Nanomedicine and Cancer

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Introduction

Nanotechnology has the power to radically change the way cancer is diagnosed, imaged and treated. Currently, there is a lot of research going on to design novel nanodevices capable of detecting cancer at its earliest stages, pinpointing it's location within the body and delivering anticancer drugs specifically to malignant cells.

Nanoscale devices smaller than 50 nanometers can easily enter most cells, while those smaller than 20 nanometers can transit out of blood vessels.[1] As a result, nanoscale devices can readily interact with biomolecules on both the cell surface and within the cell. Nanoscale devices are already proving that they can deliver therapeutic agents to target cells, or even within specific organelles.[1] Yet, despite its small size, a nanoscale device is capable of holding tens of thousands of small molecules, such as a contrast agent or drug.

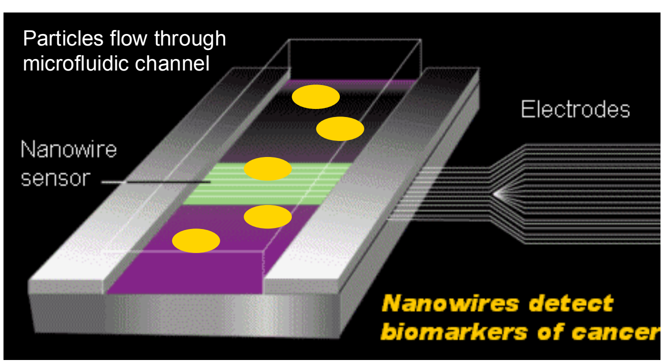
The major areas in which nanomedicine is being developed in cancer include:

- *Prevention and control*. Developing nanoscale devices to deliver cancer prevention agents and designing multicomponent anticancer vaccines.
- *Early detection and proteomics.* Developing "smart" collection platforms for simultaneous mass analysis of cancer-associated markers.
- *Imaging diagnostics.* Designing targeted contrast agents that improve the resolution of cancer to a single cell.
- *Multifunctional Therapeutics.* Creating therapeutic devices that can control the release of cancer-fighting drugs and optimally deliver medications.

Improved Diagnostics

Nanodevices can provide rapid and sensitive detection of cancer-related molecules by enabling scientists to detect molecular changes even when they occur only in a small percentage of cells. This would allow early detection of cancer – a critical step in improving cancer treatment. Nanotechnology will allow the reduction of screening tools which means that many tests can be run on a single device. This makes cancer screening faster and more cost-efficient.

Nanowires

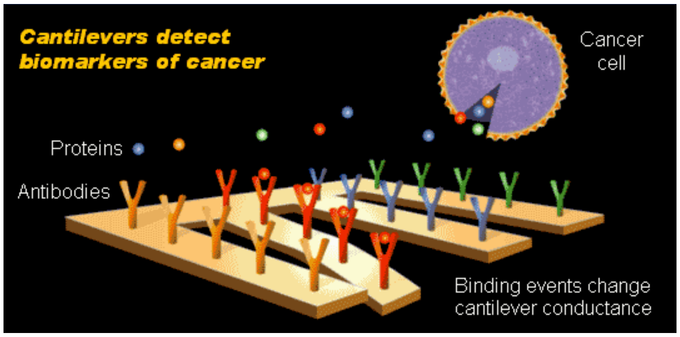


Nanowires by nature have incredible properties of selectivity and specificity. Nanowires can be engineered to sense and pick up molecular markers of cancer cells. By laying down nanowires across a microfluidic channel and allowing cells or particles to flow through it. The wires can detect the presence of genes and relay the information via electrical connections to doctors and researchers. This technology can help pinpoint the changes in the genetics of cancer.

Nanowires can be coated with a probe such as an antibody that binds to a target protein. Proteins that bind to the antibody will change the nanowire's electrical conductance and this can be measured by a detector.[2] Jim Heath, a nanotechnology researcher at California Institute of Technology has designed a nanowire detector. Each nanowire bears a different antibody or oligonucleotide, a short stretch of DNA that can be used to recognize specific RNA sequences. They have begun testing the chip on proteins secreted by cancer cells.[2]

Carbon nanotubes are also being used to make DNA biosensors. This uses self-assembled carbon nanotubes and probe DNA oligonucleotides immobilized by covalent binding to the nanotubes. When hybridization between the probe and the target DNA sequence occurs, the change is noted in the voltammetirc peak of an indicator.[3] The DNA biosensors being developed are more efficient and more selective than current detection methods.

