NANOTECHNOLOGY IN THE DIAGNOSIS AND MANAGEMENT OF COELIAC DISEASE

BY

NATALIE GENT

PASS WITH DISTINCTION

RESEARCH PAPER
BASED ON
PATHOLOGY LECTURES
AT MEDLINK 2010

ABSTRACT

The concept of doing scientific tasks at the molecular level is nothing new. Now, however, and in the next decade, the tide turns from one of nanotechnology theory to practise and then, possibly, exponential development and medicine is poised to reap the benefits. Many areas of medicine are already benefiting from ongoing research. This research paper proposes that there is a particular medical condition that is ideally suited to a nanotechnological approach to its diagnosis and treatment, coeliac disease. Current diagnostic and therapeutic options for this condition are discussed and a solution to the difficulties that they present is suggested. From an understanding at the molecular level of how this disease is caused this paper concludes that nanotechnology could greatly benefit those with the condition and those that treat them.

INTRODUCTION

Nanotechnology

The idea that the manipulation of atoms and molecules, working at sizes of billionths of a metre, could lead to important advances in science was first seriously put forward in the 1950s by an American physicist called Richard Feynman but it was not until the 1980s that the concept started to be tested in practice as technical progress caught up with the theoretical debate. The development during that decade, for example, of carbon nanotubes (figure 1) with a width 1/50,000th of a human hair, which can now be made many centimetres long, that had exceptional strength and useful electrical properties demonstrated potential uses in situations as diverse as body armour, optics, architecture and even paper batteries [1]. There are those that doubt that nanotechnology will be as useful as some people believe [2] but the expansion of research in recent years has silenced the majority of sceptics. Whether, in the future, scientists are actually able to build motors and robots of comparable size to a living cell remains to be seen but the spectrum of current research in nanotechnology arena suggests that something very near to this is a distinct possibility.

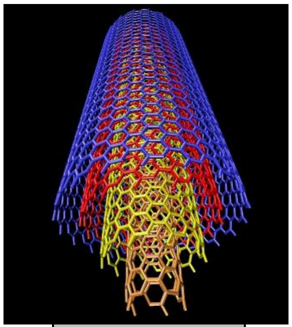


Figure 1

Nanotechnology and Medicine

It is only logical that medical research and nanotechnology have a close relationship. Much of what goes wrong in the human body occurs at a molecular level. If treatment modalities can be designed that work at that same level, such as the molecular machines that nanotechnology could utilise, then the outcome for the patient could be vastly superior to the relatively blunt scalpel of the past and the laser of the present. There is a constant desire to treat medical conditions more effectively and efficiently both from the perspective of the patient and the health economy. Minimally invasive therapies have many advantages as have been demonstrated in recent years by the widespread introduction of laparoscopic or endovascular treatments for a variety of conditions as diverse as heart valve replacements and hernia repairs. The significant benefits that have occurred from the switch from 'open' to 'minimally invasive' surgery could be multiplied many times again if the same procedures could be performed using nanotechnology. The possibilities are very exciting and in an age where financial resources to fund the health care of an ever ageing and enlarging population are increasingly restricted, technology that might significantly assist is going to be essential.

The fact that the European Union spent 280 million euros in 2007-8 on nanotechnology research[3] demonstrates the commitment of major governments to this area of medical intervention. Most of the investment in nanomedicine research in the last decade has been directed towards the fundamental research required to gain a greater understanding of this area of science but now is a significant turning point where the emphasis is moving from test tube to bedside.

Current Nanotechnology Research in Medicine

There are products already on the market that utilise nanotechnology including appetite suppressants, coatings for dressings, bone replacement treatments and immunosuppressant drugs[4]. Trials are underway where nanoparticles of iron oxide are guided to the centre of cancerous tumours. A magnetic field is then used to vibrate and therefore heat up the particles to kill off the surrounding cells [5]. Other current research includes work done by the Prostate Cancer Foundation looking at intravenous injections of nanoparticles to directly target cancerous cells within the prostate gland and secondary deposits elsewhere in the body[6]. Scientists have already managed to attach nanoparticles to individual DNA strands and attach them to frameworks in an organised and controlled manner without affecting the function of the DNA. The plan is that these structures can be organised 'bottom up' into larger devices with specific functions offering treatment modalities that are currently not available[7]. One specific disease area where nanotechnology research is progressing is macular degeneration, a common cause of blindness that is often impossible to treat, where the introduction of nanotech retinal implants (figure 2) may be only 18 months away[8]. It is clear, therefore, that although nanotechnology use within medicine is still currently quite peripheral, this is not going to be the case for much longer.

