Chapter 16
Intersection of Nanotechnology and Healthcare

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16.1 Introduction – Brief Background of Nanotechnology

Nanotechnology is the engineering of functional systems and manufacturing of materials at atomic and molecular scale. Modern word *nanotechnology* is derived from Greek term 'nano' meaning dwarf. Dr. Richard Feynman, the Nobel Prize winner in Physics in 1959, is widely recognised as the "father" of the subject, but the term *nanotechnology* was formally introduced by Professor N. Taniguchi in the year 1974 who defined nanotechnology as "the processing of separation, consolidation and deformation of materials by one atom or one molecule" [1]. Nano in the International Systems of Units (SI) is known as one billionth of a meter (10^{-9} m). The size of a structure to be classified as 'nano' usually needs to be roughly between 1 and 100 nm (nano-meter) in size at any one dimension. Regardless of the size restriction, nanotechnology implies to any structures that are developed by top-down or bottom-up engineering of individual components even if it is several hundred nanometers in size [2]. The top-down fabrication is normally applied for achieving nanometric precision and accuracy in an artefact by material removal or

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deposition (e.g. nanolithography and energy beams). In comparison, the bottom-up fabrication is a technique used for assembling components of nanometric or sub-nanometric size in creation of an artefact with functions such as molecular assembly or manipulation. According to the National Nanotechnology Initiatives (NNI), defining features of nanotechnology are as follows [3]:

- Any research and technology involving development at 1–100 nm range.
- Creation and usage of structures that have novel properties because of their size.
- Ability to control and manipulate at atomic scale.

Nanometre sized objects possesses remarkable and noble properties such as self-assembly and self-ordering under control of forces which macro objects are not capable of doing [4]. The unique features of nano objects make nanotechnology feasible for altering and improving properties and performances of conventional objects and products.

16.2 Healthcare

Healthcare is the diagnosis, treatment, and prevention of disease, illness, injury, and other physical and mental impairments in humans. It is one of those sectors in any place of any country in the world that is always looking for ways to improve and out perform their existing records. Healthcare is also among the highly invested sectors publically or privately in most of the countries since the health of a citizen is directly related to the country's level of development and progress. According to the official information supplied by the National Health Service (NHS) which is one of the largest publically funded services in the world, around £108.9 billion was budgeted for the financial year of 2012/13 in the UK [5]. This shows the calibre of healthcare investment required in order for it to function smoothly. It also shows the potential and opportunity it holds to cut down the running cost yet maintaining the quality of service or even improving it.

Nanotechnology comes into association with healthcare in various known or unknown forms. For example, one of the most well-known or prominent services where nanotechnology could contribute and aid is the imaging service/technology, such as X-rays, MRI (Magnetic Resonance Imaging) scan, and CT (Computerised Tomography) scan. According to the statistical data released from the Department of Health in the UK, the total number of imaging examinations or tests was 40.1 million during the period of 1st April 2011 to 31st March 2012 (DH, [6]). That is a total of 3.3 % (1.3 million tests) increase in the amount of examinations performed in comparison to previous year 2010–2011. Among those, X-rays (radiographs) totalled to 22.5 million, ultrasound of 9.0 million, CT scan of 4.4 million, MRI scan of 2.3 million, fluoroscopy of 1.3 million and 0.6 million were radio-isotopes. This is just an example of a fraction of the entire healthcare service provided but the amount is ample enough to demonstrate the scale of operation.

16.3 Advances of Nanotechnology in Healthcare

From engineering to designing, environmental science to textile manufacturing, many fields are able to change and benefit from a novel technology, such as nanotechnology, that is garnering pace and success at an incredible speed. Healthcare is no stranger to such revolutionary technology either and the conjugation of nanotechnology in relation to medicine is favourably named 'nanomedicine'. Nanomedicine has brought many commendable advancements in healthcare and what seemed like scientific fiction a few years back is now almost within grasp of reality. Among various fields of medicine, the pharmaceutical industry is the most adaptive, evolutionary and fast paced one getting into holds with precognitive and innovative idea such as nanotechnology, and has made a significant breakthrough as well. Nanomedicine at present is a profound part of pharmaceutical industry and is making a major breakthrough in medicine.

