Nanomedicine: The Hope, the Promise, and the Need for Precaution

Dónal P. O'Mathúna, PhD

Key words: *clinical trials, ethics, nanotechnology*

Learning Objectives

1. Define nanotechnology.
2. Describe areas where further research is needed on the risks of nanotechnology.
3. Explain why the usual risk, or cost-benefit, analysis is insufficient for nanotechnology.
4. Apply the precautionary principle to nanotechnology.

Visionary views

The vision for nanotechnology is often traced to a talk given by Richard P. Feynman at the 1959 American Physical Society annual meeting.[1] Feynman went on to win the Nobel Prize in Physics (for work done prior to his talk) and had a gift for putting physics into a format that was accessible for non-physicists. Feynman has been called one of the leading physicists of the 20th century and "the founding father of modern nanotechnology."[2] His talk did not use the term "nanotechnology," but challenged researchers to work with matter on a very, very small scale.[3] Feynman claimed that if what was then known about the laws of physics was applied to challenging questions, the whole Encyclopedia Britannica could be written on the head of a pin and computers could be built that were much smaller and faster than existed in 1959. That, and more, has been made possible by nanotechnology.

Part of Feynman's vision is yet to be realized as nanotechnology moves toward an era in which he said "we can arrange the atoms the way we want; the very *atoms*, all the way down!"[1] He envisioned intricately designed machines being built atom by atom to give, what today would be called, nanoscale devices. He thought it would be fun to build these machines, but he also considered practical applications. "You put the mechanical surgeon inside the blood vessel and it goes into the heart and 'looks' around… It finds out which valve is the faulty one and takes a little knife and slices it out. Other small machines might be permanently incorporated in the body to assist some inadequately functioning organ."[1]

Since its visionary inception, the medical applications of nanotechnology have been at its core. The idea of a tiny vessel floating through the bloodstream and delivering a surgeon to the site of injury sounds like science fiction. The movie "Fantastic Voyage" was released in 1966 and

described just such a scenario. Nanodevices and nanotechnology have regularly appeared in science fiction, something some scientists have not been altogether pleased about.[4]

While some nanotechnologists distance themselves from such machines and nanobots, others, like Robert Freitas, embrace Feynman's vision of nanomachines permanently incorporated into our bodies. Freitas claims these nanodevices will outperform and outlast our natural cells. He has already proposed detailed plans to build "respirocytes" that will carry oxygen in the blood, "microbivores" that will search out and destroy invading organisms, "pharmacytes" that will deliver drugs in targeted ways, and "surgical nanorobots."[5,6] All these, he suggests, may be available in the 2020s, although others fail to see these developing soon outside science fiction.

While the vision of nanobots floating through our bodies has not been realized, nanotechnology is making practical inroads in pharmaceutical and medical applications. Much investment is being directed toward research and development in what is now being called nanomedicine. With this are a number of ethical and regulatory issues that need to be addressed. This article will survey the major areas of development in nanomedicine and explore some of the pressing ethical issues.

Defining nano

The prefix "nano" refers to one billionth of something. Thus, one nanometer (nm) is one billionth of a meter, or 1×10^{-9} m. Nanotechnology is usually defined in terms similar to those of the U.S. National Nanotechnology Initiative (NNI), one of the largest funders of nanotechnology research in the world.

> Nanotechnology is the understanding and control of matter at dimensions between approximately 1 and 100 nanometer, where unique phenomena enable novel applications. Encompassing nanoscale science, engineering, and technology, nanotechnology involves imaging, measuring, modeling, and manipulating matter at this length scale.[7]

Objects larger than nanoscale include human cells and most bacteria, while individual atoms have diameters smaller than nanoscale. For example, hydrogen atoms are about 0.1 nm wide and gold atoms are about 0.3 nm wide. Objects that have dimensions in the nanoscale range include strands of DNA (about 2 nm wide), proteins (many are 5 to 50 nm wide), viruses (about 75 to 100 nm), and a range of new nanomaterials called quantum dots (10-100 nm), carbon nanotubes (1.4 nm wide), buckyballs (0.7 nm in diameter), and various other nanoparticles.[8] One of the major breakthroughs in the development of nanotechnology was the invention of the scanning tunneling microscope in 1981. Gerd Binnig and Heinrich Rohrer used their new instrument to produce images of individual atoms that were about 5 nm tall. Such instruments are now also able to move individual atoms and molecules around. Don Eigler and colleagues took 22 hours in 1989 to write 'IBM' in individual xenon atoms, a feat they estimate would take about 15 minutes with today's instruments.[4] Within 30 years, Feynman's vision of writing in letters that were only a few atoms wide had been far surpassed.

