetic resonance imaging** (**MRI**) using the nanoparticles of magnetic metals have the potential in improvement as the metal nanoparticle structures show variation in magnetic properties with change in size and structure. The literature survey shows a meagre advances in nanoscale research in field of radiodiagnosis, magnetic resonance imaging and radiotherapy.

Photodynamic therapy based on treatment of organs using photosensitizers in vivo using light sensitization (for example destruction of tumor cells by activation of photosensitizer by irradiation with light).[6] The metal nanoparticles and nanoconstructs using other nanomaterials such as graphene have dual properties of acting as photosensitizer and EPR for accumulation in target.[7] This fields is also progressing rapidly currently as literature and research reported is showing increased pattern of advances.

Nanochemistry of drugs design

The synthesis and construction of nanomaterial conjugates involve complex chemical procedures. There is ongoing research in developing the better and reproducible chemical reaction procedures for development of various existing as well as new nanoconjugates for nanodrug development. Many of the nanoconjugates (inorganic metal nanoparticles based as well as Organic molecules) synthesis requires complex multistep synthesis involving protection-deprotection of functional groups of intermediate compounds, necessitating the requirement of development of new and alternative chemical reactions. Such as the synthesis of cyclic and linear nanopeptides is a tedious task to obtain the final pure compound. Each addition of new aminoacid in peptide requires development of additional reaction steps. The nanopeptides have potential to use as delivery vehicles and well as drugs (that bind to specific target). The nanopeptides are prefered material due to higher possible biocompatibility and lower toxicity. The designing of peptides which can form nanoassemblies in aqueous media is itself a challenging task. A number of cyclic peptides and linear peptides have been reported recently and studied in lab settings for covalent as well as non-covalently bound drug delivery of various drugs (anti-cancer and other drugs).[8]

The development of chemistry for surface modification of carbon based nanomaterials (carbon nanotubes –single walled and multiwalled, fullerene, graphene) has helped in developing many new hybrid conjugates for diverse applications. The introduction of new organic moieties on the surface of

nanoparticles allow in tuning their chemical and physical properties in biological systems. The surface modification has been and currently is an active area of research.

The other natural products such as cellulose, glycan, lipids, steroids, are under process of evaluation for nanoassembly formation and application in diverse fields including development of newer drug strategies by researchers.

Nanoinformatics

The drug affinity and binding to target sites changes with variation in shape and size (as orientation of groups changes) of nanodrugs conjugates. The molecular modeling methods are continuously studied for in-silico evaluation of nanodrug conjugates and this field is continuously growing (as literature indicate) with reportes in application in different nanomedical fields. The nanovector designing and representation of structures of nanoassemblies prediction is useful in progressing the research for in-vivo applications.[9]

Nanotools and techniques - Nanorobotics

As the research in nanomedicine is advancing, the need for newer nanobiotechnology and biomedical nanotechnology tools and techniques for performing laborartory experimentations and assays has been advancing with time. The nanorobotics is specific research field of nanobiotechnology for development of miniaturized nanobiosystems for performing treatment task which include the surgery of internal organs, diabetes control, etc. by performing any or combination of tasks such actuation, sensing, manipulation, propulsion, signaling, information processing, intelligence, and swarm performance for big role.[10] The special sensors (i.e. physical or chemical) nanorobots can detect the target molecules in the human body for diagnosis and treatment of various vital diseases i.e. cancer, diabetes, atherosclerosis, hemophilia, kidney stones, etc. These Molecular machines (molecular robots) gain significant attention with an ultimate goal to create a theranostic platform interacting with biological system and being able to perform atomic-level tasks. Such concept requires advanced technological approach i.e. design and assembly techniques, in vivo real-time navigation system, sensing methods as well as data transfer. The four types of nanorobotic systems that have been developed and studied so far include (a) large size nanomanipulators with nanoscale manipulation capability (such as carbon nanotube based artificial nanorobotics); (b) protein- and DNA-based bionanorobotic systems; (c) magnetically guided nanorobotic systems; and (d) bacterial-based nanorobotics. The research and design has progressed in different type of robotics to laboratory scale. The field involves expertized technical and technological construction of nanorobots, the success of final product depend on procedural handling. The initial potential and boost of research in nanorobotics has slowed recently, however, it has a huge potential for application in future. More involvement of researchers, expertized constructions and additional field applications, the field of robotics is bound to see a huge boost and benefits of nanobiotechnolgy in nanomedicine.

