COMMENTARY

Antimicrobial nanotechnologies: what are the current possibilities?

Brahma N. Singh, Prateeksha, Ch. V. Rao, A. K. S. Rawat, Dalip K. Upreti and Braj R. Singh

The current challenges of multi-drug resistance development in human pathogenic microorganisms are engaging researchers in exploring the field of nanotechnology-derived approaches and products as new tools of key developments for manufacturing effective antimicrobials. But, the real contributions are still uncertain. Although there are several budding leads of nanotechnology and the growing trends in publications and patents, therapeutic microbiological applications have not yet made it to the market. Numerous reasons could explain the scarcity of commercial applications. These include high initial production investments, new nanotechnology regulation in the developed and developing countries, and public perception. The rapid progress of nanotechnology in other key areas may over time be transferred to therapeutic microbiological applications as well, and accelerate their development.

Nanotechnology-derived approaches identified by the researchers as the 'key-enabling technologies' that demonstrate its incredible applications, advances and innovations in nanomedicine and many other industrial sectors, are rapidly becoming a major driving force behind ongoing changes in the therapeutic microbiology field[1,2]. The promising chemical and physical properties of nano-sized materials suggest their applied functions are being rapidly exploited in electronics, materials science and energy sectors.

These encouraging developments also concern the antimicrobial pharmaceutical sector, in which continuous breakthrough innovations are strongly needed because of the development of antibiotic-resistant and more virulent strains of bacteria[3–6]. Since the 20th century, infectious diseases have been treated using different technological innovations, including antibiotics and vaccines, and scientific community is now seeking in nanotechnology a new paradigm in developing antimicrobials, especially for overcoming antimicrobial drug resistance[7,8]. However, the pharma industry can be seen to be clearly benefiting from nanotechnology, specifically for diagnosis, drug delivery, medical devices and vaccines (Figure 1), even though its concrete contribution to the development of antimicrobial pharmaceutical sector is still uncertain.

Research on therapeutic microbiological nanotechnology applications has been ongoing for more than a decade now, searching for solutions to microbial diagnosis, antibiotic resistance and intolerable toxicity challenges, such as enhanced drug delivery and bioavailability of existing antimicrobial drugs[9–14]. A number of studies have shown the growing trend of both scientific publications and patents in antimicrobial nanotechnologies, especially for the development of nano-antibiotics, antibiotic-free antimicrobials and nano-vaccines. Nanomaterials particularly for microbiology enhance solubility of lipophilic antimicrobial drugs, reduce the amount of applied drug by smart delivery of active ingredients, and enhance mucus and biofilm penetrations[10].

Polymeric nanoparticles-based delivery devices are also being explored for a wide range of agents, including small molecules, peptides, proteins and nucleic acids[15]. Researchers have now started using these nano-factories for developing novel antimicrobials that modulate the quorum sensing systems of bacteria rather than their viability[9]. In addition, medical devices play a critical role in modern health-care practice, but their use may increase the risks of nosocomial infection. To solve this issue, numerous nanomaterial-coated or embedded medical devices including catheters, endotracheal tubes and wound dressings have

