

APPLICATIONS OF NANOTECHNOLOGY IN  
WOUND & SURGICAL REPAIR

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## Abstract

In this paper, we will discuss the background, development and potential applications of nanotechnology in the field of wound repair in medicine. For centuries, physicians have struggled to find methods to reduce blood loss and encourage efficient and full wound healing. Up till now, the most effective solution has been standard suturing, which has served us well, however in some cases it can be inadequate. It requires training and expertise and can be time-consuming- therefore allowing more time for infection. We postulate using nanotechnology which at this point has not been developed a great deal, but which could potentially solve all these problems, and also provides a number of other advantages.

## Introduction

A universal definition of nanotechnology is surprisingly hard to find, but in the broad sense, it refers to the science of manipulating matter at the atomic level or the nanoscale (less than 100nm). The definition should also include that nanotechnology involves nano-structures which are man-made, otherwise the definition would include every natural-biomolecule, essentially redefining much of what occurs in chemistry and molecular biology into 'nanotechnology'. In addition, others would add that a true definition should include reference to molecular systems or devices or even 'functional systems' <sup>1</sup>.

One of the most vital reasons why nanotechnology is so important is because of how substances at the nanoscale have significantly different properties from those at a larger scale. The difference in bulk properties such as melting point and chemical reactivity is due to the hugely increased surface area to volume ratio. Since a greater proportion of particles in nano-structures are located on the surface, as opposed to the relatively small proportion of particles on the surface in bulk materials, more particles can experience surface interactions. They also however, display other unusual properties which can only be described by quantum physics <sup>2</sup>. The rules of quantum mechanics are very different from classical physics, explaining why the behaviour of substances at the nanoscale can sometimes contradict common sense by behaving erratically <sup>3</sup>.

Nanotechnology has incredible potential to change society, which is shown by how an estimated \$9 billion per year is invested in global research and development of nanotechnology, which is anticipated to lead to more efficient energy production, storage and transmission; better access to clean water; more effective pollution reduction and prevention; and stronger and lighter materials <sup>4</sup>. But perhaps most significantly in respect to this paper is the possibility of new medical treatments and tools.

Nanotechnology is proving to be particularly important in new developments in medicine. This application of nanotechnology to medicine, now dubbed "nanomedicine", was first postulated by Feynman in 1959, with the visionary idea of tiny nanorobots designed, manufactured and introduced into the human body to perform cellular repairs at the molecular level, metaphorically phrased by Feynman as "swallow[ing] the surgeon" <sup>5</sup>.

At the present, there have been numerous applications of nanomedicine. They include using nanoparticles to deliver drugs to specific parts of the body, as they are attracted to only the diseased cells, allowing direct treatment of those cells, and reduces damage to healthy cells. Such treatments are being developed in chemotherapy, to deliver the drugs directly to the cancer cells. In addition, nanocrystalline silver has been used as an antimicrobial agent for the treatment of wounds, and similarly a cream with nanoparticles containing nitric oxide gas has been shown to reduce

staphylococcus infections in mice. A special burn dressing coated in nanocapsules containing antibiotics is also being developed by scientists at the University of Bath and the burns team at the Southwest UK Paediatric Burns Centre at Frenchay Hospital. If an infection starts, the infectious bacteria in the wound cause the nanocapsules to break open, releasing the antibiotics, allowing much quicker treatment of an infection.<sup>6</sup> Feynman's vision of nanorobots used in medicine could also become reality, with nanorobots being designed recently which can replace faulty chromosomes in a nucleus with artificially created defect-free copies.<sup>7</sup>

## Discussion

### ***Biochemical and Physiological Interactions in Wound Repair***

Following an injury, such as a cut or a puncture wound, the body responds in a number of overlapping phases, which stops the bleeding, cleans the wound and restores cellular structures and tissue layers. These four main stages consist of:

- Haemostasis
- Inflammation
- Proliferation (Granulation)
- Maturation (Remodelling Phase)

