

Review Article

Nanotechnology in Surgery: Tiny Solutions for Titanic Problems!

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Introduction

With the revolutionary development of tools that drive manipulation of particles at the atomic level, nanotechnology is considered the biggest engineering advancement since the industrial revolution^[1,2] It began as a vision of the late Nobel physicist Richard P Feynman in 1959 who spoke at the annual meeting of the American Physical society to say, 'The principles of physics, as far as I can see, do not speak against the possibility of manoeuvring things atom by atom'. This lay largely undiscussed until the mid 1980s when an engineer published a book to popularise the potential of molecular nanotechnology, 'Engines of Creation'.^[3] Today, research into nanoscience is developing rapidly with new nanotechnological advancements holding limitless possibilities within the field of medicine and beyond. By 2015 it is estimated that the worldwide market for products produced by nanotechnology will reach US\$1 trillion.^[4] With the ever expanding realms of nanotechnology in all applicable fields, this review attempts to provide only a general summary of recent technological advancements.

What is nanotechnology?

Old rules don't apply, small things behave differently!^[5] Nanoparticles (NP) are structures of diameter 10-200nm^[6] that hold limitless possibilities for design and application in biologic systems.^[7] Nanotechnology is the

design, characterisation, production and application of structures, devices and systems that have novel physical, chemical and biologic properties secondary to control of their shape and size at the nanometric scale.^[8] Nanomedicine is its application to the preservation and improvement of human health using molecular knowledge of the human body.^[9]

Applications in Surgery

Trends towards refining surgical methods to produce minimal trauma to the body in line with enhanced recovery programmes have already begun. Smaller incisions, laparoscopic surgery, microsurgery operating under the microscope, robotics and implants have already produced a move towards the miniaturisation of surgical technique.^[10]

Nanodiagnostics

This is one of the most mature applications of nanotechnology with a variety of nanoparticles being introduced over the last decade for use as contrast agents in magnetic resonance imaging (MRI).^[7] In a study by Varallyay et al in 2002^[11], the use of an ultrasmall superparamagnetic iron oxide (USPIO) nanoparticle in intracranial tumours is compared with the traditional gadolinium MRI contrast agent. This is based on the fact that, unlike gadolinium, USPIO tends to be taken up by reactive phagocytic cells commonly found at tumour margins. As a result, areas of tumour that would not normally show up using gadolinium, may now be

seen. In addition, because of low diffusivity and phagocytosis by tumour cells within the brain tumour, USPIO nanoparticles persist longer within the parenchyma and thus more accurately delineate tumour margins. Figure I^{12,13}

Use of nanoparticles for high resolution ultrasound imaging has also been researched. Wheatley M et al^[14] describe the use of intravenous nanoparticulate contrast agents that are able to penetrate beyond vasculature to

accumulate in targets such as tumours. 'Nanometer sized, surfactant-stabilized' contrast agents are achieved by differential centrifugation to produce excellent power doppler and grey-scale pulse inversion harmonic images at low acoustic power.

Both these studies highlight the possible diagnostic and therapeutic benefits of using nanoparticles as contrast agents, be this for passive targeting and accumulation in tumors or otherwise.

