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# Advances in Nanotechnological Research and Development in Medicine from Marine Resources

**Mrinal K Ghose, PhD, DSc**
Emeritus Professor, Department of Biotechnology, West Bengal University of Technology
BF 142 Salt Lake City, Sector 1, Kolkata–700 064
E-mail: mrinal.ghose10@gmail.com



## ABSTRACT

Nanoscience suggests a solid body of theory, upon which a technology could be built. The concept of nanotechnological research in the fields of marine science and technology is quite recent. This paper discusses the potentials for applications of nanotechnology in the areas of marine biomedicines, marine toxicology, marine industrial chemicals, and others. It holds a great promise for developing countries where fish and shellfish are a major source of food, as well as an industrial commodity. This technology points out that several marine organisms contain many bioactive chemical compounds with various pharmacological properties and have provided useful drugs. Therefore, it is seen that there is an immense potential for nanotechnology in marine sciences. This paper emphasizes that today there is a great need for exploitation of biologically active compounds and untapped food resources. Marine pollution control and management with the applications of nanotechnology have also been discussed in this paper. It concludes that medical science will of course be heavily involved through the application of nanotechnology, which will impact not only human cell ultrastructure and effects on the immune system, but should also contribute to solving the riddle of allergy. This paper brings out that the advances in nanotechnological research will go a long way in innovations in chemical industries.

**Keywords**: Marine organisms, Bioactive compounds, Human cell ultrastructure, Immune system

## INTRODUCTION

Nanotechnology is defined as the design and fabrication of materials, devices and systems with control at nanometer dimensions. Nanobiotechnology and bionanotechnology refer to materials and processes at the nanometer scale that are based on biological, biometric or biologically inspired molecules and nanotechnological devices used to control biological processes, e.g., in medicine. Nanomaterials are the base components for nanotechnology and are at the leading edge of this field. Nanotechnology studies materials with morphological features on the nano-scale and especially that have special properties stemming from their nanoscale dimension. Nanotechnology with chemistry, biology, and quantum mechanics is not new: Nanotechnology is considered to be rather new, but it is by no means the only field concerned with atoms and molecules.

The nanometer length scale is creating possibilities of novel materials that can be used for the construction of devices and systems to generate services to mankind. The unique size dependent properties of nanomaterials make them superior and indispensable in many areas of human activity. In different ways, the disciplines of physics, chemistry, and biology have long dealt with atoms and molecules, their behaviour,their manipulation; and quantum mechanics is already firmly established as the science of the absolutely small.

Biology is considered to provide living proof of principles of nanotechnology. Biological structure at macromolecular and supramolecular scales are apparently assembled using the principles of self-assembly so eagerly, sought by the nanotechnologist, and these structures, mostly protein-based, often combine extraordinary lightness with extraordinary strength.India has a vast coastline of about 8,000 km and its Exclusive Economic Zone (EEZ) extends up to 370 km from the coast. The pioneering researches conducted by the Central Marine Fisheries Research Institute has shown that there are numerous species of organisms belonging to sponges, gorgonids, corals, echinoderms, and sea-anemones.The liver oil from fish is an excellent source of vitamins X and D; insulin has been extracted from whales and tuna fish; and the red alga *Digenia simplex* has been shown to contain an anthelminthic. The objective of this paper is to discuss the applications of nanotechnology to medicine from marine resources.



