Nanotechnology- Can it Fight Human Immunodeficiency Virus (H.I.V.) and is it Ethical

By

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PASS WITH MERIT

RESEARCH PAPER BASED ON PATHOLOGY LECTURES AT MEDLINK 2010

Abstract

Nanotechnology is a new discipline of science advancing in many areas. It involves the understanding of research, design, engineering and fabrication at the atomic and molecular level. Every day new inventions due to nanotechnology create advances in the field of science. But these are still being developed at this point in time. Current problems for Nanomedicine involve understanding the issues related to the environmental impact of nanoscale materials and the ethics of 'messing' with nature.

This paper discusses the use of nanotechnology in treating and preventing the world wide known virus- Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome (HIV/AIDS).

Introduction

Nanotechnology

A brief look back in time, in the year 1867 an experiment called "Maxwell's Demon capable of handling individual molecules" was proposed by a man called James Clerk Maxwell. Maxwell was the first man to discuss this new idea. Later in 1914 Richard Adolf Zsigmondy took this idea and developed it, he was the first to use nanometre for characterizing particle size, and proposed that it was 1/ 10, 00,000 of millimetre. With this he developed the first system classification based on particle size in the nanometre range. [1]

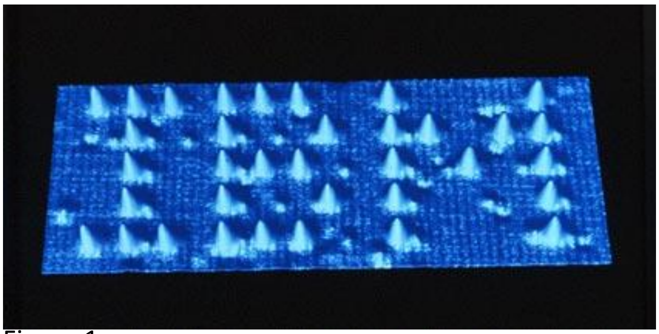


Figure 1

In the 1980's two scientists D.M. Eigler and E.K. Schweizer, cooled a nickel surface to 4K (Kelvin) in a vacuum chamber. When introducing a small amount of Xenon (Xe) gas into the chamber, some Xe atoms stuck to the nickel surface. These extremely low temperatures rendered the Xe atoms fairly immobile so the atoms stayed in place for long periods of time meaning so the scientists could manipulate the atoms into the IBM logo (figure 1). [2] During this time though scientists were inhibited by lack of technology limiting the quick pace of advances which occur today.

Nowadays, nanotechnology in medicine is offering some exciting possibilities. Even though some procedures are only imagined, verging on 'star wars' science, while other ideas are at various stages of testing, or actually being used today.

Uses in medicine

There are a wide variety of uses of nanotechnology in medicine, ranging from the use of biosensors for detection of anomalies in the body, such as high blood sugar concentration, which would suggest diabetes and even designing nanotubes that can be used in delivering insulin in insulin pumps, these would be so small (nanosize) that not even virus's can fit reducing risk of infection but still allowing insulin into the body. These delivery systems could be a way off delivering nanorobots into the body without pathogens getting in.

Nanostructures

Dendrimers are nanostructures built around a core unit and are composed of several branching units in a layered fashion, which define the growth, size and the environment within the dendrimer [15]. It could be used to entrap drug molecules and help them be soluble, controlling release, targeting or protection.
Dendrimers offer unique properties such as uniform particle size and polar end groups which allow targeting multiple receptors [15]; this would be useful when targeting the HIV virus.

