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Commentary

SMART drug delivery systems: Back to the future vs. clinical reality

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ABSTRACT

Recent advances in nanotechnology and material science have re-ignited interest in drug delivery research. Arguably, however, hardly any of the systems developed and strategies proposed are really relevant for shaping the future (clinical) face of the nanomedicine field. Consequently, as outlined in this commentary, instead of making ever more carrier materials, and making nanomedicine both science-fiction and fiction-science, we should try to come up with rational and realistic concepts to make nanomedicines work, in particular in patients.

In the past few decades, the **drug delivery** field has grown exponentially. Many different drug delivery systems have been designed and evaluated, and a large number of strategies for site-specific drug targeting to pathological tissues have been explored. One of the primary reasons for this recent explosion in drug delivery research arguably is the progress made in (polymer) chemistry, biotechnology, material science and nano-engineering: on a daily basis, tens to hundreds of novel nanomaterials are being reported, and are considered potential drug delivery systems simply because their size is somewhere between 1 and 100(0) nm. A key question in this area of research, however, is whether we should primarily focus on making ever more (and ever more advanced) drug delivery systems, or rather on better understanding the drug delivery process as a whole, and on more optimally exploiting the materials we already have, in order to eventually make them work, in particular in patients.

Examples of already available and clinically relatively well-established **nanocarrier materials** are liposomes, polymers, micelles, proteins and antibodies. These formulations have been extensively evaluated and optimized over the years, both in animal models and in patients, and several of these 'standard' nanomedicine formulations have been approved for routine use by the responsible regulatory agencies. Examples of 21st century carrier materials are even more diverse (and sometimes even exotic), ranging in nature from nanobodies, peptides, cells and viruses to iron oxide, gold, carbon and silica nanoparticles, and in shape from spheres, shells and sheets, to diamonds, cubes and tubes.

In search of **potential applications** for such intuitively highly advanced nanomaterials, people often envision drug delivery purposes. In particular for drug targeting to tumors. Because cancer is such a dreadful disease, and because blood vessels in tumors are widely believed to have 'holes' as large as 800 nm, enabling long-circulating carrier materials to effectively and selectively accumulate there over time, via the enhanced permeability and retention (EPR) effect. Enhanced vascular leakiness and potential for EPR-mediated drug targeting has also been reported for a number of non-cancerous disorders, including e.g. inflammatory and infectious diseases. Because EPR-mediated drug targeting essentially only relies on the pathophysiological properties of the target tissue, and not on any specific feature of the carrier material (apart from its 1 to 100 nm size and its long circulation time), it is generally referred to as passive drug targeting. Additional strategies frequently employed in drug delivery research include active drug targeting, both to cancer cells and to angiogenic endothelial cells (using e.g. antibody- and peptide-modified nanomedicines), as well as triggered drug release (using e.g. hyperthermia- or light-responsive carrier materials).

In the present issue of the International Journal of Pharmaceutics, **Crommelin and Florence** recapitulate the progress made in the drug targeting field over the years (Crommelin and Florence, 2013). They describe some of the advances made in the early days of nanomedicine research, address what has been learned along the way, summarize the current (pre-) clinical status, identify potential pitfalls, suggest solutions for overcoming these challenges, and highlight several 'smart' 21st century systems and strategies for taking the drug delivery field to the next level.

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In the **present commentary**, I share some thoughts on how 'smart' – in my opinion – these systems and strategies really are, and suggest ways forward to assist nanomedicine formulations in becoming valuable tools for really improving day-to-day clinical practice.

Many 21st century nanomaterials used for drug delivery purposes are dubbed to be '**smart**', meaning that they possess certain built-in properties related e.g. to triggered self- or dis-assembly, to stimuli-responsive drug release, to magnetic guidance, to heat generation and/or to photo-activation. When recapitulating the basic principles of drug targeting to pathological sites, however, and when critically judging upon the feasibility of the concepts proposed and the translational value of materials developed, one cannot help concluding that most of these novel nanomaterials are 'art', rather than 'smart'. This because they generally are highly complex multi-component formulations, with sizes often exceeding 100 nm, and difficult to synthesize and scale-up in a controllable and reproducible manner. In addition, they are often composed of non-biodegradable and pharmacologically (toxicologically) questionable materials. The former makes it almost impossible for the pharmaceutical industry to consider producing them, especially in large amounts, while not making them overly expensive. The latter would require extensive and expensive in vivo toxicology studies, both in animal models and in patients, providing long-term feedback on both deposition in healthy organs and potential side effects.

Surely, the **toxicity** of nanomaterials is often overgeneralized and/or misinterpreted – it's the dose that makes the poison, right? – but this remains to be an important issue, since carrier systems indeed tend to stay around in the body much longer than do standard (low-molecular-weight) drugs. Consequently, extensively evaluating and carefully documenting the biodistribution, biodegradation, long-term deposition and toxicity of such materials is critical for facilitating and fostering their potential clinical use.

