

NANOTECHNOLOGY: A REVOLUTIONISING
VACCINE DELIVERY SYSTEM

BY

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PASS WITH MERIT

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Abstract:

This paper explores the marrying of two of the most remarkable discoveries by man: Vaccination and Nanotechnology. Vaccination has existed in some form since 900AD, whilst the principles of nanotechnology began to be explored from around 50 years ago. There has been an explosion in the number of applications of nanotechnology as more developments have occurred and this paper looks into how the delivery of drugs and in particular vaccines could be revolutionised by this technique and the impact this can have on a world wide basis.

Introduction

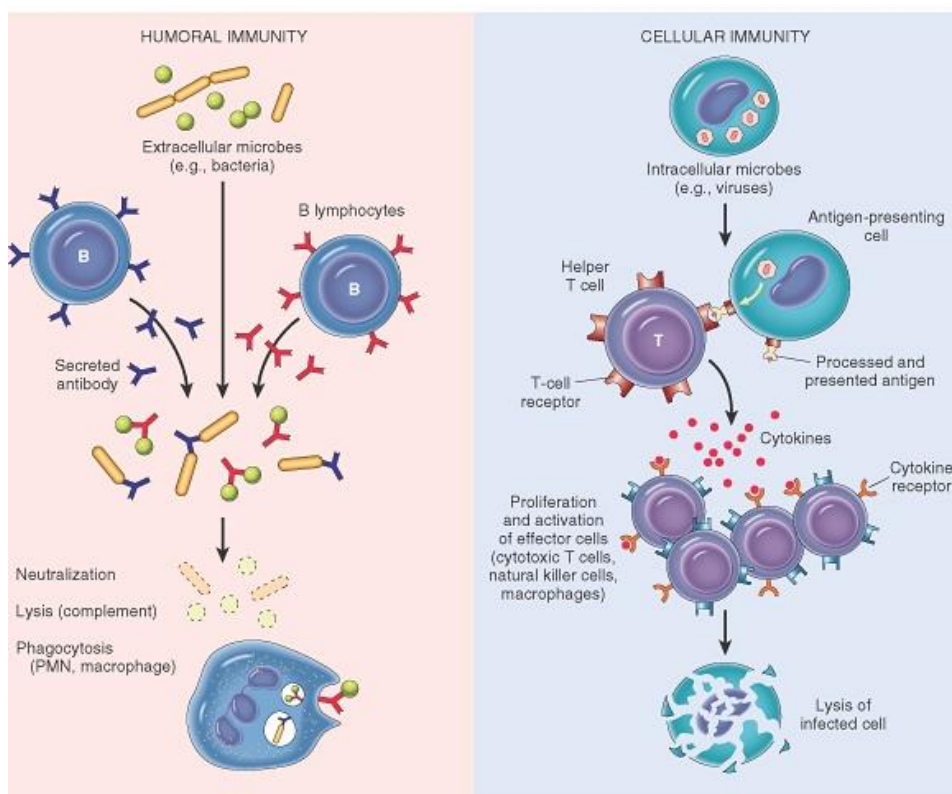
Since vaccination was first introduced it has been one of the most effective medical treatments around the world. Nanotechnology involves the use of materials in the region of several hundred nanometres in dimension and in combination with the current vaccine delivery systems, could revolutionise health care.

Development of Vaccines

Inoculation was initially discovered in a primitive form by the Chinese around 900AD, in the form of variolation. This was used as a method of protection against smallpox, and involved bringing healthy patients into contact with powdered smallpox scabs, who would then usually develop a mild form of the disease and become immune to the disease. This method reduced the mortality rate from around 20% to 2% and due to its effectiveness began to spread around the world. In 1721, the practice was first introduced in England from Turkey, and gained popularity throughout Europe in the 18th century. Several scientists tested the possibility of other methods of immunisation against smallpox, including using cowpox, but the largest breakthrough was Edward Jenner's famous experiment in 1796. Jenner's new vaccination method was significantly safer to use, and by the 1800s began to gain support, and started to spread around the world. Despite opposition, and doubt over the effectiveness of vaccination, new vaccines began to be developed, and over the next 100 years other scientists such as Louis Pasteur began to develop more of an understanding of how diseases and the immune system worked. In the 20th century, vaccines for diphtheria, tetanus, pertussis (whooping cough), and tuberculosis (TB) all became available. The polio vaccination was introduced into the UK in the 1950s, rapidly reducing the number of cases significantly. In 1956, the World Health Organisation (WHO) launched a global drive to eradicate smallpox and in 1980, smallpox the plague which had ravaged the world for the previous millennium was eradicated. 3 years ago, a vaccine was developed to protect against HPV, and ultimately cervical cancer and the cervical vaccination programme began.

