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Review Article

ROLE OF NANOBIOTECHNOLOGY IN PHARMACY AND MEDICINE: A REVIEW

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ABSTRACT

Nanobiotechnology is a term, which describes the combination of the two different worlds of engineering and molecular biology. It is a fusion of the following words: "nano" meaning very small, "bio" meaning living, and "technology" meaning use of tools. Tools and devices designed in nanobiotechnology applications are dependent directly on the current nanotechnology principles. In this review, the applications of nano biotechnology in various areas such as drug delivery, gene therapy, tissue engineering, molecular diagnostics and food safety are summarized. The multidisciplinary area of Nanobiotechnology has a powerful impact in various disciplines of scientific fields. It provides opportunities to develop new materials and techniques that improve the ability for developing quick, sensitive and reliable analytical techniques.

Key words: Nanobiotechnolgy, nanoparticles, nanobiology, nanomedicine, drug delivery and biotechnology

INTRODUCTION

Nanobiotechnology, a unique merger of nanotechnology and biotechnology is defined as the design, development and application of nanomaterials & devices to deal with functional processes of biological agents like microorganisms[1]. The field of nanobiotechnology is expected to have exponential growth and development in the future.

By this methodology, atom or molecule level devices can be constructed by incorporation of biological systems. Hence nanobiotechnology eases various aspects of biological sciences with the help of nanotechnology and information technology into biological problems. This technology has the potential to eliminate boundaries between different branches of sciences providing newer challenges and giving new directions in the field of research & diagnostics, education in the coming future [2].

Historical developments in the field of nanobiotechnology

The nanotechnological concepts were discussed for the first time in 1959 by physicist Richard Feynman during his talk "There's Plenty of Room at the Bottom". In this he described the different possible methods of synthesis by directly manipulating atoms. In 1974, Norio Taniguchi used the term "nanotechnology". With the invention of the scanning tunneling microscope in the year 1981, the visibility of individual atoms and bonds was clear. This has given the basics for manipulating individual atoms in the year 1989. Harry Kroto, Richard Smalley, and Robert Curl, discovered Fullerenes in 1985 and received a Nobel Prize in Chemistry in 1996 for his work. Initially the term nanotechnology was used regarding subsequent work related to graphene tubes (also known as bucky tubes or carbon nanotubes) which has essential applications in designing nanoscale devices[3].

The National Nanotechnology Initiative (NNI) defines nanotechnology as research and development at the atomic level, molecular level, or macromolecular levels in the range of sub-100 nm for creating structures, devices, and systems that have novelty in their functional properties. At the nanoscale, manipulation of atoms was possible to create efficient materials with tailored parameters. By giving the inherent nanoscale properties to the biological tissues, it was evident that nanotechnology could be applied to the life sciences successfully. This has given rise to the term "nanobiotechnology", a unique fusion of biotechnology and nanotechnology[4].

Relation between nanobiotechnology and bionanotechnology

Nanobiotechnology, bionanotechnology, and nanobiology are the terms referring to the intersection of nanotechnology and biology. Nanobiotechnology uses advances in nanotechnology to improve biotechnology, and bionanotechnology aims to take advantage of natural/biomimetic approaches to create devices and tools of size in nanometers. Hence, both the technologies are co-related but complementary to each other[5]. Relation between nanobiotechnology and bionanotechnology is shown in Figure 1.

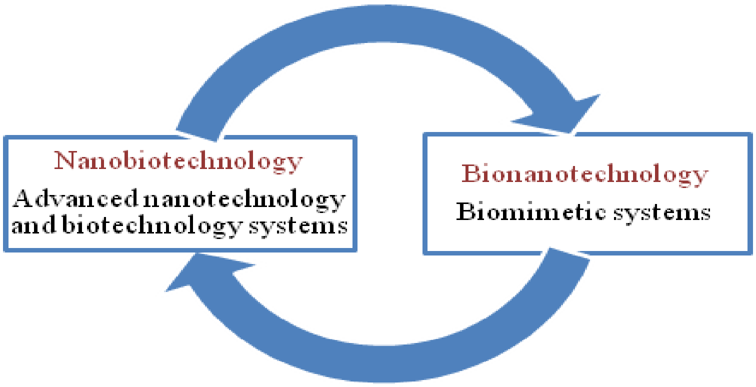

Figure 1: Relation between Nanobiotechnology and Bionanotechnology

Nanobiotechnology benefits[6]

The benefits of nanobiotechnological formulations over the conventional drug delivery systems are as follows:

