Expert Review of Anticancer Therapy

ISSN: 1473-7140 (Print) 1744-8328 (Online) Journal homepage: informahealthcare.com/journals/iery20

Impact of nanotechnology in breast cancer

Asif I Haq, Catherine Zabkiewicz, Philippe Grange & Manit Arya

To cite this article: Asif I Haq, Catherine Zabkiewicz, Philippe Grange & Manit Arya (2009) Impact of nanotechnology in breast cancer, Expert Review of Anticancer Therapy, 9:8, 1021-1024, DOI: 10.1586/era.09.72

To link to this article: https://doi.org/10.1586/era.09.72

Impact of nanotechnology in breast cancer

Expert Rev. Anticancer Ther. 9(8), 1021–1024 (2009)

Asif I Haq
Consultant in Minimally Invasive Surgery, Kings College Hospital, London, UK
Tel.: +44 208 502 1762
Fax: +44 208 502 1762
asifhaq7@gmail.com

Catherine Zabkiewicz
FY2 in Surgery, Kings College Hospital, London, UK
Tel.: +44 208 502 1762
Fax: +44 208 502 1762
catzab@doctors.org.uk

Philippe Grange
Consultant in Minimally Invasive Surgery, Kings College Hospital, London, UK
Tel.: +44 208 502 1762
Fax: +44 208 502 1762
philippe.grange@kch.nhs.uk

Manit Arya
Author for correspondence
CCT Honorary Fellow in Minimally Invasive Surgery, King's College Hospital, London, UK
Tel.: +44 208 502 1762
Fax: +44 208 502 1762
manit_arya@hotmail.com

"Between 2006 and 2010 it is estimated that funding of nanotechnology research in Europe will reach over €3 billion, the largest proportion of which is centered on health research."

Breast cancer is currently the most commonly diagnosed cancer in the UK. There are approximately 45,000 new cases each year, with one in nine women developing breast cancer at some point in their life [101,102]. Additionally, it is the second most common cause of cancer death in women, after lung cancer, with nearly 13,000 deaths each year [103]. Mortality has fortunately decreased, with 80% of patients surviving 5 years.

The incidence of breast cancer, however, continues to increase, even with the extra detection rate from screening taken into account [1]. Breast cancer detection involves self and clinical examination and radiography (including ultrasound, mammography and MRI) followed by invasive biopsy for the histological confirmation of invasive disease.

"...nanomaterials allow unique interaction with biological systems at the molecular level..."

The majority of newly diagnosed cases are at early or locally advanced stages, which can be treated with breast-conserving surgery or mastectomy with or without axillary sentinel node biopsy or clearance. This is in conjunction with chemotherapy, radiotherapy, endocrine or biological therapies depending on tissue receptor status, lymph node-positive disease or higher risk of recurrence [1]. A significant number of women who have been previously treated with curative intent subsequently develop either a local recurrence or metastases and many become resistant to endocrine, biological and chemotherapies [104].

Over many years oncology has suffered limitations in imaging modalities that are static and not sensitive to earlier, more treatable stages of disease, and from radiotherapy or chemotherapeutic agents that are not targeted sufficiently, cause systemic effects and have poor penetration at the intended treatment site.

Between 2006 and 2010 it is estimated that that funding of nanotechnology research in Europe will reach over €3 billion, the largest proportion of which is centered on health research [105]. Japan and the USA are channeling even larger funds into nanotechnology, as it offers exciting leaps forward in diagnostics and therapeutics, which tackle the current limitations in oncology. Those battling breast cancer have been some of the first to benefit from these advances, as nanotechnology progresses from the laboratory to the bedside.

What is nanotechnology?

Nanotechnology refers to the scientific field that deals with the creation, manipulation and utilization of engineered man-made functional particles in nanoscale dimension (1–1000 nm range in at least one dimension), and applies them at atomic or molecular levels [1–4].

Hence, nanomaterials allow unique interaction with biological systems at the molecular level, which has led to the development of 'nano-oncology' applications in tumor biomarker detection and profiling, diagnostic imaging of tumors *in vivo* and delivering better targeted therapies [1–4].

Laboratory diagnostics

In breast cancers, the level of estrogen receptor expression correlates directly with

 10.1586/ERA.09.72 ISSN 1473-7140

the benefit of endocrine treatments, and the presence of HER2 (ERBB2) protein overexpression or gene amplification determines benefit from the monoclonal antibody, trastuzumab [1,2]. Immunohistochemistry used for their detection on tumor specimens is limited by difficulty in quantitative analysis due to background 'noise', signal degradation and inability to detect different proteins simultaneously on the same specimen.