The Human Immune System

Humans have developed a natural immune response involving white blood cells: Phagocytes and Lymphocytes. Firstly, any antigenic material (foreign material which triggers an immune response) which enters the body will trigger the non-specific response and will initially encounter the complement system. This is a system of proteins, which: trigger inflammation; attract phagocytes; coat the pathogens to allow phagocytes to digest them more easily; and directly kill the pathogens. Phagocytes will then help to protect the body further by ingesting pathogens, in the process of phagocytosis. In this process, the pathogens are engulfed, and enzymes within the phagocytes then digest the cells.



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Figure (1) Lymphocyte Mechanism

Lymphocytes make up the specific aspect of the immune response which is much more important with regards to long term immunity. This is the principle upon which vaccinations depend. There are two types of lymphocytes, each of which is associated with its own immune response: T Cells, which make up the cell-mediated response; and B cells, which are associated with humoral immunity.

Helper T cells are activated when antigenic material is presented to them (often by phagocytes, which present the pathogens' antigens on their surface when they engulf the pathogens). These activated Helper T cells then produce cytokines (which assist the immune response) and stimulate

other T cells to divide and produce other T cells, most importantly: Killer T cells and Memory T cells. Helper T Cells activate Killer T Cells and B Cells, as well as increasing the effectiveness of phagocytes. Killer T Cells attack cells infected by the pathogens and kill them by apoptosis (the process of programmed cell death). Finally memory T cells circulate in the blood in readiness for future infection by the same pathogen. B Cells are activated by Helper T Cells, after being presented with antigens; processing them; and then presenting the antigenic material on their surface. Once activated the B Cells then divide, and produce several cells, most importantly, Plasma Cells, and Memory Cells. Plasma cells produce large numbers of antibodies, which are extremely important in killing pathogens. The antibodies do this by: producing chemicals, which attract phagocytes, marking the pathogen for ingestion; and directly killing them with the aid of some of the complement system's components. The antibodies also cause clumps of pathogens to form, through agglutination, which allows them to be ingested more easily by phagocytes. Memory cells circulate in the blood, in readiness to divide rapidly and produce more plasma cells in the case of re-infection and are crucial in the process of vaccination, as these cells are produced during vaccination to provide immunity.

Vaccine Mechanism

Active Immunity:

Vaccination involves introducing antigenic material, in the form of attenuated or dead strains of the virus or bacteria, into the patient, to stimulate the production of memory cells. These cells will then circulate in the blood, and will generate a significantly more rapid and intense response, if the body is re-infected with the same pathogen. This therefore means that vaccination provides immunity to a disease for a patient, for a period of many years (the lifespan of the memory cells). Some vaccines may require 'boosters', which involve introducing the pathogens' antigens to the immune system again to stimulate the production of more memory cells.

There are currently several vaccine types.

Inactivated vaccines contain infective organisms which have been killed by heat or chemicals. They are very safe and stable with few side effects. Their modified structure however means that they may not mount as good an immune response. Examples of inactivated vaccines are the poliovirus and influenza vaccines.

Live attenuated vaccines contain organisms which have been altered to reduce their virulence, so they can mount a strong immune response without causing illness. They may cause some mild symptoms if an

individual has a weakened immunity. Examples of live attenuated vaccines include the MMR and varicella vaccine.

Conjugate vaccines link an antigen to a protein carrier. They allow poorly immunogenic vaccines to be more powerful. Examples of these include the Meningococcal and Haemophilus B conjugate vaccines.

Subunit vaccines rely on tiny components extracted from the microbe to be used as the vaccine. They are usually dependant on adjuvants which are required to stimulate immunity. They cause few side effects. Examples of this type of vaccine include the Hepatitis B vaccine.

Recombinant and DNA vaccines are still in the experimental stage and utilise genetic material extracted from the organism in the formation of the vaccine.

Passive Immunity:

Passive immunity involves the administration of antibodies from an external source to an individual at risk of exposure to an infection. As the antibodies are not made by the individual himself, it is broken down after a short period of time by the body and not replaced. It is useful in providing short term immediate protection. Examples of these vaccines are immunoglobulin for Hepatitis B and Varicella.

