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REVIEW

Barriers for the development, translation, and implementation of nanomedicine: an African perspective

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Abstract

Nanotechnology is a branch of science, which empowers innovation to discover new medical technologies, improving current diagnostic and treatment methods. The scope of nanotechnology focuses mainly on "technology transfer", in which research aims to facilitate the application of recent nanoscience techniques to conventional medicine development methodologies. Nanomedicine is attractive to researchers who wish to target specific infectious diseases associated with poverty, which is highlighted through the many pertinent examples of recent breakthroughs in nanomedicine. An overview is provided in this study to highlight the barriers and implementation of nanomedicine for various infectious diseases in the African continent. Patient backgrounds provide the greatest of challenges for new technologies in terms of improving bioavailability and dosage. This review points out the current situation of nanomedicine in Africa and explores the possibility of how nanomedicine could improve patient drug regimens and wellbeing.

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Introduction

Nanomedicine is a science, which plays a crucial role in both health and medicine. The term nanomedicine was first established in late 1990s, with publications emerging in the early to mid-2000s (Wagner et al., 2006). The scope of nanomedicine research is impressive, having

been studied widely across multiple applications. Despite this, many experts are unable to provide a uniform definition for nanomedicine to explain their findings (Webster, 2006). Some authors' definition is born from the fact that since it is the study of particles in the nanometre range, the range should therefore be called the nanoscale or themselves be called nanoparticles. The broad definition can be termed in relation to their respective fields. For instance, researchers in the field of biological sciences extended their investigations towards the field of nanomedicine by providing nanoparticles through proteins and nucleic acids (Wagner et al., 2006).

The technology has been successful and revolutionary through the development of new drug products, such as Doxil® (Sequus, Menlo Park, CA) (liposome encapsulated Doxorubicin) and Abraxane® (Abraxis BioScience, Inc, New Zealand) (nanoparticle albumin-bound paclitaxel) which are both on the market and clinically available (Malam et al., 2009). Indeed, the application in which medicine is integrated into a nanoparticulate system allows researchers to investigate drug delivery strategies more appropriately and in greater detail. The growth in this technology has been more rapid, whereas in the drug discovery sector it is more challenging. Therefore, it is essential for researchers to understand the clinical translation process as currently the developed drug approval rate for phase I clinical trials is low at around 10% (Hay et al., 2014). Consequently, more insight into this technology in terms of progression through clinical application will lead to successful clinical translation strategies in the early stages of research.

Notably, the scale of research in terms of drug development and discovery will always be in contrast with the volume of drugs, which enter into the market. This issue arises as new drugs must be approved by various clinical trial phases prior to entry in the market. Furthermore, drugs need to be considered in relation to a multitude of factors, such as toxicity, solubility, bioavailability and efficacy. Failure to address such factors would reflect badly within the drug market in terms of "poor compliance". These issues are exemplified in Poverty Related Diseases (PRD), such as tuberculosis (TB), malaria, and HIV. There are significant factors which must be considered as although appropriate drugs are available in the market, poor drug administration (both low and high) leads to increased patient risk. Low drug solubility and bioavailability may result in low drug uptake through poor administration, which will lead to treatment failures as routes towards the emergence of drug resistant strains would be provided. The converse is also true through increased dosage quantities and frequencies, which may be employed to counter low drug solubility and bioavailability. This would lead to alternative treatment failures, especially when a physician prescribes drugs with respect to the patient's circumstances, as increased dosage and prolonged treatment can impact patients in terms of negative side effects. Hence, challenges in drug development towards PRDs are considered to be a critical issue, especially in developing countries (Anwabani, 2002). As such, nanomedicine can play a crucial role towards PRD in Africa, with technologies aimed at targeting issues such as poor solubility and limited bioavailability; the so called Class II, Class IV drugs according to the Biopharmaceutics Classification System (BSC) (Amidon et al., 1995). To address these challenges in the treatment of PRDs, the investigation of nanomedicine by African researchers has revealed promising approaches for improving treatments of TB, HIV, malaria, etc. (Choonara et al., 2011). Through consideration of this emerging field of research and development, effective drug technologies will be produced preventing life-threatening disease infections for future generations.