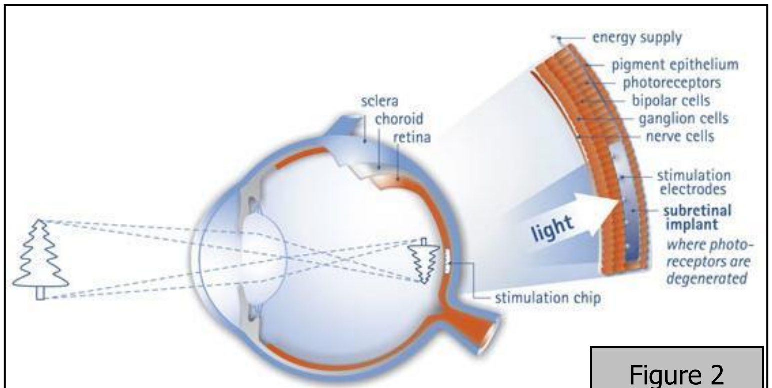
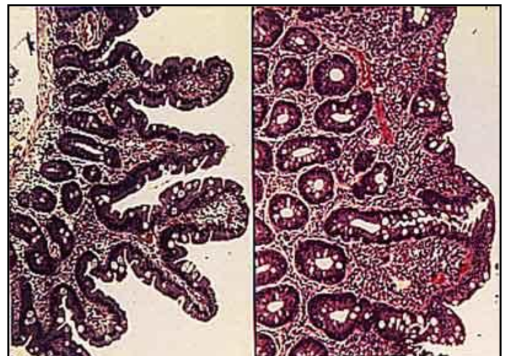


Figure 2

Many other diseases are already being researched including within the fields of oncology and nephrology[9] but, interestingly, there is little, if any, current interest in the potential for nanotechnology to play an important role in the diagnosis and treatment of coeliac disease. A condition which is not uncommon, where population screening is not currently possible, where the diagnostic tests are often invasive, where the disease process occurs at a molecular level and where the treatment options are currently very narrow is an ideal area for nanotechnology research because a positive outcome could revolutionise how we detect and manage this condition.

Coeliac Disease

There are many diseases that can affect humans which are caused by the body's own immune system attacking some part of its own body rather than its intended purpose of defending it against external threats such as infections. Well known diseases that are part of this group of disorders include type 1 diabetes mellitus, crohn's disease, rheumatoid arthritis and multiple sclerosis. They are called auto-immune diseases. Coeliac disease is also one of these conditions and affects the small intestine in the middle section of the gut of affected people of all ages. Gluten, a protein that is found in wheat, barley and rye in the diet, triggers an immune response that flattens the small finger-like projections, called villi, that line the small intestine wall (figure 3). These villi increase the surface area of the gut lining to allow important nutrients to be absorbed from the diet into the body. Without these villi, patients develop malabsorption symptoms including weight loss, tiredness and abdominal pains [10]. It is estimated that 1 in 100 people in the United Kingdom suffer from coeliac disease [11] which makes it the most prevalent auto-immune disease but because the symptoms can be quite vague and overlap with symptoms found in other illnesses, for example irritable bowel syndrome, the diagnosis can be delayed or missed completely. This is important because patients with this condition are at higher risk of complications such as osteoporosis, anaemia and lymphomas [12].



Normal villi Flattened villi

Figure 3 - Small Intestine

The 'gold standard' diagnostic test is a small bowel biopsy [13]. Although antibody blood tests are quite accurate, patients with positive results or negative results but a strong clinical suspicion should all have a biopsy to confirm the diagnosis [14]. The endoscopy procedure that has to be performed to obtain the biopsy can be both unpleasant for the patient and potentially risky [15]. This is the reason why I believe that nanotechnology research into an accurate non-invasive diagnostic test is so important.

The only current effective treatment for coeliac disease is a gluten-fee diet [16]. Strict adherence to this allows the auto-immune response to subside and the villi to grow back. The malabsorption then stops and the patients improve. Within 5 years of the introduction of a gluten-free diet the higher risk of osteoporosis and lymphoma return to normal population levels [17]. The gluten-free diet is quite restrictive as gluten is present in a large proportion of the food we eat. This restriction is life-long from the date of diagnosis. This is the reason why I believe that nanotechnology research into alternative treatments is so important.

