

# Nanotechnology and its Uses in the Treatment of Diabetes

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## **ABSTRACT**

This paper was written after a solid background of the basics of nanotechnology and a good understanding of the mechanisms of Diabetes was obtained in order to better understand current and future treatment. This paper comprises of some of this research and explores some of the ways nanotechnology may aid the treatment of diabetes in years to come. With an expected doubling of Diabetes sufferers in some countries, new treatment methods must be put into effect if the World Health Organisation is to be expected to deal with this coming crisis.

## **INTRODUCTION**

### **Nanotechnology**

#### **Origins of Nanotechnology**

Nanotechnology is the study and manipulation of matter at the atomic and molecular level, this can be working with sizes from between 1 to 100 nanometres (1 nm =  $10^{-9}$  m). While the concepts of Nanotechnology were being explored from the early 60s Nanotechnology itself did not get started until later in the early 1980s with the beginnings of cluster science and the invention of the scanning tunneling microscope (STM) allowing scientists a feasible method of exploration into the world of atoms and molecules. A few years later the discovery of the fullerenes (e.g. buckminsterfullerene or  $C_{60}$ ) and carbon nanotubes allowed the researchers to take nanotechnology further and begin to engineer their own devices for varying purposes. In 2000 the US founded the National Nanotechnology Initiative in order to better co-ordinate Federal research and development. Nanomedicine is the application of Nanotechnology in medicine.

#### **Drug Delivery**

Nanoparticles are very small and as such will not be cleared from the body where other larger particles would have been. These small particles are taken up into the cells because of their size, and because of their shape many of them are well designed to carry substances within themselves (see figure 1- buckminsterfullerene). Currently delivery mechanisms are being developed that could allow the particles through the cell membrane and into the cytoplasm. These mechanisms will have to be very efficient as many drugs need to be within a cell before they can successfully treat a disease.

A method being explored for the distribution of drugs is 'triggered response'. This could help regulate drug release as the drug would only be activated if it came into contact with a certain 'trigger', better regulated drug release would allow for greater efficiency, currently over \$65 billion is wasted each year due to the poor precision of drugs, and eliminate the problem of tissue damage due to the quick release of a drug in one location. Poor biodistribution affects normal tissues through the widespread distribution but because of the small size of the Nanoparticles the drug is released more gradually, this also prevents the drug being cleared from the body too quickly and thereby reduces the high dosages some patients have to use.

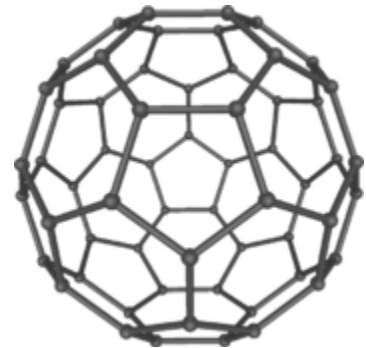


Figure 1 Buckminsterfullerene (or 'Bucky Ball')

## Nanoparticle Targeting

By tracking Nanoparticles around the body (e.g. by using luminescent tags) scientists can create images of the human body that allow doctors to find out the distribution of a drug in the body or to diagnose cancer/track a tumor, for instance using a triggered response to cancerous cells. Luminescent tags are attached to proteins that penetrate cell membranes and are made of bioinert materials so they will not interfere with the body's natural processes. They can be used at various different sizes and colours so that several can be tracked at any one time, allowing for fewer light sources to be used (the current system needed as many light frequencies as cells in order to track them all).

## Nanomaterials

Nanomaterials are usually classified into two groups: fullerenes and inorganic Nanoparticles. The fullerenes are essentially graphite sheets rolled into spheres or tubes. One such material is the nanotubes; they are currently the strongest and stiffest material known and they have excellent kinetic and electrical properties. These specific properties have sparked the interest of many researchers across the world. Research at the University of California has shown carbon nanotubes to be suitable as scaffold materials for bone formation and due to their electromagnetic properties they have been put forth as a candidate for the replacement of muscle tissue.

