

## Review Article

# Nanotechnology for energy-based cancer therapies

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Received February 16, 2011; Accepted March 5, 2011; Epub March 11; Published April 1, 2011

**Abstract:** To overcome problems of systemic toxicity associated with chemotherapy and enhance treatment resolution of cancer therapies, nanotechnology is increasingly providing many novel approaches, especially to energy-based cancer therapies. Enhancements to treatment targeting, the ability to facilitate combined therapies, and treatment imaging are but a few of the ongoing investigations in this ever growing field. This review briefly explores the modalities of energy-based cancer therapies, how nanotechnology has been allowed for improvements within them, and discusses potential future applications of combined therapies.

**Keywords:** Nanotechnology, energy-based therapies, nanoencapsulation, thermal ablation, combined modality therapy, drug delivery, chemotherapy, cryosurgery, tumor targeting, cancer treatment

### 1. Introduction

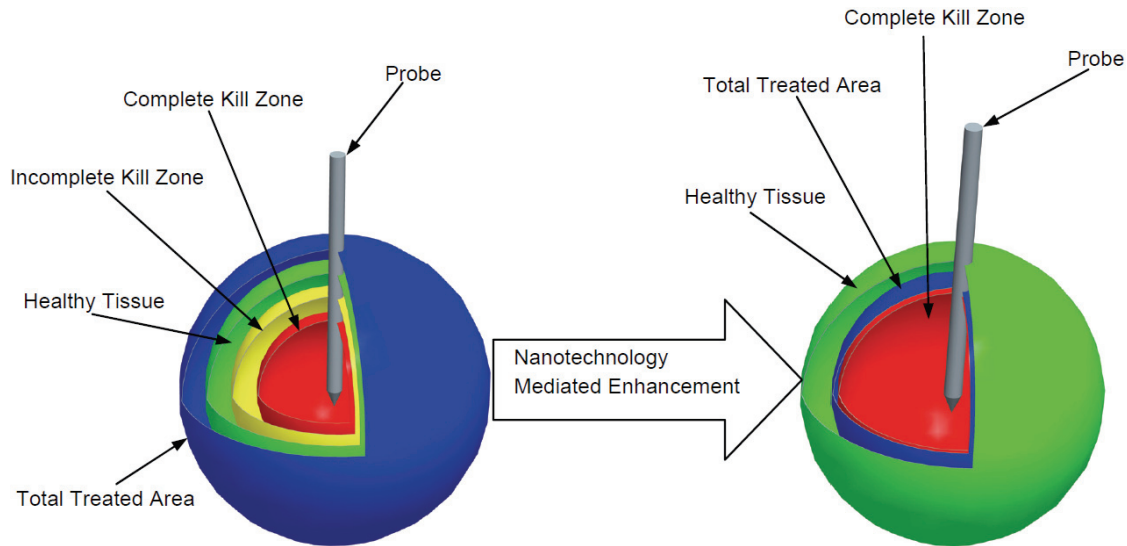
According to the American Cancer Society's 2010 statistical data, almost 1.5 million new cases of cancer were diagnosed in the United States and more than one third as many people were projected to succumb to their disease [1]. The data also lists cancer as the second leading cause of death behind heart disease with an expected total annual healthcare cost of \$263.8 billion. Even though many advances have been made in cancer diagnosis and treatment, many of the current treatments still cause considerable harm and discomfort to the patient.

A common treatment, chemotherapy, attempts to systemically deliver anticancer agents to patients in order to eradicate the uncontrolled proliferation of cancer cells. Unfortunately, because of nonspecific targeting, healthy cells can also be damaged during the treatment. This systemic approach results in hair loss, pain, anemia, and other side effects [2, 3]. In addition to the toxicity problems associated with nonspecific systemic treatments, up to 50% of approved active molecules for cancer therapy have poor solubility in physiological conditions [4].

