Gender differences, suggesting a potential role of estrogens, are seen in colorectal cancer (CRC). Premenopausal women have a lower CRC incidence than age-matched men. Most of the prospective and retrospective studies showed an inverse relationship between the risk of CRC incidence and the use of hormone replacement therapy by postmenopausal women.

An explanation for the conflict between lower CRC incidence following exposure to estrogens, known to be carcinogenic and to increase the incidence of other tumours types (e.g. breast cancer) seems to lay in the tissue-specific difference in mediators of estrogen actions - estrogen receptors (ERs).

ER nuclear isoforms encompass ERα and ERβ with predominant function and expression of ERβ in the colon. Overwhelming amount of evidence proves the inverse relationship of ERβ presence with the occurrence of CRC and estrogen signalling driven by ERβ selectively activates proapoptotic actions, inhibition of inflammatory signals in CRC. This placed the idea of improving the outcome of CRC patients after restoring ERβ levels in cancer tissue. Still, reexpression may not present full capacity of receptor action. While ER binds to target sequence, specific coregulators carry out transcriptional activation or repression. Moreover, the degree of coregulator expression is critical to their ability to influence the transcriptional potential of the ER that allows fine-tuning of target gene transcription. Previous reports and our preliminary data support hypothesis that chromatin accessibility alters in the presence of ERβ-E2 complex and that epigenetic effectors play significant roles in fine-tuning the ERβ- driven response in CRC cells.

Consequently, our main objective is to identify chromatin factors related mechanisms involved in ERβ- driven action. We will adopt CRISPR/Cas9 library screen that would allow investigating more than 1100 chromatin-associated genes. Subsequently, we will define and functionally characterize the most crucial ERβ - related response epigenetic factors. Understanding epigenetic alterations that would boost ERβ antitumorigenic effect in CRC will have a meaningful impact: 1) Guide for understanding epigenetic coregulators in ERβ driven response in colorectal and other types of cancer and diseases; 2) Identification of novel biomarkers for CRC patient’s treatment outcome; 3) Suggest of new targets for personalized medicine.