• Manipulation of Particle size and surface characteristics of nanoparticles are achieved for active and passive targeting of drugs through various routes of administration.
• Nanoparticulate drug delivery systems sustain the drug release from dosage form by changing the pharmacokinetic profile of the drug in-vivo, and maximizes therapeutic efficacy with less toxicity
• Drug targeting is achieved with the help of the specific patho-physiological conditions of a diseased tissue
• Site specific drug targeting can be attained by attaching the target ligands to the surface of the particle or by using magnetic guidance. Accumulation of nanoproducts is at a higher concentration at the site of targeted tissues when compared to conventional dosage form
• Nanosystems have better absorption capability of drug in the tumors and inflamed tissues, as there is enhanced vascular permeability along with an impaired lymphatic drainage
• Design of Nanosystems is achieved for selective localization in inflamed tissues by nanobiotechnology
• Nanoparticle carriers deliver the drugs to the brain overcoming the Blood brain barrier
• Mechanism of drug loading helps in determining the delivery of biologically active compounds with cell modification, tissue distribution thereby increasing the drug efficiency with reduced toxicity.

APPLICATIONS OF NANOBIOTECHNOLOGY

Nanobiotechnology has applications in various areas such as drug delivery, blood substitutes, gene therapy, tissue engineering, nano diagnostics and food safety (Figure 2)

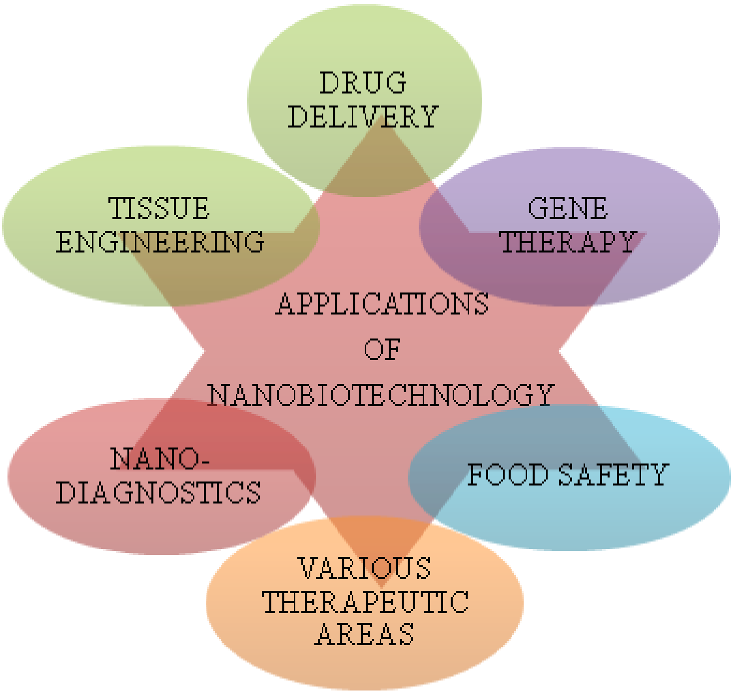

Figure 2: Various applications of Nanobiotechnology

Drug delivery using Nanobiotechnology principles

Drug delivery system designed using nanobiotechnology tools and devices have minimized the problems like less solubility, less bioavailability, instability of drug in in-vivo conditions, toxic effects and improve the drug effect at target site. Generally, the drug delivery system using this technique consists of the components like drug, a material encapsulating the drug and surface coating materials.

Examples of the nanobiotechnology dependent drug delivery systems includes the following- In Cancer therapy the administration of Doxorubicin, using nanocarriers like liposomes penetrates the tumors passively thereby enhancing the efficiency of the active product ingredient therapeutically with minimized adverse effects. By this process, the permeability and retention effect of the PEG coated liposome reduces uptake via macrophages and thus allowing the liposome to escape from the leaky vasculature around the solid tumors and enhances its accumulation at the target site. The antineoplastic agents are delivered to CNS by crossing the blood brain barrier without obstruction of microvasculature with fewer side effects depending on the nanobiotechnological approaches. E.g., Paclitaxel in PLGA nanoparticle. For the treatment of fungal infections in individuals with weakened immune system, anti-fungal agent like Amphotericin B, in the form of a liposomal formulation has been administered. Administering such toxic antifungal agent using this technology has reduced the toxicity with enhanced therapeutic effects at the systemic site of action. Delivery of nanoparticles by targeted drug delivery system is attained by binding a monoclonal antibody or cell surface receptor ligand to the surface molecules of cell developing the disease.

