Pharmaceutical BIOPROCESSING

# Nanotechnology in medicine: innovation to market

Nanotechnology based medicine is an advanced biomedical field. After producing a plethora of laboratory based nanomedicine research, nanotechnology is facing a transition into the tangible advancement of human therapeutics. If nanoproducts are to be translated into meaningful benefits for patients, innovation in the laboratory must be supported by the standard research protocols and regulatory pathways. Both for therapeutics and for medical devices now researchers and pharma-entrepreneurs have gathered at one platform to transfer innovation to market for the benefit of mankind.

**Bajwa SZ*, Munawar A & Khan WS**

National Institute for Biotechnology and Genetic Engineering, Faisalabad, Pakistan

*Author for correspondence: sadva2002pk@yahoo.co.uk

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## Nanomedicine

Nanomaterials possess exceptional unique nanoscale size dependent physical, optical, catalytic, electrical, and chemical properties that can be controlled (scalable). These properties are entirely different than their bulk counterpart. One of the exciting feature of nanotechnology is its utility in the field of nanomedicine, therapeutics, and medical devices [1]. When these small size materials are introduced into biological systems, their extremely small size and their unique nanoscale properties make it possible to use them as delivery vectors and probes for biological diagnostics, imaging and therapeutics [2]. Infact, when size decreases, the surface area to volume ratio of materials becomes very large, so that a vast suitable surface is available for chemical interactions with biomolecules. This critically implied that nanotechnology is facing a transition into the tangible advancement of human therapeutics. Recently, we have seen the beginning of multiple clinical trials of nanomaterials; both for therapeutics and for medical devices.

When we talk about nanomedicine, its aim can be broadly defined as the comprehensive production of materials to control, either repair, defence or therapy, and improvement of different human biological systems. For this purpose different nano-engineered structures are applied at molecular level. Here, nanoscale size materials can be included due to their active components in the size range from one nanometre to hundreds of nanometres [3].

Nanomaterials based drug delivery systems can interact with biomolecules positioned on both cell surface and within the cell. Thus nano based drug delivery systems not only transfer encapsulated or grafted chemotherapeutics, but can also deliver them within the cellular system once they have penetrated. Such systems can also be modified and decorated with different functionalizing agents such as antibodies to develop target specific drug delivery system [4]. At present only two families of therapeutic nanomedicine-albumin and liposomes nanoparticles are clinically established worldwide.

Nano Drug Delivery Systems (DDS) generally possess three vector generation; First generation vectors comprising nano spheres and nano capsules. Second generation vectors of nanoparticles that are coated with hydrophilic polymers such as Polyethylene Glycol (PEG). Third generation vectors which combines a biodegradable core and a Polymer Envelope (PEG) with a functionalization agent. Such systems offer inherent merits of protecting drug from being degraded in the body before it is actually delivered to its target, enhance drug absorption, better control over drug distribution to tissue and avoiding side effects by preventing interaction with normal cells. Many FDA

approved nanomedicines are available for clinical use **(TABLE 1)**.

Nanotechnology offers a different means to selectively deliver therapies at diseased cells or tissues, for instance, with application in inflammation or cancer. The behaviour of nanomaterials is based on two approaches, passive or active targeting. Passive targeting depends upon enhanced permeability and retention. Due to small size and different surface properties of nanomaterials they can drip through blood vessel walls into tissues [5]. On the other hand on active target approach, functional molecules on nanomaterials can bind specific cellular receptors to functionalize them for targeted delivery. Active

