Journal of Nanomedicine & Biotherapeutic Discovery

Vaghasia and Federman, J Nanomedic Biotherapeu Discover 2011, 1:2
DOI: 10.4172/2155-983X.1000105e

Editorial Open Access

Liposomes for Targeting Cancer: One Step Closer to the Holy Grail of Cancer Therapeutics?

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The use of plant-based medicines and various minerals to treat diseases is believed to date back to prehistoric medicine. Ancient texts from the Ramayana and The Papyrus Ebers make references to malignant diseases and their treatments [1]. However, it was not until the early twentieth century that the first modern drugs to treat cancer came about. Mustard gas, initially intended for use as a chemical warfare agent during World War I, was found to be a potent suppressor of hematopoiesis [2]. Goodman and Gilman later studied the Nitrogen Mustards as an effective treatment for cancers. Their findings were later applied successfully, however short lived, in the treatment of lymphoma [3]. Thus, the field of chemotherapy was born!

Since then, numerous chemotherapeutic agents have been designed and discovered for the treatment of various oncologic malignancies. Unable to truly differentiate cancerous from normal cells, these systemic chemotherapeutic agents often have significant bystander effects resulting in dose limiting toxicities ,and not infrequently to permanent end organ damage. The future of cancer therapy has thus rested on the development of targeted therapies that would both increase the cytotoxicity to cancer cells while limiting the deleterious effects on normal cells.

Nanotechnology has been a broad and evolving field with enormous potential to revolutionizing current anti-cancer therapies.Perhaps the oldest studied nanoparticle, liposomes, spherical and hollow nanoparticles composed of a variety of lipid molecule combinations, were serendipitously discovered in 1965 and coined "phospholipid dispersions" [4]. The past several decades have seen over 10 liposomal drugs approved by the U.S. Food and Drug Administration primarily for use in infectious diseases and cancer. Liposomal formulations are being increasingly applied to the delivery of chemotherapy with promising potential though questions and controversies remain about the way in which these nanoparticles actually improve our drug delivery to cancer cells.

Drug delivery systems with liposomes and nanoparticles take advantage of the fact that cancers particularly express an imbalance in vascular permeability factors such as nitric oxide, bradykinin, and vascular endothelial growth factor (VEGF) [5-7] ultimately causing an over-expression of these vascular permeability factors that lead to increased vascular permeability and tortuous vasculature within the tumor bed [8]. This is the basis of the central tenet of nanoparticle therapeutics, the Enhanced Permeability and Retention (EPR) effect – which describes the property that molecules of certain sizes, such as liposomes, are able to accumulate in tumor tissue much more readily than normal tissue [9]. The over-expression of vascular permeability factors and development of tortuous vessels with poorly aligned endothelial cells give way to fenestrations that lead to abnormal molecular and fluid transport dynamics, allowing for a system of passive targeting of the tumor bed. In addition,a lack of effective tumor lymphatic drainage seen within solid tumors may, contribute to the EPR effect by preventing clearance of the liposomes leading to their accumulation [10,11]. This unique phenomenon was initially applied in clinical radiology with gallium scintigraphy (Gallium 67 scan) in the diagnosis of solid tumors and areas of inflammation and now is being applied to cancer treatment. More recently, however, it has been noted that macromolecules, generally defined as greater than 40kDa, have faired better in terms of retention within the tumor bed when compared to low-molecular-weight substances. Low-molecular-weight substances, instead of being retained by the solid tumor, were returned to circulation by simple diffusion into the bloodstream [11,12]. In a chemotherapeutic application, others have confirmed this principle using HPMA [N-(2-hydroxypropyl)methacrylamide copolymer] conjugated to Doxorubicin and demonstrated an inverse relationship between tumor uptake and urinary clearance [13,14].

One of the key principles for liposomes used in drug delivery is the amount of biocompatibility and biodegradability in order to ensure adequate metabolism with minimal side effects as the drug clears. Size plays a role in clearance- the smaller the particle; the more readily it is excreted. Nanoparticles and liposomes greater than 30nm are typically cleared by the mononuclear phagocytic system (MPS) made up of macrophages in the liver and spleen [15]. In order to reduce metabolism and clearance of liposomes, grafting a "stealthing" ligand to the outer portion of the lipid bilayer, known as PEGylation (polyethylene glycol coated), helps reduce opsonization and improve the circulation time. This has been shown in Liposome-PEG doxorubicin,Doxil (Orthobiotech). The most widely used anthracycline, doxorubicin, is limited by the dose dependent cardiotoxicity side effects. Doxil has been used in HIV related Kaposi sarcoma and more recently has been FDA approved for treatment of multiple myeloma, breast cancer, and ovarian cancer in the United States.The EPR effect combined with prolonged circulation time, allowed for Doxil to prove comparable efficacy to doxorubicin, with significantly reduced cardiotoxicity, myelosuppression, vomiting and alopecia [16]. Doxil was shown to accumulate preferentially in metastatic breast carcinoma tissue and was found to have a 10-fold higher intracellular drug concentration compared to surrounding normal tissue. In addition, PEGylation of doxorubicin reduced levels of free doxorubicin in plasma, ultimately reducing drug delivery to normal tissue and toxicity [17]. Although PEGylation appears to prolong circulation time and ultimately increase penetrance into tumor tissue, it does not contribute towards specific targeting of tumor cells. It has been hypothesized that the addition of a targeting moiety onto the surface of liposomes can serve to increase

