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Summary

Molecular imaging plays a vital role in current medical diagnostics. There is a constant need for new and improved molecular imaging agents in terms of resolution, specificity, stability, safety and cost (Chapter 1). The research described in this thesis deals with the development of activatable luminescence lifetime imaging agents as well as with the use of supramolecular chemistry to introduce cell surface modifications to living cells.

The interactions between the inorganic luminophore $Ir(ppy)_3$ and the organic luminophore Cy5 were used in the design of activatable lifetime imaging agents in Chapters 2 and 3.

In Chapter 2, the potential of this concept and the nature of the photophysical interactions that led to quenching of both luminophores was investigated by directly conjugating the two luminophores via a disulfide-bridge. A Förster Resonance Energy Transfer mechanism led to the quenching of the luminescence of $Ir(ppy)_3$ and a reduction of its luminescence lifetime. The observed quenching of Cy5 luminescence was attributed to spin-orbit coupling effects of the heavy iridium atom, which opened an alternative route for energy decay. Disruption of the interaction between the two luminophores led to an activation of the luminescence of both Cy5 and $Ir(ppy)_3$. In addition, the luminescence lifetime of $Ir(ppy)_3$ was increased to its original value.

In Chapter 3 the same luminophores, $Ir(ppy)_3$ and Cy5, were conjugated to opposite sides of a peptide sequence specific for the tumor-related enzymes Matrix Metalloproteinases (MMP) 2 and 9. Quenching interactions between the luminophores were achieved by designing a charge-induced hairpin structure, which placed the luminophores in close proximity to each other. In the obtained imaging agent, quenching of

$Ir(ppy)_3$, quenching of Cy5 and reduction of luminescence lifetime were all observed. Following cleavage of the amino acid substrate, an increase of luminescence of both luminophores and an overall increase in luminescence lifetime could be realized.

The feasibility of using supramolecular host-guest interactions between β-cyclodextrin and adamantane on the cell membrane of living cells was investigated in Chapters 4 and 5.

In Chapter 4, supramolecular interactions between β-cyclodextrin and adamantane were used to functionalize a cell surface with multivalent β-cyclodextrin polymers. While reversible, this form of functionalization could also be used as a platform to introduce functional vectors to the cell surface. The last allowed for the introduction of imaging labels or the introduction of cell-cell interactions.

In Chapter 5, the multivalent supramolecular interactions between β-cyclodextrin and adamantane on the cell membrane were used to create a stepwise a layer-by-layer cell encapsulation structure on the cell surface. Cyclodextrin-containing polymers were added to the cell membrane in a similar fashion as Chapter 4, and to these polymers adamantane-containing polymers were bound. Alternate addition of β-cyclodextrin- and adamantane-polymers increased the polymer load to the cell, where each additional modification was shown to have a decreasing effect on cell viability. Although the cell surface could be efficiently covered, the functionalized surface could still be penetrated by the therapeutic agent doxorubicin.