Nanotechnology: Part 2

Tiny Technology—Tremendous Therapeutic Potential

BY BALAJI PANCHAPAKESAN, PHD

IN BRIEF

In the laboratory setting, "nano-oncology" offers much promise for cancer treatment. For example, nanovectors could potentially improve both the delivery of anticancer drugs and the localized killing of cancerous and precancerous cells. Before nano-tools can be applied at the bedside, however, numerous challenges must be addressed, including toxicity issues. In addition, clinical protocols must be established on how to effectively handle and deliver these nano-tools. The quickest way to bring this technology to community cancer centers may be for nanotechnology researchers to actively collaborate and come together to develop a single nanotechnology platform.

Despite outstanding progress in the area of cancer biology, significant challenges remain in administering highly selective, targeted anticancer therapy. Case in point: only between 1 and 10 parts per 100,000 intravenously administered monoclonal antibodies reach their parenchymal [i.e., the functional tissue of an organ] targets *in vivo*.[1,2] Yet nanotechnology holds tremendous promise for this and various other cancer treatment modalities. Specifically, nanotechnology holds great potential for the delivery of precisely targeted medical procedures that will minimize collateral tissue damage—to a far greater degree than current cancer therapies.

As nanotechnology techniques are being applied to oncology, engineering principles are increasingly being used to solve medical problems. This fusion of disciplines has given rise to the new field of "nano-oncology" for cancer treatment. All of the various nanotechnology techniques can be customized for killing different types of cancer. Nanovectors (in development today) have the potential to be a generic platform for different types of cancer treatments.

What exactly *is* a nanovector? Nanovectors are multifunctional organic and inorganic nanoparticles, nanowires, and nanotubes. Nanovectors offer the promise of:

- Targeted delivery of anticancer drugs
- Combined targeted drug delivery with targeted localized killing of cancerous and precancerous cells through thermal ablation
- Nanosurgical tools that may one day be integrated with micro- and macro-surgical tools for surgical treatment of cancer.

Nanovectors for Drug Delivery

Nanovectors designed for drug delivery have a surface modified with biological materials, such as antibodies, that can be used to target a specific receptor in cancer cells. This technology has the potential to deliver a multiphase attack against cancer cells. For example, nanovectors that are heated in a localized way *in vivo* can be used to kill cancer cells in parts of the body that may be inaccessible using traditional surgical techniques. Hollow nanovectors can be filled with anticancer agents that "deploy" when they reach their target cancer cells. Once its anticancer drug payload has been delivered, a nanovector can be destroyed using external energy sources such as optics or magnetics.

Figure 1 and 2 show how multi-functional nanovectors can be used for targeted killing of cancer cells. Two types of attack are presented. Figure 1 consists of therapeutic agents loaded into a hollow nanoparticle with biological surface modifiers. Figure 2 consists of nanotubes that are functionalized with cancer specific protein so that they will bind to specific cancer cells. These nanotubes are heated using external energy sources, killing cancer cells in a localized way.

Nanovectors designed for drug delivery may be injected directly into cancer sites or into the blood to travel to their target cancer cells. For injectable nanovectors to be highly effective, they should be selectively directed against cell clusters and should have the ability to kill both malignant cancer cells and cells that are in the early stages of transformation—all without affecting the patients' quality of life.

Therapeutic formulations of nanovectors should also include proteins that can overcome biological barri-

ers that might prevent the nanovectors from reaching to their target.

While these descriptions may sound like the stuff of science fiction, nanovector technology is currently being aggressively pursued in the laboratory setting. To date, many types of nanovectors have been proposed.

Liposomes are one of the most widely used nanovectors for different types of drug delivery modalities in the fight against cancer.[3] These include liposomes that use overexpressions of fenestrations in cancer neovasculature to increase drug concentration at tumor sites.[4]

Nanoparticles are a class of artificially engineered materials in use today as nanovectors. Their miniscule dimensions imbue nanoparticles with unique physical proper-