One of the major breakthroughs in the development of nanotechnology was the invention of the scanning tunneling microscope.

However, what is leading to even more excitement than the size of nanoparticles are their properties. Nanoscale particles often have different properties and functions to those of larger, macroscale particles of the same substance. Particles smaller than nanoscale (individual atoms) are dominated by quantum effects, whereas particles larger than nanoscale are dominated by their bulk properties. Within the nanoscale range, particles have an usual combination of quantum and macroscale properties that converge to give nanoparticles unique and interesting effects.

One of these distinctive features is how nanoparticles interact with cells and living tissues, which lie at the center of interesting and challenging developments in nanomedicine.

Molecules that are smaller than nanoscale (like many drugs) enter cells by passive diffusion. Their biological properties are strongly dependent on their solubility and concentration in tissues and fluids. Nanoparticles, however, interact with cells in ways that resemble similarly sized biomolecules like proteins.[9] The nanoparticles become coated in proteins and then use active transport systems to enter cells. On the one hand, this opens up opportunities to develop nanoparticles that can access areas of the body that were previously impermeable to drugs, such as crossing the blood-brain barrier. But on the other hand, this creates the possibility that nanoparticles may end up causing adverse effects or accumulating in tissues, leading to toxicity problems. Thus, "the very same properties that make nanoparticles potentially useful for industrial and biomedical applications have also become a safety concern."[10] Given the excitement and uncertainty, how best to proceed with nanomedicine is raising challenging ethical issues.

Funding risk assessment

The U.S. government has been a leading investor in nanotechnology, channeled through the National Nanotechnology Initiative (NNI). President Clinton started NNI in 2000 with a $270 million investment.[11] President Bush expanded this investment each year, allocating $1.5 billion for Fiscal Year (FY) 2009. President Obama has continued this trend, with $1.64 billion allocated for FY 2010, bringing the total investment between 2001 and 2010 to almost $12 billion.[7] This represents the largest federally funded, interagency scientific research initiative since the space program of the 1960s. Many other governments around the world are investing similarly. Looking back at nanotechnology spending in 2004 by both public and private organizations, $3 billion was spent in the United States, $3 billion in the European Union, $2.3 billion in Japan, and $1.9 billion in the rest of the world.[12]

Nanomedicine is an area where nanotechnology promises much and is already beginning to deliver.[13] As of 2007, about 200 companies were involved in nanomedicine research and development, 38 products were on the market with dozens more in the pipeline, and annual sales had reached $6.8 billion and were expected to double by 2012.[14]

Although huge investments are being made into nanotechnology and nanomedicine, the level of investment in risk assessment has not kept pace. The NNI published a strategy for environmental, health, and safety (EHS) research in 2008.[15] This is defined "as research whose primary purpose is to understand and address potential risks to health and the environment that engineered nanomaterials may pose."[7] Although the NNI affirms its commitment to such research, the funding allocations are small in comparison. Cumulative investment in EHS between 2005 and 2010 has been $350 million.[7] Total NNI investment for this same period can be estimated at $9 billion.[16] Therefore, EHS research makes up less than 4 percent of all nanotechnology investment. For 2010, the budgeted investment in EHS is $88 million, or 5.4 percent of the total nanotechnology budget. While other projects might include EHS dimensions, this investment represents a relatively small proportion of the funding into what everyone acknowledges is a crucial aspect of nanotechnology.

Concerns have also been expressed that funding for EHS research is not focused sufficiently on studies of the effects of nanotechnology on humans and the environment.[17] The NNI budget for EHS is based on its 2008 strategy[15] that was found to have many weaknesses by the National Research Council (NRC) at the National Academy of Sciences.[18]

While the NRC praised the collaborative way in which the strategy was developed, only federal funding agencies were involved. The views of other stakeholders such as industry, environmental, and consumer advocacy groups, and other countries were not sought. The NRC found that the document itself was flawed, concluding that it "does not describe a strategy for nano-risk research."[18] No vision or goals for EHS research were presented, nor were there any objectives that would permit accountability for results.