Cantilevers



http://nano.cancer.gov/nanotech_cantilevers.asp

Nanoscale cantilevers are built using semiconductor lithographic techniques.[1] These can be coated with molecules (like antibodies) capable of binding to specific molecules that only cancer cells secrete. When the target molecule binds to the antibody on the cantilever, a physical property of the cantilever changes and the change can be detected. Researchers can study the binding real time and the information may also allow quantitative analysis. The nanometer-sized cantilevers are extremely sensitive and can detect single molecules of DNA or protein. Thus providing fast and sensitive detection methods for cancer related molecules.[1]

Imaging and detection

Nanoparticle contrast agents are being developed for tumor detection purposes. Labeled nanoparticles and non-labeled particles are already being tested as imaging agents in diagnosis procedures such as computed tomography and nuclear magnetic resonance imaging.[4]

Super paramagnetic nanoparticles are used for magnetic resonance imaging (MRI).[5] They consist of an inorganic core of iron oxide coated or not with polymers like dextran. There are two main groups of nanoparticles: 1) superparamagnetic iron oxides whose diameter size is greater than 50nm, 2) ultrasmall superparamagnetic iron oxides whose nanoparticles are smaller than 50nm.

Quantum dots, nanoscale crystals of a semiconductor material such as cadmium selenide, whose color properties depend on particle size. Quantum dots can be linked to antibodies and combined to create assays that are capable of detecting multiple substances simultaneously. They can be used to measure levels of cancer markers such as breast cancer marker Her-2, actin, microfibril proteins and nuclear antigens.[1] Quantum dots are robust and very stable light emitters. The photochemical stability and the ability to tune broad wavelengths make quantum dots extremely useful for biolabelling.[6]

Nanoparticles can be used as tumor biomarkers. They help the detection process by concentrating and protecting a marker from degradation so that the analysis is more sensitive. Streptavidin-coated fluorescent polystyrene nanospheres used in flow cytometry to detect biological molecules have shown greater sensitivity as compared to conventional dyes.[4]

Cancer Therapy

Nanoscale devices have the potential to radically change cancer therapy by increasing the number of highly effective therapeutic agents. Nanoparticles can serve as customizable, targeted drug delivery vehicles capable of ferrying chemotherapeutic agents or therapeutic genes into malignant cells while sparing healthy cells. This may allow for smaller doses of toxic substances as the drugs are delivered directly to the target tissue. Doctors may also be able to deliver the toxin in a controlled and time-release manner.

Targeting

Currently, cancer fight drugs are toxic to both tumor and normal cells, thus the efficacy of chemotherapy is often limited by the side-effects of the drug.[4] Some nanoscale delivery devices, such as dendrimers (spherical, branched polymers), silica-coated micelles, ceramic nanoparticles, and cross-linked liposomes can be targeted to cancer cells. This increase selectivity of drugs towards cancer cells and will reduce the toxicity to normal tissue.[4] This is done by attaching monoclonal antibodies or cell-surface receptor ligands that bind specifically to the cancer cells. Some cancer targeting molecules include high-affinity folate receptor, luteinizing hormone releasing hormone and integrin $\alpha_v\beta_3$.[7]

Some research on folate nanoparticles showed higher specificity for cancerous human cells.[7] In addition, the folate nanoparticles improved the uptake of the encapsulated drugs that it carried.

Surface modification of nanoparticles can also enhance the permeability of drugs to create high-permeability nanoparticle-based cancer therapeutics. Barriers to cancer drugs can be in the form of the cell's plasma membrane or epithelial or endothelial layers of cells. Research on the covalent attachment of peptidic membrane-translocation sequences (MTS), peptides with the ability to pass through membrane, to nanoparticles have shown increased permeability through membranes.[8] With improved cell permeability, nanoparticles can become more therapeutically effective drug transport vehicles.

Nanoshells

Destruction of solid tumors using high heat has been in investigation for some time. Some thermal therapies include the use of laser light, focused ultrasound and microwaves.[8] The benefits of using thermal therapeutics is that most procedures are non-invasive, relatively simple and have the potential to treat tumors where surgery is not possible. However, to reach underlying tumors, the energy sources has to penetrate healthy tissues, often destroying healthy tissue.

Nanoshell-assisted photo-thermal therapy (NAPT), is a simple, non invasive procedure for selective photo-thermal tumor removal. It makes use of nanoshells that absorb light in the near infrared (NIR) region.