Passive immunity can also be acquired naturally for example when a foetus receives IGG antibodies through the placenta from its mother and when IGA immunoglobulin is passed to the baby through breast milk.

Vaccine delivery systems

Vaccine delivery routes are traditionally parenterally (by injection). The vaccine is usually stored between 2°C and 8°C. The cold chain must be maintained during transport and storage or else the potency of the vaccine may fail. The vaccine is given by a syringe and needle by an appropriately trained health professional, usually a doctor or a nurse. The injection is either given in the deltoid muscle of the arm or the anterolateral thigh. The injections are usually given intramuscularly or subcutaneously except for the BCG which is given intradermally. Many vaccinations will need 1 or 2 follow up injections at various intervals to maintain immunity.

Administration of vaccines via the mucosal lining is not common. Oral vaccines such as the oral polio vaccine and the rotavirus vaccine and nasally administered vaccines such as the influenza vaccine are rarely used. These vaccines are cheaper and simple to administer but run the risk of being inactivated by enzymes in the mucosal lining. They can also cause adverse reactions. For example, in the case of the oral polio vaccine, there is a small chance that the vaccine could cause polio in the patient, as well as in close contacts.

History of Nanotechnology

Nanotechnology may have been used unwittingly by humans for thousands of years, in a variety of forms, including within steel. However, the first principles of nanotechnology were first touched upon by James Maxwell, with his thought experiment Maxwell's Demon. The first measurements on a nano-particle level were conducted by Richard Zsigmondy, who was also the first to use nanometres to measure particle sizes. There were many further developments in characterising nanomaterials over the next number of years. The concepts were again brought up, in 1959, by Richard Feynman in his famous talk, 'There's Plenty of Room at the Bottom', which suggested a process by which individual atoms could be manipulated by using precise tools to build smaller sets, continuing down to the required scale. The term nanotechnology was first defined by Norio Taniguchi in a 1974 paper, and in this year, technology for depositing layers of single atoms was also developed. In the 1980s, Eric Drexler explored the concepts of dealing with individual atoms and molecules in depth. Also in this period, several major experimental advances were made. Firstly, in the early 1980s, the Scanning Tunnelling Microscope (STM) was invented, and Cluster science began. (The STM allowed individual atoms to be seen, and even manipulated, and cluster science involves the understanding of small multi atom molecules). Following these discoveries, fullerenes were discovered in 1985, followed by carbon nanotubes several years later. These were some of the most major discoveries, and have particularly useful applications within medicine. In the early 1990s, the synthesis and purification of large number of fullerenes was discovered.

Applications of Nanotechnology

Most applications of nanotechnology rely on a change in the physical properties of the material, when it is shrunk. In many examples this is the significant increase in the surface area to volume ratio of the material. Furthermore nanoparticles can affect the mechanical properties of a material, when in bulk, for example it's elasticity. Polymers reinforced with nanoparticles can also be strengthened significantly, and can be used as a lightweight replacement for metals. These improved polymers can be used to improve functionality and stability of the materials in which they are used. As nanotechnology is concerned with manipulating matter on a nanoscale, it is not surprising that it is sure to have applications within almost all areas of human technology. Within medicine, the main areas which have been suggested to develop nanotechnology within are: diagnostics; drug delivery (the focus of this paper); and tissue engineering.

Discussion

Nanotechnology will impact into almost every aspect of medicine, and in this discussion, I will look at the ways in which it will affect vaccine delivery.

New Vaccine Delivery Systems

Currently most vaccines are delivered parenterally, but nanotechnology could eliminate the use of a needle and syringe. The main principles which would allow the vaccines to be delivered without injection, involve the use of Buckyballs, and Carbon Nanotubes.

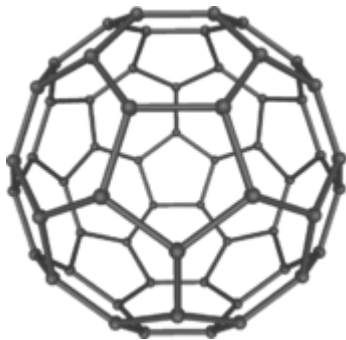


Figure (2) Buckminsterfullerene (C_{60})

Buckyballs are a spherical form of fullerenes. A fullerene is any molecule composed entirely of carbon in the form of a hollow sphere, ellipsoid, or tube. Buckminsterfullerene (C_{60}) is the most common buckyball and was the first fullerene to be discovered in 1985. Currently, Buckyballs with up to 100 carbon atoms are commonly obtained, but, Buckminsterfullerene is the most stable buckyball currently available.

