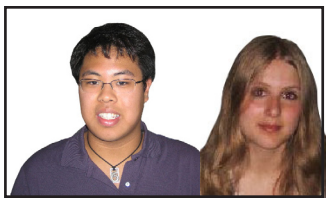
Cancer and Nanotechnology



Michael Chan & Stephanie Dreckmann

NANOTECHNOLOGY IS A RAPIDLY GROWING FIELD IN BIOMEDICAL RESEARCH WITH PROMISING IMPLICATIONS IN THE DEVELOPMENT OF NOVEL METHODS TO TARGET CANCEROUS CELLS. WITH A DIVERSE REPERTOIRE OF POTENTIAL FUNCTIONS – FROM PROPHYLACTIC IMAGING TO DRUG DELIVERY – SUCH NANO-SIZED AGENTS ARE CURRENTLY THE SUBJECT OF MUCH INVESTIGATION. THE FOLLOWING ARTICLE EXPLORES THE PROPERTIES OF VARIOUS NANOVECTOR DEVICES, THE MECHANISMS THROUGH WHICH THEY ELICIT THEIR EFFECTS, AS WELL AS RECENT FINDINGS FROM BOTH IN VITRO AND IN VIVO STUDIES.

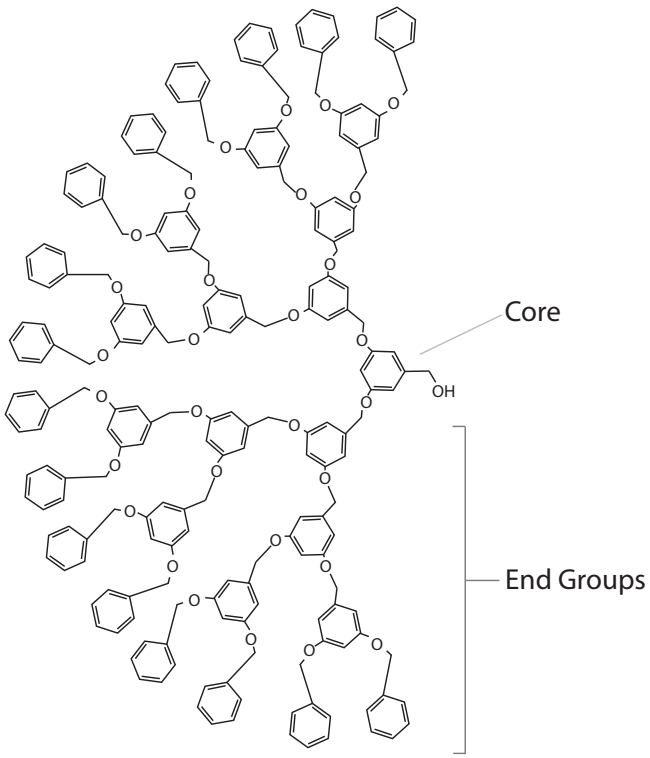


Figure 1 Generation 4 poly(benzyl) ether dendrimer consisting of OH core and end groups (Hawker, 1990).

The past few decades have seen great progress in basic cancer biology research; however, this progress has failed to translate into comparable advancements in clinical applications. One challenge accounting for this discrepancy involves the difficulty to develop agents that can evade biological barriers, and selectively target malignant cells with minimal side effects (Duncan, 1998; Ferrari, 2005). The emerging field of nanotechnology is a promising solution to this challenge. Nanotechnology is a multidisciplinary field involving the use of exceptionally small devices – at the scale of 1-100 nm – for selective delivery of drugs and imaging agents to cancer cells. This paper will discuss several of these nanotechnology platforms including nanovectors and nanoshells.