## APPLICATIONS OF NANOTECHNOLOGY TO MEDICINE

Nanomedicine involves utilization of nanotechnology for the benefit of human health and well-being. The use of nanotechnology in various sectors of therapeutics has revolutionized the field of medicine where nanoparticles of dimensions ranging between 1–100 nm are designed and used for diagnostics, therapeutics, and as biomedical tools for research.[1] It is now possible to provide therapy at a molecular level with the help of these tools, thus treating the disease and assisting in the study of pathogenesis of diseases. Conventional drugs suffer from major limitations of adverse effects occurring as a result of non-specificity of drug action and lack of efficacy due to improper or ineffective dosage formulation (for example, cancer chemotherapy and anti-diabetic agents). Designing of drugs with greater degree of cell specificity improves their efficacy and minimizes adverse effects. Diagnostic methods with greater degree of sensitivity aid in early detection of the disease and provide better prognosis. Nanotechnology is being applied extensively to provide targeted drug therapy, diagnostics, tissue regeneration, cell culture, biosensors, and other tools in the field of molecular biology. Various nanotechnology platforms,such as fullerenes, nanotubes, quantum dots, nanopores, dendrimers, liposomes, magnetic nanoprobes, and radio-controlled nanoparticles have been developed.

Usually water soluble drugs are loaded in aqueous compartment and lipid soluble drugs are incorporated in the liposome membrane.[2] The major limitation of liposome is its rapid degradation and clearance by the liver macrophages[3], thus reducing the duration of action of the drug it carries. This can be reduced to a certain extent with the advent of stealth liposomes where the liposomes are coated with materials like polyoxyethylene[4] which prevents opsonization of the liposome and their uptake by macrophages.[5] Other ways of prolonging the circulation time of liposomes are incorporation of substances like cholesterol[6],polyvinylpyrollidone polyacrylamide lipids[7], and high transition temperature phospholipids distearoyl phosphatidylcholine.[8]

Antibody Directed Enzyme Prodrug Therapy (ADEPT) consists of liposomes conjugated with an enzyme to activate a prodrug and an antibody directed to a tumour antigen (enzyme linked immunoliposomes).[9] These are administered prior to administration of a prodrug. The antibody directs the enzyme to the target tissue where it activates the prodrug selectively and converts it into its active form. This way, action of the drug is avoided in other normal tissues, thus minimizing the toxicity of drug.[10–12] Such studies are being tried with epirubicin and doxorubicin.[11,13] Ligand bearing liposomes are conjugated with specific ligands which are directed towards target structures. In ovarian cancer, overexpression of folate receptors by the tumour tissue occurs. So, the liposomal drug can be conjugated with folate so as to direct the molecule to the tumour.[14] This method is also being tried in the treatment of leishmaniasis where liposomalhamycin conjugated with mannosyl human serumalbumin are targeted towards human macrophages.[15] Asialofeutin conjugation is being tried to target liver cells for gene therapy.[16]The targeted liposomal preparations are found to have a better efficacy thannon-targeted liposomes.

The applications of nanotechnology to medicine are in nanosurgery, a development of microsurgery. Although complicated operations still require to be carried out in the traditional way, the diminished invasiveness implied by microsurgical techniques makes them very attractive. The ultimate development in nanotechnology is considered to be quasi-autonomous robots that can be released into the blood, through which they will travel to the site needing intervention. Nanotechnology offers the tools to investigate airborne particles, such as, nano photonics (integrated optics) for detecting and qualifying them, atomic force microscopy for auxiliary structural investigations, and so on. Medical science will of course be heavily involved in these investigations, which will impact not only human cell ultrastructure and have effects on the immune system, but should also contribute to solving the riddle of allergy. It is now known that several marine organisms contain many bioactive chemical compounds with various pharmacological properties. Many marine organisms have also provided useful drugs. The liver oil from fish is an excellent source of vitamins X and D; insulin is extracted from whales and tuna fish; and the red alga *Digenia simplex*is shown to contain an anthelminthic. Other such examples are:Cardiotonic polypeptides are extracted from sea anemones, adrenergic compound from sponges, potential anti-tumor compound from Caribbean gorgonians and soft corals. Antiviral and anti-tumour despeptides have been obtained from a Caribbean tunicate of the family *Didemnidae*, which inhibits the growth of DNA and RNA viruses as well as L 1210 marine leukemic cells. An outstanding example of the potential the biotechnological application offers is that of marine pharmaceuticals and drugs.

## BIOACTIVE COMPOUNDS

There are indications that tunicates may be an abundant source of bioactive compounds.