It has also been suggested that Boron Buckyballs would be more stable than those made from carbon. Buckyballs could potentially be used to deliver vaccines to patients by attaching the pathogen cells directly to the Buckyballs. This would be particularly effective with viruses, as they are significantly smaller than other pathogens, and would therefore be able to be delivered through an alternative system than injection.

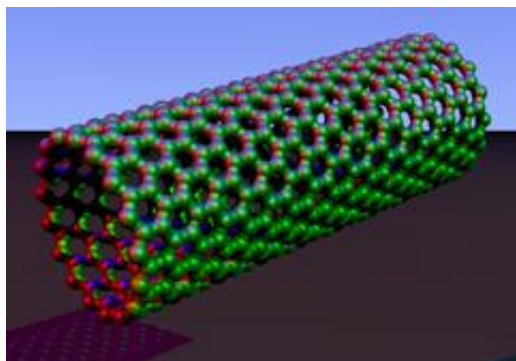


Figure (3) Carbon Nanotubes

Carbon nanotubes are cylindrical fullerenes, which consist of a single carbon atom thick strip of carbon (in the form of graphite) coiled to form a tube. These tubes often have an enormous length (up to several millimetres) in comparison to their diameter (a few nanometres).

These nanotubes conduct electricity, and as a consequence they have a wide range of applications, within medicine, especially in scanning. With regards to drug delivery, 'megatubes' may prove more useful. Megatubes

are nanotubes with a significantly larger diameter than normal nanotubes (up to 5 μ m). These megatubes therefore allow molecules to pass through them, and could potentially be used to improve the existing injection delivery system, in addition to being used in nanopatches.

One potential way to produce these nanotechnology vaccines would be through the use of diblock copolymers, consisting of one hydrophobic and one hydrophilic block. The copolymer would be mixed with the vaccine, in an organic solvent. A small amount of this solution would then be added dropwise to water. At the boundary of the water and the pathogen, the copolymers reassemble around the pathogen, with the hydrophobic blocks stabilised by the hydrophilic blocks, leading to the pathogens being encompassed, by the copolymer. This polymer coating can then be surfaced, for example with antibodies which would allow specific targeting for the vaccine. This method is currently being developed for targeted cancer treatment, but could easily be applied to other areas of drug delivery.

Using these principles, I have proposed several potential new delivery systems for vaccines.

The first potential delivery system would be oral-based. The vaccine could be delivered orally, by producing tablets containing nanoparticles attached to the pathogen. These nanoparticles could also have antibodies or other targeting substances to guide them to specific areas. The nanoparticles would be small enough to diffuse across the walls of the upper digestive tract so would therefore be able to enter the body before reaching the stomach, where most vaccines would be destroyed by the strong acidic conditions. Alternatively, the vaccine could be produced in a tablet that dissolves on the tongue, passes through the mucosa and would then diffuse directly into the capillaries beneath. The nanopatch is another possible new delivery system. The patch would contain multiple minute projections containing the vaccine together with other biochemical components. When the patch is placed on the skin, the minute projections push through the surface and allow the biochemical molecules to reach the target cells, carrying the vaccines with them. During a flu pandemic, these patches could be posted to patients or collected from a chemist, to facilitate availability of the vaccine and obviate the need to see a health professional.

The final new proposed method of vaccine delivery, which could be developed to incorporate nanotechnology, is nasal administration. A fine emulsion or powder could be mixed with the vaccine, which could then be inhaled through the nose, to enter directly into the blood stream. Research has already been conducted into using this method of delivery for Hepatitis B, using a fine emulsion of fat and water, as the inhalant.

Possible Specific Applications

These new methods of vaccine delivery would make distribution and ease of vaccine administration much simpler. I have also suggested several specific applications, which would become available with their development.

Firstly, these methods of vaccine delivery would reduce the current need for refrigeration of the vaccine. Lack of resources mean that the adequate refrigeration needed to transport and store present day vaccines is often not available in Less Economically Developed Countries (LEDCs), This is especially seen in remote and rural areas. These delivery systems would therefore mean that there would be a much greater availability of vaccines in these poorer countries. This would not only save an enormous of lives, as easily preventable diseases, such as malaria HIV and hepatitis B could be significantly cut back, but it would also greatly aid the eradication of some diseases from the planet.

