Nanomedicines and Theraonstics:

Image-guided and Targeted Treatments for Individualized and Improved Interventions

T. Lammers\textsuperscript{1,2,3},

\textsuperscript{1} Department of Experimental Molecular Imaging, Helmholtz Institute for Biomedical Engineering, RWTH Aachen University Clinic, 52074 Aachen, Germany;
\textsuperscript{2} Department of Controlled Drug Delivery, MIRA Institute for Biomedical Engineering and Technical Medicine, University of Twente, 7500 AE Enschede, The Netherlands;
\textsuperscript{3} Department of Pharmaceutics, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, 3584 CG Utrecht, The Netherlands

tlammers@ukaachen.de

ABSTRACT SUMMARY

In the present lecture, I will briefly address the basic principles of passive and active drug targeting to tumors. In addition, I will describe how non-invasive imaging techniques can be used to individualize and improve nanomedicine treatments. Furthermore, recent advances in the use of theranostic materials and methods for drug delivery to inflammatory lesions and to the brain will be summarized, as well as their suitability for tissue engineering purposes.

INTRODUCTION

Nanomedicines are 1-100(0) nm-sized carrier materials designed to improve the biodistribution and the target site accumulation of poorly soluble or poorly stable drugs. Many different nanomedicines have been developed over the years, including e.g. liposomes, polymers and micelles. By delivering drugs more efficiently to pathological sites, and by at the same time attenuating their localization in potentially endangered healthy tissues, nanomedicines aim to improve the balance between the efficacy and the toxicity of systemic (chemo-) therapeutic interventions.

Both preclinically and clinically, nanomedicines have been primarily used for drug targeting to tumors. Nanomedicines can be targeted to tumors via several different mechanisms, including passive drug targeting (based on the Enhanced Permeability and Retention (EPR) effect), as well as via active targeting to cancer cells and to tumor endothelial cells. Moreover, stimuli-responsive nanomedicines can be triggered to release their contents within tumors, as exemplified by the recent use of thermosensitive liposomes in combination with Magnetic Resonance-guided High-intensity Focused Ultrasound (MR-HIFU).

The vast majority of nanomedicines, in particular the ones which are currently being used clinically, rely on EPR-mediated passive drug targeting. It is important to take into account in this regard, however, that EPR is a highly variable phenomenon \cite{1}, with large differences between different patients and different types of tumors. Consequently, there seems to be a clear need to incorporate imaging moieties into nanomedicine formulations, to enable the pre-selection of patients presenting with sufficiently high levels of EPR.

Besides for drug targeting to tumors, combining diagnostic and therapeutic properties within a single (nanomedicine) formulation also holds significant potential for facilitating drug delivery to inflammatory lesions, as well as to the brain. And furthermore, by incorporating imaging agents in scaffold materials routinely used for tissue engineering purposes, such as collagen matrices or vascular grafts, important information can be obtained on their localization, resorption, remodeling and function.
RESULTS AND DISCUSSION

Using findings obtained both in our and in other laboratories, I will put forward concepts to overcome the high heterogeneity typically associated with EPR. These will include efforts to enhance EPR, to combine EPR, to avoid EPR and to image EPR. The latter of these strategies arguably is the most straightforward from a clinical point of view, enabling the pre-selection of patients already very early on during nanomedicine treatment [2]. Regarding active tumor targeting, findings will be presented showing that active tumor targeting does work, but only under certain circumstances, and that it generally does not lead to an increase in tumor concentration [3,4]. A head-to-head comparison of corticosteroid-containing liposomes, polymers, and micelles in rats suffering from rheumatoid arthritis is presented to highlight the importance of carefully controlling drug release kinetics [5]. USPIO-loaded microbubbles are shown to be useful for simultaneously mediating and monitoring drug delivery across the BBB [6]. And finally, USPIO-labeled collagen scaffolds and vascular grafts are shown to be suitable materials for theranostic tissue engineering purposes [7].

CONCLUSION

Based on these insights, it can be concluded that more intensively combining drug targeting and imaging holds significant potential for facilitating the clinical translation of tumor-targeted nanomedicines, as well as for enabling individualized and improved treatments. Image-guided materials and methods might furthermore be highly useful for enabling safe and more efficient drug delivery across the BBB, and for furthering the tissue engineering field.

REFERENCES

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Figure 1: Exemplary efforts showing the use of non-invasive imaging techniques for discriminating tumors with low versus high EPR (A), for monitoring the anti-arthritis efficacy of four different anti-inflammatory nanomedicines (B), and for enabling theranostic drug delivery across the BBB (C).