

## Enhanced Permeability and Retention-Effect and Nano-medicine on Backdoor

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### Editorial

Cancers are a leading cause of death today as they will be in the future. Chemotherapy is one of the major weapons we have in the ill equipped battle against this important human threat. Despite several drawbacks, nanoparticle based drug delivery systems (DDS) hold promise to ameliorate anticancer chemotherapy. From the beginning of “Nano medicine” by the discovery of liposomes by Bangham et al. in 1965 [1] till the recent boost of papers about various new materials and combined strategies in the last decade, a vast number of chemotherapeutic agents has been loaded or encapsulated into different kinds of nanoparticles. Many approaches have been successfully tested, at least in preclinical studies [2]. Unfortunately, only very few “Nano medicines” are in clinical practice today, despite the fact that they accumulate in human tumors by the same mechanism as DDS do in animal models.

While DDS are unable to penetrate the endothelial barrier in most organs, they extravasate into tumor tissues by the so called “enhanced permeation and retention effect”, often referred to as “EPR-effect”[3]. In contrast to healthy endothelial barriers, neovasculature in growing tumor tissues is usually leaky, showing gaps between 200 nm and 2 µm in size [4]. These gaps allow DDS, usually in a therapeutic range between 50 and 200 nm, to enter the tumor interstitium. Once inside the tumor, they may further penetrate the tumor by diffusion, even though this penetration is limited to a range of a few cell layers around the blood vessels [5]. Since there is no lymphatic clearance of tumor interstitium, the accumulated particles are retained in the tumor. Beside DDS targeting the tumor vasculature, the EPR-

effect is the basic entry route of all DDS that are developed for antitumor therapy.

Exploiting the EPR-effect by non-targeted DDS is also referred to as “passive targeting”, and the most successful clinically used DDS- pegylated liposomal doxorubicin – is based upon passive targeting [6]. Unfortunately, the EPR-effect is although the major bottle-neck for more sophisticated DDS, that try to specifically address tumor receptors to enhance uptake and/or specificity. Before the targeting ligand may spot its target, the particles must find their gaps into the tumor first, and so the EPR-effect becomes a bottleneck instead of a specific drain.

Despite nearly 3 decades and more than 500 citations of the original work [7], the EPR-effect is not well understood today. Beyond the original description, several unresolved puzzles remain: The amount of DDS in tumor tissue is strictly depending on the blood concentration of DDS in a linear fashion [3, 8], but a saturation of tumor tissue has not been described yet. Moreover, accumulation kinetic seems to be the same with different concentrations. Accumulation in tumor tissue is much faster than accumulation in other tissues [9], leading us to postulate the concept of kinetic targeting [10], but in contrast to accumulation of DDS in other tissues, accumulation of DDS in tumor tissue cannot be described by classical pharmacokinetic models [11]. Considering pharmacokinetic data, we further postulated that the entry of DDS into the tumor must be a one way route, a notion that is supported by recent preliminary data seen with a plasmapheresis animal model. Thus entry into tumor must follow some mechanism beyond simple diffusion through gaps. Since EPR is

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a basic principle for all DDS of appropriate size, it has become a bottleneck for new developments. It won't help to develop new materials, better targeting or highly sophisticated cell killing, only to shipwreck at limitations of EPR first hand. A more detailed understanding of accumulation of DDS into tumor tissue by EPR is urgently needed to improve the use of nanomedicine in future.

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