

remains incurable. Now, scientists are transfixed with the possible capabilities presented to us in the modern concept of nanotechnology. Cancer induced patients are notorious for having a high mortality rate – before we can begin to reduce the alarming rate, we must start at the to look at alternative methods that will be more successful in diagnosing the cancer as well as treating it. I aim to introduce the modern concept of nanotechnology as that alternative and highlight the potential possibilities of having a role within diagnosing and treating cancers, as well as improving the general prognosis for individual patients.

Introduction

Nanotechnology is an interdisciplinary and rapidly evolving branch of science that is set to revolutionise the future of medicine. What makes nanotechnology unique is the sheer scale of it: one nanometre is equivalent to one billionth of a metre, and to put that into perspective, the diameter of a human hair is 200,000 nanometres. The theoretical capabilities of nanotechnology were initially explored by Richard Feynman in 1959, as he proposed the idea of manipulating individual atoms in his talk “There's plenty of room at the bottom”. In 1986, Eric Drexler contextualised this idea into making molecular machines. So, how could this possibly be relevant to medicine?

Treatments for various diseases often cause unavoidable damage of cells that are not strictly part of the problem, simply due to the lack of precision in the instrument involved. Invasive surgery notoriously involves crudely cutting parts away. Nanotechnology on the other hand is about building things up on an atomic level to create larger molecules. This conveniently imitates nature's act of our own formation, cell by cell to form tissues, organs, organ systems and finally a living organism. If we were to manipulate atoms and design surgical instruments on a 'nanoscale', surgery would be much less invasive - the infectious risks would decrease drastically, notwithstanding any pain endured by the patient.

Further research led to the invention of the Buckminsterfullerene by Richard Smalley in 1996, and only then did medical applications of nanotechnology begin to formulate.

LATEST RESEARCH

NANOTECHNOLOGY IS BECOMING INCREASING PREVALENT WITHIN MEDICINE. BIOLOGICAL NANOPORES HAVE RECENTLY BEEN MANUFACTURED WITH THE ABILITY TO MEASURE AND ANALYSE SINGLE DNA MOLECULES. RESEARCHERS HAVE TAKEN ADVANTAGE OF THE PERFORATED NANOTUBES BY THREADING SINGLE DNA STRANDS THROUGH THE HOLES. IN THE PRESENCE OF AN ELECTRIC FIELD, A STRAND IS INSERTED AND THE HYBRID PORE-FORMING PROTEINS ARE POSITIONED IN THE PERFORATIONS. AS A RESULT, THE SPECIFIC SEQUENCE OF THE DNA CAN BE ANALYSED. THE RESEARCH FOLLOWS ON FROM THE MAPPING OF THE HUMAN GENOME IN 2003 EXCEPT WITH AN AIM TO PERSONALISE AN INDIVIDUAL'S MEDICAL TREATMENT. IN THE FUTURE THIS METHOD COULD BE REITERATED ON A WORLDWIDE SCALE – IF EVERY INHABITANT WERE TO HAVE THEIR PERSONAL GENOME MAPPED, DOCTORS WOULD BE ABLE TO DIAGNOSE DISEASES THUS IMPROVING THE PATIENT'S PROGNOSIS, ALTHOUGH ETHICAL ISSUES WOULD NEED TO BE CONSIDERED.

WHAT IS CANCER?

CANCER IS DEFINED AS ANY MALIGNANT GROWTH OR TUMOUR CAUSED BY THE UNCONTROLLABLE PROLIFERATION OF ABNORMAL CELLS. OUR BODIES REQUIRE A CONSTANT SUPPLY OF NEW CELLS, WHICH ARE PRODUCED IN THE CELL CYCLE MITOSIS. IN A HEALTHY PERSON, CELLS DIVIDE IN A CONTROLLED MANNER TO ALLOW GROWTH, REPAIR OR REPLACEMENT OF DAMAGED OR DEAD CELLS. IF A CELL BECOMES DAMAGED AND DNA MUTATES, IT MAY NOT EXPERIENCE PROGRAMMATIC DEATH AND THIS CAN ACCOUNT FOR UNCONTROLLABLE CELL

DIVISION – CANCER. CONSEQUENTLY, THIS LEADS TO THE FORMATION OF A MALIGNANT TUMOUR; THEY ARE UNLIKE BENIGN TUMOURS AS THEIR GROWTH IS ABNORMAL AND METASTASIS OCCURS.