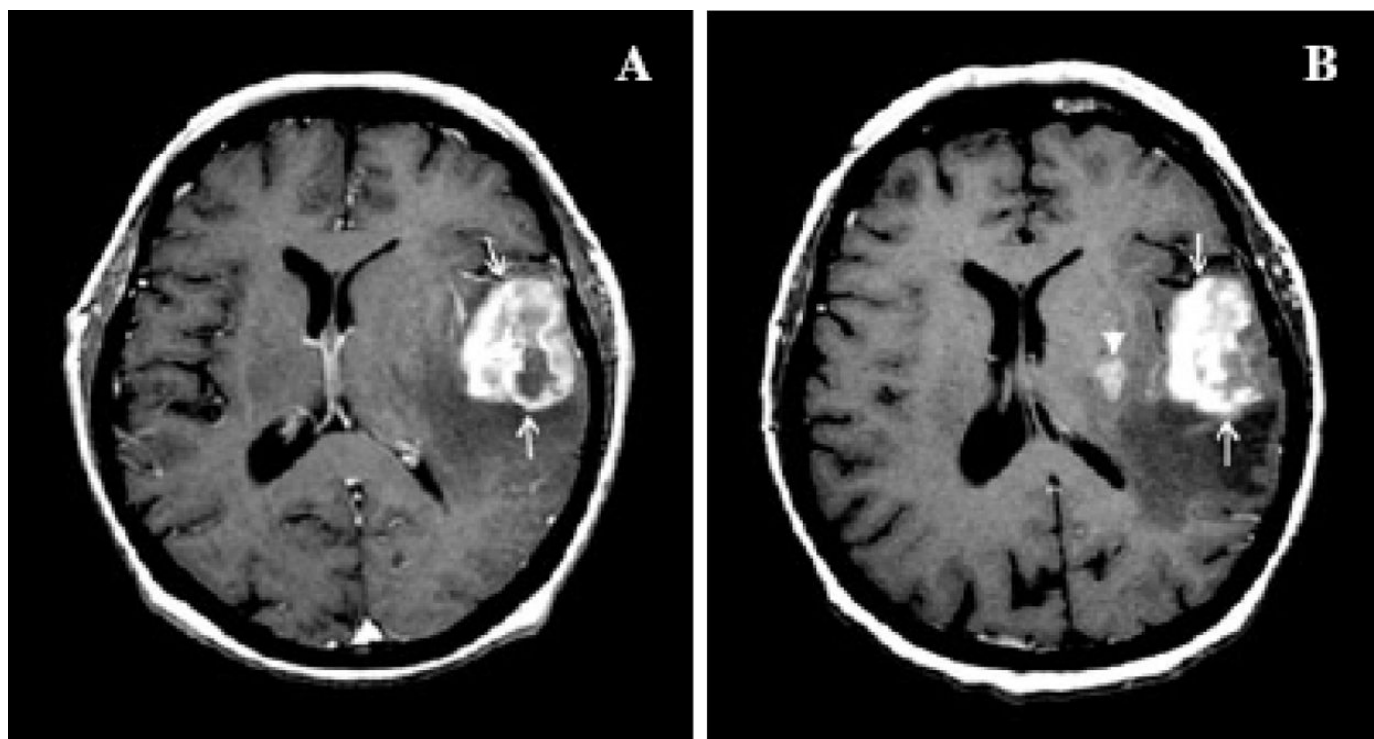


Figure I: Demonstration of differences between gadolinium enhancing areas of tumour (A) and iron oxide nanoparticle-enhancing areas of tumour (B). Note area of tumour (solid arrowhead) that enhances with iron-oxide nanoparticles but not gadolinium. (Reprinted from ref 13. Permission requested)

Nanoendoscopy

The PillCamTM capsule endoscope produced by Given Imaging Ltd (Yoqneum, Israel), was approved in 2001. This allows peristaltic movement of a video-camera capsule down the gut to produce intermittent imaging of the small intestine. Due to only a 50% success rate, it is thought that future control of positioning and movement of the capsule using nanoscale technology would greatly improve outcomes for this technique.^[10] The 'Gutbot', currently under development at a NanoRobotics Laboratory in the Carnegie-Mellon University (CMU, Pittsburgh, PA), looks to offer a possible solution. Nanotechnological sensors and sticking devices promise to offer a more accurate and efficient test with the possibility of drug/chemical release at the site of

abnormal area. Its use may be extended to introduction of a pill-sized camera through the anus designed to replace the pre-existing and much more invasive colonoscopy.^[15]

Nanooncology

Nanotechnology is increasingly finding use in the management of cancer, with impact at three main levels: early detection, tumour imaging and drug delivery.^[2] In contrast to small molecules that diffuse freely into and out of tissues, nanoparticles behave as macromolecules tending to accumulate within tumours. This effect is called the enhanced permeability and retention effect (EPR) and forms the basis of the efficient use of

nanoparticles as vehicles for diagnostic and therapeutic agents in oncology.^[7]

