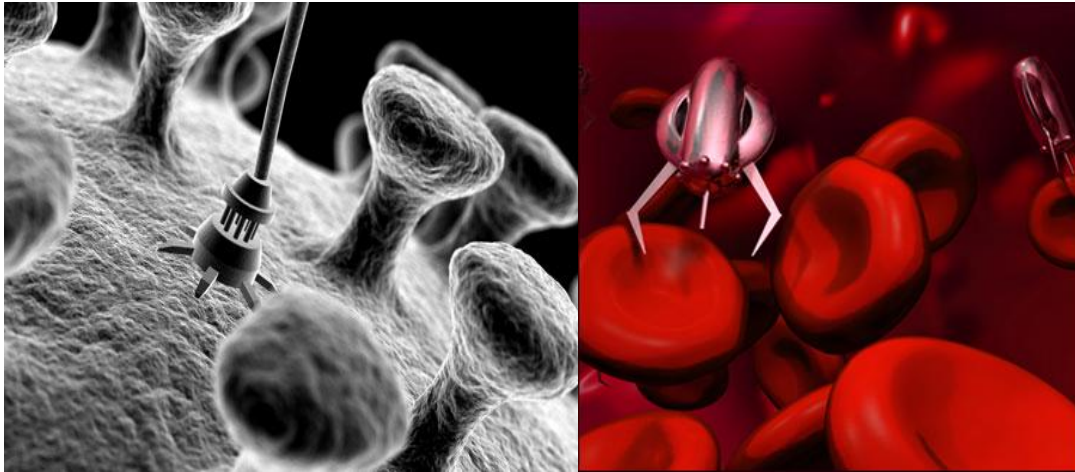


Exploring advancements in nanotechnology and their applications in antiviral medicine



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PASS WITH MERIT

Research paper
based on
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Abstract

This paper was constructed by background reading about the concept of nanotechnology and how it can be used to improve existing medical treatments and create new ones, particularly treatments to combat viruses. Viruses are the smallest pathogens at only 20 – 300 nm. This paper aims to discuss general developments in nanotechnology and why this is useful in medicine, before going on to examine how current and foreseeable-future nanotechnology stands to enhance our treatment of viral diseases.

Introduction

In 1852, a Russian Botanist D. I. Ivanovsky prepared an infectious extract from mosaic disease. When the extract was passed through a filter able to prevent the passage of bacteria, the filtered fluid was still infectious. In 1898 the Dutchman Beijerinck coined the term virus, which is Latin for poison, due to the infectious nature of certain filtered plant fluids. Although progress was made in identifying them chemically as nucleoproteins, they proved too elusive and mysterious due to their tiny size which makes them impossible to see in a light microscope. Viruses were among the first biological structures to be studied when the electron microscope was developed in the 1930s. (2)

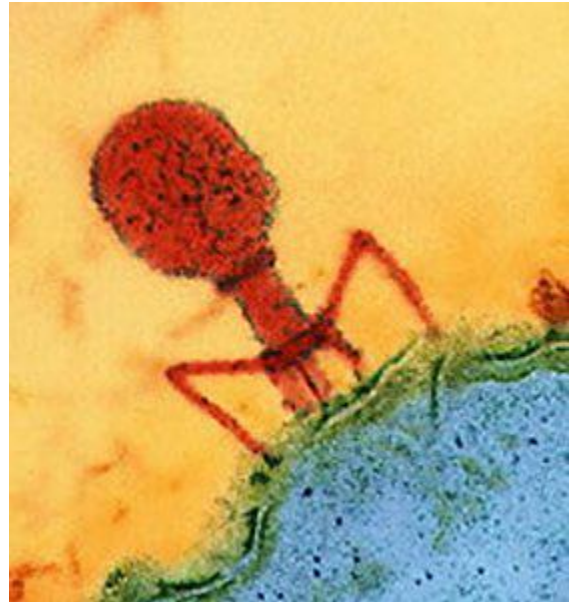


Figure 1 (17)

