NANOTECHNOLOGY AND CANCER

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General Introduction

What is Nanotechnology?

"Nanotechnology encompasses the common unifying concepts & physical laws that prevail in the Nano scale" [1]

Nanotechnology is the engineering of functional systems at the molecular scale. That covers current work and more advanced concepts of the future. Nanotechnology refers to the ability to build items from the bottom up. K. Eric Drexler popularized the term nanotechnology in the 1980's. He was referring to the ability of constructing machines on the scale of molecules, a few nanometers wide (motors, robot arms, and computers) far smaller than a cell. He spent the next ten years analyzing and defending the concept. As nanotechnology became an accepted concept, the word encompassed the simpler kinds of nanometer-scale technology. The U.S. National Nanotechnology Initiative definition includes anything smaller than 100 nanometers with novel properties.[2] Nanotechnology is very diverse, ranging from extensions of conventional device physics to approaches based upon molecular self-assembly, from developing new materials with dimensions on the nanoscale to investigating whether we can

[1] www.nanoscience-europe.org

[2] Center for responsible technology-CNR-

directly control matter on the atomic scale. Nanotechnology may be able to create many new materials and devices with a vast range of applications, such as in medicine, electronics, biomaterials and energy production.[3] Nanotechnology is a manufacturing technology that will make products lighter, stronger, less expensive, and more efficient.

Nanomedicine and Cancer

I-INTRODUCTION

Nanotechnology structures smaller than a single red blood cell could revolutionize cancer diagnosis and treatment. It is not surprising, that scientists seize upon nanotechnology for its potential in medical applications. Many nanodevices may transform cancer prevention, diagnosis, and treatment in the near future.[4] The huge scientific knowledge obtained on cancer genomics is providing significant information of how cancer develops. The result of this Human Genome Project has created new opportunities on how to attack the molecular underpinnings of cancer. However, scientists lack the technological innovations to turn those molecular discoveries into benefits for cancer patients. That is where nanotechnology can play a considerable role, providing the technological tools that will enable those developing new diagnostics and therapeutics to keep pace with this developing knowledge[5].

[3] Nanotechnology- Wikepedia-*en.wikipedia.org/wiki/Nanotechnology*

[4] Cancer Nanotech- Krock Lexi- NOVA scienceNOW- 04/01/05

[5] U.S. Department Of Health And Human Services. National Institutes of Health National Cancer Institute January 2004

The NCI (National Cancer Institute) has already conducted research on novel nanodevices capable of one or more clinical functions, including detecting cancer at early stages, determining its location within the body, sending anticancer drugs specifically to malignant cells, and determining if these drugs are killing malignant cells.[6] As these nanodevices are evaluated in clinical trials, researchers envision that nanotechnology will serve as multifunctional tools, and will change the foundations of cancer diagnosis, treatment, and prevention. This paper will encompass four main subjects. We will explore the role of nanotechnology in cancer prevention, cancer diagnosis, and cancer treatment, trying to get out the benefits and strength of that technology so far, and the risks and issues behind it. Finally, we will discuss the general ethical and regulatory issues arising from that new technology.

II- THE ROLE OF NANOTECHNOLOGY IN CANCER PREVENTION

Nanotechnology studies have already shown numerous benefits in the prevention of cancer. Although there are some identified risks, this technology is providing some critical promise for the not-so-distant future. More studies need to be done before that technology come to life clinically.

A-Benefits

Many genes, with products that protect cells against carcinogens, oxidants, and other toxic chemicals, are under the control of a simple DNA regulatory element [i.e., the antioxidant response element (ARE)].[7] One or more functional AREs are identified in the upstream region of

[6] Id.
[7] Fu, X.S., Hu, C.A., Chen, J., Wang, J. and Liu, K.J.R. (2005) 'Cancer genomic, proteomics and

many anticarcinogenic/antioxidant genes and have been shown to mediate the coordinate transcriptional up-regulation of these genes by many chemical agents [i.e., the ARE-mediated inducers].[8] It has been confirmed that increased expression of ARE-regulated genes inhibits cancer development. Many ARE-mediated inducers have been identified, and several of them have shown promising cancer preventive activity.[9] Genetic mutations can be caused by artificial or natural carcinogens. At other times, they may occur spontaneously during DNA replication and cell division. With existing technology we can't do much to prevent this spontaneous mutation from happening. In all other cases, eliminating the carcinogens is indeed a highly effective way of cancer prevention. But most patients do not recognize the problem before it occurs, which makes preventive medicine rarely utilized.[10]

Is nanotechnology able to eliminate cancer before it starts?

While there is little current research on preventive treatments using nanotechnology, the possible opportunities are showing promise.