Nanoparticles also have a role to play in medical development, particles that have been shown to have useful properties include: colloidal gold, iron and silver particles. Colloidal gold has been shown through experimentation on rats and dogs to be an effective pain reliever when injected into a joint that has been affected by arthritis; research is being done to qualify the claims made by some scientists that Iron Nanoparticles could be used as a cheaper and healthier method of water decontamination by a redox reaction and Silver Nanoparticles are used as an antibacterial/antifungal agent in bioengineering and biotechnology but there is an effort in place to incorporate silver Nanoparticles in a range of medical devices including bone cement and wound dressings.

## Diabetes

### Epidemiology

Diabetes is a world-wide epidemic that has been made worse in recent years by the rise in obesity rates, particularly in the western world. In the UK alone there are 2.8 million people diagnosed with diabetes and a further 850,000 estimated to be unaware that they have it (Diabetes UK). Worldwide there is a much larger problem as shown in Figure 2 (the work of Wild et al. that appeared in the journal *Diabetes Care* in 2004)

### Pathophysiology

There are two main types of diabetes (1 and 2) both prevent glucose from entering the cells but act in slightly different ways. Insulin is needed to allow glucose into the cells, think of it as a lock and key where the insulin (key) is

Ranking	2000		2030	
	Country	People with diabetes (millions)	Country	People with diabetes (millions)
1	India	31.7	India	79.4
2	China	20.8	China	42.3
3	USA	17.7	USA	30.3
4	Indonesia	8.4	Indonesia	21.3
5	Japan	6.8	Pakistan	13.9
6	Pakistan	5.2	Brazil	11.3
7	Russian Federation	4.6	Bangladesh	11.1
8	Brazil	4.6	Japan	8.9
9	Italy	4.3	Philippines	7.8
10	Bangladesh	3.2	Egypt	6.7

Figure 2 Global Prevalence of Diabetes: Estimates for the year 2000 and projections for 2030

needed to unlock the cell (lock) allowing it to open and accept glucose.

In type 1 diabetes the body doesn't produce any insulin; this is due to an autoimmune response in which the body destroys all of the insulin producing cells. Without a key the lock cannot open to accept glucose. Type 1 diabetes accounts for about 15% of all cases, is mostly found in the under 40s and is by far the most common type of diabetes found in childhood.

Type 2 diabetes accounts for about 85% of all cases and is most common in the over 40s in the Caucasian population and the over 25s in the Black and South Asian populations. In type 2 diabetes either the body isn't producing enough insulin to let all of the glucose into the cells or the insulin the body produces isn't working properly. This can be due to obesity as a build-up of fat in the body can stop insulin from doing its job properly, going back to the lock and key analogy, if the lock (body cells) is rusted (blocked by fat) then the key (insulin) won't be able to fit in the lock and open the door properly. However obesity is not the only risk factor as it can also happen in people of a healthy weight.

**Predictors, Risk Factors and Symptoms**

There are no sure predictors of either type of diabetes and there is at the moment no way of preventing type 1 diabetes; however there are many risk factors that can be taken into account for type 2 diabetes. These include: age, family history of type 2 diabetes, weight, high blood pressure and impaired glucose tolerance.

In type 1 diabetes the symptoms can come on very rapidly as no glucose is being produced, however in type 2 diabetes some of the insulin is still working so the onset is much slower, a person may live with undiagnosed diabetes for up to 10 years. The symptoms of both types of diabetes are the same: more frequent urination (due to the body's need to rid itself of the excess glucose in the blood), thirst (due to excess urination), extreme tiredness (lack of glucose in the cell for fuel), unexplained weight loss (an attempt of the body to get more glucose to the cells by breaking down fatty deposits, genital itching or regular episodes of thrush (excess glucose in urine encourages bacterial growth), blurred vision (glucose deposits in the lens of the eye) and slow healing cuts and wounds (bacteria breeding in flesh wounds due to high glucose content in the blood).