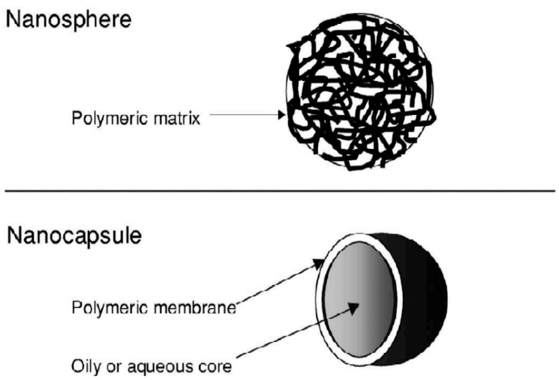
Nanoshells have a core of silica coated with an ultra-thin metallic layer, normally gold.[9] By adjusting the core and shell thickness, nanoshells can be designed to absorb and scatter light at a desired wavelength. Nanoshells for cancer therapeutic purposes have been designed to have a peak optical absorption in the NIR, as this is the wavelength that optimally penetrates tissue.

The metal shell converts the absorbed light into heat with great efficacy and stability.[10] In addition, biomaterial nanoshells are composed of elements that are biocompatible.

Due to their small size, nanoshells are preferentially concentrated in cancer cells by EPR or enhanced permeation retention.[10] Further specificity can be engineered by attaching antigens on the nanoshells which are specifically recognized by the cancer cells.

By supplying a NIR from a laser, the particle heats up and kills the tissue. Research has shown that the temperature within the nanoshell-treated tumors rose by about 40^{o}C compared to a rise in 10^{o}C in tissues that was treated with NIR light alone.[11] Thus using a NIR laser, cancer tissue can be destroyed by local thermal heating around the nanoshells.[11,12]

Nanoparticles



Nanoparticles can be in the form of nanospheres (matrix systems in which drugs are dispersed throughout the particle) and nanocapsules (drug is confined in an aqueous or oily cavity surrounded by a single polymeric membrane).[4]

Nanoparticles have the potential to overcome biological, biophysical and biomedical barriers currently faced by conventional administration of cancer drugs. If designed appropriately, nanoparticles may selectively target tumors, while protecting the drug from inactivation during transport.[4]

Poly(isobutylcyanoacrylate) has been used to make nanocapsules with an oily core for hydrophobic drugs.

Experiments have shown that nanospheres loaded with anticancer drugs successfully increase drug concentration in cancer tissues. Some nanospheres are made of poly(isohexylcyanoacrylate), poly(methylcyanoacrylate) and biodegradable poly(ethylcyanoacrylate).[4]

Further improvements to these nanospheres are being researched into by coating the nanoparticles with hydrophilic polymers like poly(ethylene glycol), poloxamines, poloxamers and polysaccharides to provide a “cloud” of hydrophilic and neutral chains at the particle surface. Molecules like poly(ethylene glycol) reduces nonspecific attachment or uptake.[13] This allows longer circulation without being taken up by the body’s macrophages, so as to direct more specific targeting.[13]

Chemists and engineers have also turned synthetic materials into nanocarriers. Dendrimers, 1 to 10 nanometer spherical polymers of uniform molecular weight made from branched monomers have been proven to provide a multifunctional cancer agent.[1] In one experiment, researchers attached folate – which targets the high-affinity folate receptor found on some malignant cells, the indicator fluorescein and an anticancer drug (methotrexate or paclitaxel) to a single dendrimer. Experiments showed that the dendrimer delivered the therapeutic drugs while simultaneously labeling the cells for fluorescent detection.

A group of scientists have used nanoparticles to deliver a gene that forces blood vessels to self-destruct. This prevents angiogenesis, or the formation of blood vessels in a tumor.[14] The group targeted the nanoparticle surface with an integrin (a protein present on growing blood vessels), $\alpha_v\beta_3$, and packed a mutant gene *Raf-1* that prevents blood vessel formation. Researchers treated mice with tumors with the nanoparticles and tumor regression was observed. On closer examination, dead blood vessel cells were observed in the tumors.[14]

Societal Implications

Presently, according to the National Cancer Institute (NCI), one out of every five deaths in the United States is related to cancer. Cancer research in the U.S. hopes to eventually see a time when cancers can become manageable, chronic diseases.[15]

Nanotechnology is an emerging technology with potential use in prevention, early detection, development of innovative diagnostics, early warning of relapse and design of effective and safe therapeutic modalities as shown above. Nanotechnology has also help speed up the process of understanding cancer as a disease process. The outcomes of cancer research has the power to transform the vision of the National Cancer Act of 1971 into an ambitious goal: the elimination of the suffering and death due to cancer by 2015.[15]

Carrying a federal five-year price tag of $144.3 million, the NIH's National Cancer Institute (NCI) is forming the NCI Alliance for Nanotechnology in Cancer, a comprehensive, integrated initiative encompassing researchers, clinicians, and public and private organizations that have joined forces to develop and translate cancer-related nanotechnology research into clinical practice. This is much more compared to the $69 million that the National Science Foundation is pumping into nanoscale science and engineering research.[20]

Despite the potential impact of nanomedicine in cancer, the societal implications of such a rapidly progressing field has to be taken into consideration. As the science leaps ahead, the ethics lags behind. There is a danger of derailing nanomedicine if the study of ethical, legal and social implications does not catch up with the speed of scientific development.