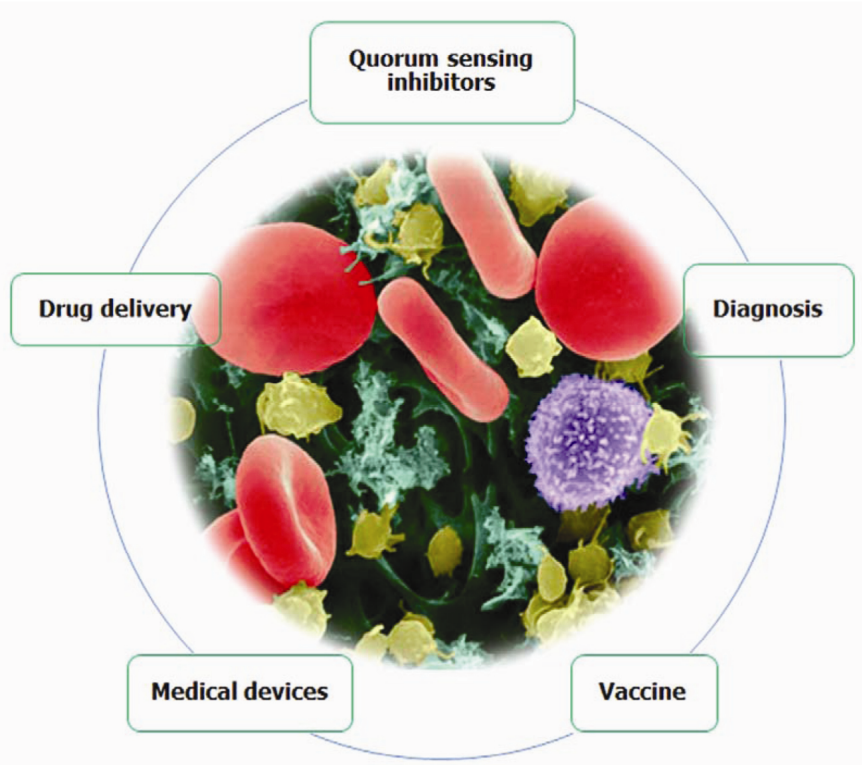

Figure 1. Applications of nanotechnology in the development of antimicrobials. Source: www.google.com

Table 1. Application of antimicrobial nanotechnologies

Application area	Drug	Developed by	Nanocomponent	Status
Quorum sensing inhibitors				
Bacterial quorum sensing system manipulation	BioMEMS	University of Maryland, USA	Nano-factories are assembled on chitosan electrodeposited	Research use only (2010)
Diagnosis				
Bacterial infection and drug resistance diagnosis	Verigene	Nanosphere, USA	Oligonucleotide-conjugated gold nanoparticle	Approved (2011)
	T2Candida	T2 Biosystems, USA	Oligonucleotide-conjugated SPION	Phase I (2014)
Vaccine				
Tuberculosis	CAF01	Statens Serum Institut, Denmark	Cationic liposome-based adjuvant	Phase I
Drug delivery				
Treatment of fungal infection	AmBisome	Gilead Sciences, USA	Lipid-nanoparticles containing amphotericin B	Approved (2005)
Treatment of invasive aspergillosis	Amphotec	Kadmon Pharmaceuticals, USA	Lipid-nanoparticles containing amphotericin B	Approved (1996)
Treatment of invasive fungal infections	Abelcet	Enzon Pharmaceutical, USA	Amphotericin B–lipid complex	Approved (1995)
	Fungisome	Lifecare Innovations, India	Lipid-nanoparticles containing amphotericin B	Approved (2005)
Chronic *Pseudomonas aeruginosa* infection	Arikace	Insmed, USA	Liposomal amikacin	Phase III
Pulmonary non-tuberculous mycobacterial lung disease	Arikace	Insmed, USA	Liposomal amikacin	Phase II
Medical device				
Wound dressing	SilvaSorb	AcryMed, USA	Hydrogel containing silver nanoparticles	Approved (2005)
	KoCarbonAg	Bio-medical Carbon Technology, Taiwan	Carbon fibre cloth and polyethylene membrane coated with nano-silver	Approved (2014)
	Acticoat	Smith & Nephew, India	High-density polyethylene mesh coated with silver nanoparticles	Approved (2005)
Root canal sealer, and dental restorative materials	IABN	Hadassah Medical Organization, Israel	Quaternary ammonium poly(ethylene imine) nanoparticle-embedded resin	Phase II
Central venous catheter	LogiCath AgTive	Smiths, UK	Silver nanoparticle-embedded polyurethane	Approved (2007)
Catheter for internal CSF-drainage	Silverline	Spiegelberg, Germany	Silver nanoparticle- and insoluble silver salt-incorporated polyurethane or silicone	Approved (2007)
Endotracheal tube	AGENTO I.C.	C.R. Bard, USA	Ag nanoparticle-distributed hydrophilic polymer	Approved (2007)
Catheter for the delivery of local anaesthetics	ON-Q SilverSoaker	I-Flow, Canada	Silver nanoparticle-coated polyvinylchloride	Approved (2005)
	NanoTite Implant	Biomet, USA	Calcium phosphate nanocrystal coating	Approved (2008)
	EnSeal Laparoscopic Vessel Fusion	Ethicon Endo-Surgery, USA	Nanoparticle-coated electrode	Approved (2005)
Ventricular catheter for cerebrospinal fluid drainage	VentriGuard	Neuromedex, Switzerland	Ag nanoparticle-embedded nonmetallic porous materials	Approved

been developed and approved for clinical use[16]. Table 1 presents an overview of the most relevant microbiological nanotechnology applications.