To demonstrate the viability of nanotechnology-based preventive treatments, let us consider melanoma for example, a form of skin cancer caused by exposure to ultraviolet radiation from the Sun. The current method of preventive treatment against this radiation is suspending a substance that absorbs or scatters ultraviolet radiation in a thick emulsion. We use sunscreen,

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clinic applications', in Dougherty, E., Shmulevich, I., Chen, J. and Wang, J. (Eds.): *Genomic Signal Processing and Statistics*, European Applied Signal Processing Inc., Hindawi Publishing Corporation, New York, NY, pp.267-408.

[8] Evan, G.I., Lewis, G.K., Ramsay, G. and Bishop, J.M. (1985) 'Isolation of monoclonal antibodies specific for human c-myc proto-oncogene product', *Mol. Cell Biol.*, Vol. 5, No. 12, December, pp.3610–3616.

[9] A strategy for cancer prevention: Stimulation of the Nrf2-ARE signaling pathway. Yuesheng Zhang and Gary B. Gordon

[10] Choi, Y., Thomas, T., Kotlyar, A., Islam, M.T. and Baker Jr., J.R. (2001) 'Synthesis and functional evaluation of DNA-assembled polyamidoamine dendrimer clusters for cancer cell-specific targeting', *Chemistry and Biology*, Vol. 12, January, pp.3543–3552.

to protect our skin prior to exposure to sunlight. This emulsion can lose its effectiveness over time, and needs to be reapplied periodically. We can also leave openings in the sunscreen coating due to macro-scale and micro-scale imperfections in our skin. The Ultra Violet (*UV)* radiation will permeate through the dead layer of skin, spreading out to a wider area. UV radiation is one of the most prominent causes of DNA damage; it can easily damage the DNA double helix. Individual nucleotide bases readily absorb UV radiation and can become excited after even short-term exposure. This can cause genetic mutations, a mutated genetic sequence and the production of defective proteins.[11]

Studies have shown that it is possible to tag specific types of cells with nanoparticles by conjugating them to targeting agents designed to recognize cell-specific surface proteins.[12] Nanoparticles attached to desired drugs can be conjugated to short peptide chains, proteins or artificial nanobodies. If we manufacture nanoparticles attached to *UV* scattering substances like zinc oxide (*ZnO*) and titanium oxide (*TiO2*), or *UV* absorbing substances like octyl methoxycinnamate and oxybenzone, and specifically target these nanoparticles to skin cell surface proteins; we can effectively coat these cells with sunscreen on the nanoscale[13] [14]. With this nanotechnology-based preventive treatment method, we would reduce the risk of melanoma. If the cells can be coated directly, the problem of diffraction in case where an area is sparsely coated will be eliminated.

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[11] http://earthobservatory.nasa.gov/Library/UVB/Images/dna_mutation.gif

[12] Greider and Blackburn, 1996).

[13] Ferrari, M. (2005)'Cancer nanotechnology: opportunities and challenges', *Nat. Rev. Cancer*, Vol. 5, No. 3, March, pp.161–171.

[14] Chen, R.J., Zhang, Y., Wang, D. and Dai, H. (2001) 'Noncovalent sidewall functionalization of single-walled carbon nanotubes for protein immobilization', *J. Am. Chem. Soc.*, Vol. 123, pp.3838–3839.

B- Risks

The most important issue to consider in this form of treatment is the toxicity of the substance used for cancer prevention. The biochemical effects of a substance on the patient's health can cause many reactions, and those reactions can be serious. We do have to consider also the diversity of human bodies. The same substance can be safe for some people, and toxic for others. Allergic reactions, especially the serious ones, should also be taken in consideration when using these new methods of prevention against cancer. The legal problem here is that sunscreens don't need premarket safety testing approval. The biochemical effects must be evaluated by standard laboratory testing procedures as well as clinical trials before this treatment can be safely implemented. The method discussed above is but one example of many possible applications of the fascinating new nanotechnology known as nanobiotechnology.[15]

III- NANOTECHNOLOGY IN CANCER DIAGNOSIS

In the field of diagnosis, magnetic resonance imaging is one of the first and up to now the most developed application of metallic particles. But beside this application, a very new generation

[15]Farokhzad, O.C., Cheng, J., Teply, B., Khademhosseini, A., Jon, S., Levy-Nissenbaum, E. and Langer, R. (2001) 'Cancer nanotechnology: drug encapsulated nanoparticle-aptamer bioconjugates for targeted delivery to prostate cancer cells', *European J. Cancer Supplements*, Vol. 3, No. 2, October, pp.229–235.

of biosensors based on the optical properties of colloidal gold and fluorescent nanocrystals, called quantum dots, seems to be ready to be implemented in diagnosis and medical imaging.[16]