Fundamentally problematic was the lack of an adequate review of EHS research to date. A baseline snapshot was obtained by examining the nanotechnology projects funded by NNI in 2006. However, the NRC found that many of the projects assumed to have an EHS component did not actually have one. Thus the EHS strategy "substantially overestimated the general nanotechnology-related research activity in environmental, health, and safety research."[18] Since that was taken as the baseline for future funding, the adequacy of the resources allocated to EHS research is seriously questionable. Yet this strategy continues to guide EHS spending in the FY 2010 NNI budget.[7]

A European report compiled through discussions in 2009 with researchers and other nanotechnology stakeholders found broad agreement on the need for more scientific knowledge of the EHS impacts of nanomaterials.[19]

The report found that further work is needed on:

- the potential toxicity and hazards of nanomaterials
- their behavior throughout their lifecycle, not just at initial use
- the fate and persistence of nanoparticles in humans, animals, and the environment
- the development of standard nomenclature, protocols, and best practice guidelines
- databases of materials, research topics, and experts in the area

However, disagreement was found regarding how progress can be made in these areas. Environmental and consumer groups, along with Members of the European Parliament, favored new regulations specifically addressing nanoparticles, while industry representatives favored regulating nanoparticles under existing guidelines for chemicals, pharmaceuticals and food.[19] Similar disagreements exist in the United States, where FDA and the Environmental Protection Agency continue to treat nanoparticles under existing regulations for macroparticles.

Consumer groups like Friends of the Earth (an environmental organization) and Consumers Union (which publishes *Consumer Reports*) are concerned about the way nanomaterials are being put into consumer products without specific EHS testing or regulation for the nanoparticles. The latter issued a report that found nanoparticles in four of five sunscreens that their manufacturers declared contained no nanoparticles.[20] Friends of the Earth issued a report that pointed out more than 100 food or food-related products on the U.S. market contain nanoparticles either in the product or in the packaging, yet no information is given to consumers about these.[21] Nanoceuticals are another developing field of products, defined as nanotechnology-enabled dietary supplements. Since these fall under dietary supplement regulations, they do not require approval before going on the U.S. market, as is required of new pharmaceuticals.[22]

Apart from EHS concerns themselves, the inconsistency and lack of transparency could tarnish all of nanotechnology, including nanomedicine. Many in the nanotechnology community worry about public protests that may arise in response to unknown risks involving nanotechnology.[23]

In France, a series of public debates on nanotechnology ran into problems. One in December in Grenoble, where the flagship center for French nanotechnology is located, had to be called off due to public protests.[24] The format for the next debate was modified to have the audience in one location and the presenters in another, with communication via video-link.

Public dialogue has been promoted as a way to address fears about the potential risks of nanotechnology. However, one of the arguments made during the debates in France was that since nano-enabled products are already on the market, these debates are not about citizen engagement in decision-making, as many hoped. Rather, some claim they have become a top-down approach to simply inform the public about decisions already made to develop nanotechnology. Whatever these protests mean about public involvement in science policy, such scenes raise concerns that nanotechnology could suffer the same fate as earlier biotechnologies that were rejected by some public groups and policy-makers based on fears of potential risks and suspicions over the motives of industry, government, and researchers.

The example of carbon nanotubes

Although much remains unclear about the risks of nanotechnology, some information is being produced. The fastest growing class of nanomaterials are carbon nanofibers (CNFs), accounting for 80 percent of the production in the nanomanufacturing sector.[25] The basic structure is a sheet of graphene, which contains carbon atoms arranged in pentagons and hexagons. CNFs are made when these are rolled into cylindrical structures. Carbon nanotubes are a groups of structures made from long tubes of these cylinders. The nanotubes typically have a diameter of a few nanometers, and can be up to 1 millimeter long. A systematic review of the health effects of CNFs found that only carbon nanotubes have been examined in EHS studies.[25]

Carbon nanotubes have been used to make "nanotweezers," "nanoscissors," and other instruments that could permit the type of nanosurgery Feynman envisioned in 1959.[1] These tools could eventually be used to manipulate and modify many biological structures within living cells.[26] Carbon nanotubes also have been examined as membranes and filters in water purification systems, especially for

developing countries.[27] To date, such devices have proved to be too expensive, but their development also has been hindered by a lack of data on their safety and environmental impact.[28] Carbon nanotubes may also be used to make improved implants such as cochlear implants.[29] Polymer-coated nanotubes (with specific proteins incorporated) are being tested both to prevent further degradation of ear cells and to transmit sound signals to the brain. Not only do carbon nanotubes have useful structural properties, they have unique electrical properties. These may give them a role in promoting electrical stimulation of nerves, and allow further advances with cochlear implants.

Very preliminary research is showing that carbon nanotubes may some day be injected into patients. A recent study injected gold-plated carbon nanotubes along with magnetic nanoparticles into mice to detect circulating cancer cells.[30] The method successfully allowed the detection of very small numbers of cancer cells that had broken away from the primary tumor. The in vivo method may lead to early diagnosis of cancer and the prevention of metastases in humans. However, use in patients will require further understanding of the short- and long-term consequences of injecting nanoparticles into people.

