EPR effect: Promising approach for tumor targeted drug delivery

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ABSTRACT

Targeted drug delivery to tumor sites is one of the ultimate goals in drug delivery. Recent advances in nanoparticles engineering has certainly improved drug targeting, however clinical effects are disappointing. Present review addresses challenges in cancer therapy and current status of tumor targeted drug delivery. Most of the efforts have been directed towards design and surface manipulation of nanoparticles with relative little attention to other aspects. EPR effect based drug delivery offers lower cost of therapy, greater therapeutic effects on more types of tumors and fewer adverse effects. Present review focuses on basic understanding of EPR effect, critical attributes of nanoparticles influencing success of EPR based drug delivery and factors involved in EPR effect. Tumor biology diversity is responsible for heterogeneity of EPR effect which reduces its universal validity. Augmentation of EPR effect overcomes heterogeneity, thus widening its application on more types of tumors. Clinical outlook of SMANCS, clinically successful macromolecular drug is presented to support the concept of EPR effect in tumor targeted drug delivery.

Keywords: EPR effect, tumor targeted drug delivery, nanoparticles, SMANCS

INTRODUCTION

Cancer remains one of the most urgent concerns in the world today. It is among the leading cause of deaths worldwide accounting for 8.2 million deaths in 2012. It is expected that annual cancer cases will rise from 14 million in 2012 to 22 within next two decades [1]. Cancer can be reduced and controlled by implementing evidence -based strategies for cancer prevention, early detection of cancer and management of patients with cancer. Many cancers have a high chance of cure if detected early and treated adequately. Research and development in the areas of nanoscience and nanotechnology promise to provide innovative, and more effective, approaches for targeted delivery to tumor. Hence there is need to focus on unsolved problems that impede progress. This review presents brief overview on cancer pathogenesis, treatment and challenges in cancer therapy. Review addresses multiple aspects of the enhanced permeability and retention (EPR) effect in cancer to explore full potential of EPR effect based cancer diagnosis, tumor targeted drug delivery or both.

Challenges in cancer therapy: With the increasing technical possibilities for evaluating diverse cancer tumors, accumulated evidence is suggesting that cancer tissue is heterogeneous at both the intratumoral and intertumoral level. Intratumoral heterogeneity is seen across many cell properties, including morphology or phenotypic expression, exhibition of primary or acquired drug resistance; and capacity for initiating new tumor growth. This heterogeneity can be attributed to random fluctuation of protein expression levels; however reasons for such extensive diversity are not fully revealed. These diverse conditions are further complexed by factors in the tumor microenvironment such as paracrine signalling from hypoxic environment or from associated stromal cells. Therefore, cancer is now not recognised as a single disease, but as many, each with varying causes, prognoses and appropriate treatments [2,3]. Also, the resistance that neoplastic cells manifest to cytotoxic drugs is a major challenge in the treatment of the disease. The resistance can be ’primary’ (present when the drug is first given) or the ‘acquired’ type which may result from either adaptation of tumor cells or
mutation with the emergence of the cells that are less susceptible or resistant to the drug. Because cancer cells can evolve in response to the selection of cancer therapy, the goal of eradicating the entire cell within a tumor by targeting a specific pathway unique to cancer cells becomes a major task. When this task is not completed, the cells that do not respond to the drugs may grow and reconstitute the tumor in the body \[^{(4)}\]. Early detection of cancer is another important challenge. It is crucial process to detect the point at which the treatment can be successfully administered \[^{(5)}\].

Current status of targeted drug delivery to tumors

Conventional approaches to treat cancer are chemotherapy, surgery or radiation. Surgical intervention is limited to removal of early stage tumors that are small and confined to a limited area, without metastasis. So the ultimate resort to control cancer is chemotherapy and to some extent radiotherapy. However; it is difficult to get tumor-selective toxicity because the biological events taking place in cancer cells are essentially as same as that of host cells. There is little difference in biochemical or molecular machinery between cancer & normal cells at cellular or molecular level. Also most conventional low molecular weight anticancer drugs have inherent character to transverse in and out of blood vessels freely. Consequently, their undesirable indiscriminatory distribution in normal tissues causes severe systemic side effects making therapy disastrous to patients \[^{(6)}\].