This promising field of research involves nanoparticles – extremely small, capable of carrying on its surface a wide variety of homing, imaging and therapeutic agents. These nanoparticles can be specifically targeted to cancer cells by a variety of mechanisms discussed below. The tiny spheres can travel through the bloodstream deep into the body to provide more accurate visualization and characterization of tumors, revealing even tiny tumors missed by conventional medical scans. They can direct chemotherapeutic drugs specifically to tumor sites and minimize unpleasant or risky side effects. And they offer more precise adaptation of treatment to the biochemical and molecular features of each patient's disease. Eventually, a single injection of nanoparticles may replace numerous medical tests, scans or other therapies.[17]

A-Examples of Nano Diagnostic Imaging

Researchers are extracting the DNA from viral particles and replacing it with imaging agents. This includes having the viral capsule adhere to a cancer cell and inject the imaging or therapeutic agent into the cell. This process would lead to early diagnosis and the development of targeted drug therapy without harming the rest of the body. Another area of research in nanotechnology is to develop nanometer sized contrast agents with ultrasound to diagnose ovarian cancer. It can pass through the smallest capillaries. These tiny bubbles light up on

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[16] Sonvico, Fabio[1]; Dubernet, Catherine[1]; Colombo, Paolo[1]; Couvreur, Patrick· Current Pharmaceutical Design, Volume 11, Number 16, June 2005 , pp. 2091-2105(15)

[17] NANOTECHNOLOGY POISED TO REVOLUTIONIZE CANCER DIAGNOSIS AND TREATMENT – *SAMUEL WICKLINE, MD-JUNE 2006*

ultrasound and can show the earliest vascular changes associated with ovarian malignancy without removing the ovary for biopsy.[18]

Gold (AU) Nano-particles are versatile materials that have a natural resistance to surface oxidation which make them ideal for a wide-range of research areas. They are being used in research to detect colorectal cancer, especially flat lesions hard to see on colonoscopy.[19]

Photo-Acoustic Imaging Nano-particles are used in research to develop a new modality of detecting tumors. Light enters the body heating the particles to produce a sound without harming the tissue, which can be detected by an external source. (Ex: Carbon nanotubes and Gold nanoparticles modified to emit sounds)[20]

Iron oxide nanoparticles coated with dextran are used to target lymph nodes for cancer spread detecting it with MRI. The particles are taken from normal cells in the lymph node, and not by cancer cells.[21] Patients will first take an MRI, then they will be injected with iron nanoparticles, and again, they will have another MRI image after 24 hours. Lymph nodes that take the nanoparticles will change color to black, cancer cells will stay bright.[22]

Gold nanoshelled microcapsules are a combination of electrostatic gold nanoparticles depositions onto microcapsules and a surface seeding method resulting in the formation of gold

[18] Researchers explore nanotechnology as diagnostic and treatment tool-Rush university medical center-August 14 2006-www.physorg.com/news74784185.html-

[19] Sanjiv Sam Gambhir, M.D., PhD; Nanotechnology in cancer imaging, dec 17 2010 Molecular imaging Center at Stanford school of Medicine –http://nano.cancer.gov/learn/impact/

[20] ID at Sanjiv Sam Gambhir, MD, PhD; Nanotechnology in cancer imaging, dec 17 2010 Molecular imaging Center at Stanford school of Medicine –http://nano.cancer.gov/learn/impact/podcasts.asp#anna-barker.

[21] Ralph Weissleder MD, Mukesh Harisinghani MD, Donald Kaufman MD, stealth Imaging with iron nanoparticles, Mass General Hospital 2008Http://nanomedicine-explorer.net/stories/stealthiron/overwiew

[22] Id.

nanoshells.[23]This process works as a theranostic agent for contrast-enhanced ultrasonic imaging, and photo hyperthermia (therapeutic).[24]

B-Advantages of Nano-Particles in Diagnostics

The use of nano-particles in the research of cancer is enhancing diagnostic imaging. In comparison with other techniques, nanotechnology has four major advantages in improving imaging, and as a result, early diagnosis of cancer.

-The first advantage is that a larger surface allows for multi functional ability to interact with more molecular agents or particles.

-The second advantage derives from the fact that a stronger amplifier can be detected outside the body, which helps to detect micro metastasis.

-Nanoparticles have multi modality competence. It can enhance signaling of several imaging modalities.

