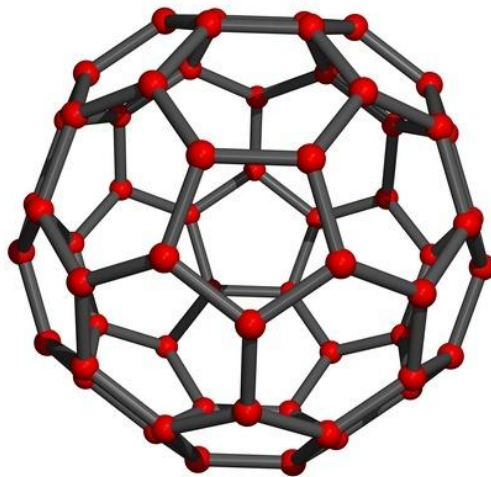


Is nanotechnology the medicine of  
the future, and how will revolutionise  
drug delivery systems?



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PASS WITH MERIT

Word count 3,979

Research paper based on

Pathology Lectures

Medlink 2010

## Abstract

The two key areas that I will be discussing in this paper are: firstly the use of fullerene nanotubes as a method of transporting drugs to specific areas of the body with little blood supply such as abscesses, and secondly the use of Truncated icosahedrons such as a Buckminster fullerene to carry drugs around the body without interacting with themselves or the body combined with synthetic antibodies designed to attach the drug to a cell with a specific antigen. These two areas aim to mitigate the extent to which drugs effect areas of the body for which the drugs were not intended for.

## Introduction

Aspirin is from the past, radiotherapy is the present, but will nanotechnology be the future? Nanotechnology isn't yet a well known science but is potentially the future of medicine. Nanotechnology was first conceived in 1959 and aims to control matter at an atomic level. This has extreme potential, nanoparticles are much more toxic and reactive than their bulk counterparts, gold is an excellent example, it is generally an inert metal but when in groups of eight or twenty two particles it acts as a catalyst (see Landmans research.)

There is the potential to transport a drug to the specific part of the body it affects, which would increase the effect of the drug whilst reducing side effects. This is currently being trialled in prostate cancer and tumours; the problem was that large amounts of drugs were being given because it was being broken down, reducing its levels in the body. Nanoparticles are used to encase the cisplatin, the drug used to treat prostate cancer, to make it hydrophobic where it was previously hydrophilic; this approach means that less of the drug is broken down and removed from the body because it is less likely to interact as most reactions take place in solution, this means that a smaller dose is needed. This is highly beneficial because as well as destroying cancer DNA, cisplatin is known for causing nerve damage and nausea.

Nano structures are very strong and light; they have similar properties to both diamond and graphite. Carbon nanotubes are 300 times stronger than steel and marginally harder than diamond; these are properties that could be useful in creating longer lasting artificial body parts for things such as hip replacements. It is also possible to create nano electronics, atom force microscopes are used

to manipulate individual atoms to create robots capable of travelling round the body (see Nano-car gets an engine).

A key part of nanotechnology is the ability to create nano tubes and other nano structures capable of containing drugs. This was started in 1985 when Buckminster fullerene was first made; those responsible were later given a Nobel prize. Bucky balls are 60 carbon atoms bonded to form a sphere; this creates a space that has the potential to carry drugs. Nano tubes are currently being trialled with insulin patients as a way of getting small amounts of insulin into the body, through the skin, without the risk of infection because the tubes are too small for even viruses to get through, it also allows better more regular control of insulin levels.

## Discussion

Modern medicine is becoming more precise than it ever was, the attention to detail is immense, innovations in most walks of the profession allows doctors to see clearer, and influence functions at deeper levels; yet despite all this, we have yet to find an effective way of giving drugs to an individual place in the body.

Pharmacologists are forever improving the effectiveness of drugs on their targeted area, the challenge they face is to make drugs that only target specific areas of the body. Undesired affects caused by drugs, known as side effects, can cause damage and generally degrade a person's health. This limits the doses in which they can be prescribed which means that the good done by the drug is also limited. A way to help alleviate this problem aims to deliver the drug only to the cells that it is intended for, therefore reducing the area and magnitude of these effects.