#### **Haemostasis**

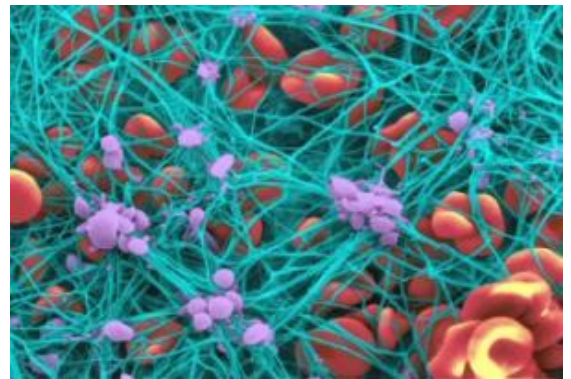
Initially a clot is formed due to the fibrin rich blood formed from coagulation of red blood cells and platelets (thrombocytes) within the wound/puncture. They serve to stem the blood flow from severed vessels and to fill the gap in the wound. This clot provides a 'provisional matrix' through which cells migrate and repair, such as keratinocytes, fibroblast and epithelial cells (which are involved in the granulation and remodelling stages). The clot also acts as a reservoir of cytokines and growth factors, released as activated platelets de-granulate.

Platelets react to the wound by liberating cytokines and cell mediators such as PDGF (platelet – derived growth factor), TGF-a and TGF-b (transforming growth factor alpha and beta) and ADP (adenosine diphosphate). ADP promotes coagulation and further platelet activation. PDGF and TGF-a and TGF-b, both being modulators of fibroblastic mitosis (tissue reconstruction), are responsible for inducing new tissue generation

Haemostasis provides chemotactic cues to recruiting inflammatory cells, initiating re-epithelialisation, stimulating wound angiogenic response (formation of new blood vessels) and connective tissue contraction.

#### **Inflammation**

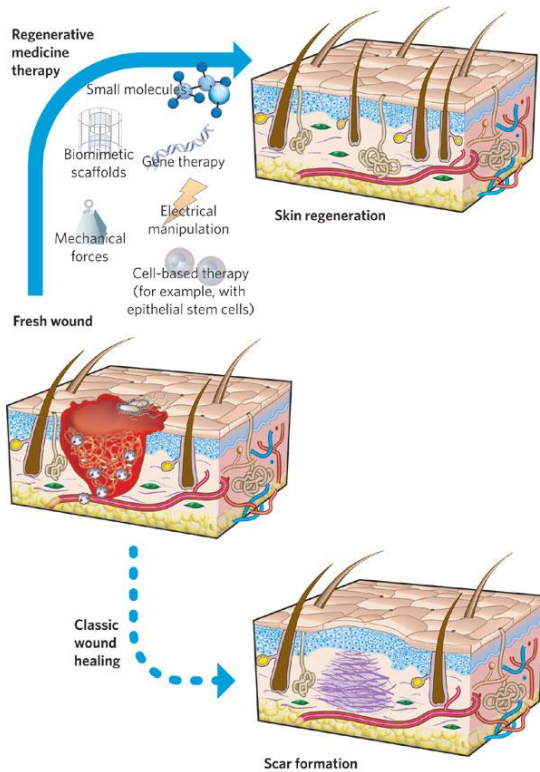
From chemotactic cues from platelets and bacteria polymorphonuclear leukocytes (PMNs) (neutrophils) are attracted to the site followed by monocytes which develop into macrophages. PMNs



*Figure 1: A colorized scanning electron microscope image of a whole blood clot. The fibrin fibres are blue, platelet aggregates purple, and red blood cells red. (Credit: Yuri Veklich and John W. Weisel, University of Pennsylvania School of Medicine)*

clean the wound of bacteria and debris by phagocytosis; they also activate fibroblasts and keratinocytes for later phases. Macrophages continue to clean the site; they also release various growth factors and manipulate endothelial cells with new blood vessels and smooth muscle cells for contraction of the wound and reconstruction.

This stage is vital for preventing infection within the tissue or blood and to initiate the next phase in wound repair.



## Proliferation

At the beginning of this phase, fibroplasia (formation of fibrous tissue) takes place, fibroblasts migrate into the wound and synthesise the production of collagen in the wound, forming a new extracellular matrix (ECM).