**Table 1. List of drugs approved by FDA.** Source: Adapted from US-FDA and EMA.

| Trade name | Year approved | Active pharmaceutical ingredient | Indication | Nanotechnology |
|---|---|---|---|---|
| Visudyne | 2000 | Verteporfin | Photodynamlic therapy for age-related muscular degeneration | Liposome |
| Doxil/Caelyx | 1995 | Doxorubicin | Antineoplastic | PEGylated liposome |
| AmBisome | 1990 | Amphotericin B | Fungal infections | Liposome |
| Abelcet | 1995 | Amphotericin B | Fungal infections | Liposome |
| Definity | 2001 | Octofluoro-propane | - | Liposome |
| Myocet | 2001 | Doxorubicin | - | Liposome |
| DepoCyte | 1999 | Cytarabine | Lymphomatous meningitis | Liposome |
| DepoDur | 2004 | Morphine | - | Liposome |
| Daunoxome | 1996 | Daunirubicin | Antineoplastic | Liposome |
| Octocog alfa | 2009 | Factor VIII | - | Liposome |
| Abraxane | 2005 | paclitaxel | Metastatic breast cancer | Albumin bound nanoparticles |
| Rapamune | 2000 | Rapamycin | Immunosuppresant | Nanocrystal Elan |
| Emend | 2003 | Aprepitant | Anti-emetic | Nanocrystal Elan |
| Tricor | 2004 | Fenofibrate | Hypercholesterolemia | Nanocrystal Elan |
| Megace ES | 2005 | Megestrol | Anti-anoretic | Nanocrystal Elan |
| Triglide | 2005 | Fenofibrate | Hypercholesterolemia | IDP-P Skyepharma nanocrystal |
| Mepact | - | Mifamurtide | - | Liposome |
| Amphotec | 1996 | - | Fungal infections | Micelle |
| Estrasorb | 2003 | - | Vasomotor symptoms associated with menopause | Micelle |
| Taxotere | 1996 | - | Antineoplastic | Micelle |
| Somatuline depot | 2007 | - | Acromegaly | Nanotube |
| Feraheme injection | 2009 | - | Treatment of iron deficiency anemia in patient with Chronic Kidney Disease | SPIO Polymer- |
| Krystexxa®/ Pegloticase (Horizon) | 2010 | Improved stability of protein through PEGylation; introduction of unique mammalian protein | Chronic gout | Polymer-protein conjugate (PEGylated porcine-like uricase) |
| Marqibo® (Onco TCS) | 2012 | Increased delivery to tumour site; lower systemic toxicity arising from side-effects | Acute Lymphoblastic Leukemia | Liposomal Vincristine |
| Abraxane®/ABI-007 (Celgene) | 2013 | Improved solubility; improved delivery to tumor | Breast cancer NSCLC Pancreatic cancer | Albumin-bound paclitaxel nanoparticles |
| Invega® Sustenna® (Janssen Pharms) | 2014 | Allows slow release of injectable low solubility drug | Schizophrenia Schizoaffective Disorder | Paliperidone Palmitate |
| Adynovate (Baxalta) | 2015 | Improved stability of protein through PEGylation | Hemophilia | protein conjugate (PEGylated factor VIII) |

and passive targeting can be combined to boast chemotherapeutic, achieving more significant disease control at lower drug doses [6]. Nano-based materials are also being investigated as regenerative medicines. Regenerative medicine is the procedure of generating functional and living tissues, to replace or repair damaged organ or tissue due to congenital defects, age, damage or disease. The main aim behind for nano-based regenerative medicine is the availability of cost-efficient, user friendly disease treating techniques that will permit for in-situ tissue regeneration [7]. Nanomaterial assisted gene delivery for employing stem cells has an energetic role in recognizing the potential of regenerative medicine. The major goal of continuing and future efforts in this field will be to effectively exploit the enormous newly discovered self-repair capability that has been observed in adult stem cells [3,8]. Here, two main objectives are perused; firstly recognising signalling systems in order to power the self-healing potential of endogenous stem cells. Secondly, emerging efficient targeting systems for adult stem cell therapies. Whereas, another possible application of regenerative medicine strategies is to evade pre-seed a nanostructured biomaterial scaffold/matrix of a patient's own cells.

Nanotechnology is an excellent mean to develop different structures and materials that mimic the biological but also promises to provide efficient delivery systems. The application of nanotechnology in this field is a wide topic. It includes the fabrication of different unique materials, such as nanoparticles, nano patterning and scaffolds for tissue engineering [9-11]. Future biomaterials must instantaneously improve tissue regeneration while reducing immune responses and preventing infection.

## Medical diagnostics

*In vitro* diagnosis for medical problems has conventionally been a laborious task; different tissue samples or body fluids are directed to a laboratory for an examination, which could take hours, days, weeks or months. Different disadvantages include cost, sample deterioration, lengthy waiting times (not suitable for urgent cases), imprecise results for minute sample quantities, and poor standardisation and management of sample collection. Different properties on a single device, nano industry, have led to the expansion of a new generation of sensing devices that are smaller, cheaper, user friendly, laborious free, provide accurate reading system, and faster [12]. These nano devices require small sample and will provide more accurate and complete biological data from a single test/measurement/reading. Nanotechnology refines the diagnostic techniques/devices, resulted in high throughput screening and resulted to the development of Point-of-Care (POC) diagnostics [13]. Nanoimaging includes numerous approaches for the study of *in vivo* molecular proceedings and molecules management. Main purpose of *in vivo* diagnostics research is to create highly sensitive, specificity and reliable detecting agents that can be used to deliver and monitor therapeutic agents. This is the 'Find, Fight and Follow' (FFF) concept of early diagnosis and therapy [14]. Now molecular imaging is a basic tool for monitoring and diagnosis of disease and in developing *in vivo* nano medical application [15]. For wide range of diagnosis, targeted molecular imaging is important for different purposes such as (assessing drug distributions, controlled drug release and early diagnosis of unexpected and potentially dangerous drug accumulations) [16].