Another common treatment, radiation therapy, provides a more narrow treatment region, but still has side effects due to its indiscriminate nature. Moreover, this treatment modality has limited applications due to site specificity [5, 6]. However, using more direct methods such as the surgical removal of cancerous tissue may cause permanent disfigurement, is also location dependent, and may cause post operational infection or complications [3]. In an attempt to eliminate or reduce the disadvantages associated with traditional techniques, minimally invasive energy-based therapies are being investigated, with many clinical trials currently underway [7-11]. The purpose of this paper is to review nanotechnology enhancements to energy-based cancer therapies and discuss results that may be applicable for combined therapies.

### 2. Energy-based therapies

Some promising focus areas in energy-based therapy research are photodynamic, alternating magnetic field, microwave, radio frequency (RF), high intensity focused ultrasound (HIFU), and cryoablation therapies, each with their own advantages and disadvantages [8, 12-14]. An advantage of these methods over systemic treatments or surgical resection is a more localized



**Figure 1.** Illustration of nanotechnology mediated enhancements that can improve energy-based cancer therapies. Classical energy-based treatments have limitations in treatment area visualization causing the total treated area to overlap with healthy tissue. Also, unquantified thermal distribution causes an uncertainty in the complete kill zone (left). By using nanotechnology mediated combined modality treatments, the total treatment area can be visualized to minimize healthy tissue overlap, and the complete kill zone can be expanded to the treated area edge.

destruction of diseased tissue while minimizing possible side effects such as systemic toxicity or infection. Also, these methods are considered minimally invasive and are primarily investigated as outpatient procedures. Energy-based therapies destroy tumor cells by causing a local temperature excursion within the designated treatment area. Commonly, this procedure is applied through a minimally invasive probe insertion technique or the focusing of external high energy sources. Although the individual implementation of these thermal ablation methodologies are different depending on the energy source, the fundamental therapeutic mechanisms for these therapies can be divided into two categories, damage from heating to hyperthermic temperatures (usually  $> 43^{\circ}\text{C}$ ) or damage from cooling or freezing to cryothermic temperatures (usually  $< -20^{\circ}\text{C}$ ). The therapeutic benefit from both of these types of treatment are strongly temperature and time dependent with differing degrees of damage existing throughout a given treatment gradient, as shown in **Figure 1** (left).

In the complete kill zone, hyperthermic damage has been characterized by protein denaturation, cellular membrane damage, and vascular injury [12]. Alternatively, cryothermic damage has

been characterized by mechanical damage from ice formation, cellular dehydration, ischemia from vascular damage, and post treatment immunological response [15]. Of the energy sources mentioned, all induce hyperthermic damage with the exception of cryoablation, which induces cryothermic damage. Although these methodologies have promising potential applications, they have problems that cannot be overlooked. Thermal ablation treatments are susceptible to uneven distribution of temperature profiles, and in the case of hyperthermic treatments, the treated area is not readily visible during the procedure and must be estimated from models or experimentation. Furthermore, the methods of implementation for the delivery of the thermal energy required for these treatments cause unintended damage to surrounding healthy tissue. In contrast, the iceball formed during cryothermic ablation treatment is visible through ultrasound or CT and easily tracked, but the determination of effectively treated area with temperature  $< -20^{\circ}\text{C}$  within the iceball is uncertain and must either be directly measured or estimated through models and experimentation [16-18]. The fluctuation in temperature gradient and uncertainty in treated area causes ablation treatments to be less specific than intended and in some cases possibly

incomplete, as shown in **Figure 1** (left) [7, 12, 19].

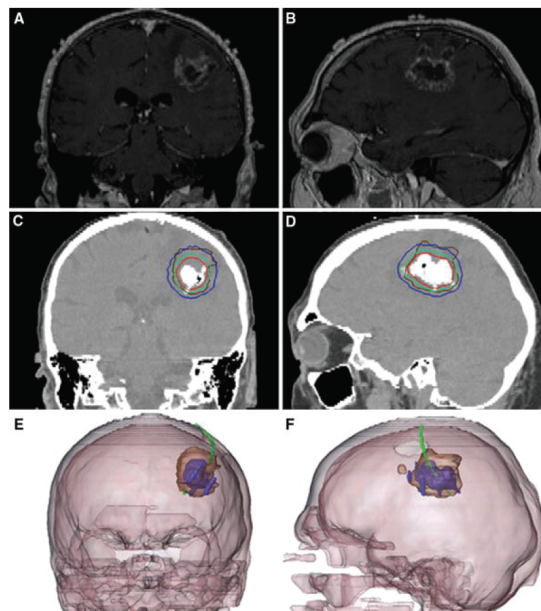
### 3. Adjuvants for energy-based therapy

