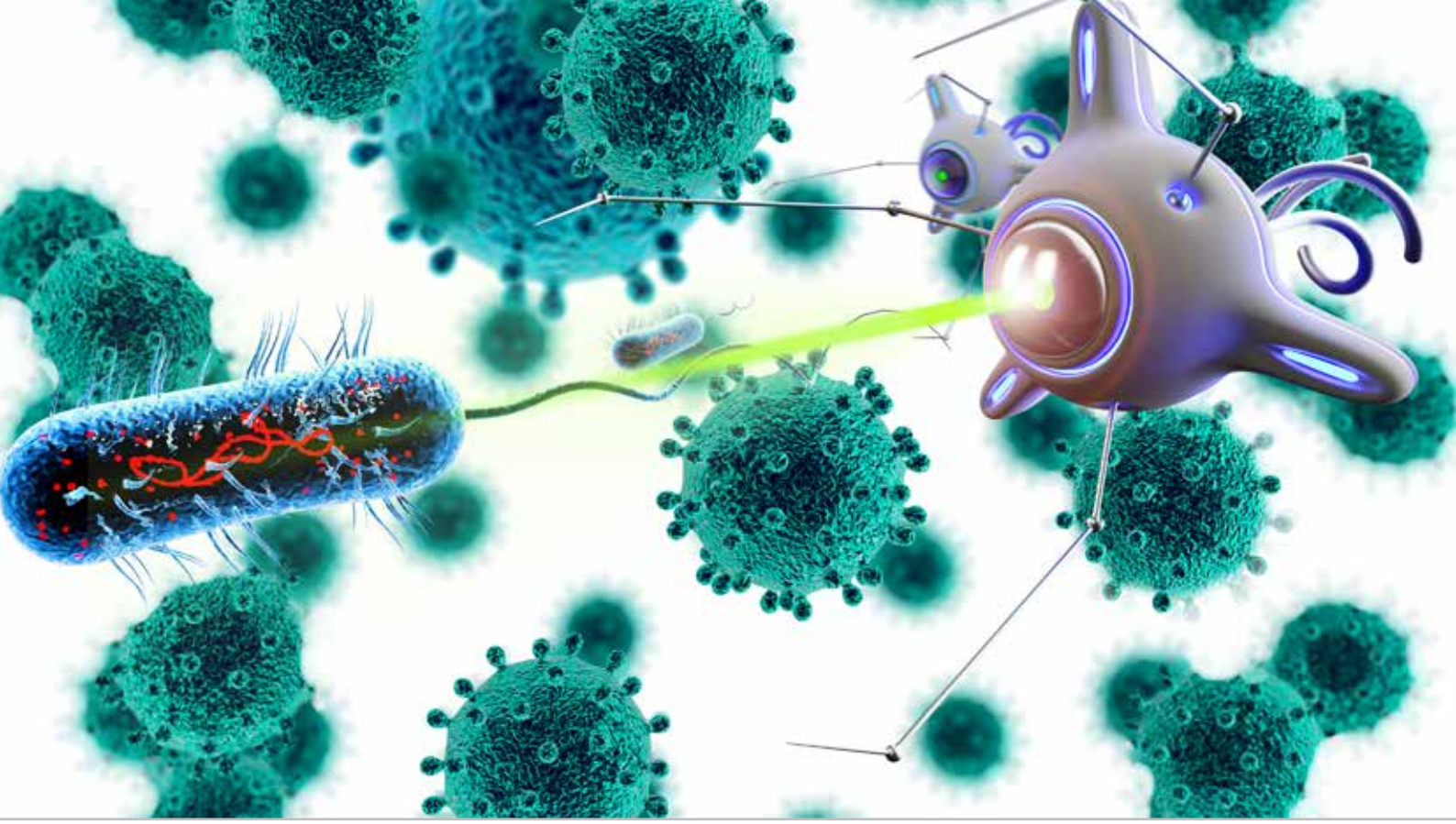

Nanotechnology

What does the future look like for the medical devices industry?