Tumor targeted delivery has received great attention due to increased anticipation of achieving it using nanotechnology-based delivery systems and to overcome difficulties associated with conventional anticancer drugs including rapid clearance, insolubility under aqueous condition, lack of selectivity resulting in nonspecific toxicity towards normal cells and lowering the dose of drug to cancer cells. For simplicity, all nanostructures including drug-polymer conjugates, drug-protein conjugates, polymer micelles, liposomes, dendrimers, DNA polyplexes and drug nanocrystals will be referred to as nanoparticles. The following Table No. 1 classify much discussed targeting approaches in literature as active, passive, inverse and combined targeting based on drug targeting strategy used \[^{(7)}\]. However, nanoparticles based targeted drug delivery has not fulfilled its expectations even after efforts of whole decade of 2000s. Recent article by Kinam Park et al explains the uncomfortable facts in targeted drug delivery \[^{(8)}\]. According to authors, present targeting approaches does not result in targeted biodistribution of nanoparticles as they rely on blood circulation to reach the target as conventional drugs do. Ligand targeted drug delivery may increase the cellular uptake of drug if the cells in contact with nanoparticles happen to have overexpressed receptors. However, overexpression of molecular signatures on tumor cells is relative to normal cells which suggest that normal cells also express the receptors to some extent. This leads to capture of considerable amount of ligand bound drug by normal cells as total number of normal cells are much larger than number of cancer cells. Also great diversity exists with kinetics of drug uptake and receptor recycling which needs to be considered. Thus efficacy of such therapy is only 4-5% which is only useful as adjuvant/ supplementary. Thus low efficacy & high cost makes therapy unacceptable. The benefits for patients undergoing these treatments is a 1-2 month extension of the usual 3-10 years overall survival. Furthermore, neither the intensity of adverse effects nor the frequencies of medical emergencies are reduced. Most cases demonstrated resistance after several months of its use \[^{(8)}\]. Thus, rationale for drug-targeting method based on enhanced permeability & retention (EPR) effect is lower cost of therapy, with greater therapeutic effects on more types of tumors and fewer adverse effects.

UNIQUE FEATURES OF TUMOR VASCULATURE CONTRIBUTING TO EPR EFFECT

Rapid growth of tumor is due to the phenomenon called angiogenesis in which new tumor blood vessels are formed. These newly formed blood vessels have defective architecture and produce extensive amounts of various vascular permeability factors such as bradykinin, prostaglandins, vascular endothelial growth factor (VEGF) which causes enhanced vascular permeability; so that sufficient supply of nutrients & oxygen to tumor tissues for rapid growth is ensured \[^{(9,10)}\]. Enhanced retention is attributed to the fact that tumor tissues exhibit poor lymphatic drainage. Small molecules do not show the EPR effect, because they can freely pass through the blood vessels into tumor as well as the normal tissue, & diffuse back into blood capillaries. In contrast, nanoparticles pass through the blood vessels around the tumor & do not diffuse back into blood capillaries or end up in lymphatic system. In addition, lymphatic metastasis is one of the most formidable consequence of cancer progression although the lymphatic system does not function properly in tumor tissues. Lymphotrophic accumulation of nanoparticles thus can be utilized for effective diagnosis and treatment of lymphatic metastasis. These anatomical and architectural characteristics of tumor blood vessels constitute the foundation of the EPR effect \[^{(9-11)}\]. Therefore nanoparticles exhibiting tumor targeting characteristics can be directed for targeted drug
delivery using principles and understanding of EPR effect.

**CRITICAL ATTRIBUTES OF NANOPARTICLES INFLUENCING EFFICACY OF EPR EFFECT**

**Molecular size:** Since molecular weight is an important determinant of EPR effect, particles or molecules larger than 40 kDa (threshold of renal clearance) show an active EPR effect with prolonged circulation time, increased plasma half life as a result of their very slow clearance from body [12]. Prolonged circulation time allows molecules to gradually permeate into tumors and remained accumulated in tumors for a relatively long time (e.g. several days). As discussed earlier not only macromolecules but also drug-polymer conjugates, liposomes, micelles, nanoparticles, lipid particles and DNA polyplexes show EPR effect. For e.g. investigation of copolymer N-(2-hydroxypropyl) methylacrylamide HPMA with molecular size up to 778 kDa and protein α-macroglobulin (720 kDa) suggested that both macromolecules exhibits the EPR effect [13].