### How can carbon nanotubes be used?

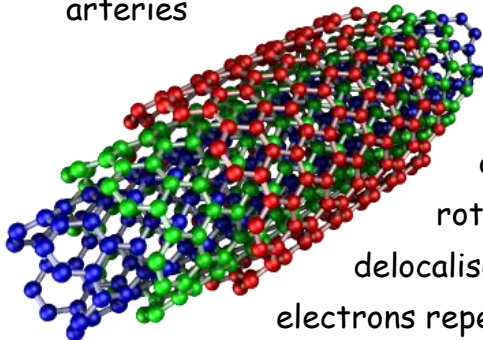
Nanotubes have already been used to continually deliver small doses of insulin directly into the blood stream through the skin, this closely mimics the natural homeostasis of the pancreas in a much more realistic way than current diabetic treatment; because of this success I believe that it would be possible, not only

to use them as a way of giving drugs intravenously, but to send them to each individual tissue, or even individual groups of cells.

It is possible to insert numerous nano tubes into one large accessible artery, such as the Tibial artery in the leg or an artery accessible in the arm and shoulder region; from there the tubes could travel through the circulatory system to any area of the body, because of their small size they would not significantly reduce blood flow. The nanotubes could even go through the capillaries delivering drugs to specific groups of cells.

One challenge facing this suggestion would be navigating the arteries and getting the nanotubes to the desired place. To solve this problem it would be possible to emulate the process that is currently used to insert stents into the heart; during this procedure a catheter is guided to the coronary arteries by a guide wire which can be viewed by x-rays which help to determine the path which it takes; the wire is then removed leaving behind it a hollow tube.

The use of nanotubes would allow a catheter to reach areas with much narrower arteries



and even capillaries. Nanotubes are suited to having layers of telescopic tubes inside one another; this would allow greater control over the direction of the tubes as it the inner tube is free to rotate inside the outer sheath because of the delocalised electrons on both tubes. The delocalised

electrons repel each other which pushes the two tubes apart, this means that the friction between the two tubes is negligible. If the end of the inner tube was curved then this rotation would affect the direction in which the tube points. Unlike with large scale catheters there is insufficient resolution in microwaves to accurately perceive the position of the tube; the wavelength of X-rays are 10nm which is up to ten times the width of nanotubes, in order to get a better view it would be necessary to use high frequency gamma rays.

Once the tube is in place the inner tube can then be removed which would allow the drug to be delivered and the larger outer tube can be left in as a permcath. This can then be used for future or ongoing treatment without the risk of infection; the small size preventing pathogens from entering.

The blood in the body circulates in as little time as a minute, delivering a drug to a specific place in the body is therefore relatively pointless unless it were deposited into a place of little blood flow. This method would see the most success in infected areas such as an abscess where the infection is contained in a sack. Abscesses have very poor blood supplies making it difficult to get antibiotics into contact with the bacteria. If a nanotube were to be inserted into an abscess then the drug would be contained within the sack and unable to affect the rest of the body.

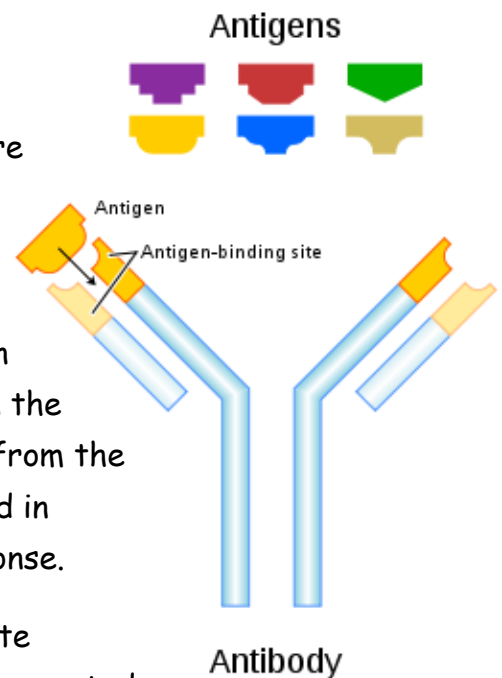
Current nanotubes are not open at either end, instead the carbons bond together to form a rounded end like a semi sphere cap; this currently prevents drugs being easily inserted into the tube. To mitigate the difficulty of accessing the tube, you would require a way of leaving the end of the tube open; a variation on current carbon nanotubes would bond an oxygen molecule to pairs of carbon atoms at the end of the tube thus ending the carbon chain whilst leaving the lumen of the tube free to access.

