Research program P3-0449

Translational molecular endocrinology for womens health

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Summary and objectives

The program addresses the unmet clinical need for early diagnosis, reliable prognosis and new treatment options for hormone-dependent gynecological diseases that affect women throughout their lives and are associated with enormous health burden and economic loss. Endometriosis, characterized by the growth of endometrial-like tissue outside the uterine cavity, affects up to 10% of women of reproductive age. Hormone-dependent cancers are most common after menopause and account for more than 35% of all cancers in women, with endometrial cancer (EC) being the most common and ovarian cancer (OC) the most lethal gynecological cancer. There is a lack of appropriate models for endometriosis, therapies to reverse chemoresistance and clinically relevant diagnostic/ prognostic biomarkers for endometriosis, EC and OC. The program has the following goals: 1. elucidation of pathophysiological mechanisms at the molecular level; 2. identification of new targets, particularly in relation to chemoresistance; and 3. development of diagnostic/ prognostic multiomic algorithms. We plan to achieve these goals using state-of-the-art methodological approaches and in collaboration with the Department of Gynecology at UMC Ljubljana and a number of established collaborations worldwide.

To improve the understanding of pathophysiology, we are focusing on new models for endometriosis, OC and EC. We plan to establish endometriosis cell lines, co-cultures and 3D models as well as the use of organoids and explants. As a part of the program, we are investigating the molecular basis of the disease and the mechanisms of chemoresistance, using omic approaches, metabolic and functional studies with a focus on the involvement of steroid hormones and aldo-keto reductases (AKR). Using mathematical modeling, we aim to create a model to identify the most appropriate drug targets in steroid hormone biosynthesis/metabolism. As drug targets we are examining enzymes of steroid hormone biosynthesis/metabolism and the corresponding receptors and AKR1Cs associated with resistance to chemotherapeutics; and as antiproliferative agents and agents to prevent chemoresistance, known drugs and newly synthesized compounds. To restore response to chemotherapeutics, the efficacy of combined

treatment with known AKR1C inhibitors and platinum-based drugs is being explored in models of chemoresistant cancers. In collaboration with UMC Ljubljana, we are expanding the GynecoEndo biobank, enabling further omics studies to discover and validate diagnostic/prognostic markers. Using machine-learning approaches we plan to develop diagnostic/prognostic algorithms based on the combination of omics and clinical data. External validation of the created models will be performed on separate patient cohorts within the existing EU collaborations. We expect the research program to contribute in the long term to the definition of new diagnostic tools and patient-tailored treatment strategies for hormone-dependent diseases.