## Nano medical Implants

Nanotechnology also has different implications for *in vivo* diagnostic tools such as the new endoscopic instruments and swallow able imaging 'pill'. Monitoring and observing of circulating molecules is of important for some chronic diseases such as AIDS or diabetes. Different nano sensors (for example catheters), will provide immediate data to surgeons. Nanoscale entities could identify defects/pathology; and the subsequent removal or correction could also set a future vision [17]. Implanted drug delivery devices–DDD–can be benefited by nanotechnology. Nanotechnology enable to fabricate and design the ultra-small devices (pumps, reservoirs and actuators) for accurately and targeted release of drug. Due to their small size viscosity, and low invasiveness, these Drug Delivery Devices (DDD) can be introduced within the body, even in the brain [18]. Smaller devices offer less damage and invasiveness so these can even be implanted for different purposes. Ultra-miniaturisation: Sensing part lies in the ultra-small size of the biological sample like some biopsies. Low concentrations: On the contrary, measuring of biological molecules (blood, urine) like some biomarkers in large samples like blood drops requires some initial steps for concentrating these molecules. There are different types of implant-nano materials in the market e.g. orthopaedic, wound management, dental/dental care products, cardiac implants, bone replacement scaffold,

nano-hydroxyapatite, silver NP solution, nano-hydroxyapatite, nanoporous hydroxyapatite, ultraporous beta-tricalcium phosphate NPs, boneSource (Lebinger), Silvagard (AcryMed, 2005), UltraDEX Recalcifying (Periproducts), Vestasync (MIV Therapeutics), Vitoss (Orthovita, 2000), these amount to about 10 billion USD market.

Nanobiotechnology offers important inputs to the development of detection/sensing devices and of the tagging/following of disease related indicators, that results to the advancement in imaging. The combination of *in vitro* diagnosis and *in vivo* imaging (by nanoparticles) could results in targeted diseased cells disruption or removal. Tagging diseased cells with functionalised nanoparticles, that can respond to external stimuli, consents for in situ, local 'surgery' (breaking/heating of nanoparticles by magnetic fields, laser, microwaves, etc.) without inappropriateness within the human body [19]. Theranostic, used for the combination of diagnosis and therapy. Imaging can be used to trace the drug delivery system within the body. In other hand imaging can also be used to activate the drug release, by some external stimulus. Such external stimuli such as temperature, laser light, or ultrasounds [20].

## Limitations

The global nanomedicine market was valued at $53 billion in 2009, and is forecast to increase at a Compound Annual Growth Rate (CAGR) of 13.5% to reach more than $100 billion in 2014. The vision of producing a more efficient system to the development of nano-product, following limitations are encountered. Understanding of the bio-distribution of nanomaterials in the body is very crucial step. This is connected to a second constraint, which requires imaging modalities for investigating the bio-distribution of nanomedicine over time. Another important issue is the determination of mass transport of medicine across biological barriers in the body. The bio-distribution of medicine is a function of their biological affinity, however, in case of nanoparticles, it is primarily managed by their ability to negotiate compartmental barriers. This issue is further compounded by further hurdles as degradation of enzyme, uptake by phagocytic agents, hydrostatic pressure at target cell, abnormal flow of blood, and molecular and ionic efflux pumps that tend to eject drugs from target site. There is a dire need to establish bioinformatics models. Very less research efforts are being directed to develop new mathematical and computer tools or softwares. Equally important is the establishment of reference materials and testing methods that can provide standard yardsticks for the development of novel classes of medicines. Many scientists who specialize in nanomedicine have no prior experience with the regulatory procedures. It is valuable to educate about the approval process of medicines. For drugs often 10 years are required with expenditure of hundreds of millions of dollars. Published materials, conferences, training workshops can produce a meaningful pool for faster drug approval system.

## Conclusion

The early impact of nanotechnology on medicine is beginning to get realized, with novel nanoscale therapeutic and diagnostic modalities under development or in clinical practice today. In this commentary the field of "nanomedicine" is briefly reviewed form the perspective of where are today in wake of nanomedicine, therapeutics, and devices. All these strenuous and laborious efforts doesn't reach to the end benefit owing to different sort of technical issues. A full understanding of the basic science of nanoparticle transport, biological barriers, understanding of basic biology, control over possible adverse effects, and as well as training about the scientific and official procedures of drug approval can yield advanced generation of therapeutics in market.

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