To investigate enhancements to energy-based therapies, chemotherapeutic agents have been used as treatment adjuvants. It has been shown that both types of thermal ablation therapies, hyperthermic and cryothermic, have the potential to enhance the uptake of chemotherapeutic agents as well as induce a secondary immunological response that can enhance the extent of the removal of diseased tissue [15, 20-31]. Additionally, various salts, chemotherapeutic agents, and immunological factors have been tested for enhanced cryoablation treatment outcomes [15, 32-37].

While promising results and discoveries have been elucidated using adjuvants to enhance thermal ablation therapy, there are significant drawbacks associated with this treatment methodology that warrant further investigation. In particular, unquantified systemic toxicity, tumor specific targeting, and intratumoral drug distribution have left areas for improvements and research [38-55]. The focus of further research in this field has been to improve the treated area versus non-treated area by using nanotechnology as a resolution enhancing mechanism to expand the complete kill zone into the incomplete kill zone, sharply define treatment boundaries, and reduce the total treated area, as shown in **Figure 1** (right).

### 4. Nanotechnology mediated enhancements to energy-based therapies

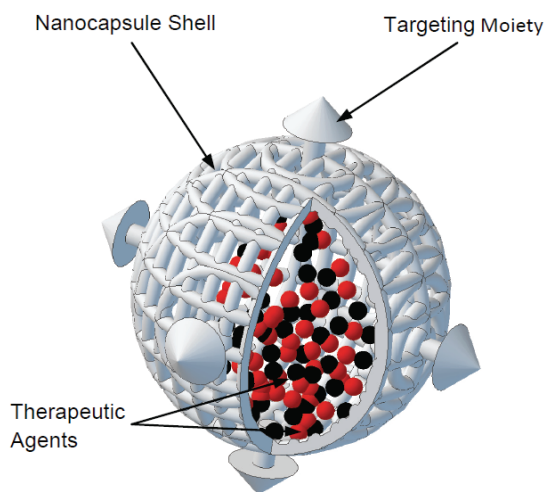
Over the past decade, nanotechnology has begun to be explored as a tool to increase the resolution of thermal ablation treatment area, tumor visualization, and improve treatment effectiveness [13, 14, 19]. The most direct method used for the enhancement of thermal therapy has been the systemic or local introduction of nanoparticles given concurrently with energy-based ablation treatments [56, 57]. For hyperthermic therapies, carbon nanotubes, gold nanoshells, and iron oxide nanoparticles have proven extremely useful for enhancing heating effects due to energy absorption by the nanoparticles during treatment [13, 19, 58]. Previous research has shown that the nanoparticles preferentially associate with tumors when



**Figure 2.** Imaging results from a preliminary study of locally delivered metallic nanoparticles in hyperthermic treatment of brain cancer: (A,B), pre-treatment brain MRI; (C,D), post nanoparticle delivery CT scan showing magnetic nanoparticle deposits as hyperdense areas with the colored lines indicating calculated treatment temperatures between 40°C (blue) and 50°C (red) and the brown line representing the tumor area; and (E,F), 3-D reconstruction of fused MRI and CT showing the tumor (brown), magnetic fluid (blue) and thermometry catheter (green) [144].

given systemically or locally under the premise of the enhanced permeability and retention effect (EPR), which is often found in tumor vasculature [52, 53, 59-61]. Furthermore, the use of metallic or carbon nanoparticles as treatment adjuvants enables the treated region to be visualized through noninvasive means such as MRI and CT, as shown in **Figure 2** [56].

