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Molecular tools for light-navigated therapy

Reeßing, Friederike

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MOLECULAR TOOLS FOR LIGHT-NAVIGATED THERAPY

Friederike Reeßing

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OUTLINE OF THIS THESIS

Even though constant advances and innovations in modern medicine continue to improve the health and quality of life of millions of people, challenges such as the need for more selective drugs still remain unmet. The activity of medicines outside their intended site of action may cause severe side effects, especially in the case of cancer chemotherapy. In order to minimize these problems, new ways of targeted therapy, such as photoactivated chemotherapy and photopharmacology, have emerged. Their current status in the context of cancer treatment is summarized in [CHAPTER 1](#) of this thesis.

A common limitation of the aforementioned approaches is that UV light is most often needed for activation of the responsive medicines. This type of radiation is heavily absorbed in biological tissue and may have cytotoxic effects. In contrast, visible or near-infrared (NIR) light is generally considered non-toxic and stands out due to a much higher penetration depth. Therefore, new molecular structures, responsive to visible or NIR light, are urgently needed for the advancement of light-activated therapies. A synthetic strategy for this purpose is described in [CHAPTER 2](#) and is based on a multi-component reaction allowing the simultaneous coupling of two different moieties, e.g. a drug and targeting moiety, to a visible light responsive core structure.

However, a general prerequisite for light activated therapy is the exact localization of the target tissue, i.e. diseased organ(s). The success of photoactivated therapy is therefore inevitably connected to medical imaging. A variety of corresponding imaging modalities are available in the clinic with each method having its advantages and drawbacks regarding resolution, penetration depth, sensitivity and availability of contrast agents, as illustrated in Fig. 1. For instance, positron emission tomography (PET) and single photon emission tomography (SPECT) stand out due to their high sensitivity but are largely limited by their low resolution. Moreover, the patient is exposed to radiative burden when undergoing these types of scans. The same holds for X-ray computed tomography (X-ray CT), a technique that affords high resolution images but offers very limited choices of contrast agents. Similarly, the use of ultrasound and optoacoustic imaging has constraints in respect to available contrast agents and is furthermore limited by the shallow imaging depth. In this thesis, the focus lies on new approaches and optimization of contrast agents for (i) magnetic resonance imaging (MRI) and (ii) optical fluorescence imaging.

OUTLINE OF THIS THESIS

Fig. 1: Overview of commonly used medical imaging techniques depicted according to the possible imaging depth, resolution and sensitivity.

MRI is a widely used imaging modality, which allows whole-body anatomical imaging with very high resolution. Beyond that, its application has been explored not only for diagnostic purposes but also for monitoring of drug delivery, as described in [CHAPTER 3](#). Despite numerous promising results, the implementation of the presented strategies is still restricted by false positive outcomes. The research presented in [CHAPTER 4](#) addresses this problem by introducing a new approach to MRI contrast agents for simultaneous imaging and drug delivery based on photoresponsive liposomes.

The advantage of using light to provoke a change in MRI contrast, envisioning the application of light-emitting targeting moieties, is the possible signal amplification as one such moiety could activate several contrast agents. Another example built on this principle is described in [CHAPTER 5](#). In contrast to the previously described nanoscopic probe, this agent is a small molecule for the exploration of distinct mechanisms to change the MRI signal.

The subsequent part of this thesis deals with the synthesis of new tracers for optical fluorescence imaging. This technique stands out due to its relatively simple instrumental setup, offering unique applications, such as intraoperative imaging, for which the low penetration depth presents only a minor problem. [CHAPTER 6](#) describes our efforts to develop fluorescent tracers for the imaging of different targets (parathyroid glands, fungal infections). The synthesized agents show fluorescence in the visible light spectrum which is still not ideal for *in vivo* imaging. Implementation of NIR fluorescent tracers would significantly enhance the imaging depth and therefore we proceeded with the synthesis of targeted NIR-dyes, as outlined in [CHAPTER 7](#).

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In summary, this thesis describes various novel approaches to medical imaging and pharmacotherapy aimed to enhance the safety and effectiveness of pharmacotherapy by early diagnosis and increased selectivity of drug treatment.