Figure 1. Multifunctional Nano-Drug Delivery Vehicle for Killing Cancer Cells

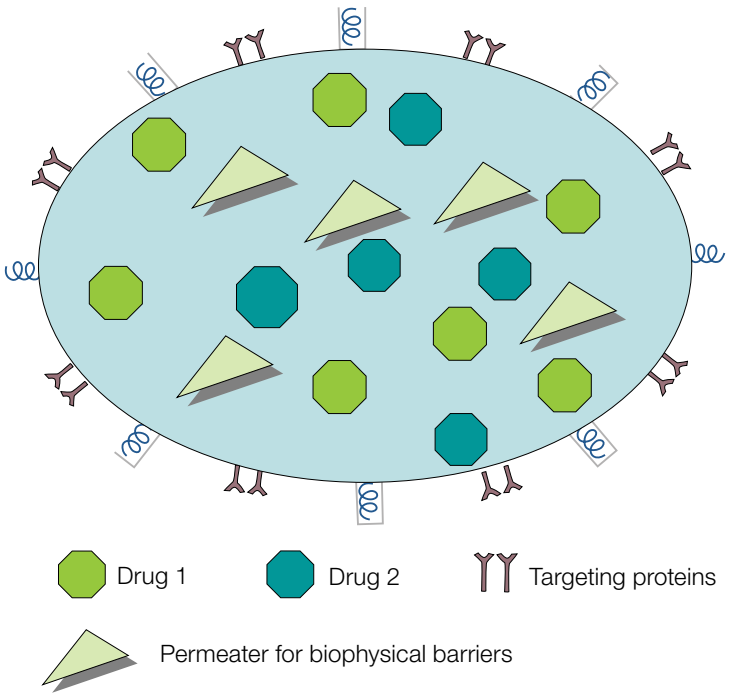
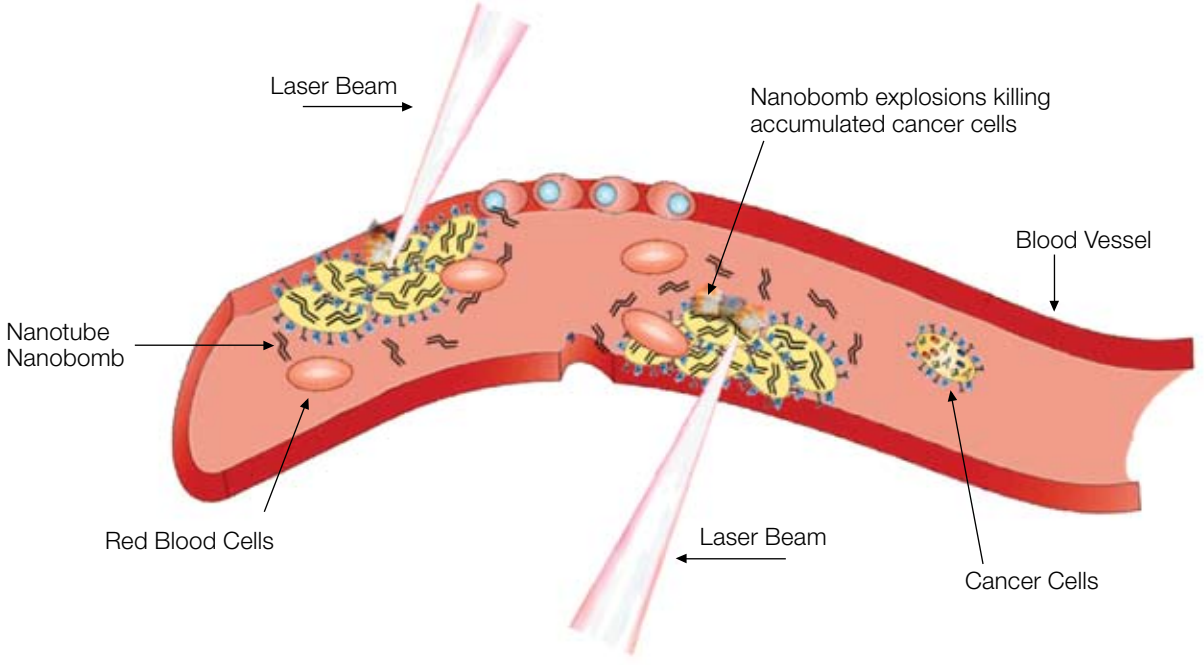


Figure 2. A Multi-Component Cell Killing Strategy Using Nanoparticles and Nanotubes and Employing Laser Irradiation on a Cancer Cell Cluster



ARTWORK COURTESY OF DR. PANCHAPAKESAN, UNIVERSITY OF DELAWARE

Nanoparticle Applications

Polyethylene glycol-coated gadolinium-based iron oxide nanoparticles have been used to target cancer cells and detect apoptosis using magnetic resonance imaging techniques.[5,6] Magnetic fields are also induced to heat the iron oxide nanoparticles to kill the cancer cells.[7] This can be accomplished—with little modification—using the same MRI equipment already in place in many hospitals.

Silicon- and silica-based nano- and micro-particles have been used as a class of injectable nano-vectors.[8,9] Porous silicon is biodegradable, and therapeutic agents that are encapsulated inside the nanoparticles can release drugs in a matter of minutes to kill cancer cells.

