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A perspective on
Nanomedicine:
Focus on
**cardiovascular
diseases**



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Abstract

Background

Nanomedicine refers to the application of nanotechnology to improve the diagnosis, monitoring and treatment of diseases. Although the primary application was originally in oncology, nanomedicine has witnessed substantial scientific interest and growth beyond chemotherapeutic drug development.

Approach

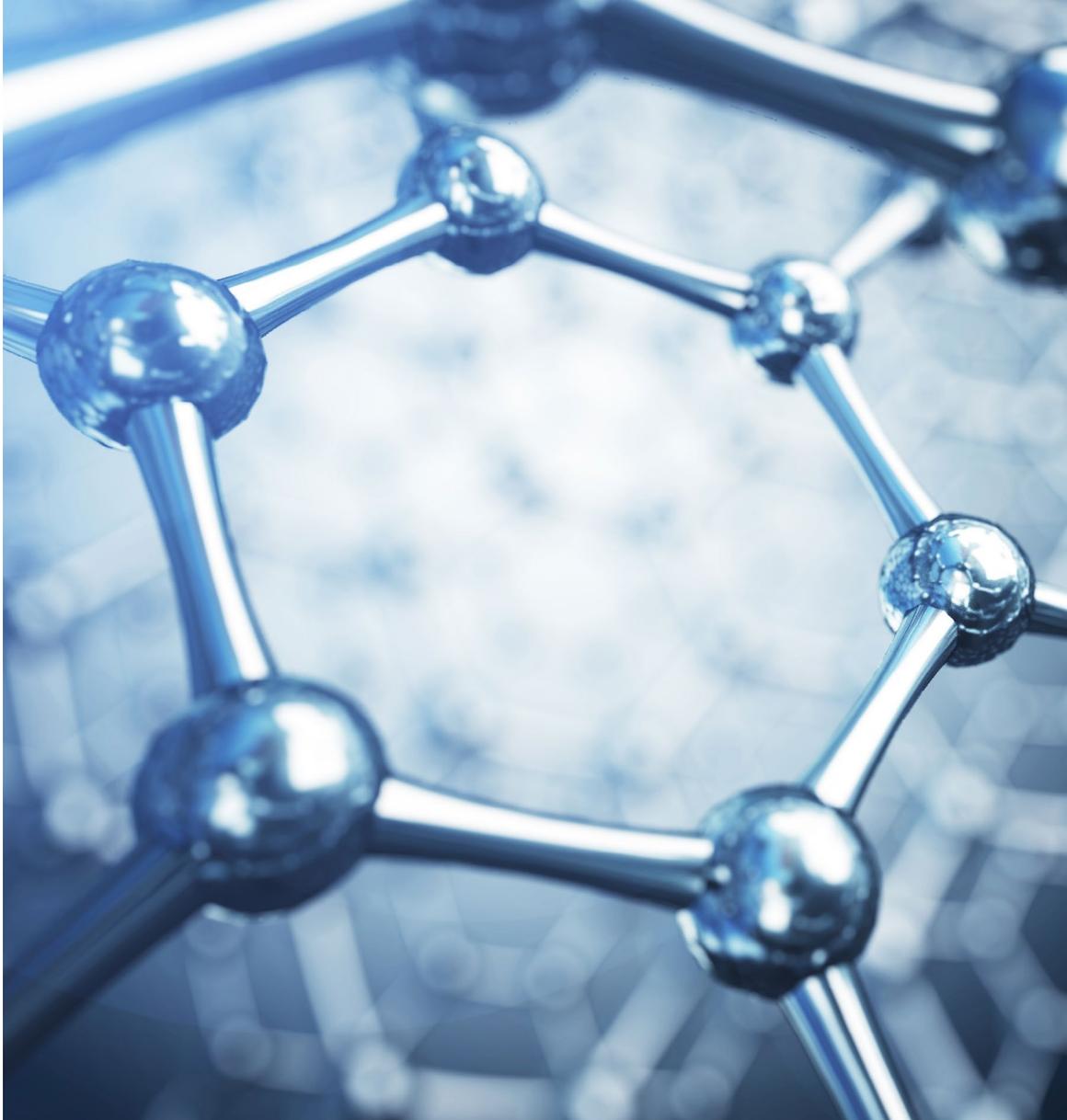
Despite the widespread prevalence of cardiovascular diseases (CVDs), limitations remain in their clinical management regardless of the major technological advancement in diagnostic and therapeutic modalities available. In the present context, flourishing research in cardiovascular nanomedicine is expected to address the current challenges and bring about much sought for solutions to the identification and management of the progression of CVDs.

Practical Implications

As the research portfolio of nanomedicine expands, it can have a significant impact on the management of CVDs, particularly atherosclerosis. Nanotechnology presents an opportunity to address the components of atherosclerotic plaque and enhance the therapeutic approaches to atherogenesis.

Keywords

Nanotechnology (NT); Nanomedicine (NM); Cardiovascular Diseases (CVDs); Atherosclerosis

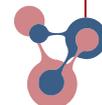


Nanotechnology

Nanotechnology is the design, production, characterisation and application of materials, structures, devices and systems on the nanoscale (Abeer, 2012). The advent of nanotechnology is linked to Richard Feynman's concept of synthesis by the direct arrangement and manipulation of atoms (Feynman, 1960). The applications of nanotechnology extend to diverse domains, such as electronics, computers, medicines, cosmetics, foods, purification processes, etc. (Abeer, 2012; Ventola, 2017). The global market size of the nanotechnology industry was worth US\$300 billion in 2011; it is estimated that its value in 2041 will be US\$35,000 billion (Antunes et al., 2013).

The European Commission (2011) defines nanomaterials based on their size distribution. A material is classified as a nanomaterial if 50% or more of the constituent particles in the number size distribution has one or more external

dimensions in the size range 1-100 nanometres (nm). The nanomaterial could be natural, incidental or manufactured. It can exist in a free form, or as an aggregate or agglomerate (Rauscher et al., 2017). A nanometre is approximately 1/80,000 of the diameter of a human hair, or 10 times the diameter of a hydrogen atom (Shetty, 2006). The past decade has witnessed a growing interest in advanced nanomaterials among researchers, medical practitioners and industrialists for a wide spectrum of commercial, industrial and clinical practice applications. The main reason for this development has been the understanding that particles with a diameter less than 100 nanometres have more surface area to volume ratio; they also have enhanced properties, such as conductivity, strength, biochemical, electronic, magnetic and optical properties compared to bulk-sized materials (Thorley and Tetley, 2013; Ventola, 2017).