A Breast Cancer

Breast cancer is currently the most commonly diagnosed cancer in the UK, with approximately 45 000 new cases each year. It is known that one in nine women will develop breast cancer at some point in her life.^[16,17] It is perhaps hardly surprising therefore, that between 2006 -2010, an estimated funding for nanotechnology in Europe will reach over three billion euros in an attempt to bring nanotechnology from the laboratory to the bedside.^[18]

i) Laboratory diagnostics:

The level of oestrogen receptor expression in breast cancer correlates directly to benefits of endocrine treatments, where as the presence of HER₂ (ERBB₂) protein over expression determines potential benefit from the monoclonal antibody, trastuzumab.^[19] Immunohistochemistry currently in use for their detection on tumour specimens is limited by back ground 'noise', signal degradation and inability to detect the different proteins simultaneously.^[18] Semiconductor fluorescent nanocrystals, such as quantum dots, have been conjugated to antibodies to allow simultaneous labelling and accurate quantification of these targets in one breast specimen. This would allow correlation between gene products/ proteins in real time, expression of target protein to be monitored before and after treatment, and provide an accurate measure of efficacy of targeted therapy.²⁰

ii) Imaging:

The use of blue dye and injection radioisotope in the intra-operative detection of sentinel lymph node for breast cancer staging is currently in use.^[18] As nano-dimensions of the quantum dot mean they do not flow past the sentinel lymph node, infra-red quantum dot injections into the skin of a breast tumour bearing animal have been used for its easy location by following lymphatic flow. Their use *in-vivo* could simplify sentinel lymph node biopsies into becoming a more precise and safe procedure.^{21,22}

iii) Drug delivery:

One of the greatest challenges in translating novel chemotherapeutics into the clinical realm is developing efficient means of therapeutic delivery.^[23] Tumour targeting principles include systemic passive targeting and active receptor targeting through incorporation of molecular sensors that are able to respond physical or biological stimuli.¹⁵

Traditional systemic anthracyclines such as doxorubicin, a first-line chemotherapeutic agent for metastatic breast cancer, are known to have potentially poor tissue penetration along with significant cardiotoxic side effects.^[18] Randomised control trials using the addition of a simple nanoparticle such as liposome, have shown that although liposomal doxorubicin achieves similar efficacy in time to disease progression, those taking the modified preparation had significantly fewer cardiotoxic and neutropenic side effects.^[20,24] Although liposomal doxorubicin is approved for treatment of metastatic breast cancer in Europe, it is not currently recommended by NICE (National Institute for Clinical Excellence).^{25,26} Studies with similar use of nanoparticulate delivery of tamoxifen in breast cancer mice has also shown polymer bound drugs to have greater tissue penetration.²⁰

B Colorectal cancer

Colorectal cancer is the second most commonly diagnosed cancer in the UK with 36 500 new cases diagnosed each year.^[27,28] Although surgery continues to have a major role in the removal of detectable tumour in early colorectal disease, micro-metastasis are often known to cause relapse, ranging from 3->50% depending on stage of cancer.²⁹

Guanylyl cyclase C (GCC) is an intestinal receptor for bacterial diarrheagenic heat-stable enterotoxins (STs) which are selectively expressed in the apical membranes of intestinal mucosal cells in normal and colon cancer cells but not extra-gastrointestinal cells/tumours.^[30] Studies are currently underway into the incorporation iron oxides into nanoparticles for use in targeting specific GCC receptors to enhance *in-vivo* diagnosis of colorectal cancer using MRI imaging.^[31]

Nanotechnology clearly holds immense potential for targeting cancer, but this needs to be paralleled carefully with safety evaluations before they can translate themselves into surgical clinics.^[2]

Nanoorthopaedics:

New methods of repairing bone using nano-HA/collagen/PLA composites have been successfully implemented for fractures, spinal fusion and tumour removal in China. This bone scaffold is made of nano-tubes and, being non-biodegradable, behaves like an inert matrix encouraging bone cells to grow, proliferate and deposit new living material on. As a result, normal functional bone is formed. In a similar fashion, new

techniques to encourage regeneration of cartilage defects are being developed using the fine electrospun poly (L-lactide) scaffold.^[15]

