Potential ability of tumour cells to spread to other tissues/organs and to form metastases is a characteristic feature of malignant neoplasms, which include colorectal cancer (CRC). The gold standard for treatment in CRC remains surgical resection. However, despite radical operation combined with (neo)adjuvant chemo/radio-therapy, recurrence is rather common in patients with this malignancy. Therefore new prognostic markers of CRC and novel therapeutic targets are still needed. Development of efficient diagnostic and therapeutic strategies requires complete understanding of CRC progression and metastasis. For these reasons, there is an urgent need to expand the knowledge of cellular processes responsible for the spread of tumours and to searching for the new and specific molecular markers of their invasiveness. The ability to determine the degree of tumour progression and the risk of metastasis, based on reliable molecular signatures, would allow for better selection of optimal therapies.

In the proposed project we hypothesize that molecular components characteristic for colorectal cancer cells can be released and transported by exosomes (nanovesicles) to other cells and tissues, which is associated with the mechanism of invasiveness and metastasis of colorectal cancer. Exosomes released by tumour cells into body fluids, enriched in biomolecules characteristic for cancer cells, have become attractive for their potential as carriers of prognostic biomarkers. Moreover, we assume that proteins, metabolites and lipids characteristic for tumour tissue could be found in body fluids (serum) both in the form of exosomal "cargo" and in the "soluble" form, and their level could determine and reflect stage of disease progression and type of response to treatment.

The main goal of the proposed project is to characterize molecular factors associated with the progression of CRC, in the context of the participation of tumour-derived exosomes in progression and metastasis process. We assume that the project will allow the identification of specific molecular components (proteins, lipids and metabolites) characteristic for tumour tissue and present in blood and/or colorectal cancer-cell-derived exosomes. For this purpose, we plan a systematic qualitative and quantitative assessment of proteins, lipids and metabolites present in colorectal tissue, to select specific molecular components which differentiate tumour from healthy tissue. In the next step we plan identification and quantitative analysis of selected specific molecular components (characteristic for CRC tumour tissue) in serum and/or exosomes isolated form serum, using targeted mass spectrometry techniques (MRM, SRM). Retrospective design of the study (minimum 5-year follow-up after treatment and collecting of material) allows to correlate molecular profiles with the long-term effects of treatment.

Identification of colorectal cancer-cell-derived exosomal marker, could help in developing potential non-invasive (“liquid biopsy”) tool to determine the degree of tumour progression and the risk of metastasis. Moreover, the identification of cancer cell-derived specific molecule/s present on the surface of exosomes could allow specific detection and isolation of cancer-cell-derived exosomes in the circulation. One of the important and original aspects of the proposed project is the availability of a unique clinical material preserved for the high-throughput “multi-omics” studies, especially metabolomic and lipidomic. Moreover, one of the most innovative aspects of our project is using serum-purified exosomes for MS-based “omics” studies. Original method of exosome isolation, optimized for proteomic analysis by different mass spectrometry techniques, was recently worked out by our research group. High throughput mass spectrometry techniques optimized for multi-omics-based exosome analysis could be used in future in validation and screening research.