

THE POSSIBLE USE OF NANOPARTICLE SEMICONDUCTORS IN
PRODUCING A THREE DIMENSIONAL IMAGE OF A SOLID SURFACE
TUMOUR.

BY

ROSEMARY HERRINGTON

ELEANOR ROBERTSON

PASS WITH DISTINCTION

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Abstract:

Nanotechnology is used to manipulate individual atoms. This capability has a wide variety of applications, which include medicine - both human and veterinary. Nanoparticles, such as Buckminster Fullerenes (commonly known as 'Buckyballs') could be used, in conjunction with semiconductors, to form a nanoprobe. This could be used to trace the three dimensional extent of a solid surface tumour – e.g. a melanoma. Such semiconductors, if exposed to an electric potential, may emit photons of various wavelengths could be used to detect photon emissions. The use of two semiconducting compounds which emit photons of different wavelengths could enhance such a technique. The difference in absorption of the two wavelengths as they pass through the in vivo tissue could allow the outline of the surface tumour to be seen in three dimensions.

Introduction:

Nanotechnology is an exciting new field with applications in medicine. It is the capability to assemble atoms or molecules to create nanoscale structures. "There's always room at the bottom" as Nobel Prize winning physicist Richard Feynman (Figure 1) first established in 1959. Since then, nanotechnology has been developed for uses such as machines and transport systems on the molecular scale. It could also be used in the field of medicine. A nanometre is one billionth of a metre. It is smaller than the wavelength of light and one thousandth of the width of a human hair. Objects of this size are small enough to enter and leave a cell in our bodies with ease. The invention of the electron microscope meant that individual atoms could be seen for the first time in the 1980s. This led to the development of such inventions as self-cleaning glass, insulin pumps, car airbags, diagnostic imaging, and drug delivery systems. Effectively, in the biological field, nanotechnology is allowing the creation of man-made cells, which are nature's nanomachines.



Figure 1

Current concepts which are being explored are the disinfection of wounds, drug delivery systems and cell repair. Quantum dots (specific nanoparticles) are being used in medicine to locate tumours by use of antibodies and fluorescent agents. The quantum dots bind themselves to the tumours and glow. Used in combination with an advanced imaging system, a melanoma can be located accurately. An accurate location means that surgery can become more efficient as the location of the cancer cells are precisely known. This decreases the chance of cancer reoccurrence after surgery.

Cancerous tumours are a major cause of mortality, with over 70% of deaths being caused by the disease. The figure is large in part due to the number of cancers that reoccur due to the first removal being unsuccessful. Unless all cancerous cells are removed, a new tumour can recur. Cancer is currently the leading cause of death worldwide, responsible for 7.6 million deaths each year. The figure is predicted to increase to 11 million in 2030 by the World

Health Organisation. Thus, a more accurate and efficient way of locating and removing tumours would be highly beneficial to the field of medicine.

Tumours, specifically surface tumours, are mutations that sporadically and spontaneously form. However the likelihood is increased by the presence of mutagenic agents (carcinogens) such as; x-rays, ultra-violet rays and excessive exposure to certain chemicals. There are various methods of ridding the body of the surface tumour. The most commonly used is a combination of radiotherapy, chemotherapy, and removal of the melanoma with invasive surgery. There are many drawbacks to this method: the side effects of chemotherapy; the removal of healthy cells during surgery; the low success rate of complete melanoma removal; and the risk associated with the use of radioactive material (isotopes) to locate the tumour. A method of accurately and safely identifying such cells would be highly beneficial in the treatment. Using nanotechnology, such a method could be devised.

A procedure currently used to find tumours is isotope localisation. In this technique, a radioactive isotope is injected into the patient's bloodstream. The substance becomes concentrated in the proximity of the surface tumour, and this allows detection by use of an x-ray machine. However, this method has a number of flaws. The main one being that the substance injected is radioactive. Even if it is injected in low doses it may be harmful. An alternative treatment which uses nanotechnology could resolve some of these flaws.