HOW IS CANCER DIAGNOSED NOW?

REGARDLESS OF SYMPTOMS PRESENT, CERTAIN TECHNIQUES ARE NEEDED TO PRODUCE A DIAGNOSIS OF CANCER. A COMMON, NON-INVASIVE METHOD IS THAT OF IMAGING, WHICH IS USED TO FIND OUT WHERE THE CANCER IS LOCATED AND BY HOW MUCH (IF AT ALL) METASTASIS HAS OCCURRED. AS WELL AS THE LIMITING SENSITIVITY OF THE PROCEDURES, THEY INVOLVE EXPOSURE TO IONISING RADIATION AND COULD ENCOURAGE CARCINOGENESIS IN SURROUNDING HEALTHY TISSUE; IF THE EXPOSURE IS MINIMAL, THIS COULD PREVENT TINY REGIONS OF DISEASED TISSUE FROM BEING DETECTED. A BIOPSY IS THE ONLY FOOLPROOF METHOD IN DETERMINING WHETHER A TUMOUR IS BENIGN OR MALIGNANT. IT INVOLVES THE REMOVAL OF A SMALL TISSUE SAMPLE, WHICH IS EXAMINED UNDER A MICROSCOPE BY A PATHOLOGIST. A RATHER INVASIVE METHOD, NEEDLES AND OFTEN SURGICAL TREATMENT IS NECESSARY FOR TISSUE ACQUISITION. BEFORE A BIOPSY IS PERFORMED, PRECISE MAPPING TECHNIQUES ARE CARRIED OUT TO LOCALISE THE AREA OF SURGERY; RADIO-ISOTOPIC MARKERS (OFTEN CONTAINING DYES) ARE INJECTED AND THE CANCEROUS AREAS ARE STAINED. NEVERTHELESS, THE DYES CAN BECOME FAINT DUE TO PHOTOBLEACHING AND THE LIMITED HALF-LIFE OF THE RADIOACTIVE MARKERS MAY RESULT IN THE NECESSITY OF EXTRA TREATMENT. THE ISSUE WITH BIOPSIES HOWEVER IS THEIR INACCURACY IN DETECTING EARLY STAGES OF METASTASIS, SO IT IS ESSENTIAL THAT WE FIND ALTERNATIVE METHODS IN WHICH TO DO SO.

HOW IS CANCER TREATED NOW?

TRADITIONAL METHODS OF TREATING CANCER ARE SURGERY, RADIATION AND CHEMOTHERAPY.

THE SURGICAL APPROACH INVOLVES REMOVING MALIGNANT CELLS VIA AN OPERATION. IT HAS ALWAYS BEEN NECESSARY TO REMOVE AS MUCH TISSUE AS POSSIBLE TO PREVENT THE RISK OF RECURRENCE. NEVERTHELESS, MANY ADVANCED STAGE CANCERS HAVE EITHER *METASTASISED* OR ARE DIAGNOSED TOO LATE TO BE ERADICATED BY SURGERY.

RADIOTHERAPY INVOLVES USING IONISING RADIATION TO DESTROY TISSUE. THIS TECHNIQUE IS USEFUL WHEN A TUMOUR IS SITUATED BESIDE VITAL ADJACENT TISSUES THAT WOULD OTHERWISE BE AT RISK OF DAMAGE IF SURGERY WAS TO TAKE PLACE. IF THE TUMOUR IS LARGE AND THEREFORE INOPERABLE, RADIOTHERAPY CAN BE USED TO SHRINK IT PRE-SURGERY FOR EASE. THE MAJOR RISK OF RADIOTHERAPY IS THAT HIGH DOSES OF IONISING RADIATION MAY CAUSE ADJACENT, NON CANCEROUS CELLS TO BECOME DAMAGED.

Chemotherapy involves using drugs to treat cancer. Tumours can sometimes be situated in inaccessible areas for surgery or radiotherapy, so chemotherapy drugs are distributed in the bloodstream. Besides destroying the cancer, the goal is to control toxicity and reduce the risk of resistance. If cancer cells become resistant to the drugs, a multiple combination must be taken in order for the chemotherapy to be effective.

