

ADVANCEMENTS IN NANO TECHNOLOGY WITHIN MEDICINE AND  
THE POTENTIAL EFFECTS ON THE GENETIC DISEASE CYSTIC FIBROSIS

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PASS WITH MERIT

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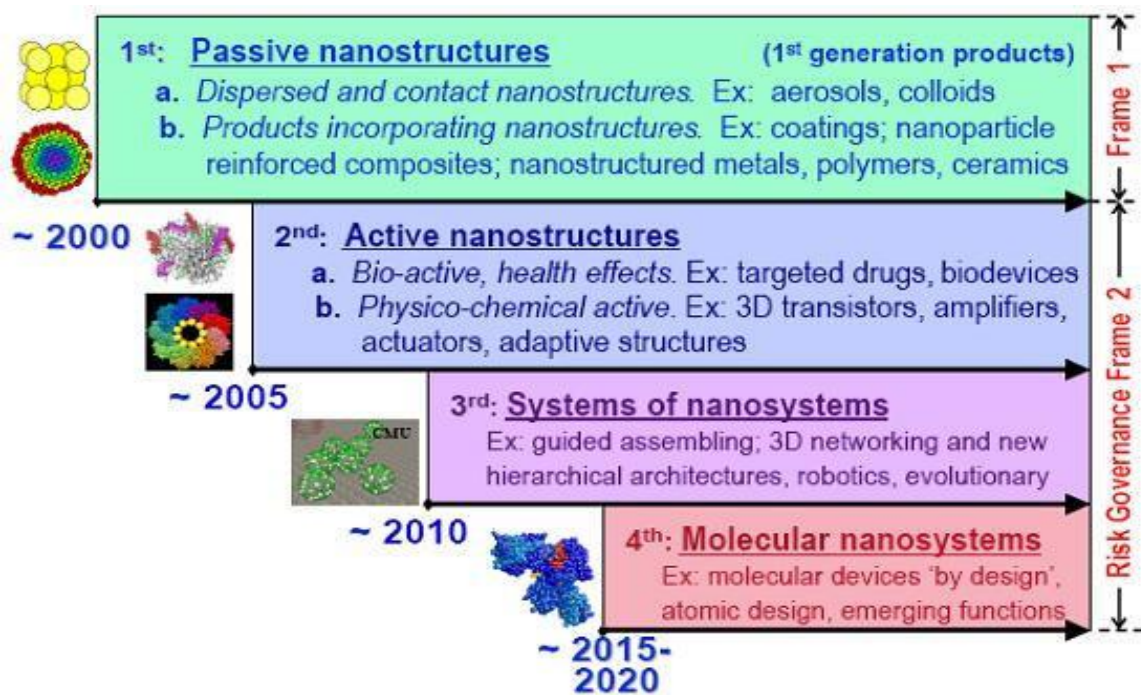
## Abstract

In recent years, nanotechnology has developed and has begun to have an impact of our way of life, being used in industry, food and medicine. It holds large amounts of potential to medicine as it can deal with issues at a microscopic level, which no medical tool can. Nanotechnology is being used more often and being developed in our society due to treating problems with great precision, and has begun to show great results.

The subject area of this paper is to develop ideas surrounding the uses of nanotechnology and to incorporate this technology in improving the detection, diagnosis, prevention and eventually a cure for the genetic disease, Cystic Fibrosis (CF). Our main aim is to develop an idea using nanotechnology which can be used to improve the quality of life of a patient suffering from cystic fibrosis and even reduce costs associated with treating the symptoms.