It is clear from papers on the use of drug delivery systems in the locating of surface tumours that a technique that combines the current theories of biochemistry and nanotechnology might produce a three dimensional image of a tumour pre-surgery. This could allow minimal invasion of healthy cells, benefitting the patient's recovery.

Discussion:

Buckminsterfullerenes are hollow, spherical, cage-like structures composed of carbon atoms arranged in hexagonal and pentagonal faces. They were first produced in 1985. The smallest is made out of 60 carbons arranged in truncated icosahedrons. This structure has a diameter of only 1 nanometre, which would be impractical for the containment of semiconductors, which are large in comparison. However, another fullerene, C₅₄₀, has a diameter of 2.4 nanometres but remains small enough to pass through the phospholipid bilayer of a cell without drastically altering it.

The toxicity of these structures was determined through testing on mice. It was concluded that there were no toxic properties, and the technique was deemed suitable for in vivo procedures. They are currently used for superconductors, lubricants and catalysts as well as drug transportation of molecules in medicine. It has been proved that these fullerenes are capable of safely containing chemicals without leakage. For this reason, there is a possibility that semiconductors, some of which are recognised to have toxic properties, can be safely

transported to surface tumour. These are skin tumours, thus the semiconductors would be most efficient on such types as the light transmitted would be most easily detected.

A semi-conductor is a chemical with an electrical conductivity that lies between that of a conductor and an insulator. Currently they are used in the production of light emitting diodes, microchips and transistors. Certain semiconductors are very sensitive, and produce light when a low voltage is applied across them. This is due to the electrons becoming excited by the voltage applied and changing energy level. They later decay back to a lower level, and so release photons. The bandgap determines the energy of the emitted photon and therefore the colour of the light. A wide bandgap results in blue and a narrower one red.

A proposed use for semiconductors is in vivo illuminating of cancer cells. This could be achieved by containing the semi conductors within a fullerene molecule and passing a voltage, using skin electrodes, through them in order to make them emit photons. However it is unlikely even then that sufficient potential difference would be achievable across the individual nanoprobe to activate the semiconductor. A more feasible approach would be to attach a metal electrode directly to the semiconductor substrate and use the body's own electrolytes as an ionic power source. One possible electrode material is titanium which produces a potential in the region of 2.2V when coupled via an electrolyte to graphite. Whether this holds for fullerenes would need to be investigated

A possible semiconductor is cadmium sulphide, which has a diameter of 2.3 nanometres and a bandgap of 2.42 electronvolts. This results in it producing blue light when a voltage is applied to it. This semiconductor is currently being used in the manufacturing of photoresistors and is associated with sulphate reducing bacteria. Another possibility is gallium phosphide. This has a diameter of as little as 0.8 nanometres and a bandgap of 2.26 electronvolts, and emits green light. The contrast between the green/blue light and the red body tissue could allow the surgeon to distinguish between the highlighted cancer cells and the normal ones throughout the procedure should the voltage be constantly applied.

However blue and green light would be significantly absorbed by the patients body, which has a red interior, and this could compromise the quality of the image. The differential absorption could be detected by CCD detectors with narrow bandpass filters. Therefore, infrared and red light could be possible alternatives as certain wavelengths of infrared are less absorbed than some wavelengths of red; thus you can estimate depth by differential absorption, therefore creating a more accurate image. A semiconductor that produces red light is gallium phosphide doped with zinc oxide. This emits a wavelength of 700 nm. If used in conjunction with Indium Gallium Arsenide, which produces infrared light at a wavelength of 980 nm, it could produce a more accurate image.

Furthermore, these wavelengths used could present complications, as infra-red light is currently used in pulsoximetry. Oxygen level in the blood could therefore make the results less accurate.

However the oxygen concentration does not affect the absorption at all wavelengths, such as the ones we have selected.