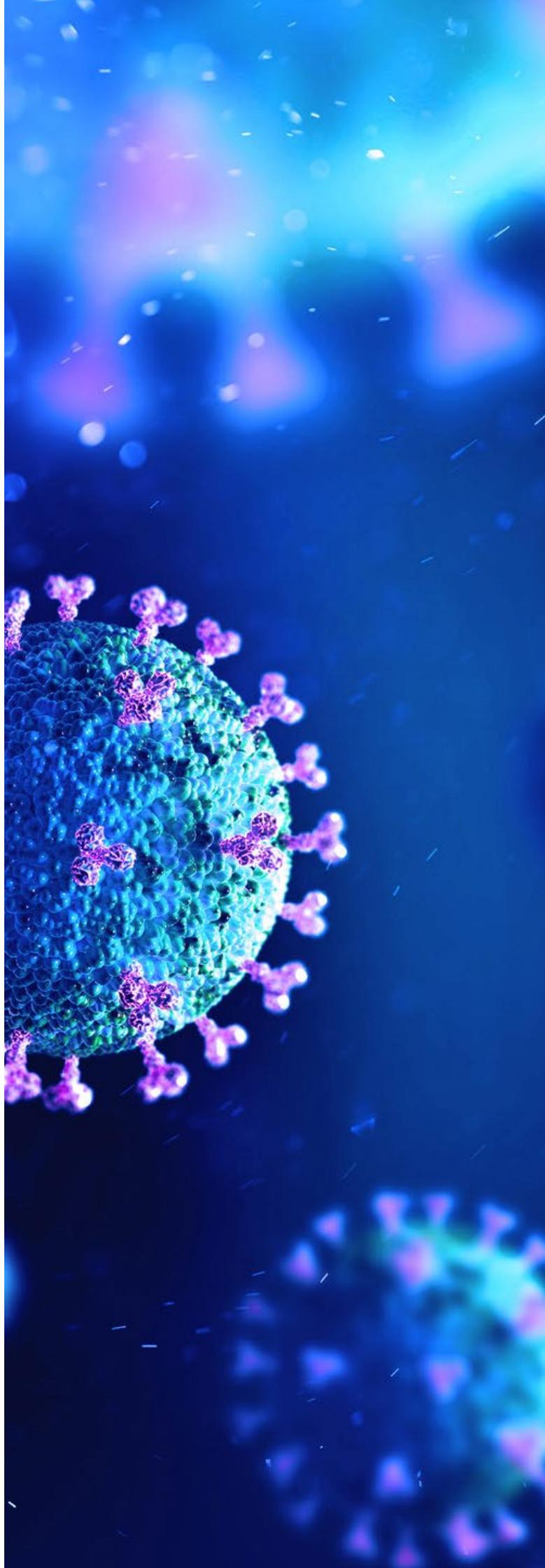


Nanomedicine

The term 'nanomedicine' was put forward by Robert Freitas (1999). Nanomedicine involves the application of engineered nanosystems to gain a deeper insight into the complex core pathophysiology of diseases and enhance people's quality of life (Sahoo, 2005; Rizzo et al., 2013). Nanomedicine focusses on the identification of targets (cells and receptors) related to specific clinical conditions, and suitable nanocarriers to achieve the desired response at the target site (Moghimi et al., 2005). Compared to conventional medicines dispersed in a free base, as in the case of tablets, capsules and injections, nanomedicines have numerous advantages (Ventola, 2017; Hua et al., 2018). The benefits include enhanced drug solubility, pharmacokinetics, and tissue selectivity, leading to improved efficacy and reduced toxicity (Ventola, 2017). The application of nanomedicine lies not only in manufacturing advanced and novel drugs but also in reformulating marketed drugs in order to enhance efficacy and delivery, and decrease adverse effects (Rizzo et al., 2013).

The worldwide nanomedicine market was valued at US\$248 billion in 2014 (Pandit and Zeugolis, 2016). It is anticipated that the market size of nanomedicine will grow at an annual growth rate of 11% and reach US\$351 billion by the year 2025 (Grand View Research, 2019).

At present, there are 77 products in clinical trials and 51 Food and Drug Administration (FDA) approved nanomedicines in the market (Bobo et al., 2016; Patra et al., 2018; The British Society of Nanomedicine, 2019). In 1995, liposomal formulation of an anti-cancer drug, doxorubicin, was one of the first nanomedicines to be approved for clinical use (Lobatto et al., 2011). The approval was based on lower cardiotoxicity compared with conventional doxorubicin (Ventola, 2017); it is still widely used as a gold standard injectable nanodrug (Tinkle et al., 2014). The majority of nanosystems approved so far are based on improved stability, half-life, bioavailability, and safety of current drugs (Cicha et al., 2018).



Nanomaterials as Novel Drug Delivery Systems

Efforts to explore nanomaterials for drug delivery applications date back to the 1970s. One of the major focus areas of current nanomedicine research is on developing novel drug delivery systems with new or improved features. The upper size limits of nanomaterials employed as drug delivery systems are often variable (Boverhof et al., 2015). These include micelle (10-100nm), liposome (40-1000nm), polymer nanoparticle (20-1000nm), solid lipid nanoparticle (50-1000nm), dendrimer (3-20nm), carbon nanotube (0.5-3.0nm × 20-1000nm) and metallic nanoparticle (60-150nm) (Mishra et al., 2012; Katsuki et al., 2017). Other delivery vehicles are carbon or organometallic based, virus-like, or inorganic particles (gold, silver) and metal oxides.