Nanomedicine is a powerful and revolutionary development that is likely to have significant impact on society, the economy and life in general. As quoted from Langdon Winner's *Technologies as forms of life*, technologies are not merely aids to human activity, but also powerful forces acting to reshape that activity and meaning. A very important area of nanomedicine would be to not only pay attention to the making of the physical instruments and processes, but also to the production of psychological, social and political conditions as a part of any significant technological change.

Potential toxicity

Fears about the potential toxicity of nanoparticles and nanoshells to the human body. While the small size of nanoparticles is what makes them so useful in medicine, it is also the factor that might make them potentially dangerous to human health. Nano-sized particles are able to evade the detection by the body's immune system as well as have the ability to pass through the blood brain barrier. Nanoparticles have almost unrestricted access to the human body.[16] Normally, exogenous particles or foreign substances that enter the bloodstream are absorbed by specialized phagocytes that are responsible for protecting the body from "foreign substances". However, anything smaller than 200nm is no longer absorbed by phagocytes thus nanoparticles can travel though the blood and move randomly throughout the entire body.[16]

Nanoparticles have increased surface area to volume ratios that dramatically increase their reactivity. The surface reactivity of nanoparticles can, depending on the type of coating, cause chemical damage to surrounding tissues. In addition, the miniaturization of materials to the nanoscale has seen emergent properties which have not been characterized before. Full analysis of any new nanomedicine should be undertaken to completely characterize the new product before application so that we can help avoid any unintended side-effects.

Do these nanoparticles accumulate in the body system or are they excreted? The exact distribution of nanoparticles in the body depends on the coating. Biodegradable substances are normally decomposed and their waste products excreted by the kidneys and intestines.[16] However, non-biodegradable nanoparticles have been studied and it seems that they accumulate in certain organs, especially the liver. It is not known how long the deposits stay, the potential harm they may trigger, or the dosage that causes harm. Thus, this is a huge area of concern.

Special attention has to be paid to vulnerable organs such as the brain, since the potential to impair health is generally greater. What might happen if nanoparticles enter the brain that they were not intended to reach?

The body has many biological processes that are carefully regulated and controlled. We need to be sure that nanoparticles do not impair any of these processes that can trigger a whole flood of reactions that interrupt normal bodily functions.

Before we leap into using nanomedicine to cure cancer, we first have to assess how human contact with nano products will affect us. It is not yet known exactly how nanomedicines will interact with our immune system and other body tissues, thus unintended side effects may results from nanomedicine therapy if we are not careful. Research in these fields are still in its infancy, the body's many repair and compensatory mechanisms must be taken into account. Clearly, a great deal more information to determine the possibilities of nanoparticle interaction with the body is required.

Environmental concerns

Depending on the excretion and disposal of nanomedicines, these nanoparticles can be released into the water or the air. Concerns about how these nanoparticles may affect the environment has to be assessed to see if these materials will adversely affect our surroundings or would they require processing before disposal.

Artificially manufactured nanoparticles will be new to the environment in type and quantity.[16] They would constitute a new class of non-biodegradable pollutants. With the little that we know of these products now, it is very difficult to foresee its effects in the environment.

Nanoparticles in the air may adversely influence human health.[16] Nanoparticles are so small that they rarely aggregate or land on surfaces. They can remain airborne for extended periods of times and may be inhaled by people. Other worries are pollution to soil, water and then the absorption of nanoparticles into the ecosystem through plants.

If indeed nanoparticles did exert harmful effects on the environment. Clearly, the elimination of nanoparticles from the environment would be extremely difficult. So a lot of research has to be done with respect to the disposal techniques of nanoparticles.

Efforts are being made towards understanding the effects of nanotechnology on the environment. The U.S. environmental protection agency (EPA) has added the funding of research projects that explore the environmental dangers of nanotechnology to its list of prioirities.[17]

Definition of benefit or progress

Nanomedicine for cancer has the ability to improve health care by leaps and bounds. However, who will benefit from the advances in nanomedicine in cancer?

