

How about 'the use of nanotechnology in efficiently fighting  
pathogens

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PASS WITH MERIT

RESEARCH PAPER  
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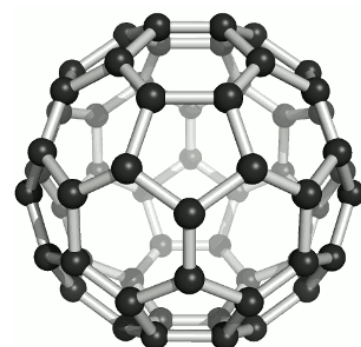
## Abstract

This paper started out by looking at the problem of drug delivery systems' inefficiencies and the potential solution in a targeting system. We looked at several attempts to create targeting systems with nanotechnology, alongside general ways to improve drug delivery. We used this to theorise about the possibility of creating long lasting nanoparticles in the blood to act as a preemptive measure, and how they may be useful in fighting diseases that the human body cannot become immune to, such as HIV.

## Introduction

A very costly problem that we have with drugs at the moment is that drug delivery systems (the movement of the drug, from how it enters the body to where it goes) can be inefficient. The inefficiency results from the drug that the patient takes not reaching the desired areas in our body and being unused by the body. The study of what the drug undergoes is called pharmacokinetics, and it is hoped that nanotechnology can alter this so that more of the drug goes to areas where it is needed.

When a patient is given a drug, it can distribute itself across the body in a way that may not be as helpful as possible- if left to its own devices a drug can simply spread across the body, which may mean that it moves further away from the desired area. While this may be effective against a virus that has spread throughout the body as well, it is not very effective against something affecting only a specific site of the body, such as a cancer. This means that the amount of drug administered to the patient must always be more than the amount that their condition requires to be treated; some will be lost before it even moves into circulation (the amount that enters circulation is called the bioavailability of the drug), some of the amount that does become circulated may move to an area of unimportance and some of this can be excreted by the body, or act on an area that does not require it. Even worse, the drug may also cause harmful effects to the rest of the body as well (it may be carcinogenic, for instance), so increasing the dosage to compensate for this loss can have both financial and health implications.



However, it is beginning to seem that nanotechnology can solve this problem. This has only recently been possible, though. The difficulty in dealing with this problem is that it is one on a molecular level. As far as it seems, there is little we can do about the inefficiency of drug delivery systems above this level without nanotechnology. We can, for instance, administer drugs intravenously, but using injections has its own set of problems in fields of money (the cost of using injections over a simple pill) and other more patient-based problems (many patients are a lot more nervous of having an injection, and may refuse it on these or other grounds). Even if these problems are ignored, injections only solve the problems in bioavailability and have no effect on pharmacokinetics. So it would seem that this problem falls onto the shoulders of nanotechnology, a science dedicated to things that can be as small as atoms.

Figure 1: A buckminsterfullerene, made of sixty carbon atoms, bonded three times, resulting in a sphere with a face made of pentagons and hexagons.

The march of progress in this area arguably started with the discovery of the third macromolecular form of carbon in 1985: the buckminsterfullerene (see

figure 1). The potential for this was quickly realised- the sphere possessed a hollow space in the centre- so what if something could go inside it? This could solve several problems in one swoop.

It is possible that the substance held inside the fullerene could only be released at a site where needed, or upon another condition being fulfilled. This has led to what is probably the most important concept in this entire field of nanotechnology: targeting. The problem was first presented with the work of Paul Ehrlich in 1900, where he created the theory of the magic bullet, where antibodies are released into the body in search of their corresponding pathogen, which they would treat without affecting the rest of the body (Medicine in Stamps Paul Ehrlich (1854–1915): man with the magic bullet). The key to perfecting this system of drug delivery was, he observed, a way to target the pathogen. This idea, if used in our context of fullerenes, could solve the problem of an inefficient drug delivery system in all ways: while there would be nothing to prevent the drug from spreading out into the body, the coating could be altered to break down at a certain site, delivering the drug. Not only would this reduce the quantity of drug wasted by excretion, it would also drastically reduce the quantity of (potentially dangerous) drug acting on sites where it would be used in the wrong place. If the particles could be administered intravenously then the bioavailability issue would also be solved.