By making use of nanobiotechnological principles, Scientists from Osaka University have developed nanosphere to deliver nasal vaccines. Introduction of the tetanus antigen in the form of nanosphere in the immune system of human being crossing the barrier of mucus membrane has shown potential results. Multifunctional nanodevices are developed by using different targeting molecules such as thiamine, folate, aptamers and peptides which are receptor specific in nature. These are able to detect cancerous cells in biological milieu, thus providing newer therapeutic methods or better use of current techniques to destroy cells that are malignant[7].

Drug formulations developed with the carriers like nanoparticles deliver the drug with the application of stimuli such as pH resulting in the degradation of the nanocarriers concentrate at site of action. This releases the drug from encapsulated material at a controlled release rate. The extracellular pH of solid tumors is 6.2-6.9 and that of a normal tissue is 7.2- 7.4. As a result of this pH difference, nanoparticles develop sensitivity to pH-stimuli, thereby releasing the drug at a controlled rate from this type of drug delivery system[8].

FDA has approved many nanobiotechnological products such as Rapamune, Emend, Abraxane. Rapamune, consists of an immuno-suppressant drug, Sirolimus, used in children after transplantation of organs like liver in order to prevent graft rejection. Emend, consists of aprepitant MK 869, used to treat emesis developed as a result of chemotherapy in cancer patients, and Abraxane, an albumin bound Paclitaxel which is used in cancer treatment. Drug delivery systems using nanobiotechnological principles are used to target immune system cells and provides new opportunities for treating numerous diseases such as Brucellosis, Listeriosis, Leishmaniasis, etc., where the sources responsible for causing the diseases are intracellular agents.

Production of blood substitutes using nanobiotechnology

Based on Nanobiotechnology fundamentals first generation RBC substitutes such as poly Hb, conjugated Hb, has given effective results for removing infective HIV agents, Hepatitis virus etc. Poly Hb is approved and recommended for the use of human in South Africa, whereas the test for using of conjugated Hb is under trial. Recombinant and cross linked molecular Hb and has Second generation RBC substitutes like poly Hb-SOD-CAT (poly Hb-superoxide dismutase catalase). Production of Third generation RBC substitutes using nanobiotechnology principles are considered to be under clinical trial process.

Gene therapy by nanobiotechnology

Nanobiotechnology principles are used in Gene therapy, used for the treating of genetic disorders by correcting a defective gene by inserting a normal gene into a nonspecific location within the genome or by swabbing an abnormal gene for a normal gene via selective reverse mutation, which returns the gene to its normal function. The use of nanodevices has the advantage of penetrating the cells easily as compared with larger devices so that they can interact effectively with the cells[9].

Delivery of the genetic material into the target cells may be possible by using Liposomes of size below 100 nm. Liposomal formulations developed with the incorporation of polyethylene glycol, galactoses are effective in targeting liver cells because of their fast uptake using Kupffer cells of liver. In this way, gene therapy can be achieved to treat numerous liver disorders[10].

Niu et al has transfected STZ diabetic rat via gastrointestinal tract using human insulin gene incorporated with chitosan nanoparticles and reported a potential reduction in the levels of fasting blood glucose test, enhancement in the plasma insulin range and human insulin gene mRNA expression in the test rats. This work can develop foundation to develop new approaches for type 1 diabetes mellitus therapy in future[11].

A "hybrid nanodevice" was designed by the Northwestern University and Argonne National Laboratory consisting of nanoparticles made up of Titanium dioxide (TiO_2) with 4.5 nm dimensions attached by covalent bonds to oligonucleotide DNA. The hybrid nanodevice can be directed to the corresponding DNA segment in the nucleus of cell with the sequence of oligonucleotide DNA. Upon light or x-ray stimulation, nucleic acid endonuclease is induced by TiO_2 which is responsible for the cleavage of particular fragment of a DNA. However, laboratory testing of this device is yet to be performed in test models. This may be used effectively usage in future to treat different malignant cells[12].

Tissue engineering via nanobiotechnology

Tissue engineering is a branch of science useful for creating, repairing, replacing organs, tissues and cells with bioactive materials thereby producing structures resembling native tissues of the body[13]. Nanobiotechnology and micro technology may be combined with bioactive materials so that scaffolds, for tissue engineering can be generated. These scaffolds are necessary for maintaining and regulating the cell functions. Micro patterning and nanopatterning, cell shape influences cell properties within the scaffolds, which regulates cell migration and angiogenesis process[14].

Electro spinning is the widely used techniques used for constructing biomaterials to be cultivated with cells. The principle involved in Electro spinning is electrostatic principle, where the solution is supplied to the system by a syringe and then subjected to a difference in electrical voltage, yielding solid fiber at the end of the process. Coaxial electro spinning is a modification or extension of the electro spinning technique. Using this compound spinneret method, two components can be fed through different coaxial capillary channels and are integrated into a composite fiber of core–shell structure[15].