Carbon nanotubes could eventually be used to manipulate and modify many biological structures within living cells.

Even without the results of safety studies, production of carbon nanotubes is being increased. About 500 tons of carbon nanotubes were produced globally in 2008, while Japanese companies alone are planning to produce thousands of tons annually within five years.[31] Some predict that millions of tons of carbon nanotubes will be produced worldwide every year.[32] A large workforce will therefore be exposed to carbon nanotubes. However, research into the potentially toxic effects of these nanoparticles is lagging far behind their development and implementation. What is even more concerning is that almost all the data published to date points to serious concerns with carbon nanotubes.

Two similar studies published in 2004 on the impact of carbon nanotubes on mice came to contradictory conclusions.[32] This led to much debate about toxicity and the precautions necessary for those producing and working with carbon nanotubes. The National Institute for Occupational Safety and Health conducted an extensive study to resolve this conflict. Mice breathed suspensions of carbon nanotubes, and their lungs were later found to have an unusual acute inflammation that led to the production of granulomas and fibrosis. Lung lesions were progressive and dose-dependent. The authors concluded that carbon nanotubes were "intrinsically toxic" and cautioned that workers exposed to airborne particles from carbon nanotubes could be at risk of developing lung lesions.[32] Subsequent research has confirmed that if carbon nanotubes reach the lungs, they will have toxic effects. This research is limited because unnatural routes of administration were used and only animal and cell models have been tested. In addition, carbon nanotubes as currently produced contain many impurities that may contribute to the observed effects.

A systematic review in 2009 could still find no epidemiological data on the exposure of humans to carbon nanotubes. Twenty-one animal and cell studies were located and summarized in a meta-analysis that "demonstrated statistically significant and very large differences between the exposure and control groups."[25] When account was taken of the unnatural nature of the experiments, heterogeneity in the studies, and likely inter-species differences, the reviewers concluded that workers in carbon nanotubes manufacturing plants were "at a 'somewhat possible' health risk resulting in strong cytotoxic response (e.g., alterations in cell viability, cell death, cell inflammation, and DNA damage)."[25] They recommended engineering controls to limit exposure to carbon nanotubes and "rigorous personnel protective equipment" for workers.

Addressing risk responsibly

How research and development should respond to potential risk is a challenging question. While these are not new topics for medical research, nanotechnology research has highlighted the importance of focusing on this area. In

many ways, clinical research has developed in response to concerns about the risks of new pharmaceuticals. Different protocols are in place to ensure that very risky (unsafe) chemicals are abandoned (or highly restricted) as potential pharmaceuticals. Such protocols help to identify the dosages and routes of administration that minimize risks.

However, nanomedicine raises further complications because of its novelty. Part of what is most interesting and enticing about nanomedicine are the unique and distinctive ways in which nanoparticles interact with cells and tissues. This opens up exciting opportunities for new drug delivery systems and targeting of tissues and organs. At the same time, it raises concerns about the uncertain risks of nanoparticles.

Given that risk is a part of daily activity, surprisingly little philosophical analysis has examined the concept of risk or how it should be addressed ethically.[33] Risk involves at least four components. One aspect is the claim that there is uncertainty about something bad happening from using, for example, a new nanomedicine. A second is that the nanomedicine is alleged to be the cause of something bad. A third is that there is a probability of the bad event happening, say 1 percent chance or 50 percent chance. The fourth aspect is the expected outcome, say that a certain number of people will develop a particular adverse effect.

Risk analysis, or cost-benefit analysis, typically focuses on the third and fourth aspects of risk. Hence, a pharmaceutical might have a 1 percent chance of a certain side effect developing, or possibly that 1 in 10,000 people may have a specific adverse reaction. This approach is attractive because it is numerical and allows comparison with other risky actions.

However, such an approach is inherently problematic when the scientific data necessary to calculate probabilities or establish causation are lacking. In most situations, and especially with developing technologies like nanomedicine, uncertainty is the rule. With nanotechnology "so little is known about the possible dangers that no meaningful probability assessments are possible."[34] Using a risk-benefit analysis with nanomedicine can therefore be deceptive if the uncertainty behind the numbers is forgotten when decisions are eventually made.