## Introduction

Nanotechnology is the engineering of function systems at an atomic level. This means by general definition, dealing with matter at the scale of one billionth of a meter, the average size of 3 atoms. In comparison with eukaryotic and prokaryotic cells, a bacterium is 1,000 nanometres (nm), a single virus is 100 nm and 1 DNA molecule is 1 nm. This instantly shows the huge implications nanotechnology holds for medicine. It allows nanotechnology to create molecular machines which recreate nature from the bottom up, and instantly holds potential to revolutionise modern day medicine in treating the human body and disease. Below, (Figure 1.) shows the recent uses and future possibilities of nanotechnology. With technological advances it allows technology and medicine to work together in helping others

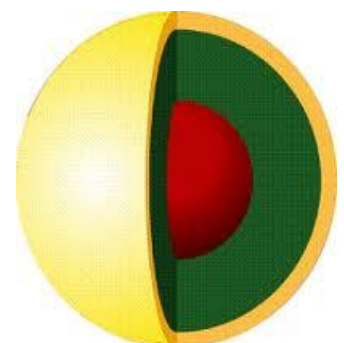
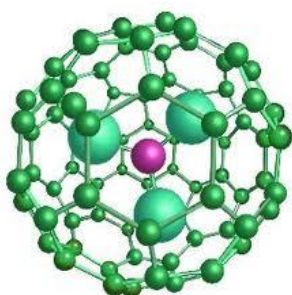


Nanotechnology has been a recent discovery and concept, only being realised in the mid 20<sup>th</sup> century. Prof. Richard P. Feynman (1959) a physicist gave a talk entitled, 'There's Plenty of Room at the Bottom,' about the use of micro-technology in being the new frontier for

science. It was not until K. Eric Drexler (1980s), when scientific depth and analysis was taken into account for the prospects of nanotechnology and the term became popularised in the science community. During this period, the Scanning Tunneling Microscope (STM) was invented by Binnig & Rohrer (1981) which allowed individual atoms to be identified and moved. Soon after Smally & Kroto (1985) created the first carbon Buckminsterfullerene at Rice University. With Feynman's and Drexler's theoretical idea for the future of nanotechnology and the inventions of the STM and Buckminsterfullerene, nanotechnology became a reality.

Since 2000, nanotechnology has made an impact on modern day medicine with research promising advances in anything from drug delivery to cancer detection and treatment. In 'nanomedicine,' there are a number of different nanoparticles which are being used or developed. These include:

- Fullerenes (Buckyballs & Nanotubes), probably the most common type of nanoparticles used. These are manufactured from carbon atoms in a regular lattice structure. They have a high tensile strength and stiffness, unique electrical properties allowing them to pass charge, ideal for stimulating drug delivery in patients and imaging; and are porous, allowing them to pass molecular matter in and out of cells. (figure 2)
- Liquid Crystals, organic liquid molecules which substitute naturally occurring biomolecules such as proteins and enzymes. Ideal for dealing with enzyme deficient patients, such as in cystic fibrosis, since it allows synthetic doses of these enzymes to aid the patient's digestion. They are also very specific and precise, because the crystals line up in arrangements, this, when applied to cystic fibrosis, could target the worst affected areas of the patient, the lungs and the pancreas, helping relieve symptoms. (figure 3)
- Nanoshells, spherical cores of a particular compound which is then surrounded by a shell or coating of another compound, a few nanometres thick. Nanoshells have been used to kill cancerous cells and tumours. This is done by nanoshells being injected into the cells, and then an amount of infrared radiation is applied which destroys these cells as the gold core heats up and vibrates. Although very small, in large numbers this is very effective. Applying this to cystic fibrosis, large amounts of mucus and phlegm cause problems for drugs and treatment when reaching the lung tissue, the potential for using nanoshells and infrared radiation is to suppress the large build up which could be a viable treatment and also allow certain drugs or liquid crystals to reach the epithelial cells of the lungs. (Figure 4)



## **Cystic Fibrosis**

Cystic Fibrosis is one of the UK's most common genetic diseases and the most common genetic disease affecting babies and young people in the US. It affects over 8,500 people in the UK and 30,000 people in the US. Most patients diagnosed with cystic fibrosis spend the majority of their time in hospitalised care or under constant care at home. Some cases spend 26 weeks out of 52 weeks in hospitalised care. The average life expectancy of cystic fibrosis patients is up to 38, but with future developments, life expectancy could increase for newborn cystic fibrosis patients.

