

Research project J3-60065

The role of steroid hormones in chemoresistance of ovarian and endometrial cancers: impact on therapy

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Project description:

Ovarian and endometrial cancers comprise 10% of all cancers in Europe. Ovarian cancer (OC) represents the most deadly and endometrial cancer (EC) the most common gynaecological malignancy. Drug resistance is the major cause of death of these patients. Even though the initial response rates to chemotherapy are high the majority of OC patients develop resistance, leading to subsequent recurrence or progression of disease thus only 47% of patients survive five years after the first diagnosis. Similarly, due to chemoresistance the survival of patients with advanced EC is currently less than 20%. Chemoresistance is a complex phenomenon that includes many underlying mechanisms including altered intracellular drug transport, and changes in levels of cellular enzymes responsible for detoxification, involving enzymes from the aldo-keto reductase (AKR) superfamily. AKR1C enzymes have been associated with chemoresistance of various cancers and pan-AKR1C inhibitors have been used to restore sensitivity and showed efficacy in cancer explant mouse models. AKR1C enzymes have been linked to resistance of OC but their action in OC and EC has not been determined. OC and EC are hormone-dependent malignancies that predominantly affect post-menopausal women and thus rely on the local formation of active steroid hormones. Although published studies indicate that steroid hormones have roles in chemoresistance of OC and EC, these roles of the individual steroid hormones in chemoresistance have not yet been studied. The proposed project has the following aims; i) to examine interplay between steroid hormones and chemoresistance of OC and EC using publicly available omics data and experimental omics data, ii) to investigate role of AKR1C in chemoresistant OC and the options for combined treatment with AKR1C inhibitors and platinum-based drugs and iii) to evaluate prognostic and predictive potential of estrogen, androgen and progesterone metabolites in OC patients. These aims will be achieved by using 2D and 3D cell models, explant cultures, organoids and nontargeted and targeted transcriptomics, nontargeted and targeted metabolomics, functional studies and modelling of omics and functional data. The project aims to contribute to better understanding of molecular mechanisms associated with chemoresistance, to clarify options for combined treatment to reverse chemoresistance and options for stratification of OC patients for personalized treatment. The proposed project is a collaboration between the Faculty of Medicine Ljubljana, the University Medical Centre Ljubljana, the National Institute of Chemistry Ljubljana, the Catholic University of Leuven, Belgium, the University of Maastricht, the Netherlands, and the Stellenbosch University South Africa.

The phases of the project and their realization:

WP1 Steroid hormones and chemoresistance:

Months 1-12: Analysis of publicly available omics data

Months 1-36: Studies in model cell lines and tissue samples

WP2 AKR1C enzymes in chemoresistance

Months 1-36: Studies of AKR1C enzymes in cell lines and explants

WP3 Targeted metabolomics for biomarker discovery

Months 1-24: Collection of blood samples

Months 24-36: Blood targeted metabolomics study