The **size** of drug delivery systems, often (mis-) assumed to be ideal at around 100 nm, adds yet another layer of complexity to the design of 'smart' nanomaterials. In the 1990s and early 2000s, many scientists were synthesizing drug and gene delivery vehicles with sizes of up to 500 nm. In vitro, these materials always work very well, most likely because they simply sediment onto target cells in well-plates, and thereby indirectly force cells to take them up, at least to some extent. In vivo, however, nanoparticles with sizes exceeding ~100 nm are cleared very fast by the mononuclear phagocytic system (MPS; formerly known as the reticulo-endothelial system (RES)), and because of their ultra-short circulation times and strong and rapid accumulation in liver and spleen, they are unable to exploit the EPR effect to accumulate in tumors and at sites of inflammation. In addition to this, many (especially cationic) nanoparticles tend to aggregate in vivo, leading to strong and rapid accumulation in liver and lung, and frequently also to embolisms and lethality. Moreover, it has become increasingly apparent that the EPR effect is a highly variable phenomenon, with blood vessels in some mouse tumors indeed presenting with a small number of holes as large as 800 nm, but with the majority of tumor blood vessels – in particular those in patients – with much lower levels of leakiness and with very high intra- and interindividual differences in vascular permeability. Also, people often forget that even if nanoparticles with sizes of 50–100 nm would efficiently extravasate within tumors, that they would then subsequently fail to properly penetrate into the matrix-rich and highly dense tumor interstitium. This situation is further complicated by the high interstitial fluid pressure (IFP) which is typical of solid tumors, and which is responsible for 'pushing' extravasated nanomaterials back into systemic circulation.

Taking these notions and the fact that vascular leakiness remains to be the main rationale for the (pre-) clinical use of nanomedicine formulations into account, it appears to be extremely important to **better understand EPR**, and to be aware of its principles, peculiarities and limitations. With respect to principles, for instance, it is reasonable to conclude that a size just large enough to avoid rapid renal excretion, i.e. 5–10 nm, might be ideal, as this would allow not only for long-circulation and efficient extravasation, but also for proper penetration and retention. With respect to peculiarities and limitations, in particular its very high intra- and inter-individual variability, one could argue that by simply monitoring EPR in patients, i.e. by visualizing and quantifying how well image-guided nanomedicines accumulate at the target site, patients can be preselected. By doing so, only patients presenting with sufficiently high levels of EPR could then be treated with the formulation in question, as these are most likely to beneficially respond, whereas those with moderate to low levels of EPR would be sent on for treatment with other established or experimental therapies.

Image-guidance consequently seems to be a smart (i.e. rational, simple and straightforward) strategy for **improving the clinical performance** of nanomedicine formulations. Similarly, the rational implementation of these formulations in combination therapies, e.g. together with surgery, with radiotherapy and/or with (standard) chemotherapy, is considered to be a smart and straightforward means for improving their therapeutic efficacy (see below). In spite of this, however, the vast majority of efforts in the nanomedicine field are focusing on making ever more (and ever more exotic) drug delivery systems, rather than on establishing smart strategies to eventually make them work.

Let us therefore, like Crommelin and Florence do in their landmark review (Crommelin and Florence, 2013), briefly go **back to the basics** of drug delivery research, rather than "back to the future" (i.e. making nanomedicine science-fiction and fiction-science), and summarize what we have learned thus far. And then, taking the current clinical reality into account, turn toward the future, to see where we can take things from here.

So where are we? And how '**smart**' are the materials we have developed thus far really, especially in the clinic and/or in advanced stages of pre-clinical research? Aren't all of these materials 'smart' only because they are '**S**ystems (slightly) **M**odulating **A**dverse **R**eactions and **T**oxicity'? Or '**S**ystems (somewhat) **M**ore **A**ble to **R**each the **T**arget site'?

Like it or not, but when critically looking at the **clinical data** available in the literature, this really is as good as it gets at the moment, and for the vast majority of drug delivery systems evaluated over the years, these two features actually are the only two things we can confidently claim for 'smart' drug delivery systems. Regarding the former, we can nowadays indeed make nanomedicines able to prevent certain adverse effects, both during infusion (e.g. Abraxane; which overcomes castor oil-induced local inflammatory reactions during paclitaxel administration), and during circulation (e.g. Doxil; which attenuates cumulative doxorubicin-induced cardiomyopathy). Both are prototypic examples of '**S**ystems **M**odulating **A**dverse **R**eactions and **T**oxicity', and are clinically highly successful because of improved patient tolerance and compliance. In addition to this, in the case of Abraxane, up to 50% higher doses can be given per cycle (260 mg/m^2 vs. 175 mg/m^2), potentially leading to improved therapeutic outcomes.