- Nanotechnology has both diagnostic and therapeutic potential.[25]

1- In Imaging[26]

Current imaging methods can only readily detect cancers once they have made a visible change to a tissue, by which time thousands of cells will have proliferated. And even when visible, the

[23] Ke H, Wang J, Dai Z, Qu E, Xing Z, Guo C, Yue X, Liu J. Gold microshelled microcapsules: a theranostic agent for ultrasound contrast imaging and photothermal therapy, Angew Chem Int Ed Engl. 20011 Mar 21;50(13):3017-21
[24] Id.
[25] Sanjiv Sam Gambhir, MD, PhD; Nanotechnology in cancer imaging, dec 17 2010 Molecular imaging Center at Stanford school of Medicine – http://nano.cancer.gov/learn/impact/podcasts.asp#anna-barker.

[26] BENEFITS FOR DIAGNOSIS- NCI ALLIANCE FOR NANOTECHNOLOGY IN CANCER- NATIONAL CANCER INSTITUTE

nature of the tumor and the characteristics that might make it responsive to a particular treatment must be accessed through biopsies. Nanotechnology allows cancerous, even pre-cancerous cells to be detected by two things: something that specifically identifies a cancerous cell and something that enables it to be seen. For example, antibodies that identify specific receptors found to be over expressed in cancerous cells can be coated on to nanoparticles such as metal oxides which produce a high contrast signal on Magnetic Resonance Images (MRI) or Computed Tomography (CT) scans. Once inside the body, the antibodies on these nanoparticles will bind selectively to cancerous cells, effectively lighting them up for the scanner. Similarly, gold particles could be used to enhance light scattering for endoscopic techniques like colonoscopies. Nanotechnology will enable the visualization of molecular markers that identify specific stages and types of cancers, allowing doctors to see cells and molecules undetectable through conventional imaging. This earlier and more precise identification of cancer cells should result into more effective treatment.

2- In Screening[27]

Screening for biomarkers in tissues and fluids for diagnosis will also be enhanced by nanotechnology. Individual cancers differ from each other and from normal cells by changes in the expression and distribution of tens to hundreds of molecules. As therapeutics advance, it may require the simultaneous detection of several biomarkers to identify a cancer for treatment selection. Nanoparticles such as quantum dots, which emit light of different colors depending on their size, enable the simultaneous detection of multiple markers. The

[27] Id.

photoluminescence signals from antibody-coated quantum dots could be used to screen for certain types of cancer. Different colored quantum dots would be attached to antibodies for cancer biomarkers to allow oncologists to discriminate cancerous and healthy cells by the spectrum of light they see.

C-Risks Behind Using Nanotechnology

With the development of nanomaterials, and their use in medical imaging, we are capable to detect the smallest details and transformations in the human body. With the potential that this technique possesses, even pre-carcinogenic cells could be detectable. The concerns are that this form of imaging and diagnosis could lead to a state of panic in the medical and human environment. The ability to detect a serious disease before it happens, or even more, to detect a risk of disease that might never happen, would have psychological and critical effects on the population. A human body can be full of tumors that might never transform in malignant ones. The detection of those tumors can affect an individual life, leave him with unnecessary psychological fears, and cause over-use of irrelevant medical resources.

A research model of rats which made them inhale carbon nanotubes showed that their lungs reacted to the nanoparticles and inflammation was identified. Most of the inflammation did clear out with time.[28] Currently, there is lack in regulation of nano production due to the very little data available on its toxicity.[29]We will be discussing this issue in the ethical and regulatory part of this paper.

[28] Gillian Lieberman, MD- Saif Aljabab 2011
[29] Id.

IV- NANOTECHNOLOGY APPLICATIONS IN CANCER TREATMENTS

A-Applications Areas

Most efforts to improve cancer treatments through nanotechnology are still at the research stage, although several of them have moved to the pre-clinical stages[30]. Nanotechnology offers some exciting possibilities in that area, including destroying malignant tumors without harming, or with minimal damage to, the healthy tissues, as well as the detection and destruction of cancer cells before they transform into tumors.[31]

Examples of clinical trials

1-Cytlmmune has published the preliminary results of a phase 1 clinical trial of a targeted chemotherapy method.[32] They attach gold nanoparticles to a molecule of a tumor-killing agent called tumor necrosis factor alpha (TNF) and to a molecule of Thiol-derivatized polyethylene glycol (PEG-THIOL), which hides the TNF bearing nanoparticles from the immune system. [33]The PEG-THIOL allows the nanoparticles to flow through the blood stream without being attacked. The combination of PEG-THIOL is named Aurmine. The nanoparticles carrying the TNF tend to accumulate only in cancer tumors. That limits the toxic effect on healthy cells[34]. TNF has shown to be more effective with other chemotherapy drugs. Cytlmmune is planning a phase 2 trial

[30] Understanding nano.com- www.understandingnano.com/cancer-treatment-nanotechnology.html
[31] Id.
[32] Id.