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Contents

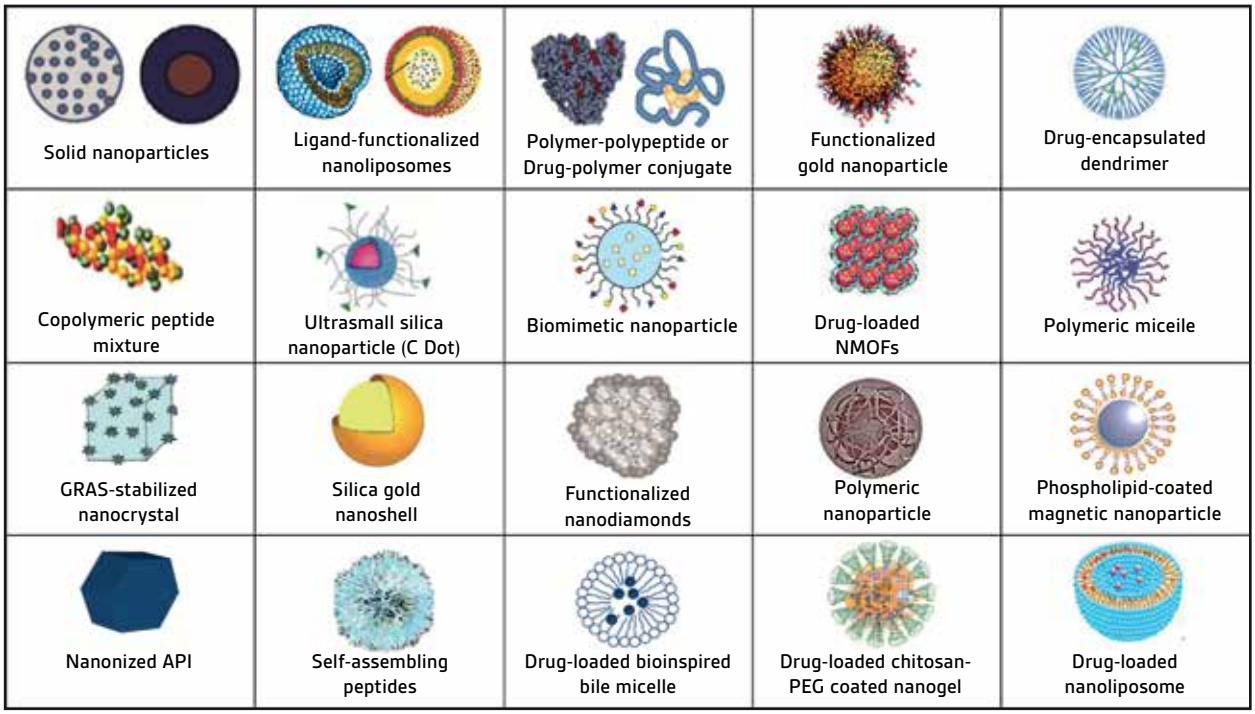
1 Introduction

Nanotechnology is now a mature subject in terms of the basic science, and while there were many claims for what it could achieve 20 years ago, when the funding in the area was beginning to ramp up, there is now much more realism in most areas of application. The application to medicine and healthcare is certainly now much more well defined. There have also been some harsh lessons learned in the past 15 years or so as to the limitations being set by regulation, professional and public acceptance and by the funding agencies, both public and private.

First, we should define what in implied by the word 'nanotechnology'. In terms of sizes, this means that at least in one or more dimensions, sizes of between 1 and 100 nm are involved. This has been adopted for pragmatic reasons rather than purely scientific reasons. New optical, electrical and mechanical properties of materials become manifested as the size of materials is reduced. The number of atoms at the surface relative to those inside the material increases, and small particles are generally more reactive. With the sizes of much smaller than cellular levels, there are possibilities for new biological functionalities and hence the excitement about possible new medical applications (see Figure 1).

So, how will things develop in the years ahead? It is probably best to divide the medical devices field into five main sectors and look at each in turn. For this purpose we will consider: medical image enhancement; drug delivery vehicles; nanomaterials for functional coatings; therapeutic aspects of nanomaterials that make use of their small size and properties and finally biosensors that make use of nanoparticles. While each of these fields is posing many new questions, there are common themes that apply to all of them and in this review we will summarize these and identify gaps in understanding and opportunities.

Figure 1 – The large range of possibilities for designing nanoparticles for use in the medical sector is shown; From: Bawa, R. (2018). Immunogenicity of biologics and nanodrugs: An overview. *In:* R. Bawa, J. Szebeni, T. J. Webster and G. F. Audette. (Editors): *Immune Aspects of Biopharmaceuticals and Nanomedicines*, Pan Stanford Publishing, Singapore, Chapter 1 (in press).



Part 1 Future developments in the medical devices industry

2 Medical image enhancement

Nanoparticles can be designed so that they can enhance the contrast for different imaging modalities. For example they can have attached to their surface a molecule that binds to a specific disease state and thus hold the nanoparticle onto the cells and tissue of interest. So, one can enhance X-ray contrast using nanoparticles made from high atomic number material; MRI contrast can be enhanced using superparamagnetic particles; optical imaging can be enhanced either by luminescent nanoparticles or surface plasmon resonance particles; ultrasound imaging can be enhanced using nano/microbubbles. The building blocks to achieve the aforementioned are to make the particles under well-controlled conditions and to design, or have available, the appropriate linker between the nanoparticle and the disease state of interest.

2.1 Nuclear and radiology image enhancement

This requires nanoparticles to be created that have a radioactive component added to give some form of specialized image enhancement or a high atomic number to absorb X-rays to give additional contrast on X-ray images. For the former, it is possible to attach particles containing a radioactive gamma-emitting tracer to give single-photon emission computed tomography (SPECT) images, or Flourine-18 to give positrons for the positron emission tomography (which is detected by having two gamma rays emerging in opposite directions) that is becoming more widely used for neuroimaging of the brain.

2.2 MRI image enhancement

The most widely used image enhancers for MRI have been based on gadolinium compounds, either chelates or oxide nanoparticles. These give a positive T_1 contrast (white on grey) in images. But there is increasing use of superparamagnetic iron oxide nanoparticles (SPIONs) which give a black on grey T_2 image contrast. These have an advantage in being less toxic than gadolinium but also lend themselves more readily to being used in combination with image enhancers based on complementary techniques, such as radio-labelled, luminescent labelling and so forth.

2.3 Luminescence enhancement

Traditionally there are a number of approved dyes that have been used, especially during surgery to identify diseased tissue. However these dyes can suffer from bleaching and changes due to the chemistry in the local environment. There is increasing use being made of highly luminescent quantum dots, nanodiamonds and other nanoparticles because these can be designed to be not so dependent on local chemistry, but they can be functionalized to detect particular disease states.