Nanovectors

Nanovectors are multifunctional devices usually comprising three components: (1) a core material, (2) a therapeutic or imaging agent, and (3) biological surface modifiers with or without a targeting group. The core material, which is usually made of biodegradable polymers, may carry one or more therapeutic agents. Biological surface modifiers are designed to increase the half-life of drugs in the body, protect drugs against enzymatic degradation, as well as avoid other obstacles. For example, polyethylene glycol (PEG) is a biological surface modifier that has been shown to prevent uptake of nanovectors by macrophages or other cells of the reticulo-endothelial system. In addition, nanovectors are designed to selectively deliver therapeutic

agents to cancer cells. This can be achieved by attaching ligands or antibodies to the surface of nanovectors that recognize certain epitopes on the diseased tissue or organ. This process is termed targeted delivery-active transport. Nanovectors can also be delivered passively through enhanced permeation and retention effect (EPR) due to their long circulation half-life (Matsumura, 1986; Ferrari, 2005). The EPR mechanism takes advantage of the increased fenestrations in vasculature that allows for the extravasation and accumulation of nanovectors in tumours (Ferrari, 2005; O'Neal, 2004). Another targeting method involves externally activating nanovectors in certain parts of the body to prohibit systemic cytotoxicity (O'Neal, 2004; Yan, 2003).

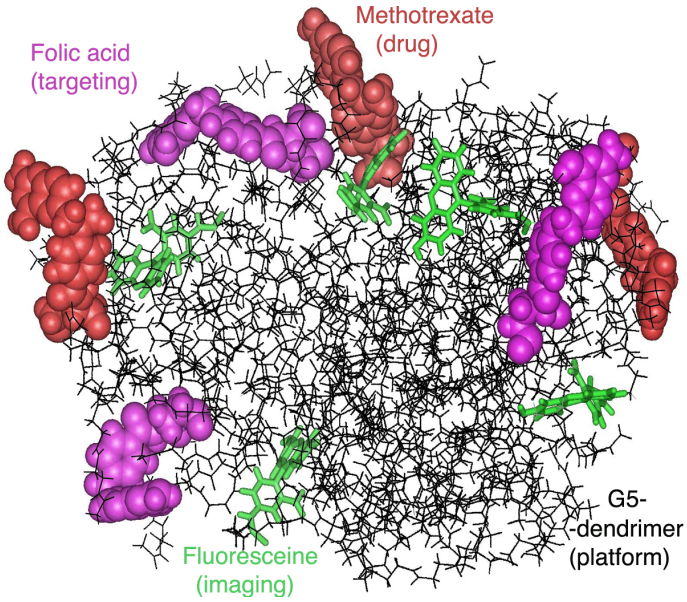
Dendrimers

A novel approach to cancer therapy involves the use of dendrimers as nanovectors (Hawker, 1990). These are repeatedly branched symmetrical molecules, consisting of a polyfunctional core bound to multiple end groups (Figure 1) (Hawker, 1990). A large number of dendrimers with different properties can be synthesized due to variations in their size, shape, and reactivity (Tomalia, 1995). One such property is the ability to target, detect, and destroy cancer cells (Majoros, 2006). Studies conducted at the Michigan Nanotechnology Institute showed that dendrimers could effectively detect and eliminate cancerous cells when linked to therapeutic, fluorescent, targeting, and contrast agents (Figure 2) (Majoros, 2006).

Cancer Cell Detection and Internalization

As previously described, there are several ways to target cancer cells. One method involves conjugating cancer-specific receptor ligands to drug-carrying dendrimers. For example, the unregulated proliferation of cancer cells increases the cell's requirement for folate, a water-soluble vitamin. Consequently, folate receptors are upregulated in different carcinomas, including cancers of the ovary, kidney, uterus, testes, brain, colon, blood, and lung. By conjugating folic acid to a drug-carrying dendrimer, these cancers are preferentially targeted. The dendrimer internalizes into lysosomes through folic acid receptors and releases chemotherapeutic drug into the cell, resulting in cell death (Majoros, 2006). Another example involves the overexpression of human epidermal growth factor receptor 2 (HER2) in many breast carcinomas. By coupling a dendrimer to herceptin (a HER2 ligand), these cancers can also be eradicated (Shukla, 2006).

Figure 2 Generation 5 dendrimer linked to a cancer drug (methotrexate), a targeting agent, and an imaging agent. Another optional attachment not pictured above includes a high density contrast agent, such as gold, which would be useful for MRI detection (Kukowska-Latallo, 2005).



Studies to Date

Successful dendrimer testing has occurred both *in vitro* and *in vivo* (Majoros, 2006; Navarro, 2008). The dendrimer was conjugated to folic acid, and the final product has successfully killed cancer cells (Majoros, 2006).