WHY DO WE NEED ALTERNATIVE DIAGNOSTIC TECHNIQUES AND TREATMENTS FOR CANCER?

The answer is simply down to statistics:

CANCER INCIDENCE IN THE UK (2007)

- Men – 149,364 cases

WOMEN – 148,633 CASES

Total – 297,997

CANCER MORTALITY IN THE UK (2008)

- Men – 81,587 deaths

WOMEN – 75,007 DEATHS

Total – 156,594 deaths

THESE STATISTICS SHOW THAT OF THE TOTAL INCIDENCE, 53% OF CASES RESULTED IN DEATH. THIS SHOCKING FIGURE IS OBVIOUSLY MULTI-FACTORIAL, BUT ASIDE FROM EXTERNAL CAUSES, PROGNOSIS AND MORTALITY HAS A DIRECT RELATION TO:

- How early the diagnosis has been made

HOW SUCCESSFUL THE TREATMENT IS

If we are to improve prognoses, we must improve current methods or devise new ways to diagnose and treat cancer. I therefore propose that we encourage further developments and applications of nanotechnology in these fields.

DISCUSSION

How can cancer be diagnosed using nanotechnology?

Nanoparticles

Conjugated gold nanoparticles can be used to detect low density tumour cells circulating in the bloodstream. Epidermal Growth Factor (EGF) receptors are bound to the surface of the gold nanoparticles and are specifically engineered to distinguish tumour cells from non-tumour cells. When external illumination is applied, it targets the biomarkers on cancer cells so with further research, we may be able to develop methods of detecting metastasis and micro-metastasis. The sensitivity of this method would be extremely beneficial in detecting cancer during the early stages and help to improve the prognosis dramatically. White blood cells are unaffected by the laser. The EGF receptors have purposely been engineered to be less sticky than antibodies in order to distinguish between the tumour cells and white blood cells, which are of similar size.

Another possible application of nanoparticles is in improving Magnetic Resonance Imaging (MRI). Iron oxide nanoparticles coated with tumour-binding peptides are injected and their minuscule size enables them to navigate through the bloodstream undetected by the immune system. The magnetic element of the iron oxide enhances the contrast between the liquid and solid states of matter, allowing cancerous clusters to be more visible on the scan.

Quantum dots

Quantum dots are semiconducting nanocrystals which emit fluorescence upon excitation when bound to a particular antibody or molecule. The emission spectra is determined by the size of the crystals, and various colours can be seen depending on the wavelength produced. Due to the multitude of colours, a collective assay of quantum dots can be used to simultaneously detect multiple substances. One specific application of this technique is identifying cancer cells that have metastasised to the lymphatic system. The advantage of quantum dots over using dye is that they have a much higher photobleaching threshold and the emission can be seen clearly through the tissue prior to an incision; in some cases a biopsy will no longer be necessary, removing

unnecessary trauma due to invasive surgery. The lymphatic systems of the visceral organs are more complex than those of other regions of the body, so mapping techniques are tailored carefully. For instance, pigmented lymph nodes will require several emission wavelengths of various sized quantum dots in order to obtain highly sensitive and contrasting images.

Biosensors

A biosensor is an analytical device for the detection of an analyte (a chemical constituent determined in an analytical procedure). They consist of three parts:

- A sensitive biological element (eg. tissues, cell receptors, enzymes, antibodies etc.)
A transducer (acts as a physicochemical interface to transform the signal from the analyte-biological element interaction into another. For instance: Magnetic, electrochemical, piezoelectric)
A detector element (amplifies the transducer signals and converts them into sensible units necessary for efficient analysis)

Carbon nanotubes

Single-wall carbon nanotubes are coated with particular antibodies allowing single cancer cells to be detected at a high accuracy. This technology has several significant applications in nanotechnology, one of which is the recognition and ability to distinguish between proteins. So far, nanobiosensors with electrochemical transducers are capable of detecting the E7 oncoprotein associated with the human papillomavirus (HPV). HPV is notoriously linked to cervical cancer, and the screening age put in place has attracted much controversy over recent years. The HPV protein is tracked directly by the nanotube sensor and chemical markers are not required. If the cluster of protein-coated carbon nanotubes are able to discriminate between varieties of the E7 oncoprotein, this could enable us to determine the stage of the cancer (or pre-cancer), thus eliminating the age cap. Alternative diagnostic techniques often involve weeks of laboratory analysis whereas protein detection is rapid, allowing diagnoses to be formulated much quicker.

