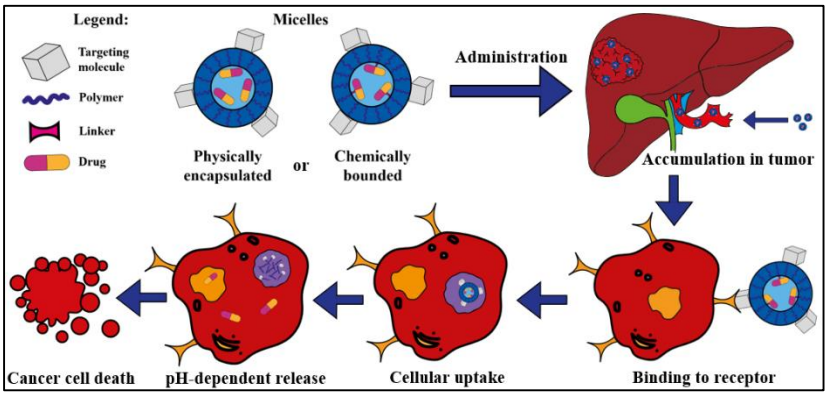
Primary liver cancer (PLC) is in the fourth position regarding the number of deaths worldwide and seventh in terms of incidence, with a prediction of an increase of 55% by 2040. Currently ongoing therapies, including surgical treatment and chemotherapy, are far from being satisfactory. The 5-year survival ranges from 16 to 55%, depending on the stage of the disease. Moreover, the currently applied therapies are invasive, toxic, and negatively contribute to the life quality. The poor outcomes of the current therapies are mainly associated with PLC cell resistance to drugs, which is related to the low cellular uptake of applied drugs and the augmented number of ABC transporters that pump out drugs from the cells. **The poor outcomes of current PLC therapies constitute a driving force for searching for better alternatives.** One of them concerns novel drug delivery systems (DDS) for applied drugs to increase their efficacy. The idea of DDS relies on the conjugation or enclosure of active pharmaceutical ingredients (API) in the carrier, which further improves the therapeutic effect and diminishes its toxicity. Nanoparticles reveal significant advantages over conventional DDS as their nanometric size and stability allow for prolonged circulation in the bloodstream and effective accumulation in dedicated tumor tissues. Moreover, DDS protect nanoparticles from the undesirable leakage of APIs and their unwelcome inactivation. It is worth noting that distinctive features of the tumor tissue can be considered for further enhancement of anticancer DDS efficiency. Therefore, the more acidic conditions present within the tumor tissue can be applied to construct DDS that can release drugs only in the dedicated environment. Moreover, nanoparticles can be equipped with targeting molecules, which direct DDS towards specific receptor present on the surface of cancer cells and thus allowing to increase cellular uptake and accumulation of drugs in tumors.



In the given background, developing a novel drug delivery system equipped with specially dedicated targeting molecules constitutes a promising tool prospectively allowing to cope with the challenges of primary liver cancers. The idea of the current project is to bind, chemically or physically, drugs used in primary liver cancers to poloxamer, a material that forms micelles at low concentrations. Poloxamer is a base material for the DDS, which was chosen due to the vast spectrum of beneficial physicochemical and pharmacological properties, including lack of toxicity, good stability, extended blood circulation time, and sustained drug release. Moreover, the material is rich in appropriate chemical groups allowing it to bind chemically or physically to various drugs or targeting molecules. In the current study, poloxamer will be chemically modified with targeting molecules – simple sugar galactose and their derivatives, which have proven their specific affinity towards specific receptors present on the PLC cells' surface. DDS equipped with both specific drugs and targeting molecules will be captured by specific cancer cells and, after internalization, will deliver and release the connected or embedded drugs at the target site. Also, for the chemical conjugation of drugs to poloxamer, a special acidic-sensitive linker equipped with ortho ester moieties, which will be applied for binding with drugs and poloxamer, is envisaged.

In the project, the following main tasks were considered: (*i*) chemical modification of poloxamer chemical groups – bounding spacers and targeting molecules; (*ii*) chemical conjugation of APIs to the modified polymer; simultaneously, for the comparative study, poloxamer nanoparticles with physically bound APIs and without APIs will also be obtained; (*iii*) physicochemical characterization of the new DDS, including structural study, phase transition, nanoparticle imagining, drug encapsulation, critical micellization concentration, drug release in different media, determination of swelling properties; (*iv*) interaction with serum proteins and with membranes, MTT-based *in vitro* toxicity study of nanoparticles on cancer cell lines with the uptake and DNA fragmentation assessments, oxidative stress measurement and detection of apoptosis. **In summary, the proposed studies will verify** whether it is possible to obtain poloxamer-based DDS containing targeting molecules and drugs for their application as targeted nanoparticles in primary liver cancer chemotherapy. The study will allow for comparing the potential of different types of targeting molecules to liver cancer cells in more sophisticated DDS. The project will be conducted at the Chair and Department of Chemical Technology of Drugs Poznan University of Medical Sciences, which demonstrates long-term experience in medicinal chemistry and nanotechnology, as well as within cooperation and secondments at domestic and international scientific institutions.