[33] ID -CHEMOTHERAPY: NANO MEDICAL CURES COMING CLOSER? - UNDERSTANDING NANO.COM-

[34] Id.

with Aurmine combined with other chemotherapy drugs. They are also performing pre-clinical trial of another combination in which TNF, PEG-THIOL and chemotherapy drug known as paclitaxel is bound to the surface of nanoparticles

2-Nanobiotix, a nanomedicine company, announced recently that preclinical follow-up data regarding long-term toxicity evaluation suggests that its patented NBTXR3 nanoparticles are a safe and effective treatment for radiosensitive and radioresistant tumors.[35] The preclinical studies were performed at NAMSA Biomatech.[36] The method used is called nanoXray therapeutics. It resolves radiation's problems including the destruction of the healthy tissue and the side effects results.[37]

"Our nanotechnology is designed to allow for the precise destruction of cancer cells via the controlled application of an outside-the-body energy source-in this case, an X-ray. We have aggressively worked to achieve our goal of completing this preclinical program in order for nanobiotcs to be able to start the first- in-man clinical trial by the end of this year. We are highly encouraged by these latest results, with confirmation of good tolerance and negligible toxicity observed in animals," Laurent Levy, PhD, President and CEO of Nanobiotix and Co President of the French Technology Platform on Nanotechnology, (FTPN).

3- Nanospectra Biosciences, Inc. in Houston Texas announced in July 1, 2008 that it has commenced a human pilot trial of its AuroLase Therapy in recurrent head and neck cancers. The

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[35] TARGETED X-RAY THERAPY FOR CANCER TUMORS - UNDERSTANDING NANO.COM-

[36] Id.
[37] Id.

Company's opened Investigational Device Exemption allowing for the enrollment of up to 15 patients at up to four hospital sites in the United States.[38]

"This is our first-in-human study of this novel therapy" said J. Donald Payne, President and CEO of Nanospectra. "We believe a principal benefit of this approach may be highly selective and rapid tumor destruction with minimal damage to surrounding tissue and no systemic toxicity. This pilot human trial is designed to establish a safety profile for our therapy and to determine the optimal treatment parameters in humans. The result of this study will allow us to design a subsequent, larger study that would be necessary for FDA approval. In addition, the safety data from this trial can be used to initiate subsequent investigational trials in other types of cancer."

AuroLase Therapy is designed to thermally destroy solid tumors with particles activated by a near-infrared-laser. These AuroShell particles are injected into the blood stream of the body, and are allowed to accumulate in solid tumors through the leaky blood vessels related to the tumor's rapid growth. Then, the area is illuminated with a laser that emits near-infrared light having a significant penetration through human tissue. The particles are designed to absorb this wavelength, converting the absorbed light into heat, to destroy the solid tumor.[39]

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[38] TARGETED HEATED THERAPY FOR CANCER TUMORS - UNDERSTANDING NANO.COM-

[39] Id.

B-Benefits of Nanotechnology in Cancer Treatments

1-Nanocarriers

Conventional chemotherapy drugs kill tumor cells effectively. But these drugs kill healthy cells in addition to tumor cells, leading to side effects such as nausea, hair-loss, fatigue, and compromised immune function. Nanoparticles can be used as drug carriers for chemotherapeutics to deliver medication directly to the tumor without damaging healthy tissue. Nanocarriers have several advantages over conventional chemotherapy. They protect drugs from being degraded in the body before they reach their target, enhance the absorption of drugs into tumors and into the cancerous cells themselves, have better control over the timing and distribution of drugs to the tissue, and prevent drugs from interacting with normal cells, thus avoiding side effects.[40]

2-Passive Targeting[41]

There are several Nanocarrier-based drugs, which rely on passive targeting through a process known as "enhanced permeability and retention." Because of their size and surface properties, certain nanoparticles can escape through blood vessel walls into tissues. Tumors tend to have leaky blood vessels, allowing nanoparticles to accumulate in them, and concentrating the attached cytotoxic drug where needed, protecting healthy tissue and reducing side effects.

[40] BENEFITS FOR TREATMENT AND CLINICAL OUTCOMES- NCI ALLIANCE FOR NANOTECHNOLOGY IN CANCER- NATIONAL CANCER INSTITUTE

[41] Id.

3-Active Targeting[42]

There are nanoparticles on the horizon that will actively target drugs to cancerous cells, based on the molecules that they express on their cell surface. Molecules that bind specific cellular receptors can be attached to a nanoparticle to actively target cells expressing the receptor. Active targeting can be used to bring drugs into the cancerous cell, by inducing the cell to absorb the nanocarrier. Nanotechnology can combine active and passive targeting which increases the efficacy of a chemotherapeutic, achieving greater tumor reduction with lower doses of the drug.