Unfortunately, doping semiconductors greatly increases their diameter, raising the issue that the fullerene may not have the capacity to contain it. This could possibly be the most challenging theoretical issue to overcome with this proposal. However, a possible alternative would be to use carbon nanotubes. Although these possess a smaller radius, the length that can be created has no such restrictions. We would thus need to investigate the possibility of semiconductor monocrystals within a nanotube scaffolding

The method currently used in tumour removal is one that could be improved. The surgeon performing the procedure must discover the full extent of the melanoma during surgery. There is no estimation of skin tumour depth before surgery. This results in a swathe of healthy cells having to be damaged, or removed, to ensure that no remaining cancer cells cause re-growth. A wider margin surrounding the surface tumour would result in a slower rate of recovery for the patient. The procedure is often halted in order for diagnostic imaging to take place so that any remaining cancer cells can be located. However if even one cell is left that there is a possibility of re-growth. This one cell cannot be picked up by such a method.

If the Breslow thickness, the depth that is used as a prognostic factor in melanomas, were determined before surgery the surgeon would have a clear idea of the excision needed and a smaller margin would be necessary. This is where a major advantage over the current procedure lies, this technique could potentially show surface tumour depth estimates before surgery, therefore furthering the accuracy of the procedure. Also, use of this imaging pre-surgery would be of a great advantage to the surgeon as it would decrease the extent of invasive surgery required. If the semiconductors were constantly exposed to voltage then they could continuously illuminate the cancerous cells. This would mean that the surgeon could easily identify the cells for removal without halting the procedure: the less time on the operating table, the less the risk of anaesthesia related difficulties.

In order to achieve the loaded fullerenes transportation and attachment to the tumour two possible methods could be used. The first of these is angiogenesis, as illustrated by Figure 2. This is the creation of new blood vessels from existing ones. This takes place naturally during the growth of a surface tumour, due to the secretion of proteins and growth promoting factors. An example of a growth factor is basis fibroblast growth factor (bFGF). Present in normal tissue, it is activated by the production of a heperan-sulphate degrading enzyme. This is most commonly created during the healing of wounds and in embryonic development, but it has also been found to occur during the growth of a surface tumour. The production of this enzyme results in an increase in capillary growth. This increases the blood supply to the tumour, and is currently exploited for the transportation of drugs.

However, angiogenesis, although giving the general area of the tumour, does not have a particularly high degree of accuracy. The concentration gradient could be very small in the vicinity of the surface tumour, making the tumour margins difficult to identify accurately.

The possibility of using antibodies to bind to the tumour could be an alternative option. An antibody structure, as shown in figure 3, consists of four polypeptide chains arranged in a quaternary structure. This takes a shape similar to that of the letter 'Y'. The humoral immune system produces these proteins, which belong to a family of molecules named Immunoglobins. These antibodies attach themselves to specific antigens and foreign bodies, such as bacteria, fungi and abnormal cells. The tips of the 'Y' are paratopes, which are areas specific to the epitope of an antigen. These epitopes are short sequences of amino acids, which enable an antibody to recognise the foreign body. It is for this reason that antibodies can only bind to one antigen - making them specific. This specificity could be manipulated for the purpose of recognising particular cancerous cells. Specifically, it is monoclonal antibodies which are used. They are produced under man-made conditions in a laboratory from a single cell. This means that there is indefinite capacity for the growth of the cells which produce the desired antibody.