16.3.1 Applications of Nanotechnology in Imaging

Molecular imaging is an emerging technology which intends to improve the accuracy of disease diagnosis, and the association of nanotechnology has aided molecular imaging to further have the capacity of disease pathology characterisation. This has been achieved by using a number of nanoparticles (NPs), such as liposomes, dendrimers, gold, iron oxide and perfluorocarbon NPs, which are very sensitively and selectively responsive to specific disease [7, 8]. In addition, in combination with other advantages such as small size, high surface area to volume ratio, long circulating hour, high affinity for target tissue, easy production, less toxicity and immunogenicity, it makes NPs highly attractive to be used as the contrast agents [9, 10]. For example, tailored NPs (e.g. dendrimers) could be used as advanced contrasting agents for MRI scan by shortening the spin–lattice relaxation time T1 and spin-spin relaxation time T2, resulting in sharper and brighter images. Herein, T1 and T2 are two different types of MRI scans that help differentiates types of abnormalities in accordance to density. T1 is effective in imaging solid organ pathology (e.g. liver and spleen), whereas T2 is effective in imaging soft tissues. Furthermore, the NPs (e.g. iron oxide NPs) that have superparamagnetic properties are able to change the spin-spin relaxation time of neighbouring water molecules. Thus, they could be applied to monitor the expression of genes, detect tumours, artherosclerotic plaques, and tissue inflammation, etc. The NPs can also be targeted actively or passively in favour according to the subject of interest to differentiate normal and diseased tissues.

Furthermore, NPs could have multiple binding sites which increases affinity for target tissues immensely [10]. Intracellular imaging is possible with NPs like quantum dots which have high-fluorescence intensity making it easier for tracking of cells throughout the body. They are more desirable then conventional fluorescent since they are more stable, allowing images to be sharper and crisp over long period

of time. In addition, they have the ability to detect multiple signals at the same time [11]. They emit bright lights which mean small amount of quantum dots can be sufficient to produce desired signal which makes them promising candidate for detection and diagnosis of various diseases. Due to their small size it is easier for them to enter and interact with biomolecules within the cells.

Atomic force microscopy (AFM) is another powerful tool for imaging which incorporates nanotechnology providing results with high-resolution and three-dimensional images [12]. An AFM functions with a microscale cantilever which has a sharp tip, used as a probe to scan specimen surfaces under focus. Deflection of the probe is detected and recorded as a result which happens due to the presence of attraction and repulsion force between the close contact of probe and surface of the specimen which is normally within 1–10 nm in distance. Deflection of the probe is quantified by the beam bounce method where lasers beam on top of the cantilever into range of photodiodes providing a three-dimensional profile of the specimen on scan. The development progression in AFM has allowed tumour detection, detection of erythrocytes influenced by diabetes and studying the structure of C-reactive protein that are a risk for coronary artery disease and peripheral arterial diseases [12]. Also the application of nanotechnology in molecular imaging is giving ways for further development of specialised medicine like personalised medicine and is sure to bring about a huge revolution and transform the way of disease diagnosis, treatment and prevention.

16.3.2 Applications of Nanotechnology in Drug Delivery

When talking about nanotechnology in healthcare, drug delivery system is one of the most conspicuous topics that attract a huge amount of interests from both civil society and industry. Pharmaceutical company's quest to develop targeted drug delivery systems with existing drugs whilst incorporating nanotechnology for effective medical treatment is evolving on daily basis. Effective drug-targeting system based on therapeutic efficacy, appropriate concentration and longer circulation time, could be achieved by utilising nanotechnology [2, 7, 13, 14]. For example, nanoparticles (NPs) could be employed to deliver drugs to specific types of cells (e.g. cancer cells) whilst overcoming barriers such as heat, light and various physiochemical environments. These NPs are engineered in specific way such that it is able to adhere to targeted diseased cells and delivers direct treatment to those cells alone. They could further help to reduce damage to healthy cells significantly, decrease side effects and even allow earlier detection of diseases.

In terms of the improved drug delivery system via a better and innovative formulation, some drug nanocrystals have already been commercially developed [15]. For instance, Elan Nanosystems developed a process called nanonisation to solve the problem of poor water solubility of a drug. This was achieved by reducing the drug crystals until they became particles of 400 nm in diameter or less. A thin layer of polymeric surface modifier was used for absorptions onto the crystal surfaces to

prevent aggregation and for stabilisation of the particles produced. The result was a suspension that looked and functioned like a solution which can be used in various forms of dosage such as pills, sprays or creams.