Next, these vaccine delivery systems could also further advance the way in which passive immunity can be delivered to patients.

This would be useful in treating cholera and other intestinal diseases which are associated with extreme diarrhoea. By delivering antibodies through nasal administration or through patches, antibodies could enter the body, which would significantly aid the body in recovery from these diseases.

Another new possibility would be providing antibodies for foetuses, in utero. This would be particularly useful if the mother had a disease like rubella, or cytomegalovirus which can seriously damage an unborn baby. The nanoparticle attached antibodies could pass across the placenta and protect the baby from the disease. This technology could also be used to provide short-term immunity to babies, for other diseases from just before they are born, until they are given the active vaccines at 8 weeks.

Ethical Issues

Vaccines

Vaccines prevent diseases and save at least 9 million lives a year world wide. However, the ethics of giving vaccines is not straightforward. Vaccination is compulsory in some countries such as Canada, Italy and the USA before children can go to school. In the UK, vaccination is not compulsory. The NHS free vaccination programme and the work of GPs, nurses and health visitors in educating and encouraging parents to get their children vaccinated has resulted in childhood vaccination, uptake of 94%. The MMR uptake in the UK dropped to 81% some years ago following an article by Andrew Wakefield where he linked the MMR

vaccine with an increased risk of developing autism. Since the article was disproved, MMR uptake rates are slowly climbing. There are those that say that vaccination should be compulsory except for very few exceptions, in order to maintain herd immunity. This is the concept where the large vaccinated immune population confers protection to the un-immune population. Where the herd immunity falls below a certain threshold, there will be outbreaks of disease. This was seen when parents chose not to give their children the whooping cough vaccine due to the fear of developing fits and more recently the MMR due to fears of autism. As recently as last year during the pandemic flu outbreak, individuals were refusing the H1N1 vaccine because of fears of developing neurological problems. The ethics of giving vaccines particularly for contagious diseases balances the rights of the individual against the rights of the whole community. People may choose to decline vaccines due to reading about adverse reactions, due to needle phobia or due to religious beliefs. Due to the relative rarity of most of the common communicable diseases, which previously had significant mortality and morbidity rates, people have focused more on the adverse reactions of the vaccines rather than the much more serious consequences of the diseases themselves.

Nanotechnology

This new technology will revolutionise vaccine delivery systems and have a major impact in the world. As with any new innovation it will create a vast array of opportunities but also create its own problems. The immediate advantage proposed is that vaccines created this way will be cheaper more efficacious and more simply delivered. There is also no need for refrigeration or a highly trained health professional to administer the vaccine. The need for needles and syringes which were at risk of being unsterile is removed, thereby also removing the risk of needle stick injuries to health care workers. Many cases of HIV in Africa arise from unsafe medical practices such as reusing needles and syringes. Therefore, the risk of poor disposal of used needles and syringes in high HIV prevalent countries is removed. Currently many people especially in poorer countries do not complete the entire course of vaccination as they cannot afford to come up 3 times for injections. 'Nano vaccines' may need only 1 or 2 courses to give full immunity. There is a huge unmet need for vaccines in world's poorest countries. If topically applied vaccine against HIV becomes available, it could reverse the death toll currently seen in Africa and other areas with high HIV prevalence. The concern about any new technology is the knowledge gaps that exist within it when it is still in its infancy. The immediate benefits can be seen, but potential harm or toxicity to individuals and the environment may not become apparent for

a much longer time. There is also the risk that in order to recoup the massive investment put in, multinational drug companies may be keen to try out the new vaccines before they have been adequately evaluated. Individuals should not be exposed to research or the new vaccines without informed consent and there should be robust clinical trials.

Conclusion

In the next 20 years we are going to see nanotechnology transform almost every aspect of medicine. This technology may allow development of vaccines not just against infectious diseases but also against chronic diseases such as cancer, strokes and Alzheimer's disease allowing us to immunize those in high risk groups. Traditional vaccination has been proven to be safe, cost effective and well tolerated. However it is evident that in much of the developing world there is lack of equity in accessing these vaccines. There are also no vaccines currently available for malaria and HIV, which kill millions each year. If 'nanovaccine' research and trials give us high quality new vaccines which can be available for all, we may see the dawn of a just and fair world for all.

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