Despite these potential leads, full potential of nanotechnology in the development of antimicrobials and antimicrobial vaccine sectors, are still comparably marginal and have not yet made it to the market to any large extent in comparison with the other sectors as approximately 20 nano products already permitted for commercialization ranging from drug delivery and imaging to implantable biomaterials and medical devices[17]. Below we list numerous areas that have not been well explored, which may help discover real breakthroughs in the exciting field of antimicrobial nanotherapies in the years to come. The wave of research discoveries seems to be mainly claimed by the research organizations, academic sector and small enterprises; however, multi-national industries reveal a large patent ownership. The trends of patent applications are continuously growing, but no new nano-antimicrobials in managing microbial infections for the pharmaceutical sector have reached the market. This suggests that researchers are actively patenting and keeping broad patent claims in order to assure future freedom to work and prevent misuse in the case of potential commercial developments in future.

Multinational industries are searching the potential that nanotechnology interventions offer in the antimicrobial sector. Based on industry expert's opinion, antimicrobial nanotechnologies so far do not demonstrate a sufficiently high economic interest. Nano-based formulations/or products need huge initial investments that can be counterbalanced only by marketing at large scale, which is not currently the case. Among the reasons for the problems of nano-medicine developments at commercial level, the industries mention regulatory issues (toxicity aspects) and public opinion.

The most crucial aspect of regulating nanomaterials is the need for approved definition of the terms 'nanoscale' and 'nano-medicine' approved among the involved parties and, possibly, synchronized at international level. The definition of nanoscale and nano-medicine seems not to be straightforward and is not just a matter of size. The nanoscale could be used to one or more dimensions and the form of the particles can be in aggregate, agglomerates or nano-scaled materials. Additionally, nanomaterials are used in different pharmaceutical sectors, but the clinical approval process is structured to ensure that sponsors demonstrate adequate safety and efficacy before a product is released in the market.

Several nations are now providing definitions and regulatory frameworks for the application of nanotechnology in medicine[17]. In the European Commission (EC), the main regulation covering nanotechnology applications is the REACH (Registration, Evaluation, Authorization and Restriction of Chemicals)[18]. The EC has recently (2011) adopted a recommendation on the definition according to which 'nanomaterial' means a natural, incidental or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50% or more of the particles in the number size distribution, one or more external dimensions are in the size range 1–100 nm. According the US Decision-Making Concerning Regulation (DMCR), some definitions apply the size range to two or more dimensions – using either external or internal structures as units to be measured. Some definitions also include criteria related to physical or chemical characteristics (e.g. size distribution, shape, charge, or the ratio of surface area to volume), or to the display of unique or novel properties or 'nanoscale phenomena'.

In addition to economic and technological benefits, the challenges associated with the safety of nanomaterials and nanotechnologies are global. The commercial benefits may be outweighed by the potentially unsafe characteristics of nanomaterials. Meanwhile, nanomaterials and nanotechnologies are assuring the ability of key pharmaceutical sectors to compete globally; their success also demands a guarantee of their safety. But, some survey-based studies on consumer preferences reveal that overall public opinion (from the US and UK) is not negative or neutral towards nanotechnology[19], and that it is particularly influenced by perceived benefits and usefulness of the technology. The outcomes of the investigations recommend that nano-based products with vibrant properties and acceptable/minimum risks for the users, if launched first into the market can drive the reception of other applications introduced later on, for example, reactive antibiotics, where societal concerns already exist.

