Nanotechnology and its Potential to the Future of Medicine:

Possibilities of its role in nerve reconstruction

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ABSTRACT
The potential medical advances that will be made possible by successful nanostructures span a wide range of practical applications. We intend to convey the potential of some of these practical applications of nanotechnology in the subsequent passages. Furthermore, we will provide possible developments in the methodology of nanotechnology and its approach to modern medicine. Currently, biological samples can be screened with nano-sized mechanical devices that bind to specific genetic sequences. But what would happen if we refined this technique further? We look to apply a similar procedure to alternative areas in medical health such as repairing the nerves in the spinal cord. This radical development could potentially lead to a cure for locked-in syndrome paralysis and other such dysfunctions of the central nervous system.

INTRODUCTION

-What is Nanotechnology?

The word 'nano' is derived from Greek for dwarf; a nanometre is one billionth of a metre. It is for this reason that it has a significant role in the continued advancement of modern medical understanding and treatment. Nanotechnology has been used since medieval times in stained glass windows, which contained different sized gold nanoparticles which were incorporated into the glass [ii]. The word 'Nanotechnology' was first given to describe machining with tolerances of less than a micron by Nario Taniguchi in 1974. The famed talk "There's Plenty of Room at the Bottom", by Caltech Physicist Richard Feynman in 1959, outlined the potential for atomic engineering. In 1985, Robert Fuller and Richard Smalley discovered the (Buckminster) Fullerene form of carbon, which consisted of 60 Carbon atoms. This entire structure was found to be about 1nm in diameter and was a discovery that sparked a new era in technology.

-Current Research into Medical Nanotechnology

One such advancement in medicine is the use of nano-sized molecules that act as contrast agents by increasing the brightness of their location, allowing them to improve the resolution of an image, which could be produced by a magnetic resonance imaging (MRI) scan [iii]. In MRI scans, nanoparticles of gadolinium metal serve as contrast agents but there is always a chance of the particles leaving the delivery vehicle, which may have detrimental side effects on the health of the patient. Currently researchers are attempting to utilise fullerenes as housing for the contrast agents [3]; thus eliminating the health risks. Contrast agents could detect problems at more treatable stages. They may for instance, reveal malignant tumours only a few cells in size.

Furthermore, researchers are trying to discover new ways in which to treat diseases. For example, gold nanoshells because of their size are able to manoeuvre around within the body to deliver treatments to specific targeted areas, which may otherwise be inaccessible to standard drugs. This enables the nanoshells to reach and bind to targeted tumours, and then by reflecting infra-red light they are able to heat up their surroundings sufficiently to destroy the cancerous cells. This is because gold, which at normal scale reflects yellow light, is actually able to reflect red light at nanoscale [2]. The reason for using gold in particular is simply because of its inert nature, and therefore it does not corrode and damaging the body.

On a different note but still within the boundaries of medical development, researchers at the University of Texas- Medical Branch and the University of Michigan succeeded in making the world's first direct electrical link between nerve cells and miniscule nanoparticles with the ability to turn light into tiny electrical currents that can produce responses in nerves (2007). This radical development opened up the possibility of nanoparticle-based artificial retina being produced in the future.

-A Current Application of Nanotechnology in Medicine

Currently in hospitals, cardiologists and surgeons tend to use 'stents', an artificial tube, to relieve blockages in the major blood vessels of the body, i.e. relieving a localised flow constriction [4]. As Fig.1 shows, by inserting the stent into the blood vessels, in this case the coronary artery, and expanding them using 'balloons' the size of the lumen increases, dilating the vessels, sufficiently to allow blood to flow through and treat conditions such as (myocardial) ischaemia and coronary stenosis (Angina). Aside from this, there are numerous uses of stents in surgery.