Cardiovascular active substances have been isolated from sponges, N-methylated histamines and histamines from *Verongia fistularis,* asystolic nucleoside from *Dasychalnia cyathnia* and the nucleosids spongosine from *Cryptotethya crypta*. These are just a few examples. The fact is that it is uneconomical to extract and purify material from the organisms that have to be captured in large quantities from various remote areas. This necessitates the need for culture of these organisms. Further, there is a lack of knowledge concerning the basic chemistry of many of the marine natural products which has limited the use of these sources for the development of useful drugs. Genetic engineering can change this situation dramatically by revealing the vast and diverse genetic composition of marine life for pharmacological application. Marine biofouling is highly destructive to vessels and underwater and floating structures used for marine aquaculture. The ability of bacteria to find, attach, adhere, and elaborate specific primary films are the crucial stages in biofouling. If these factors are understood, it is possible to manipulate them by employing biotechnology techniques. Two approaches are being tested to elucidate the molecular basis of biofouling. Many powerful chemical toxins have been isolated from various toxic organisms. They have specific functional groups in the molecule and show strong toxic physiological activity. Many toxins have potential applications as a drug or pharmaceutical agent. Even when the direct use as drug is not feasible, because of potent or harmful side effects, these toxins still serve as models for synthesis or providing suitable derivatives which improves their suitability as drugs. One is to identify the genes involved in each of these processes using recombinant DNA technology. The second is the use of transposing mutagenesis, when a transposing mutant deficient in the expression of adhesion gene is discovered, it could be easy for further elucidation of the factors involved in microbial adhesion and then it might be possible to manipulate these factors at a genetic and biochemical level. This also has implication in aquaculture by enhancing spat settlement of cultivable mollusks.

## MARINE PHARMACOLOGY

A dramatic example of biotechnology applications is that of marine pharmaceuticals. Extracts from a tunicate belonging to the family *Didemnidae*, inhibit the growth of DNA and RNA virus as well as leukemic cells. Marine toxins besides being pharmacological chemicals, also serve as models for development of new synthetic chemicals. The strategy to be undertaken in marine pharmacology would be initial screening of marine organisms for bioactive agents. The most useful bioactive compound can be tested and characterized. Thereafter,two prolonged strategies could be undertaken. One for evolving techniques for mass culture of the organism and the other for using recombinant DNA technique to identify and clone genes responsible for synthesizing the bioactive compounds.

## MARINE POLLUTION CONTROL AND MANAGEMENT

Marine pollution control and its management is more important because natural organisms cannot produce enzymes necessary for transformation of the original compounds so that the intermediates are produced which can enter into common metabolic pathways and metabolized completely. Synthetic compounds are relatively more resistant to biodegradation compared to the natural products which create significant problems for waste management and environmental protection. Groups of microorganisms useful in treating specific types of man-made compounds have been complied and are known. Selective use of microorganisms, including actinomycetes, fungi, bacteria, phototrophic microorganisms, anaerobic bacteria, and oligotrophic bacteria are known in certain applications, such as wastewater treatment for biological removal of nitrogen via sequential nitrification and denitrification. The treatment of selected industrial wastes in reactors using controlled mixed cultures is currently in use in Japan. Various methods of genetic engineering will certainly prove to be very useful for this purpose.

The engineering of microorganisms to be added to wastes that are to be discharged into the marine environment has to be found out. Pollutants entering the marine environment can interfere with the integrity of the ecosystems. A few examples of such pollutants are synthetic organic compounds, chlorinated chemicals, dredged spoils, litter, artificial radionuclide, trace metals, and fossil fuel compounds. Toxaphene, a group of about 200 compounds, produced by chlorination of wood waste products and comphors under ultraviolet light contains carcinogenic and mutagenic chemicals. These chemicals/compounds may be more persistent in the environment than Dichlorodiphenyltrichloroethane (DDT) and its degradation products. The modifications of genetic information resident in microorganisms can be used for pollution control. The enzyme concentration may be amplified either by selection of constitutive mutants, increase in the number of copies of the gene for the enzyme or both, so that enzymatic degradation can be made. Rearrangement of regulatory mechanisms controlling the expression of specific genes in response to specific stimuli may also prove to be useful.

