

The application of nanotechnology in the
treatment of Rheumatoid Arthritis and
Osteoarthritis

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PASS WITH MERIT

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Abstract:

Application of nanotechnology in areas such as electronics, biomaterials and energy production is a rapidly developing field. An area in which nanotechnology is set to have a huge impact on is medicine. Research into the application of nanotechnology for imaging, diagnosis and treatment of diseases is going to revolutionise medicine.

Arthritis is a group of diseases which affect mainly the joints in the body and cause pain and disability. This paper discusses how the role of nanotechnology in drug delivery systems to treat cancer could be applied to rheumatoid arthritis as well as the prospect of it being used for bone and cartilage tissue regeneration in the treatment of osteoarthritis. It will also look at the ethical issues surrounding the use of nanotechnology in medicine.

Introduction:

As medicine advances and doctors strive to achieve quicker and earlier diagnoses and more effective treatments, scientists throughout the world are looking to nanotechnology for the solutions. Nanotechnology is the study and manipulation of matter at an atomic level. The word 'nano' is derived from the Greek word for 'midget' and is a measure of magnitude to the order of 10^{-9} m. Nanotechnology involves building up nanoparticles to form structures which have unique properties and are very different to the properties of the same structure at a larger level.

Nanoparticles are of immense importance in medicine due to their relative surface area; being less than 100nm in size, their surface area to mass ratio is very large. Various substances can therefore bind to the large surface area or the particles can be used as carriers to transport drugs and probes around the body. The size of nanoparticles also allows them to enter cells and some of the organelles within the cells as well as potentially cross biological barriers such as the blood brain barrier (BBB) which introduces the possibility of new methods of delivering drugs to the brain ^[1]. These nanoparticles could be used to deliver drugs to specific cells in the body in the case of cancer, heart disease, respiratory distress syndrome or arthritis, improving the efficiency of the drug and reducing the toxicity of the drug elsewhere in the body ^[2].

As well as drug delivery, nanotechnology is being used in early diagnosis and monitoring of diseases. Combining structures called fullerenes, which are hollow carbon compounds (such as buckminsterfullerene [see fig.1]), with an imaging agent and then using ultrasound or magnetic resonance techniques enables us to visualise soft tissue organs in greater detail ^[3]. New devices have also been designed which enable physicians to continuously monitor various parameters in the body such as blood glucose levels, blood pressure and cholesterol levels.



Figure 1

One example of a recent invention is an insulin pump prototype in which nanotubes puncture the skin and analyse the blood to determine the glucose levels. They then pump

insulin down the tube constantly. The insulin molecule is 5nm in size therefore the tubes are 10 to 20nm in diameter. Because bacteria are on average of an order of magnitude of 100nm they are too large to pass through the tubes. This reduces the risk of infection which was prevalent previously and necessitated the replacement of needles every few weeks.

Nanotechnology has also found a use in cosmetics with most sunscreens now containing titanium dioxide, giving high protection against U.V light whilst also being colourless due to the relatively small size of the titanium dioxide particles. However as the titanium dioxide is able to penetrate the skin, it raises ethical questions about the health risks which this paper will discuss ^[4].

This paper will also explore in more detail the new drug delivery systems involved in treating cancer and the use of nanotechnology in tissue regeneration using nano-scaffolds. It will go on to explore how these processes could apply to the treatment of arthritis. However before exploring the details of how nanotechnology can affect medicine in the future, it will discuss the ethical issues involved in using nanotechnology in this way.

Ethics

The major ethical issue which arises from the development of nanomedicine is whether nanotechnology should be used only for therapeutic purposes or also for cosmetic purposes such as the enhancement of body parts. Due to the variety of fields which come under the heading of nanomedicine, for example advanced diagnostics, drug delivery and tissue engineering, the ethical issues which present are also varied.