**Biocompatibility:** Not only molecular size but also biocompatibility of nanoparticles is critical to achieve long plasma half life and in turn, functional EPR effect. Biocompatibility issues are predominant in case of protein therapeutics. Most proteins, when they are denatured or highly chemically modified become less biocompatible and therefore cleared rapidly from the circulation via scavenger receptors or other mechanism [14]. Ligand targeted drug delivery system utilizes active targeting wherein nanomedicine is coupled with ligands which have specific affinity towards molecular signatures expressed on the surface of cells requiring clinical intervention.

Among the proteins and peptide class of ligands antibodies, antibody fragments and diabodies are widely investigated. Other protein based targeting moieties include carrier proteins such as transferring [15] & low density lipoprotein (LDL) [16], natural ligands of cell receptors such as hormones & lectins [17], and molecules derived from toxins and pathogens such as cell permeating peptides [18]. Other classes of ligands include small molecules such as folate [19] & vitamin B12, nucleic acids such as aptamers and certain sugars such as the monosaccharide mannose [7].

However only proteins and peptides, antibodies are widely investigated and used. These ligands are coupled with nanomedicines using various coupling strategies like co-synthesis, chemical conjugation [19] or bioconjugation [20]. These coupling strategies make conformational changes in native macromolecule or even in unmodified polymer leading to their identification by RES system and rapid clearance from plasma which is undesired for functional EPR effect. However, this challenge can be overcome by coupling with PEG [21,22]. Another newer approach is by coupling to peptides derived from protein CD47 which binds to SIRPα on leukocytes thereby preventing phagocytosis and prolonging plasma circulation time [23].

Ideally, the drug carrier should be eliminated after drug release. But, unless the nanocarriers are biodegradable, it will remain in the body and be dealt with as a foreign body. Foreign body causes activation of macrophages which in turn phagocytose & attempt to degrade the nanocarriers in its lysosomal compartment. If macrophages fail to do so, then foreign body giant cells will be formed by fusion of multiple macrophages or monocytes & ultimately forms lesions resembling granulomas [24]. Also, prolonged inflammation & frustrated phagocytosis can lead to induction of malignancy on chronic accumulation of non-biodegradable materials [25].

**Surface charge:** The presence of many sulphated & carboxylate sugar moieties on luminal surface of blood vessels gives them negative charged surface. This fact leads to rapid clearance of polymeric drugs with high positive charges as they will nonspecifically bind to luminal surface of vascular walls leading to reduced plasma half life. Whereas particles with high negative charges not only get trapped in liver but also trigger coagulation cascade which ultimately leads to blood coagulation (clotting). In worst cases, clot can block brain capillaries, which may lead to stroke & finally patient may die [26]. Therefore, desired surface charge is weakly negative to near neutral. Figure 1 explains the effect of surface charge.

**Release rate:** The ultimate goal of targeted drug delivery is to deliver most of the administered drug to the target site at optimal release rate. Too slow release rate results in subtherapeutic drug level at target site whereas too fast release rate would lead to a high concentration of free drug in circulation but no drug accumulation at target site resulting in undesired systemic toxicity and lower therapeutic effect. Basically nanoparticles can be formed by either encapsulation (micelles, liposomes) or conjugation (drug-polymer conjugate) [27,28]. Encapsulation based micelles shows very rapid drug release (micellar burst) after injection e.g. nearly 50% release within about 30 minutes for several drugs whereas liposomes with adequate shelf life or stability in solution shows too slow...
release rate as they possess cholesterol-enriched harder lamellar structures. Conjugate based nanoparticles are synthesized through chemical bonds between drug and polymer for e.g. amide, ester, urethane, azide, imide and hydrazone etc. Release of drug from its conjugate depends on temperature, pH or enzymatic cleavage. For e.g. ester linkages ensures a rapid release due to abundance of esterases in plasma whereas amide linkage will ensure slower release profile. Therefore, choice of linker in case of conjugates and selection of suitable encapsulation based nanoparticles is critical determinant of rate of drug release.

**FACTORS INVOLVED IN EPR EFFECT**

Most of these factors are common mediators in inflammation & cancer and are highly expressed (as shown in Figure 2). A major difference between the two pathological lesions is the clearance rate of extravasated macromolecules such as plasma proteins, nanoparticles which results in a prolonged retention time in tumor tissue compared with that in inflamed tissue [31-33]. Consideration and studies of these factors will help the development of new strategies to modulate the EPR effect, angiogenesis and thus tumor growth.