2.4 Plasmonic effects

Gold and silver particles of sizes in the range 20–40 nm can give a large enhanced optical scattering caused by the excitation of surface plasmons. These two metals show particularly sharp and optically intense surface plasmon effects (surface plasmons result from an oscillation of the conduction electrons in small particles of these two metals). While these particles could be used in the body, they are currently used mainly for in vitro studies especially for some forms of widely adopted biosensors (see 6.2).

2.5 Ultrasound enhancement

Bubbles are the main agent for introducing additional contrast for ultrasound, and these are in the form of liposomes filled with a gas such as argon. The outer surface of the liposome is usually functionalized so that the bubbles

preferentially attach to the target that is being investigated. Generally these are larger than the usual definition of nanoparticles, that is they are larger than 100 nm diameter.

3 Drug delivery vehicles

Precise targeting of drugs to specific sites is also possible using the approach outlined earlier. In this case the drug payload is carried by the nanoparticles and many possible approaches are possible. The drug could be contained in a liposome and allowed to leak out when it reaches its target; drug molecules could be hidden inside a porous matrix, of nanosilica or a polymer, and leak directly into the target; the drug could also be wrapped around nanoparticles and possibly even guided to the target and triggered in some way, possibly using magnetic or electric fields. There are two particularly challenging topics in this area. One is connected with the enhanced permeability and retention (EPR) effect whereby nanoparticles could (it is suggested) be designed with the right size to be captured in the leaky vasculature of tumours. This has also led scientists to question the capture or 'sticking probability' more generally for these new targeting methods. The second is the possibility of designing drugs to cross the blood–brain barrier and open up the possibility of treating neurological diseases.

3.1 Drug carrying

There are many possible ways of carrying a drug using nanoparticles, and the prime reason for doing so is to try to reduce the dosages and get them to the place where they will be effective using their size or targeting functionality. Hence there are strategies for incorporating existing drugs in or on biodegradable 'packages'. These packages could be made from biodegradable polymers, porous, benign substances such as silica or any material that is safe when introduced into the body. This has the advantage from a regulatory point of view that the drug compounds have already been approved, and it is the delivery mechanism that has to be approved. This is seemingly popular with investors because such new ideas are classed as 'devices' and consequently the time to revenue generation should be shorter because the approval route is simpler.

3.2 The EPR effect

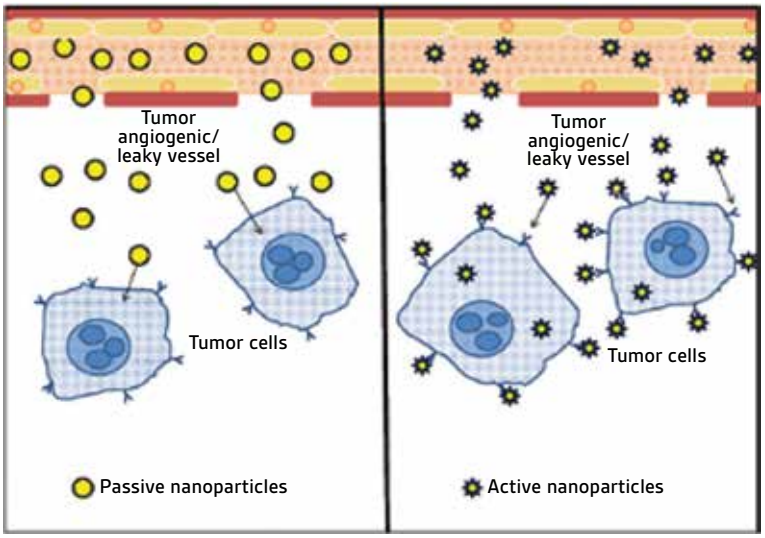
There has been a lot of faith attached to the idea of the enhanced permeability and retention (EPR) effect for cancer treatment. The basis for this idea is that the regions around a tumour allow for the entrapment of particles of a certain size range (20–200 nm) in the intravasculature around a tumour, without the need for active targeting, and then allow for the outwards diffusion of the active ingredient to destroy the cancerous cells (see Figure 2).

After extensive research in this area, it is emerging that while some mouse experiments showed evidence for this EPR effect, the same cannot be said to apply to humans. There is now a detailed appraisal of whether work should continue on human trials. Research is now being directed at possible methods for adding additional compounds to try to improve the EPR effect by changing the tumour microenvironment to allow for this to happen.

3.3 Triggered release

If a drug-carrying nanoparticle can be guided to a particular organ or site and attached there to cancerous or endothelial cells by having appropriate binding ligands, there is the question of 'release'. In some cases one might rely on the natural diffusion of the active drug into the nearby cells as the nanoparticle carrier releases it by diffusion or biodegradation. There are several ideas of triggering the release. This could be for example by changes of local pH because this tends to be slightly lower in tumour regions due to higher lactic acid concentrations; it could be triggered by an electric or magnetic impulse, or a light pulse via an optical fibre or an ultrasound impulse. All of these triggered releases do; however add another layer of complexity and additional components to the drug delivery nanoparticle. The fate of these additional trigger-enhancing layers does also need to be established.

Figure 2 – Schematic illustration showing nanoparticle accumulation in tumours (a) passive mechanism via the EPR effect that allows preferential build-up of nanoparticles near tumour tissue using leaky vasculature. (b) Site-specific active tumour targeting through ligand–tumour cell surface receptor interactions. From: Patel V, Papineni VL, Gupta S, Stoyanova R, Ahmed MM (2012), 'A Realistic Utilization of Nanotechnology in Molecular Imaging and Targeted Radiotherapy of Solid Tumours', *Radiation Research* Volume 177, pp 483-495.