Another issue is whether the clinical information presented to a doctor is sufficient enough to conclude that a disease or condition is present, due to the sensitivity of advanced diagnostics. As Dr. Raj Bawa says, *"Diagnostic nanotechnologies eventually will provide the ability to detect... subtle molecular changes in DNA... scenarios that will likely cause pause and reconsideration of what it means to be a 'healthy person' versus a 'person who has a disease'. In a 'nanoworld,' we might have to reconsider how to diagnose someone who has, say, cancer. Is the presence of a genetic mutation known to have a predisposition for causing cancer in a single cell a diagnosis? Or is it simply a risk factor? How many cells from the body must be of a cancerous nature for it to be defined as cancer?"*^[5]

As suggested previously, there are ethical issues about how the health benefits of using nanomedicine compare to the risks of using it. Due to it being a relatively new technology, it is unclear how the nanoparticles will react with the biological pathways in the body and whether they will be toxic in the long-run. In the case of sunscreen, the titanium dioxide particles are able to penetrate the outer layer of dead skin cells (stratum corneum) but it is unclear whether they can penetrate through the live cells; if they could then there is evidence to suggest that the particles can induce the formation of free radicals when exposed to light and this could damage the cells ^[4].

A further aspect of concern is about privacy and confidentiality. Using nanodevices for monitoring the body will provide hospitals and institutions with continuous 'real-time' data and it is questionable whether this vast amount of data about patients can be kept confidential.

Discussion:

Arthritis

There are two forms of arthritis: osteoarthritis and rheumatoid arthritis.

Rheumatoid arthritis is a chronic, autoimmune disease which causes inflammation of joints and the tissue surrounding the joints. It can occur in people of all ages but most commonly affects those over the age of 40 and there are over 400,000 people in the UK with the disease ^[6]. Degeneration of the joints and tissues is possible due to the chronic nature of the disease and its ability to affect other organs makes it a systemic disease. Scientists are unsure about the actual cause of arthritis but suspect that it has something to do with infectious agents. This leads to an immune response in which the immune system attacks the body's own cells and causes inflammation of the joint.

A normal joint [see fig. 2] allows movement without any pain or discomfort due to the synovium (joint capsule lining) producing synovial fluid which lubricates the movement of the smooth cartilage at the ends of both bones.

In an inflamed joint the synovium becomes much thicker due to plasma B cells which secrete antibodies including rheumatoid factor (an autoantibody which acts against the antibody Immunoglobulin G and forms an immune complex) and anti-collagen antibodies. These antibodies then stimulate an immune response known as the inflammatory cascade which leads to acute inflammation. Chronic inflammation occurs when the chemicals present in the joint are permanently changed and there is some evidence to suggest that this is caused by B cells (which secrete rheumatoid factor) being seen by the body as antigen presenting cells ^[7]. The chemicals secreted by the antibodies cause a swollen and tender joint and can cause fatigue if released into the bloodstream.

Figure 3 compares an inflamed joint with a normal joint; the synovial membrane becomes inflamed, eroding the bone and cartilage, and the amount of synovial fluid increases.