4-Destruction from within[43]

Nanoshells are being used in the laboratory to thermally destroy tumors from the inside. They are designed to absorb light of different frequencies, generating heat (hyperthermia). Once the cancer cells take up the nanoshells (via active targeting), scientists apply near-infrared light that is absorbed by the nanoshells, creating an intense heat inside the tumor that kills tumor cells without damaging healthy cells. New targeted magnetic nanoparticles are in development that will both be visible through Magnetic Resonance Imaging (MRI) and can also destroy cells by hyperthermia.

C-Risks behind Nanotechnology Treatments in Cancer

The risks behind that technology are really limited in comparison to the benefits that can result from using this technology in cancer. The benefits appear to outweigh the risks which appear to

[42] Id.
[43] Id.

be similar to those mentioned above in the applications of nanotechnology in diagnosis, such as potential for unanticipated toxic effects and allergies. Those risks can be controlled when proper studies are completed, and ethicals rules are followed, as we will be discussing in this paper.

V- OVERVIEW OF THE ETHICAL AND REGULATORY ISSUES IN NANOMEDICINE

As the science of nanomedicine speeds ahead, ethics and the law struggle to catch up. The most significant concerns involve risk assessment, risk management of engineered nanomaterials (ENM), and risk communication in clinical trials. Questions of social justice, access to health care and the use of nanotechnology for traits enhancement becomes important.

A- Ethical Issues

Before nanomedicine products can be used in diagnosis, prevention, or treatment of disease, they must undergo extensive pre-clinical and clinical testing. The U.S. Environmental Protection Agency, the National Institute of Environmental Health Sciences, the National Science Foundation and the National Institute of Occupational Safety and Health have launched a variety of programs to study the risks of nanomaterials. The National Cancer Institute has

established a laboratory for characterizing the in vitro response to ENM used in cancer diagnosis or treatment.[44]

1-Applications risks

Nanomaterials vary in size and shape, and can have unpredictable effects. A substance that is non-toxic at 50 nm may be toxic at 1 nm or vice versa. They are heavily dependent on their microenviroment, they may change in size or shape inside an organism, and could behave differently in an organism than they do in cell culture.[45]

Nanomaterials can translocate from the exposure site to other parts of the body. They can also cross cell membranes and the blood-brain barrier.[46] Inhaled nanomaterials can enter the capillaries, and once in the circulatory system, they may enter the liver, lymph nodes, spleen, and bone marrow.[47] Nanoscale materials can accumulate in parts of the body and produce adverse effects. A particle that is benign when ingested may be toxic when inhaled.[48]

Ethical guidelines require that risks to human subjects be reasonable compared to the potential benefits to the subjects and society and that risks be minimized, as much as possible. Scientists have to be very careful with substances that can trigger an immune response, such as

[44]. Resnik D, Tinkle S. Ethical issues in clinical trials involving nanomedicine. *Contemp Clin Trials.* 2006 Nov 17; [Epub ahead of print]. Considers ethical issues in nanomedicine clinical trials.
[45] Hoet P, Brüske-Hohlfield I, Salata O. Nanoparticles—known and unknown health risks. *J Nanobiotechnology.* 2004;2:12–27.

[46] Id.
[47] Oberdörster G, Oberdörster E, Oberdörster J. Nanotoxicity: an emerging discipline evolving from studies of ultrafine particles. *Environ Health Persp.* 2005;113:823–39. Useful review of nanotoxicology.

[48] Donaldson K. Resolving the nanoparticles paradox. *Nanomedicine.* 2006;1:229–34.

antibodies and antigens. Substances that are safe in a particular animal species at a particular dose may not be safe in human beings.

To minimize these risks, a clinical study must have a Data and Safety Monitoring Board (DSMB) to keep track of adverse events, adverse reactions, and other problems with the product under investigation. The DSMB should review the data frequently enough to spot any dangerous trends and control potential harm to human subjects.[49] Other strategies for minimizing risks in nanomedicine clinical trials include careful review of the relevant literature, sound research design, appropriate inclusion and exclusion criteria, clinical monitoring, well-trained personnel, timely adverse event reporting, protection of confidentiality, and standard operating procedures, and follow-up with subjects after they complete the study.[50]

It is important for physicians to report all problems to the relevant safety agency (such as the FDA). Though the FDA does not require companies to conduct post-marketing studies, it should consider making this research mandatory for some nanomedicine products. Long-term studies (5–10 years in duration) may be needed to monitor the safety of some nanomedicine products.[51]

Ethical and legal rules require that an investigator inform a potential research subject (or his or her representative) about the study, procedures, benefits, risks, and other information the subject would need to decide whether to participate. Researchers should educate the public about how nanotechnology can be used in medicine, the benefits and risks of nanomedicine.