Silicon Nanowires

Arrays of silicon nanowires have been engineered with a coating of monoclonal antibodies, and they act as receptors for cancer marker proteins. An antibody binds to a cancer marker protein and as a result, the change in the conductance of the nanowire is significant enough for detection. Inactive in normal body cells, the activity of the enzyme telomerase can be monitored in tumours due to the sensitivity of the array. In a clinical setting, a blood sample is taken and many cancer markers are detected, allowing the blood to be tested directly without need of laboratory analysis. With further developments, this technology could have huge potential and advantage over others. While prevailing tests identify only the presence of cancer, nanowire arrays may be manipulated to determine specifically the type of cancer.

Cantilevers

Microfabricated cantilevers can be used as a component of nanobiosensors. Although we describe the cantilevers as 'micro' fabricated, they bend in the nanometer-scale. Their flexible beams are coated with antibodies of binding sites complementary to specific DNA sequences. The physical properties of the cantilevers alter as a consequence of the binding, and researchers can detect its presence and the concentration of the molecules in real time.

Nanopores

These nanodevices are perforated with tiny holes that allow a single strand of DNA to pass through at a time. The DNA is characterised for genetic sequencing applications, although only recently have researchers been able to determine what particular individual molecule has passed through one of the minuscule holes. The research involved decoding the electrical signals of a nanopore in an artificial cell membrane. As a molecule passes through a nanopore, it causes a change in the ionic

current that flows across the membrane. Depending on the size, type of the molecule and its ability to attract ions, the current is reduced by a certain amount and time. If we were to substitute the molecules for DNA strands, we could ultimately differentiate between normal genetic coding and abnormalities in the genetic coding due to cancer.

HOW IS CANCER TREATED USING NANOTECHNOLOGY?

Nanoscale materials have a greater surface-area to volume ratio than larger particles, so there is a higher possibility of biochemical reactions taking place due to the nature of reactivity at the surface of a material.

NANOPARTICLES

THE SUCCESS OF CHEMOTHERAPY IS VERY DEPENDENT ON THE METHOD OF DRUG DELIVERY. AS CANCER CELLS CAN BECOME RESISTANT TO THE EFFECTS OF A SINGLE DRUG, IT IS IMPORTANT THAT A COMBINATION IS ADMINISTERED TO THE PATIENT. NANOPARTICLES HAVE BEEN MANIPULATED TO SELECTIVELY DELIVER HIGH CONCENTRATIONS OF TOXIC AGENTS TO TUMOUR CELLS. AS WELL AS THEIR NANOSCALE SIZE, THEIR CHEMICAL STRUCTURE AND SURFACE PROPERTIES ENABLE THEM TO HAVE THE SPECIFIC TRANSPORTATION METHODS REQUIRED TO REACH THE TUMOUR; THEY ARE ABLE TO DIFFUSE ACROSS THE VESSEL WALLS INTO THE *INTERSTITIUM* WHERE THE DELIVERED DRUGS CAN TAKE EFFECT. BECAUSE THE DRUGS ARE EXTREMELY TOXIC, PATIENTS OFTEN ENCOUNTER SEVERE SIDE EFFECTS (EG. HAIR LOSS, SICKNESS) DUE TO THEIR ACTING UPON SURROUNDING HEALTHY CELLS. ACTIVE TARGETING OF THE DRUGS USING NANOPARTICLES WOULD HELP TO ALLEVIATE SIDE EFFECTS.

Conventional uses of nanoparticles in drug delivery were to completely coat the nanoparticles in polymers – this meant that hydrophobic and hydrophilic drugs could not be carried simultaneously. However, new technology involves engineering nanoparticles to deliver precise doses of two or more types of drug to cancer cells of the prostate. Drug molecules are hung from individual units of polymers before they are assembled into a single nanoparticle, enabling the concentration and rate of entry of the drug molecules to be controlled. Surfaces of prostate tumour cells are then tagged with a binding molecule for the drugs so healthy cells are unaffected. The main advantage of this technique is the ability to personalise medicine for the individual, an option rarely available within the realms of cancer treatment.