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Received September 02, 2011; **Accepted** November 08, 2011; **Published** November 10, 2011

Citation: Vaghasia N, Federman N (2011) Liposomes for Targeting Cancer: One Step Closer to the Holy Grail of Cancer Therapeutics? J Nanomedic Biotherapeu Discover 1:105e. doi:10.4172/2155-983X.1000105e

recognition of either tumor cells or tumor endothelium. It follows that specific targeting could then increase selective cellular binding and internalization into the tumor cell via receptor mediated endocytosis. It has been debated whether active targeting increases tumor localization. However, enhanced cellular internalization, when compared to non-targeted liposomes, has been shown in delivery systems targeted to endocytosis prone receptors [18].

Studies have shown, with promising results, that active targeting of the cancer cell can be achieved via a variety of receptors- the most commonly studied include the transferrin receptor, folate receptor, and cellular glycoproteins such as HER-2 and EGFR. [19-21]. Such systems are considered single strategies of active targeting. $\alpha_v\beta_3$ integrin targeted liposomes are considered as double targeting delivery systems because these integrins are expressed in both tumor cells and tumor endothelium [22]. A recent study evaluated the effect of active targeting with passive targeting in HPMA copolymer-docetaxel conjugates and $\alpha_v\beta_3$ integrin targeting conjugate HPMA copolymer-docetaxel-RGDfk. The results demonstrated that the $\alpha_v\beta_3$ integrin targeting liposomes had better water solubility, improved clearance, and decreased toxicity, making dual targeting delivery systems a possible new avenue for improved outcomes [23].

While liposomes are pioneering the way for novel chemotherapeutic delivery systems, there still remain many unknowns and kinks to be worked out. With nanotechnology comes "nanotoxicology," and we are still searching for the short and long term list of implications that come with new alternatives to therapy. As a new discipline in medicine, it will be a significant amount of years from now that we will be learning of such late effects from nanomedicine. Discovering the balance between circulation time and tumor accumulation is still being investigated, making the trends in liposomal size and PEGylation a moving target. Too small of a size or too little PEGylation and they are cleared too quickly. Too large and they cannot cross the fenestrated vasculature to gain access to the tumor bed. And too many PEG layers and they remain in circulation possibly leading to off-target toxicities [24]. One of the best examples of this is Palmarplantar erythrodysesthesis (PPE), also known as hand-foot syndrome.This is a painful erythematous and edematous rash that presents on the hands and feet typically occurring 2-14 days after treatment with chemotherapy. The incidence and severity of PPE associated with Doxil is substantially increased compared to patients receiving conventional doxorubicin. The pathophysiology of PPE in association with the PEG-liposomal doxorubicin formulation is incompletely understood and likely due to multiple variables unique to the palms and soles, such as increased skin cell division, unique vascular anatomy, temperature gradients, and increased drug concentration in the sweat glands [25,26].

Other architectural debates of liposomes involve ligand placement in an optimal fashion. Ligands must be selected to have the correct conformation, high affinities for their corresponding receptors and successful internalization into the tumor cell. The placement of these ligands upon the liposome must be done in careful fashion- the greater the density the more likely a liposome will achieve successful active targeting. However, the high surface coverage with ligands has been shown to also cause macrophage recognition and faster clearance from the circulation, ultimately rendering the PEG layer non-functional [18]. A balance between the aggressiveness of active targeting with ligand grafting and circulation time still is being sought.

Liposomes and nanoparticles have emerged as a promising potential drug delivery system. Current uses of approved liposomal formulations of chemotherapy have already shown advantages in the treatment of cancers when compared to conventional chemotherapies. Their ability to lower significant toxicities, improve drug circulation time, and target specific tissues while sparing others make liposomes an attractive forerunner in the future of drug therapy in cancer treatment. Currently, approved liposomal chemotherapeutic formulations rely on the concepts of passive targeting and the EPR effect. The improvements that active targeting can achieve in specifically affecting tumor cells would only serve to improve clinical outcomes, changing the field of chemotherapy with these customized "homing devices." However, while revolutionary in concept, active targeting has yet to be successfully demonstrated and applied in a clinical setting. There may be barriers still unrecognized within the tumor microenvironment that could render this quest for "the holy grail" unachievable. The concept of double targeting may help to improve specific targeting strategies and is currently under investigation.

The history of medicine shows that even in ancient times human societies had medical beliefs that provided explanations for disease. Initially reasoning that these misfortunes stemmed from witchcraft, the will of the gods, or astrological misalignments, society still found ways to search for remedies and cures. Modern medicine has come a long way from using single agent therapeutics for the treatment of cancer. Now a multimodality system exists between drug therapies and technology in the combination of chemotherapy, surgeries and radiation therapy. However, one cannot argue against the potential liposomes and other nanoparticle formulations hold in the application of cancer therapeutics for improving outcomes in clinical medicine. While there are many questions that remain in the field of nanomedicine and much work that remains to be done, they remain a strong promise for upcoming platforms of drug delivery applications.

Acknowledgement

Neha Vaghasia is supported by the NIH T32 ICPTP Grant T32 CA09056.

Noah Federman is supported by the St. Baldrick's Career Development Award and Hyundai Hope on Wheels Award.

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