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Editorial

Current Challenges and Future Directions in Nanomedicine

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Nanomedicine research focuses on the medical application of nanotechnology and emerged as a field from the early success of nanoparticle based drug delivery systems, in particular for treatment of cancer, and the advances in nano- and biotechnology over the past decades. The field is globally highly active due to the tremendous potential to advance disease diagnostics, monitoring and treatment, and many universities and companies are increasing their focus in this area in all regions of the world. The use of nanoparticles for drug delivery is one of the areas that are attracting the greatest attention and in the last few years the focus on nanoparticles have expanded to include diagnostic imaging. This is now providing highly interesting new possibilities as nanoparticle drug delivery systems are perfectly suited for being co-developed with companion diagnostic imaging systems that can select patients that will benefit from the particular treatment, thus providing a perfect example of the newly initiated era of theranostics and personalized medicine [1]. Nanomedicine is moving in many new directions, e.g. in tissue engineering where it has been realized that nanostructure in advanced biomaterials is highly important for how materials interact with the biological interface [2]. Another example includes, micro- and nano-structured lab-on-a-chip systems for highly sensitive diagnostics e.g. for detection of disease markers in blood [3]. The field is progressing at an unbelievable speed and there is no doubt that many new technologies will be introduced that provide better disease diagnostics and treatments for the benefit patients and society in the years to come. Even so, there are also certain challenges that the field faces at a fundamental level. Common to perhaps all technology developments within the field is a poor understanding of the complex interaction between the artificial materials we are developing and the biological environment they are placed in. This lack of understanding is at protein, cellular and whole organism level. It is clear that surface chemistry, nanoscale to macroscale morphology and material softness are parameters that all affect the biological behavior of the technologies we are trying to develop but our ability to understand and map these effects needs to be improved further over the next decades. We would like to exemplify this point by discussing the current understanding of nanoparticle based drug delivery systems for intravenous administration and the challenges we are faced with in improving this understanding.

The interest in polymer and lipid based drug delivery systems, which were the first examples of nanosized structures that today falls into the nanoparticle category started in the 1950's and 60's

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and the first products reached market in the 1980's and 90's. The first liposome drug, DOXIL, reached market in 1995 and is the best selling nanomedicine drug to date. We will argue that there were three important findings that allowed for the invention of DOXIL: 1) The discovery of the enhanced permeation and retention (EPR)-effect in 1986; 2) The discovery of the shielding effect against opsonization of poly(ethylene glycol) (PEG) nanoparticle coatings in 1991; 3) The loading of doxorubicin by the ammonium sulfate gradient. DOXIL has in many ways been a gift and a curse to the field. A gift, as it showed that it was really possible to reformulate a drug, in this case doxorubicin, into a more effective drug using nanoparticle technology. A curse, because it led to a number of assumptions that to some extent still exist, about the biological challenges a drug delivery system for treating solid tumors faces. The result was that researchers moved very quickly and established a number of technologies and companies based on these assumptions that led to a negative view on nanoparticle based drug delivery from big pharma and venture capitalists as early expectations were not fulfilled. Today, it even remains difficult to challenge some of these assumptions. The report of the EPR-effect in solid tumors and the use of nanoparticle PEGylation to secure long blood circulating due to reduced immune system clearance, has led to thousands of articles and patents describing innovative strategies for delivery of drugs to solid tumors using nanoparticles. From a tremendous amount of articles it is clear the EPR-effect ensures high uptake of PEGylated nanoparticles in solid tumors based on xenograft models, where usually 4-8% of the injected dose reaches the tumor depending on the nanoparticle and the model under investigation. However, it was generally neglected to investigate if the EPR-effect is a common phenomenon in larger animals and humans with spontaneous tumors, partly due to regulatory challenges. A couple of studies have been published [4], but it has now been realized that a detailed evaluation of the EPR-effect in humans is highly warranted [5] and improved imaging techniques such as positron emission tomography (PET) will allow us to conduct these types of studies. Another challenge is the simplistic view of the EPR-effect, which we have generally illustrated and conceptually understood as leakiness in the blood vessels due to 200-800 nm sized gaps between the endothelial cells. However, another important aspect of this is the barrier constituted by the extracellular matrix, which is very poorly