The final stage of this phase is re-epithelialisation, which involves the migration of cells from the nearby structures peripheral to the injury. The cells will divide and an epithelial layer formed. Contraction is caused by myofibroblasts which act as muscle cells, contracting and re-aligning the walls of the wound.

## Remodelling

The weaker collagen which was originally laid down is degraded and replaced with stronger collagen. Originally disorganised collagen fibres are re-arranged, cross-linked, and aligned along tension lines<sup>8</sup>. The tensile strength then increases over several weeks during this phase and only reaches up to 80% strength of normal skin.

Figure 2- regenerative medicine therapy and classic wound healing

Section Reference: 8, 9

## Gold Nanoshells

Nanoshells are spherical nanoparticles comprising of a dielectric core and an outer metal shell. The core, in the case of gold nanoshells, is made of silica nanoparticles (SiO<sub>2</sub>), with dielectric properties. A dielectric is an electrical insulator that can be polarized by an electrical field. Once this silica core has been synthesised via the Stöber process, the next step is to functionalize the silica core, which allows gold to be seeded onto the core. The cores are placed in a solution of 3 aminopropyltriethoxysilane, which self assembles into a single layer on the silica surface, this process is called Silanization.

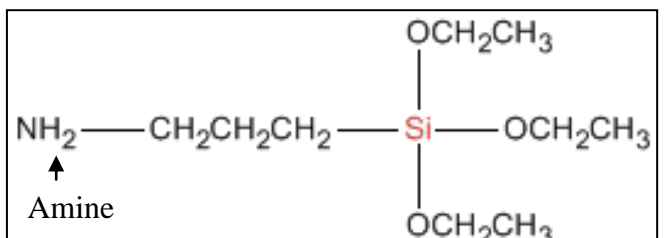
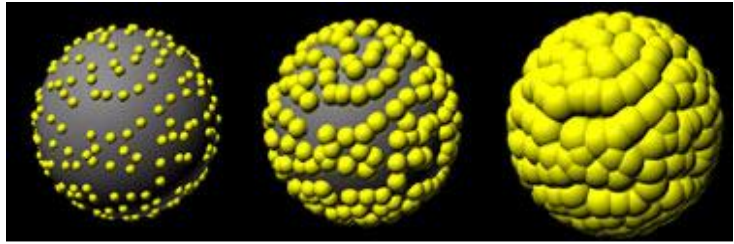


Fig 3: 3 aminopropyltriethoxysilane

One nm gold nanoparticles are then 'seeded' onto the silica cores by adding concentrated gold colloid, a suspension of under 100nm gold particles in a liquid such as water. When this colloid is added up to 2000 gold nano particles will covalently bond to the amine groups from the 3 aminopropyltriethoxysilane; see Fig 3. These act as seeds or nucleation site allowing a continuous layer of gold to be formed. The seeded cores then have Chloroauric acid added which reduces at the gold seeds with formalahyde. The formalahyde reduces the chloroauric acid allowing the negative gold ion to bond to the gold seeds as they gain electrons forming a continuous shell. See Fig 4.



*Fig4: From left to right, the formation of 'seed' particles, and the formation of a continuous layer of gold.*

Finally the gold Nanoshells are tuned; this is the process whereby the ratio of core thickness and shell thickness is adjusted. This controls the light level at which the Nanoshells undertakes surface plasmon resonance and releases heat. Surface plasmon resonance in its simplest terms is the oscillation of electrons between a dielectric, like the silica core and the metal outer shell. For tissue welding purposes a core of 55nm and an outer shell of 10nm is ideal as it will resonate and release heat when NIR light is shone on it.

## **Medical use**

Gold nanoshells have a huge array of medical applications one of which is tissue soldering; the gold nanoshells can act as exogenous absorbers to facilitate NIR laser soldering. It can absorb the NIR light and through SFC release heat. The solder is albumin; a water soluble protein. When the gold nanoshells resonate releasing heat the albumin solder in which it is suspended denatures. The Beta pleats which make up the albumin's structure unfold and make new bonds between itself and the tissue membranes it is surrounded by.