**Current Treatment Options**

Diabetes cannot yet be cured but it can be successfully managed. In type 2 diabetes a person may be able to control the diabetes with regular exercise and a change in diet as well as losing any weight that may be appropriate, however as type 2 diabetes is a progressive disease most people will have to use some form of medication (figure 3) to deal with it, in some cases insulin may have to be used. Type 1 diabetes cannot be helped by diet and physical activity so insulin must be used from the start.

Figure 3 Medication Reference Chart for Type 2 Diabetes

<b>MEDICATIONS FOR TYPE 2 DIABETES</b>				
<b>Classification</b>	<b>Medication</b>	<b>Route</b>	<b>The way it works</b>	<b>Time and Dose</b>
Sulfonylureas	Glimepiride (Amaryl) Glipizide (Glucotrol) ER Glipizide (Glucotrol XL) Glyburide	Oral	Increases insulin production	1 or 2 times a day

Biguanides	Glucophage (aka Metformin) Glucophage XR	Oral	Lowers glucose from digestion	2-3 times a day, XR once a day
Alpha-Glucosidase Inhibitors	Glyset and Precose	Oral	Slows digestion, slows glucose production	Take before each meal
Thiazolidinediones	Actos and Avandia	Oral	Lowers glucose production	Once daily with or without food
Meglitinides	Prandin and Starlix	Oral	Increases insulin production	5-30 minutes before meals
DPP-4 Inhibitors	Januvia	Oral	Lowers glucose by blocking an enzyme	100 mg. once a day
Incretin Mimetics	Byetta	Injectable	Helps the pancreas make insulin, slows digestion	10 mcg. Inject within an hour of AM and PM meals
Anti-hyperglycemic	Symlin	Injectable	Controls postprandial blood glucose	15 mcg. Inject before major meals

All people with type 1 and some with type 2 diabetes need insulin. Insulin cannot be administered orally as it is a protein and would be digested before being absorbed into the bloodstream so it is injected with syringes or an insulin pump is used. There are many types of insulin, all acting in slightly different ways as shown in figure 4.

Figure 4 Insulin Types and Actions

<b>INSULIN TYPES AND ACTIONS</b>				
<b>Brand Name</b>	<b>Generic Name</b>	<b>Onset</b>	<b>Peak</b>	<b>Duration</b>
<i>RAPID ACTING</i>				
Apidra	Insulin Glulisine	<15 minutes	1-2 hours	3-4 hours
Humalog	Insulin Lispro	<15 minutes	1-2 hours	3-4 hours
Novolog	Insulin Aspart	<15 minutes	1-2 hours	3-4 hours
<i>REGULAR</i>				
Humulin R	Regular	1/2 - 1 hour	2-3 hours	3-6 hours
Novolin R	Regular	1/2 - 1 hour	2-3 hours	3-6 hours
<i>INTERMEDIATE ACTING</i>				
Humulin N	NPH	2-4 hours	4-10 hours	10-16 hours
Novolin N	NPH	2-4 hours	4-10 hours	10-16 hours
<i>LONG ACTING</i>				
Levemir	Insulin Detemir	3/4 - 2 hours	minimal peak action	up to 24 hours
Lantus	Insulin Glargine	2-4 hours	no peak	20-24 hours

### Insulin Pumps

Insulin pumps have been in circulation around 20 years, they allow tighter control of blood glucose levels and have been reported to increase the patients quality of life in comparison with injections and medication, mainly due to the relative freedom from the structured meals and exercise regimes previously needed to control the disease. Pumps also offer greater convenience and discretion and in some cases where neuropathy has complicated treatment there have been reports of alleviation or

total disappearance of pain. However pumps are much more expensive than injections and have the added risk of breakages and long term damage.

## **DISCUSSION**

The current cost of Diabetes to the NHS is £9bn a year (10% of the NHS England and Wales budget) that's £1 million an hour or £16,666 every minute. A report from the NHS recently stated that in the past 5 years the cost of diabetes treatment and medication had risen by 40% from £458.6 million in 2004/5 to £649.2 million in 2009/10. The high costs of current diabetes treatments coupled with the new possibilities Nanomedicine is bringing in daily is a strong incentive to research treatments particular to diabetes. As there is no clear indicator of when Diabetes could appear in a patient (or even at all) and no certain preventative measures to be taken, the main focus of research has been on improving treatment and quality of life instead of prevention or curing the disease.