4 Nanomaterials for functional coatings

In the new applications of nanoparticles being used for diagnosis or therapy, the 'functional coating' plays a key role. There are also many issues with implants in the body, even if they are only temporary, such as with catheters, because of bio incompatibility, infection, mechanical wear and so forth where coatings play a key part. Nanocoating materials can now be designed to mitigate against most of these risks. For example it is possible to design both active and passive antimicrobial coatings for catheters and stents and so forth; it is possible to protect prosthetic joints and moving parts with nanocoatings to reduce friction and wear; and it is possible to design coatings that resorb into soft or hard tissue. At a more pragmatic level, there is growing evidence that nanoparticles can be used to design surface coatings for benches, handles, keyboards and so on, with antimicrobial properties and this could have immediate application in clinics and hospitals.

4.1 Functional coatings to improve biocompatibility

Biocompatibility can be defined as the 'acceptance of an artificial implant by the surrounding tissues and by the body as a whole' and this places constraints on the approaches that can be used. There are also going to be differences between the nature of the body tissues, so hard tissue such as bone will have very different requirements to soft tissue environments. First, if we look at the requirements of hard tissues, where metals such as stainless steel and titanium alloys are frequently used, there are issues associated with wear and corrosion and the general interaction with living cells. To overcome these, nano-composite materials are being increasingly deployed and these should have the following characteristics: they should adhere strongly to the metal implant, and inhibit wear and corrosion, and the body-contact surfaces should encourage bone cell growth, with porous hydroxyapatite as the most favoured material. It should be emphasized that there is a tendency for these coatings to consist of several layers, that is: adhesion layer, anticorrosion/strength layer followed by the biocompatible layer and they have to be made under strictly controlled conditions.

Soft tissue coatings have very different requirements and characteristics but as in the earlier case there has to be some matching of the mechanical properties and this case it is elasticity, and the ability to follow deformation. There has to be some element of similarity with the surrounding soft tissues, so collagen and other polymeric biomaterials can be used.

4.2 Functional coatings for targeting

The scientific literature is full of methods to put some molecule recognition entities on the surface of particles that are intended for either imaging diagnostics or drug delivery. These entities range from fragments of DNA/RNA to antibodies and aptamers or smaller molecular units. There is very little quantification about the efficacy of these approaches, apart from some proof, from the imaging perspective that they have attached to the intended target. In other words, we do not know the 'sticking probabilities' of these functional nanoparticles. The situation is also complicated by the addition of poly-ethylene glycol (PEG) to help increase the circulation time in the blood. So, the role and behaviour of PEG is another uncertainty in this area.

4.3 Functional coatings for antimicrobial action

There is currently growing interest in rendering surfaces in hospitals and clinics and surfaces of medical equipment that come into contact with patients to have some antimicrobial action. There are really two approaches to achieve this aim, one is to prevent adhesion of bacteria to a surface and inhibit biofilm formation and the other is to kill the bacteria by some means. Traditionally this was achieved by employing metals such as zinc, copper or brass, where antimicrobial action is provided by the release of metal ions that kill or inhibit bacteria. This solution is tending to come back into fashion, but there are many plastic fittings and furnishings already in healthcare centres, and there will be new innovations to render such surfaces to be antimicrobial. An untreated plastic surface is often ideal for biofilm formation and antimicrobial attachment. The current approaches that are being tried include the use of silver nanoparticle composites, again, where the metal ions released perform the bacterial killing; very fine nanoparticles (<3 nm) of gold often in conjunction with a dye such as crystal violet; fine particles of the anatase form of titanium dioxide which is a potent generator of free radicals when exposed to light. The latter two methods are attractive because they rely on free radicals or possibly energetic electrons to do the microbial killing. It is unlikely that microbes can evolve to counteract these effects.

5 Therapeutic nanoparticles

Particles can be designed to produce a therapeutic effect without direct application of drugs. Most of these effects are brought about by having the particle designed to create locally, free radicals or energetic electrons to kill specific cell types. This is really an extension of the now well-established photodynamic therapy used to treat skin cancer. However, by injecting such particles locally into say, a tumour, and using X-rays to activate the free radicals, the efficacy of radiotherapy can be greatly enhanced. There is a further possible way to treat diseased tissue by destroying it with local heat produced by nanoparticles that are designed to get warm in radiofrequency fields or infra-red light.

5.1 Free radical generation

The formation of free radicals by exposure to light has been referred earlier in 4.3. The free radicals are a very effective way of destroying any cells, and it is hard to see any living cell adapting to resist such attack. For this reason, they form the basis of antimicrobial and antiviral therapies and also, if they can be localized, to the destruction of cancer tumours and other undesired cell types. Free radical formation by light exposure can be extended to X-ray exposure with similar results, possibly accompanied by the formation of energetic electrons that have a chemical reducing activity on the cells. This might have promise for increasing the effectiveness of radiotherapy treatments, by locally injecting around a tumour, nanoparticles that absorb X-rays and generate reactive oxygen species and/or energetic electrons.

5.2 Hyperthermia

Living cells can be destroyed by slightly elevated local temperatures of around 43 degrees Celsius. There are currently three main approaches to achieve this: one uses focussed ultrasound and does not have to rely on any addition of nanoparticles. (this method might also rely on cavitation of body fluid, locally to destroy cells and possibly also

create local free radicals); the other methods use either light to locally heat highly absorptive nanoparticles or long wavelength electromagnetic (radio frequency) waves to heat magnetic nanoparticles or metallic nanoparticles.