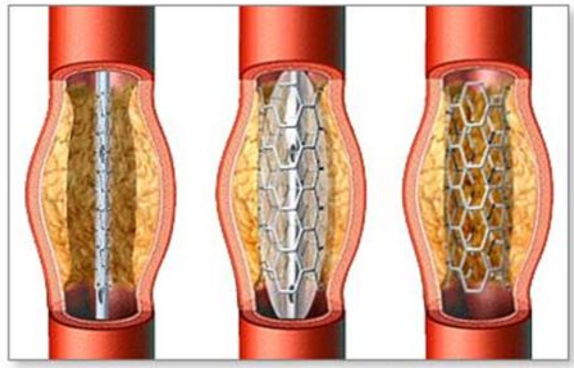

Fig. 1

However, there are many associated risks with this method that could incur disastrous effects on the patient. Vascular implants, such as stents, can cause inflammatory reactions, such as restenosis and thrombosis, within the body. To abstain from these risks, Ho-Wook Jun, Ph.D., an assistant professor at the University of Alabama at Birmingham, in 2008, presented his design of a nanomatrix coating for stents which mimics the natural endothelium that lines blood vessels [5]. This synthetic coating promises to prevent post-operative tissue scarring along the blood vessel wall, greatly reducing the possibility of future thrombosis or blockage at the stent site. However, although this carbon nanomatrix coating promises to alleviate the possibility of harmful side effects caused by metal corroding within the body, there also is evidence to suggest that carbon nanotubes can cause cancer if they found their way into the lungs. A more refined solution was later discovered, in 2010, by researchers at the 'University of California' (UCSF); by using nanotubes made of titanium dioxide the above risks are greatly reduced [6].

Although we have found different fields of medicine where nanotechnology has been utilised to advance treatments, we have realised that such technology has yet to be incorporated in other areas of the body, specifically that of the central nervous system. Presently, there is no standardised treatment to repair damaged vertebrae and the associated nerves of the spinal cord.

DISCUSSION

The development and refining of these and other medical procedures involving nanotechnology promise to change the very nature of medical invention.

-An Introduction to Nerves

"A nerve is a bundle of neurones/nerve cells enclosed in a sheath of connective tissue. Nerves may contain sensory neurones, which conduct impulses from the receptors in sense organs, motor neurones, which conduct impulses to effectors, or they can be mixed, containing both sensory and motor neurones."

A nerve cell, or a neurone, has a relatively long axon- as shown below in Figure 2-, which is a cytoplasmic tube, insulated from other axons by its myelin sheath. The responsibility of an axon is to carry electrical impulses, more specifically outgoing messages, from the cell.

Nerve cells also have many tiny branches called dendrites (as Fig. 2 shows), located along the cell body and axon. Although dendrites are situated at the ends of all neurones, the dendrites of one nerve cell do not actually touch those of neighbouring cells. The miniscule space between dendrites of one cell and another cell is called the synapse.

At any time there is either a full nerve impulse generated or none at all. Only by varying the frequency of the impulse can information about the strength of the stimulus be extracted. These impulses cannot be transmitted directly from one neurone to another; they must cross a non-conductive space, known as a synapse.

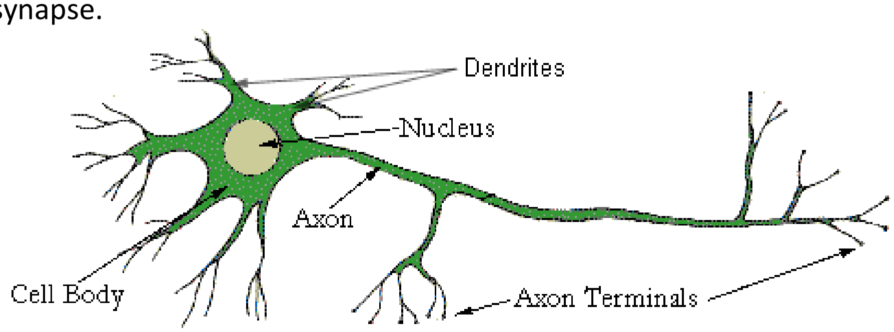

Fig. 2

There is no electrical connection between neurones; a neurone secretes chemicals called neurotransmitters into the space of the synapse. This bridges the gap between nerve cells: therefore allowing the impulse to pass. Interfering with these neurotransmitters can slow reaction times. As a result, many drugs work by inhibiting this chemical process.

<u>-Can Nerves be Repaired or Replaced?</u>

Nerve damage or neuropathy normally occurs when the myelin sheath of the nerve cells degenerates, as Figure 3 shows. If this protection is not present the electrical signals are not correctly transferred, much like how water flow in the xylem vessels of plants will be affected if the lignified wall is damaged at any point. As the damage to the nerves gets worse, they either lose their ability to transmit information (numbness), or begin sending false signals (pain and tingling).