The use of nanotubes is currently limited by the technologies available. Fullerene nanotubes theoretically have an endless limit, you can continue increasing the length of the tube without compromise; despite this potential, as of 2010, the longest nanotube that has been created is 18cm, this has a length to width ratio of 134million:1 which compared to the m6, which is 4500:1, is an amazing achievement. The problem still remains however and until tubes of at least one meter in length are created, it may not be possible to reach all areas of the body.

Another issue with nanotubes is that only drugs with a very short half live and are highly reactive may succeed. This is due to the fact that the drug will very quickly circulate to the rest of the body, therefore defeating the point of releasing the drug in a specific place. Therefore this method would see the most success in infected areas where large amounts of infected fluid collect, a good example of this would be an abscess. Abscesses have very poor blood supplies making it difficult to get antibiotics into contact with the bacteria. If a nanotube were to be inserted into an abscess then the drug would be contained within the sack and unable to affect the rest of the body.

### Using antibodies to locate cells

Many new technological advances currently look to nature for inspiration; one type white blood cells, called B lymphocytes, produce antibodies. These antibodies are designed to attach themselves to a specific bacteria or toxin; this allows the human body to distinguish between itself and foreign objects. Antibodies have been used in the lab for many years now, they were originally extracted from the spleen of inoculated mice. However, this couldn't be used in medicine because it regularly triggered an immune response.



It is only recently that chemists have been able to create synthetic enzymes. At Ohio University they successfully created a synthetic catalyst with similar properties to its natural counterpart whilst reducing the adverse affects of an immune response. The ability to create a specific shape could be used to replicate the properties of the antigen-binding site, if this were to be incorporated into a drugs structure then it would be possible for drugs to differentiate between cells within the body. However the problem of how to prevent the drug from interacting with the rest of the body before finding the correct site would still remain.

Antigens could be used to improve radiopharmaceuticals in the treatment of any cells with a distinctive antigen, such as a tumour. If an antigen could be isolated from the tumour cell then it could be used to create an antibody. It should be possible to create the correct shape for the antibody because it will be the exact opposite of the antigen, if mice were to be used then the antigen would have to be used to trigger an immune response and the antibodies could be harvested and then used. Once the antibodies had been obtained then  $^{131}\text{I}$ -MIBG (metaiodobenzylguanidine) a radioactive source currently used to treat tumours, could be attached to one of the arms. This would then attach itself to the antigen of the tumour and bind the metal too it. The radiation would then kill the tumour; this method would reduce the radiation absorbed by the rest of the body as the radioactive source would spend the majority of its time at the site of the tumour.

Antibiotics would also benefit from the use of antibodies; because they have different antigens to the human body cells, they are easily identifiable. If an

antibody were to be incorporated into the drug then it would be possible to bond it to the bacteria it was designed to fight.

### Using Buckminster fullerene

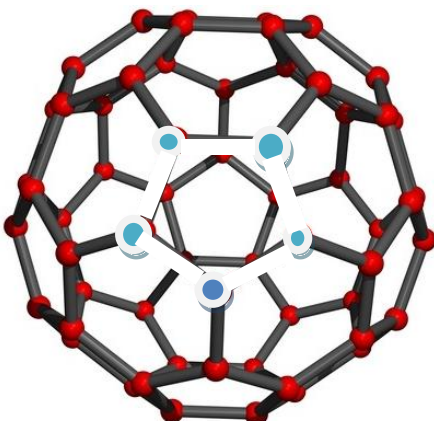
One possible method of transporting drugs whilst preventing them from interacting with the rest of the body would be to use Buckminster Fullerene; this has similar properties to nanotubes but is spherical instead of tubular. This would have the capacity to carry most drugs in around the body.