The methods involving light require nanoparticles that strongly absorb; so silver and gold either in particle or nanorod form are being suggested because of their very strong plasmonic properties. These two metals can be designed for application in the visible and infra-red wavelengths to allow for some light penetration into the body, although this will never be more than a few millimetres. If this approach is to be used, for anything other than skin cancer treatment, the light would have to be delivered via an endoscope to achieve sufficient heating. Magnetic hyperthermia on the other hand could be used almost non-invasively. It relies on the heating effect of either eddy currents induced in a metal or on the magnetic domain rotation or even the whole particle movement in a high frequency electromagnetic field. The uptake of these techniques is currently limited by the safety and possible toxicity of the particles that are introduced and on the inability to measure the local temperatures achieved with sufficient accuracy.

6 Ex situ biosensors that use nanoparticles

This category is much more widespread than many realize. For example the well-known pregnancy test devices can use gold nanoparticles although the earlier ones were based on blue latex microparticles. There are several types of optical sensors that rely on nanoparticles to 'capture' molecules and detect them via changes in refractive index or optical absorption or Raman enhancement. There are also types of electrochemical and electrical impedance sensor that use the high surface areas of nanoparticles to capture and detect specific analytes via their redox or electrical impedance behaviour.

6.1 Lateral flow sensors

Lateral flow sensors are popular because they provide a simple and quick visual record of the presence of a biomolecule. While these are widely deployed for pregnancy detection via the detection of human chorionic gonadotropin (HcG) which is released into the urine during pregnancy via the original Unipath Clearview test, we can expect the use of lateral flow sensor technology to increase for many other medical conditions and diseases, especially in developing countries. The original test used blue latex microparticles for the attachment of the HcG, giving a blue line on the test strip along the region that was functionalized with HcG antibodies. There is now a trend to use nanoparticles of gold in the size range of 15–40 nm, possibly enhanced in some way to increase the visual contrast. This is because the surface plasmon for gold nanoparticles in that size range results in a high contrast 'line' that appears red. The technology changes that are happening to broaden the application this technique are based on the identification of new biomarkers that are indicators of specific medical conditions. There are also developments to provide a more quantitative readout, especially by using the mobile phone camera as a miniature spectrophotometer or optical density recording instrument.

6.2 Plasmonic and SERS

The plasmonic behaviour of gold and silver also play key roles for these sensors. For many years, the Biacore instrument, now marketed by GE Healthcare Life Sciences has been the workhorse in biochemical research labs to detect the presence of biomolecules in in vitro experiments. This is likely to remain the case, but we could expect some miniaturization and extension to cheaper and simpler instruments for use in the field, possibly based again on mobile phone camera technology. Surface enhanced Raman spectroscopy (SERS) also depends strongly on the local light amplification brought about by surface plasmons. Most such analytical instruments use gold nanoparticles attached to a substrate. These can be used in a 'label-free' way to identify the molecules that adsorb on or near the gold nanoparticle surface, or they can employ gold that has a molecular capture agent.

6.3 Impedance sensors

There are several forms of electrical impedance sensor but the most common is to use interdigitated electrodes and measure impedance changes when the space between the electrodes is populated with biomolecules. The biomolecules can be selected using some form of molecular recognition molecule bound to the electrodes or

substrate and the use of nanoparticles in between the electrodes is used to increase the number of surface binding sites and hence increase the sensitivity. This method is more complex and indirect than others and it does usually require a variable frequency impedance analyser to get the best results.

Part 2 Nanomaterials, standards and EU medical device regulations

7 Regulations and the common issues

Most of the ideas described earlier demand a deep understanding of the fate of particles and the components that make up these particles inside the human body. There is still some research to be done in this area, but it can build upon some of the detailed trials and approvals of materials from the past. Much is now known about the excretion and retention of chemical components and particles in the body although there are many important gaps in our knowledge. In particular these hinge on a better understanding of the size dependency of capture and retention of nanoparticles and of the surface chemistry. The latter has profound effects on the behaviour of particles when attached to cells and tissue. The translation and adoption of many of the exciting new concepts outlined earlier will have to await detailed and carefully designed trials. There is a current feeling among scientists that if they can engineer their nanoparticles to carry an already approved drug, then the regulatory rules for 'devices' will apply rather than the more rigorous trials for a new drug. This is questionable! Regulators will want to see evidence that the new entity is fully understood, especially what happens to the drug carrier after it has 'delivered'. There are two main regulatory bodies that are addressing the issues. In the USA, the Food and Drug Administration issues guidelines that are continually updated as new evidence emerges https://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/ucm301114.htm and in Europe, The European Medicines Agency adopts a similar approach and there is clearly much common agreement in their approaches. The most recent policy is described here http://www.enatrans.eu/public/services/ecosystem-of-nanomedicine/ecosystem-for-nanomedicine

The designers of new medical technologies are now much more multidisciplinary and are engaging with engineers who are expert in up-scaling the new products under conditions of good manufacturing practice (GMP). It is also possible now to define clear roadmaps for innovation in this field and identify the unknown risks at early stages of development. This will help to define the standards and protocols needed for the application of nanotechnology to medicine and healthcare (see Figure 3).

If we have to make a prediction about the uptake of nanotechnology in healthcare it is probably going to happen as indicated in Table 1. There are quite a number of nano-based products already advanced through some of these stages such as those by BIND Bioscience, Abraxis Bioscience and Nanobiotix.

