The absorption of orally administered drugs is determined not only by the physicochemical properties of the drug itself but also depends on a range of biological factors, including the activity of transport proteins (transporters) involved in transferring drugs across biological membranes. The main organs that determine the amount of drug that will be absorbed after oral administration, known as bioavailability, are the gastrointestinal tract and the liver, along with the enzymes and transporters located within them. Colorectal cancer is a leading cause of cancer-related deaths worldwide. Despite advances in therapy, drug resistance remains a major limitation, affecting 90% of patients with metastatic colorectal cancer. There is scientific evidence supporting the role of certain drug transporters in the development of multidrug resistance in colorectal cancer. There are also various regulatory mechanisms that influence the amount of transporters in tissues. It has been proven that mechanisms such as DNA methylation or the presence of various miRNAs (single-stranded RNA molecules 21 to 23 nucleotides long) play a key role in drug resistance in colorectal cancer.

There is a lack of detailed information in the literature on the occurrence and localization of drug transporters in the intestine and liver, both in healthy individuals and in patients with metastatic colorectal cancer. In particular, there is a lack of data concerning samples from the same donor. Possible differences in the occurrence and localization of drug transporters or regulatory mechanisms between colorectal cancer tissue and metastatic tumor tissue may influence future pharmacotherapy modifications, and in the case of inoperable tumors, also palliative therapy modifications. Identifying differences in samples from the same patient offers an opportunity to optimize and personalize pharmacotherapy in colorectal cancer. Therefore, the aim of the study is to determine the quantity and type of drug transporters in four types of tissues: healthy colon, colorectal cancer, metastatic colorectal cancer in the liver, and healthy liver. This is crucial for understanding drug action and the pathophysiological processes of the colon. Another aspect examined in this project is the determination of mechanisms involved in the different occurrence of drug transporters in various tissue types, both in terms of quantity and type. The goal of the project is thus to determine the role of miRNAs that may influence protein formation and DNA methylation affecting gene expression in all examined tissue types. The obtained results will allow for the characterization of regulatory mechanisms determining the occurrence of drug transporters in metastatic colorectal cancer. The results of this study will be unique on a global scale due to the origin of the samples – from each patient, a set of four types of tissues (healthy colon, colorectal cancer, metastatic colorectal cancer in the liver, healthy liver) was collected. Importantly, all samples were obtained from patients who had not undergone neoadjuvant therapy prior to surgical resection. These tissues were collected and stored in a private biobank approximately ten years ago, at a time when neoadjuvant treatment was not yet commonly implemented for metastatic colorectal cancer patients. Today, obtaining such a comprehensive set of tissues from a single patient without prior systemic treatment would be nearly impossible, due to the widespread adoption of neoadjuvant therapy as the clinical standard of care. This further highlights the exceptional value of this study – both in terms of the completeness of the biological material and the ability to generate reliable data on the natural (treatment-naïve) levels of gene and protein expression, as well as regulatory mechanisms. Moreover, these results will provide new information on the molecular mechanisms regulating the expression and function of drug transporters, which are crucial for the optimization and individualization of pharmacotherapy in colorectal cancer. The discoveries may also contribute to the development of more accurate pharmacokinetic models for predicting clinical responses.