Viruses do not have a cellular structure; instead they consist of simple, uncondensed strands of genetic material, in the form of either DNA or RNA. Viruses are, by their nature, parasites, called 'obligate endoparasites', because they can only live in other cells, splicing their own genetic material into that of the host cell and so using the hosts' own mechanisms to synthesise new viruses. Their simple structure, however, belies their incredible variety, and remarkable capacities for rapid adaption. (2)

AIDS (acquired immunodeficiency syndrome) was first reported in 1981 and is caused by HIV (human immunodeficiency virus) which is a retrovirus. Retroviruses possess only RNA but are able to convert their RNA into DNA using an enzyme called reverse transcriptase to insert the necessary gene sequences into host cell DNA.(2)

Since Richard Feynman first made his speech 'there's plenty of room at the bottom' in 1959, nanotechnology has emerged as one of the most exciting, potentially paradigm-altering scientific breakthroughs of our time. It promises to

grant humanity unprecedented control of the natural world at the tiniest scales, hence unlocking a previously unimagined world of potentials on the macro-scale we inhabit. Perhaps nowhere is this potential greater than in medicine, where nanotechnology has fortuitously arrived just as we have made incredible leaps in our understanding of life on the cellular, even molecular level. Potentially this could allow us to control the most basic processes of life itself and hence tackle seemingly unsolvable medical challenges and diseases.

On a practical level, these promises have already translated into tangible benefits. A basic example is in materials science, where improved materials available due to nanotechnology, such as carbon nanotubes, have made surgical instruments and devices more precise and durable than ever. Carbon 'cages' such as fullerenes (shown in figure 2) are also being developed to carry water-insoluble drugs which are otherwise difficult to get into the body. CytImmune sciences, Inc, for example, published a paper (2010) outlining the phase 1 trials of anti-cancer drug delivery system based on this nanotechnology. (4)

These advantages come from nanotechnology's ability to replicate natural phenomena. On the smallest scales, matter behaves radically differently, allowing scientists to create materials which behave like biological structures. For example, researchers from the Air Force Research Laboratory and Chung-Ang University in Korea (2010) have created synthetic photovoltaic gels, which use graphite nanomolecules and chlorophyll-like pigments to mimic the way plants harness light energy. This is but one of a huge array of exciting applications which take their inspiration from the natural world around us. (15)

However, if nanotechnology is to avoid falling into obscurity, and truly maximise its potential justifying the excitement it has generated, then what is needed are truly unique, practical applications. One area with the potential for such success is in treating viral infections. Antibiotics are totally useless in this respect, affecting only bacteria, whilst substances used to kill viruses in the environment are generally just as toxic to us. Antiviral drugs are the best hope, but controlling the pharmacokinetics of these treatments (that is, how the drugs enter, circulate inside, and leave the body) is difficult. Hence it is often difficult to target the drugs where they are needed, which means unnecessary side-effects, higher dosage requirements, and ultimately an upper limit on the efficacy of these drugs. The nature of viruses' means they must hide in the body's own cells, using them to replicate, and evade the immune system at the same time. This makes them even harder to treat, and makes it all the more important that

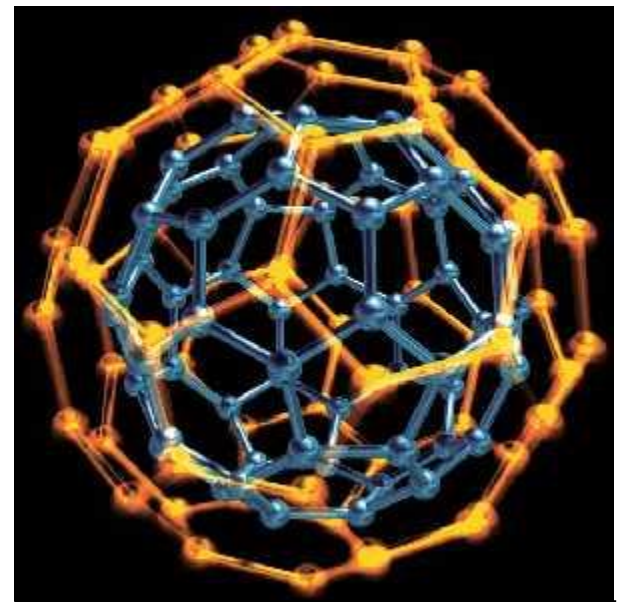


Figure 2 (18)

drugs be targeted to the cells that need them and are taken up into the cells themselves in order to completely eliminate the virus.