Nanomedicine has the ability to make a positive impact to people from all walks of life. If not managed appropriately the possibilities to improve health care will not materialize. There Is a possibility that the application of nanotechnology will be too expensive such that we further segregate the rich and the poor. By introducing nanotechnology into the health care market, would the technology be able to bring down the cost of health care or would it make health care more expensive?

Even before the introduction of nanomedicine, enormous social gaps now exist in the world, both at national and international levels.

Nanomedicine is a technology that embodies certain political connotations in the way that its use would affect the distribution of power, authority and privileges in society. Ideally, nanomedicine should help to bring down the cost to treat cancer so that everyone who is afflicted by this disease can seek this treatment. However, if the technical arrangement of the technology is not well managed, we might end up creating a nanomedicine "have" or "have not" society – "nanodivide".

Should the fruits of nanomedicine reach everyone or just the wealthy? Are we benefiting the world or the world who pays?

America's system of medicine policy making is currently steered by narrowly interested technical elites.[18] For several decades, research and development have produced high tech treatments but at the expense of propelling costs of health care to dizzying levels. According to the World Health Organization, the U.S. ranks only 24th in the quality of medical care actually delivered to its populace.

What is the point of having technology to cure cancer that does not benefit everyone, but only the privileged few?

Before nanomedicine is introduced into the market, considerations for how it would affect health care costs and the distribution of technology should be analyzed. Policies should be made to ensure the equal distribution of benefits of this new technology.

Addressing social and ethical issues

While nanotechnology is still in the fledging stages, and applications are speculative and the ethical considerations follow speculatively. However, it is a good time to start addressing ethical implications. A good place to start is to examine our experiences with biotechnology and information technology as these fields are likely to share similar issues with nanotechnology.

Have appropriated funding strategies for nanomedical research. The U.S. should spend part of the nanotechnology research budget on funding the study of ethical, legal and social implications. Funding often determines the direction of research.[19] To help spur research on ethical and social implications, the U.S. has to commit a percentage of the research funding to developing this research. The U.S. seems headed down this path for nanotechnology though it has not yet made a percentage commitment.[17]

The study of the social implications of nanomedicine should not be conducted in isolation from a few major players. Instead, it should have an intersectoral approach.[17] Those studying ethical and social implications should have regular opportunities to interact with, and represent, scientists, different activist/pressure groups, government and industry. In Langdon Winner's testimony to the Committee on Science of the U.S. House of Representatives, he mentioned that there should be forums where social scientists and philosophers present their findings to people from business, laboratories, environmental organizations, churches and other groups to join the discussion.

Most importantly, there should be public engagement. The active engagement of everyday folks in the shaping of public understanding of emerging issues and controversies in this area could bring about extremely valuable contributions to issues; problems and possible solutions.[18] Journalists need to be involved in the early stages of nanotechnology research as they are an important influence on public perception. More innovative mechanisms such as plays can be used to engage the public. Science museums should consider how it might include exhibits on ethical and social implications. Nanotechnology education can be developed for students in high school and college, so that citizens can be engaged early in balanced discussions of issues.

Future Implications

Nanotechnology will radically change the way we diagnose, treat and prevent cancer to help meet the goal of eliminating suffering and death from cancer. Nanotechnology can provide the technical power and tools that will enable those developing new diagnostics, therapeutics, and preventives to keep pace with today's explosion in knowledge. With nanomedicine, we might be able to stop cancer even before it develops.

With such technology, nanomedicine has the potential to increase the life span of human beings. It will create populations with a large proportion of elderly people – an aging society. The elderly are going to require more health attention and consequently more health expenditures. One scenario that we have to imagine is whether the savings from more efficient cancer nanomedicine will counterbalance the expense of an increased aged population.[21]

In addition, as nanotechnology improves cancer treatment in terms of efficiency and quality. There waits to see if the costs of health care would rise or fall. In reality, nanomedicine, especially in the diagnostic realm should reduce diagnosis charges as more cost-efficient diagnostic tools are developed. However, there is always the danger of charging exorbitant prices for this new technology and cause health care to rocket up sky high.

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This student-produced report is part of a larger pamphlet on nanotechnologies circa 2005, the partial output of a course on "Nanotechnology and Society" (Science and Technology Studies, Section 84405, by C. Tahan) which was taught in the spring semester of 2005 at the University of Wisconsin-Madison. Visit http://tahan.com/charlie/nanosociety/course201/ for the other reports and more information.