Cystic fibrosis is caused by 2 recessive genes, one faulty gene from the paternal and one from the maternal. These are found in chromosome 7, which controls salt and water movement in the body. If both parents are carriers of this gene, they have a 1 in 4 chance that their baby will have cystic fibrosis. The biggest problem with cystic fibrosis is that there is no known cure for it. However with the prospects for nanotechnology, there is a possibility of a treatment which can cure cystic fibrosis, discussed later in the paper.

Patients suffer a variety of symptoms, such as coughs, frequent chest infections, diarrhoea and malnutrition. It affects mainly the lungs and the digestive system, causing a range of complications such as in other aspects of life; infertility, difficulty breathing and malnutrition.

Cystic fibrosis affects the pancreas by reducing the production of essential enzymes such as amylase, proteases, and lipases in digesting food. This causes difficulty to gain weight, and consequently develop due to malnutrition. Therefore nutrients and sometimes a drip are used to add weight and give the patient the vitamins and enzymes they need. Cystic fibrosis affects the lungs by causing a large build up of thick mucus which causes coughs and therefore becomes a prime breeding place for the growth of harmful bacteria, which cause the frequent chest infections. Antibiotics are frequently taken to treat infections and prevent damage to the lungs. Patients use a, 'vest,' where they wear a vibrating vest which is used to shake the excess mucus build up in the lungs and throat.

As mentioned above, cystic fibrosis affects a patient's digestive and respiratory system. The patient takes a large number of antibiotics and nutrient pills and has frequent visits to the hospital a majority of the year, which can restrict them often from living a normal life. This has obvious negative effects on the patient, but also on the healthcare system, as treatment is often regular and expensive. From our research we feel that in the future it will be possible to reduce these costs, but more importantly improve the quality of life of cystic fibrosis patients.

## **Discussion**

The advances mentioned have provided the technology necessary for medicine to progress to new territory. The nanotechnology has and will have the potential to greatly improve four loose groups within medicine. These seem to be detection; by utilising technologies that enable different scanning techniques, drug delivery systems; by using particles to target specific cells, destruction of cells; for instance of cancer cells and finally by nano-robots, to do specific jobs such as cell repair. Concerning Cystic fibrosis, each is to have a profound effect on the detection, relieving of symptoms, increasing life expectancy and eventually curing of the disorder.

## **Detection**

Initially, whilst screening and tests are available the detection of cystic fibrosis, they involve tests that are non-specific and often unreliable. The first is the 'Sweat Test', this involves initiating a new born baby, usually around 3 weeks old, to sweat profusely on a patch of skin, normally the forearm or thigh. This is done using the drug Pilocarpine and a weak electrical current is passed through the area. The sweat is collected after ten minutes of the treatment, for around 30 minutes until it is tested. The test is for excess sodium chloride, for which an excess is secreted in the sweat for reasons to do with a ion imbalance in cells. On a scale a level of sub 30 is considered normal and post 60 is thought to have cystic fibrosis.

The second most common test, the test for immunoreactive trypsinogen is also done at this age, by drawing blood from the heel of the baby. If the IRT level is raised there is a strong chance of cystic fibrosis or pancreatic abnormality when producing enzymes. However the test often produces false positives and needs to be repeated.

This leads onto a more reliable and nano-technological advance that is being researched by Southampton University. A genetic test is available by which DNA is tested to be mutated by the process of differential denaturation, in which mutated DNA breaks down at a lower temperature than normal DNA due to more instability because of non complementary nucleotides. The research shows that if the DNA strands are attached to gold nanoparticles with sulphur linkages the DNA breaks down under an applied gradient of an electric current. This could have huge benefits in detecting not only cystic fibrosis but all other genetic disorders. The potential for this technology is clear, a portable device could feasible be made at low cost, which in turn, means that hospitals and even doctor's surgeries could make quick diagnosis for patients. This would make diagnosis, when potentially combined with the other tests, much more reliable and effective from even before birth. The other benefits include the cost, the 'sweat' test and IRT test are both reasonable costly and specific to cystic fibrosis meaning special equipment has to be bought. With this more portable DNA testing equipment it can be used more generally and so should be able to reduce costs of detection.