Gold nanocages have also been developed for treatment as well as diagnosis. Described as a 'magic bullet' for cancer treatment, they are injected intravenously selectively accumulate in tumours without harming surrounding tissue. The thin leaky walls of the tumour vessels allow the nanocages to enter efficiently. Moreover, upon exposure to a laser, the light is converted to heat and it is this which kills the tumour cells. It could be possible to personalise the treatment by altering the wavelength of emitted light subject to tumour size and stage.

Nanotubes

Carbon nanotubes are becoming increasingly seen as a treatment alternative as well as a diagnostic one. One of the major problems of conventional treatments is the inevitable damage of healthy tissue. Carbon nanotubes can be inserted into cancer cells and when exposed to a source of near-infrared light, they heat up resulting in cell death. In contrast, the healthy cells without inserted nanotubes are ultimately unharmed. In order to allow differentiation between healthy and cancerous cells, the nanotubes are coated with folate, a vitamin complementary to the receptors on the surface of cancer cells.

The human immune system produces naturally occurring T cell antigens against cancerous tumours. However, they could either be suppressed by the tumour or simply in too short a supply to have a significant effect. Scientists have amalgamated adoptive immunotherapy with carbon nanotubes:

blood is extracted from the patient and carbon nanotubes are added to promote the clustering of T cell antigens in high concentrations. Compared to other substances, the nanotubes encouraged more immune cell proliferation; the perforations of the nanotubes enabled a greater adsorption of antigens thus improving immune response.

Ethical issues surrounding nanotechnology

The theoretical concepts of nanotechnology and its applications in medicine are very promising indeed. Nevertheless, many of the concepts are still at a stage where evidence on their effectiveness is unavailable at this time. Research is currently ongoing and apparent breakthroughs, particularly in nanomedicine are becoming a regular occurrence; it is impossible to foresee the long term effects of nanoscale diagnostic/treatment methods simply because it is new technology. Therefore it is important that the stance surrounding nanotechnology is not conveyed as false and fantastical to the oblivious public.

Although the methods I have outlined may progress to revolutionise cancer treatment, they could instead have opposing effects. Individuals who undergo nanotechnology based treatments could unknowingly accumulate a vast number of nanomaterials within their body, concentrated in a region that could prove fatal. An accumulation of nanomaterials would be extremely dangerous in the bloodstream; they could be positioned in an irregular manner that makes it sharp and susceptible to puncturing vessels. Alternatively, an accumulation could become large enough to block certain vessels or the respiratory tract.

Quantum dots contain heavy metals. If this method is used frequently on a patient and the metals accumulate, this will have a detrimental effect on surrounding cells (as well as their functions). A possible solution to this would be to use diagnostic tests where only tissue samples are exposed with nanomaterials, as opposed to exposing the nanomaterials to the patient. This is only one way and there are probably at least a million others that are currently inconceivable.

Conclusion

It is evident that a wide range of diagnostic techniques and treatments based on nanotechnology could completely change how we view medicine. However, there are still aspects of this technology which are at a premature stage.

We are seemingly able to manipulate materials on a nanoscale for a particular function in the body. What is not yet considered is how we are to safely remove the nanomaterials once they have performed their function in diagnosis or treatment. As mentioned in relation to ethical issues, accumulations of these materials could have a contradictory effect on the body - after all, one of the main purposes of using nanomedicine is to eliminate the risk of damaging healthy cells. Moreover, we cannot be sure of the long term effects of the nanomaterials. Most chemicals have unpredictable side effects, but because nanotechnology is very recent, we are unable to determine those effects presently.

One project that ought to be followed through is the mapping of the human genome. Although we would have to consider ethical issues, we should eventually be able to offer genome mapping to cancer induced patients who request it. If they accept the opportunity, treatment in particular can be personalised and tailored to the individual's needs. I believe that the combination of genome mapping and nanotechnology is the next logical step we can take towards curing cancer once and for all.

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