To overcome problems with systemic toxicity and enable target specificity, nanocapsule carriers with targeting moieties have been investigated to preferentially deliver therapeutics to diseased tissue via cell surface receptors, as shown in **Figure 3**. Some cell surface receptors help transmit messages from the extracellular environment to the intracellular environment, and in many cancerous cells are overexpressed. Overexpression of these surface receptors and other similar hallmarks specific to cancer can serve as potential target areas due to their in-



**Figure 3.** Illustration of nanocapsule containing therapeutic agents for targeted delivery to tumor cells. Nanoencapsulation technology has the potential to offer many combined modality approaches for treatment enhancements and personalized treatment targeting.

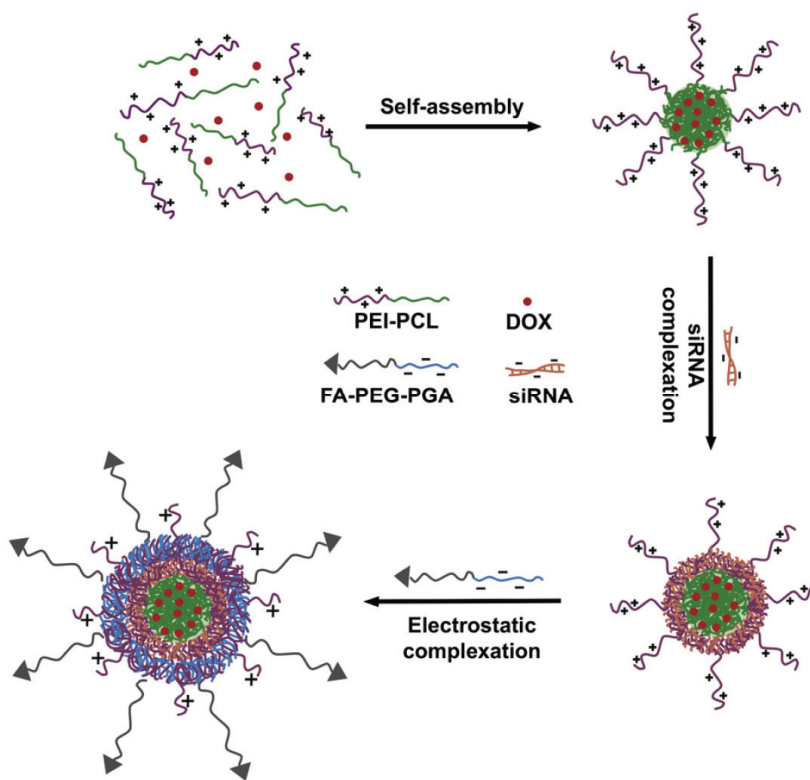
creased concentration in diseased tissue. Specifically, receptors to estrogen, folic acid, epidermal growth factor and others have been explored for potential treatment targets. Using the various cellular targeting moieties, preferential uptake of nanoparticles into target expressing cancer cells has been shown [23, 62-67].

In addition to small molecular compound drugs, a Nobel-prize winning discovery of RNA interference (RNAi) has been extensively applied with the progress of delivery systems in several different experimental models and more recently in treatment of numerous diseases, including neurodegenerative disorders and cancer [68-72]. Small interfering RNAs (siRNAs) promote the cleavage of complementary mRNA to reduce protein production in mammalian cells and play a pivotal role in triggering RNAi [73, 74]. siRNAs have short plasma half-life, fast degradation times in the physiological milieu, inefficient translocation into the cytoplasm, and lack of targeting ability. Therefore, successful siRNA-based gene targeting relies on the following conditions: improvement on stability and prevention of degradation by serum RNAses, efficient cellular uptake and subsequent intracellular release into the cytoplasm, as well as avoidance of intracellular immune responses, in vivo toxicity or rapid elimination in the liver or

kidneys [73, 75-77].