## **Drug Delivery**

The symptoms of cystic fibrosis are most severe in the lungs, because of chronic infections that thrive in the excess mucus. In a normal lung, epithelial cells produce thin watery mucus that is constantly moved by the cilia into the stomach, where the bacteria caught are killed. However, in a person with cystic fibrosis the faulty gene codes for protein which is not produced properly as a result of the gene mutation. This particular protein is attached to the outer membrane of a cell and acts a channel for chloride, iodide and more interestingly thiocyanate ions. This restricted channel slows the uptake of these ions into the cytoplasm of the cell, which results in exocrine secretions (secretions such as mucus) with altered ion content, reduced water content and higher viscosities. These therefore clog up the ducts by which they should be secreted and contain more ions and potential nutrients than usual.

This means that bacteria are able to colonize in such secretions and thrive. Furthermore, in the lungs, because of the slower transfer of thiocyanate ions the body's immune system is unable to produce the weak acidic and effective bactericide called hypothiocyanate, from which thiocyanate is reacted with oxygen. This acid is used by the immune system especially well in the lungs, although this cannot be done in a person with Cystic Fibrosis. Therefore the bacteria in the accumulations of mucus are able to multiply without an effective bactericide.

This is where the recent technologies of nanotechnology are very effective. The drug delivery systems that are possible because of nanotechnology are groundbreaking. Firstly the structure the particle is currently thought to be most effective within drug delivery has these features; a hollow centre that encases the drug, for larger drugs this may be numerous shells that group together. This encasing has the benefit of shielding drugs that would normally cause very negative symptoms or be toxic to the body, until at the site where the drug is most needed or will cause least harm. The shell needs to be coated with a layer of material which stops proteins binding to the particle, which in turn stops the body's immune system recognising it and attacking it. The difficulty with the molecule is making the drug be delivered to the right area. Current thoughts on this suggest that the use of heat could be a way of breaking the molecule, or the use of light to highlight the area needed. However whilst this may be effective for tumours, this is less useful in the lungs. Potentially the nanoparticles could deliver the drugs where there is an increased concentration of thiocyanate, such as in the mucus secreted in the pancreas and lungs. This would involve a potential trigger being attached to the outer shell which reacts in high concentrations of any of the ions present in the mucus. This could provide a system to deliver new drugs such as VX-770, which has been shown to decrease mucus production by 10% in cystic Fibrosis patients when taken orally.

An alternative method of breaking the nano-shells would be to use temperature, as already stated, but the cause of the temperature not a tumour but because of an exothermic reaction that has taken place because of a chemical attached to the nano-shell. The issue is

with this method that resulting products would be made that would not be wanted; although they could be breathed out if the products were in a gaseous state.

### **The Potential Cure**

Perhaps the ultimate goal with all this research is to alleviate the symptoms associated with cystic fibrosis and extend life expectancy, of course the most obvious way of doing this would be to 'cure' the disorder, although this provides some obvious challenges. Firstly the disorder is genetic, meaning it is coded for in every single cell in the body, so cells are always going to be reproduced containing the faulty gene. Secondly, no physical molecule has infected the person that can be destroyed, thus curing the disease. Therefore in order to 'cure' the disease, one must consider changing the DNA of the patient, by using gene therapy, to stop the faulty gene reproducing. Currently the main way being researched that could achieve this without very negative side effects is the use of a virus containing the altered DNA. This virus would be breathed in and then would infect the cells of the lungs and in doing so stops the production of the faulty protein by forcing the cell to produce proteins according to its DNA, which would be genetically engineered to be correct. This research is being conducted mainly by the Fred Hutchinson Centre.