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[49] Slutsky A, Lavery J. Data safety and monitoring boards. *N Engl J Med.* 2004;350:1143–7.

[50] Gallin J. *Principles and Practice of Clinical Research.* Academic Press; San Diego: 2002.

[51] Id.

2- Economical issues

The price of the new product decreases when other firms develop competing products and the manufacturer's patents expire. The price also decreases when generic products enter the market. It may take a long time for the price of nanomedicine products to decline, due to its complexity. In the short term, intellectual property can exacerbate health inequalities, because economically disadvantaged people may not be able to afford new and expensive medical innovations.[52] It is likely that nanomedicine products will also be very expensive when they first enter the market, and that nanomedicine may temporarily make health national and international inequalities worse. This problem could be a serious issue in countries where there is no guaranteed health care coverage, such as the U.S.

To promote national and international justice in access to nanomedicine, intellectual property laws should not give manufacturers excessive control over the market, countries should develop health care financing systems that help poor people receive nanomedicine, negotiate fair trade agreements, and encourage companies to institute stratified policies that make nanomedicine affordable.[53]

Another ethical issue related to social justice concerns the use of nanomedicine for physical enhancement rather than therapy. Doctors can prescribe anabolic steroids to help patients recover from traumatic injuries, but athletes may also take these drugs to improve their performance. Applications of nanotechnology to neurology that help to reduce or replace

[52] Menifoff J. *What the Doctor Didn't Say.* Oxford University Press; New York: 2006.

[53] Resnik D. Fair drug prices and the patent system. *Health Care Anal.* 2004;12:91–115.

memory loss could be used to enhance human memory. Nanomedicine therapies designed to help people with learning disabilities could allow healthy people to become super-intelligent. Enhancement can produce unfair competition. A person with an enhanced body or mind has an unfair advantage over someone with a normal body or mind. Enhancements can help people acquire a competitive edge in athletics, school, the job market, and other aspects of life. It can exacerbate socioeconomic inequalities if only the rich people can afford enhancements, and they are able to convey their advantages to the next generation. The rich will get richer. It can lead to discrimination or bias against people who are not enhanced and to social inequality. [54]

Although there are good reasons for society to anticipate and respond to the use of nanomedicine for enhancement purposes, this may not be easy. First, the distinction between enhancement and therapy is not well-defined, because both of these concepts depend on the concept of "normality."

Second, it may be difficult to enforce any laws pertaining to restricting the use of nanomedicine for enhancement. [55]Therefore, future methods shall have to be regulated and controlled to help promote access to the enhancement technology by low income people.

[54] Rothman S, Rothman D. *The Pursuit of Perfection.* Pantheon Books; New York: 2003
[55] Buchanan D, Brock D, Daniels N, Wikler D. *From Choice to Chance: Genetics and Justice.* Cambridge University Press; Cambridge: 2001.

B-Regulatory Issues

1-Potential Issues with Medical Malpractice and Products Liability

Until tested on humans, we can only talk about speculation as to issues of liability. When it concerns nanomedicine, two parties that are likely to be held liable, the manufacturers and the doctors.

The Restatement of Torts defines a person "subject to liability" as an actor, whose conduct is the legal cause of another person's injury, thereby making him liable for that person's particular claim unless he has an applicable defense.[56]In a typical products liability case concerning a medical device, there is a bright line between the negligence of a doctor and a manufacturer.[57] The presumption, generally, is against holding the doctor liable and instead the blame turns to the manufacturer of the medical device. Under products liability law, a manufacturer can be held liable for a defect in design, a defect in the manufacture of the product, or due to a failure to warn about all of the reasonably foreseeable inherent risks.[58] When it comes to nanomedical devices, it may be impossible to determine liability because the small size of the components of the device makes it incredibly difficult, to determine whether the doctor or manufacturer was negligent. The complexity of nanotechnology may also require a restructuring of the law

[56] RESTATEMENT (SECOND) OF TORTS § 5 (1965).
[57] Id.
[58] Morrison, *supra* note 25, at 240.

regarding manufacturing defects.[59] A manufacturing defect occurs when the "product departs from its intended design even though all possible care was exercised in the preparation and marketing of the product."[60] Currently, under the law, "a manufacturer is *always liable* for a defectively manufactured product."[61] The complexity of the product being manufactured is irrelevant. Consequently, manufacturers will be taking risk creating nanotechnology devices because no matter how complex the design is or how unpredictable, they can be held liable if the product malfunctions.