If doctors can diagnose diabetes faster the huge amount of damage done to people who don't know they have diabetes can be reduced significantly, thus cutting the cost of drug treatment to the side effects of diabetes for the NHS by a large amount. Single molecule detection (SMD) is a prime candidate for the detection of diabetes, whilst it has in no way been applied to diabetes at this time it has many features that could be of major assistance in the future. SMD allows assessment of the pattern distribution of a single molecular species instead of measuring the average distribution of a molecule; this would make the detection of abnormal glucose levels a much simpler task and provide a diagnosis in days/weeks as opposed to the 10 years some people can be left living with undiagnosed diabetes. Another method of potential diagnosis is targeted molecular imaging, a molecule that tracks glucose could easily be bonded to a colloidal molecule giving off a traceable signature. Targeted molecular imaging is already used in some cancer scans and is a tested method that has been proven to be effective in tracking other molecules. The difficult part of this method would be to find a non-toxic molecule that could bond to glucose and still be safely removed from the body without causing hypoglycemia because it was bonded to the glucose. This method has the same advantages as SMD apart from it having been used in different tests and having been itself tested in different situations, overall targeted molecular imaging seems to be the most reliable but a suitable molecule must be found before it can be considered as a viable option.

One of the major problems diabetes sufferers have to deal with is the finger-prick glucose self monitoring test, this is a painful invasive process that causes numbness in the fingers of diabetes sufferers after prolonged use. Currently this is a test that must be taken several times a day and research has found that patients have even stopped taking the test in order to reduce the stress and mental strain and pain it had placed on them. Aside from this dangerous habit the very process itself is flawed; the tests are at best intermittent and cannot be taken at times when hyper/hypoglycaemia are most likely to occur (e.g. when driving or when asleep). They also will miss any spikes or drops in an irregular glucose pattern due to their intermittency. Clearly there is both a need and a market for a non-invasive device that will allow constant glucose monitoring.

Several designs have been put forward the first of which is a 'smart tattoo'; small glucose responsive nanosensors are implanted into and onto the skin and could be tracked using the florescent monitoring now common in some medical scans, this is implemented through tiny nanotubes that allow the user to transfer small molecules (such as glucose) without any risk of bacterial infection as

the tubes are simply too small to allow bacteria through. This would be a non invasive procedure that would be pain free but allow the patient 24 hour glucose monitoring, lowering the risk of hyper/hypoglycaemia and keeping track of the overall glucose level trends throughout the day and night. It would also be much more convenient for the patient as they would not need to carry the finger prick equipment with them and could check their levels with minimal effort. The expected pricing of such a device would be expected to be lower than the current cost of the medication and the long term savings would make it almost certainly so. However the major flaw in the design seems to be its main feature, the fluorescent light is currently too difficult to decipher and as such the glucose level reading is uncertain.

Another solution put forward is a glucose-binding protein (GBP) that uses similar florescent monitoring technology but instead of detecting the glucose it binds to it creating a glow that grows with the quantity of glucose available, this allows a greater readability that would be more suited to patients, particularly in this modern age where more people are developing diabetes from an earlier age. This however is not currently a viable option; it has been shown that the sensors are particularly susceptible to degradation, denaturation and leakages from the human body. These major flaws have prevented its use as the sensors can only last a day (or in a few cases a little longer), therefore the cost of replacing the sensors would far outweigh the benefits.

However these solutions have not yet been combined, the flaws of each work to the others advantage, if the GBP could be contained within a nanosensor so that the readability of the GBP could be maintained with the longevity of the nanosensor to protect it then an ideal monitoring device could be produced. Unfortunately the cost of such a hybrid may be too high for the average diabetes sufferer and the production rate of nanodevices is so low that without further research this option may not be able to reach the mass production scale needed to meet the public demand. Another improvement could be the implementation of a light emitting particle attached to the nanosensor; many radioactive Nanoparticles have been attached to cell bodies for medical tests so it isn't too much to presume the same could be done with the nanosensor body, this also allows for the longevity of the product to be maintained whilst making the sensor more user friendly.