Researchers in Kyoto University developed a smart drug that got activated in specific circumstances [16]. In this case, the novel drug molecule released antibiotic only in presence of an infection. A molecule of gentamicin was bound to a hydrogel with a peptide linker which is cleavable to a proteinase enzyme produced by *Pseudomonas aeruginosa. Pseudomonas aeruginosa* is a common bacterium that can cause disease in animals and humans. This smart drug was tested on rats, which showed that in presence of a bacterium, the enzymes produced by the microbes cleaved the linker releasing gentamicin which then killed the bacteria. But in the case where there was no presence of bacteria or the enzyme produced, the drug remained unaffected.

Freitas Jr Robert A. designed a spherical nanorobot the size of a bacterium and made up of 18 billion atoms which were arranged precisely in a crystalline structure to form a miniature pressure tank (Freitas Jr, [17]). The design was of an artificial red blood cell called respirocyte. The miniature tank would hold as much as nine billion oxygen and carbon dioxide molecules. When the artificial blood was to be injected into an individual's bloodstream, the sensors on the surface of the robots would detect the level of oxygen and carbon dioxide in the blood and signal the time to load oxygen and unload carbon dioxide and vice-versa. These nanobots could store and transport gas 200 times more than red blood cells and also consists of glucose engine which releases glucose when there was a deficiency in the body. Even though this is a conceptual idea, there have been uses of artificially engineered microbes already to produce human hormones. Such example is incorporation of human DNA in the genome of bacteria which then starts producing human hormones used for curing endocrine diseases.

16.3.3 Applications of Nanotechnology in Gene Delivery

Nanotechnology has been applied in gene delivery with help of NPs such as liposomes and dendrimers [14, 18, 19]. In able to be successful in this venture, understanding gene therapy is important. Gene therapy is a technique which involves altering, removing or inserting gene at particular loci in order to treat various genetic disorders. In order to do so, a factor able to transfer the gene to a desired location is required which is known as a vector. A vector can be viral or non-viral of origin and mostly includes retroviruses, adenoviruses, lentiviruses and adeno-associated viruses which are very useful in utilising the natural mechanism of an infection [7].

Gene delivery replaces defective gene with a normal one or delivers genes into the disease cells to cure and treat diseases. It was applied as a method to treat hereditary diseases earlier but now have been proven very helpful in treating diseases like cancer. Even then, there are certain limitation points that the technique faces which have been able to overcome by help of nanotechnology, with introduction of non-viral

vectors like liposomes and dendrimers which are less immunogenic than the conventional viral vectors. The properties that NPs behold which make them better vectors than currently used vectors are as follows [20, 19]:

- They are cationic in nature and encapsulates negatively charged DNA by electrostatic interactions;
- Safe and simple in use;
- Easily reproducible;
- Even with decreased efficiency in transfection compared to viral vectors, adjustments are easy to make which overcomes the shortcoming.

Dendrimers are known for being efficient in gene delivery and have the ability to protect DNA from the action of DNAse enzyme. The transfection efficiency can be increased by performing heat treatment with solvents like water and butanol which enhances flexibility, allowing dendrimers to become compact when compounded with DNA. The dendrimer that is most commonly used is Polyanidoamine (PAMAM) because it has the highest transfection efficiency [14, 19].

Another such use of NPs, as gene delivery carriers, are liposomes which have certain advantages [19]. Their size can be easily controlled and modified to add a targeting agent but they do have a downfall of having low efficiency in encapsulating DNA. However, the issue of low efficiency can be solved or avoided by using cationic liposomes because they consist of lipid bilayers which are positively charged and combine spontaneously with the negatively charged DNA. The liposomes are mixed with cholesterol and further modified with functional ligands to increase transfection efficiency.

16.4 Impacts of Nanotechnology on Healthcare

The Impact of nanotechnology is extending, from medical, environmental, biology, computing, material science to even communications and military applications. Even though nanotechnology is showing promising development and positive results are being demonstrated steadily, the fact that it is still an emerging field which cannot be blindsided easily. The sole fact that it is an emerging field has roused numerous heated debates about the extent till where the technology benefits and the risks for human health it may bear. Based on the impact of nanotechnology on human health strictly, the subject could be divided into two categories: (1) Potential of nanotechnology holds for innovative medical applications in curing diseases; (2) Potential health hazard it may pose with exposure to nanomaterials. The sustainability of nanotechnology would thus depend on social acceptance, minimised risks and maximised benefits.