Quantum dots are semiconductor strongly fluorescent nanoparticles that can be tuned to fluoresce under a light source of specific wavelength, between 450 and 850 nm (from UV to near infrared) [2–4]. The unique fluorescent emission peaks of different quantum dots can be easily detected and quantified with spectrometry [2–5].

Thus, different quantum dots can be conjugated to different antibodies, each targeted to specific proteins. The spectra of multiple quantum dots targeted to different tissue proteins can then be simultaneously detected and quantified on one sample. They also have enhanced photostability, allowing the emission of fluorescent light over a length of time without a brisk decrease in emission, and the strength of their fluorescence means that low-level proteins can also be detected, thus increasing diagnostic sensitivity [2–6].

Yezhelyev and colleagues have developed an assay, using bioconjugated quantum dots, that allows simultaneous quantitative detection of estrogen receptor, progesterone receptor and HER2 (ERBB2) in paraffin-embedded cultured breast cancer cell lines and paraffin-embedded human breast cancer clinical tissue sections [2,6,7]. Quantitative expression of the breast cancer biomarkers correlated with conventional immunohistochemical analysis and semi-quantitative western blotting [2,6,7].

Quantum dots have also been used to improve detection of receptor gene expression, which may improve FISH [5,6]. DNA probes for HER2 labeled with quantum dots were incubated with breast cancer cells and detected HER2 even at low levels of expression, providing greater sensitivity than standard FISH [6,8].

Although quantum dot profiling of breast tumors has clear potential for providing enhanced sensitivity and specificity, the conjugation of antibody to nanoparticle in a 1:1 ratio is still in development, and the equipment used for spectroscopy detection is currently expensive, thus limiting its widespread use [2,6].

Imaging

Detection of sentinel lymph nodes is routine for staging breast cancers intraoperatively, as it allows selective axillary clearance, thus reducing postoperative morbidity. Currently, this involves the use of blue dye and injection of radioisotope.

The nanodimensions of quantum dots means they don't flow past the sentinel lymph node [9]. Their use has been demonstrated by injection of near-infrared quantum dots into the skin of a breast tumor-bearing animal, where lymphatic flow was followed to the sentinel lymph node and its location easily identified [2,9]. High-intensity fluorescence, specific high-density tissue accumulation and decreased degradation means less background 'noise' and the ability to image brightly over longer time periods under one simple near infrared light source. Their addition to *in vivo* imaging could simplify and improve precision and safety in sentinel node biopsy.

Quantum dots conjugated to HER2 antibodies have recently been tracked *in vivo* after injection into live, breast tumor-bearing mice. Data were collected on the dynamics of these targeted nanoparticles as they passed through blood vessels into tumor tissue [10]. However, use for human *in vivo* imaging has so far been limited by the toxic effects of the quantum dots' heavy metal core [2,4,5], and research continues to refine their structure so that translation to human studies may begin.

> "...the (nano-)liposome ... takes advantage of the fenestrated tumor neovasculature, leading to enhanced extravasation and extended lodging of the liposome ... within the tumor tissue."

Supermagnetic nanoparticles (such as ultrasmall superparamagnetic iron oxide [USPIO] nanoparticles) are of particular use to enhance MRI as they themselves generate a magnetic field, which affects the surrounding tissue, giving significant signal amplification to the area on the scan [4,5,11,12]. They have been used in breast cancer rat models to highlight the leaky microvasculature of breast carcinomas (using the MRI data), which can correlate with tumor grade and differentiate them from benign breast lesions [13]. Additionally, luteinizing hormone-releasing hormone (LHRH) conjugated USPIOs have been shown to enhance MRI and microscopy of LHRH receptor-expressing breast cancers (and their lung metastases) in mouse models [12]. These supermagnetic nanoparticles have also been conjugated with antibodies against HER2, which potentially enables simultaneous imaging and therapy of breast cancer [2,11,14].

As with quantum dots, further research into how these contrast agents may behave at a cellular level in humans is needed prior to their clinical use.

Drug delivery

First-line chemotherapy for metastatic breast cancer consists of an anthracycline in conjunction with one or two other agents. Traditional systemic anthracycline preparations can have poor target tissue penetration and significant cardiotoxic side effects requiring regular monitoring of cardiac function [1,13]. Nanoparticle anthracycline preparations have been developed to address these issues and are now licenced for use in the USA and Europe [1,2].