Research is also being done into the possible improvements in insulin delivery. As insulin is a protein is cannot pass through the digestive system without being denatured and losing its purpose. The current methods of insulin delivery both cause pain and inconvenience for the patient. Type 1 diabetics can choose between Insulin injections or having a pump installed, both of which are invasive procedures (the pump highly so). While the pump has brought some improvement to insulin delivery through a more natural schedule it is imperfect in its timing, poor glucose control can lead to the build-up of glucose around the body including the eye and kidney causing irreversible damage.

Oral insulin delivery methods have not been successful up till now for the previously mentioned reasons but in 2007 there was a breakthrough with inhaled insulin, the insulin molecules are bound to other molecules that easily pass through the alveolar membrane. These molecules bring the insulin with them as they diffuse through the membrane directly into the blood where the insulin can be of the most use. This system unfortunately was never accepted for general use in the UK as claims it could be linked to lung cancer surfaced but were later rejected on lack of evidence; it was also shown to be very short lasting so much so that basal insulin injections had to be taken as well as the inhaler. Recently a new product has been developed, Afresa is an improved inhaler that works via the same

methods but is bound to a different molecule allowing faster diffusion rates and a longer action time that allows for the number of insulin injections to be significantly lowered. If research was undertaken to find another even more suitable molecule the effectiveness of the inhaler could potentially remove any need for the injections, creating a pain-free non-invasive method of insulin delivery.

None of the research so far has touched upon potential methods of curing diabetes, whilst they are few in number and still in their infancy they are under development. The most prominent of these is the artificial pancreas, a concept that has been looked at in several different ways. One; a bedside device that is attached to glucose monitoring devices inside the body would allow for constant glucose monitoring, as a pancreas does, and as it is attached to an insulin store outside the body it can react in the same way as the pancreas by delivering insulin when glucose levels are too high. This constant monitoring would significantly lower damage caused by intermittent insulin delivery and by extension reduce costs to the NHS by a large sum. However the earlier problems with glucose monitoring systems would still play a part as no working model has yet been successful in the long run. This would be a great risk to patients using the device if the reading was off or the glucose monitors had stopped working as they could easily go into hyperglycaemia whilst asleep. This method would also be just as invasive (if not more so) than the current treatment options so until a better functioning glucose monitor is developed the risks and disadvantages of this method are too high to outweigh the benefits.

The second of the artificial pancreas plans is a non-mechanical artificial nanopancreas. The development of this device is still in the early stages but most of the components have been successfully created including the all important beta-cells (insulin producing cells), and the various nanocapsules that would be needed. The greatest challenge for these scientists in the future will most likely be to mimic the high level of interfacing that goes on within the human pancreas in order to create a fully functional nanoorgan. This device could replace the function of the pancreas and provide the closest thing available to a cure for diabetes. By building a new pancreas the beta-cells that have been previously destroyed would be replaced and so the production of insulin within the body would be able to return to normal, almost like a transplant organ. Unfortunately whilst this method holds the most likely method for finding a cure it also brings up some of the most difficult questions, the moral implications of this device will have to be carefully examined.

## **CONCLUSION**

The moral implications of nanotechnology within the human body are very important to understand for instance if scientists can create an artificial organ successfully where does it stop, people could argue that creating an organ is a small step away from creating an organism and that man cannot meddle in the creation of life. On the other hand the leap from organ to living creature is immense and no technology available today or in the foreseeable future would be able to make that jump. Also before any treatment is developed scientists must give serious thought to the toxicity of Nanoparticles, as of yet there has been no indication of Nanoparticles causing illness or harm through toxicity however the small size of these particles cause them to spread over a larger surface area than their larger chemical counterparts and their ability to pass into cells would cause disastrous results if a harmful Nanoparticle were to be used. In conclusion the future of nanotechnology in diabetes is open with many possibilities and will no doubt be of huge importance in times to come.

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