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Mini-Review

Bionanotechnology: The Novel Nanoparticles Based Approach for Disease Therapy

Adel M. Mahasneh*

Department of Biological Sciences, Faculty of Science, University of Jordan, Amman 11942, Jordan

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Abstract

Bionanotechnology has probably been the most developing field in the last decade as an integration of biotechnology on the molecular level and nanotechnology. It provided new avenues of research and development to produce novel and new nanomaterials of medicinal applications which paved the way to the vibrant field of nanomedicine. This is dependent on combining biological norms with unique characteristics of nano-sized particles to carry out very specific functions. This will hopefully lead to the elucidation of our understanding of disease therapy and the biology of different life forms. The prospects of using nanoparticles in such fields would include drug and gene therapy, tumor control, detection of pathogens and proteins, tissue and cell engineering, DNA probing, pest control in agricultural fields and many other applications. Knowing the expected implications of novel nanoparticles applications in nanoparticle based medicine and research, it became important to compile literature relevant to this subject in a single publication. Thus, this mini review was aimed to be a contribution to this emerging volatile area of bionanotechnology, where efforts are being exerted to apply basic scientific ideas in clinical practice.

Keywords: Bionanotechnology, Nanoparticles, Nanomaterials, Delivery Systems, Disease Therapy.

1. Introduction

Nowadays, global concern has emerged as we are entering the post antibiotic era with reduced capabilities in some areas to combat microbes and disease (Blecher *et al*., 2011). Hence, the development of novel therapeutic approaches to these challenges constitute a focal point of modern research (Carpenter *et al*., 2009; Hentzer and Givskov, 2003; Al-Hussaini and Mahasneh, 2009 a, b; Al-Hussaini and Mahasneh, 2011; Taleb *et al*., 2012; Taleb and Mahasneh, 2010a; Taleb and Mahasneh, 2010b; Taleb and Mahasneh, 2012; Knipe *et al*., 2013). The alternative to traditional therapies would be through investigating new and novel avenues of molecular therapies to include, for example, use of probiotics (Mahasneh and Abbas, 2010; Elbaz and Willner *et al*., 2012), quorum sensing regulation where the virulence of many pathogens is regulated by quorum sensing mechanism (Abudoleh and Mahasneh 2012) and last but not least the combination therapy. In this case, chemotherapy is given in combination with other means such as probiotics and nanoparticles to target specifically the diseased cells or tissues (Taleb and Mahasneh, 2012; Day *et al*., 2009). Such approaches will definitely improve the outcomes of both traditional, as well as, novel bionanotechnology approaches in nanomedicine, stem cell and gene therapies (Lin *et al*., 2013). The nanomedicine arena, if exploited properly, would have far reaching implications on medicinal professions, definition of disease, their diagnosis and treatment. Nanomedicine is based upon the use of nanoparticles at the level of 1-100 nm (Caruthers *et al*., 2007; Pissuwan *et al*., 2011; Knipe *et al*., 2013).

In the last two decades, nanoscaled technologies in health sciences have witnessed ample efforts in research, development and patenting (Caruthers *et al*., 2007). These efforts formed the cornerstone for the transfer of nanotechnological research into clinical settings (Elbaz and Willner, 2012) and it was expanded to shape what is known nowadays as nanomedicine. The aim of this activity was and still is to maximize efficiency in controlling diseases. To achieve this, nanomedicine concepts are used in the early diagnosis which leads to suggesting the treatment program with the least possible side effects and finally to evaluate its efficacy and feasibility (Park *et al*., 2010). Conversely, the European Science Foundation defined nanomedicine as "the science and technology of diagnosing, treating and preventing disease and traumatic injury, of relieving pain, and of preserving and improving human health, using molecular tools and molecular knowledge of the human body" (Bawa *et al*., 2005). Nanodrugs, particularly nano-particulate drugs, offer advantages over their bulk counterparts in one or more properties such as solubility, bioavailability, half life, stability, ability to cross biological barriers, toxicity, dose delivery and specificity

* Corresponding author. e-mail: amahasneh@ju.edu.jo.

(Blecher *et al*., 2011; Paulo *et al*., 2010). To elucidate nanomedicine implications in medical practice, such as cancer therapy, development of specific drug delivery system (Figure 1) and nanorobots have attracted a great deal of research where now we know exactly what such systems specifications would be (Arcese *et al*., 2012). The fully functional nanorobot should be able to carry a payload (drug), direct mobility to specific targets in patient body, adhere or attach to tumor cells and finally release the payload. Further researchers' efforts would no doubt be turned to design very specific nanorobots and nanoparticles.

