1. Raziskovalna organizacija (*Research organisation)*:

Univerza v Ljubljani, *Medicinska fakulteta*

2. Ime in priimek mentorja (*Name and surname of a mentor*):

Tea Lanišnik Rižner

3. Področje znanosti iz šifranta ARRS (*Primary research field*):

3.07.Medicinske vede, Metabolne in hormonske motnje

4. Kontaktni e-naslov mentorja (*Contact of a mentor)*:

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5. Kratek opis programa usposabljanja (*Short description of the program)*:

Izhodišče raziskovalne naloge MR: Hormonsko odvisne oblike raka, kot so rak dojk, rak endometrija in rak jajčnikov predstavljajo 25 % vseh oblik raka pri ženskah. V svetovnem merilu se te vrste raka pojavljajo pri več kot 1,6 milijonih žensk/leto in predstavljajo 15 % smrti povezanih z rakom/leto**.** Hormonsko odvisne oblike raka se razvijejo predvsem pri ženskah po menopavzi in so tako odvisne od lokalne sinteze aktivnih steroidnih hormonov. V perifernih tkivih se aktivni androgeni in estrogeni lahko sintetizirajo iz neaktivnih prekurzorskih oblik, predvsem dehidroepiandrosteron-sulfata (DHEA-S) in estron-sulfata (E1-S), po prehodu v celico s pomočjo transportnih proteinov iz proteinskih družin OATP in OAT. **V okviru raziskovalne naloge** želimo razjasniti vlogo transportnih proteinov iz proteinskih družin OATP in OAT pri razvoju raka endometrija in raka jajčnikov. Raziskava bo potekala v sodelovanju z Ginekološko kliniko, UKC Ljubljana, z »Institute of Enzymology, Research Centre for Natural Sciences, Hungarian Academy of Sciences", in z »Department of Pharmaceutical Chemistry, Faculty of Vienna«. **Delovna hipoteza:** Pri raku endometrija in raku jajčnikov je spremenjeno izražanje genov prenašalnih proteinov OATP in OAT, kar omogoča pospešen vnos steroidnih prekurzorjev, pospešeno biosintezo estrogenov in aktivacijo ustreznih receptorjev, proliferacijo ter nadaljnjo maligno transformacijo. **Metode:** Zastavljene cilje bomo dosegli s pristopi tarčne transkriptomike, z uporabo tkivnih mikromrež in imunohistokemijskega barvanja, s študijami metabolizma z uporabo LC-MS/MS in študijami proliferacije v realnem času. Transport steroidnih prekurzorjev bomo proučili v modelnih celičnih linijah raka endometrija in raka jajčnikov, kontrolnih celičnih linijah pa tudi v vzorcih tkiva. Preverili bomo: 1. izražanje genov transporterjev, encimov povezanih z biosintezo in metabolizmom in receptorjev za estrogene; 2. zmožnost za vnos steroidnih prekurzorjev DHEA-S in E-S, nadaljnjo biosintezo aktivnih estrogenov ter metabolizem; 3. aktivacijo receptorjev za estrogene in vpliv na proliferacijo, migracijo in invazivnost. Na osnovi teh rezultatov bomo 4. predlagali model biosinteze in delovanja estrogenov pri raku endometrija in jajčnikov. Z raziskovalno nalogo želimo prispevali k razjasnitvi mehanizmov prenosa steroidnih prekurzorjev v rakave celice endometrija in jajčnikov in s tem opredeliti pomen posameznih OATP in OAT kot možnih novih tarč za razvoj zdravilnih učinkovin.

Background of the research project: Hormone dependent cancers as breast cancer, endometrial cancer and ovarian cancer represent 25% of all cancers in women. Worldwide, these cancers occur in more than 1.6 million of women/year and are associated with 15% of cancer-related deaths/year. Hormone-dependent cancers develop mainly in the postmenopausal women and thus rely on the local formation of active steroid hormones. In peripheral tissues, active androgens and estrogens can be formed from inactive precursor steroid hormones, mainly dehydroepiandrosterone-sulfate (DHEA-S), and estrone-sulfate (E1-S) after their translocation into cells through the transporter proteins of the organic anion-transporting polypeptide (OATP) and organic anion-transporter (OAT) families. **Goals of this research project** are to clarify the role of transporter proteins of the OATP and OAT families in development of endometrial and ovarian cancer. The research project will be performed in collaboration with the Department of Gynaecology, University Clinical Centre Ljubljana, the Institute of Enzymology, Research Centre for Natural Sciences, Hungarian Academy of Sciences and the Department of Pharmaceutical Chemistry, Faculty of Vienna. **Work hypothesis:** Genes encoding OATP and OAT transporters are differentially expressed In endometrial cancer and ovarian cancer, which leads to increased uptake of steroid precursors, enhanced estrogen biosynthesis and activation of corresponding receptors, followed by increased proliferation and further malignant transformations. **Methods:** The aims of this project will be accomplished by targeted transcriptomic approach, tissue microarrays and immunohistochemical staining, metabolism studies by LC-MS/MS and real-time proliferation, migration and invasion studies. The transport of steroid precursors will be investigated in model cell lines of endometrial cancer and ovarian cancer, in corresponding control cell lines, and in tissue samples. We will examine: i) the expression levels of transporters, enzymes responsible for local estrogen biosynthesis and metabolism, and estrogen receptors; ii) the capacity for steroid uptake and formation of active estrogens and their metabolites from DHEA-S and E-S; iii) the activation of estrogen receptors and further effects on proliferation, migration and invasion. Based on this data we will iv) build a model of estrogen formation and action in endometrial and ovarian cancer. The project will contribute to understanding of the mechanisms of steroid precursor uptake in the endometrial and ovarian cancer cells and will elucidate the importance of individual OATP and OAT proteins as potential novel drug targets.