

# Considerations for Using Genetic Material in Medical Nanotechnology

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## **Introduction**

“Nanotechnology” is a term used by scientists to describe the technologies and processes involving materials, devices and structures that occur on the scale of nanometres (a nanometer is one billionth of a metre), involving atoms or groups of atoms. The smallest nanostructures are more complex than man-made polymers like polyethylene, nylon or Teflon and more complex than natural objects like sugars, proteins and cellular membranes.

The nanotechnology market in 2003 was worth over \$26 billion in sales worldwide, which demonstrates the widespread impact this new technology has had on development of consumer products. Products currently available that have been produced using nanotechnology include chemicals with microscopic catalytic particles, sun block lotions with zinc-oxide particles, paint emulsifiers and plastic resistant coatings to extend the life of industrial tools and eyeglass lenses.<sup>1</sup>

The use of nanotechnology to produce structures and products for medical therapeutics has so far been limited to gold nanoparticles for clinical trial cancer treatment,<sup>2</sup> quantum dots for photo-imaging of living tissue<sup>3</sup> and containers for delivery of drugs or materials to target cancer tumours.<sup>4</sup> However, the market for future therapeutics, molecular nanotechnology products, medical devices and diagnostic tools promises to be substantial. The use of DNA (Deoxyribonucleic acid) derived tools in the fields of molecular and medical nanotechnology promises a plethora of medical

benefits with potential applications for drug delivery, health diagnostics and gene therapy. However, underlying the positive applications of this emerging technology is the potential for unknown hazards. As little has been mentioned of possible problems associated with using genetic material in the nanotechnology field to target drug delivery to specific cells and tissues so far, the technology should be regulated.

## **Just How “Nano” is Genetic Material?**

DNA is composed of two strands that form a very stable double helix (much like a ladder) and acts as the physical carrier of genetic information. DNA is composed of many nucleotides that each consists of a sugar, a phosphate group and one of four bases (adenine, thymine, guanine or cytosine).<sup>5</sup> Molecular biologists have been working on a nanoscale to manipulate genetic material from a variety of organisms (human, animal, insect, plant, bacteria, virus) for over 25 years, with the ability to isolate, cut, move, join, splice together, synthesize and copy DNA.<sup>6</sup> In terms of scale, to better understand nanotechnology, most mammalian cells are between 20,000–30,000 nanometres (nm) in size, with some exceptions like neurons (brain cells, spinal cord) that can reach lengths up to 1 metre. The molecules in our body, including DNA and its component parts vary in size but range between 0.2 – 20 nanometres.<sup>7</sup> Each cell contains 3 billion nucleotide base pairs or 2 metres of DNA packed into the cell nucleus only 6,000 nm.<sup>8</sup>



## ***Use of DNA in Nanotechnology to Create Drug Delivery Structures***

The properties of DNA, including its size, structural stability and its ability to replicate combined with the pre-existing tools derived from molecular biology make it an ideal focus for nanotechnology applications.<sup>9</sup> DNA-dependent nanotechnology exploits the properties of DNA by harnessing it to act as a backbone to arrange ligands, proteins and gold particles<sup>10</sup>, to form DNA-based nanowire<sup>11</sup>, to assemble molecular switches<sup>12</sup> and to provide the basis for molecular-based computing<sup>13</sup> and molecular motors.<sup>14</sup>

While our hereditary material found on DNA is located on chromosomes contained within the nucleus of our cells, the genetic material used in molecular nanotechnology applications will come from a synthetic chemical synthesis using much shorter stretches of single stranded DNA, no longer than about 4 nm. The single DNA strands can be joined together and then can be joined to one another to create longer 'scaffolded' structures including ribbons, grids, lattices, cages, knots and octahedrons.<sup>15</sup> These scaffolded DNA structures have the potential to be used in medical therapy for the delivery of labile, highly reactive or extremely cytotoxic compounds. Encapsulating drugs will protect them from degradation or activity before being released into the cells or tissues being targeted for treatment. The scaffolded DNA can have specific receptors added to its surface, which will recognize cancer cells, attach and release the therapeutic drugs exactly where needed. Thus, the main use will be to hold, deliver and target chemotherapy drugs, or other therapeutic compounds, to specific tissues, cells, organs or cancer cells.

The fate of nanotechnology derived DNA structures used in medical treatment Scaffolded DNA with the potential for drug delivery applications will impact the efficacy of both the drugs and the treatment itself. Both during and after drug delivery the fate of the DNA carrier used to deliver the drug should be examined and understood.