What is needed is a means to deliver these drugs exactly where they are needed, keep them in place as long as possible, and then remove them from the body as rapidly as we can. This will mean lower doses, better treatment, and lower side effects at every stage. Nanotechnology could see this dream become reality, in the very near future.

Discussion

Nanotechnology fits into the problem of viral treatment perfectly. It has already been shown that nanotechnology solutions can massively improve the efficacy of drugs, by increasing their 'half life', the time taken for half the quantity of an administered drug in the body to be eliminated. Indeed, this has been one of the most effective uses of nanotechnology, with drugs being delivered as nanoparticles, and hence massively increasing the time they spend in the body, as discussed by P.Lim Soo et al. in 'nanotechnology in drug delivery' (2008), explaining that the nanoparticles are readily taken up by cells, far more rapidly than conventional suspensions, and remain in cells, releasing their drug content, for far longer periods as a result, rather than remaining poorly absorbed and being eliminated from the body. (11)

This technology is especially useful where viral treatments are concerned. Because viruses operate inside our own cells, it is crucial that drugs be absorbed into the cytoplasm of the cells where they can directly counteract the virus. The most common antivirals, for example, inhibit the activity of the reverse transcriptase and similar proteins which viruses depend on to 'hijack' human DNA replication systems. Hence unless they can be taken into the cells where these proteins are active, they will have no effect, making the nanoparticles delivery systems an ideal method for drug delivery in such cases. (7)

Further applications are also apparent in vaccine development. Firstly, nanoparticles allow for a more gradual, sustained release of the viral antigens, which drastically improves the potential for immune responses to develop, as the bodies white blood cells are exposed for a longer period and so are more likely to respond and generate the memory cells required to confer long term immunity. This could also eliminate the need for the booster shots which, though not a significant disadvantage, do tend to inconvenience patients, as the antigens would remain in the body longer and allow more time for immune memory cells to duplicate, increasing the length of immunity. Even more exciting, however, is the potential discussed by Tewodros Mamo in the article 'Emerging Nanotechnology Approaches for HIV/AIDS Treatment and Prevention: Nanotechnology for HIV/AIDS Prevention' (12) to design nanoparticles which, much like

macrophages, can 'present' viral antigens to the body's T and B cells directly. This would again massively improve the likelihood that the immune cells react to the presence of the antigen. This is another incredible example of nanotechnology's ability to mimic natural processes on a molecular level, interacting with the very cells and proteins we use when acquiring immunity naturally. There is growing concern, however, that this nanotechnology may be rendered useless by the inherent dangers of the carbon nanomolecules themselves. Fullerenes, for example, may be carcinogenic, rendering them useless for drug delivery, a function it was once hoped they would fulfil. It is therefore crucial that we research fully all the potential effects of this technology, and follow rigorous clinical trial procedures to ensure that these technologies are not adopted too hastily, which could lead to unanticipated side effects.

The process of vaccine development itself may also be aided by nanotechnology. Normally, vaccines are based on weakened forms of the target virus which cannot replicate themselves, or their isolated antigens. Therefore the ability to alter these viruses on a genetic level would be invaluable. Nanotechnology may allow us to do exactly that, for example, in a paper originally published in *science*, by Nadrian C Seemans, it was demonstrated that a nanotechnology 'cassette'-like device could be used to easily alter DNA structure. In future this could be used to selectively eliminate undesirable genes from viruses (perhaps those allowing replication or conferring resistance) and therefore easily create the weakened viruses for use in vaccine development. This technology could also prove problematic, with the potential to alter viruses for use as biological weapons all too obvious. It is therefore crucial, as with any emerging technology, that it be treated at all times with a moral conscience, and that legislators act quickly to control and limit this technology so that it does not fall into the wrong hands or be misused. (8)