The biggest concern related with nanotechnology in regards to its applications in healthcare would be the unknown outcome when exposing to nanomaterials. Due to the scarcity of systematic studies and established regulations, nanotechnology is not easily accepted by many fields even with its promising and positive results.

Healthcare is in no exception since it holds responsibility of millions and billions of people and their health with any small decision they make that has anything to do with treatment, diagnosis and cure. Showing promising results is still not convincing enough for medical society to accept nanotechnology without hesitance because of the technology lacking long documented track record like those of conventional and traditional technologies. Nanotoxicity is being pursued with rigorous pace and through experimentation but it still is not being able to reach the standard required by many healthcare organisations. Especially with the case like asbestosis where the symptoms usually appeared 30-40 years after the exposure period when the damage was catastrophic and unmanageable, the requirement for a more comprehensive investigation of nanotoxicity in relation to nanomaterial exposure is urged and becomes imperative in healthcare.

16.4.1 Nanotoxicity

Materials possess very different properties in comparison to their initial bulk form, such as surface area, surface properties and chemical properties. These different properties have intrigued many scientific innovation and experiments which have made many ground-breaking progress over the years. Nanomaterials have some unique properties in comparison to their larger counterparts due to the quantum size effects and large surface area to volume ratio. Hence, manipulation of substance at nanoscale will have variety of effects in manufacturing, engineering, environmental technology, information technology, health, pharmaceuticals and many other industries. In other words, the resulting nano-sized materials may offer a safe solution or pose a threat to the environment and to human beings [21]. Since there still are no sufficient data available for identifying, monitoring, and controlling the toxicity of nanomaterials, this concern gets brought upon time and again by environmental activist and regulatory bodies, etc. [22].

With respect to our body system in particular, nanomaterials which are very fine could easily be inhaled. They can re-disperse within body to different organs after initial stage of introduction inside the body. Some of the routes which nanomaterials adapted to enter the body are as follows [23, 24]:

- Respiratory system
- Ingestion
- Dermal exposure
- Medical implants (e.g. orthopaedic)

Since there is no cut-off point below about which particles are suddenly classed harmful, in relation to NPs, two factors in mixture may determine the potential harm caused (esp. in lung injury).

1. Large surface area and reactivity of the surface
2. Smaller particles which are more likely to be harmful

Once NPs are inside the human body, they could mix with blood during gas exchange and get transported to different organs of the body during circulation. They could get deposited even in nervous system due to their ability to overcome the blood brain barrier. Collectively, some in vitro studies have already identified that the oxidative stress related changes of gene expression and cell signalling pathways may underlay the toxic effects of NPs [24, 25]. Similar effect in role of transition metals and certain organic compounds on combustion generated NPs were also found [25, 26]. Recently, according to Health and Safety Executive [27] nanomaterials are classified hazardous under following criteria:

- Thinner than 3 μm
- Longer than 10–20 μm
- Biopersistent
- Do not dissolve/break into shorter fibers

16.4.2 Nanopharmaceuticals and Food and Drug Administration (FDA)

Lots of pharmaceutical companies are in trouble with patent expirations on numerous 'blockbuster' drugs, resulting in a loss of multi-billion dollars [28]. There has been an argument over big pharma companies being more focused on shareholder profits than innovative therapies. In today's global economy, big pharmaceutical companies face huge pressure to deliver high-quality products while maintaining profitability. Because of this rising issue, nanotechnology has been applied by numerous pharmaceutical companies to revisit their shelved drugs that were difficult to formulate due to their solubility profiles. The existing nanopharmaceuticals in market that have been approved by the FDA are in absence of any special testing in accordance to the pre-existing laws [28, 29]. However, the approval of new nanodrugs and 'nano-reformulations' has challenged FDA's regulatory framework, which as forced FDA to evaluate submitted products for market approval on the category based-system. A drug, biologic or device has been assigned to Centre for Drug Evaluation and Research (CDER), the Centre for Biologics Evaluation and Research (CBER) or the Centre for Devices and Radiological Health (CDRH) for evaluation respectively. Certain therapies which comprises of two or more components (drug, biologic or a device) that are physically, chemically or otherwise combined or mixed to produce a single entity is 'combination entity'. However, this arrangement has resulted in inconsistency when approved by the FDA in basis of category-based approval which had been deemed "arbitrary and capricious". With issues such as this, nanopharmaceutical is more likely to complicate the combinational products with potential to further blur the lines in distinguishing these categories [29]. In addition, nanopharmaceuticals may also present safety issues for FDA knowing the unpredictable nature of interactions between nanoparticles and biological systems since the surface charge and shape associated with a NP is known to influence its