**Bradykinin:** Bradykinin is a major mediator of inflammation that induces extravasation & accumulation of body fluids in inflammatory tissues leading to edema & major cause of pain in inflammation. In addition to bradykinin, tumors have hydroxypropyl bradykinin, which is a derivative of kinin that has the third amino acid replaced by hydroxyproline. High levels of derivative were found in blood plasma & in peritoneal & pleural fluids in carcinomatosis in patients with advanced cancer. Recently it was found that bradykinin also activates endothelial cell-derived nitric oxide synthase; which ultimately leads to an increase in nitric oxide (NO), which is an important mediator of tumor vascular permeability [31].

**Nitric oxide (NO) and its derivatives:** NO has multiple direct & indirect roles as a signalling messenger & hence it is a vital molecule in living creatures. NO is produced from L-arginine by nitric oxide synthase (NOS) in presence of oxygen. NO is extensively produced using iNOS from a greatly increased number of infiltrated leukocytes. Oxidized products of NO including ONOO- and nitrogen dioxide potentiates the EPR effect [31,32]. ONOO- is a strong oxidizing and nitrating agent, which forms via the reaction of NO with superoxide anion (O$_2^-$).

**Collagenase (Matrix Metalloproteinase (MMP)):** ONOO- activates matrix metalloproteinase. MMP’s are zinc-dependent neutral endopeptidases which are overexpressed in tumor cells. Activated MMP’s cause disintegration & remodelling of extracellular matrix as a result of collagenolytic action and thus facilitates vascular permeability. Further, activated MMP’s cause activation of plasminogen & in turn activated prekallikrein, thus activates bradykinin cascade. In addition to activation of MMP’s, ONOO has other roles such as decomposition of ONOO$^-$ to generate NO and nitration of amino acids in protein (e.g. nitrotyrosine) & nucleic acids (e.g. nitroguanosine) as a result of its high reactivity. These nitro compounds release nitrite (NO2$^-$) which may serve as source of NO [11,33].

**Prostaglandins (PGs):** PGs are enzymatically derived form arachidonic acid by the action of cyclooxygenases (COXs) & are lipidic in nature. PGs are important mediators in inflammation & are upregulated by inflammatory cytokines & bradykinin. Among the various PGs, prostaglandin E & prostaglandin I2 exhibit effects similar to those of NO [11,33].

**Angiotensin-converting enzyme (ACE) inhibitors:** ACE inhibitors are important class of antihypertensive drug which acts by preventing conversion of angiotensin I (AT-I) to angiotensin II (AT-II). Since the amino acid sequence of angiotensin I is similar to that of bradykinin at the C-terminal end, ACE inhibitors blocks degradation of bradykinin as well. Therefore, ACE inhibitors potentiate the pharmacological actions of kinin & acts as vascular permeability factor [32].

**Vascular endothelial growth factor (VEGF):** Solid tumors are characterized by the angiogenesis which is important for rapid growth of tumor. VEGF plays important role in any angiogenesis, enhancement of vascular permeability; both facilitate & sustain rapid growth of tumor. VEGF is highly upregulated in most tumors [33]. Recently, inhibitors VEGF (angiogenesis inhibitors) are approved to treat cancer for e.g. bevacizumab (Avastin) [34], ranibizumab (Lucentis) [35].

**HETEROGENEITY OF THE EPR EFFECT**

The EPR effect is not perfect or effective for all solid tumors, because tumors of different patients vary greatly in actual clinical setting. Therefore, one can say that heterogeneity of the EPR effect reduces its universal validity. The heterogeneity is due to the tumor biology diversity.

**Tumor doubling time (TDT):** While designing EPR based anticancer nanoparticles, TDT is crucial...
factor to consider as it is highly heterogeneous. It exhibits heterogeneity at both intratumor and intertumor level with respect to different tumor types, tissue origins, stages and grades. Therefore, while designing EPR based anticancer nanoparticles one should consider doubling time variation when planning the release mechanism of active chemotherapeutic agents from its nanocarriers, as well as internalization rate of macromolecular complexes into tumor cells [36] for e.g. polymer-drug conjugates with slow releasing amide bond, or slowly internalized liposome, could be good choice for tumors with a slow TDT. In contrast, fast releasing micelle or an ester bond linkage can be a better fit for rapidly dividing tumors as described in above section.