The most obvious way to avoid making a wrong decision is to reduce the uncertainty. With nanomedicine, this involves conducting further nanotoxicity studies to provide more complete results to guide decision-making. Further research to establish causal links between nanoparticles and outcomes (good and bad) also is needed and will help reduce uncertainty. However, there are limitations in this area, as exemplified by the connection between risks and duration of exposure. Short-term studies may reveal a lack of risk, but this may not address uncertainty about long-term risks. A very tiny risk in short-term studies may be evidence that the risk will never become more common, or it could be early evidence that the risk will get larger as exposure continues. Decisions will need to be made regarding whether early results are sufficient to warrant proceeding with the product, abandoning it, or continuing to conduct research while delaying release of the product onto the market.

The precautionary principle

One approach to decision-making in the face of uncertainty is to adopt a precautionary approach. Such thinking is expressed in common expressions like "proceed with caution" rather than "full steam ahead," or "better safe than sorry" rather than "go for broke." However, serious questions remain about what a precautionary approach means when deciding how to conduct research on nanoparticles, what standard operating procedures to develop for researchers handling nanoparticles, or what to include in informed consent forms for clinical trials involving nanoparticles.

While a precautionary approach is generally accepted, wide variation occurs in the formulation of the approach. Also called the precautionary principle, it has come to prominence in recent decades in environmental contexts. The principle first emerged during the 1970s in response to "acid rain" destruction of German forests.[35] The ensuing German legislation introduced air quality regulations even before scientific studies had firmly established that the damage was due to air pollution. The precautionary principle was first included in an international treaty in the 1992 United Nations' Rio Declaration on Environment and Development. The principle has since been included in proposals and regulations in the European Union (EU), the World Health Organization (WHO) and the United Nations Educational, Scientific, and Cultural Organization (UNESCO).[4] The Wingspread Statement is a consensus definition of the precautionary principle: "Where an activity raises threats of harm to the environment or

human health, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically."[36]

The precautionary principle is one of the underpinning principles of the EU's new regulatory system for chemicals, the Registration, Evaluation, Authorisation, and Restriction of Chemicals (REACH).[37] In 2008, the European Commission adopted a voluntary code of good conduct for research in nanosciences and nanotechnologies (N&N). This code explicitly included the precautionary principle although, as with most other documents, without clear guidelines on how to apply it.

> N&N research activities should be conducted in accordance with the precautionary principle, anticipating potential environmental, health, and safety impacts of N&N outcomes and taking due precautions, proportional to the level of protection, while encouraging progress for the benefit of society and the environment.[38]

The precautionary principle is rarely named in U.S. regulation, but the general approach has been adopted regularly. For example, a precautionary approach has been taken in the United States on certain initiatives long before Europe adopted similar legislation. Examples include bans on scrapie-infected sheep and goat meat from animal feed, removal of chlorofluorocarbons from aerosols, and preventing the use of the steroid DES as a growth promoter in cows.[35] So, while the precautionary principle has not been clearly enunciation, the approach has had wide acceptance.

Applying the precautionary principle

The precautionary principle has developed in environmental contexts for reasons that are particularly relevant to health contexts.[33] Both involve complex systems that are characterized by feedback cycles. Small changes have the potential to have large and significant consequences, some of which may be irreversible. The example of rabbits in Australia is a prominent environmental example. Several dozen rabbits were introduced in 1859 to permit hunting. By the time their population reached 600 million in the mid-1900s, untold environmental destruction had occurred. This led to the deliberate introduction of the disease myxomatosis, to which rabbits have become resistant. Most recently, another rabbit disease has been introduced via calicivirus. "The upshot of this example is that apparently trivial and benign acts can have catastrophic consequences."[33]

Science fiction has been quick to pick up on hypothetical scenarios in which nanotechnology could cause significant harm. Probably the best-known is Michael Crichton's novel, *Prey*, although many other stories capture the same storyline.[4] The recent blockbuster movie, "I am Legend," shows how almost any scientific scenario can be extrapolated into a global catastrophe. In this movie, scientists introduce the cure for cancer, only to discover a few years later that an unpredicted side effect has led to the annihilation of almost the whole human race.

Much discussion of the precautionary principle drifts into application of the "catastrophe principle."[33] This is the situation where it is suggested that a new technology or product may give rise to such catastrophic harms that the only precautionary approach is to ban its production. While such scenarios help in theoretical discussions, they are not the practical situations facing most researchers, regulators, or patients. Nor do they give a fair portrayal of the value of the precautionary principle.

Situations in which the precautionary principle is applied generally involve three components.[39] The first is the activity or technology under consideration, the second are the potential effects of that activity, and the third are a group of remedies to avert harms. When uncertainty pervades the activities and the effects are uncertain, various remedies should be proposed. As more becomes known about the damaging effects, or the degree of certainty about the causal connections (or lack thereof) becomes better established, proposed remedies should be adjusted. If the damage becomes more severe, the remedies should become more restrictive, or as causal connections are shown not to exist, the remedies should become less restrictive. Such an approach takes account of the uncertainty involved and the importance of flexibility in responding to a growing scientific knowledge base. In the case of nanomedicine, it points once again to the importance of producing relevant information from EHS research.