siRNA, similar to DNA, carries a net negative charge on the sugar phosphate which prevents its contact and entrance to the lipid bilayer of the cell membrane, whose head groups are also negatively charged. In the early 1970s, Calcium phosphate (CaP) precipitates were used as transfection reagents of viral DNA as they are believed to be non-toxic [78]. CaP effectively protects the nucleic acids from enzymatic degradation and aided cellular delivery, but uncontrollable rapid growth of calcium phosphate crystals greatly reduced the transfection efficiency [79, 80]. To facilitate higher genocompatibility and lower toxicity, non-viral delivery vectors became a good choice for gene-based therapies and in drug development. Non-viral delivery vectors include cationic lipids (e.g. DOTAP and Oligofectamine), cationic polymers (e.g. PEI and DAB dendrimers) and non-ionic (uncharged) polymers (e.g. poly HPMA and PEG) [81-87]. Nanoparticles (NPs) such as the cationic polymer, polyethyleneimine (PEI), can act as envelopes to protect the siRNA from metabolism and excretion, but can also carry specific molecules designed to target the siRNA to specific tissue types. For example, hydrophobic DOX obtained by deprotonation accumulated in the PCL core of the cationic micelle assembled from PEI-PCL, as shown in **Figure 4** [88]. More recently, gold nanoparticles were directly conjugated to siRNA, increasing the serum half-life more than six fold compared to free RNA duplexes [89]. Also, biodegradable nanoparticles have been developed and have shown good potential as carriers for anticancer drugs with a spherical structure [90].

Within the past decade, the use of siRNA for RNAi has proven to be an effective nanomedicine for gene silencing therapy [91-96]. However, research into the delivery of siRNA via nanoparticles to target cells is still in its infancy. In cancer therapy, siRNA delivery via nanoparticles needs to satisfy two major concerns: to improve the therapeutic range by including more than one siRNA which acts on specific targets, but keep minimal toxicity and maximum patient safety; and to develop novel or modify established carrier systems to induce gene changes on siRNA mediated gene silencing, but avoid enhancing the off-target gene changes [97-99]. These emerging different new types of nanoparticles (biodegradable, gold, etc.) will



**Figure 4:** Formation of hierarchical nano-assemblies for combinatorial delivery of siRNA and anticancer drugs [88].

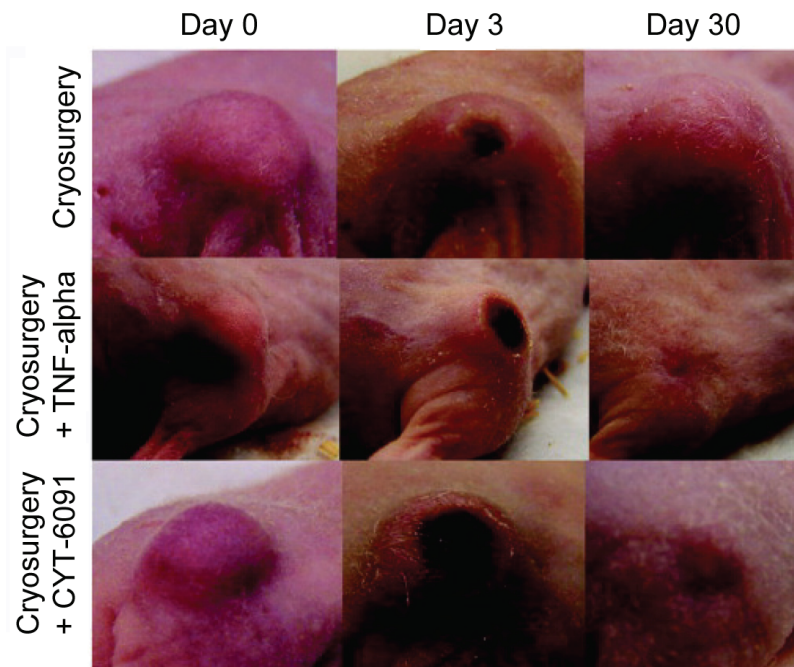
changes. Utilizing the nanoparticle aided target delivery approach allows drugs released via a temperature controlled mechanism to be preferentially distributed at the tumor location with an increased uptake caused from the energy-based treatment. Use of nanoencapsulation technology also has the potential to reduce systemic toxicity because of localized delivery of agents to the treatment area for controlled release. Consequently, this combined treatment has the potential benefit of reducing the overall treatment area by allowing for an increase in the complete kill zone aided by chemotherapeutic agents [115, 116]. Preliminary results in animal studies for temperature sensitive carriers (liposomes) have prompted several currently ongoing clinical trials in various phases, I-III

facilitate the brilliance of RNAi and promote its application in clinical trials targeting specific tissues and diseases.