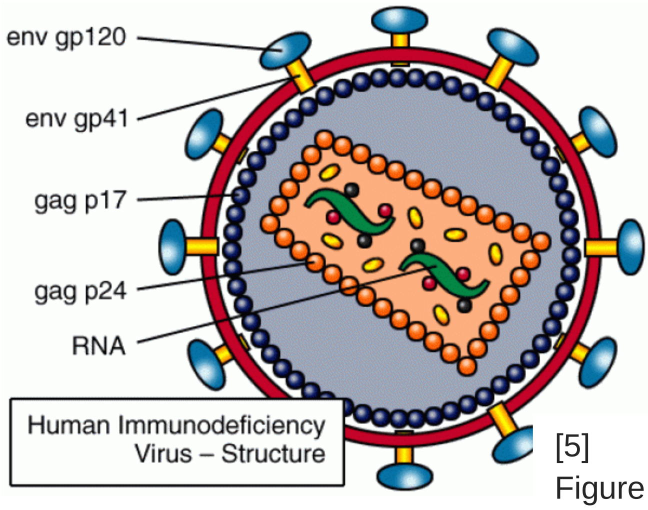
Nanosuspensions which are particles that are produced by suspensions with macro- or micro sizes particles. The could be used to improve dissolving “solid” drugs that are insoluble in both water and oil at high melting points into solutions.[15]

Polymeric micelles are nanostructures of more than 100 nm in diameter, made of hydrophobic cores and hydrophilic shells. They could protect against metabolism which is problematic due to the breaking down of many ‘normal’ sized drugs, they can be used for controlling the release of drugs into the body and used in targeting cells.

Other ideas which are being developed at this present time are scientists creating and engineering nanomaterials so that artificial tissues can be produced, this would replace diseased kidneys and livers and possibly repair nerve damage. [3] More on different parts of nanotechnology are discussed further in the paper.

H.I.V virus and A.I.D.S. (Acquired Immunodeficiency Syndrome)

To know how to stop HIV it is important to know what it is and how it affects the body.



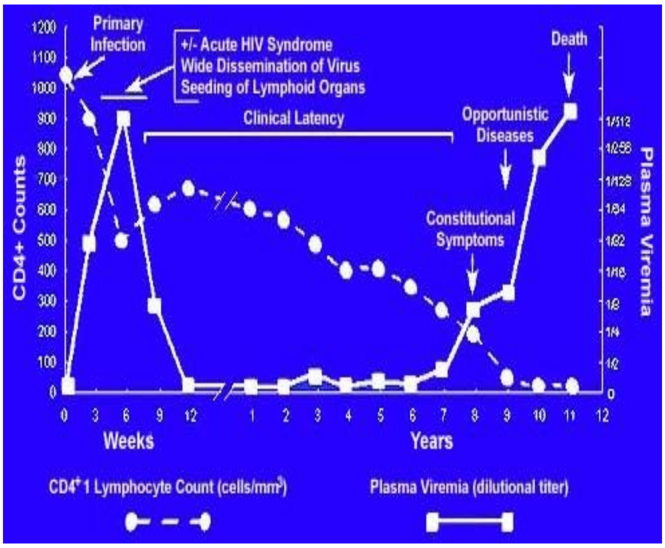
[5]
Figure 2

H.I.V is a virus which has caused chaos worldwide causing over 25 million deaths [4] with no known cure or. What is H.I.V? It’s a virus which “attacks” the immune system, disables it and causes A.I.D.S. Although the virus itself is not fatal it allows other diseases that the host can’t fight off to take hold which ultimately is fatal (opportunistic diseases). It is contracted through bodily fluids i.e. blood and seme.. through mucus membranes. Like all viruses HIV cannot grow or reproduce on its own. In order to make new copies of itself it must infect the cells of a living organism. So what it actually does to the body is, the virus (which is only 0.1 microns [5]) infects the $CD4^+$ T helper cells, and macrophages (a sub-group of lymphocytes and T-cells can be known as CD4 cells). The T-helper cells main function is to find and isolate pathogens, in one sense they ‘watch’ the body so that the immune system be activated and can destroy the pathogens. In a person with the HIV virus, the destroyed T-helper cells means that the virus can then infiltrate and destroy the immune system.