Another useful modification is the introduction of new enzymatic functions into organisms not having them. The alteration of the characteristics, such as substrate specificity, kinetic instant, and pH optimum, of specific enzymes can also be used. These modifications can be achieved by undertaking in vitro modifications via transposing mutagenesis or other transposing mediated gene manipulation, genetic exchange via transduction, transformation, or conjugation, protoplast fusion, site-specific mutagenesis, and specialized selection procedures to enrich for mutants. The engineering of microorganisms capable of flourishing in the marine environment, optimized proliferation and maintenance of selected populations has to be considered. The need for algaecides and antifouling agents is so great that discoveries of such compounds with these activities will produce marketable success.

## MARINE AQUACULTURE

The pathology and diseases of organisms under marine aquaculture have to be studied and their control using genetic engineering techniques as well as immunological methods have to be found out. Also, the post-harvest technologies to increase the quality and value of the final food products have to be improved. The other significant area which needs our attention is the transportation of seeds of the organisms from the hatchery to the farm or field for marine aquaculture. Today, the transportation of seeds poses a high risk of mortality. Coelenterates, alcyonarians, sea-urchins, molluscs, pearl and edible oysters, clams, seaweeds and algae, seagrass, etc.,are found in our coastal waters. Screening of these for their bioactivity and isolation and characterization of the chemical compounds responsible for these activities is the first step needed. Already a few researches have been conducted by Central Marine Fisheries Research Institute (CMFRI), Central Institute of Fisheries Technology (CIFT), National Institute of Oceanography (NIO), Central Drug Research Institute (CDRI), and Indian Drugs and Pharmaceuticals Private Limited (IDPL) but they are only peripheral. The other biotechnological strategies needed in marine aquaculture activities are, the farm engineering and harvesting technology which have to be designed and perfected for producing the maximum yield.

Chromosomal manipulation techniques may be utilized and perfected to improve fish production in marine aquaculture. Fish nutrition is another aspect which has to be considered from the point of view of marine aquaculture. The feed for the organisms to be reared has to be carefully compounded with due regard for increased growth rate and breeding so that their culture is profitable. By far, the importance of the applications of genetic engineering techniques is greatest to the marine biotechnological field. It will also provide an untapped gene pool representing the transport system for minerals, metal concentration, novel photosynthetic systems, and marine pheromones, i.e., communicator substances produced by marine organisms as well as the hydrogen sulphide utilizing and microbial mediated ecosystems. With the advent of the tools of genetic engineering, the potential of the sea as a significant source of protein food can be assessed. The stock assessment and the migration of fish can be known which will make it easier to know when and where to fish at a particular period. The management and stock breeding can be made more preciseusing these biotechnologies for fish and shellfish in a more profitable way so as to provide food and favourable returns to the country.



## CONCLUSION

From these,it is seen that there is an immense potential for biotechnology in marine sciences. The greatest need of today is for exploitation of biologically active compounds and the hitherto untapped food resources. India has a vast coastline of about 8,000 km and its Exclusive Economic Zone (EEZ) extends up to 370 km from the coast. The pioneering researches conducted by the Central Marine Fisheries Research Institute has shown that there are numerous species of organisms belonging to sponges, gorgonids, corals, echinoderms, and sea-anemones.Medical science will of course be heavily involved through the application of nanotechnology, which will impact not only human cell ultrastructure and effects on the immune system, but should also contribute to solving the riddle of allergy.