The inside of the ball bears a slight positive charge this is due to the delocalised electrons trying to distance themselves from one another, this would mean that the drug within the ball would not touch the sides preventing it from interacting. The converse of this is that the outside has a slight negative charge, this would increase the chances that it would interact with the ions in the body making this a potential problem, this however shouldn't be an issue because the charge isn't great enough to form a strong bond, the main noticeable affect is that they are very hydrophilic which allows it to dissolve easily into the blood due to its high water content. The negative charge is able to form hydrogen bonds with the polar bonds in water; this is what makes all ions dissolve.

To guide the Bucky balls to the site of the drug antigens can be used. As previously explained they can attach themselves to an antibody specific to a particular bacteria or cancer.

The only problem with Bucky balls is that because of the strong covalent bonds holding it together it would be difficult to release the drug into the body. A way would need to be found to open the structure once it has reached where it needs to be in the body.

One possible way to solve this would be to replace five of the adjacent carbon atoms with hydrogen; the human blood is naturally alkali and would attack the hydrogen with an oxidation state of +1 this allows it to act in a similar way as  $H^+$  ions in acids. This reaction would take time during which the antigens can bind to the individual cells.



It would also be possible to wait for the fullerene to combust; Bucky balls naturally react with oxygen to form  $CO_2$ . The slight negative charge on the outside of the ball means that electrons are readily available to the oxygen which is naturally bonded to the iron in the haemoglobin, once the oxygen is attracted to the carbons electrons, it will enter an intermediate stage where it accepts the carbon electron and breaks the bond with the iron, much like in a nucleophilic substitution reaction. The  $C^+$  ion would then be removed from the Bucky ball to create a double bond with the oxygen. This would then react with the oxygen being carried by another haemoglobin to form  $CO_2$ . Over time the whole Bucky ball would react and the drug released.

The reaction time would be affected by the  $CO_2$  levels in the blood, if levels were increased the haemoglobin would become taugh giving it a low oxygen affinity, this means that the bond to the oxygen is weaker allowing it to react with the carbon more easily. The only problem with this is that once the carbon is removed from the main structure it will form carbon monoxide; this is poisonous and will form a strong bond to any unbounded haemoglobin. This means that unless there is oxygen readily available it may reduce the level of haemoglobin in the blood potentially causing oxygen deprivation within the body. However unless large quantities of drugs were given in under four months the effect would be minimal as only the minority of the carbon will attach to the haemoglobin because unlike in the lungs the haemoglobin is already bonded, also the blood is completely recycled every 100 days. Despite this it would be unsafe to use without considerable testing to find out the exact levels of  $CO$  produced.

### Creating Buckminster fullerene

When using Bucky balls to form inclusion compounds it is very difficult to get the molecule inside the Bucky ball in the first place. Any molecule that is to be trapped within a Bucky ball has to do so whilst the ball is being made, this is problematic because of the conditions needed to produce the balls. Bucky balls are made by firing a high energy laser at graphite which is in helium or another similar inert gas. This causes the graphite to form Buckminster fullerene as well as other carbon compounds; the specific compound can be controlled by altering the timing of the laser. To trap a compound into the ball it is simply placed in the presence of the graphite when the laser light is shone on it; it is then

merely by chance that it is trapped within its structure, because of this there is a low success rate and not all the Bucky balls will contain the compound.

During the process of making the balls the compound will also be subjected to the laser light, this could cause it to be broken down or altered in some way because the laser would provide enough energy to break the bonds and even ionise the atoms; when the atoms reform bonds they are unlikely to return to their original structure. This would also be more likely with drugs because of their large size; they are also designed to react within the body but may also react with the carbon because of the high levels of energy they are exposed to. In the future it may be possible to create fullerenes with much more precision and accuracy; there are already new ways being tested, few of which are shared because of their potential uses in pharmacology.