Life cycle of the virus

HIV fuses to the CD4 receptor on a human cell using glycoprotein 120 (envelope glycoprotein [9]) seen in figure 2 which binds to the CD4 protein that is found on the cell membrane. This allows the viral envelope of HIV to fuse with the cell membrane and the contents of the virus (viral core and all the necessary enzymes) can then enter the cell into the cytoplasm. Once inside the cell the RNA of the virus is converted/ retrotranscripted (using an enzyme known as viral reverse transcriptase) [6] into compatible Deoxyribonucleic acid (DNA) with human DNA which is moved to the nucleus. This DNA is combined with the DNA of the cell and is then known as provirus [5]. One of the enzyme's which are needed for the virus to be made, is the enzyme protease as it 'chops' up protein strands so they can be used to construct the viral cores (the shell of protein that protects the nucleic acid of a virus). [5]

This new DNA may lie dormant in the cell until an immune response is required the cell treating the virus DNA as if it is human DNA. "Resting cells" do replicate the virus but at a much slower rate than an activated cell. This mix of human DNA and HIV DNA is converted into RNA ready to be replicated outside the nucleus. The cell produces complete copies of the HIV genetic material along with the cells genetic material. These copies gather together with HIV proteins and enzymes made from the cell and form new virus which then "burst" out of the cell.



Once the new viruses are out of the cell they carry on infecting other cells and this process is repeated over and over again. This is why the virus spreads very quickly. The problem with this virus is there is no cure, opening a doorway for other viruses to infect the body, including some cancers.

Figure 3 Figure three shows the viral load and CD4+ counts as a function of time shows the progression of the disease and also the time line it takes to lead to death.

People can live with HIV for a long time, this is due to the fact that the virus can lay dormant in the cells and the immune system has not been stimulated. The origins of where the virus came from but many people believe it came from monkeys in Africa [7]

Discussion

A brief discussion of the various methods of nanotechnology will follow before possible solutions to the problem of HIV discussed as well as the ethical arguments.

Nanorobotics

Another possible aspect of nanomedicine is nanorobotics. Although hypothetical at present, it’s the development of building a nanosize robot which can ‘live’ inside a human body without disturbing natural body functions. These devices would be ranging in size from 0.1-10 micrometers and are constructed of nanoscale or molecular components. Even though last year nobody has yet built an artificial non-biological nanorobot, scientists are gleaning their inspiration from living cells and their biological motors. This then allows the scientists to understand protein dynamics in order to develop and power micro size and nanosize machines with catalytic reactions. [3]

If nanorobots could be made, it would change so much in battling the virus. Just imagine if we could insert these machines into someone infected and the programmed robots could then target and destroy the virus itself before it duplicates, it would completely eradicate the virus from the planet.

Sadly the technology is still for future development being in the hypothetical stages and is impossible to build such machines at this present time. It can’t be known as ‘star trek’ medicine because scientists have been working on developing it, for instance in 2010 scientists have been designing software on how the future nanorobots would react to the body and destroy cancer cells (simulations) like ones made by scientist Adriano Cavalcanti (the CEO and chairman of the Center for Automation in Nanobiotech (CAN)) who created 3D imaging in reference [8]. Even though these are just simulations other scientists are actually trying to build the nanorobots. So far (in building the prototypes) we have only developed micro robots like the Researchers at the UW and Stanford University who have developed an insect like robot with hundreds of tiny legs. [10]

Targeting cells-similar concept as nanorobots

As we all know, cancer is just as devastating as HIV maybe even more. Chemotherapy is an effective method for the treatment of cancer. It is a medication that is usually delivered intravenously travelling in the bloodstream destroying any detected cancer cells. The problem is that as well as destroying the cancer cells it destroys healthy cells as well. The drug is unable to distinguish between cancer cells and normal cells. This treatment alone can make the person very ill.

In May 2007 a reported treatment was found to deliver anti-cancer drugs to the specific cancer by the use of nanotechnology [9]. This treatment involves micro-machines and possibly treats cancer much better than chemotherapy. The nanotechnology cell known as ‘EnGeneIC’ delivery vehicles delivers the cancer treatment with antibodies that become attracted to the tumours [9]. Once the cell reaches the cancer it releases the drug onto the cancerous cell. It has been tested on animals specifically dogs and has been effective. Researchers Jennifer MacDiamid who tested these on dogs said: “There is no other system where you can get so much concentrated into a little parcel. We haven’t yet found a drug that you couldn’t load. Because they have rigid membrane they won’t break down when injected.”[10].