toxicity. Another particular safety issue to be raised by nanopharmaceuticals is the potential for bioaccumulation of NPs with prolonged use [28]. For example, buckminsterfullerene has shown to impair DNA repair mechanism with additional report of certain NPs shown to cause brain damage in fish and lung toxicity in mice.

16.5 Regulatory Challenges to Nanotechnology

Application of existing regulatory frameworks and space for tailoring rules implementing new technologies and products development is questionable when it comes to nanotechnology. This puts pressure on regulators capacity to keep in pace with developments such as nanomedicine and other new applications. Difficulties arise in balancing technological benefits to risks for expertise in regulatory bodies. New innovations such as nanotechnology require practical regulators, who are able to facilitate responsible development in order to gain trust of stakeholders for such areas to prosper.

As a fact, the knowledge gaps in product formulation and concentration of NPs have raised questions about the applicability of European regulations on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) [30]. Another debatable issue involving nanotechnology is to do with uncertainty and ambiguous risk that rise dilemma in regulators on either to wait until there is sufficient knowledge available or to act promptly. Another knowledge gap in nanotechnology is to do with the toxicological aspect of nanotechnology and the potential risk it pose on health and environment, which challenges safety regulations to its limit. As recorded, toxicological studies conducted with NPs have indicated that free NPs could penetrate through the blood–brain barriers or remaining lodged in capillaries [25]. There has been prediction for possible impact of these particles on immune system and consumption by macrophages. Uncertain biocompatibility imposed by NPs in relation to it being used in medical products and materials is another challenge on its own. It has been evaluated that the toxicological risks of NPs depend on material properties, exposure route, dose and frequency of doses which accounts for risks with usage of NPs among other things such as distribution of particles in the body [24, 25]. Even worse, further toxicological risks of NPs are yet to be known. Previous drug disaster in late 1950s with thalidomide, of which effects are still being projected till today, regulation bodies have thereafter ensured to higher the level of public health protection in terms of safety, efficacy and quality.

16.6 Rules Governing Nanomedicine

There is still no specific rule regarding nanomedicine by the European Union to date. Having said that, nanopharmaceuticals have been classed as advanced therapy medicinal products and can only be approved by centralised procedure. In cases

where nanomedicinal products are in combination with medical devices and/or regular medical products, certain aspects of regulatory regimes for both medical devices and pharmaceuticals apply, regardless of the manner in which the other features have been combined in the product [30]. The application of regulatory regime depends on the category in which the product falls in regards to the definition of medicinal products, advanced therapies medicinal products or medical devices. The primary mode of action depends on the criteria in which the products falls majorly in application to the regulatory regime. The market authorisation depends on positive outcome of risk-benefit balance. Applicant must be able to demonstrate sufficient product safety, quality and efficacy in comparison to large set of objective scientific data. It is mandatory for scientific evaluation of applications to be based on highest level of expertise and standards.

16.7 Marketing Prospects of Nanotechnology

Nanotechnology is bound to have a substantial impact on the world's economy and market volumes, which are a good indicator for such economic significance. Despite all the controversies and hesitance in its acceptance, if successful the technology will contribute substantially. There were plenty of market forecast originated for nanotechnology during the early 2000s with timeline going up to the year of 2015. Among all, the best compiled forecast has to be the one published by the National Science foundation (NSF) of US in 2001. The NSF forecasted that the estimated world market of nanotechnology would worth 1 trillion US dollars by 2015 [31]. In addition, by combination of other technologies, nano-enabled products and markets are expected to be of the largest share in the world. Nanotechnology has already been attracting significant amount of investments from government and various business communities around many parts of the world. In 2007, it was estimated that the total global investment nanotechnology held was around five billion Euros of which two billion Euros were from private sectors [32].