Together, what these advances offer is the possibility of a cure for viruses which we can only presently inhibit and keep controlled. HIV, for example, is one of the most common viruses globally, and although in recent years it has received less media attention, cases are in fact on the rise, with the number of infections doubling between 1997 and 2003. At present, the use of antiretroviral drugs, especially in combination, is the most effective treatment, and has in fact managed to reduce the number of fatalities from almost 2000 in 1995 to only 516 in 2009, according to AIDS awareness group AVERT (6). If vaccines could be developed, however, it would mean a permanent solution, eliminating patients' dependency on a lifetime of medication and also protecting the population from infection in future. Not only would this help to save millions of lives directly, but also, as HIV/AIDS is especially endemic in the world's poorest nations, would help to lift the oppressive burden of disease on these nations and so accelerate their escape from poverty. If a disease as well recognised as AIDS could be eliminated, in the same way that smallpox was so successfully in the last century, this would cement nanotechnology's position as a crucial medical tool, and surely boost public support for further research and development into the area.

Nanoparticles have also been used to examine how our immune responses work. For example, Cytotoxic T cells are vital to our antiviral defences, as they destroy infected cells to limit the spread of the virus in the body. A team at the University of Alberta used nanoparticles as markers to track the interactions of a particular protein (CD45) known to have a role in triggering T-Cells. (10) It was found via this method that the protein was attached to the cell cytoskeleton, and the particular proteins it was attached to. There are many possibilities available if we could find out when CD45 is turned on or the other molecular partners that enable CD45 to work. An inhibitor could possibly be produced. Potentially, if the proteins that connect CD45 to the cell cytoskeleton were removed or denatured The T-cell would cease to function, treating cases of overactive T-cells. The converse could also be possible, allowing T cells to propagate rapidly to support those with weak immune systems such as in the case of AIDS. This discovery was made possible by the use of nanoparticles as tracking devices. By developing our knowledge in this way, nanotechnology could eventually allow us to enhance the natural immune capabilities of our bodies to fight off infections more rapidly and effectively. Ethically however, there is an inherent concern in altering our bodies' standard functioning. Thus it will be crucial not only to ensure there are no damaging side-effects, but also to question who will have access to this kind of enhancement, and whether it will be used as a treatment for existing infection or administered to all citizens as a pre-emptive defence against disease.

Being able to effectively inhibit T-cells could be instrumental in drug delivery systems. Often drugs encapsulated in nanoparticles have been intercepted by the immune response. Inhibiting the immune response for just long enough for the nanoparticles to reach their destinations could resolve the issue. Obviously however, as with any immunosuppressant treatment, we risk exposing the body to other infections, hence it is vital doctors administer such treatment as minimally as possible to limit this risk

Other methods of allowing the nanoparticles to inactivate or bypass the immune response are being implemented. One such method is coating the nanoparticles with water soluble polymers which cause the surface to appear water-like and therefore essentially immunologically unidentifiable. This must be done carefully as the surface must be compatible with biological surfaces but not trigger our immune responses as most antigens do. The key hurdle to achieving this success will come from being able to synthesise bio molecules as precisely as possible to narrow their effects to those we deem beneficial. Nanotechnology can help us to achieve this, by improving our analysis of the naturally occurring molecules inside us, and allowing us more control and precision than ever over the synthesis of molecules on the smallest scales.(3)

Nanotechnology evidently has a variety of applications, but in spite of this, there remains relatively little public awareness of the benefits it offers, whilst more alarmist coverage of the potential downsides finds favour in the media. All of this makes it harder to generate support and funding for nanotechnology research, ultimately slowing the rate of progress in a promising field. Whilst it would be equally irresponsible to rush blindly into developing this field without considering the risks, what is needed is a more balanced and better informed public debate on the issue. It has been demonstrated that once informed of the potential risks and scientific fundamentals of nanotechnology, people are more likely to support its development. Thus our aim should be to tackle ignorance of nanotechnology itself whilst remaining transparent about the dangers. Only once this happens can a general consensus begin to form and scientific research be focused into the areas most likely to yield beneficial results for the whole of society.