Regarding the latter, i.e. '**S**ystems **M**ore **A**ble to **R**each the **T**arget site', more drug molecules can indeed be delivered to pathological tissues, but this is often mistakenly assumed to automatically result in improved therapeutic efficacy. In patients, systematic and quantitative head-to-head comparisons of free drug vs. nanodrug levels in target tissues are lacking, but convincing imaging evidence is available showing that under certain circumstances (e.g. in certain

types of tumors, such as sarcomas), nanomedicines do efficiently localize to pathological sites. In animal models, an overwhelming amount of head-to-head data is available, showing improvements in tumor accumulation over time from 10% to 1000-folds, which is generally paralleled by promising in vivo antitumor efficacy. In patients, on the other hand, significant improvements in therapeutic efficacy for '**S**ystems **M**ore **A**ble to **R**each the **T**arget site' are scarce. Doxil, for instance, i.e. PEGylated liposomal doxorubicin, is approved for various different types of tumors, but only works well in very specific subsets of patients. In cisplatin-responsive ovarian carcinomas, it did significantly prolong patient survival as compared to topotecan treatment, but in cisplatin-resistant and non-stratified cohorts, it did not. Similarly, Doxil has been shown to be able to double response rates in Kaposi sarcoma vs. triple chemotherapy with doxorubicin, bleomycin and vincristine, but failed to significantly prolong the survival of KS patients. In line with this, in multiple myeloma and metastatic breast carcinoma, Doxil has arguably only been approved because it is a '**S**ystem **M**odulating **A**dverse **R**eactions and **T**oxicity', and not because it improves efficacy. This in spite of the fact that as compared to free doxorubicin, it undoubtedly is a **S**ystem **M**ore **A**ble to **R**each the **T**arget site, even in relatively non-leaky tumors, such as breast carcinomas.

So **what to do next**? Is making the materials we have 'smarter' a viable option? If yes, then how? Should we try to make them even longer circulating, or smaller, or self-(dis)assembling, or actively targeted, or stimuli-responsive? Would this really significantly improve clinical outcome? In the vast majority of cases probably not... At least not really. For multiple reasons, e.g. because EPR is a highly variable phenomenon (underlining the need for imaging), because active targeting is only marginally useful (arguably only if therapeutically active targeting ligands are used), because stimuli-responsive formulations and treatment regimens are highly complex (indicating we should try to come up with simpler and more broadly applicable approaches), and because chemotherapeutics are hardly ever used alone (stressing the need for rationally integrating nanomedicines in combination therapies).

These insights imply we should go back to the basics, rather than "back to the future", if we want to make nanomedicines part of **clinical reality**. And that we should try to come up with 'smarter' strategies, rather than with 'smarter' systems. What e.g. about '**S**ystems for **M**onitoring **A**ccumulation and **R**etention at the **T**arget site?' Or '**S**ystems for **M**ultidrug delivery and/or **A**dvanced **R**adiochemotherapeutic **T**reatments?' In particular in the case of cancer, these options might be much more viable.

If we could, for instance, systematically **integrate imaging** in nanomedicine research and clinical practice, to preselect only those 10–50 out of 100 patients presenting with high levels of EPR, and then only treat those 10–50 preselected patients with the image-guided nanomedicine formulation in question, wouldn't it then be very likely that response rates and survival times would substantially increase? And that treatments could then be individualized and improved? Consequently, '**S**ystems for **M**onitoring **A**ccumulation and **R**etention at the **T**arget site' seem to hold significant potential for personalizing nanomedicine-based (chemo-) therapeutic interventions.

Similarly, if we would rationally integrate nanomedicines in **combination therapies**, e.g. by using them to deliver multiple drugs to tumors simultaneously, or by combining them with clinically relevant regimens of fractionated radiotherapy (routinely applied to patients on every weekday for several consecutive weeks; and thereby likely strongly potentiating the higher accumulation and retention of nanomedicines at the target site), wouldn't then cancer treatments be much more effective? Especially when taking into account that cancer is hardly ever treated with a single chemotherapeutic drug, but virtually always with combinations of surgery, radiotherapy, chemotherapy and/or anti-angiogenic therapy. Therefore, '**S**ystems for **M**ultidrug delivery and/or **A**dvanced **R**adiochemotherapeutic **T**reatments' seem to hold significant potential for improving the efficacy of combined modality anticancer therapy.

In **conclusion**, it seems science-fiction to believe that by simply synthesizing ever more drug delivery systems (i.e. by making nanomedicine fiction-science), we are going to change the face of 21st century clinical practice. This is especially obvious in the case of cancer, but likely equally applies to all other pathologies to be treated with nanomedicine formulations at some point in the near to distant future. Rather, we should carefully (re-) consider the basic principles of drug targeting to pathological sites, and we should try to come up with simple and straightforward formulations, and rational, easily translatable and broadly applicable strategies, to make drug delivery systems a 'smart' part of clinical reality.

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