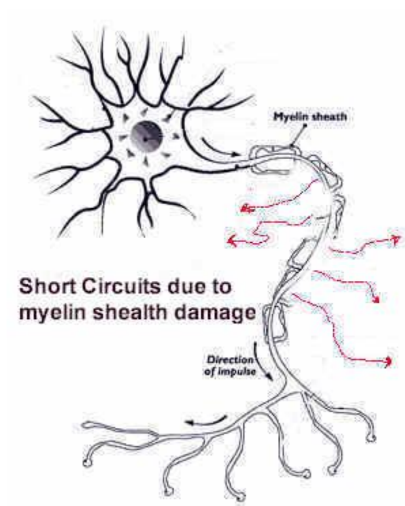

Fig. 3

If the body of the nerve cell is not damaged then the axon can grow back, though there may be impaired conduction [10]. A Canadian scientist has discovered a new way to coax damaged cells to repair themselves [11]. However, this therapy is still in its developing stage. Another theoretical solution to repairing truly damaged nerves is by the use of stem cells. Stem cells are now being found in the brain and eyes of an adult human and these may be able to repair or replace damaged nerve cells. However, the pace of stem cell repairs in humans is very slow and in some cases it can even impede healing. Stem cells in an injured spinal cord can create a sticky scar that blocks nerve regeneration, according to Dr. Philip Horner, an assistant professor in the Department of Neurosurgery at the University of Washington. Axons that try to regenerate after an injury could get caught in the scar [12].

Furthermore, there are numerous medical ethics against the use of stem cells and stem cell research, which include religious beliefs such as the sanctity of life and that researchers are trying to 'play God'. We believe that because of the faults with this treatment and the ethics against stem cell research, that our idea for repairing nerve cells may be better received by the community.

-Using Nanocrystals to do the impossible?

The central nervous system is like an electrical circuit, if there is a break in the circuit, it does not repair itself, nor does the wire grow back; the circuit is no longer able to conduct. In order to repair the circuit you need to fill the gap with a conductor, or semiconductor, to allow the circuit to resume its function.

Our salient notion is an innovative application of utilising semi-conductor 'quantum dots' or Nanocrystals to aid the reconstruction of nerve cell endings in the spinal cord of the central nervous system. This possible technique could lead to a radical new development in medicine as we may finally be able to treat and possibly cure certain dysfunctions of the CNS and the brain such as locked-in syndrome paralysis. A cause for Locked-in syndrome paralysis is damage to nerve cells, particularly destruction of the myelin sheath [13].

Currently, if the axon of the neurone is damaged, then the cell is no longer able to repair itself and therefore loses conductivity. By using semiconductor nanocrystals, we may be able to bridge the gap and repair the conductivity of the neurone. This is dependent on the fact that a nerve provides a pathway for electrochemical nerve impulses; and that the transmission of the electrochemical impulses occurs at the interface of an electron conductor or a semiconductor [9]. Furthermore, if we could create nano-sized mechanical devices to convert electrical energy into the impulses that the nerve cells conduct, this technique may well be possible.

-Alternative Applications of Artificial Nerves

<u>-Replacing Damaged Vertebrae</u>

Currently neuro-pharmaceuticals are able to target different areas of the nervous system. If we can utilise this technique, we may be able to erase the need for a surgical operation if the components of the artificial nerves were to travel to the targeted area and assemble themselves. By negatively charging the nano-sized mechanical devices to 'bind' to the Ca^{2+} ions in the original vertebrae we can link them to the side of our nanocrystal the nerve. In essence, we can link the nerves in the spinal cord using a chain of semiconductor nanocrystals. We can also use a device to convert the neuro-electrical impulses that are be conducted by the axons of nerve cells to electricity, which the nanocrystal can conduct.

Fig. 4

Artist's impression of the structure of the spinal cord (light blue) held in place by vertebrae

Furthermore, after the electrical signal is passing successfully, we may be able to coat the nanocrystals inside a carbon nanotube, preventing the nanocrystals from escaping.

Then by covering the nanotube in composite material, which is not harmful to the body, we could create an artificial vertebra as the composite material could represent the bone. This possibility could eradicate the need for a patient to endure serious operations on the spinal cord such as corpectomy and 'strut grafting' procedures.

These are complex, difficult operations and are done for extremely serious problems that are unlikely to respond to any other type of treatment.

-Treating Brain-stem Lesions

A lesion is cut or break caused by a sudden dynamic impact. When this occurs in the brain stem, the victim is likely to suffer from initial unconsciousness; if this state is sustained the victim may suffer from locked-in syndrome paralysis.