Lipid-based nanoparticles (solid lipid nanoparticles, micelles, nanosuspensions, nanoemulsions) represent one of the most widely employed nanocarriers for delivering drugs (Schiener et al., 2014). Nanoparticles can display strong interactions with biomolecules, such as enzymes, receptors and antibodies, both on the surface and inside the cell. The surface of the nanoparticles can be modified by engineered coatings and integration of a variety of bioconjugated molecules for selective detection and treatment of several diseases (Fan et al., 2014). On reaching the desired site of action, nanocarriers should be able to release the drug in therapeutically effective concentrations without affecting healthy tissues. Many cases require the drug to reach its intracellular target, for example, the cell nuclei, cytoplasm or other cell organelles

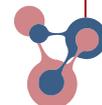
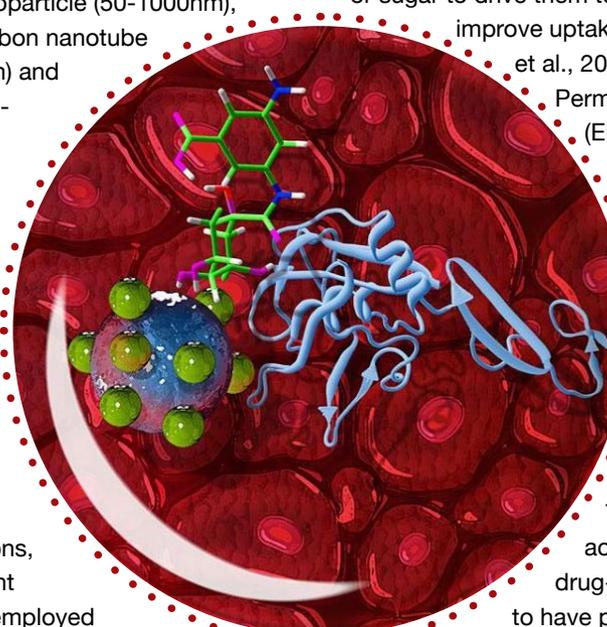
(Schiener et al., 2014).

Drug loaded nanoparticles deliver drugs via various transport mechanisms: active targeting, passive targeting and triggered release (Hua et al., 2018). Active targeting is also known as ligand-targeting or receptor-mediated targeting. Nanocarriers can be functionalised with active recognition moieties, such as antibodies, peptides, or sugar to drive them to the target site and

improve uptake and efficacy (Minelli et al., 2010). The Enhanced Permeability and Retention (EPR) effect refers to the preferential localisation of the nanocarriers in diseased tissues (e.g., tumours, inflammatory conditions) compared to normal tissues; this is due to the enhanced permeability of the abnormal vasculature (Hua et al., 2018). This leads to passive accumulation, for which the drug-loaded nanocarrier needs to have prolonged circulation in the bloodstream. This can be facilitated

by conjugating polyethylene glycol (PEG) to the surface of the nanocarrier. Properties like pH, temperature, and shape influence the passive uptake of drugs (Minelli et al., 2010; Patra et al., 2018). In triggered release, also referred to as stimuli-responsive release, the nanocarrier releases the drug in response to endogenous stimuli (local environment at the disease site, pH, enzymes) or exogenous stimuli (temperature, light, magnetic field, ultrasound) (Hua et al., 2018; Patra et al., 2018).

Nanotechnology-enabled delivery of drugs is a dominant research field in nanomedicine,



contributing to more than 75% of total sales (Mir et al., 2017). Green nanodrug delivery systems based on environmental friendly synthesis routes or natural biomaterials (such as plant extracts and microorganisms) are now producing innovative safer materials with higher potentials for scale-up and commercialisation (Jahangirian et al., 2017). Other areas of application are *in vivo* imaging agents, *in vitro* diagnostic sensors, nanoscale therapies, biomaterials, and active implants (Nature Publishing Group, 2007). Manufacturing of an old drug into a new nanotechnology-enabled product leads to a compound with

modified pharmacokinetic properties. In fact, a majority of patents and currently available nanomedicines are based on novel drug delivery to enhance bioavailability and targeting of existing medicines (Toit et al., 2007; Berger, 2013).

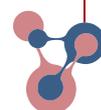
Technological developments in research areas (including molecular and cellular biology, genetics, proteomics, lipidomics, material science and bioengineering), make nanotechnology one of the primary prospective players in the detection and management of cardiovascular diseases.

Cardiovascular Diseases

Cardiovascular diseases (CVDs) is the collective term for a number of linked pathologies of the heart and blood vessels. It includes diseases of the arteries supplying the heart (coronary heart disease), the brain (cerebrovascular disease), the periphery, especially leg muscles (peripheral arterial disease), rheumatic heart diseases, congenital heart diseases, and venous thromboembolism (Stewart et al., 2017). CVDs account for approximately 31% of global deaths annually (17.9 million people) (Benjamin et al., 2017; 2018), and are the leading cause of mortality and loss of disability-adjusted life years (DALY) worldwide (Vilahir et al., 2014). Mathers and Loncar (2006) projected that global cardiovascular deaths will reach 23.3 million in 2030. The underlying and dominant pathology of most CVDs is the deposition of fatty plaques within the arterial walls making the artery harder and narrower, a condition known as atherosclerosis, leading to subsequent thrombosis (Viles-Gonzalez et al., 2004). Atherosclerosis originates with the dysfunction of the endothelium and a cascade of events involving various cells and molecules (Nakhlband et al., 2018). Atherosclerotic plaque formation results from complex cellular interactions in the intima of arteries between the cells of the vessel wall (smooth muscle cells and endothelial cells) and inflammatory cells (macrophages and T lymphocytes) (van der Wal and Becker, 1999). Atherosclerotic plaques consist of fatty substances, intracellular and extracellular lipid,

cellular waste products, calcium, collagen and fibrin (a clotting material in the blood) (van der Wal and Becker, 1999; Insull, 2009). High total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) are modifiable risk factors of CVDs (Peterson and Greenland, 2019). The worldwide prevalence of high cholesterol in adults over 25 years is about 39% (Alwan et al., 2011; Farzadfar et al., 2011). LDL-C plays a major role in the progression of atherosclerosis (Soran et al., 2017), and an elevated level of cholesterol is estimated to account for 4.5% of total deaths (2.6 million lives) (World Health Organization, 2009; Alwan et al., 2011).