Anti-viral therapy

The virus (including retro-virus such as HIV) infection treatment using nanoscale conjugates of drugs has been evaluated and reported using all different type of nanosystems such as liposomes (majority), micelles, metal nanoparticles, polymers etc. Virucidal nanoconjugates and drug delivery nanocomposites have been used mainly for the fighting human immunodeficiency virus (HIV), Dangue, H1N1 virus, hepatitis (type A, B, C and E), influenza andherpes simplex virus (HSV-1 and HSV-2) infections.[11] The research and application of nanobiotechnology in virology has been increasing exponentially in the past decade. The search of articles in Scopus and Google Scholar show increasing number of articles year wise after 2000. The nanocomposites are being continuously evaluated in diagnostic, prophylactic and therapeutic applications. The nanoparticles have been used for imaging / diagnosis of viral infection, and/or as drug delivery nanocomposite to enhance virucidal properties. Though a number of research have been reported, still the use of nanoparticles and nanocomposites for virucidal treatment (anti-viral therapy) is still under investigation in laboratories and has not been approved for clinical or pre-clinical trials. The moleular drug development of anti-viral therapy is itself a progressive and active field of research as effective drugs are required and being discovered for many lethal viral infections. In correspondence to it, the research in nanomedicine is advancing in parallel as active field of research.

There is contineous moderate research advances in following fields of nanomedicine research:

Nanotoxicology

Nanotoxicology is concerned with study of toxicity of nanobiomaterials and nanoconjugates that are used nanomedicine. This field includes the study in toxicity of nanomaterials on the human beings (possible side effects) and also the toxic effect of used or discarded nanomaterials on biotic life. The environment impact on the quality of natural phenomenon such water contamination by discarded nanomedical substances form the part of nanotoxicology studies.

Nanotoxicology has become a well established subfield of nanoscience and as well as toxicology over the past decade. It is currently a rapidly developing area of toxicologic interest internationally. The properties of naomaterials depends upo the size, shape, surface characteristics, including charge and other aspects of the physical nature of a nanomaterial, so commensurable would be their toxicological effects. The evaluation and reports by nanotoxicologists have been a steady increasing pattern in last decade.[12]

Nanobiotherapeutics

Application of nanoscale research with biological macromolecules used for drug development such as proteins,

peptides, monoclonal anti-bodies, anti-body fragments, and evaluation of their properties is included in this field.[13]

Nanopharmaceutics

The pharmaceutical evaluation on combination of drugs with nanosystems or interaction studies of existing pharmaceutics with nanoparticles and nanoconjugates is also being reported continuously.[14]

Nanophytopharmaceuticals

The application of nanoscale systems to plant medicines indicate increasing trend of reports as therapeutic potential of many phytopharmaceuticals is found to have better profile on combination with nanosystems.[15]

Clinical Nanomedicine

The clinical evaluation of newly developed nanotherapeutics and nanodiagnostics is parallel research field with developments in nanomedicine. The detailed clinical evaluation reports are being published in different journals with continuous stable pattern.[16,17]

Mechanistic and invivo nanobiotechnology

The nanomedicine research is a thorough study field about behavior of each different type of nanoparticles inside the body, their distribution pattern, excretion, biocompatibility, interaction with different biomolecules (including in healthy person as well as biomarkers of diseases in patients) and their mechanism of interaction at target and crossing of memberane. The mecahnistic nanomedicine study of nanoconjugates will provide a clear picture of their behaviour inside the body and will provide directions for future research. The current studies that are being reported in nanomedicine should include the mechanism of interactions or reason of pattern observed.[18]

Green Nanoscience

The environment friendly development of nanomedicine techniques and nanoconjugates through adoption of non-hazardous chemicals is advancing actively and being reported in different journals.[19]

Green synthesis(Plant extracts)

There is plethora of research undergoing in synthesis of metal nanoparticles using plant extracts while it is already well established concept. The plant extracts contains reducer molecules as well as stabilizer biomolecules, so adding a metal salt generally yield nanosize particles. The each new report in this field is becoming useless as simply changing the plant or plant part and extract of it, is not giving any new results. Generally the nanoparticles size reported in these reports varies in a range, and with variations in repeat reactions. This field is more than a decade old with same conclusions.[20]

The need of hour is the size control of nanoparticles in green synthesis and reproducibility of it. The green synthesis of metal nanoparticles with size control is the main desired activity to real application of nanoparticles, and getting the reproducible results. Mixture of different sized nanoparticles give an average of end property or final physiological result while a more accurate property or result can be possibly obtained with specific size controlled particles.

CONCLUSION

The nanomedicine is a highly active field of research with huge potential in development of translational medicine. The current trends in research advances indicate expansion of field in different application areas and also in breadth with types of nanoconjugate systems along with different drug formulations. Though selected fields have been explored extensively, these require a redefined concept to get the practical solutions by using new and improved nanosystems. The nanomedicine and nanobiotechnology research is expanding with new vistas and possibilities. The future research would expectedly require robust thorough explorations and involvement of less explored field such as radiotherapy and radiodiagnosis.

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