## REFERENCES

1. Medina C, Santos-Martinez MJ, Radomski A, Corrigan OI, Radomski MW. 2007.**Nanoparticles: Pharmacological and Toxicological Significance**. *Br J Pharmacol* **150**: pp. 552–558

2. Gregoriadis G, Ryman BE. 1972.**Fate of Protein-containing Liposomes Injected into Rats: An Approach to the Treatment of Storage Diseases**. *Eur J Biochem* **24**: pp. 485–491

3. McCormack B, Gregoriadis G. 1994. **Drugs-in-cyclodextrins-inliposomes:A Novel Concept in DrugDelivery**. *Int J Pharm***112**: pp. 249–258

4. Illum L, Davis SS. 1984. **The Organ Uptake of Intravenously Administered Colloidal Particles can be Altered Using a Non-ionic Surfactant (Poloxamer 338)**. *FEBS Lett***167**: pp. 79–82

5. Senior J, Delgado C, Fisher D, Tilcock C, Gregoriadis G.1991. **Influence of Surface Hydrophilicity of Liposomes on Their Interaction with Plasma-protein and Clearance from the Circulation—Studies with Poly (ethylene glycol)-coated Vesicles**. *BiochimBiophysActa* **1062**: pp. 77–82

6. Kirby C, Gregoriadis G. 1983.**The Effect of Lipid Composition of Small Unilamellar Liposomes Containing Melphalan andVincristine on Drug Clearance after Injection in Mice**. *BiochemPharmacol* **32**: pp. 609–615

7. Torchilin VP, Shtilman MI, Trubetskoy VS, Whiteman K, Milstein AM. 1994. **AmphiphilicVinyl Polymers Effectively Prolong Liposome Circulation Time *in vivo***.*BiochimBiophysActa* **1195**:

pp. 181–184

8. Forssen EA, Coulter DM, Proffitt RT. 1992. **Selective *in vivo*Localization of Daunorubicin Small Unilamellar Vesicles in Solid Tumors**. *Cancer Res* **52**: pp. 3255–3261

9. Torchilin VP, Trubetskoy VS, Milshteyn AM, Canillo J, Wolf GL, Papisov MI. 1994. **Targeted Delivery of Diagnostic Agents by Surface Modified Liposomes**. *J Control Rel* **28**: pp. 45–58

10. Bagshawe KD, Sharma SK, Springer CJ, Antoniw P, Boden JA, Rogers GT. **Antibody Directed Enzyme ProdrugTherapy (ADEPT) — Clinical Report**.*Dis Markers* **9**: pp. 233–238

11.Vingerhoeds MH, Haisma HJ, van MM, van de Rijt RB, Crommelin DJ, Storm G. 1993. **A NewApplication for Liposomes in Cancer Therapy:Immunoliposomes Bearing Enzymes (immune enzymosomes) for Site-specific Activation of Prodrugs**. *FEBS Lett* **336**: pp. 485–490

12.Vingerhoeds MH, Haisma HJ, Belliot SO, Smit RH, Crommelin DJ, Storm G. 1996. **Immunoliposomes as Enzyme-carriers (immune enzymosomes) for Antibody-directed Enzyme ProdrugTherapy (ADEPT) : Optimization of Prodrug Activating Capacity**. *Pharm Res* **13**: pp. 604–610

13. Xu G, McLeod HL. 2001. **Strategies for Enzyme/ProdrugCancer Therapy**.*Clin Cancer Res*7: pp. 3314–3324

14. Forssen E, Willis M. 1998. **Ligand-targeted Liposomes**.*Adv Drug Del Rev* **29**: pp. 249–271

15. Kole L, Sarkar K, Mahato SB, Das PK. 1994.**Eoglycoprotein Conjugated Liposomes as Macrophage Specific Drug Carrier in the Therapy of Leishmaniasis**.*Biochem Biophys Res Commun***200**: pp. 351–358

16. Wu J, Liu P, Zhu JL, Maddukuri S, Zern MA. 1998. **Increased Liver Uptake of Liposomes and Improved Targeting Efficacy by Labeling with Asialofetuin in Rodents**. *Hepatology***27**: pp. 772–778v