The focus of current treatments for CVDs is on restoring normal blood flow through or around the damaged vasculature and the prevention of cardiovascular events (Chandarana et al., 2018). A plethora of therapeutics such as statins, beta-adrenergic receptor blockers, antiplatelet agents, coronary stents and surgical interventions have been prominent contributions in dealing with CVDs (Ismail et al., 2015). However, there are limitations in the management of CVDs, regardless of the major technological advancement in the diagnostic and therapeutic modalities (Godin et al., 2010). The available therapeutic options are not sufficient to stop or significantly reduce the progression of CVD and may cause harmful side effects (Giménez et al., 2017). Early detection of diseases and cell-specific delivery of therapeutics



bears the potential to improve the prevention of cardiovascular morbidity and mortality (Cicha et al., 2013). Nanomedicine aims to address the existing therapeutic challenges of CVDs by providing more effective and safer therapeutic alternatives. Endothelial cells represent the first point of contact for nanoparticles administered via the intravascular route (Cicha, 2016). Therefore,

medicines targeting impaired endothelium remain a significant need (Tang et al., 2012). Nanoparticles can be engineered to reach and target endothelial cells directly from the circulation; this is due to the high expression levels of specific adhesion molecules and increased cellular gaps in early stages of atherosclerosis (Tang et al., 2012).

Cardiovascular Nanomedicine

Cardiovascular nanomedicine focusses on enhancing the diagnosis and therapy of CVDs by advancing biomarker detection and imaging, as well as by targeted enhanced delivery of drugs and tissue regeneration devices (Godin et al., 2010). Currently, two nanomedicines have been approved for the management of CVDs. Nanocrystals of fenofibrate and Colesevelam HCl in polymeric forms were approved for hyperlipidaemia in the United States in 2000 and 2004, respectively (Schütz et al., 2013; Su et al., 2017; The British Society of Nanomedicine, 2019). The solubility and bioavailability of fenofibrate were increased by micronisation and nanoformulation, rendering it bioequivalent in fed and fasting conditions (Ling et al., 2013). Nanocrystalline fenofibrate enhanced therapeutic efficacy as well as reducing the adverse effects (Khairnar et al., 2017). Colesevelam, a polymeric sequestrant of bile acids, was based on hydrophobically and cationically modified crosslinked poly(allylamine). The secondary binding forces provided by the hydrophobic decyl groups significantly increased the potency of colesevelam (Li et al., 2015).

Despite the abundance of promising lab-scale results in cardiovascular nanomedicine, some of which will be discussed below, the number of clinical trials remains low (Cicha et al., 2018). There were 13 clinical trials for nanoparticles for CVDs compared to 176 completed or ongoing studies for cancer registered on the homepage of clinicaltrials.gov up to 2018 (Cicha et al., 2018). Most of the trials for cardiovascular applications were related to the clinical use of iron oxide nanoparticles for enhanced detection and characterisation of atherosclerotic plaques (ferumoxtran, SineremVR) (Trivedi et al., 2006; Howarth et al., 2009; Sadat et al., 2013), aortic aneurysms (ferumoxtran, SineremVR) (Richards et al., 2011), and the detection of inflammation in myocardial infarction (ferumoxytol, FerahemeVR) (Alam et al., 2012; Yilmaz et al., 2013; Florian et al., 2014). NanoAthero was a large-scale 5-year multinational project to demonstrate the benefits of the use of nanoparticle technologies. It included several studies for the diagnosis and treatment of atherosclerosis and stroke (Chauvierre and Letourneur, 2015). As a part of the NanoAthero project, a clinical study was conducted by van

der Valk et al. (2015) with a Good Manufacturing Practice (GMP) steroid (prednisolone) encapsulated in PEGylated liposomal formulation on the basis of previous preclinical studies. Although the formulation had no anti-inflammatory effect in atherosclerotic lesions, it improved the pharmacokinetic profile and provided guidance for the future development of nanomedicine for CVDs.



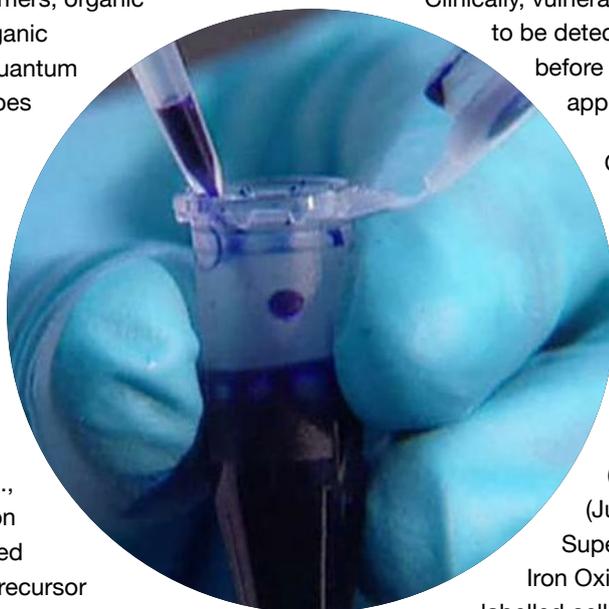
Diagnostic Nanomedicine

Nanotechnology-based diagnostic techniques can offer higher sensitivity and improved image resolution with respect to current methods. This can enable early detection of disease, better understanding and improved therapeutic outcome (Boulaiz et al., 2011). The characteristics of nanomaterials that make them valuable for medical imaging are size distribution (enabling incorporation with various bio-components), high penetration ability, targeted delivery at a specific site, image contrasting power, tuneability at nanosurface, increased stability and lifetime (Deb et al., 2015). To date, some of the materials utilised to manufacture nanomedicines for applications in imaging include lipids, polymers, organic precursors (dendrimers), inorganic molecules (gold, iron oxide, quantum dots), carbon (carbon nanotubes and pipes), metal oxides, and biological constituents, such as proteins (Chung et al., 2015). Nanosystems functionalised with contrast agents and ligands directed towards specific biomarkers can be used for molecular imaging of cardiovascular pathologies (Chauvierre and Letourneur, 2015; Juenet et al., 2015). Design and construction of nanomaterials with enhanced characteristics yield several precursor materials enabling the design of contrast agents for imaging applications, optical switches for initiating drug release or for therapeutic purposes (Sahoo, 2005).