Nanomedicine will be such a new and developing field that patients who agree to be treated by the devices are likely going to be warned and made to sign waivers until nanomedicine becomes the norm, if it ever does. If there are any lawsuits under this claim, they would be filed against the doctor because when it comes to prescription drugs and medical devices, the Learned Intermediary Rule allows a manufacturer to "Discharge its duty to warn the end-user by warning that person's doctor," making the doctor responsible for properly warning the patient. Despite the presumption for holding manufacturers liable in medical device lawsuits, the doctors controlling the devices must face possible liability for any errors made concerning control of the device, or for prescribing outside of the approved use, such as off-label use. Some nanorobots will be powered by chemicals or the human body temperature[62]. What happens when the doctor has minimal control over the functioning of the device? It may be necessary for hospitals to retain nanoexperts to be present during procedures to ensure that

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[59] John C. Monica, Jr. & Patrick T. Lewis, *Preparing for Future Health Litigation: The Application of Products Liability Law to Nanotechnology*, at 16, 26 (Nov. 3, 2005), http://www.nanolawreport.com/tags/powerpoint; *cf.* John C. Monica, Jr., *ProductsLiability in the Age of Nanotechnology: Understanding a Manufacturer's Duty to Warn,*Richmond Journal of Law & Technology Volume XVI, Issue 2 12

[60] Id.

[61] Id.

[62] *See* Morrison, *supra* note 25, at 245

the nanodevices are functioning properly.[63] "Physicians . . . must observe that degree of skill, learning, care, and diligence ordinarily possessed by the average, competent practitioner in their professions, and must exercise reasonable and ordinary care and diligence in the exercise of such skill and the application of such knowledge."[64]

These liability dilemmas are but a drop in the well of all the issues that will emerge from nanomedicine once it enters into society.

The unpredictable nature of nanotechnology requires the development of a regulation plan to keep the public safe. As noted by Fiedler and Reynolds, "the law of unintended consequences operates with a vengeance where technology is concerned."[65] On who will be given the responsibility to oversee regulation? Would nanomedicine operate under the current regulations? Or it would require new regulations? Our current laws for regulating medical drugs and devices may not be adequate to regulate, safely and effectively, the manufacturing and distribution of nanomedicine. So far no formal regulations have been created. Nanotechnology is regulated by the FDA (the Food and Drug Administration).

2- Regulations by the Food and Drug Administration

Under federal law, medical devices are subject to the jurisdiction of the FDA, according to the Food, Drug and Cosmetic Act, to ensure that they are safe and effective. The FDA is charged with regulating nanomedical devices and drugs.[66] The FDA determines that the nanodevices are

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[63] John C. Monica, Jr. & Patrick T. Lewis, *Preparing for Future Health Litigation: The Application of Products Liability Law to Nanotechnology*, at 16, 26 (Nov. 3, 2005), http://www.nanolawreport.com/tags/powerpoint; *cf.* John C. Monica, Jr., *Products Liability in the Age of Nanotechnology: Understanding a Manufacturer's Duty to Warn,* Richmond Journal of Law & Technology Volume XVI, Issue 2 12

[64] *Id. at* Morrison, *supra* note 25, at 245

[65] Fiedler & Reynolds, *supra* note 18, at 603.

[66] Morrison, *supra* note 25, at 233–34.

safe, that the probable benefits to health outweigh any possible risks of harm, and that they are efficient.[67]

The FDA has chosen to attempt regulation of nanomedicine by applying current regulations to the emerging technology.[68] The FDA made a similar decision when it confronted the issue of regulating biotechnology.[69] The FDA did not create any new regulations or new centers to handle its regulation; it incorporated the biotechnology products into the current regulatory system by looking at products on a case-by-case basis.

Same thing for nanotechnology, no formal regulations have been created; we must look to the existing statutes to predict how the field will be regulated. We need to wait until nanotechnology becomes part of our lives to see if specific regulations would be needed.

VII- CONCLUSION

There is no question that nanotechnology is about to revolutionize technologies in general, and medicine in particular. It is still an unpredictable science, and not yet mature enough to be fully trusted. Yet, foreseeable promises, especially in medicine, make it worth all our attention and support without ignoring the risks and issues behind this technology. Ethical guidelines should be followed, and regulations and policies must catch up with this science. Safety, equality, and protection to all the individuals must be maintained. Nanotechnology is a main station in history; related discoveries remind us of the importance of science to our existence. Without

[67] Wolfson, *supra* note 5, at 384.
[68] *See* Morrison, *supra* note 25, at 247 (noting that as of February 2007
[69] Miller, *supra* note 4, at ¶ 62.

being able to accept reasonable risks as part of discoveries, we would still be shivering in the jungles, unable to start a fire.