Locked-in syndrome is an unfortunate condition whereby the patient is conscious but lacks the ability to communicate verbally due to complete paralysis of nearly all voluntary muscles in the body, with the exception of the eyes. Locked-in syndrome commonly results in 'quadriplegia' and the inability to speak. Although the vocal cords are not paralysed themselves, the lack of coordination between breathing and voice restricts the production of voluntary sounds. The majority of Locked-in syndrome victims never regain motor control [13].

A technique of stimulating muscle reflexes with electrodes has been known to alleviate the paralysis to some extent, with some patients regaining some muscle functions. However, it is extremely rare for any significant motor function to return. 90% of victims die within the first four months. In other words, currently, there is no treatment available for locked-in syndrome and it is completely incurable.

This is where our idea comes in. By incorporating nanocrystals into a possible treatment for a brain stem lesion, we may be able to treat and hopefully cure this critical condition. The nanocrystals could be contained within a carbon nanotube and possibly be used to reconnect the nerves.

-Further Possible Applications of Nanotechnology

-At last, a Cure for Immotile Cilia Syndrome and Chronic Bronchitis?

Motile ciliated epithelial cells [14], located in the trachea, bronchus and bronchioles of the lungs, are a vital component to the life-sustaining respiratory system. These finger-like projections line the airways and waft rhythmically in a coordinated pattern in order to move the mucus out of the lungs.

Conversely, some diseases can interrupt the work of the cilia. Particularly in the lungs of smokers, the toxic substance, tar, can destroy or paralyse the cilia; so they are unable to move the mucus away. Furthermore, the tar stimulates further production of mucus from the goblet cells and mucus-secreting glands; which then causes a build-up of mucus in the airways. In effect, the cilia immobility instigates the perfect conditions for bacterial growth, and this could lead to chronic bronchitis.

Chronic bronchitis is the respiratory disease which involves the inflammation of the bronchi. This is a long term condition which can cause the sufferer to cough frequently. Additionally, as the disease progresses, the airways become more and more narrow: resulting in breathlessness which may condemn patients to developed disabilities.

Immotile Cilia syndrome is an inherited disorder caused by the absence of dynein structures and subsequently inability of the cilia to beat effectively and marked by recurrent sinopulmonary infections, reducing fertility in females and sterility in males [15].

In response to these critical conditions, we suggest that it would be possible to synthesise artificial projections, which are designed to imitate the motion of the cilia. In particular, many 'nanotubes' could be brought together into a cluster, perhaps not in a nine-by-two arrangement currently in cilia: which then could replace the microtubules in cilia and also be lined with a membrane to contain them. Therefore, with the use of careful programming, these 'nanotubules' could contract on one side, then the other, in a rhythmic pattern: creating an effect which follows closely onto the movement of the cilia. Further radical developments in this field could include the creation of a whole tissue which is covered in these artificially produced 'cilia'. Therefore, if the tissue were to be implanted directly into the airways, the eradication of diseases such as immotile cilia syndrome and chronic bronchitis could possibly be cured.

The advancement and development of such a treatment for damaged or disabled cilia would be applicable to a vast number of patients across the world. However, this remedy must be introduced with caution because there will undoubtedly be detrimental ethical issues that could arise. Smoking is a major contributor to chronic bronchitis. Generally, people take their first cigarette due to a variety of reasons such as peer pressure, or other factors; which then can advance into an addiction and lead onto many harmful diseases. If this treatment proves to be effective, many of our patients may actually turn out to be smokers. Do we really want to create a cure for such smoking diseases? Wouldn't it encourage more people to take up smoking if they were to believe that there are fewer health risks associated with it, especially if the danger of bronchitis was alleviated?

People will be more encouraged to smoke because they will subconsciously think that there is a cure if the worst happens. For example, the only thing preventing some people from taking up smoking may well have been the fear of contracting the harmful diseases associated with it. However, if there is a successful treatment then this will be less of an issue for them. Should we limit the use of this treatment for the non-smoking community?

Having a widespread cure for illnesses similar to chronic bronchitis will cause more people to become more nonchalant about the consequences of smoking. Therefore, some people may argue that the treatment may be abused: at the cost of the health system if it is to be subsidised. So, what are the cost implications?