The components of atherosclerotic plaques can be explored for the application of nanotechnology to improve the diagnostic and therapeutic approaches to atherosclerosis (Jayagopal et al., 2010). The endothelia, fibrin, collagen III, macrophages and biomarkers of angiogenesis are some of the potential targets for imaging atherosclerotic plaques. The promising targets examined for the nanotechnology-based imaging and therapy of atherosclerosis and targeting mechanism are presented in Table 1. Fibrin deposition marks one of the initial hallmarks of atherosclerotic plaque rupture. Rupture of

susceptible and exacerbated atherosclerotic plaques can have several damaging consequences. Fibrin and tissue factors remain potential targets for imaging arterial thrombi by ultrasound and Magnetic Resonance Imaging (MRI). The ligand nanoparticle conjugation specifically interacting with $\alpha v\beta 3$ -integrin is an example of angiogenesis targeting (Kraft et al., 2014). The number of prospective targets within the lesions containing a plethora of specific cell types, such as macrophages, and the up-regulation of cell surface receptors, such as vascular cell adhesion molecule-1 (VCAM-1) has stimulated research in this area (McCarthy, 2010).

Clinically, vulnerable lesions need to be detected and identified before the symptoms appear (McCarthy, 2010).

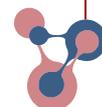


One of the first nanosystems to reach the market is Ultrasmall

Superparamagnetic Iron Oxides (USPIOs) for MRI (Juenet et al., 2015).

Superparamagnetic Iron Oxide (SPIO) or USPIO labelled cells in combination with

MRI have been used for the diagnosis of CVDs, multiple sclerosis, and neurodegenerative brain disease (Riehemann et al., 2009). Contrast generating nanomaterials have been employed as multidimensional approaches to detect and characterise initial phases of disease before the manifestation of gross pathological symptoms. Fluorescent, radioactive, superparamagnetic, paramagnetic, electron-dense and light scattering particles represent a few of the contrast agents engineered on a nanoscale for imaging of CVDs (Kraft et al., 2014). Gold nanoparticles (GNPs) have shown promise in preclinical studies for imaging of CVDs. Due to their strong light scattering properties, they have been utilised as contrast agents for optical or X-ray imaging modalities to detect atherosclerotic plaques,



intravascular thrombus, or fibrotic tissue (Ambesh et al., 2017; Varna et al., 2017). Nahrendorf et al. (2006) functionalised multivalent monocrystalline magnetic nanoparticles (MNPs) with peptides that direct MNPs to cells expressing VCAM-1, a biomarker of inflammation in atherosclerosis (Jiang et al., 2017). Intra-arterial thrombosis remains a common underlying pathological cause of various CV syndromes, including myocardial infarction (MI), cerebrovascular accident (CVA), and pulmonary embolism. Some of the diagnostic techniques employed for the detection of thrombosis are

doppler ultrasound, X-ray computer tomography (CT) imaging or MRI. However, the characterisation of clots, including the constituent components or biological age, remains a challenge. This could support the efficacy of the treatment modalities. Therefore, several molecular imaging approaches have been engineered to aid visualisation of the formation of thrombus, such as fluorescently labelled platelets, and fluorescently or radiolabelled ligands targeted to other components, such as fibrin and coagulation factors (McCarthy, 2010).

Table 1: Targets examined for nanotechnology-based imaging and therapy of atherosclerosis

Target	Description of the targeting mechanism	References
Endothelial cell (ICAM-1, VCAM-1)	Internalises imaging agents or therapies bound to cell adhesion molecule-specific peptides or antibodies	Muro and Muzykantov (2005); Nahrendorf et al. (2006); Zhang et al. (2008)
Macrophage scavenger receptor	Internalises dextran-coated iron oxide nanoparticles for MR contrast, or antibody-linked imaging agents, and/or therapies via scavenger receptor endocytosis	Raynal et al. (2004); Amirbekian et al. (2007)
Apoptosis	Phosphatidylserine residues on apoptotic cells, or the caspase family of enzymes, can be targeted by molecular imaging agents	Johnson et al. (2005); Faust et al. (2007); Smith et al. (2007)
Neovascularisation	Neovessel-specific integrins, extracellular matrix molecules, and cell adhesion molecules enable targeted molecular imaging and therapy	Matter et al. (2004); Lanza et al. (2006); Winter et al. (2006)
Matrix metalloproteinases (MMPs)	Nanoparticles featuring MMP-cleavable can be used to develop a variety of site-specifically activated imaging and drug delivery reagents. Several emerging nanotechnologies are based on functional actuation by MMPs	Wagner et al. (2006); Lancelot et al. (2008)
Extracellular matrix	Collagen subtypes present in the plaque such as I, III, and IV can be imaged in the plaque using a collagen-binding protein linked to contrast agents	Megens et al. (2007)
Thrombus	Activated platelet integrins and exposed fibrin can be targeted by antibodies, peptides, and small molecules linked to contrast agents to image vulnerable plaques, or drug delivery vehicles for delivery of antithrombotic agents	Winter et al. (2003); Sirol et al. (2005); Lanza et al. (2006); Srinivasan et al. (2010)

ICAM: intercellular adhesion molecule, MMP: matrix metalloproteinase, MR: magnetic resonance, VCAM: vascular cell adhesion molecule

Source: Jayagopal et al., 2010



Therapeutic Nanomedicine

The added values of nanomedicines in therapeutics include improved pharmacodynamics, pharmacokinetics, efficacy and safety (Ventola, 2017). Nanomedicines can be designed to enable entry to previously impermeable locations, longer circulation, enhanced accumulation, controlled site-specific drug delivery and reduced adverse effects (Ventola, 2017).

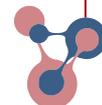
In the field of cardiovascular research, some of the major focus areas of application have been the therapy of atherosclerosis, recurrence of stenosis, and targeted clinical imaging (Kraft et al., 2014). Atherosclerotic plaques and new or thickened layers of arterial intima present a range of stage-specific molecules during progression stages that can be employed as targets in CVDs, for example, intercellular adhesion molecule (ICAM), vascular cell adhesion molecule-1 (VCAM-1) and others (Godin et al., 2010). An interventional approach to atherosclerosis has some issues, such as long-term antiplatelet therapy and restenosis associated with stents (Cicha et al., 2013). Cyrus et al. (2008) showed that $\alpha v\beta 3$ -integrin-targeted rapamycin loaded paramagnetic nanoparticles significantly reduced stenosis without affecting endothelial healing. Nanocoatings on drug-eluting stents (DES) deliver the drug at the targeted site of plaque accumulation (Karimi et al., 2016).