DISCUSSION

Coeliac Disease Treatment

An exploration of the process occurring in this disease at the molecular level is required to understand how nanotechnology could play a part in the delivery of an accurate and safe diagnostic test.

The human diet contains storage proteins called prolamins. Gliadin is the prolamin found in wheat that triggers the immune response seen in coeliac disease [which explains the anti-gliadin antibody diagnostic blood test]. Gliadin attaches to the small bowel villi superficial membrane and disturbs the function of the sealant that exists between the surface enterocytes, allowing larger protein molecules than normal through, such as gliadin itself, which then stimulates the auto-immune response in susceptible people. Research has shown that rotavirus infections can cause small intestine villous atrophy and may, in fact, be the initial trigger for coeliac disease to begin [18].

I propose that partially inactivated rotavirus could be used as a delivery mechanism for a nanoparticle attached to the surface of the virus. The nanoparticles arrive naturally at the small intestine after ingestion in tablet/liquid form and gain access via the virus' normal targeting mechanism to the superficial membrane still attached to the virus. The body's normal defence mechanism would attack and destroy the rotavirus in the usual way leaving the detached nanoparticles to carry out their intended function. The nanoparticle would be so similar chemically to the surface membrane sealant that it would not be attacked by the immune system. The membrane sealant of the small intestine lining normally allows proteins of 3 amino acid lengths to pass through [19]. Gliadin is much larger – the most active section that triggers an immune response is 33 amino-acids in length [20]. The nanoparticle will bind to the sealant layer and, due to its own properties, will allow small amino-acid length proteins to pass through as normal but will not allow gliadin to disrupt the tight enterocytes layer. This will prevent the nanoparticle from causing malabsorption itself which would happen if it were to completely block off the sealant layer. The nanoparticle will therefore protect the surface layer from the effect of gliadin and prevent gliadin from entering the small bowel epithelium and triggering the auto-immune response.

The technology to use deactivated viruses therapeutically is already well established, for example in the childhood measles, mumps and rubella vaccination [21]. It is also currently possible to use genetically modify viruses to carry out tasks including directing them to produce proteins [22]. The virus would act as a carrier for the nanoparticle. Therefore this research is not beyond the scope of current practice. A nanoparticle that has the correct properties in terms of small bowel service layer adhesion, protein permeability and an ability to stay in position for long enough to allow administration frequencies that promote good patient compliance needs to be developed and tested in the normal in-vitro and then in-vivo way. The rotavirus has been chosen as the carrier mechanism as it is already known that this virus reaches and has an affect on the small intestinal lining [18].

Medical research takes time and costs money. Many prototype drugs do not make it through to the market due to unforeseen complications including side-effects and lack of efficacy [23]. For this reason I propose that the same nanotechnology that is proposed for the treatment of coeliac disease can also be used in an adapted form for its diagnosis.

Coeliac Disease Diagnosis

Patients with coeliac disease who are on a diet containing gluten, ie those at the time of diagnosis, have flattening of the small bowel villi as described previously and the superficial layer membrane sealant layer is damaged. The same nanoparticle/inactivated rotavirus combination can be used diagnostically in the following way.

In a well patient or in a coeliac sufferer on a gluten-free diet in whom it is important to confirm villi normality, a test dose of nanoparticle can be given. The virus will be taken up by the small intestine surface membrane as usual and the nanoparticle will be released as the virus is broken down by the body's immune system. At this point, however, as the sealant layer is intact, the nanoparticle does not attach itself. This is where this exciting potential of nanoparticles can be demonstrated. They are not simply passive structures but can be designed to perform more complex or multiple tasks [24]. The nanoparticle will enter the venous circulatory system in a passive manner along with other substances absorbed by the gut and will attach itself within the blood stream to a substance that is excreted from the body by the kidneys that is not present in the small bowel superficial layer membrane such as creatinine. It will then be excreted renally and can be easily detected using a simple and cost-effective urine dip test in a similar way to that used for urine pregnancy tests. Just as pregnancy tests performed this way are now extremely reliable [25] there is no reason why a coeliac test should not also be. A positive result in the urine test would indicate the absence of coeliac disease or the adherence to a gluten-free diet in an affected individual.