Nanoshells (metal-based nanoparticles) have been used to kill venereal tumors in mice.[10] These nanoshells consist of a silica core with a top layer of gold. By changing the thickness of the gold layer, it is possible to change the optical absorption properties of the nanoshells. When radiated with near-infrared light, the nanoshells heat up to 55° to 70° C, and are able to kill cancer cells thermally.

Fullerene-based derivatives have been recently proposed in pharmaceutical formulations as anti-HIV, as well as anti-cancer agents, and are used in clinical practice today.[11] Both empty and metallo-fullerenes have low cyto-toxicity *in vitro* and *in vivo* and can be effectively used for drug design and delivery. The cage-like structure of fullerene is ideal for packing with anti-cancer drugs or even radiological materials to increase treatment efficacy for killing cancer cells.

Carbon nanotubes are a close cousin of fullerenes, which have recently been shown to kill cancer cells. How? First, the surface of the nanotube is modified with proteins for cellular uptake. Then the nanotubes are heated with near-infrared light to kill cancer cells.[12] Due to their heat confinement, nanotubes have also been used as nano-bombs to destroy cancer cells *in vitro*.[13] Nano-bombs may offer a highly effective method of killing cancer cells that are malignant as the temperatures attained in a localized way are much higher compared with other nanovectors used in thermal ablation of cancer cells. Further, the complete destruction of nanotubes inside the body may make them ideal for handling toxicity problems that may be associated with nanotubes and nanoparticles. Nano-bombs offer the further potential of killing cancer cells over a wide area that may serve the biological cell signaling pathways thus promoting cancer remission.

ties that offer enticing possibilities for cancer therapeutics (see box on this page).

To date, only liposomes and fullerene-based derivatives have been translated into the clinic. Most other nanovectors are still being used in the laboratory, and it may take another five to ten years before these can be translated from the lab to clinical advances.

Small Particles Equal Small Pain

While nanovectors for killing cancer are being developed in the laboratory, some existing nanovectors have the potential to integrate with current cancer-fighting techniques, such as the use of an endoscope for cancer treatment. For example, it may be possible to integrate nanotechnology approaches, such as nano-bombs, as probes with existing laproscopic techniques. This surgical tool could be used to kill small lesions without blood loss and post-operative pain. Because patients who undergo such procedures should experience minimum collateral damage, this combined technique may also lead to faster recovery times for patients.

Even if such nanovectors do not kill all the cancer cells simultaneously, once approved, these procedures could be applied at regular intervals without compromising the patient's quality of life. In other words, these nanotools hold potential for treatments with a much-reduced impact on patients' quality of life. In the future, nano-surgical tools that integrate micro- and macro-surgical tools may become a reality for use in the surgical treatment of cancer.

Looking far into the future, with advances in 3-D imaging, nanovectors, and nano-surgery, it's possible to envision a day when cancer treatment may be a matter of going into the clinic for a small procedure that integrates all of these above-mentioned techniques for the imaging and killing of cancer without the side effects patients with cancer experience from current cancer therapeutic modalities.

Nanomedicine: Roadblocks Ahead

While rapid advances are being made, significant roadblocks must be surmounted before nanovectors can be applied in a clinical setting.

For example, most of the nanovectors used in high-contrast imaging (such as quantum dots) are toxic and cannot be applied to the body. Injectable nanovectors (such as nanoparticles and nanoshells) while not necessarily toxic,

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still pose a tremendous risk if left in the body. Over long periods of time, nanoparticles may aggregate, potentially blocking arteries and veins or even blocking the kidneys, and thereby creating a host of new problems. For any nanovector to be successful in clinical application, it must be either completely destroyed or biodegradable *in vivo*.

Secondly, nanovectors might also trigger sensitization reactions. For example, antibodies specific to fullerenes have been described; dendrimers and protein-dendrimer conjugates have shown strong immunogenic response in these studies.[14] Therefore, counter measures to suppress such reactions for killing cancer cells must be devised.

Numerous biophysical barriers, such as increased osmotic pressures in malignant cancer tissues, present additional obstacles.[15] Due to these increased pressures within the cells, diffusion of therapeutic agents and nanovectors may become problematic. Hence, new solutions are necessary for overcoming these biophysical barriers. One creative approach may be the use of multiple agents and multiple approaches within a single nanovector. For example, one can envision using both chemo-drugs, as well as radiological drugs encapsulated within nanoparticles. Release of both of these different types of cancer-fighting drugs to kill cancer cells may be highly successful in overcoming the biophysical barriers. In short, hundreds of nanovectors have been proposed in the literature; however, some of these techniques will have to be combined in a single nanovector to improve targeting efficacy, overcome biological barriers, and also kill cancer cells.