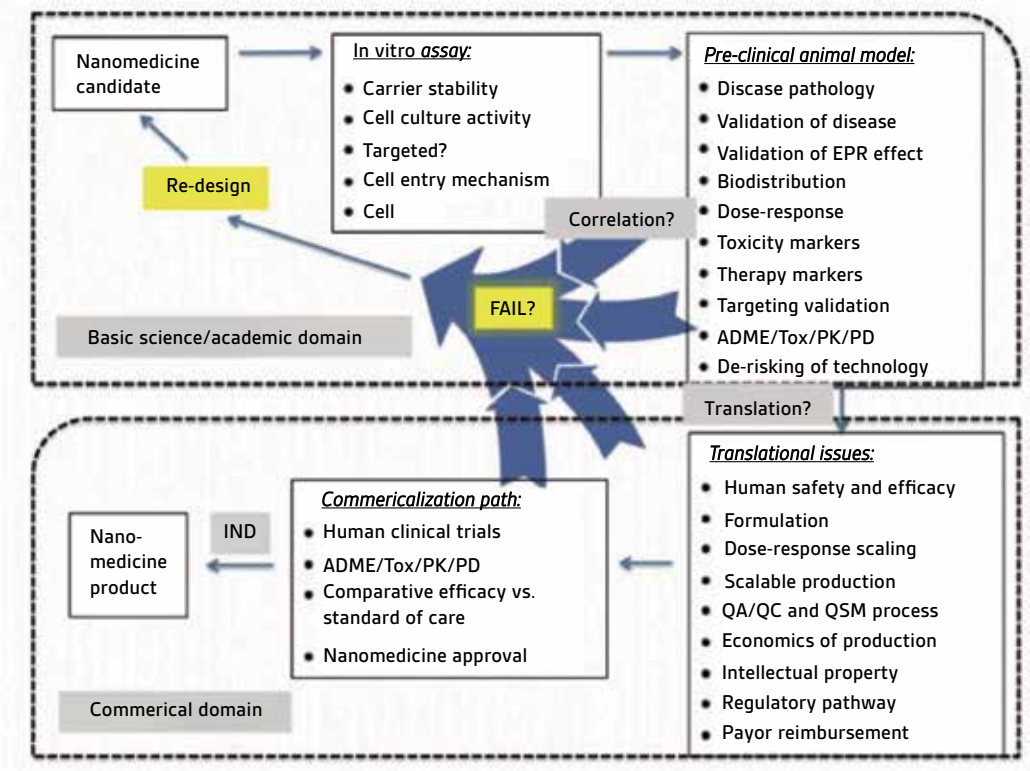
The main point to get across here is that the 'revolution' promised in nanomedicine is not going to be as rapid as many academic scientists hoped or predicted. This whole process takes considerable time, probably 10–15 years (at least) and hence it does not always attract investors)!

8 Regulation and guidance in the EU

8.1 The EU medical device directives

The current EU medical devices directives (AIMD - 90/385/EEC, MDD - 93/42/EEC, IVDD - 98/79/EC) do not contain explicit requirements on nanomaterials. However, all risks must be assessed and eliminated/reduced as far as possible primarily by device design (93/42/EEC, Annex I, Sections 1, 2 and 6). There are also requirements related to material toxicity, compatibility with substances and products the medical devices comes into contact with and contaminants, residues and leachants must be evaluated as part of the risk management and biological evaluation process (93/42/EEC, Annex I, Sections 7.1–7.3 and 7.5). Finally, risks must be evaluated in relation to the physical features/dimensions of the medical device (93/42/EEC, Annex I, Section 9.2). There are similar requirements in the AIMD and IVDD.

Figure 3 – Nanomedicine product development task set from conception through basic science assessment to pre-clinical proof-of-concept and then to translation for clinical use via commercialization. ADME, absorption, distribution, metabolism, excretion; Tox, toxicity; PK, pharmacokinetics; PD, pharmacodynamics; QA, quality assurance; QC, quality control; QSM, quality system management. From 'Barriers to advancing nanotechnology to better improve and translate nanomedicines', Wang, Y and Grainger, D W (2014). Reproduced by permission from Springer Nature, *Frontiers of Chemical Science and Engineering* Volume 8, pp. 265–275.



8.2 EU SCENIHR report

Following a public consultation, the EU Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) produced a report in January 2015 on the determination of potential health effects of nanomaterials used in medical devices. This report identified examples of devices consistent with those described above, spanning active and non-active, invasive and non-invasive technologies. This report advocated taking a risk-based approach by classifying devices based on invasiveness (non-invasive and invasive), freedom of the nanoparticles (free, fixed and embedded) and the potential for release (inadvertently released into the body or deliberatively intended to be released). The report also contains guidance on suitable characterization methods of nanomaterials based on the properties to be analysed and the size of the nanomaterial (e.g. transmission electron microscopy, TEM, for particles measuring a few nm compared to SEM for larger particles). The report indicates medical devices with the highest potential for release of nanomaterials are as follows:

- in which the nanomaterial is intended to be released
- that are composed of free nanomaterials
- containing free nanomaterials
- release/loosening of nanomaterials present as coatings on medical devices
- chemical breakdown or wear-and-tear processes due to (bio)degradation of medical devices
- grinded, polished or shaped during application

Exposure routes outlined include inhalation, dermal, mucosal, oral, parenteral and ocular. Criteria for classifying the risk of exposure are based on type of devices (invasiveness), tissue contact, duration of contact and freedom of the particles. This exposure can be used to inform the biological evaluation plan.