An alternative area for research here would be to label the nanoparticles in a way that allows their presence and position to be identified by an external scanning device. The localisation of the nanoparticles to the small intestine wall a certain period of time after the administration of a test dose would indicate the presence of disruption of the superficial layer sealant and the attachment at that site of the nanoparticles. This is more technical than the renal excretion method and may turn out to be more accurate in terms of sensitivity and specificity but in practice would require complicated equipment and trained staff with the associated costs.

The National Institute for Health and Clinical Excellence has advised screening for first degree relatives of coeliac disease sufferers [26] and as a screening test has to be accurate, easy to perform and affordable to the health service the chosen method for use in coeliac disease has to be mindful of this.

The Future

Newcastle University has a Biomedicine Department Research Institute for Nanoscale Science and technology and they believe that nanotechnology will become one of the basic technologies for healthcare delivery in the next twenty years. They believe that by 2020 nanotechnology will have developed to the extent that we will be able to monitor, repair and control cellular function for example by building artificial mitochondria which would be able to take on the metabolic functions of a failing cell. Later we might build nanocomputers to travel within the body identifying cancer cells, then releasing agents to kill these cells before moving on to next ones [27]. There are also hopes that we will be able to repair free radical damage within DNA that could reverse the ageing process that has been linked with cancer, arthritis, dementia and diabetes [28]. The development of a nano-scale artificial kidney is years away but not beyond the realms of possibility. The benefits to millions of patients worldwide would be huge [29]

It is clear that nanotechnology medical developments in the next few years could potentially save many lives. Nanotechnology is already moving to being used in active ways, through more targeted drug therapies which have already been shown to cause fewer side effects and to be more effective than traditional therapies. In the future, nanotechnology will also aid in the formation of molecular systems that may be similar to living systems which could be the basis for the regeneration or replacement of body parts that are damaged by infection, accident or disease. These predictions are realistic and should encourage nanotechnology research and development [30].

Ethical Issues

Undoubtedly the diversity of potential nanotechnology developments in the future will unearth a large number of ethical concerns that will have to be dealt with appropriately for the protection of patients, their physicians and indeed society as a whole. Medical research currently undertaken in the developed world is already tightly regulated for this purpose but debate is inevitable when extreme opinions exist, which is usually the case. The recent interest concerning genetically modified food and stem cell research are two good examples. If nanotechnology develops to the extent that nanorobots travel within the human body repairing or replacing tissue and prolonging life then there will be a heated debate. Professor Alfred Normann at the Department of Philosophy at Darmstadt University in the United States says "trends [in nanotechnology] were deeply unsettling to many patients and physicians in the 20th century and are likely to raise eyebrows in the 21st. Accordingly, the group on ethical and societal aspects recommends explicit agenda-setting for nanomedicine that begins with a clear understanding of achievable benefits and the ways in which it is, indeed, novel" [31]. I do not, however, believe that what is proposed within this research paper will raise any ethical concerns.

CONCLUSION

Nanotechology is obviously entering an exciting phase. When we look back in 10 or 20 years it will be interesting to see how current predictions compare to reality. What is certain, however, is that the scientific ability to develop nanotechnology exists and there is a need and desire within medicine to use this technology in a multitude of ways. I believe that I have highlighted one of the situations where it could be used in a way that is far superior to that which is currently available. By combining a new method of diagnosis for patients with coeliac disease with a new treatment I believe that the process has been simplified and that the chances of success are improved – both from a financial perspective but also due to there still being a potential use for this technique if one arm of the research study were to fail for any reason.

Potential problems that may be encountered include the inability to develop a nanoparticle that can be attached to the inactivated rotavirus that serves the purpose of sealing the intestinal surface membrane, side effects possibly caused by the protein's effect on the absorption of other [non-gluten] substances through the intestinal wall and problems with the accuracy of the detection of the protein within the patient's urine in the absence of villous atrophy. Although it is often impossible to predict these sorts of problems prior to commencing trials the interesting thing about nanotechnology is that any solution to an encountered problem may actually come from within the field of nanotechnology itself. For example it may be possible to send images from the intestinal wall to a monitor outside the patient from a nanodevice that is able to 'read' the intestinal superficial membrane and detect whether the sealant layer has been repaired. Perhaps one day these two nanotechnologies could be combined in one product that not only seals the surface layer but also images the repair for the treating physician to see which may seem improbable now but could well be reality not just for our descendants but ourselves.