Recently, thermally responsive nanoencapsulation systems have been developed using temperature sensitive carriers designed to deliver chemotherapeutic agents preferentially to tumor sites. During the temperature change associated with energy-based treatment, a conformational or structural change in the delivery vehicle causes the release of chemotherapeutics from the carrier. Once released, therapeutic agents are free to diffuse away from their carrier and act on nearby targets with promising results [64, 100-114]. Additionally, as previously mentioned, the solubility of many chemotherapeutic substances in physiological conditions is very poor. Therefore, an added benefit of nanoencapsulation is the expansion of available chemotherapeutic agents that can be used for treatment. Moreover, an effect of energy-based treatments is enhanced uptake of chemotherapeutics possibly due to permeability

[117-121].

To provide additional improvements to the nanoparticle aided delivery methodology, facilitated drug release and treatment visualization, some experimental systems have co-encapsulated metallic nanoparticles alongside chemotherapeutic agents. This co-encapsulation paradigm allows metallic nanoparticles to act as agents for imaging and controlled release of chemotherapeutics through their energy absorbing properties [100, 101, 122-124]. Moreover, the delivery of metallic nanoparticles and chemotherapeutic agents simultaneously provide an approximated visualization of drug delivery localization and treatment area [125-129]. Therefore, this combined approach has the potential to reduce the total treatment area due to the energy absorbing properties of metallic nanoparticles, provide an increase to the complete kill zone from both targeted heating and chemotherapeutic agent delivery, and visual definition of treatment boundaries. However, more research into the



**Figure 5.** 30 day observation of tumor size in mice treated with cryosurgery, TNF- $\alpha$  with cryosurgery, or gold-TNF- $\alpha$  nanoparticles (CYT-6091) with cryosurgery. CYT-6091 was found to have less systemic toxicity than free TNF- $\alpha$  and provided a similar benefit in tumor size reduction as the more toxic free TNF- $\alpha$  [135].

development of this approach is necessary for clinical application to be realized, especially in the area of intratumoral nanoparticle distribution.

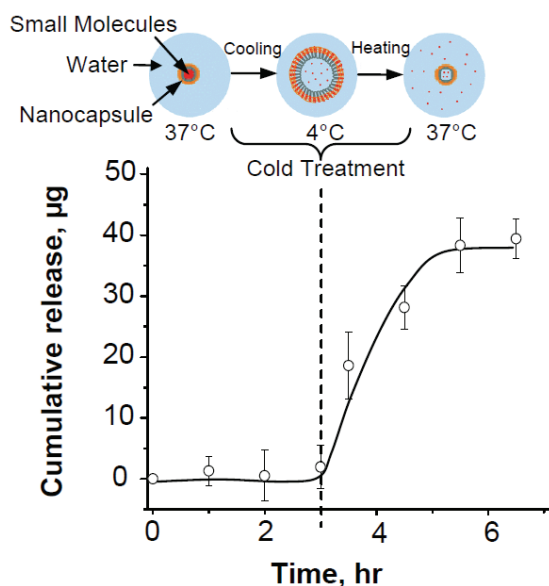
Exploration into immune response to enhance treatment has also been studied by conjugating TNF- $\alpha$  onto the surface of gold nanoparticles [130-135]. Results from animal model studies have shown a preferential biodistribution of gold-TNF- $\alpha$  within tumor locations with less systemic toxicity than free TNF- $\alpha$ . Furthermore, hyperthermic and cryothermic ablation treatment given after gold-TNF- $\alpha$  nanoparticle delivery increased the complete kill zone in animal models, as shown in **Figure 5**. From these initial studies, further tumor model applications and combinations with chemotherapeutic and co-encapsulation treatments are warranted [115].