In conclusion, antimicrobial-nanotech innovative products/drugs are facing complications in reaching the market, making antimicrobial drugs still a marginal sector for nanotechnology. This is due in specific to the high production costs, unclear technical benefits and judicial uncertainties, as well as public opinion. However, the research and development landscape is encouraging and the opportunities offered by nanotechnology in the development of nano-medicines for combating microbial infections are being actively explored. Moreover, nanotechnology is becoming the driving force behind a variety of developments in other fields as well. The knowledge gained in other emerging research areas, including diagnosis, targeted drug delivery, medical devices, energy and packaging, may over time be transferred, or provide spill-overs, to antimicrobial drug development applications as well. For example, surface modifications of antimicrobials using nanoparticles could also enhance their antimicrobial effect along with the range of combined therapy (antibiotics plus antimicrobial nanoparticles), and quorum sensing nano-inhibitors can provide real solutions for effectively combating infectious diseases.

1. Zhu, X., Radovic-Moreno, A. F., Wu, J., Langer, R. and Shi, J., *Nano Today*, 2014, **9**, 478–498.
2. Aruguete, D. M. *et al.*, *Environ. Sci. Process. Impacts*, 2013, **15**, 93–102.
3. Hadinoto, K. and Cheow, W. S., *Colloids Surf. B*, 2014, **116**, 772–785.
4. Huh, A. J. and Kwon, Y. J., *J. Control Release*, 2011, **156**, 128–145.
5. Reardon, S., *Nature*, 2014, **513**, 471.
6. Hede, K., *Nature*, 2014, **509**, S2–S3.
7. Meziane-Cherif, D. and Courvalin, P., *Nature*, 2014, **510**, 477–478.
8. Reardon, S., *Nature*, 2014, **509**, 141–142.
9. Fernandes, R., Roy, V., Wu, H. C. and Bentley, W. E., *Nature Nanotechnol.*, 2010, **5**, 213–217.
10. Nafee, N. *et al.*, *J. Control Release*, 2014, **192**, 131–140.
11. Singh, B. N. *et al.*, *RSC Adv.*, 2015, **5**, 5809–5822.
12. Guo, Y. *et al.*, *J. Chromatogr. B*, 2013, **942–943**, 151–157.
13. Hsieh, S. H., Huang, H. Y. and Lee, S., *J. Chromatogr. A*, 2009, **1216**, 7186–7194.

14. Fernandes, R., Luo, X., Tsao, C. Y., Payne, G. F., Ghodssi, R., Rubloff, G. W. and Bentley, W. E., *Lab. Chip*, 2010, **10**, 1128–1134.
15. Blecher, K., Nasir, A. and Friedman, A., *Virulence*, 2011, **2**, 395–401.
16. Mahmoudi, M., Azadmanesh, K., Shokrgozar, M. A., Journeay, W. S. and Laurent, S., *Chem. Rev.*, 2011, **111**, 3407–3432.
17. Etheridge, M. L., Campbell, S. A., Erdman, A. G., Haynes, C. L., Wolf, S. M. and McCullough, J., *Nanomedicine*, 2013, **9**, 1–14.
18. Parisi, C., Vigani, M. and Rodríguez-Cerezo, E., *Nano Today*; doi.org/10.1016/j.nantod.2014.09.009.
19. Satterfield, T., Kandlikar, M., Beaudrie, C. E., Conti, J. and Herr Harthorn, B., *Nature Nanotechnol.*, 2009, **4**, 752–758.

ACKNOWLEDGEMENTS. We thank the Director, CSIR-National Botanical Research Institute, Lucknow, for encouragement and support. B.R.S. also thanks the CSIR, India, for awarding Pool Scientists Scheme [13(8595-A) 2012-Pool].

Brahma N. Singh, Prateeksha, Ch. V. Rao, A. K. S. Rawat and Dalip K. Upreti are in the Pharmacognosy and Ethnopharmacology Division, CSIR-National Botanical Research Institute, Lucknow 226 001, India; Braj R. Singh is in the Centre of Excellence in Materials Science (Nanomaterials), Z.H. College of Engineering and Technology, Aligarh Muslim University, Aligarh 202 002, India.*
**e-mail: brahmasingh99@gmail.com*