Table 1 – The timelines for the translation of nanotechnology-designed drugs and diagnostics in clinical practice

	To year 3	**To year 6**	**To year 9**	**To year 12**
Ex vivo tests and sensors (animals)	Lab research to prove concept	Trials on animals		
Ditto for humans	Ditto	Define human trials	Trials and beta product?	Sales
In vivo imaging (animals)	Lab research to prove concept	Trials on animals		
Ditto for humans	Ditto	Define human trials phase I	Further trails phase II	Trial phase III and first sales
In vivo therapy (animals)	Lab research to prove concept	Trials on animals	More animal trials	
Ditto for humans	Ditto	Define human trials phase I	Further trials phase II	Trials phase III and first sales
In vivo drug delivery (animals)	Lab research	Trials on animals	Further animal testing	
Ditto for humans	Decisions regarding device or drug?	Await animal trial results	Human trials phase 1	Human trials phases 2 and 3
Implants and tissue regeneration (animals)	Lab results	Trials on animals	Further animal testing	
Ditto for humans	Lab research	Await animal results	Human trials phase 1	Human trials phases 2 and 3

8.3 EU MDR and IVDR

The EU Medical Device Regulation 2017/745 entered into force on 25 May 2017 and there is a 3-year transition to the date of application on 26 May 2020. There are more specific and prescriptive requirements in this regulation due to 'scientific uncertainty about the risks and benefits of nanomaterials used for devices' (Whereas (15)). The definition of a nanomaterial in the MDR is consistent with the definition from 2011/696/EU noted in Section 1 earlier; however Article 3 allows the definition to be amended based on technical and scientific progress. The MDR (Article 2) also includes definitions of nanoparticles, nanoagglomerates and nanoaggregates which is consistent with PAS 71:2011.

Annex I (general safety and performance requirements – GSPRs), Section 10.6, of the MDR contains a specific requirement that manufacturers must address in relation to the chemical, physical and biological properties and reducing the risk (by device design and manufacturing processes) linked to the size of particles that can be released into the patient's or user's body, in particular nanomaterials. Medical devices containing nanomaterials will need to address this requirement in the risk management process and risk controls related to this GSPR will need to be verified in the pre-clinical evaluation.

There is also a new classification rule in the MDR (Rule 19 in Annex VIII) covering devices incorporating or consisting of nanomaterials. Classification (and hence regulatory scrutiny) depends on the risk of internal exposure as follows:

Class III	High/medium potential of exposure
Class IIb	Medium potential of exposure
Class IIa	Negligible potential of exposure

Guidance, standards and/or common specifications will need to be developed to define these levels of exposure to enable manufacturers to classify medical devices containing nanomaterials.

9 Standards and ISO 10993-22

9.1 Standards

BSI has produced a number of publically available standards (PAS) on nanotechnology including on vocabulary and terminology. ISO/TC 229 are also working on developing and publishing standards for nanotechnologies covering areas such as characterization, toxicology, risk evaluation, vocabulary, materials specifications and OHS/MSDS.

9.2 ISO 10993-22

ISO 10993 is a series of standards covering the evaluation of biocompatibility of medical devices. These standards are harmonized to the EU medical devices directives; manufacturers who comply with these standards can presume conformity to the relevant parts of the medical device directives that the Annex Z's of these standards outline. This series of standards covers the medical device biological evaluation process (Part 1), animal welfare requirements (Part 2), biological testing (Parts 3–6, 10, 11 and 20), ethylene oxide residuals (Part 7) and chemical/material characterization (Parts 9, 13–15 and 17–19).

A recently published addition to this series is the technical report ISO/TR 10993-22:2017 Biological evaluation of medical devices – Part 22: Guidance on nanomaterials. The scope of this standard covers medical devices composed of or containing nanomaterials and also medical devices that generate nano-objects either intentionally (e.g. iron oxide nanoparticles for injection and heating of tumours) or unintentionally (e.g. wear debris from joint replacement articulating surfaces or dental fillings that are polished in situ). The standard includes additional considerations in the evaluation process compared to ISO 10993-1 include:

- Surface nanostructures
- Nano-objects bound to or incorporated within a medical device; without intention to be released
- Nano-objects/nanostructures on the surface of or within a medical device; with intentional/expected release from the device
- Release kinetics (rate and quantity) of the nano-objects and contact duration of the medical device
- Potential cellular or tissue effects due to direct interaction with nano-objects/nanomaterials (beneficial or adverse).
- Characterization of physicochemical properties of the released nano-objects
- Toxicokinetics and tissue distribution of the nano-objects
- Biological evaluation of the nano-objects
- Potential of nano-objects to be generated by degradation, wear or mechanical treatment processes (e.g. in situ grinding or polishing)

ISO/TR 10993-22:2017 also has details on characterization methods (similar to the SCENIHR report discussed earlier), information on reference materials, sample preparation, release toxicokinetics (covering absorption, distribution, metabolism and excretion/elimination) and the toxicological evaluation. There are a number of challenges in the evaluation of nanomaterials due to their nature including increased reactivity, partial dissolution, aggregation/agglomeration and transformation via hydration.

ISO/TR 10993-22 advocates asking three fundamental questions when evaluating nanomaterials:

- Physical description: What does it look like?
- Chemical composition: What is it made of?
- Extrinsic properties: How does it interact with the surrounding environment?