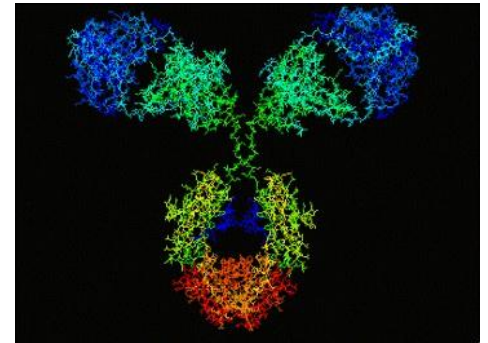
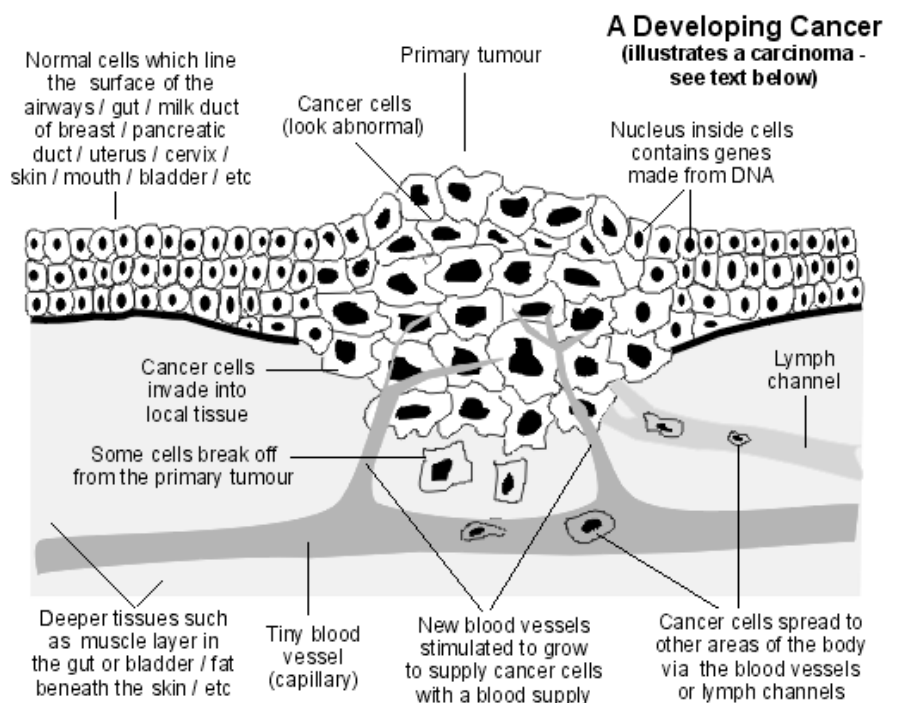


Figure 3

It was George Kohler and Cesar Milstein who first cultured such antibodies in 1975. Since then, they have been used

for a wide variety of treatments. For instance, anti-bodies are currently being produced for radioimmunodetection and radioimmunotherapy of cancer cells, as well as identifying specific pathogens. Based on these tested techniques, it is plausible that by coating a fullerene with the antibody specific to the antigen produced by the surface tumour, a complete surrounding of the tumour



could take place, using semiconductors to produce an image.

The antibody for this purpose would be produced as follows and demonstrated in Figure 4. First, in order to create the antibody, a specimen - such as a mouse - would be injected with the appropriate antigen. This would induce the production of the antibody protein.

Following this, the newly induced cells would be abstracted from the spleen. These would then be fused to myeloma cells (cancer cells). The fusion would be brought about by either polyethylene glycol, a virus or electroporation. (Such fused cells are called Hybridomas.) Myeloma cells that do not bind to antibodies would die, as they can not divide indefinitely. Finally, the cells would be observed to confirm that they are producing the required antibodies. Once this has been ascertained, the cells would then be grown and monoclonal antibodies abstracted.