One of the simplest forms of nanoparticle is the (nano-) liposome, which, due to its size, takes advantage of the fenestrated tumor neovasculature, leading to enhanced extravasation and extended lodging of the liposome (and the therapeutic agent which it carries) within the tumor tissue. This is a tumor-targeting mechanism known as enhanced permeation and retention (EPR) [1,14,15]. By adding polyethylene glycol to the vector, clearance from the system is prolonged [4,13–15]. Liposomal doxorubicin and pegylated liposomal doxorubicin have been compared with conventional (systemic) doxorubicin in first-line treatment of patients with metastatic breast cancer. These randomized trials have shown that although liposomal doxorubicin has similar efficacy in time to disease progression,

those taking the modified preparation had significantly fewer cardiotoxic and neutropenic effects [2,4,13,16]. Liposomal doxorubicin (in combination with cyclophosphamide) is approved for the treatment of metastatic breast cancer in Europe, but is not currently recommended by National Institute for Clinical Excellence (NICE) [15,16].

In the UK, after anthracycline therapy has been offered, taxanes are the next step in chemotherapy for advanced breast cancer that has not responded and is HER2 negative (or HER2-positive disease unresponsive to trastuzumab) [101] . Paclitaxel is a widely used taxane whose synthetic delivery vehicle causes significant toxic effects. In preclinical trials nanoparticle albumin-bound paclitaxel (a nanoparticle with a core containing paclitaxel surrounded by albumin) demonstrated an improved side-effect profile and higher tumor penetration with improved disease response [2,4,13,16]. Nanoparticle albumin-bound paclitaxel has been licenced for use in the USA and UK but is not currently recommended by NICE [2,13,15,16]. Similar use of nanoparticles to deliver tamoxifen therapy in breast cancer mouse models has shown that polymer-bound tamoxifen has significantly increased tumor penetration [2].

> "The National Cancer Institute has recognized the importance of nanotechnology in the future of breast and other cancers and delivered large grants to further achievements in this field."

In conjunction with the aforementioned nanoparticle imaging technology, doxorubicin-loaded, quantum dot-labeled liposomes conjugated with anti-HER2 antibody have shown successful delivery to HER2-expressing cells *in vitro* with efficient anticancer activity in comparison with controls [17]. This theoretically paves the way in multifunctional nanoparticles for diagnostic breast cancer imaging that simultaneously delivers chemotherapeutic, targeted endocrine or biological agents, and provides dynamic data on their effects in real time.

Gene therapy

Although still very much in its early stages nanotechnology has been applied to breast cancer gene therapy research. Nanoparticles loaded with wild-type p53 DNA have greater antiproliferative activity on breast cancer cell lines than wild-type p53 DNA alone [18], and transfection of tumor cells with siRNA that inhibits breast cancer cell growth and downregulates HER2 (ERBB2) has greater stability and higher tumor uptake in mouse models when delivered attached to nanoparticles [19].

Thermal ablation

Nanoshells consist of a silica core surrounded by a thin gold shell. Surface thickness is specifically tuned to be activated by near infrared irradiation and the particle then emits thermal energy causing local tissue ablation [2,13,15]. When conjugated to a specific targeting antibody, the nanoshells should accumulate in the desired target tissue to localize ablation of cancer cells. This has been applied in animal models to demonstrate targeted thermoablation of breast cancer cells using anti-HER2 conjugated nanoshells [2,16,20]. Nanotubes (tube structure with walls one carbon molecule thick) have shown similar thermoablative effect when conjugated to IGF1R and HER2 antibodies and applied to *in vitro* breast cancer cell lines [21].

Conclusion

As evidenced earlier, there is great potential application for nanotechnology in oncology. Diagnosis and therapy for breast cancer is one of many malignancies now seeing the benefits of this application in the clinic. The National Cancer Institute has recognized the importance of nanotechnology in the future of breast and other cancers and delivered large grants to further achievements in this field [106].

Ultimately, it is hoped that the current separate strands of research will provide the greatest gains by combinations of the strategies described, so that one may specifically identify a patient's unique tumor profile in great detail (using nanotechnology to detect hundreds of thousands of biomarkers simultaneously) and tailor a nanoparticle for that patient that will provide highly specific and sensitive *in vivo* imaging, while also delivering chemotherapeutic agents whose effectiveness can then be followed over weeks in real time.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

References

1 Tanaka T, Decuzzi P, Cristofanilli M *et al.* Nanotechnology for breast cancer therapy. *Biomed. Microdevices* 11(1), 49–63 (2009).

2 Yezhelyev MV, Gao X, Xing Y, Al Hajj A, Nie S, O'Regan RM. Emerging use of nanoparticles in diagnosis and treatment of breast cancer. *Lancet Oncol.* 7(8), 657–667 (2006).

3 Ferrari M. Cancer nanotechnology: opportunities and challenges. *Nat. Rev. Cancer* 5(3), 161–171 (2005).

4 Wang X, Yang L, Chen ZG, Shin DM. Application of nanotechnology in cancer therapy and imaging. *CA Cancer J. Clin.* 58(2), 97–110 (2008).