Their research shows that a small virus called the Adeno Associated Virus shows huge amounts of promise as a carrier of genes. It is a small virus that carries only a single strand of DNA. There are many advantages to using this specific virus as a vector for carrying the correct gene, for instance it creates little or no immune response as it is not disease causing. It also transfers genes to the human chromosome with almost one hundred percent efficiency. These factors mean that extensive research has been conducted into using it for gene therapy. However it has its drawbacks, and according to the research of David Schaffer professor of chemical engineering at UC Berkeley, one of the main of these is that respiratory diseases are not particularly contagious, surprising, but thought to be because high infection rates would wipe out the host too quickly as the lungs are so vital for life. This problem has been partially helped with Schaffer's development of the gene to make it much more infectious, which in turn increases the chance that it will get into the cells of the host and implant the DNA. However this has not solved the problem completely, because although it is more infective in normal patients, with cystic fibrosis the mucous acts as an effective barrier to cells. This would be fine if the idea was just to cultivate the virus in the lung, but entry to cells is needed if the treatment is to be successful.

Nanotechnology could help increase the ability of the virus to enter more cells and the way in which this could be done is to travel through some of the viscous mucus. Some research conducted by Benjamin C. Tang provides an effective nano particle to do this, it is a biodegradable diblock copolymer of poly(sebacic acid) that shows massive increases in diffusion speeds in normal human mucus, and although this would be slower in the more viscous Cystic Fibrosis mucus, this increase in ability to reach cells could increase the ability to transfer DNA. The potential in this could be to either attach the virus to the nano particle

and then have the virus released to enter the cells or merely inhale both and hope the virus will diffuse along with the nanoparticles. Although this relies on chance of diffusion and could have no beneficial effect it does solve the problem of releasing the virus into the cells. On balance, the attaching of nanoparticles seems more promising and beneficial. An alternative is to break the mucus down, this could be done in numerous ways; including the use of nanoshells containing gold centres that, when infrared waves are subjected to, heat up, destroying the cells they are in. This could be adapted for use in mucus. The nano particles could be attached to particles which are attracted to high concentrations of ions, as present in the mucus. This would ensure that the nanoparticles did not damage the epithelial cells in the lungs. Currently the use of the virus to transfer genes is in its tertiary stage of human testing, as shown by the table. This method therefore has a promising future and could provide a huge leap forward, whether aided by nanotechnology or not, in the curing of Cystic Fibrosis.

### **Conclusion**

As stated, the future of nanotechnology has much scope within medicine and has the potential to not only save many lives, but to ease the suffering of those it cannot save.

The use of nanotechnology within the diagnosis of genetic disorders is well on its way to being implemented within medicine, through the use of separation of DNA on an applied current gradient. Although this is non-specific for cystic fibrosis, this makes it all the more important, as it can be used for all genetic disorders. The potential then, is monumental and therefore why we think more research is paramount.

The use of potential targeted drugs within the lungs is less far on the research timeline. It also holds scope to relieve many people however and holds great importance in the collective attempt to eradicate cystic fibrosis as a genetic killer. Advancements could be improved by future technology, for instance a better way of releasing the drugs, which is less specific to cancer. Therefore this treatment is still very much in the pipeline.

Finally the use of a virus to potentially cure the cystic fibrosis gene holds the most scope for improvement of lives. This combined with potential future nano-bots which could improve the system by which the DNA enters the host cell seems to be a very successful idea. However the technology is still very limited for the use of nano-bots. Current nanotechnological advancements, such as the particle which diffuses through the mucus, could further the research into this field of genetic therapy.

When all is taken into account, we feel that it is only a matter of time before a treatment or diagnosis is available to the general public that can save or relieve some of the many people who have cystic fibrosis in England, and the world.

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