The research within this paper, however, is for the present and hundreds of thousands of undiagnosed coeliac patients around the world can hopefully be relieved of the chronic symptoms and dangerous complications that they are currently exposed to.

REFERENCES

1 "Beyond Batteries: Storing Power in a Sheet of Paper". Eurekalert.org. August 13, 2007. http://www.eurekalert.org/pub_releases/2007-08/rpi-bbs080907.php

2 Nanotechnologyscepticism http://amssolarempire.blogspot.com/2006/08/im-nanotechnology-skeptic.html

3 Chrstos Tokamanis quoted from 'Nanomedicine in Europe: present and for the future'. 2 June 2010, European Parliament, Brussels

4 Current Nanotecnology Projects http://www.nanotechproject.org/inventories/medicine

5 Dr. Andreas Jordan, MagForce NanotechnologiesAG, Berlin http://www.magforce.de/

6 Prostate Cancer Foundation http://www.news-medical.net/news/2008/01/29/34762.aspx

7 DNA reaearch http://www.cesar.ornl.gov/nanotechnology.html

8 MacularDegenerationRetinalImplants http://www.amdsupport.ca/2009/05/01/nanotech-retinal-implant-for-macular-degeneration/

9 Nephrology Research http://www.physorg.com/news6334.html

10 Coeliac Symptoms http://www.patient.co.uk/health/Coeliac-Disease.htm

11 Bingley PJ, Williams AJK, Norcross A, Unsworth J, Lock RJ, Ness AR, Jones RW. (2004). Avon Longitudinal Study of Parents and Children Study Team. BMJ 328:322-3

12 NICE (2009) Coeliac Disease: Recognition and assessment of coeliac diseases. www.nice.org.uk

13 Abdulkarim AS & Murray JA (2003) Review article: the diagnosis of coeliac disease. Alimentary Pharmacology and Therapeutics. 17: 987-995.

14 Coeliac Diagnosis. http://www.coeliac.org.uk/healthcare-professionals/diagnosis-of-coeliac-disease

15 Diagnostic Endoscopy. http://digestive.niddk.nih.gov/ddiseases/pubs/upperendoscopy/

16 Coeliac Management. http://www.coeliac.org.uk/healthcare-professionals/management-of-coeliac-disease

17 Holmes GKT, Prior P, Lane MR, et al (1989). Malignancy in coeliac disease - effect of a gluten free diet. Gut. 30: 333-338.

18 Rotavirus: A trigger for coeliac disease? http://www.nature.com/ajg/journal/v101/n10/full/ajg2006431a.html

19 Amino acid transport in the small intestine. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2653457/?tool=pmcentrez

20 Disruption of small intestine surface layer. http://gut.bmj.com/content/55/7/1037.full

21 Deactivated viruses in childhood immunisation. http://jvi.asm.org/cgi/content/full/76/20/10524?view=long&pmid=12239331

22 Viral modification for thrapeutic puroses
http://www.newscientist.com/article/dn12839-gm-virus-shrinks-cancer-tumours-in-humans.html
23 Medical research costs.
http://www.sciencedirect.com/science
24 Nanoparticles ability to perform complex tasks.
http://books.google.co.uk/books?id=nanoparticles+complex
25 Pregnancy Test sensitivity.
http://www.womenshealth.gov/faq/pregnancy-tests.cfm
26 National Institute for Health and Clinical Excellence (2009): Recognition and Assessment of Coeliac Disease.
27 *Advances in Anti-Aging Medicine*, Vol. I, edited by Dr. Ronald M. Klatz, Liebert press,1996,pages277-286
http://www.zyvex.com/nanotech/nanotechAndMedicine.html
28 DNA free radical repair.
http://www.ncl.ac.uk/biomedicine/research/groups/nanomedicine.htm
29 Sohal R, Mockett R, Orr W (2002). "Mechanisms of aging: an appraisal of the oxidative stress hypothesis". *Free Radic Biol Med* **33** (5): 575–86.
30 Research and Development.
http://en.wikipedia.org/wiki/Nanomedicine#Medical_applications_of_molecular_nanotechnology
31 Alfred Normann lecture notes.
http://www.nanomedroundtable.org/system/files/private/Speakers'biographiesandsummaries.pdf