For many years now, a huge amount of money has been invested in the development of new treatments for conditions associated with smoking. We expect that nanotechnology used in the context of cilia will be no exception to this. First, there is the initial designing expenditure; then the manufacture of a prototype. After which, follows the clinical trials; and if successful, mass production and surgical distribution. This technique of curing patients is a currently a visionary one: intended to cure genuine cases where people are prepared to change their lifestyles. It is not, on the other hand, designed to be abused. In that case, how many repeated treatments should be administered to one single patient?

If a patient is going to continue to smoke, even after the treatment, then what is to stop them from continuing to smoke and damage the artificial cilia again? This may result in a continued course of treatment for a single patient: at a large cost as well as being unfair for other sufferers who are genuine cases, especially those with immotile cilia syndrome. This technique of repairing damaged cilia could also be incorporated into treatment for other diseases where the cilia are also damaged.

<u>-'Nanosheets', a revolutionary treatment for osteoarthritis</u>

Osteoarthritis commonly occurs in people over the age of 50, especially in woman, and is the number one form of arthritis in Britain. The NHS in England and Wales performs over 140,000 hip and knee replacement operations every year [16]. Osteoarthritis is a disease affecting joints, particularly the knee and hip. Fig.5 is a diagram to shows cartilage in the optimum position to reduce friction between the bones at a joint; if the cartilage is lost, this may result in damage to the underlying bone. The condition is a painful one and affected people experience difficulty in moving the joint concerned.

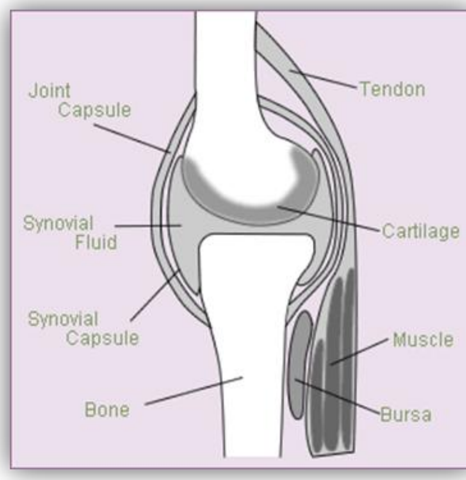

Fig. 5

Currently, we have carbon nanotubes (rolled sheets of graphite). Nanosheets would simply be a sheet of graphite flattened out.
In addition, there would be nanotubes lining the sheets to ensure the desired structure is held, almost like a barrel-lined water raft; and these could be adapted to change the shape of the nanosheets depending on where they may be used. These structure providing nanotubes could, if possible, be made from titanium dioxide, which has recently been discovered to be efficient as a stent.

We may be able to incorporate 'nanosheets' as a possible treatment for osteoarthritis. We could treat this condition by applying layers of nanosheets, which are flexible and able to slide over each other, to the area of the joint where the cartilage was lost and the bone is damaged. The loss of cartilage may cause the bones to grind against each other, resulting in erosion and fractures.

An alternative application of 'nanosheets' may be to utilise them as a protective layer during complex surgeries, particularly to the neurosurgery. They could ensure that certain parts of the brain are almost sealed off, reducing the risk of unintentional damage. Surgery currently takes place without this type of protection and is fairly successful; is it worth the extra costs of incorporating 'nanosheets' as extra protection during delicate surgeries?

CONCLUSION

By using our innovative 'nanocrystal nerves', 'nanotubules' and 'nanosheets', we could potentially treat a multitude of critical conditions. Unfortunately, despite the meticulous nature of our procedures, they still have some shortcomings.

Firstly, it may be difficult to programme the devices to convert the neuro-electrical impulses of the nerves into electrical energy which can be conducted by a nanocrystal, and then to convert this back without affecting the impulse. If the information relayed wasn't completely accurate, the impulse may not have the desired effect.

In addition to this, we acknowledge that it will be incredibly difficult to repair damages that occur along the dendrites and axon terminals of neurones, utilising our proposed technique. Furthermore, it may also be difficult to simulate the function of the synapse, so we would be unable to treat damages in these areas.

With regard to using 'nanotubules' to replace the microtubules in cilia, we may be able to repair the effects of chronic bronchitis and potentially cure immotile cilia syndrome. However, in reality, it may be challenging to individually replace disabled cilia with our artificial implants; we may be forced to perform large tissue implants.

Providing that we overcome these issues, we believe our proposed treatments could fulfil the potential of nanotechnology to the future of medicine.

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