The evaluation should be a multidisciplinary process with input from toxicologists, physical chemists, engineers and other experts. Additional considerations are shown in the following table compared to the existing series of ISO 10993 standards noted:

Table 2 – ISO 10993-22 - Key considerations and corresponding other parts of ISO 10993

General **ISO 10993-1**	• Different properties to bulk form (dose) • Nanoparticles can translocate downstream of site of administration • Crossing cellular/intracellular membrane • Interrupt DNA synthesis and other cellular functions • Interaction with proteins
Genotoxicity, carcinogenicity and reproductive toxicity **ISO 10993-3**	• In vitro testing must demonstrate exposure to the cell nucleus (DNA damage) • In vivo testing must ensure nanomaterial reaches target organ
Haemocompatibility **ISO 10993-4**	• Nanoparticles can translocate from device to systemic circulation in blood • Can induce prothrombotic effects and platelet activation • Surface area • Complement system activation – inflammatory and hypersensitivity reactions

Cytotoxicity
 	
ISO 10993-5
	• Cellular uptake
	• Cell type
	• Oxidative stress
	• Aggregation
	• Electric charge/optical properties can interfere with test
	• Dose metrics – all of the following should be documented in testing
	  • Mass concentration
	  • Surface area
	  • Number concentration

Pyrogenicity and implantation **ISO 10993-6 and -11**	• Various implantation sites • Direct injection into appropriate tissue • Controls
Immunotoxicity, irritation and sensitization **ISO 10993-10 and -20**	• Nanomaterials enter mononuclear phagocyte system (MPS) cells which play a central role in immune system • Nano-object protein complex can result in sensitization • Skin penetration dependent on size and shape
Systemic toxicity **ISO 10993-11**	• Cannot be predicted by bulk material toxicity • Potentially crossing all protective barriers including the nuclear membrane, blood–brain and foeto–placental barriers • Special emphasis on the MPS (liver, spleen), kidneys, brain, bone marrow

Summary

- Nanotechnology can be used to design novel medical devices and entities
- New methods of enhancing medical images can be achieved using nanoparticles to improve functional contrast
- Novel methods of drug delivery and new approaches to therapy and antimicrobial action can be developed
- Coatings can be designed to improve biocompatibility
- There are a number of nanomaterial-containing devices on the market (covering all classifications and technologies)
- Global regulators are aware of these and are evaluating risks and developing regulations

- Risks need to be considered and evaluated for devices which contain/generate nanomaterials
- Existing 'state-of-the-art' characterization techniques (chemical, physical, biological) used for macro materials may not be appropriate for nanomaterials

Glossary of some of the terms used in this article

FDA: The US Food and Drug Administration

Free radicals: Atoms, molecules or ions that have an unpaired electron, making them very reactive. They are especially important for inducing oxidation and being able to destroy tumours or microbes

GSPR: General Safety and Performance Requirements

IVDR: In Vitro Diagnostic Regulation

MDR: Medical Device Reporting

Liposomes: Spherical vesicles of a lipid bilayer membrane that encapsulates a fluid. The sizes could range across the nanometre to micrometre sizes

Microparticles: Particles that have dimensions of greater than 100 nm

Nanoparticles: Particles that have dimensions less than 100 nm

Nanorods: Particles that are shaped like rods, but with diameters of less than 100 nm

Nanocomposites: Composite materials that have one phase that has dimensions of less than 100 nm

Nano/microbubbles: Bubble structures in a fluid which have dimensions of <100 nm for 'nano' and >100 nm for microbubbles

Nanodiamonds: Diamond particles of <100 nm that usually have nitrogen vacancy centres that luminesce with an intensity that depends on the local magnetic field and can be used for bio-labelling

OHS/MSDS: Occupational Health and Safety/Materials Safety Data Sheets

QMS: Quality Management System

Quantum dots: Semiconducting particles with their electronic and optical properties controlled by size and show quantum size effects. They are used for luminescent bio-labelling

Surface plasmons: Oscillations in the surface electron density, usually of metal particles and usually of the noble metals, silver and gold. The plasmons give these metal particles unique colours and they can be used for bio-labelling. Surface plasmons also give rise to local high electromagnetic fields and can enhance the vibrational spectra observed by Raman Spectroscopy

Raman spectroscopy: Inelastic light scattering that can be used to identify different molecules from their vibrational spectrum

SEM: Scanning Electron Microscope or sometimes it refers to "Standard Error of the Mean"

Superparamagnetic particles: Small particles of a magnetic material can exhibit superparamagnetism such that they only show magnetic behaviour in the presence of a magnetic field. These particles are useful for enhancing the contrast in MRI and they may play a role in the killing of cancer cells via heat, when these particles are treated with electromagnetic fields

TEM: Transmission electron microscopy

UDI: Unique device identification (term used by the FDA)

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BSI (British Standards Institution) is the business standards company that equips businesses with the necessary solutions to turn standards of best practice into habits of excellence. Formed in 1901, BSI was the world's first National Standards Body and a founding member of the International Organization for Standardization (ISO). Over a century later it continues to facilitate business improvement across the globe by helping its clients drive performance, manage risk and grow sustainably through the adoption of international management systems standards, many of which BSI originated. Renowned for its marks of excellence including the consumer recognized BSI Kitemark™, BSI's influence spans multiple sectors including aerospace, construction, energy, engineering, finance, healthcare, IT and retail. With over 70,000 clients in 150 countries, BSI is an organization whose standards inspire excellence across the globe.

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