Dextran-coated magnetofluorescent nanoparticles were functionalised with a photosensitiser,

which released oxygen upon exposure to light of a certain wavelength. Detection and lysis of macrophages by the oxygen released proved to be vital for the future diagnosis and management of atherosclerosis (Jiang et al., 2017). Iron oxide nanoparticles have been examined for the magnetically targeted delivery of thrombolytic agents (McCarthy et al., 2010). Magnetic targeting encompasses the utilisation of a magnetic field to the targeted site, followed by injection of the bioactive molecule-magnetic nanoparticle injectable complex (Giménez et al., 2017). The agent accumulates within the magnetic field at the desired site as it passes through the circulation (McCarthy et al., 2010).

D-Phenylalanyl-prolyl-arginyl Chloromethyl Ketone (PPACK) functionalised perfluorocarbon-core nanoparticles were developed; this led to enhanced anti-thrombotic activity in a mouse model of arterial thrombosis. However, there have been limitations in clinical use due to rapid clearance (Rhee and Wu, 2013; Giménez et al., 2017). Although Peters and group demonstrated the *in vivo* ability of hirudin entrapped micelles functionalised with fibrin binding peptides to target fibrin rich clots, thrombolytic efficacy is yet to be established (Rhee and Wu, 2013).

Table 2 highlights various nanotechnology-enabled approaches that have been researched for CVDs, such as hypertension, hyperlipidaemia, myocardial



infarction and thrombosis (McCarthy, 2010). Low nitric oxide (NO) bioavailability is a key factor in the manifestation and progression for CVDs such as hypertension (Giménez et al., 2017). Gold and silica nanoparticles have been engineered to enhance the supply of NO to manage hypertension. High levels of reactive oxygen species (ROS) are often linked to CVD progression. Cerium nanoparticles (CeO₂ NP) possessing antioxidant potential were found to reduce microvascular dysfunction and oxidative stress associated with hypertension (Giménez et al., 2017). Raju et al. (2014) formulated solid lipid nanoparticles loaded with simvastatin that showed controlled release and improved bioavailability. A novel approach of

anti-apolipoprotein B100-poly(lactide) nanoparticle conjugates showed up to a six-fold decrease of LDL-C levels in a mouse macrophage cell line without toxicity (Maximov et al., 2010). Some nanoparticles possess therapeutic benefit on their own; for example, silver nanoparticles with size-dependent antiplatelet activity and magnesium oxide nanoparticles with antibacterial efficacy reducing infections linked to medical implants and devices (Jiang et al., 2017). Polizzi et al. (2007) decorated gold nanoparticles with amine ligands for sustained release of nitric monoxide (NO); these are capable of mediating endothelial and vascular smooth muscle cell functions.

Table 2: Synopsis of nanotechnological approaches for CVDs

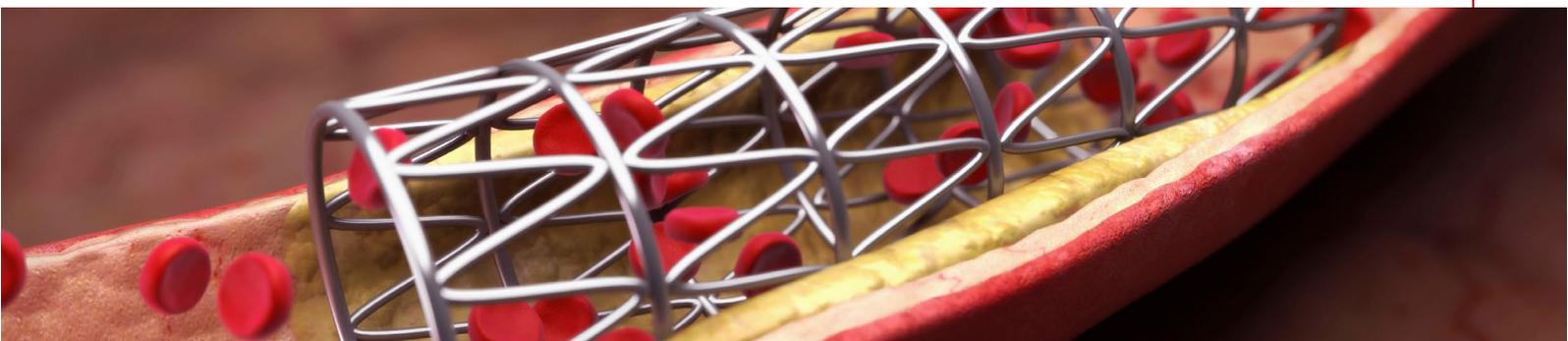
S. No.	Diseases	Nanotechnological approach	Drug
1	Hypertension	Nanoemulsion system Solid-lipid nanoparticles Dendrimers Nanosuspension Nanoparticles	Curcumin Carvedilol Candesartan dilexetil, Nifedipine Nevibinol Telmisartan
2	Hyperlipidaemia	Polymeric drug Nanocrystal Solid lipid nanoparticles Nanoemulsion system Nanosuspension Nanosponge Nanostructured lipid carrier Polymer nanovesicles Nanoparticles	Colesevelam HCl Fenofibrate, Atorvastatin Simvastatin Curcumin, 17-β E, Paclitaxel, Simvastatin Fenofibrate, Simvastatin, Ezetimibe Atorvastatin, Fenofibrate, Lovastatin Lovastatin Pravastatin Pitavastatin
3	Pulmonary Hypertension	Nanoparticles	Bosentan; NF-Kappa β antagonists
4	Myocardial Infarction	Nanoparticles Liposomes Silica nanoparticles Nanofibers	Contrast agents for stem cell therapy; irbesartan poly-(lactic-co-glycolic) acid (PLGA) Phosphatidylserine Adenosine Vascular endothelial growth factor (VEGF)
5	Thrombosis	Nanoparticles	Tissue plasminogen activator (tPA), D-Phenylalanyl- prolyl-arginyl Chloromethyl Ketone (PPACK)

Source: Giménez et al., 2017; Khairnar et al., 2017; The British Society of Nanomedicine, 2019