5 Jain KK. Applications of nanobiotechnology in clinical diagnostics. *Clin. Chem.* 53(11), 2002–2009 (2007).

6 Yezhelyev MV, Al Hajj A, Morris C *et al.* *In situ* molecular profiling of breast cancer biomarkers with multicolor quantum dots. *Adv. Materials* 19, 3146–3151 (2007).

7 Xing Y, Chaudry Q, Shen C *et al.* Bioconjugated quantum dots for multiplexed and quantitative immunohistochemistry. *Nat. Protoc.* 2(5), 1152–1165 (2007).

8 Xiao Y, Telford WG, Ball JC, Locascio LE, Barker PE. Semiconductor nanocrystal conjugates, FISH and pH. *Nat. Methods* 2(10), 723 (2005).

9 Song KH, Kim C, Maslov K, Wang LV. Noninvasive *in vivo* spectroscopic nanorod-contrast photoacoustic mapping of sentinel lymph nodes. *Eur.J. Radiol.* 70(2), 227–231 (2009).

10 Tada H, Higuchi H, Wanatabe TM, Ohuchi N. *In vivo* real-time tracking of single quantum dots conjugated with monoclonal anti-HER2 antibody in tumors of mice. *Cancer Res.* 67(3), 1138–1144 (2007).

11 Artemov D, Mori N, Okollie B, Bhujwalla ZM. MR molecular imaging of the Her-2/neu receptor in breast cancer cells using targeted iron oxide nanoparticles. *Magn. Reson. Med.* 49(3), 403–408 (2003).

12 Zhou J, Leuschner C, Kumar C, Hormes JF, Soboyejo WO. Sub-cellular accumulation of magnetic nanoparticles in breast tumors and metastases. *Biomaterials* 27(9), 2001–2008 (2006).

13 Sunderland CJ, Steiert M, Talmadge JE, Derfus AM, Barry SE. Targeted nanoparticles for detecting and treating cancer. *Drug Dev. Res.* 67, 70–93 (2006).

14 Pan D, Lanza GM, Wickline SA, Caruthers SD. Nanomedicine: perspective and promises with ligand-directed molecular imaging. *Eur. J. Radiol.* 70(2), 274–285 (2009).

15 Peer D, Karp JM, Hong S, Farokhzad OC, Margalit R, Langer R. Nanocarriers as an emerging platform for cancer therapy. *Nat. Nanotechnol.* 2(12), 751–760 (2007).

16 Zhang L, Gu FX, Chan JM, Wang AZ, Langer RS, Farokhzad OC. Nanoparticles in medicine: therapeutic applications and developments. *Clin. Pharmacol. Ther.* 83(5), 761–769 (2008).

17 Weng KC, Noble CO, Papahadjopoulos-Sternberg B *et al.* Targeted tumor cell internalization and imaging of multifunctional quantum dot-conjugated immunoliposomes *in vitro* and *in vivo*. *Nano. Lett.* 8(9), 2851–2857 (2008).

18 Prabha S, Labhasetwar V. Nanoparticle-mediated wild-type *p53* gene delivery results in sustained antiproliferative activity in breast cancer cells. *Mol. Pharm.* 1(3), 211–219 (2004).

19 Urban-Klein B, Werth S, Abuharbeid S, Czubayko F, Aigner A. RNAi-mediated gene-targeting through systemic application of polyethylenimine (PEI)-complexed siRNA *in vivo*. *Gene Ther.* 12(5), 461–466 (2005).

20 Hirsch LR, Stafford RJ, Bankson JA *et al.* Nanoshell-mediated near-infrared thermal therapy of tumors under magnetic resonance guidance. *Proc. Natl Acad. Sci. USA* 100(23), 13549–13554 (2003).

21 Shao N, Lu S, Wickstromand E, Panchapakesan B. Integrated molecular targeting of IGF1R and HER2 surface receptors and destruction of breast cancer cells using single wall carbon nanotubes. *Nanotechnology* 18, 315101 (2007).

Websites

101 NICE. Advanced breast cancer: diagnosis and treatment www.nice.org.uk

102 Cancer incidence and mortality: trends in the UK and constituent countries www.statistics.gov.uk

103 Cancer research UK www.cancerresearchuk.org

104 NICE. Early and locally advanced breast cancer: diagnosis and treatment www.nice.org.uk

105 Technology Transfer Centre. Government funding, companies and applications in nanotechnology worldwide www.nano.org.uk/reports.htm

106 National Cancer Institute www.cancer.gov