The nanofibers obtained by these methods have been used in many biological applications, as follows.
Electro spinning aims at improving adhesion and expansion capability of hematopoietic stem cells at 3D nanofiber mesh18. This acts as carriers in bone marrow for hematopoietic stem cells; Electro spinning also causes cell differentiation, behavior of neurons, oligodendrocytes, and astrocytes into mature neural lineage cells. Electro spinning helps to develop starch/polycaprolactone nanofiber starch which induces stretching in cell morphology and moreover enhances its activity, and viability in cell cutures of Human osteogenic sarcoma. Electro spinning helps in attachment and cell migration along the axis in human coronary artery smooth muscle cell culture with poly (L-lactic-co-ε-caprolactone). Electro spinning promotes the formation of integrated spheroidenanofiber construct in rat primary hepatocytes culture with poly (e-caprolactone-coethyl ethylene phosphate).

Photolithography provides improved groove topography for primary human osteoblasts helping in cellular adhesion, osteospecific function, for determining the cellular response and also used in “patterned cell co-cultures” for Human osteogenic sarcoma cells on Photo-cross linkable chitosan using lysozyme enzyme. Photolithography helps in maintaining 3D structure of cell in hepatocyte culture with poly (ethylene glycol) and it is also capable in maintaining phenotypic functions for prolonged weeks in primary rat hepatocytes and primary human hepatocytes culture with polydimethylsiloxane.

Soft lithography helps to regulate the behavior and structure of Human mesenchymal and embryonic stem cells under specific conditions. Soft lithography combined with a definite design gives suitable oxygen and nutrient mass transfer so as to maintain viability in hepatoma cells culture and primary rat hepatocytes culture with polycarbonate and polydimethylsiloxane.

Replica molding helps to maintain cell morphology and functions e.g. bovine aortic endothelial cells can be cultured using high cell alignment frequency and smaller circular index is used when they are cultured on poly(glycerolsesebacate) on sucrose-coated micro fabricated silicon. Replica molding helps also in maintaining controlled microenvironment and it is integrated with inverted microscope for monitoring the accurate time of any change in the cell size of articular chondrocyte. Micro-contact printing technique helps in formation of synaptic connections with polystyrene and polydimethylsiloxane and also on rat hippocampus neurons when cultured with silicon oxide, they showed initial resting potential and after one day of culture, they were able to reach action potential.

In biosensor systems to detect pathogens

A nanoparticle with specific optical, electrochemical or magnetic properties increases the detection ability of the diagnostic methods by incorporating them into biosensor systems. Further, the possibility of using them in a variety of configurations allows implementing these nanoparticles as point of care systems for human health or multiplexed devices[16].

In nano-diagnostics

The use of nanobiotechnology in the molecular diagnostics is defined as nanomolecular diagnostics or “nanodiagnostics”. Multifunctional nanoparticles, that are able to incorporate diagnostic or therapeutic properties, are used in in-vivo conditions to protect the drug in the systemic circulation, inhibits access of the drug to the chosen sites and to deliver the drug at a controlled and sustained rate to the target site are commonly used in nanodiagnostics.

Gold nanoparticles, with the strong electron absorbing properties are used for staining samples with poor contrast, such as tissue samples in transmission electron microscopy are also used in nano-diagnostics. Gold nanoparticles are used as sensors for detecting sensitive DNA. Their optical properties may vary depending upon their binding to specific molecules; this allows detecting and quantifying the presence of analytes. The absorption spectrum of gold nanoparticles differs at a wide range when many particles are closer to each another.

Using Magnetic nanoparticles, a potential diagnostic tool in biomedicine, incorporation of desirable quantities of super paramagnetic iron oxide nanoparticles into cells has become possible. This helps to enable their diagnosis in in-vivo conditions using Magnetic resonance imaging.

Quantum dots are widely used in place of traditional fluorescent dyes like fluorescein isothiocyanate FITC, in diagnostic purposes because of their photo stability and size dependent fluorescence properties. Functionalized Quantum dots are useful in fluorescent in-situ hybridization assays and for labeling DNA probing of genomic DNA.

DNA proteins and nucleic acid conjugates developed by either covalent coupling method, or by non-covalent bimolecular recognition methods, like receptor-ligands of complementary nucleic acids are potential diagnostic tools used in immunological detection assays, and in the biomimetic bottom-up approach to synthesize nanostructured supra-molecular tools[17].