Monoclonal Antibody Production

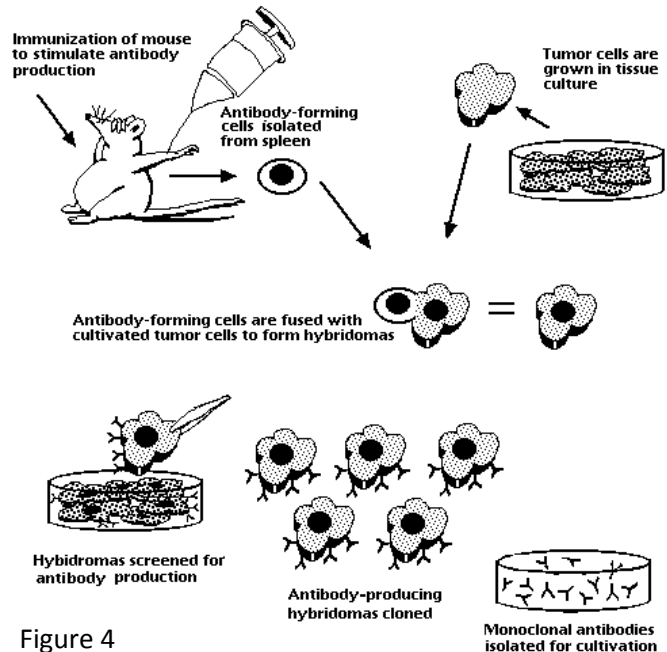


Figure 4

After the binding of the semiconductor loaded fullerenes to the surface tumour, the intention would be to detect the wavelengths of light emitted by the semi-conductors. This could be achieved through the use of a Charged-couple device (CCD) detector, as shown earlier. These are currently used in digital photography, for astronomy as well as in medicine. Such a detector could have a narrow spectrum filter, therefore only detecting the wavelength of light required. Two CCD's could be used, one for each of the coupled semi-conductors that were mentioned previously. If these detectors were integrated with a photoelectric device and the differential absorption between the two wavelengths were recorded, a ratio could be calculated which allows a three dimensional image to be created. The image would show the perimeter accurately and the depth approximately.

Another possible setback is the unavoidable Rayleigh Scattering effect. This is the elastic scattering of light. However, as the light emitted by the semi-conductors would be travelling only a short distance through the body tissues before being detected, this should simply result in a slight 'blurring' of the final ratio produced. However, it is possible that it could have a minimal effect on the image synthesised, particularly if red and infra red wavelengths of light were used. Using these colours would reduce the variation in the image, in comparison to the blue or green wavelengths, as scattering is inversely proportioned to the fourth power of the wavelength, i.e. the red light scatters less.

Once the three dimensional image were synthesized, surgery would be aided by visual identification of the cancerous cells. A possible extension of use would be a robotically performed operation by the use of the previously mentioned CCDs with narrow bandpass filters and a scalpel. It is possible that a mechanically operated scalpel could be programmed to cut around a particularly light intensity created by the photon emissions. The field of healthy cells being removed would thus be reduced further, and the risk of human error removed. However, a laser scalpel would not be appropriate as the light intensity of the laser would interfere with the light detected by the CCD detectors.

All the loaded fullerenes bound to the surface tumour should theoretically be removed with the cancer cells, however unbound nanoprobs will remain in the body. There has been little conclusive scientific evidence to prove that magnets affect the blood negatively. Therefore, it is possible that by doping the fullerenes with a small amount of a magnetic metal, the fullerenes could be removed through whole blood filtration used in conjunction with a magnet. This could ensure that all fullerenes are removed as the chemicals held within could be toxic. Uncertainties also remain on the grounds of toxicity and environmental problems of nanoparticles themselves. The Council of Science and Technology stated that "We are very conscious of the extent to which knowledge about the potential health and environmental impacts of nanomaterials lags significantly behind the pace of innovation" Allowing any to remain within the body would be undesirable.

Conclusion:

The field of nanotechnology is currently being explored through many fields. The capabilities introduced by the manipulation of individual atoms in medicine could improve current surgical procedures immensely. A technique which enabled individual molecules to be transported securely to a particular site such as a surface tumour would be a great advance in medicine. Even more extraordinary, and of more immediate value would be the use of the nanoparticle delivery system to delivery chemical markers which would be visible, through magnification, to a surgeon. Surgery to remove a melanoma in this way would be quicker and much less prone to error. All parts of the melanoma would be clearly marked, and even fragments which broke away from the melanoma would be marked and traced more easily. The three dimensional image of the skin melanoma that could be synthesised also holds the possibility of improving the accuracy of surgery further by allowing the depth to be determined before surgery begins.

Despite some significant issues such as semiconductor crystal size and energy requirements, we remain confident of the feasibility of this proposal and that ongoing research will prove fruitful in progressing development. The technique is in its infancy. The prospects are immense. The potential for development in his field could allow us to " have more power in the volume of a sugar cube than exists in the entire world today", as has been visualized by Dr Ralph C Merkle, co-founder of 'Nanofactory Collaberation'.

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