The hopes surrounding nanotechnology in different fields, including medicine, are immense (Salvador-Morales *et al*., 2012). It does not offer improvements to existing techniques only, but provides leads to new tools and applications (del-Pozo-Rodriguez *et al*., 2013). Among these would be drug manipulation at the nanoscale with what impact such manipulation would leave upon the bioactive characteristics such as controlled release, solubility, retention time and probably environmentally triggered controlled release (Douglas *et al*., 2012). It is also realized that nanoparticles' surface area provides increased functionality which lends itself to further biomedical as well as environmental applications (Chunbai *et al*., 2013) and gene therapy (Pissuwan *et al*., 2011).

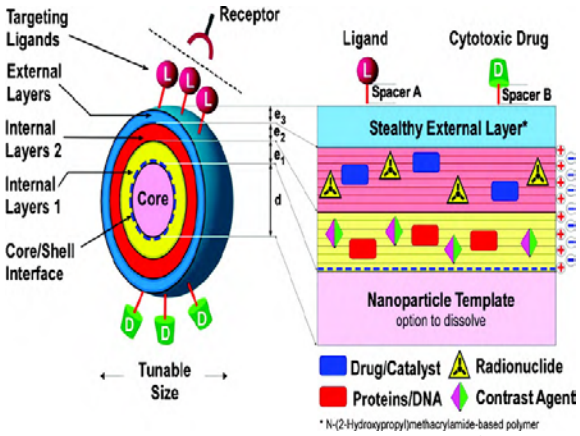

Figure 1. Core/shell drug delivery system consisting of cytotoxic stealth carrier particles based on nanoparticles. Usually the core is surrounded by several layers and chemical groups could be added to the external layer thus allowing attachment of biomolecules.

2. Applications of Biocompatible Nanoparticles

The distinct characteristics of the varying types of nanoparticles presented them for a wide variety of applications in medicine (Sih *et al*., 2013), in biological sciences for the development of biosensors, DNA probes (Tang *et al*., 2006), in medicine (Mukherjee *et al*., 2007), in controlling pathogenic bacteria (Raja *et al*., 2012) and fungi (Min *et al*., 2009), and in ecological applications pertaining to water treatment (Lyon *et al*., 2006) and plant diseases (Jo *et al*., 2009; Aguilar-Mendez, 2010; Kim *et al*., 2008).

Nanoparticles of the size 1-10 nm were capable of readily interacting with HIV virus through selective binding to glycoprotein thus inhibiting viruses from binding to host cells (Elechiguerra *et al*., 2005). Metallic nanoparticles such as silver nanos are being used in medical implants and devices to prevent microbial infections (Geethalakshmi and Sarada, 2010). Furthermore, some nanoparticles have been tested for their probable use in burnt tissues, alternative dental materials and textile fabrics (Duran *et al*., 2007).

Gene therapy is an emerging field where nanoparticles would no doubt play a major role in elucidating means and ways of introducing and delivering genes into target cells or tissues. In here, nucleic acids are delivered through special delivery systems thus controlling gene flow and expression. Pedro *et al*. (2008) recall the great advances in human gene therapy which were driven by interest in understanding of the molecular mechanisms of diseases and what they implicate of vector design in the quest for producing more efficient and safe drug in addition to gene delivery systems thus bridging bottlenecks through new technologies. In this context, it is worthy to mention research efforts in the search for designer bionanoparticles in the form of viral like particles (VLPs). These nanoparticles are unique in their diversity in terms of structure, shapes, architecture and production means (Figure 2). In this direction, new administration routes are being sought through oral and pulmonary means although intravenous route is the one of choice for most current nanoparticles delivery (Uchegbu and Siew, 2013). It should be noted that an array of cell types exist in the human body, which means that higher organisms, including our bodies, are just compilations of multifunctional nanosystems (Suh *et al*., 2009). Research on nanoparticles usually involved organic, inorganic and composite nanos to be produced, characterized and then used in drug delivery, bioimaging and other applications which necessitates further biocompatibility studies (Salvador-Morales, 2012). The shortage of effective and safe *in vitro* delivery systems has been a challenging obstacle in developing new nanoparticle based therapeutics (Troiber and Wagner, 2011). To secure an acceptable level of safety, other aspects of nanoparticles have to be considered. Priority aspects include routes of administration, therapeutic dose and frequency as well as reproducibility (Mohanan, 2010; Azzazy and Mansour,2009).