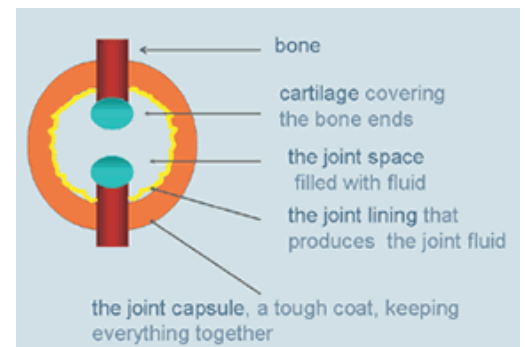


Figure 2

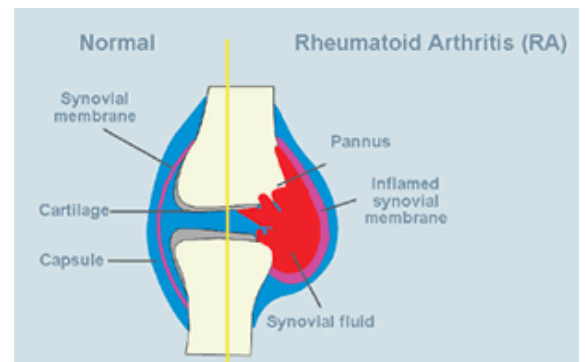


Figure 3

Currently, there is no cure for rheumatoid arthritis but to reduce joint inflammation and pain two sets of medications are given. The 'first-line drugs' such as aspirin and cortisone help to reduce the pain and inflammation and then the 'second-line drugs' such as gold salts and methotrexate are used to induce remission and prevent any further joint destruction. However these 'second-line drugs' are slow-acting and could take weeks or even months to start becoming effective.

In order to develop a fast-acting, effective treatment for rheumatoid arthritis, nanotechnology could be used. To explore this further, we need an understanding of how the drug delivery system works.

Drug Delivery

When developing nanoparticles for use in drug delivery, the drug itself could be delivered in its nano-form, or it could be carried by a separate nanoparticle. To improve the system, certain factors need to be addressed:

- "More specific drug targeting and delivery,
- Reduction in toxicity while maintaining therapeutic effects,
- Greater safety and biocompatibility." ^[1]

The substance to be used as a carrier must be biocompatible with the drug and have a specific life-span to last until the drug has reached its target organ or cell. The advantage of using nanotechnology is that the drug is delivered straight to the target cell which improves the efficiency of the treatment and reduces the toxic effect of the drug elsewhere. In the case of cancer for example, chemotherapy drugs would just kill the tumour cells and not cause damage to other cells which would have resulted in side effects such as hair loss and fatigue.

Researchers at the University of Illinois have recently developed a nanoparticle combining aptamers (short strands of DNA or RNA which bind easily to biomolecules) and liposomes (drug-delivery vesicles) containing the drug Cisplatin for killing tumour cells. The aptamers used in this case bind specifically to nucleolin receptors, which are found in certain breast cancer cells ^[8]. A similar process could be used for Rheumatoid Arthritis.

In rheumatoid arthritis a messenger protein in the joints called tumour necrosis factor (TNF) begins the process of inflammation. Therefore, using a TNF-blocker to intercept the protein before it acts on its receptor could theoretically stop the process of inflammation from even starting ^[9]. Nanotechnology could be used to ensure that the TNF-blocker (the aptamer) was effectively transported to the joint where the inflammation needed to be prevented. This could be attached to a liposome containing a 'second-line drug' such as methotrexate which would improve the efficiency of the treatment.

Osteoarthritis is the more common form of arthritis, affecting 8 million people in the UK usually those above the age of 40 ^[10]. Osteoarthritis also causes degradation of joints in the body which leads to pain and stiffness and potentially deformity. However the degradation is caused by the cartilage roughening and wearing thin and the two bones in the joint rubbing together and forming osteophytes. There may also be inflammation when the synovium expands and all this can cause the shape of the joint to change, causing deformity [fig. 4].

Currently there is no cure for osteoarthritis either, but analgesics are usually given to alleviate the symptoms of the disease and non-steroidal anti-inflammatory drugs are prescribed if the inflammation in the joint is contributing to the pain. Physiotherapy is also recommended for improving the mobility of the joints affected and surgery is often given to replace joints like the knee and hip if the pain is severe.

The drug delivery system suggested for treating rheumatoid arthritis would be ineffective against osteoarthritis due to the nature of the damage to the joint. Supplying drugs to the joint would not prevent further degeneration of the cartilage and bone. An alternative way of treating osteoarthritis would be to develop a way in which the tissue around the joint could be induced to regenerate in order to counteract the degeneration.

Tissue regeneration

To create functional tissue its features must represent real structures. Taking the outer connective tissue supporting the cells as an example, the features of the matrix such as the fibers, adhesion proteins and proteoglycans must be mimicked at the nanoscale. In order to build up new tissue, electrospinning and self-assembly are some of the methods used to create a scaffold of the fibres, known as a nano-scaffold [fig. 5]. Proteins are then added to the surface to promote cell differentiation and growth. Adding a charged covering on the surface can also help to increase the concentration of growth factors which would aid proliferation of the cells. Nanoparticles such as carbon nanotubes are then used to enhance the mechanical and electrical conductive properties of the tissue. They also improve adhesive properties and control the release of growth factors, and can physically shape the tissue to create the necessary structure.