In another study by O'Neal et al. (2004), nanoshells that are composed of a silica core and a thin metallic gold shell were shown to be effective against subcutaneously implanted tumours in mice. These nanoshells were designed to become activated at near infrared (NIR) wavelengths, an optimal wavelength for light to penetrate into deeper tissues (Weissleder, 2001). Nanoshells were systemically introduced and externally activated by a laser.The resulting increase in temperature caused irreversible damage to surrounding cancer cells. Results indicated that there was a selective accumulation of nanoshells in tumours, as opposed to in healthy tissue, which could be attributed to the EPR effect. In addition, nanoshell-treated mice exhibited complete destruction of the tumour within ten days of beginning treatment, while all control group animals exhibited uncontrolled tumour growth and had to be euthanized according to study protocols.

The Future

The use of nanotechnology in cancer research is an exciting field that is receiving increasing international recognition. Through careful design of nano-devices, scientists will be able to use various combinations of therapeutic agents that specifically target cancer cells, avoid biological barriers, and eliminate tumours without damaging healthy cells. In addition, these devices may also be used for early detection of cancer cells even before they develop into the disease. Nevertheless, there could be some safety issues associated with the use of these devices. Are they compatible with humans? How reliable are the production protocols of these agents? Due to their nature, nanoparticles will fall under several categories such as drugs, medical devices, and biological agents. Thus, the time required for regulatory approval may be lengthy. Despite all of these challenges, it is clear that the future holds countless possibilities for nanotechnology research.

References

Duncan, R. (2003). The dawning era of polymer therapeutics. Nature Review Drug Discovery, 2, 347-360.

Ferrari, M. (2005).Cancer nanotechnology: opportunities and challenges. Nature Reviews 5, 161-171.

"Golden slingshot: The next generation of cancer treatments may be delivered by nanoparticles."The Economist 6 Nov 2008 25 Nov 2008 <http://www.economist.com/science/displaystory.cfm?story_id=12551598>.

Hawker, C.J., Fréchet, J.M.J. (1990). Preparation of polymers with controlled molecular architecture. A new convergent approach to dendritic macromolecules. Journal of the American Chemical Society, 112, 7638-7647.

Kukowska-Latallo, J., Candido, K.A., Cao, Z., Nigavekar, S.S., Majoros, I.J., Thomas, T.P., Balogh, L.P., Khan, M.K., Baker, J.R. (2005). Nanoparticle targeting of anticancer drug improves therapeutic response in animal model of human epithelial cancer. Cancer Research, 65(12), 5316-5324.

Majoros, I.J., Myc, A., Thomas, T. Mehta, C.B., Baker, J. (2006). PAMAM dendrimer-based multifunctional conjugate for cancer therapy: synthesis, characterization, and functionality. Biomacromolecules, 7(2), 572-579.

Matsumura, Y. & Maeda H. (1986). A new concept for macromolecular therapies in cancer chemotherapy: mechanisms of tumortropic accumulation of proteins and the antitumor agents SMANCS. Cancer Res. 6, 6397–6392.

Navarro, G., Tros de ILarduya, C. (2009). Activated and non-activated PAMAM dendrimers for gene delivery in vitro and in vivo. Nanomedicine, 10: 1016.

O'Neal, D.P., Hirsh L.R., Halas N.J., Payne, J.D. & West, J.L. (2004). Photothermal tumor ablation in mice using near infrared-absorbing nanoparticles . Cancer Letters. 209(2), 171-176.

Shi, X., Wang, S., et al. (2007). Dendrimer-entrapped gold nanoparticles as a platform for cancer-cell targeting and imaging. Small, 3: 1245-1252.

Shukla, R., Thomas, T.P., Peters, J.L., Desai, A.M., Kukowska-Latallo, J., Patri, A.K., Kotlyar, A., Baker, J.R. (2006). HER2 specific tumor targeting with dendrimer conjugated anti-HER2 mAb. Bioconjugate Chemistry, 17(5), 1109-1115.

Tomalia, D.A. (1995). Dendrimer molecules. Scientific American, 272(5), 62-66.

Weissleder, A. (2001). Clearer vision for in vivo imaging. Nat. Biotechnol. 19, 316–317.

Yan, F. & Kopelman, R. (2003). 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. 78, 587–591.