**Variations in tumor vascular density:** Vascular density is largely dependent on the type of cancer & varies largely within each tumor type. Also, metastatic tumors tend to posses higher vascular density compared to non-metastatic tumors. Also; it has been found that large variation in expression of vascular permeability factor like VEGF exists. Thus, while designing the nanoparticles, the properties of the targeted tumor tissue such as cancer type, the microvascular density & the secretion of tumor vascular permeability factors such as VEGF should be considered to take full advantage of EPR effect. Tumor diameters can be less than 1 cm to larger than 10 cm; & tumors can be highly hypoxic to normoxic, can have different pathological classes, are genetically diverse, can have partial or extensive necrosis, can have occluded or compressed vascular systems with or without blood coagulation in or around the tumor mass [13,36]. This heterogeneity can be overcome in a number of ways as discussed in following section.

**APPROACHES TO POTENTIATE THE EPR EFFECT**

As we have identified many permeability factors such as NO, bradykinin, & prostaglandins, that facilitates extravasation or the EPR effect in cancer tissues. These factors are not generated in normal benign tumors and therefore these systems are not activated under normal circumstances. Therefore, augmentation of these factors will affect only tumor or influenced tissues, with the results being tumor- selective enhanced vascular permeability & improved delivery of drugs to tumors. In this way, heterogeneity of EPR effect can be overcome. Following section describes two approaches by which EPR effect can be potentiated namely by targeting tumor vasculature or stroma and reducing tumor cells barrier to drug delivery by killing them.

**Targetting Tumor Vasculature or Stroma**

**Increased delivery of nanoparticles to tumors under Angiotensin-II induced hypertension**

Tumor blood vessels lack a smooth layer or pericytes needed for vasoconstriction, so tumor blood vessels on infusion of AT-II show very little vasoconstriction, whereas blood vessels of normal tissues show constriction. Therefore; by inducing hypertensive state by using AT-II, normal blood vessels will constrict while tumor blood vessels will be open, thus facilitating vascular leakage. The final result would be increased blood flow volume in tumor tissues & hence increased drug delivery [37].

**Use of nitroglycerin for enhanced delivery to tumors**

As described in factors involved in EPR effect, NO is major facilitator of EPR effect. Hence, tumor targeted delivery of macromolecules can be enhanced by use of NO or NO-relasing compounds such as nitroglycerin. These NO releasing agents generate NO from NO2 selectively in hypoxic tumor tissue compared with normoxic tissues. Thus, such nitro agents facilitate the EPR effect via local NO generation in tumors, with enhanced drug delivery up to 2-to 3-fold & improved therapeutic effect [38]. Clinically used agents which are investigated include nitroglycerin and isosorbide dinitrate.

**Using ACE inhibitors**

As described in the above section, solid tumors generate bradykinin which would aid the EPR effect. ACE inhibitors inhibit degradation of bradykinin, thus raising the local bradykinin concentration in tumor tissues in the body [39].

**Generating carbon monoxide (CO)**

Enzyme heme oxygenase-1 (HO-1) is upregulated in most solid tumors & serves as important role by producing CO which has physiological function similar to the vasoconstrictor function of NO. Therefore CO also has a key function in EPR effect. Therefore, use of OH-1 inducers like PEgylated hemin or similar agents or CO-releasing agents (e.g. Carbon monoxide-releasing molecule, CORM2), can facilitate the EPR effect [40]. Other possible options include use of prostaglandin (PG) I2 analogue such as beraprost sodium or use of TGF-B inhibitor (TGF-B is tumor growth & differentiation factor. It facilitates production of extracellular matrix.)

**Reducing Tumor Cells Barrier to Drug Delivery by Killing Them**

Tumor cells themselves acts as a barrier to deeper penetration of nanoparticles. Short term application of radiation, photo-dynamic therapy or chemotherapeutic agents to kill cancer cells can
Recent advancements in imaging and therapeutics have led to a better understanding of how to effectively target cancer cells. These developments have been enabled by the EPR effect, which is the increased permeability of blood vessels in tumors compared to normal tissues. This increased permeability allows nanoparticles to accumulate in tumors, providing a potential therapeutic target.

Theranostics is a concept that combines the imaging and therapeutic properties of a drug in a single platform. This allows for targeted delivery of therapy and real-time monitoring of therapeutic efficacy. For example, theranostic nanosystems can be used to deliver drugs to specific locations in the body while simultaneously imaging the location of the drug to ensure it is reaching the target site.