In addition to the nanoparticle mediated combined modality treatments, recent developments such as nanoscissor technology in conjunction with gene and gene product specific targeting and manipulation may bring about

new areas of research focus for even more combined modality therapies with patient specific cancer targeting treatments [136-140]. Specifically, targeted DNA sequences have been manipulated through localized disruption by the utilization of the energy absorption properties of gold nanoparticles [136]. Furthermore, gold and polymeric nanoparticles have also been used for DNA/oligonucleotide conjugation to regulate transcription and translation in cell models [137, 140]. Considering that this research has used energy absorption, metallic nanoparticles, and targeted delivery techniques similar to that used in previously mentioned research areas, it is not a far stretch to imagine that combined therapy applications with the correction or elimination of damaged DNA or initiation of apoptotic signaling through nanomanipulation techniques may be of future relevance.

These techniques are still in their infancy and much more research and technical advancement is needed in order for this to become a practical and economic reality. However, the pace of advancement toward affordable and accessible gene research technology for potential treatment personalization applications is increasing rapidly [141].

While the majority of the advances made for nanotechnology derived delivery vehicles have been in the area of hyperthermic treatment, recent studies in our laboratories have focused on advancing cryoablation treatment using hypothermally responsive nanocapsules [142, 143]. The goal of this research has been to improve the effectiveness of cryoablation treatment by moving the complete kill zone closer to the edge of the ice ball (the total treated area) by releasing drugs from a nanocapsule carrier within the incomplete kill zone. If successful, the subsequent outcome of this treatment enhancement would yield a smaller ice ball needed to achieve a greater clinical response



**Figure 6.** Cumulative release of ethidium bromide(EB) encapsulated in hypothermic temperature sensitive nanocapsules during dialysis. Before cold treatment, the nanocapsule solution was kept at 37 °C to keep the encapsulated EB trapped within the capsule core to prevent release. After 3 hours, a cold treatment was given for 15 minutes to expand the nanocapsules and increase the wall permeability to allow the encapsulated EB to be liberated (released) out of the nanocapsule. As a result, a burst release of EB during dialysis is observable after the cold treatment [143].

and thus less peripheral damage to adjacent tissues. As shown in **Figure 6**, our initial studies have shown that a thermally responsive nanocapsule system for delivery of chemotherapeutic agents during cryothermic ablation treatment is theoretically possible and further research in this area is warranted and ongoing.

The potential benefits offered by nanotechnology (target specificity, reduction of systemic toxicity for chemotherapeutics, and coencapsulation of adjuvants), bring nanoparticle mediated combined therapies to the forefront of potential enhancements to energy-based cancer therapies. Coupled with further understanding of host immune response and the possibility of patient specific treatments, nanoparticle mediated therapies can also provide the basis for many more interesting and novel treatment options previously not investigated. Further research into the nanoparticle mediated enhance-

ments to energy-based therapies mentioned in this review should result in the final goal of expanding the complete kill zone while minimizing the total treatment area (or incomplete kill zone) and providing visualization of boundary zones needed to give energy-based therapies more clinical relevance and certainty, as shown in **Figure 1** (right).

## 5. Summary and Conclusion

Through advanced understanding and application of functional nanomaterials, cellular targeting, and immune response, improvements in energy-based therapy have seen promising results. Furthermore, as gene sequencing technology advances to a much more affordable level, the personalization of nanotechnology derived delivery vehicles and therapeutics will make nanoparticle mediated combined therapies a much more focused and patient specific treatment option. Through further investigation and clinical trials, energy-based therapy assisted by nanotechnology may bring about a paradigm shift in primary cancer treatment in the not so distant future

## Acknowledgments

This work was partially supported by a grant (to X.H.) from the Wendy Will Case Cancer Fund and a grant (to X.L.) from the American Cancer Society (119135-RSG-10-185-01-TBE).

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