Nanomedicine – The Scope of Poverty Related Diseases (PRD)

Nanomedicine can be categorised as one of four types: nanocarriers, polymer therapeutics, solid drug nanoparticles (SDN), and inorganic nanoparticles (NPs) (Niemirowicz et al., 2012; Busquets et al., 2015; McDonald et al., 2015; Giardiello et al., 2016; Saravanan et al., 2018). The conjugation between drugs and water-soluble polymers is aimed at overcoming bioavailability issues through drug encapsulation onto nanoparticle surfaces or within nanocarriers. This conjugation between the drug and nanocarrier can be simply intermolecular or as a covalent linkage, which is cleaved as the nanocarrier arrives at its target site allowing the drug to dissociate from the nanocarrier, offering controlled release.

Nanomedicine has many impressive applications in drug product development and research (Etheridge et al. 2013). This technology has a great implication in the design of personalised medicine that promises diagnostic methods and the ability to effectively treat patients individually. The primary benefits are related to drug dosage and treatment times, which can be lowered for more effective therapy with fewer side

effects. This greater effectiveness is achieved through targeting drug conjugated nanoparticle to increase drug uptake specific to the individual, which both enhances systemic concentrations and residence times (Wang et al., 2011).

Furthermore, nanoparticles have the significant potential to be targeted specifically to the disease receptors. The binding takes place both actively or passively through bioconjugation of antibodies and specific ligands (McCarron et al., 2008; Kamaly et al., 2012). This mode of target specific drug release would give rise to an overall increase in the blood circulation time of the drug (Kamaly et al., 2012). There are several advances in nanomedicines targeted at passage through the blood brain barrier (BBB) and fine capillary blood vessels, which in turn offers improved drug uptake across other barriers (e.g., lung and intestinal) (D Jong and Borm, 2008; Onoue et al., 2014).

Significantly, nanomedicine has great applicability towards early stage diagnostics of cancer. This is achieved through semiconductor devices designed to image the fluorescence (Farias et al., 2009) of samples either within blood or specific tissues. This challenge plays a crucial role in reduction of cancer related death rates (Niemirowicz et al., 2012; Choudhary and Kusum Devi, 2015). The advancement in early diagnosis is more accurate and patients will be highly benefited both financially and through reduced treatment times and medication (Pericleous et al., 2012). Navalakhe and Nandedkar, 2007 reported that the small size and large surface area of nanoparticles increases their ability to interact internally within cell surfaces (Clift et al., 2008). The phenomenon in terms of tumour tissue accumulation is referred as "Enhanced Permeability and Retention" (EPR) effect. Therefore, similar approaches in terms of cellular and tissue accumulation of drugs specific to PRDs will have advantages in terms of treatment of bacterial infections like TB (Meerovich et al., 2008).

African Perspective of Nanomedicine

In order to enhance the global contribution of African countries in the field of nanotechnology, the Nanosciences African Network (NANOAFNET) was established in 2005, with around 27 African countries engaged in this network. In the case of nanomedicine, their activities focus on the improvement of therapies for infectious diseases related to poverty, including TB, malaria, HIV, etc. Moreover, in 2011 the CSIR (Council for Scientific and Industrial Research) Nanomedicine Platform in South Africa hosted the first "International Workshop on Nanomedicine for Infectious Diseases of Poverty". Importantly, the CSIR Nanomedicine Platform in South Africa collaborated actively with the "Pan-African Centre of Excellence in Nanomedicine" to discuss the application of nanomedicine research and training, in partnership with industry and academia, to significantly enhance the development of therapeutic compounds for infectious diseases of poverty (Chang et al., 2015).