In addition to the booming nanotechnology assisted market, there was also a remarkable increase in published patents of nanotechnology, which ranged from 531 total patents in 1995-1976 total published patents by 2001 (Royal Society [33]).

16.8 Public's Concern & Prospects on Nanotechnology

It is evident that nanotechnology have bought about remarkable differences in ways of diagnosis, patient care and other medical and non-medical implications, yet it has not been able to establish itself in full positive light within the general public's eye due to the lack of communication in interpretation of it. There are very few studies that have been carried out about the media coverage of nanotechnology [34]. Mass media plays a significant role in shaping public attitude towards nanotechnology or

any other field of discovery and development since they are the major source of information to the general public. According to a survey conducted in the US and the UK, some common conclusions were drawn [34]:

- Media interest in nanotechnology has grown immensely since 1999 and in 2003 it began spreading from opinion-leading elite press to the general press hence addressing wider population;
- Media coverage of nanotechnology throughout the period of analysis (1984–2004) has been overwhelmingly positive although there are articles about risks nanotechnology bear;
- Majority of media had presented nanotechnology in terms of progress and economic prospects.

Even when media has been positive towards nanotechnology, the public can be more sensitive to possible impacts of new technologies. A good example of it is the toxicity of NPs. The word 'nano' has been embedded in the national consciousness and is an area of public debate and often concern. From scientific fictional tales of self-replicating 'nanobots' engulfing the word to legit concerns on effect of NPs used in everyday products such as sun creams, it is inevitable for nanotechnology to be out of public view. Factors such as emotive, ethical and political implications also come in to play a major role. One of the best known example of such an issue is the stem cell research. It has managed to gain the highest scientific profiles in both medical community and the general public in the past decade.

Due to the novelty of the technology, a full acceptance is yet to be achieved and acknowledged. Main concern lies in public's view on the development and effective way to convey the novel method. It always is our human nature to have curiosity around new subject and have the expectation to know more about it. There are a few of ways where the message can be conveyed efficiently as follows [34]:

- Learning from previous cases, avoid the same mistakes;
- Aim to elucidate the public's knowledge and attitude towards the technology;
- Public workshops;
- Focus groups;
- Sources that give further information about genuinely considered beliefs of public towards nanotechnology instead of currently uninformed opinions;
- Assessments of nanotechnology as positive and major benefits, especially from health application of nanotechnology;

On the other hand, from the academic point of view, there are also a few of things which could help to dilute the issue and enhance a better future for nanotechnology, including nanomedicine in healthcare [34]:

- Possible ways to deal with inherent uncertainty concerning the potential impacts and future developments;
- Urge the governmental bodies as well as industry to take decisions for the benefit of general public;
- The potential risks and risk management of nanotechnology.

16.9 Conclusions and Future Perspectives

Nanotechnology has come up with many solutions to previously unsolved pharmaceutical, medical and technical problems. It has revolutionised healthcare with its contribution to the betterment of biomarkers, imaging, drug discovery, development and delivery, etc. The applications of nanotechnology in healthcare thus have been growing exponentially, along with increasing interests in investment from both government and industry [35].

However, in healthcare, the unique and novel properties of nanomaterials could become a particular issue in regulatory department due to insufficient information of their toxicity profile and being very different to regular pharmaceuticals. This has caused dilemma among expertise in regulatory body to categorise the nano-related products before getting evaluated for the market approval. The line among many categories are merged and blurred when coming to evaluating nanopharmaceutical. The knowledge gaps on the subject and lack of expert in the field employed among regulation institutes has also created numerous obstacles.

It has also been shown that the public awareness and understanding of nanotechnology in healthcare is still immature and sometimes may be biased and prejudiced due to the concerns of nanotoxicity. Meanwhile, the use of nanotechnology may be promoted too extensively in a sense that it becomes a hype far detached from the reality [36].

Despite such dilemmas, there is no doubt that the future of health will be closely interlinked with developments in nanotechnology which is being used in an evolutionary manner to improve and/or replace many existing therapeutics and healthcare products. It shouldn't be a surprise that in the near future we will have smart 'nanobots' which could be safely be taken by the human body and then automatically repair or destroy specific diseased cells/tumours.

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