Nanoparticles have since moved on from their simple roots. There are now tube-shaped nanoparticles, and these present another set of possibilities, but we are going to stay focused on fullerenes and forms close to them. The next step was to see if these structures could be created using different molecules that would change the property. For instance, fullerenes are hydrophobic, which presents problems when trying to use them in a substance like blood. However, it is possible to bond hydrophilic molecules to the structure, overcoming this problem. This advance has also furthered possibilities like allowing the fullerenes to cross the cell surface membrane and act within the cell itself.

One of the current research projects is the trial of nanoparticles called Aurimmune (Cytimmune sciences, 2011) made of a gold compound shell, which enables the particles to be attracted to a certain area under the right conditions. This is based on the original idea of the metalfullerene, a fullerene containing something. These gold nanoparticles are also too large to fit through the blood vessels, ([www.understandingnano.com](http://www.understandingnano.com)) so they will remain in the body until they reach the cancerous areas they are supposed to treat. The blood vessels in these areas are 'leaky', resulting in the particles being able to slip through. The contents also have to be hidden from the rest of the body's immune system, which requires the use of polyethylene glycol (or PEG-THIOL, for short), which prevents the red blood cells from attacking the particle. The final component is the cancer-killing TNF, which resides at the centre of the particle. The product is currently undergoing phase II trials, showing that it at least works, and has survived the jump from a theoretical paper to practice- something which is still a rare occurrence for medicine.

All of these advancements have helped reduce the wasting of drugs, by targeting a specific area and releasing the dangerous drugs there. This is the research that I will be building upon.

## Discussion

As has already been said in the introduction, certain materials will naturally be attracted to areas of the body, and to cancerous cells. Therefore, what I propose is that the same sort of technique could be applied to a nanoparticle designed to destroy a particularly dangerous pathogen. All that would be needed is a way to target the pathogen. If such a thing is found, the result would be nanoparticles that can reside in the blood, too large to be secreted, carrying a cure in order to destroy these harmful cells. Of course, our bodies already produce antibodies to combat pathogens, working along the same principal (bond to a pathogen in order to release a cytotoxic substance) but this is a system that suffers from two flaws:

- The short lifespan of the plasma cells that produce antibodies; they last only a few days. This means that the time it takes to make an effective number of these plasma cells causes a period in which little is being done to fight the disease.
- The pathogen may not immediately be recognised as a dangerous substance by the body because it has not yet come to the right white blood cell that is specific to it, meaning no stimulation of the division of these plasma cells.

However, a nanoparticle can overcome these difficulties and even outdo the body's immune system and regular drugs. Firstly, these particles can last for a lot longer than the fleeting plasma cells. Using the techniques described in the introduction of Aurimune, they could stay within the blood for a considerable amount of time, undetected by the body and too large to escape. A further advantage of being too large to escape through blood vessels is that the best way to administer the particles is by an injection. If they were administered intravenously into the bloodstream then they would overcome the first problem of bioavailability. Secondly, since these particles are already in the blood, they do not require the time that the body does to produce an immune response; they are numerous and already present in all areas of the body.

