Understanding the influence of structure and functionalisation of nanocarriers for targeted drug delivery on cell-nanostructure interactions by advanced NMR methods and cellular assays

Despite the efforts of researchers, both in academia and industry, fighting cancer is still a major worldwide challenge. In 2020, as many as 18 million cancer cases were diagnosed, with liver cancer being one of the most common cancers (more than 900,000 cases worldwide in 2020). Limited selectivity, low cellular uptake, poor water-solubility and short stability in aqueous media of many anticancer agents translates into the occurrence of side effects or the systemic toxicity and makes anticancer therapy extremely costly and challenging, both for the patients as well as for the healthcare system. Furthermore, the patients' diagnosis at an advanced stage of the cancer, that is common for liver cancer, significantly decreases efficiency of the treatment as well as desirable clinical outcomes (e.g. five-year survival rate). Therefore, there is an unmet need to develop a novel therapeutic approaches and new drug carriers enabling delivery of the anticancer agents directly to the cancer cell.

Over the past few years, a number of targeted drug delivery systems (e.g., silica nanoparticles, liposomes, micelles) has been developed. Due to the ability of drug loading inside these nanoparticles and functionalisation their surfaces with specific ligands, they can deliver the drug directly to the desired cell. Such use of nanomaterials can reduce the side effects associated with standard chemotherapy, but the way their surface structure affects their cellular uptake is yet to be fully understood. Also, detailed analysis of the surface of such materials is challenging due to the small amount of ligand attached to the surface of nanoparticles, their dual organic-inorganic nature and size in the 150-250 nm range.

Studies of the structure of such nanomaterials have typically been carried out using a combination of infrared (IR) and nuclear magnetic resonance (NMR) spectroscopy. However, study of nanomaterials by traditional NMR methods in the solution-state is difficult due to strong dipolar interactions and chemical shift anisotropy, which cause peak broadening, making NMR spectrum analysis difficult. The use of advanced techniques, such as HR/MAS NMR (High Resolution Magic Angle Spinning NMR), allows to average out these interactions by spinning the sample at an magic angle, which results in a significant narrowing of the peaks, enabling detailed structural characterisation. Direct observation of the cell-nanoparticle interactions, using NMR spectroscopy is also challenging due to large size of cells, high viscosity of the analysed suspensions and immobilisation of molecular targets in cellular membranes. Therefore, NMR hybrid techniques can be used along with solution and solid state to study interactions of nanomaterials with biological systems.

The goal of the project is to synthesise complex functionalised nanomaterials for targeted drug delivery and understand their interactions with model cells using novel "hybrid" NMR techniques. This will be achieved by synthesising nanomaterials (MSN, liposomes, liposome-coated MSN) and incorporating the drug inside the particles. The next step of the project will be functionalisation of the surface of the synthesised materials with functional groups (e.g. saccharides, PEG), which will increase biocompatibility and allow the particles to be directed to a molecular target. In the final stage of the project interactions between the synthesized materials and cells using "on-cell" NMR will be investigated supported with microscopic imaging and cell assays for the confirmation of receptor targeting.

The obtained results could significantly impact the development of new targeted drug delivery systems and expand the knowledge of cell surface interactions. The aforementioned techniques would provide insights into the mechanisms of intercellular communication pathways, and due to the improved quality of the spectra this approach might be used to study interactions of nanomaterials with biological systems that has not been involved in such characterisation so far to a large extent.