Synthetic epidermal growth factor receptor inhibitor conjugated with nobel metal nanoparticles as a potential drug for targeted therapy against pancreatic cancer

Pancreatic ductal adenocarcinoma (PDAC) is one of the most malignant diseases. More than 80% of patients are diagnosed with locally advanced and metastatic stage. It is one of the lowest 5-year survival rate, which is 6.9% (average for Europe). Epidermal growth factor receptor (EGFR) is overexpressed in 30%-89% of PDAC, which involved in tumor growth, vascular changes cancer metastasis and resistance to classical chemotherapy. Because EGFR is expressed in both cancer cells and normal cells, to develop a target-EGFR inhibitor treatment is necessary. Nanoparticles (NPs) have a high surface to volume ratio which allow to decrease the dosages of therapeutic agents. NPs, as drug delivery platforms, have target preference and potential anti-tumor properties. Therefore, it reduces the side effects and costs of therapy.

In the project, we will synthesize, characterize, and evaluate NPs conjugate with EGFR inhibitors in biological systems as therapeutic agents in PDAC. We will evaluate the potential toxicity, biocompatibility and safety within *in vitro* and *in vivo* studies by using cells and mice model. Especially, we will use organoids as model, which is a miniaturized and simplified version of an organ produced *in vitro* in three dimensions (3D) that shows realistic micro-anatomy of cancerous tumor. Firstly, we will perform cytotoxicity assay using cancer and non-cancer cells, receptor binding, toxicity and pharmacokinetic study to select EGFR inhibitor-NPs conjugates with the best potential anti-tumor properties. Then, we use CRISPR-Cas 9 system which is a good genome editing technique to mutate pancreatic cancer cell line. We will detect expression of cytokines and proteins in relative signaling pathway of EGFR, which explore the specific molecular target and underline mechanism of action of NPs conjugates. Finally, the selected NPs conjugates will be investigated on patient-derived organoids, which depending on gene information of organoids, and target locus of NPs conjugates. Accordingly, these organoids will be transplanted into pancreatic tissue of mice to imitate *in vivo* tumor progression, and the anti-tumor, anti-angiogenetic and anti-metastatic effects of NPs conjugates will be determined.

In summary, the project aims to determine the toxicity, pharmacokinetic and anti-tumor activity of EGFR inhibitor-NPs conjugates in commercially available cell lines, patient tissues-derived organoids and patient-derived organoids xenograft which form the basis for further clinical investigation and ultimately can lead to patent application and the launch of a new drug.