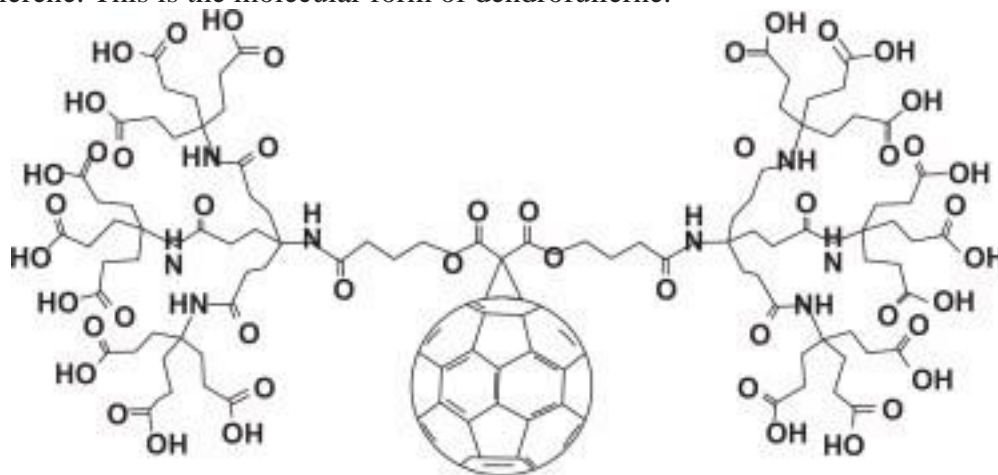
The possibilities of the technology would potentially allow a targeting system to work based on something that is common to viruses may allow for a general cure to all virus-related diseases. Provided that a specific area is targeted with the particles (an ability that some gold particles have based on size and charge, according to an article on *Nature*: Nanomedicine: Sizing up targets with nanoparticles), like the kidney or the liver, all viruses in the area could be wiped out. This would be safe to do, if something was picked to be targeted that was common to viruses but not to human cells (such as the protein coat surrounding virus. Our cells' plasma membranes are made of phospholipids and some proteins. If it was ensured that the fullerenes did not target the proteins in our membranes then it could theoretically be possible).

However, this general targeting may have several adverse effects if used like this. The first is that some bacteria in the body may cause damage if destroyed. There are some bacteria, for instance, that are not pathogens but do compete with other bacteria that are. If they were to be wiped from the body because a general killer was released then there would be no one to compete with the other pathogens. The only way to stop

an infection then would be to inject the body with more of these nanoparticles, something that would not be helpful for patients, as they would need to be re-injected over a period of time.

Instead, the best use of this technology (for the near future, at least) would be to create a nanoparticle that is specific to one pathogen. Given the ordeal of the treatment, involving many injections, it would be best used in situations when the human body cannot effectively fight a disease, such as tuberculosis (where pathogens are still left after the immune response), or where the body cannot fight a disease at all, such as HIV. By injecting nanoparticles that can target a specific pathogen before infection, the body will be able to fight these infections before they become serious.

This has already been done, to some extent. Research by H Urakami et al (1989) suggests that some antiviral compounds have shown the ability to suppress the development of viruses. Fullerene based substances have this ability inhibit viral activity, most notably the human immunodeficiency virus (HIV). This is mainly due to the specific molecular shape of the compound. Dendrofullerene, water soluble form of fullerene, can create a complex with the HIV protease. Once bound, the protease can no longer cause the mRNA to split and thus preventing the replication of the viral gene. The fullerene itself is not soluble in water, so hydrophilic amino acids must be added for it to dissolve in the blood, as mentioned in the introduction. Scientists had to use specific amino acid chain to prevent alteration of the fullerene part itself. They did this by adding hydrophobic areas in the protein chain, which protects the fullerene. This is the molecular form of dendrofullerene.



We theorise, then, that it would be possible to create similar fullerenes that can extend to other harmful diseases, this time carrying cytotoxic chemicals in place of a cure, if one does not exist. They, due to their long-lasting nature, could be administered as a preemptive drug, and would only deliver their dangerous chemicals at the right places due to targeting unique features of the pathogen, resulting in an effective drug delivery system. However, the particle must only be used when there is no other option. Careless use of the technology for all pathogens is not advisable, for several reasons.