Finally, toxicity problems associated with nanovectors have to be researched, and currently there is a lack of sufficient data in this field. The safety of patients and clinicians who handle nanovectors in the future are of primary concern. Clinical protocols must be established on how to handle nanovectors and how to deliver them effectively. Considering the length of time associated with obtaining FDA approval for each nanovector, it may take a few years before the nanovectors can be translated to the clinic setting. One way of eliminating such long waiting times is for scientists who develop different nanovectors to actively collaborate and come together to integrate all these different principles into one potent and powerful platform. Such collaboration will also ensure faster translation into the clinic.

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Acknowledgments

The author wishes to acknowledge the many useful discussions during the preparation of this manuscript with Dr. Eric Wickstrom of the Thomas Jefferson University in Philadelphia, Pa., and Dr. Nicholas Petrelli and Dr. Thomas Bauer of the Helen F. Graham Cancer Center, Christiana Care Health System in Newark, Del.

The author also wishes to acknowledge the help of Lee Stein, Joachim Spencer, and Sonam Gupta with the artwork illustrating this article. The artwork for Figure 2 was inspired by "Cancer nanotechnology: opportunities and challenges." in the *Nat Rev Cancer*. 2005;2:750-763 (see reference 2 below).

References

[1] Li KC, Pandit SD, Guccione S, et al. Molecular imaging applications in nanomedicine. *Biomed Microdevices.* 2004;6:113-116.
[2] Ferrari M. Cancer nanotechnology: opportunities and challenges. *Nat Rev Cancer.* 2005;5:161-171.
[3] Park JW. Liposome-based drug delivery in breast cancer treatment. *Breast Cancer Res*. 2002;4:95-99.
[4] Allen, TM. Ligand-targeted therapeutics in anti-cancer therapy. *Nature Rev Cancer.* 2002;2:750-763.
[5] Oyewumi MO, Yokel A, Jay M, et al. Comparison of cell uptake, biodistribution,and tumor retention of folate-coated and PEG-coated gadolinium nanoparticles in tumor-bearing mice. *J Control Rel.* 2004;24:613-626.
[6] Schellenberger EA, Bogdanov A Jr, Hogemann D, et al. Annexin V-CLIO: a nanoparticle for detecting apoptosis by MRI. *Mol Imaging*. 2002;1:102-107.
[7] Bergey EJ, Levy L, Wang X, et al. DC magnetic field induced magnetocytolysis of cancer cells targeted by LH-RH magnetic nanoparticles in vitro. *Biomed Microdevices*. 2002;4:293-299.
[8] Cohen MH, Melnik K, Boiarski A, et al. Microfabrication of silicon-based nanoporous particulates for medical applications. *Biomed Microdevices.* 2003;5:253-259.
[9] Yan F, Kopelman R. The embedding of meta-tetra (hydroxyphenyl)-chlorin into silica nanoparticle platforms for photodynamic therapy and their singlet oxygen production and pH-dependent optical properties. *Photochem Photobiol.* 2003;78:587-591.
[10] Hirsch LR, Stafford RJ, Bankson JA, et al. Nanoshell-mediated near-infrared thermal therapy of tumors under magnetic resonance guidance. *Proc Natl Acad Sci U S A*. 2003;100:13549-13554.
[11] Cagle DW, Kennel SJ, Mirzadeh S, et al. In vivo studies of fullerene-based materials using endohedral metallofullerene radiotracers. *Proc Natl Acad Sci U S A.* 1998;96:5182-5187.
[12] Shi Kam NW, O'connell M, Wisdom, JA, et al. Carbon nanotubes as multifunctional biological transporters and near-infrared agents for selective cancer cell destruction. *Proc Natl Acad Sci U S A.* 2005;102:11600-11605.
[13] Panchapakesan B, Lu S, Sivakumar K, et al. Single wall carbon nanotube nanobomb agents for killing breast cancer cells. *Nanobiotechnology.*2005; vol. in press.
[14] Lee SC, Parthasarathy R, Botwin K, et al. Biochemical and immunological properties of cytokines conjugated to dendritic polymers. *Biomed Microdevices.* 2004;6:191-202.
[15] Sarntinoranont M, Rooney F, Ferrari M. Interstitial stress and fluid pressure within a growing tumor. *Ann Biomed Eng.* 2003; 31:327-335.