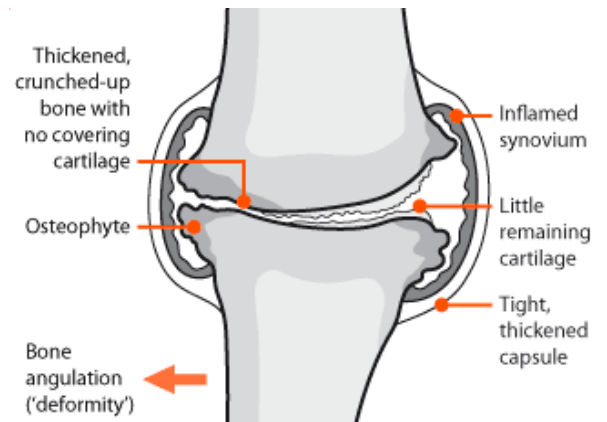


Figure 4

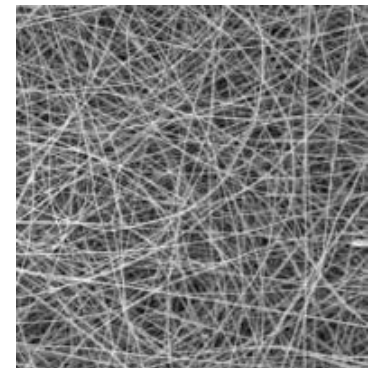


Figure 5

Once the tissue is created, nanoparticles can also be useful for triggering desired biological functions and for monitoring engineered tissues before transplantation, to ensure they will function as intended ^[11]. If this type of engineered tissue could be targeted, using nanoparticles in a similar way to drug delivery systems, specifically to the degenerated joint, it could be used to regenerate the bone and cartilage tissue there, reducing the tenderness and inflammation.

Recently, Ms. Beatriz Olade, research scholar at the Health Unit of Tecnia, has found that a combination of the polymer polylactic acid, a bioceramic hydroxyapatite and carbon nanotubes successfully grow healthy bone tissue ^[12].

Conclusion:

The underlying cause of arthritis is currently unknown although there are theories about possible causes; infectious agents and smoking are suspected for rheumatoid arthritis, and osteoarthritis is related to old age but not caused by it. However research is ongoing and once the causes are established, developing a cure for arthritis will follow on from that.

However in the meantime, nanotechnology could go some way in improving the treatment for arthritis. Although both forms of arthritis explored in this paper are diseases which affect the joints, the differences in how they do this means that treatment would have to differ too. For osteoarthritis, the degenerative nature of the disease suggests that using tissue regeneration techniques would be the most effective way of treating the cause of the pain and stiffness in the joints. For rheumatoid arthritis, however, degeneration is possible only after the synovium has inflamed, so a more effective treatment would be to prevent the inflammation by neutralising the tumour necrosis factor which promotes the inflammation. However, for these treatments to be as effective as possible the diagnosis needs to be made as early as possible; drug delivery targeting TNF will be of maximum use if it is used before the inflammation has started.

For both diseases, nanotechnology will play a part in making the treatment possible and effective. This paper supports the use of nanotechnology in trying to find an effective treatment for arthritis because it is a disease which affects many people, causing them to live in pain and discomfort; osteoarthritis affects over 1 million adults in the UK and rheumatoid arthritis affects 400,000 ^[13] and it is the main cause of chronic disability in the USA ^[14]. On the other hand, although nanotechnology makes it possible to have huge advances in medicine, it is important not to let the ethics of what is acceptable in medicine lag behind.

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Images

Fig. 1:

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Fig. 2 and Fig. 3:

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Fig. 4:

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Fig. 5:

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