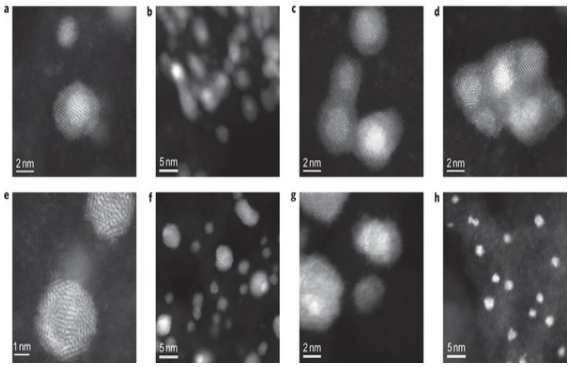

Figure 2. Images of nanoparticles showing diversity in terms of structure, shape, architecture and arrangements.

3. Nanoparticles Preparation Methods

Synthesis of nanoparticles has emerged in the last decade as an intersection between nanotechnology and biotechnology; hence the coining of the new expanding bionanotechnology (Raja *et al*., 2012). Due to the possible wide application of nanoparticles, this emerging science put nanoparticles at the tip of modern material science research. These nanoparticles are expected to exhibit new and/or novel characteristics associated with size, morphology and distribution (Veerasamy *et al*., 2011). Such characteristics are deemed to meet different applications of nanoparticles (Sayed and Ahmad, 2013). To improve the functionality of nanoparticles, it is mandatory to be functionalized accordingly with probably protein or biocompatible surfaces to reduce their toxicity if they are of inorganic origin such as the quantum dots (Sayed and Ahmad, 2013). Recent literature lists several possible means of nanoparticle synthesis ranging from totally chemical methods to fully biological processes (Veerasamy *et al*., 2011) such as reduction in solutions, chemical and photochemical reactions, thermal decomposition, radiation-assisted (Bhuvanasree *et al*., 2013), electrochemical and finally most recently green synthesis (Raja *et al*., 2012; Sayed and Ahmad, 2013; Gopinath and Velusamy, 2013). Nanoparticles synthesis using mostly toxic chemicals with low rates of conversion and laborious purification methods with high energy physical procedures prompted investigators to search for biologically mediated methods including microorganisms such as fungi, bacteria and plant systems including plant extracts (Gopinath and Velusamy, 2013; Sayed and Ahmad, 2013). These biological processes offered great deal in developing new methods to produce nanoparticles. They offer cost-effective methods and they are easily sealed up and economize energy demands and finally they are ecofriendly (Ponarulselvam *et al*., 2012; Song and Kim, 2009; Ahmad *et al*., 2011). Table 1 highlights the most used methods of nanoparticle preparation.

Table 1. Brief description of the most common and emerging nanoparticles preparation methods; (+): produced; (++): experimental optimization.

Method	Advantages	Scale-up
Nanoprecipitation of polymers	Fast; reproducible	++
Polymerization of alkylcyanoacrylates	Easy to produce core-shell nanos	++
Interfacial polycondensations	Modulation of nanos thickness	++
Formation of polyelectrolyte complexes	Positive or negative charge nanos are produced	++
Nanos from neutral nanogels	Organic solvent-free; controlled release of drugs	++
Ionic gelation	Possibility of controlled drug release in response to a stimulus	++
Gelation of emulsion droplets	Hydrophilic and biocompatible	++
Emulsification-reverse salting-out	Less stress upon fragile drugs	++
Emulsification-solvent evaporation	Encapsulation of hydrophilic and lipophilic drugs	++
Colloidal mill	Controlled nano size	++
Natural organisms-Fungi	Simple; non-toxic; reliable; ecofriendly	++
Natural organisms-Bacteria	Well defined size and distinct morphology; biocompatible; ecofriendly	++
Natural products-plant extracts (green synthesis)	Cost-effective; simple; ecofriendly	++

4. Molecular Therapy and Delivery Systems

The ample amount of information pertaining to the understanding of molecular mechanisms of diseases that was gathered in the last two decades coupled with advances at the gene therapy level has prompted research for more efficient, effective and safe delivery systems (Pedro *et al.,* 2008; Bansal *et al.,* 2012; Neves *et al.,* 2012). In cancer treatment, current research include development of delivery systems that allow very specific dosing routes and unusual therapeutic targets (Brannon-Peppas and Blanchette, 2012; Mignani *et al.,* 2013).

In the last few years we observed the emergence of many new and improved intelligent nanoscale platforms which is suitable for drug and gene delivery as well as imaging. It also witnessed the search for smart functionality in delivery systems to include cell and receptor specific targeting in the context of nano-bio interaction (Lehner *et al*., 2013) in nanomedicine (accepted). Nanotechnology-based carriers have shown very successful results in terms of low toxicity and efficient delivery to targets including cells and/or tissues of mammalian systems (Seth *et al*., 2012; Shen *et al*., 2012). Different nanotechnology systems would provide solutions for improved delivery with least toxicity which is the core for translating effectively basic medical sciences into enhanced clinical practice (Liu and Zhang, 2011; Singh *et al*., 2012).

