Supramolecular host-guest chemistry for applications in theranostics

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CHAPTER 7

Future perspective

Due to the high heterogeneity among human cancers, the therapeutic efficacy varies between individual patients. Personalized therapy, or precision medicine, has the potential to overcome this shortcoming. In order to realize such precision medicine, careful control is required on the local accumulation of drugs, either via targeting of disease related molecular pathways or via local therapy. Both have provided the foundations for synthetic developments in the rising field of molecular imaging. In this setting technologies rising from the field of nanotechnology, in particular supramolecular chemistry can be employed to meet today's clinical needs.

The advantage of using non-covalent supramolecular interactions over covalent bond formation is that multivalent interactions between relatively simple building blocks allow for the realization of complex systems under physiological conditions. A prime example of an endogenous supramolecular system is DNA. When supramolecular chemistry is applied during the development of molecular imaging strategies, synthesis of a library of building blocks followed by a stochiometric mix-and-match strategy can tailor different needs. As such a generic chemical toolbox can hold building blocks that serve a different purpose and supramolecular systems support multiplexing with different and or complementing target-, imaging- and therapy-entities.

While clinical studies with ICG-^{99m}Tc-nanocolloid have already underlined the power of supramolecular imaging in the field of molecular imaging, this thesis provides evidence that employing more complex supramolecular systems may provide value also. For example, the targeting of receptors with vectors that were functionalized with a host- or guest-moiety can direct secondary agents with complementary guest- or host-moieties, respectively, to these receptors. Chapter 2 provides evidence that this pre-targeting strategy can successfully be used to direct functionalized polymers and even functionalized whole-body cells to CXCR4 receptors, little imagination is required to see how this approach can be widely implemented. For example, in the future cocktails of various receptor targeting groups could be used to realize a higher labelling density (read host-or guest-moiety density) and as such supports strong multivalent interactions with a complementary secondary entity. Uniquely, non-specific background stainings are not likely to reach the appropriate loading density, thereby decreasing the chance of nonspecific labelling during the second step. Applications of the above pre-targeting strategies reach beyond imaging and accommodate image-guided interventions via theranostic approaches. When applied during local therapy, like the local administration of host-or guest functionalized

nanoparticles, supramolecular pre-targeting concepts open the door for a range of alternative applications and synthetic variations. Chapters 3 and 4 demonstrate the first steps towards the application of the supramolecular concepts in hepatic radioembolization therapy. The success of these imaging studies indicates that it is worthwhile to extend these efforts towards the targeted delivery of therapeutic isotopes and/or drugs.

While the efforts presented in this thesis stressed the translational potential of the developed supramolecular strategies, they also underline the influence that synthetic modification have on the *in vitro* and *in vivo* behavior of chemical entities. Clearly in future designs a lot can be gained by optimizing these chemical aspects.