The use of nanomaterials in cancer therapy has led to the development of drugs that can be targeted to specific locations in the body. These drugs can be designed to be taken up by cancer cells and then release their therapeutic payload. This targeted delivery of therapy can help to reduce side effects and improve the effectiveness of treatment.

Theranostics is an important area of research for cancer treatment. Advances in this field will continue to improve the efficacy of cancer treatments and reduce side effects for patients. The development of theranostics nanomedicine requires significant advances in imaging and nanomaterials, and considerable research with respect to their safety.
for very long periods, several weeks or months gave sustained drug delivery with marked therapeutic effect. 

*Extended applications of SMANCS/Lipiodol therapy*

With SMANCS/Lipiodol therapy it is now possible to treat advanced, difficult to treat solid tumors. This includes massive and multiple metastatic liver cancers, pancreatic cancers and their metastatic nodules in the liver, or bile duct carcinomas and cholangiocarcinomas. Advancements in tumor targeting was achieved by infusing SMANCS/lipiodol intra arterially under conditions of AT-II induced high blood pressure (e.g. from 100 Hg mm to 150 Hg mm). The blood pressure of 150-160 Hg mm was achieved via slow i.v. infusion of 0.5 µg/ml AT-II, which is set in a 20 ml infusion syringe-pump. Benefits of this method are improved therapeutic effect & diagnostic value. The improved diagnostic value is due to highly sensitive detection, by means of computed tomodraphy (CT) of the tumor selective uptake of Lipiodol; even in small tumor nodules with diameters of 3-5 mm. Improved therapeutic effect can be obtained on more types of tumors. Poor drug delivery to tumors due to heterogeneity of EPR effect can be overcome. Another benefit of this method is the reduced time required for tumor regression & less frequent drug administration needed.

**TABLE NO. 1: DRUG TARGETING STRATEGIES [8]**

<table>
<thead>
<tr>
<th>STRATEGY</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PASSIVE</strong></td>
<td>Relies on physiological body features e.g.:</td>
</tr>
<tr>
<td></td>
<td>- reticulo-endothelial system (RES)</td>
</tr>
<tr>
<td></td>
<td>- monocyte-macrophage system</td>
</tr>
<tr>
<td></td>
<td>- enhanced permeability and retention (EPR) effect</td>
</tr>
<tr>
<td><strong>INVERSE</strong></td>
<td>by blockade/saturation of passive targets</td>
</tr>
<tr>
<td></td>
<td>- RES blockade by sugar polymers/ lipid microemulsions</td>
</tr>
<tr>
<td><strong>ACTIVE</strong></td>
<td>Based on imposing targeting properties to drug:</td>
</tr>
<tr>
<td></td>
<td>- intrinslic: drug designed to target a specific molecule</td>
</tr>
<tr>
<td></td>
<td>- extrinsic: drug coupled to targeting features</td>
</tr>
<tr>
<td></td>
<td>*physical targeting: programmed release (pH, temperature etc)</td>
</tr>
<tr>
<td></td>
<td>*ligand based: coupling to affinity moieties: as conjugates or through carriers</td>
</tr>
<tr>
<td><strong>COMBINED</strong></td>
<td>By combining any of the above strategies</td>
</tr>
</tbody>
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**CONCLUSION**

In the current arena of anticancer drug development, the need for a wide range of knowledge about cancer genomic & tumor biology is not fully explored. Drug development based on EPR effect is certainly an important first step, but some problems still remain. Even after a drug is delivered to cancer tissues, it must be taken up by tumor cells, & free active drug must then be released & interact with target molecules to achieve full potential of EPR effect based targeted drug delivery.

*Srinivasan et al., World J Pharm Sci 2014; 2(8): 881-889*
Figure 1: (A) Quick internalization due to electrostatic adsorption, but are not suitable in vivo; (B) negatively charged carriers are quite stable in vivo, but cause biocompatibility problems; (C) PEGylated nanoparticles are internalized slowly because of steric hindrance [29]. (Reprinted with permission from author)

Figure 2: Various vascular mediators commonly found in inflammation and cancer that contribute to the EPR effect [30]. (Reprinted with permission from author)

REFERENCES

Sriniivasan et al., World J Pharm Sci 2014; 2(8): 881-889