The first is that they could reduce the capabilities of the human immune system. Experiencing and fighting new diseases allows our immune system to become

effective, so creating a blanket disease killer could weaken our immune responses and result in more serious consequences when it fails, due to our dependence on it.

Also, while the use of cytotoxic chemicals would be useful in some cases, as they would break down the cell membrane and kill the pathogen in much the same way an antibody works, the risks of injecting someone with these chemicals would be great—especially if the targeting system works on a feature that is common to human cells, like proteins. There may be cases where the nanoparticles targeted the human cells instead, because they shared a protein with this hypothetical disease. Proper testing must be ensured to make this safe.

There are also ethical issues surrounding such a practice, and these must be addressed. The first is that, since these are drugs, there does exist a certain amount of copyright on them. This may prevent people from building on the work of others and it may extend to using gold or PEG-THIOL as compounds using them may be copyright protected. Some may say that this is unethical, but this is a right that must be respected, often at technology's expense.

Ever since the magic bullet, animal trials have been necessary for the development of this science. This, combined with the requirement for all drugs to undergo an animal testing phase, means that some may refuse the treatment. The argument goes that we alone have asserted our right to experiment on animal, and that we have assumed our superiority. For this reason of animal rights, many may refuse treatment.

However, this only provides another problem. If there was to be a vaccination programme that included this nanoparticle, there could be a risk of the disease staying in some members of a population if they refused to have the treatment. This would endanger the lives of the people around them, but it would also be wrong to force people to undergo treatment.

More serious, though, is the question on how future nanotechnology will be regulated. Just as Marie Curie was not aware of the dangers of the field she was beginning to research, so scientists of today are not yet fully aware of how dangerous nanotechnology can be. The effects of fullerenes in the body are still being observed in the trail of Aurimune, and we have yet to see the effects in a wider context that can only be provided outside the controls of a laboratory. For instance, there may be side effects that are dangerous or are only prevented by abstaining from a substance like alcohol. Whilst this can be controlled in a laboratory, it is completely different in real life, where many patients do not follow the advice of their doctor completely when using a drug.

A great fear of ours is that serious regulations will only be set up as a response to a crisis, instead of a preventative measure. Luckily, though, there do seem to be shoots of these regulatory bodies of the future. The FDA, for instance, is already monitoring nanoparticles. In the future there may be whole new bodies dedicated to them, but they appear to be starting here.

## Conclusion

In conclusion, the possibilities of nanotechnology to create these preemptive drugs should be researched. The potential effects upon HIV have been observed, so it is possible for us to prepare against worse infections. There are problems: it is expensive, it is time consuming and it may be dangerous if not properly tested and regulated. But these are the safeguards against carelessness- while these ideas may sound good on paper the difficulties surrounding nanoparticles like their size and the complexity of using several layers make it hard to properly design them. Each property of the particle must be decided upon, and each one has, up until recently, required extensive research. While designers can now build on the discoveries made today, such as the properties of charged gold compounds and where their nanoparticles can go, they may have to make new discoveries when certain features are incompatible. But vigilance must be maintained. Capsules were, after their use in medicine, often replacing pills as a preferred method of orally ingesting solids. This had little to do with the effects of the capsule and more to with the public's attraction to them because of how new and impressive they were. In this case capsules posed no danger but, going back to Curie, another example can be seen uranium where the new products it made were dangerous.

<http://smj.sma.org.sg/5111/5111ms1.pdf> magic bullet

[http://www.cytimmune.com/download/posters/ASCO\\_Poster.pdf](http://www.cytimmune.com/download/posters/ASCO_Poster.pdf) and

<http://www.cytimmune.com/go.cfm?do=Page.View&pid=19>

<http://www.understandingnano.com/medicine.html>

<http://www.nature.com/nnano/journal/v3/n1/full/nnano.2007.433.html>

<http://www.ncbi.nlm.nih.gov/sites/ppmc/articles/PMC267681/>