In theory this can be applied to stopping HIV, because the “micro-machines” could target and attach themselves to the important receptors (glycoprotein 120) on the HIV virus. It can be done by passive or active targeting [11]. Passive targeting is based on the properties of the delivery system and the disease pathology, in order to preferentially accumulate the drug at the site of HIV and distribute the drug evenly [12].
Active targeting to the disease site relies on addition to Polyethylene Glycol (PEG) modification of nanocarriers to enhance circulation time and achieve passive targeting coupling of a specific ligand on the surface that will be recognized by the cells present at the virus site [12].
If the nanosystems can inhibit the important receptors on the virus, then the virus can’t attach itself onto the ‘host’ cells which stop the process right in its tracts. The problem could still be that the virus is present in the body it would just be inactivated but at least it wouldn’t cause any harm.

Drug delivery

Another idea which is being developed and is even used today is that as well as having the drug delivery system (nanotubes) on a small scale, the administrated drug itself can be extremely small. This is happening with insulin pumps and nanoscale tubes. The small drug would also mean that there would be a smaller surface area: volume ratio meaning that reactions of the drug with what it’s targeting will be faster. Also because of how small the drugs would be they could pass through digestion without being destroyed so more of the drug is taken up making it more efficient, cost effective and lengthening the time between doses. [3]

In delivering antiviral drugs nanotechnology lends itself to being useful and could be the beginning of eradicating the virus. A current treatment to HIV is Highly Active Antiretroviral Therapy or HAART. It is a mixture of different antiretroviral agents and is therapeutic, the problem with the treatment is that it causes its’ own problems. If we could find a way of reducing the size of the HAART molecules but still keep their characteristics, it could pass through the tissue membranes more easily than a normal sized molecule, reaching parts off the body difficult to get to. Nanosized versions would reduce the toxicity of the drug as it is in smaller doses (usually) which is very important with HAART. Other useful things is that nano-molecules can easily be encapsulated, enabling a monitored drug- release (e.g. instead of every six hours have it every three), high drug payloads, and could have a relative low cost [11]

With the ideas already stated there are many more applications that nanomedicine already has and can do, and it is certain that many more uses will come to light over the next few years. It has already been said that the successful development of a medical nanorobot would “change the world of medicine forever”. [3]But with any new technology it raises concerns about the potential effects of nonmaterial’s on the environment. It is this reason that advocacy groups as well as the government are debating on whether special regulation of nanotechnology is needed.

So what else can we do?

'If they can put a man on the moon, why can't they make something we can use to protect ourselves from HIV/AIDS?' Peer educator, Uganda, 1991 in Grant et al [9].

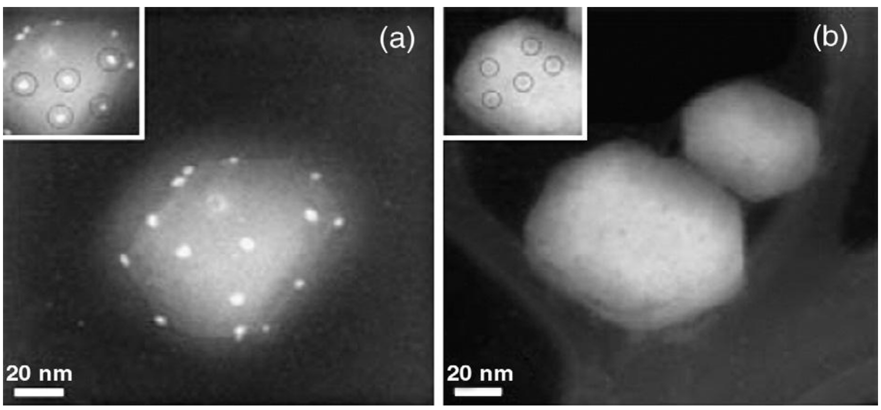
In today's age there are very few vaccines that work against sexually transmitted diseases as they have in recent years only started with the Human Papillomavirus (HPV) vaccine which is directed towards stopping cervical cancer. With vaccines there are ways to increase the lifespan off the infected or uninfected person so they can live longer and have a better quality of life.