In situations of scientific uncertainty, both risk-benefit analysis and the precautionary principle are important.[33] As more information comes available, risk-benefit analysis can be given higher priority. But when uncertainty predominates, numerical calculations will not be sufficient. During those stages of research and development, priority

should be given to evaluating the structure and validity of the arguments made for various precautionary remedies.

Decisions involving great uncertainty, such as those currently being made about nanomedicine, fall prey to "mere possibility arguments."[34] In these, some favor proceeding with development just because a great benefit is possible, while those on the other side call for halting development just because a catastrophe is possible. To arrive at a more balanced decision, all the potential effects of a proposed technology must be examined. At the same time, causes other than the new technology should be examined for those effects. In all likelihood, multiple causes and multiple effects are likely. Identifying these will not resolve disputes or dictate the best way forward. Instead, it should help avoid simplistic decision-making based on whether the argument for benefit or for harm is made first or made loudly. Having identified several benefits and harms, remedies can be put in place to maximize the former and minimize the latter. In other cases, the potential harms may be so great, and the benefits so hypothetical, that work should be put on hold or allowed to proceed only under strict safely regulations.

Precaution in nanomedicine clinical trials

In some ways, the ethical issues with nanomedicine are similar to those arising with all forms of medicine and medical research. New products should be tested and evaluated for effectiveness and safety; clinical research should be conducted according to widely accepted ethical guidelines; and approved treatments should be offered, along with the information necessary for patients to make informed decisions about different treatments.

Developments in nanotechnology are said to be "revolutionizing the future of medicine," but currently "most of these visions are hypothetical."[40] However, some nano-enabled medical products are already on the market. Several drugs have been reformulated into nanoparticles to give products that have better solubility, more targeted delivery, or fewer side effects.[40]

As these nano-enabled pharmaceuticals and other nanoparticles reach clinical trials, precautionary approaches should be included in the methodologies. Standard protocols have been developed over years of closely-monitored drug trials. But nanoparticles are of interest precisely because they do not act in the same way as conventional pharmaceuticals. The more unique and innovative a nanomedicine, the greater the possibility of unexpected outcomes. The tragic example of the TGN1412 phase 1 trial in 2006 highlighted the importance of a precautionary approach with new classes of drugs.[41] Early warning signs from preclinical studies were not given sufficient emphasis and the experimental drug was delivered in accordance with standard protocols, rather than being treated with due precaution. As a result, the healthy volunteers who received the drug suffered severe adverse effects from a "cytokine storm."

TGN1412 represented a completely new class of drug, and this was the first time such drugs were given to humans. TGN1412 was not nano-enabled, but the study highlights important ethical issues that need to be considered as new classes of drugs and devices are delivered by nanomedicine research. The British body set up to investigate the TGN1412 trial concluded that additional caution is needed when testing biological molecules with a novel mechanism of action, new agents with a high degree of species specificity, or new agents targeting the immune system.[42] Many nanomedicines will fall into one or more of these categories.

Earlier recommendations had been made regarding the ethical review needed by certain types of clinical research ,which will also apply to developments from nanomedicine.[43] A more precautionary approach was called for when research projects involved: 1) translating new scientific advances into human beings using interventions that are novel, irreversible, or both; 2) known or credible risk for significant harm without benefit to the participants; and 3) ethical questions about the research itself for which there is no consensus or there are conflicting or ambiguous guidelines.

Adopting a precautionary approach does not mean that clinical trials in nanomedicine should be abandoned; but neither should they proceed without adaptation when test items involve scientific uncertainty and novelty. Each new nanomedicine will need to be considered on a case-by-case basis until a sufficiently large database of effects has been generated. From the small amount of research done to date, carbon nanotubes warrant a high degree of precaution. That same level of precaution may not be necessary with other nanoparticles, but their health and safety testing is even further behind than that of carbon nanotubes. The remedies should

vary depending on the degree of uncertainty regarding causal connections and types of harms suggested by early research. The remedies could include conducting more preclinical research before testing on humans, giving lower doses over longer periods of time, observing each participant longer before administering the drug to the next participant, and a range of other possible adjustments to protocols.