It is known that when short double stranded DNA oligonucleotides are injected that they dissipate widely in

the body, are internalized into cells by endocytosis and easily cross membranes before the majority of it is degraded.<sup>16</sup> Larger scaffolded DNA structures are likely to suffer the same fate of degradation once in the human body. In laboratory animal research it has been shown that DNA injected intravenously into pregnant mice was detected in the fetuses, suggesting that if scaffolded DNA is used in nanotechnology, fragments would likely dissipate and persist internally within the patient.<sup>17</sup> Tens of millions of particles would be introduced for cancer or gene therapy

treatments and the scaffolded DNA carrying the drugs will reach distant cells, cells that are not the subject of the treatment, and will persist. The drugs inside the scaffolded DNA could cause a great deal of harm to those other cells. For example, anti-cancer cytotoxic agents damage cellular DNA, anti-angiogenic drugs inhibit the formation of new blood vessels, growth factor inhibitors prevent cell growth and maturation and cell signal transduction

modulators alter enzyme pathways inhibiting cell growth.<sup>18</sup> These drugs could have far reaching effects, carrying cancer drugs into germline cells, inducing serious genetic damage and even affecting gamete development.

Aside from the effects of the drugs, the safety of the use of the DNA itself should also be considered. The injected, scaffolded DNA structures or DNA nanodevices can be joined to other foreign proteins and antibodies as a way to target them to specific cell surface receptors and tissues. Medical nanodevices based on organic and inorganic components should do no damage to the DNA of the host and should not cause an immune reaction from the formation of small DNA-protein complexes. DNA itself is not highly antigenic (able to cause an immune response) but the large amounts that may be injected for efficacy during treatment may cause a weak immune response and lead to immune reactions in some people.<sup>19</sup> For example, a severe immune reaction and death occurred when 18-year-old Jesse Gelsinger was treated in a gene therapy attempt with 38 million double stranded DNA adenovirus particles (Adenovirus is about 90 nanometres and slightly larger in size compared to scaffolded DNA structures that will be used in nanotechnology).<sup>20</sup>

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## Regulation of Molecular Nanotechnology

Science explores the unknown and it is therefore difficult to predict the outcomes of innovative research before any actual discoveries are made. However, it is possible to see from currently known lines of nanotechnology research using DNA that some potential problems may arise and require special attention by both scientists and regulators. Nanoscale DNA constructs would have the ability to be absorbed into tissues directly through the skin by contact and as such, considerations for handling, allergenicity and toxicity should be addressed by specifically regulating the technology.<sup>21</sup>

In the United States the National Institutes of Health (NIH) Guidelines on Recombinant DNA technology is an example of self-regulation taken by the biotechnology research community over two decades ago.<sup>22</sup> In 1973, the first restriction enzyme capable of cutting DNA was discovered and it was realized that the techniques of manipulating genetic material had evolved to the point where any two pieces could be put together. Recognizing that the public would fear the creation of new, potentially dangerous chimeras (creation of designer bacteria, animals or viruses), scientists urged proposed rules for its use.<sup>23</sup> Initial broad guidelines were developed by 1976 to provide a system of guiding principles for molecular biology and other derivative technologies that could not have been predicted *a priori*. The NIH Guidelines illustrate that a pre-emptive, voluntary framework can be effective. Although the NIH Guidelines have been relaxed since they were first released with several amendments, they did achieve their intended effect by providing researchers with a set of guidelines and practices for constructing and handling recombinant DNA, as well as micro-organisms and viruses that contained recombinant DNA molecules.<sup>24</sup>

Even though the artificial molecular nanodevices of the future will be very different from the current basic research that is occurring today, similar initial scientific and ethical policy guidelines, such as those that were laid out for biotechnology, have proven to be effective, and should there-

fore be adopted. Commercialization of active medical nanotechnology products by both private and public sector researchers will be widely accepted if considered to be safe to humans, animals and ecosystems. Voluntary, self-regulation was used by the biotechnology community developing and adhering to the NIH Guidelines due to the far-reaching transformative ability of the research. While the voluntary regulations were not binding for private sector ventures, public sector peer review was deemed essential for public trust; similarly, nanotechnology has the same transformative ability and would benefit from voluntary regulations that would provide a sense of collective responsibility for this emerging technology.

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## Conclusions

While we are a long way from realizing such therapeutic benefits in nanotechnology described herein, there are currently several main research

areas using DNA. Initial nanotechnology research using DNA and molecules borrowed from nature are rapidly developing new areas including the construction of nanotransistors,<sup>25</sup> nanowires,<sup>26</sup> simple devices (DNA tweezers),<sup>27</sup> DNA motors<sup>28</sup> and microcomputing<sup>29</sup> with very promising initial results.

There is much interest in using scaffolded DNA to be used in medical and non-medical nanotechnology applications. If we extrapolate the use of genetic material in nanotechnology into the future it is likely that the majority of applications derived originally from DNA based molecular nanotechnology will have utility in many applications as well as use in medical treatments. In the future we can be certain that DNA based nanodevices that have utility, and are novel and non-obvious will be patented for commercial gain and their development will be proprietary. The pace of research into creating more complex devices will continue rapidly. Co-operation by both private and public researchers in the area of active medical nanotechnology devices is therefore required to provide a framework of guiding principles.

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