Another potential solution in the future is quantum tunnelling; this is where a particle is fired through a barrier which it should be unable to pass through because it lacks the required energy. In quantum tunnelling, due to wave particle duality, the quantum object can "tunnel to the other side". The probability of this occurring is still quite low but is still possible. This can currently only be done with objects the size of protons and neutrons but in the future may be possible with larger molecules; this is because Bucky balls are currently the largest molecule shown to act as a single quantum object. If in the future quantum tunnelling became feasible with large molecules then it could be used to fire the drugs into the Bucky ball without damaging them in any way.

It is perfectly viable to create synthetic enzymes however bonding it to Bucky balls poses a problem; simple reactions such as electrophilic addition can take place with fullerenes but they have yet to become part of a large structure. There is no theoretical barrier to this; however it would be necessary for the overall success of the antibodies as a method of locating specific cells.

#### Using other elements other than carbon

Buckminster fullerene is very slow to break down, however, similar structures are being trialled with different elements. Molecules such as silicon dioxide would produce a larger ball, the bonds are more spread out and due to the differences in electro negativity, the bonds are more polar; this increases the chances that it will interact and decompose faster than carbon fullerenes.

However this instability means that they are less likely to reach the site where the drug is to be released, silicon dioxides when joined together to create a larger structure aren't one large molecule like fullerenes but are distinct polar molecules which are bonded together in a similar in structure to ionic compounds, this means that it would quickly break down and dissolve because of the water in the blood.

Other molecules offer a greater degree of control over the time at which they release the drug. Boron has been predicted to be a chemically stable ball, however, it has however been criticized because the shape is shown to be vibrationally unstable because of an unusual symmetry. This symmetry means that it is easy to create a standing wave around the ball, these oscillations can build up energy to eventually break the ball. It would however be possible to use boron in a medical environment because it takes time for the standing wave to build up, throughout this time a constant vibration at precisely the right frequency needs to be applied, these aren't conditions found within the human body so it would be stable under standard conditions.

It would be possible however to induce the standing wave whilst it was in the body, if ultrasound was used to send the correct frequency through the body, the boron would break down, releasing the drug, this would enable doctors to wait for the drug to be in the correct place before releasing the drug. The limitation with this is it would be impossible to break up an individual molecule because the vibrations used are longitudinal; therefore refraction causes them to spread out through the body.

With any of system where the drug is contained inside a spherical container with an antibody attached, on release, the drug would be directly on the cell vastly increasing the probability that it is absorbed by that particular cell. Some of the antigens would not reach the correct cells as it is purely by chance that the two meet, this is therefore not an ideal solution as there is still no guarantee of success.

## Conclusion

In summary, nanotechnology, in some form or another, will be used in the future development of pharmaceutical drug delivery systems. Despite having discussed two distinct key areas in isolation I do not believe that there is a clear way

forwards. The future will be built around many separate ideas, drawing on different areas of research, with the key being integrating to suit the situation.

In my opinion the use of antibodies will be successful over the use of nanotubes because of its practicality in everyday situations, also nanotubes are mostly limited to abscess, the convenience and versatility of antibodies will make them more practical and also desirable in the future. Out of all the methods of containing drugs I believe that boron offers the greatest level of control.

We can be sure then that the use of nanotechnology will continue to expand, it will however raise many controversial issues along the way. To achieve the current technologies there have been large amounts of animal testing, this is an issue which is deeply opposed by many people. Not only would this pose a threat to future research but any developments would have to overcome this opposition before being accepted into mainstream medicine

If in the future we have the ability to take over the processes of the individual cells, it would raise the question of whether too much was being done to preserve life. If it were possible to prevent cancers and tumours, fight disease, and otherwise prevent the deterioration of the body then would it be the best thing for the patient? Just as when it is decided that a life support machine should be switched of, when should it be decided that enough medication has been given?

Also, if mortality rates were to significantly drop then the population may grow at an ever increasing rate. The money needed to provide such sophisticated medical techniques to everybody would be impossibly expensive, only people with the money to spare would be able to afford it. This would raise the question of whether it is right that money determines the treatment you can afford and therefore how long you can live.

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