understood in a drug delivery context. For example, tumor penetration of the nanoparticle drug carriers is highly important for the therapeutic benefit but we only have limited data from xenograft models in mice and essentially no data in larger animals and humans with spontaneous tumors. The challenge of not having such data is that we may miss important aspects in relation to drug delivery system design as almost all studies only evaluate total tumor accumulation and therapeutic end point. In addition, the lack of understanding of the extracellular tumor matrix is a challenge to us in relation to optimizing active targeting where targeting ligands such as peptide and antibodies that binds to over-expressed receptors on the tumor cells are conjugated to the nanoparticles. We do not understand the interplay between the targeted nanoparticles and its interaction in the extracellular matrix and with the cell surface receptors. We also have very poor ability to evaluate cellular uptake *in vivo* in a quantitative way. The result has been that the importance of targeting over-expressed receptors on cancer cells in solid tumors is one of the heavily debated questions in the field. Some groups claim it works very well and provide significantly higher tumor accumulation than non-targeted nanoparticles that rely on the EPR-effect for tumor accumulation, and other groups claim that there is no difference in tumor accumulation. It should be noted that most targeted systems rely on the EPR-effect to get in contact with tumor cells and it is therefore not obvious that there should be an improved accumulation effect. Even so, there might be an important therapeutic effect if the targeted nanoparticles enter the tumor cells effectively, but as mentioned, this is not easily quantifiable with currently available techniques and has only been evaluated in a qualitative manner. Lastly, the real question here is whether the targeted nanoparticles will prove more effective in non-xenografts, i.e. large animals and humans with spontaneous tumors, which is not yet known. Future studies in large animals and humans should therefore include quantitative evaluation of tumor and cellular uptake as well as the therapeutic benefit.

Naturally, one prerequisite for nanoparticulate drug delivery systems to be effective in treating solid tumors, is tumor accumulation as described above, another is effective release of the drug payload at the target site. A tremendous amount of nanoparticle based drug release strategies have been proposed that can be classified into certain areas. The simplest and most successful strategy so far, probably due to relative simplicity, is based on utilizing certain physico-chemical characteristics of drugs to obtain a slow drug leakage from the formulations after accumulation in the cancerous site, which is the principle of DOXIL. However, this strategy is only applicable to a relatively small range of drugs and cannot be applied to biologicals. Many advanced drug release strategies have therefore been investigated. Such strategies include utilization of heat, light and ultrasound sensitive systems, and in particular pH sensitive systems where the lower p^H in tumors and endosomes can potentially induce drug release. Highly interesting are enzyme sensitive systems that are utilizing over-expressed disease associated enzymes to trigger drug release. The p^H and enzyme based strategies are particularly interesting as they require no prior knowledge

of the tumor localization. However, these strategies suffer from difficulty in transferring *in vitro* optimization to *in vivo* efficiency, and we believe that most researchers in this area will agree that there is certain aspects of the *in vivo* conditions we do not understand. As an example, enzyme sensitive drug delivery systems have been designed for activation by phospholipase A2 or matrix metalloproteases, which are classes of extracellular enzymes that are secreted into the extracellular matrix. The presence and activity of the enzymes can be evaluated by various techniques, however, it is a major challenge to quantify how the extracellular matrix components competes with the nanoparticle substrates. Ideally, with all delivery systems we would like to evaluate the drug release kinetics from the carriers directly in the tumor, but no such studies have been published yet.

Lastly, for all nanoparticle drug delivery systems, independent on strategies used, we are greatly challenged with understanding protein adsorption to the particles and how this changes their biological behavior. It is clear that PEGylation reduces opsonization and allows for long blood circulation of the particles, however, this is currently more or less what we know. To our knowledge the only mechanistic understanding of the effects of protein adsorption originates for studies of complement activation related to nanoparticles [6]. Enhancing the understanding of the biological effects of protein adsorption is probably one of the most important steps forward for the field but we are limited by the techniques we have available to study these phenomenon.

Despite the challenges of understanding the biological interactions of artificial materials such as nanoparticles and the consequences thereof, it is without doubt that the nanomedicine field is going to provide multiple new solutions and products that will solve healthcare challenges in the coming decades and it is going to be very interesting to follow this development.

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