Regenerative Nanomedicine

The technological applications based on nanotechnology have also been applied to the field of regenerative medicine for cartilage repair, bone reconstruction, and the regeneration of skin, nerve and cardiac tissue (Perán et al., 2013). The promotion of new blood vessels from existing ones is essential for the regeneration of cardiac tissue after myocardial ischemia (Bejarano et al., 2018). A synthetic biomaterial, nanofibrous scaffolds made of L-lactic acid with trimethylene carbonate (LLA-co-TMC), has demonstrated its ability to enhance cardiac muscle cell proliferation for myocardial regeneration. Tissues have been engineered to produce fully functional artificial heart valves, and nanoparticles have been employed to modify

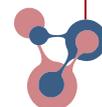
the structure and function of diseased valves. Functionalised nanoparticles that serve as drug carriers can target atherosclerotic progression involving degeneration of heart valves (Perán et al., 2013). The application of nanotechnology into stent design and technology has also presented innovative approaches for delivering drugs from mesoporous substrates and enhanced biocompatibility from nano-textured surfaces (Godin et al., 2010). The m can be prevented without hindering the healing of endothelium and causing endothelial dysfunction by local drug delivery based on nanotechnology (Cyrus et al., 2012).



Theranostic Nanomedicine

Theranostic nanomedicine is based on the exciting concept of combining three functions, namely targeting, diagnosis, and therapeutics, within a single formulation (Lammers et al., 2010; Ventola, 2012). Theranostic nanomedicine contains both a therapeutic drug and a diagnosing label (Lammers et al., 2010), enabling the tailoring of the properties of the engineered nanomaterials (McCarthy, 2010). The findings of preclinical studies gradually applying theranostics to CVDs have been encouraging (Tang et al., 2012) and a step closer to personalised medicine (Jiang et al., 2017). De Olivera Gonçalves et al. (2015) functionalised 5-aminolevulinic acid (ALA) gold nanoparticles with polyethylene glycol (PEG) and administered them to rabbits. ALA was converted into endogenous protoporphyrin (PPIX)

in atherosclerotic plaques. An increase in blood and faeces porphyrin emission indicated that it could be utilised for early diagnosis and therapy of atherosclerosis. Macrophages play a vital role in the progression of atherosclerotic plaques (Shetty et al., 2019). McCarthy (2010) designed light-activated cross-linked dextran-coated iron oxide nanoparticles for targeted macrophage ablation in mice. The developed theranostic nanoagent had therapeutic and imaging functionalities in inflammatory atherosclerosis. Research is also being focussed on utilising the extensively studied and established nanoparticulate agents for the imaging of atherosclerosis strategies to deliver two or more therapeutic agents simultaneously (McCarthy, 2010).



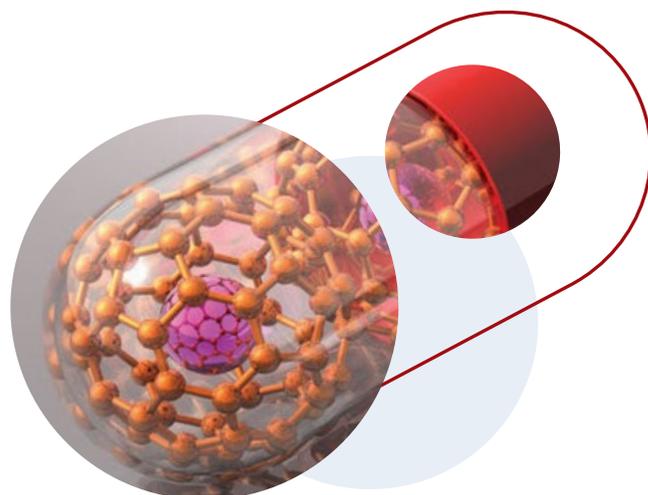
Challenges

There are several scientific, analytical, environmental, regulatory and cost-benefit issues posing a variety of challenges to the clinical translation of nanomedicines (Chavda, 2016; Ventola, 2017). Therefore, very few nanomedicines have reached the clinical studies and market from the research bench (Godin et al., 2010; Cicha et al., 2018). Some of the issues are a lack of repeatability in the synthesis, the limited number of methods and standards available for their characterisation, regulatory approval, and a degree of resistance to switch from traditional to more innovative medicines. Any subtle variations or contaminant in the production process and testing could lead to altered physicochemical properties; this would affect therapeutic efficacy and safety (Ambesh et al., 2017; Ioannidis et al., 2018). In addition, the development of nanomedicines has evolved faster than the regulations (Fornaguera and García-Celma, 2017). There are no specific regulatory guidelines to ensure standardised GMP production and quality control of nanomedicines (Ventola, 2017; Hua et al., 2018). The complexity of nanomedicine patents and intellectual property rights also poses challenges (Hua et al., 2018). Handling and control of materials, structures and devices on a nanoscale presents greater scientific and technical challenges than conventional medicine (Hua et al., 2018). The increasing use of engineered nanoparticles can increase their levels in the groundwater and soil, raising environmental concerns (Jeevanandam et al., 2018). In addition, conventional medicine manufacturing facilities lack the capability of manufacturing nanomedicines (Agrahari and Hiremath, 2017). The major unknown risks associated with nanosystems include translocation to undesired cells, potential toxicity, and uncertainty of the clearing process (Chavda, 2016; Ambesh et al., 2017).

Furthermore, there are other challenges associated with the development of cardiovascular nanomedicine. The optical and fluorescence techniques generally used to image molecular changes in *in vitro* studies require further advancement in instrumentation, assessment of contrast agents, and data analysis for direct

clinical translation (Pysz et al., 2010). Many of the stimulating preclinical results have not progressed beyond the developmental phase (Soares et al., 2018), and it remains to be studied if the results from one species can be extrapolated to another (Chan et al., 2018). This could be due to pathological differences (Tang et al., 2012), for example, murine atherosclerosis is vastly accelerated compared to humans (Schiener et al., 2014; Nakhband et al., 2018). A perfect animal model that completely replicates all stages of human cardiac disease does not exist to enable a thorough investigation of nanoparticle interaction. Identification and standardisation of appropriate *in vitro* and animal models to mimic CVDs remain a challenge considering the discrepancies in scientific research (Fitzgerald et al., 2011). The immune system contains multiple pathways to maintain homeostasis. In addition, delivering the benefits of anti-inflammatory bionanomaterials to the management of chronic inflammatory conditions in CVDs, should not compromise the host defence mechanism provided by the immune system. Although atherosclerotic plaques may be less structurally complex or heterogeneous than tumours, plaque volumes are significantly smaller than tumours (Chan et al., 2018).