The problem with HIV is the fact that it infects the body at a quicker rate if the immune system is already stimulated. If we could prevent its attachment to the 'host' cells then it would be far easier to destroy, then just creating something that destroys the virus after it's already infected many cells. Another problem is the fact the virus can lay un-noticed, almost dormant in inactivated cells which could make it extremely difficult to find the virus.

This is where nanotechnology comes to light with stopping this virus from destroying more lives. With the other techniques further back in the discussion there is something else which is being researched and developed and it could be the cure. This research is called Nano-Microbicides. Microbicides are compounds that can be applied inside the vagina or rectum to protect against sexually transmitted infections (STI's) including HIV. They can be found as gels, creams, films, or suppositories.

They can keep you safe at an affordable rate against HIV but, this is directed more at women than men due to the fact women (sometimes use them as contraceptive techniques) are more likely to have the virus transmitted as the barrier between the mucus membrane in the vagina and the blood is much thinner then the penile membrane. The nano-based microbicides could create a barrier between the HIV virus and the cells being targeted and thus preventing the spread of the virus. At present, an effective microbicides to put to the public is not available.

The first detergent with high expectations used was called nonoxynol-9 and was the first microbicide to enter the efficacy trial. From it, it was observed that the result was that it only enhanced HIV transmission [17]. Further trails on different microbicides have been conducted. If these were nanosized molecules then (referring back to drug delivery) there may be a better chance, because the microbicides would last longer and be more effective.
Silver nanoparticles interacting with microbicides have been useful which could be harnessed to cure HIV. Silver nanoparticles have been proposed to undergo interaction with the HIV gp120, there is interaction of the
Silver nanoparticle with the exposed disulfide bonds of the gp120. If this interaction could be used to inhibit the gp from being used by the virus, it would stop the virus binding with 'host' cells.



This is shown in figure four, High angular annular dark

field images of the HIV-1 cells (a) with silver nanoparticle treatment (inset depicts the arrangement between
Groups of three nanoparticles) and (b) without silver nanoparticle treatment (inset shows the spatial arrangement on the surface of the untreated HIV-1 virus).
Research [14] has depicted that "silver nanoparticles showed size-dependent interaction with HIV, inhibiting the virus from binding to CD4+ T cells" whilst other metals i.e. gold joins to other receptors [14]. (Molecule SDC-1721 a fragment of the strong HIV inhibitor "TAK-779") [15].

Ethics of nanotechnology research

Every day scientists are gaining more and more knowledge of the effects of nanotechnology, there is so much more that isn't understood. The research itself could push moral, legal, social and political boundaries. Like any new technology, the lack of knowledge to what the effects of nanotechnology on the environment could be disastrous. Drugs that would usually be harmless because of their molecule size, made smaller to allow them to pass through membranes they wouldn't normally be able to could potentially cause toxicity problems to that individual. It is great to say that nanotechnology could change the future of medicine but, in some areas more research is required to view the long term effects of a drug/vaccine that can cure/prevent A.I.D.S. but has the adverse effect of causing lung cancer.

It could also be stated once a drug is available worldwide, only the rich or developed countries could access these new technologies, which leave a vast swathe of humanity unable to afford them. If these new drugs contaminate the environment, the size of the particles could prove dangerous to nature.

Conclusion

So to conclude there are many possibilities to help stop HIV from causing more havoc. With our understanding growing for both HIV and nanotechnology we can slowly make impossibilities more impossible. With nanorobots changing from being a hypothetical idea to actually manifesting itself into something we could use. The problem is now which I have already pointed out is, at this point in time, there is more research to be undertaken, as we are only scratching the surface. From what I have researched in the above, it seems that even though we have not created a cure for HIV we are becoming very close. If we can find a suitable nano-microbicide to provide the barrier between HIV and our T-cells or create something which could block the gp 120 receptor on the virus then we truly can say that this virus will become history.

Also some of the techniques potentially creating smaller particles will hopefully allow an easier transmission between outside cell membranes and inside, but could have toxic side-effects on both the body as a whole but especially the cell. An exciting but nail biting times for researchers as they race to use nanotechnologies to cure some of mankind's most deadliest diseases.

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Figure 2 and 3 - http://uhavax.hartford.edu/bugl/hiv.htm Human Immunodeficiency Virus and HIV Disease

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