Synthesis of Biomaterials for use in Drug Delivery to the Brain

The need for new treatments of brain diseases is growing with the increasing lifespan of western populations. Drug delivery to the central nervous system (CNS) is generally perceived as a tremendous challenge. Drug transport across the brain endothelium forming the blood-brain barrier (BBB) is a particularly great challenge because of the low intrinsic permeability of the barrier to most solutes and the presence of active efflux transporters.

Malignant glioma constitutes the most frequently diagnosed type of malignant brain cancer. The current benchmark for treatment of malignant glioma is a combination of surgical resection, radiotherapy and chemotherapy. Unfortunately, due to the distinct invasive nature of malignant glioma there is poor recovery prognosis, and a high probability of incurable recurrence, which is ascribed to the current insufficient treatment platform. Major progress within sophisticated tumor targeted multifunctional nanoparticles, can provide a wide range of unique opportunities for site-specific targeting of therapeutic agents to many areas within the vasculature. This potentially offers a new and improved platform for medical diagnostics, therapeutics or theranostics of glioma.

The objective of this PhD thesis was to expand the knowledge about nanoparticle delivery to the brain, by developing targeted hard and soft nanoparticles that could be sensitized towards glioma pathological conditions. The first study attempted to improve the understanding of TfR-mediated transcytosis of nanoparticles across the BBB. Specifically, we have studied the impact of the targeting ligand’s affinity, avidity and valency on the subsequent uptake of gold nanoparticles (AuNP) in brain. Following systematic investigations of the functionalized AuNPs both in vitro and in vivo, showed a very interesting potential of boosting the transcytosis of the BBB by tuning the avidity of the targeting moieties on the surface of the AuNPs.

The second and third study presents the development of two mechanisms to release the encapsulated drug inside the nanoparticles in order to create the desired efficacy. The two mechanisms utilizes the intrinsic bioreductive potential of cells and (over)expressed cancer specific enzymes to activate liposomes, respectively. In both studies it was demonstrated that the systems were potential tools for stimuli-responsive drug release targeting glioma cells. Lastly, a more indirect measure to elicit an anti-cancer response is by targeting sub-types of immune cells to ‘teach’ them to eradicate tumor cells. Here we present a thorough mechanistic study, that by fine-tuning the liposomal charge; it was possible to show substantial specificity towards a specific cell-subtype of the immune system. Hence, this methodology could potentially offer a tool to specifically stimulate and activate differentiation of cell-subtypes of the immune system, making it a viable platform for e.g. cancer vaccines.

In conclusion, during this PhD we have managed to develop multiple strategies to address the pressing issue of brain drug delivery using multifunctional liposomal formulations. Multiple of the developed systems are still in further in vitro testing to clarify their therapeutic application.