Conclusion

The unique properties of nanoparticles are at the center of both excitement and worry about nanomedicine. "Although the use of nanotechnology in drug imaging, diagnosis, and cancer therapy may be beneficial, it may also cause unintentional human exposure with unknown health effects that can only be imagined at present."[40] Some people are imagining the worst, which may run the risk of abandoning useful new therapies and treatments. Careful evaluation of the harms and benefits of each new product is needed on a case-by-case basis.

In clinical trials with nanomedicine, a precautionary approach needs to be taken because these new drugs and devices have novel mechanisms of action and therefore involve much uncertainty. As more scientific information becomes available on each product, a more usual risk-benefit analysis can guide subsequent decisions. Thus, the precautionary principle should not be seen as a hindrance to scientific and technological development, but requires "more and better science."[44]

A precautionary approach is based on the ethical priority of protecting patients and the environment. It should help reduce the risk of disasters like TGN1412 in which people were seriously harmed. At the same time, it may add costs and will tend to slow down some areas of research and development. While the pace of discovery within nanomedicine is exciting, it raises concerns about how well safety, regulatory, and ethical oversight can be maintained.

> The economic pressure to see a return on the massive investment in nanomedicine puts pressure on researchers and manufacturers to push through clinical testing and to bring products to market. While this is not incompatible with due precaution, it does create forces that will require strong ethical resolve to resist.[4]

At the core of this resolve is the commitment to protect patients, both from their illnesses and from adverse effects caused by efforts to treat those illnesses.

Ideas for this article developed in part during discussions at the Biomedical Diagnostics Institute at Dublin City University, which is funded by Science Foundation Ireland.

References

1 Feynman RP. There's plenty of room at the bottom. *J Microelectromechanical Systems.* 1992;1:60-66.
2 Gazit E. *Plenty of Room for Biology at the Bottom: An Introduction to Bionanotechnology.* London: Imperial College Press; 2007.
3 Toumey C. Plenty of room, plenty of history. *Nature Nanotechnology.* 2009;4: 783-784.
4 O'Mathúna DP. *Nanoethics: Big Ethical Issues with Small Technology.* London and New York: Continuum Press; 2009.
5 Freitas Jr RA. Nanotechnology, nanomedicine, and nanosurgery. *Int J Surgery.* 2005;3:243-246.
6 Freitas Jr RA. Pharmacytes: An ideal vehicle for targeted drug delivery. *J Nanosci Nanotechnology.* 2006;6:2769-2775.
7 NNI. Research and Development Leading to a Revolution in Technology and Industry. Supplement to the President's FY 2010 Budget. Washington, DC: Office of Science and Technology Policy; 2009. Available at www.nano.gov/NNI_2010_budget_supplement.pdf. Accessed Dec. 19, 2009.
8 Royal Society and Royal Academy of Engineering. Nanoscience and Nanotechnologies: Opportunities and Uncertainties. 2004. Available at: www.nanotec.org.uk/finalReport.htm. Accessed Dec. 22, 2009.
9 Lynch I, Dawson KA. Protein-nanoparticle interactions. *NanoToday.* 2008;3:40-47.
10 Myllynen P. Damaging DNA from a distance. *Nature Nanotechnology.* 2009;4: 795-796.
11 Lane N, Kalil T. The National Nanotechnology Initiative: Present at the creation. *Issues Sci Technology.* 2005;12:49-54.
12 Bhushan B. *Springer Handbook of Nanotechnology.* 2nd ed. New York: Springer; 2006.
13 Sanhai WR, et al. Seven challenges for nanomedicine. *Nature Nanotechnology.* 2008;3:242-244.
14 Resnik DB, Tinkle SS. Ethics in nanomedicine. *Nanomed.* 2007;2:345-350.
15 NNI. Strategy for Nanotechnology-Related Environmental, Health, and Safety Research, Washington, Office of Science and Technology Policy; 2008. Available at: www.nano.gov/NNI_EHS_Research_Strategy.pdf. Accessed Feb. 14, 2009.
16 NNI. Funding. Available at: www.nano.gov/html/about/funding.html. Accessed Dec. 19, 2009.
17 Hanson D. Nanotech strategy. *Chem Engineer News.* 2008;86:29-30.
18 National Research Council. Review of Federal Strategy for Nanotechnology-Related Environmental, Health, and Safety Research. Washington, DC: National Academy of Sciences Press; 2008.
19 Hart D, Boschung N, Riediker M. Identified Stakeholders and Their Interests in the Field of HSE Impacts of Nanomaterials. 2009. Available at:

www.nanoimpactnet.eu/object_binary/o3039_Stakeholder_Report_4%201_FINAL.pdf. Accessed Dec. 19, 2009.
20 Beveridge & Diamond. Consumers Union requests FDA safety assessment on use of nanoparticles in cosmetics and sunscreens. Accessed Dec. 11, 2008. Available at: www.bdlaw.com/news-436.html. Accessed April 5, 2009.
21 Friends of the Earth. Out of the Laboratory and Onto Our Plates: Nanotechnology in Food & Agriculture. 2008. Available at: www.foe.org/pdf/nano_food.pdf. Accessed Dec. 19, 2009.
22 Erickson BE. Nanoceuticals. *Chem Engineer News.* February 9, 2009. Available at: http://pubs.acs.org/cen/government/87/8706gov3.html. Accessed April 13, 2009.
23 Satterfield T, et al. Anticipating the perceived risk of nanotechnologies. *Nature Nanotechnology.* 2009;4:752-758.
24 le Hir P. Le débat public sur les nanotechnologies risque de tourner court. Le Monde. December 10, 2009. Available at: www.lemonde.fr/planete/article/2009/12/10/le-debat-public-sur-les-nanotechnologies-risque-de-tourner-court_1278722_3244.html#ens_id=1278325. Accessed Dec. 19, 2009.
25 Genaidy A, et al. Health effects of exposure to carbon nanofibers: Systematic review, critical appraisal, meta-analysis, and research to practice perspectives. *Sci Total Env.* 2009;407:3686-3701.
26 Leary SP, Liu CY, Apuzzo ML. Toward the emergence of nanoneurosurgery: part III—Nanomedicine: Targeted nanotherapy, nanosurgery, and progress toward the realization of nanoneurosurgery. *Neurosurgery.* 2006;58:1009-1026.
27 Meridian Institute. Nanotechnology and the Poor: Opportunities and Risks. 2005. Available at: www.meridian-nano.org/gdnp/NanoandPoor.pdf. Accessed April 10, 2009.
28 Hillie T, Hlophe M. Nanotechnology and the challenge of clean water. *Nature Nanotechnology.* 2007;2:663-664.
29 Clark GM. Personal reflections on the multichannel cochlear implant and a view of the future. *J Rehabil Res Development.* 2008;45:651-694.
30 Zemp RJ. Detecting rare cancer cells. *Nature Nanotechnology.* 2009;4:798-799.
31 Ray PC, Yu H, Fu PP. Toxicity and environmental risks of nanomaterials: Challenges and future needs. *J Env Sci Health. Part C. Env Carcinogenesis & Ecotoxicology Rev.* 2009;27:1-35.
32 Lam C-W, et al. A review of carbon nanotube toxicity and assessment of potential occupational and environmental health risks. *Crit Rev Toxicology.* 2006;36:189-217.
33 Allhoff F. Risk, precaution, and emerging technologies. *Studies Ethics Law Technology.* 2009;3:1-27.
34 Hansson SO. Great uncertainty about small things. *Techné.* 2004;826-35.
35 Harremoës P, et al (eds). Late Lessons from Early Warnings: The Precautionary Principle 1896–2000. Copenhagen: European Environment Agency; 2001. Available at: www.genok.org/filarkiv/File/late_response.pdf. Accessed June 18, 2008.
36 Ashford N, et al. Wingspread Statement on the Precautionary Principle. 1998. Available at: www.gdrc.org/u-gov/precaution-3.html. Accessed April 20, 2009.
37 European Group on Ethics in Science and New Technologies to the European Commission. Opinion on the Ethical Aspects in *Nanomedicine.* 2007. Available at: http://ec.europa.eu/european_group_ethics/activities/docs/opinion_21_nano_en.pdf. Accessed Feb. 7, 2007.
38 European Commission. Code of Conduct for Responsible Nanosciences and Nanotechnologies Research. 2008. Available at: ftp://ftp.cordis.europa.eu/pub/fp7/docs/nanocode-recommendation.pdf. Accessed March 9, 2008.
39 Manson NA. Formulating the Precautionary Principle. *Env Ethics.* 2002;24:263-272.
40 Bawarski WE, et al. Emerging nanopharmaceuticals. *Nanomedicine.* 2008;4:273-282.
41 O'Mathúna DP. Phase 1 clinical trials in the aftermath of TGN1412. *Research Practitioner.* 2008;9:74-81.
42 Expert Scientific Group on Phase One Clinical Trials. Final Report. Norwich: The Stationary Office; 2006. Available at: www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_063117. Accessed Feb. 16, 2008.
43 Levine C, et al. "Special scrutiny": A targeted form of research protocol review. *Ann Intern Med.* 2004;140:220-223.
44 Martuzzi M. The precautionary principle: In action for public health. *Occupational Env Med.* 2007;64:569-570.