The need is significant. Around 6 million people are affected annually, many of whom losing their lives, due to the poor compliance with the aforementioned diseases. According to the World Health Organisation (WHO), 2010 Global TB report, one third of the world's population is currently infected with *Mycobacterium tuberculosis*. Additionally, an estimated 1.7 million people died from TB in 2009 with the highest number of deaths occurring in Africa (Global Tuberculosis control, WHO report, 2010). Malaria remains one of the world's most prevalent infectious diseases, with 40% of the world's population at risk of infection. In 2009, there were an estimated 225 million cases of malaria reported worldwide and an estimated 781,000 deaths (WHO, 2010). Additionally, the somewhat neglected tropical leishmaniasis affects more than 1 billion people annually for those living in tropical and subtropical climates. Additionally, a further 500,000 people are affected annually with new cases of leishmaniasis arising in Southeast Asia and East Africa (Davidson et al., 1996). Specifically, visceral leishmaniasis is more life threatening in cases where no proper treatment is available. In terms of HIV, Sub-Saharan Africa still bears the largest global share of the burden, with the highest number of people living with HIV as well as the highest number of new HIV infections, AIDS-related deaths and the highest adult HIV prevalence (UNAIDS, 2010). HIV infection weakens the immune system and as such exposes the patient to other infectious diseases such as TB, malaria and leishmaniasis. Consequently, HIV is gaining popularity for further investigations towards diagnosis as well as therapeutic research.

The antimicrobial properties of nanomedicines have been extensively investigated (Azam et al., 2012; Islam et al., 2013; Neyrolles et al., 2013). Although there are currently drugs available for the treatment of tuberculosis, the deep in-sights of their mechanism are yet to be properly understood. Therefore, nanomedicine in terms of anti-mycobacterial application needs more investigation (Hussain et al., 2013). In 2001, Hussain et al. reported on the accurate targeting and drug

delivery applications of particles in both the micro and nano size range, where nanoparticles were shown to engulf and subsequently co-localise *Mycobacterium tuberculosis*, which resides in macrophages, within the micro-organism. Hence, the role of nanoparticles has been understood, demonstrating the targeting of specific sites instead of other sites (Hussain et al., 2001). These findings have clearly shown that nanomedicine has laid a foundation to the scientific community for further improvements in the therapeutic field of TB. In the case of malaria, the encapsulation of primaquine in liposomes and solid-lipid nanoparticles has proven advantageous. Additionally, towards the treatment of toxoplasmosis as well as leishmaniasis, a recent study reported the effectiveness of silver nanoparticles (Islan et al., 2017). Specifically, silver NPs can be prepared by using physical, chemical or biological methods (Barabadi et al., 2017a, 2017b). However, further investigations are required before these products reach the market.

Adverse Effects or Limitations of Nanomedicine to Patients

Kermanizadeh et al., 2014 reported that the mode of action of nanoparticles related to toxicity has not been extensively investigated. Bio-distribution studies have shown that the liver is the primary site and exposure route. Toxicity mainly exists through oxidative stress, inflammation, ROS production, carcinogenicity and genotoxicity (Johnston et al., 2015; Kermanizadeh et al., 2014). Additionally, the route of administration and size of the nanoparticle will also play a significant role in producing adverse effects (Kermanizadeh et al., 2014).

Remarkably, more that 70% of the clinically available nanomedicines are administered *via* non-patient-friendly, intravenous routes leading to a reduction in patient adherence to treatment. Furthermore, the regulations for nanoproducts and nanomedicines are still at a very early stage as traditional regulations are not appropriate for nanoproducts. Consequently, there is a significant necessity for regulatory reform in order to establish "nanoguidelines", facilitating the translation of nanomedicine from research laboratories to the clinical market (Fornaguera and García-Celma, 2017).

Conclusions

There is much to be investigated and learned from nanomedicine and TB. This study provides the recent updates from the previous literature and provides an explanation of nanomedicine and its applications. Combining the collective expertise from a range of disciplines is required to allow an amalgamated, coherent and thorough evaluation of where the next steps of research should be taken. A further understanding of how drugs are penetrating the lung cavities is required which may allow a more tailored nano-based regime to be designed to exploit the unique properties NPs have to offer. Faster disease diagnosis and initiation into treatment programmes is paramount if TB is ever to be controlled. Significantly, a cohesive effort between governments, funding bodies, scientists, clinicians and patients akin is essential to combat this disease. In conclusion, more screening of substances is required to identify anti-mycobacterial compounds as MDR/XDR TB levels escalate. Moreover, metal/metal oxide NPs have the potential to be integrated into clinical medicine. Hence, their inherent anti-bacterial properties should be exploited.

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None.

Conflict of Interest

The authors report no conflicts of interest.

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