In this context, consideration should be given to the size of delivery vehicle, ease of penetration into the cellular membranes and sustainability in the cytoplasm (Li and Huang 2010). Among the best studied nanocarriers are those synthesized from liposomes, dendrimers, carbon nanotubes and nanoclusters (fullerenes), polymers and metal and metal oxides nanoparticles. Table 2 presents some delivery systems and some of their unique characteristics that make therapy more effective.

From the aforementioned table, it is rather clear that the best fit delivery system is one that exhibits characteristics of both non-viral as well as viral delivery vectors coupled with disarming such systems from undesired properties.

Table 2. Diversity of different delivery systems available and under testing and could be used for the treatment of different diseases.

Delivery system	Main characteristics	Comments
Liposomes	Biocompatible and biodegradable; most suitable for DNA, RNA delivery into mammalian cells; persistence in blood circulation; increased specificity for gene therapy	Pharmaceutical and medical applications; easy to synthesize and easy storage
Dendrimers	Highly symmetric; many functional groups at surfaces; better encapsulation of genes; high payload delivery	May act as multifunctional delivery application; modifiable surface groups thus tuning their activity
Fullerenes	Carbon nanoclusters; possibility of functionalizing it in different ways such as making it water-soluble; less toxic than cationic liposomes	It forms protective sheath over bound DNA expanding chances of incorporation into chromosomes
Carbon nanotubes	Gene and drug delivery; compatibility with aqueous environments; nontoxic in mammalian cells and tissues	Very successful in gene delivery for disease therapy
Quantum dots	Extremely small; mainly of heavy metal origin; very effective in imaging enhancement	Often they undergo leaching in biological environment leading to toxicity in mammalian cells
Gold, silver magnetic nanoparticles	Highly noted in biomedical application, biodiagnostics, imaging, gene and drug delivery for disease and gene therapy	Nontoxic nature of gold nanos; non-opsogenic and of stealth properties; used in magnetic hyperthermia therapy cancer cells
Viral systems – oncoviruses	Specific gene therapy; stability during genome integration; insert large gene segments; infect only dividing cells	During gene therapy trials, possible recombination with endogenous human retroviruses
Viral systems – Adenovirus	Gene therapy; low pathogenicity for humans; infect non-dividing cells	It induces strong immune response; no integration into the host
Viral systems – Adeno-associated-virus	No pathogenicity and toxicity; infect non-dividing cells; long-term transgene expression	No specific integration' may mutagenize cells
Viral systems – Lentivirus	Can carry large gene inserts; stable expression; infect non-dividing cells	Biosafety problems

However, more work is needed to overcome problems such as lack of specific targeting, toxicity, low transfection efficacy and expression in case of gene therapy and specificity, all of which hindered advancement in molecular and regular therapy approaches (Knipe *et al*., 2013).

Finally, it seems that nanotechnology, especially bionanotechnology is expanding at a speedy pace exploring novel methods at both the traditional and the molecular levels of therapy.

It is also clear that progress of the new emerging field of nanomedicine is dependent on exploring bionanotechnology potential in terms of translating the laboratory based trials and observations into the real clinical settings. These necessitate further research on scale-up, inconsistencies from batch to batch, confirmation of stealth properties of nanoparticles *in vivo*, improved specificity of the different nanoparticles and finally improved targeting means through nanorobots development. The concept of smart nanosystems for new and novel biomedical applications is being exploited. Solution of all or part of these concerns would no doubt open new frontiers for the nano-based diagnostics for the detection of tumors, infections and neurological diseases among many others. At this stage of scientific discovery I would dare to say that nanoparticles-based nanomedicine would in the very near future transform the understanding of the human biological structure and function. This transformation will no doubt furnish new nanoparticle based applications to include chemotherapy, activity monitors (blood pressure, glucose monitors), biochips, pacemakers, insulin pumps, needleless injectors, medical flow sensors, drug delivery systems and finally designer gene therapy systems. This would expand the prospective horizons of nanoparticles use as well as the need for further investigations pertaining to the final fate and probable interactions of these bionanoparticles in biological systems.

5. Conclusion

Science has greatly advanced into the area of applied nanotechnology and the internal components of living cells are of the same scale. This lead bionano-technologists to look to cell biology for medicinal applications using biological structures, processes and information. Much of bionanotechnology is molecular biology based applications. Individual molecules, bacteria and viruses can be easily detected. Nano-particles are already in use for drug delivery trials, biological labeling, medical imaging and various other analytical purposes for clinical use. Other new and more complex bionanodevices are being produced and investigated for novel applications.

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