Food safety through nanobiotechnology

The nanobiotechnological research in food involves mainly adding antioxidants, antimicrobial, biosensors, and other nanomaterials at packaging stage. The applications of bio-nanocomposites for food packaging along with edible and biodegradable nanocomposite films are used in recent days.

Biocompatible polymeric silver nanocomposites are prepared using natural polymers (gum acacia, starch, and gelatin, sodium alginate, and carboxy methyl cellulose), as the combination of silver nanoparticles with water soluble biopolymers produces newer antimicrobial agents. Chitosan, a natural polymer interacts with bacteria easily and attaches with DNA, glycosaminoglycans, and many proteins, so as to increase the antimicrobial effect of silver nanoparticles.

Butnariu and Giuchici, worked on studying the therapeutic effeciency of nano-emulsions made using aqueous extracts of an antioxidant, lycopene and propolis. The results proved 100% reduced inflammation levels due to antioxidant lycopene in the nano-emulsion. Moreover, the moisturizing property of this nano-emulsion improves the skin ability to protect against harmful sun rays[18].

The curcumin, a natural polyphenol with various therapeutic properties extracted from the Curcuma species rhizomes was used to develop a nanogel by Gonçalves et al. The authors developed a dextrin nanogel, which was used as an effective "nanocarrier" for lipophilic curcumin formulation with enhanced solubility, improved stability, and controlled drug release rate. The smaller size of this system can be useful to target the tumorous tissues passively[19].

THERAPEUTIC APPLICATIONS OF NANOBIOTECHNOLOGY

Nanobiotechnology has found its use in every aspects of human healthcare.
To diagnose cancer, nanoparticles are developed in order to optimize nuclear medicine imaging, magnetic resonance imaging, and ultrasound imaging. The effective advantages of cancer therapy by nanoparticles engineered by nanobiotechnology are faster destruction of tumor with less damage to a normal tissue. This increases the potential of standard chemotherapy and radiation.

Nanoparticles deliver chemotherapy drugs in a potent way than standard treatment methods, directly to tumor cells by giving a signal after destruction of the cells. When the gold nanoparticles combinations are used followed by X-ray treatment minimize the tumor size, or eradicate them completely in mice. Prior researches have given an indication in capability to deliver the approximate range of infrared light at a 15cm depth depending on the tumor tissue. Tumor ablation in mice by Photo-thermal methods has attained using near-infrared-absorbing nanoparticles with maximum success.

Applied nanobiotechnology used for regenerating and protecting the central nervous system will effectively provide advantage from nanotechnology research conducted at basic level in conjunction with advanced neurophysiology, nanopathology and cell biology. Nanomaterials are used to deliver the therapeutic effect, directly to the site, requiring a lower dose. These materials use a specific molecular structure which interacts with protein structures or neurons of the cells.

In cardiovascular diseases, plaque components are targeted with nanoprobes for detecting patient's having maximum risk of disorder. Antimicrobial nanoemulsions, consisting of alcohol, water, soybean oil, detergent agents with size range of 200 to 400nm destroy the micro-organisms potentially without toxic effects[20].

CURRENT ASPECTS OF NANOBIOTECHNOLOGY

Nanobiotechnology is best described as a field helping the modern medicine progress program from treating symptoms to generating cures and regenerating biological tissues. Three patients from America have received whole cultured bladders using nanobiotechnology principles. By conducting studies on animals it has been demonstrated that it is possible to grow a uterus in in-vitro conditions and then introduced in in-vivo conditions of the body. In the United States, Stem cell treatments to cure cardio disorders are under clinical trials. Funding is provided for research into allowing individuals to have new limbs without having to resort to prosthesis. Artificial proteins without any harmful chemicals and costlier equipments may become available in the future with the application of nanobiotechnology tools.
Example of the current nanobiotechnological research is fluorescent polymer coated nanospheres, where fluorescence of polymer is quenched when they encounter with specific molecules. These polymer-coated spheres as a part of new biological assays, might someday lead to particles which can be introduced into the human body to find out the metabolites linked with various diseases like tumors etc.

CONCLUSION

Nanobiotechnology is the beneficial progressing research field of science and engineering. It is present at the boundary layer between nanotechnology and biotechnology dealing with the investigation and applications of the newly produced nanomaterials as well as the development of functionalized nanobiosystems. It creates effective implementation of many new materials and devices in the various scientific fields. Nanobiotechnology leads to innovations by playing a prominent role in various biomedical applications starting from drug delivery and gene therapy to molecular imaging, biomarkers and biosensors. Detailed research and careful clinical trials are required to introduce diverse tools of nanobiotechnology in random clinical applications with potential success.

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