Who should get access to these treatments? Nanotechnology in many areas is in its developing stages and is expensive as a result of research costs and the expense of creating and using such tiny instruments. The small scale in which nanotechnology operates would require specialist equipment and training, further escalating the costs. This raises the issue of who these costs should be pushed onto; Individuals or health insurance companies? Many individuals would not be able to afford what is likely to be in some cases necessary and possibly expensive treatment. Would these people be left to suffer with whatever ails them or potentially be left to die? In the UK and other nations with a national health service, careful consideration would also be required to decide what nanotechnology requires public funding. Tellingly, surveys reveal peoples' support for nanotechnology increases when it is framed as being therapeutic. Thus perhaps the best course of action would be to focus on developing therapeutic, popular nanotechnology, which would receive plentiful funding, and so gradually decrease naturally in cost over time as technology and scientific understanding improves. It is typical for cutting edge technology to be initially expensive, but then fall in cost with wider adoption, so cost alone is no reason to shy away from further development. (5)

A problem common to all medicine is that of preventing infection. In modern medicine, this remains one of the greatest challenges we face, with viruses rapidly spreading in hospitals, and the threat of global pandemics such as swine flu and SARS (severe acute respiratory syndrome) making infection control more important than ever. As demonstrated by EcoTru in 2003, chemicals which were normally considered unsafe for use as disinfectant could be made less hazardous by suspending active ingredients as nanoparticles, thereby preserving their effectiveness whilst requiring a lower quantity. This allowed a disinfectant capable of destroying the SARS virus to be produced. In future, this

may become a common practice, creating increasingly effective disinfectants, whilst also making them safer than ever before. (16)

Although nanotechnology is important in treating those who are already infected, nanotechnology can play an important role in preventing further infections, especially in water treatment. Nanofiltration materials such as carbon nanotubes, alumina fibres and nanoscopic pores in zeolite filtration membranes can purify water to previously impossible degrees. Having filtration on such a small scale would be more effective at preventing the smallest pathogens, viruses, from entering our drinking water. Even if any contaminants or pathogens managed to get through all these defences, we could be informed of this by the nanosensors such as those based on titanium oxide nanowires, which would alert authorities to contaminations, allowing immediate action even before outbreaks occur. For example, sending health workers to affected areas to prepare for potential cases would vastly improve their readiness and ensure that patients be treated immediately. Additional benefits of nanofiltration are that less pressure is needed to run the water through the filter and it is more efficient due to the incredibly large surface area. Hence these filters not only defend against viruses more effectively, but do so more cheaply and requiring less energy than present solutions. This is especially useful as the areas most in need of effective water purification tend to be the poorest nations, with poor general infrastructure. This could therefore extend the clean water enjoyed by the first world to a much wider population. (9)

Conclusion

We have discussed extensively the scientific application of nanotechnology in treating, preventing, and eliminating viral diseases. Ultimately this comes down to three main areas. Firstly, nanotechnology's direct treatment of current diseases, and enhancing our present treatments. Secondly, nanotechnology is useful in researching and improving our knowledge of disease by allowing us to interact directly with viruses and cells on the molecular level. Thirdly, nanotechnology can be used in disease prevention by providing better cleaning and filtration materials.

A crucial issue, as with any new technology, comes in funding. With a divided public opinion, government funding may be impractical, at least until greater consensus can be fostered. At least in the short term, the research and supplies are likely to be funded by major pharmaceuticals and private companies, in turn limiting access to those who can afford the market price. If the technology is to be enjoyed by everyone, then either the price must be allowed to fall naturally, or the government must subsidise treatments to improve access.

Cures that could be made by using nanotechnology could actually save money. Those suffering with currently incurable diseases are on prescribed drugs that help them to survive although in the cases of diseases like AIDS, this only lengthens the person's life span by 30 years on average. The disease isn't being cured, it is just being suppressed and while the person lives they have the daily AIDS combination therapy which consists of 3 or 4 drugs. This leads to a poor quality of life and persistent drain on medical resources, which a cure could avert (14). As has been previously discussed some methods of transportation using nanoparticles such as fullerenes could actually cause cancer due to their carcinogenic nature. Possibly in the near future nanoparticles that lack carbon could be used but currently the risk of treatment using carcinogenic nanoparticles and the risk of using low-efficiency drug delivery must be weighed up. Ultimately the balance of harms must be evaluated on a case by case basis for each different application.

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