Nanotechnology for haemostasis during surgery

Research undertaken at MIT and Hong Kong University has shown the potential use of simple liquids in haemostasis of open wounds in several different types of rodent tissue: brain, liver, skin, spinal cord and intestine. These liquids composed of peptides, when applied, self-assemble into nanoscale protective barrier gel that seals the wound and stops bleeding in <15s. After healing, the gel breaks down into molecules that the cells can then use for building blocks of tissue repair.¹⁰

Atomic Force Microscopy (Afm) With A Nanoneedle

AFM is a type of microscopy in which a probe is scanned across the sample to obtain information about its surface investigating specific properties by contact and indentation of the cell with an ultrathin nanoneedle.^[8] Obataya et al^{32,33} investigated the mechanical response during insertion of the nanoneedle into living cells. It was found that the needle could be accurately inserted into the nucleus of the cell without causing fatal damage. This cell surgery technique could be used to induce differentiation from stem cells to prepare healthy cells for donation of functional cells to a patient.^[8]

Femtosecond laser surgery:

Nanoprocessing in this respect is 'achieved by the generation of high light intensity (10^{12}Wcm^{-2}) by diffraction-limited focusing of the radiation of an NIR (740 and 800nm) femtosecond laser on a subfemtolitre volume.'^{33,34} Konig et al³⁴ were able to perform a minimum cut size of 110nm with chromosome dissections within living cells. The potential applications for this technology include eye surgery, neurosurgery, tissue engineering, laser-assisted in vitro fertilisation (IVF) and gene therapy.^[8]

Nanomics: The Economics of Nanotechnology

In an attempt to bring nanotechnology from the laboratory to the bedside, an estimated three billion Euros will be allocated to nanotechnological research in Europe between 2006 and 2010.¹⁸ In comparison, the

USA alone invested approximately US\$1.4 billion to this project in 2008.²⁸ There is no doubt that nanotechnological platforms provide a unique niche for medical advancement in the future but various challenges to commercialisation must also be addressed. These include: cost of equipment, quality of nanomaterials, regulatory guideline uncertainties, lack of trained workforce, lack of understanding about nanotechnology potential and a need for analytical tools to evaluate product quality and environmental/health and safety issues.³⁵

Side Effects and Ethical Implications

Nanotechnology now at the leading edge of rapid development with many potential health benefits, raises apprehensions over the possible toxic health effects associated with human exposure to nanoparticles that are relatively unknown.^[1] Numerous epidemiologic investigations have already shown a direct credible relationship between ambient air particulate pollution and association with increased health effects attributed to cardiovascular disease.¹ Delfino et al in 2005 showed clearly such pathophysiologic changes associated with ultrafine particles (UFPs). Another problem that may limit the wide use of this technology, is the potential for radical change, and as yet unpredictable effects, of particulate behaviour that occurs when molecules are translated to the nanomolecular level.^[36]

The ethical considerations in nanotechnology can be related to the following: risk assessment in general, therapy on somatic cells versus germline cells, the enhancement of human capabilities, research into human embryonic stem cells along with the self-assembly and uncontrolled function of nanoparticles in nanosystems.⁸ It should be noted however, that despite ethical questions in nanotechnology being more complex than those in general medicine, the same principles apply.

Conclusion

Applications of nanobiotechnology are already beginning to show great impact on the practice of conventional medicine in practice today.¹⁵ The National Cancer Institute has recognised the great importance of nanotechnology in the future of all types of benign and malignant cancers and have delivered large grants for

achievements in this field for the future.^[37] The Office for Science and Technology in the UK has recommended more research into the toxicological aspects of nanotechnology which will undoubtedly pose challenges to researchers as we delve yet deeper into the realms of this field.^[28] Despite this, it appears certain that advances in nanomedicine offer the possibility of new and exciting opportunities in nanoparticulate detection, diagnosis and treatment of surgical disease.

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