The gold nanoshells proven biocompatibility and the fact it is non toxic make it ideal as the exogenous absorber. The fact it can be tuned is also useful allowing different batches to be made for various purposes depending on the site of injury and needed penetration depth. However the most useful feature is its ability to be tuned to near infra red light frequencies. This counteracts the conventional limitations of tissue soldering allowing greater penetration depths and very limited thermal damage compared to the previous techniques which had dangerous side effects.

The albumin in the solder is gradually replaced by collagen as the wound heals and the epithelium reforms normally. This laser technique also stops the usual inflammatory response of the tissue.

The relatively weak starting strength of the tissue after healing means that this technique is ideally suited to artificial wounds.

This technology could be applied in a variety of ways. Most obviously perhaps, is to seal a surface cut or shallow wound, as an excellent substitute for standard sutures. They would be relatively straightforward to apply, only requiring the solder to be applied to the wound, holding it together with tweezers and then exposing it to the near infrared source. This could be well utilised in an Accident and Emergency situation for example in the hospital, but could also be used post operation to seal the incisions with minimal scarring, since the scars diminish over time. It could also be

extremely useful in military and disaster applications, providing a way for superficial, and some less serious muscular wounds to be easily sealed quickly, allowing time to be saved compared to conventional suturing. The technology also needs very little previous training to use, which is useful where medical attention and time is at a premium. This type of treatment might not be suitable at this stage for more serious internal organ injuries, since so far it has only been tested on skin and muscular tissue, and it is unknown whether it is capable of successfully fusing the more complex and specialised tissue of organs to a sufficient degree without impairing their function.

If the solder could be used to fuse arteries, which theoretically it could be, it could potentially make cardiovascular surgery far more efficient and less time-consuming. For example for a coronary artery bypass grafting, the vessels from which an artery is taken and the coronary arteries onto which they are attached could be quickly and easily sealed up with an application of the solder and using the NIR source to fuse it instantly. The technique would obviously require some practice but would theoretically be a more straightforward way to close or attach an artery as opposed to the small sutures used today.

Section references: 10, 11, 12

## ***Ethics***

There are some ethical issues involved in the development, experimentation and possible application of this treatment.

One of these is the animal testing which took place and most likely will continue to take place if this technology is to be improved and perfected for medical application. In the experiments to test the technology live rats were used in addition to chicken tissue. The rats were anaesthetised, and deep incisions were made in their flesh, half of which were sutured in the standard way with stitches, while the other half had their wounds closed with the solder and laser. While care was taken to minimise the suffering of the rats (a key ethical issue in the area of animal testing) by anaesthetising them, some could see testing of the technology on the animals as unethical since it was not fully known if there would be any severe negative effects on the living animals, and if they would be injured. Perhaps more importantly than this however, the rats were euthanized in order to remove their fused tissue and test its strength. For some, particularly those who believe life is sacred in all its forms, it might be hard to accept such a treatment, the development of which resulted in the deaths of numerous rats. This obviously is a question of animal rights, whether the rights of the animal are equal to that of a human.

Section references: 13, 14

Another of the ethical issues concerns the financial cost of this treatment. At the present, the manufacture and use of these gold nanoshells is very expensive, similarly to how most new technology starts off as. Some may argue that the use of technology such as this would divide medical treatment severely into the expensive and clearly more effective treatment for the wealthy, and the more outdated and less effective treatment for the poorer, which they would see as unethical. Therefore some would protest against the usage of such treatment, at least until the technology is able to be manufactured in a way that is cheaper to the extent that it can be covered by the government.

## **Conclusion**

Theoretically, we believe that this method would be a significant improvement to modern sutures and would improve many areas of medical care as a result. In trauma medicine, it would mean quick and efficient sealing of wounds, and in vascular surgery, could allow for quicker and easier attachment and sealing of vessels. Theoretically it is predicted that the soldered tissue should have 100% of the tensile strength of normal, undamaged skin, however at present this is not the case, due to how the gold nanoshells release heat which inhibits the full healing of wound. If they were made to oscillate at a lower frequency then 100% tensile strength could be achieved.

In conclusion, if these technical flaws could be rectified, this could become an excellent replacement for sutures.

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## Images

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Figure 2. <http://www.nature.com/nature/journal/v453/n7193/images/nature07039-f4.2.jpg>

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