Several issues need further investigation, such as interaction with plasma proteins, endothelium, the effect of targeting ligand with different cell types and extracellular components, internalisation kinetics, the pathway of uptake and fate of nanoparticles after entering the atherosclerotic plaque (Chan et al., 2018; Kim et al., 2019).

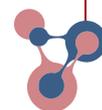


Conclusions and Future Perspectives

In the years to come, nanotechnology will serve a vital role in providing creative opportunities for the early diagnosis of diseases and therapeutic options for targeted drug delivery and patient-tailored therapy, thereby improving people's quality of life. With the better characterisation of nanomaterials and guidelines established to bridge the gap between conventional medicine and nanomedicine, nanomedicine bears the enormous potential to diagnose and manage several diseases. However, with expanding interest and continuing research, each formulation is bound to face unique biological and technological challenges in its clinical translation. Interdisciplinary collaboration with an exchange of knowledge and skills of academia, drug manufacturers, supported by regulatory agencies, will be vital in translating from the bench to clinical application.

There is tremendous scope for nanomedicine in cardiovascular diseases, and further research is warranted to improve tissue-specific targeting and to reduce toxicity. There is a need for extensive

studies on nanoparticle interactions with vascular endothelium to establish the relationship between physicochemical properties of nanoparticles and their delivery efficiency. The expanding list of preclinical applications of nanomaterials highlights the growing interest in the field of atherosclerotic nanomedicine. There are prospects for a number of nanotechnology-enabled formulations since several polymeric and lipid-based nanoformulations are being tested in preclinical and clinical trials. Plaque-targeted drug delivery, site-specific targeting, fabrication of multifunctional nanomaterials, and design of nanoscale devices presents promising avenues for enhancing the clinical management of atherosclerosis. The future of cardiovascular nanomedicine indeed seems very exciting with newer molecular targets, deepening knowledge, better understanding and concerted research efforts. Certainly, there is plenty of room for further advancement of nanomedicine.



Competing Interests: Perspectives

There are no conflicts of interests to be reported.

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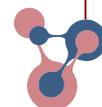
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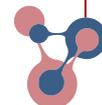
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Biography

Sony Chandi Shrestha is a PhD scientist from London Metropolitan University and the National Physical Laboratory, United Kingdom. She studied pharmacy in Nepal where she gained five years work experience of pharmaceutical product development, marketing planning and regulatory affairs. She graduated with an MSc in Pharmaceutical Science with distinction from London Metropolitan University in 2015. Some of her research interests include nanoparticle formulation and characterisation, nanomedicine, pharmaceutical formulation and analysis, novel drug delivery systems and pharmacovigilance.

Dr Kenneth White studied Chemistry at Oxford University and stayed there to carry out his DPhil in the Department of Pharmacology, where he developed an interest in drug pharmacodynamics, metabolism and toxicology. Following post-doctoral training at the National Institutes of Health, Bethesda, MD, USA and Kyoto University, Japan, he returned to the UK. At Guy's Hospital Medical School he established his own research focussing on gene regulation. For the last 20 years Dr White has pursued a variety of research interests at London Metropolitan University, most recently focussing on electrohydrodynamic methods for creating novel nanoformulations for drug delivery.

Dr Caterina Minelli is a physicist at the UK National Physical Laboratory (NPL) working in the field of nanomaterials' metrology. Caterina studied High Energy Physics in Florence, Italy, and obtained a PhD in Nanotechnology from the École Polytechnique Fédérale of Lausanne (Switzerland) in 2004. She was subsequently awarded two fellowships to work in the field of nanomedicine at research institutions in Japan and the UK, including the prestigious EU Marie Curie individual fellowship. Caterina has been at NPL since 2010 where she is currently working at developing the metrology infrastructure underpinning the industrial exploitation of particle-based technologies and supporting innovation in medicine manufacturing.

Dr Ihab Tewfik is a Registered Nutritionist (Public Health) who has expertise in planning, implementing and evaluating sustainable nutrition intervention programmes at the population level. He has developed an independent academic research career that underpins the pivotal role of nutrition science in modulating complications of

global chronic diseases through tailored functional recipes (TFRs). These innovative TFRs are optimised using locally produced food ingredients that are formulated into meals to nourish vulnerable populations and ascertain their optimum health. In addition to his PhD from London South Bank University, Ihab holds Master of Public Health (MPH) and Doctorate of Public Health (DrPH) from Nutrition Department, University of Alexandria.

Professor Panna Thapa studied Pharmacy (BPharm, MPharm) at the University of Dhaka, Bangladesh. He received his PhD in Formulation and Drug Delivery from the University of Strathclyde in Glasgow, United Kingdom. He is one of the founding members of the Department of Pharmacy at Kathmandu (KU) University, Nepal where he has held several positions; these include Lecturer, Assistant Professor, Associate Professor, Professor; HOD in the Department of Pharmacy and Dean, School of Science. He has been serving KU as the Controller of Examinations since 2013. His research interests include the development of novel drug delivery systems (DDS), mucosal bioadhesive DDS, pharmacokinetic studies, regulatory affairs, quality management issues, pharmaceutical education and practice, social pharmacy and implementation of effective teaching methods.

Dr Sundus Tewfik is a qualified Biologist. She holds an MSc in Applied Microbiology and a PhD in Pharmacognosy. Dr Tewfik employs the new concept that combines tailored functional formulae hand-in-hand with standard pharmacological therapies. Her nutraceutical research exploits the use of pharmacology and clinical nutrition in nutrition intervention programmes that combat chronic diseases related to immunity, cancer, cardiovascular and cognitive disorders. Research techniques start from the authentication of botanicals; biochemical evaluation, antimicrobial testing, isolation/identification of "biologically active" components (in-vitro/in-vivo tissue systems), quality control, product formulations and randomised clinical studies. Dr Tewfik's research portfolio includes the use of nanomolecules in health and disease management. Dr Tewfik is contributing to the future of pharmaceuticals with advanced drug delivery systems, e.g., Solid Lipid Nanoparticles [SLN]. Dr Tewfik provides client advisory service to Pharmaceutical, Cosmetic, Natural products and Functional Food businesses.

