Kratek opis usposabljanja mladega raziskovalca (*Short description of the Young Researcher's training)*

1. Raziskovalna organizacija (*Research organisation)*:

Univerza v Ljubljani, Medicinska fakulteta

2. Ime, priimek in elektronski naslov mentorja (*Mentor's name, surname and email*):

Tea Lanišnik Rižner, tea.lanisnik-rizner@mf.uni-lj.si

3. Šifra in naziv raziskovalnega področja (*Research field*):

3.07 Medicina, Metabolne in hormonske motnje

4. Kratek opis usposabljanja mladega raziskovalca (*Short description of the Young Researcher's training)*:

Navedite tudi morebitne druge zahteve, vezane na usposabljanje mladega raziskovalca (npr. znanje tujih jezikov, izkušnje z laboratorijskim delom, potrebne licence za usposabljanje…).

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Izhodišče raziskovalne naloge MR: Rak jajčnikov je šesti najpogostejši vzrok z rakom povezanih smrti v Evropi. Pri večini bolnic rak diagnosticirajo v kasnejši fazi, ko ima bolezen že slabo prognozo. Poleg operativnega zdravljenja se običajno uporablja kemoterapija z derivati platine in taksanov. Čeprav je prvi odziv na to zdravljenje ugoden, pa se kar v 2/3 primerov razvije na kemoterapevtike rezistentna oblika raka. Trenutno le 30-40% bolnic z rakom jajčnika preživi pet let. Študije v rakavih celičnih linijah so razkrile, da so v kemorezistenco vpleteni tudi steroidni hormoni. V sodelovanju z »University of Vienna« smo pred kratkim pokazali, da se metabolizem estrogenov v celičnih linijah raka jajčnikov razlikuje glede na odzivnost na kemoterapevtike. Pri celičnih linijah odzivnih na karboplatin, v primerjavi s kemorezistentnimi celičnimi linijami, je pospešena konjugacija do neaktivnih sulfatov in glukuronidov, kar kaže, da je intrakrino delovanje estrogenov povezano s kemorezistenco.

V okviru raziskovalne naloge želimo razjasniti mehanizem vpletenosti steroidnih hormonov v kemorezistenco raka jajčnikov. Raziskava bo potekala v sodelovanju z Ginekološko kliniko, UKC Ljubljana. **Delovna hipoteza:** Pri kemorezistentnem raku jajčnikov je spremenjena lokalna sinteza estrogenov in androgenov, kar vpliva na odzivnost raka na zdravljenje s kemoterapevtiki. Razumevanje mehanizmov vpletenosti steroidnih hormonov v kemorezistenco lahko prispeva k odkrivanju novih možnosti zdravljenja. **Metode:** Zastavljeno hipotezo bomo preverili s študijo izražanja celotnega genoma (RNA sekvenciranje), s pristopom tarčne transkriptomike in proteomike, z uporabo tkivnih mikromrež in imunohistokemijskega barvanja, s študijami metabolizma estrogenov in androgenov z uporabo LC-MS/MS, z utišanjem genov s pristopom siRNA in študijami proliferacije, invazivnosti in migracije v realnem času. Vlogo steroidnih hormonov bomo proučili v modelnih celičnih linijah kemorezistentnega in kemosenzitivnega seroznega raka jajčnikov visokega gradusa, kontrolnih celičnih linijah pa tudi v vzorcih tkiva. Proučili bomo: 1. razlike v metabolizmu estrogenov in androgenov in 2. razlike v transkriptomu in proteomu med kemorezistentnimi in kemosenzitivnimi celičnimi linijami in 3. pomen ključnih encimov biosinteze estrogenov in androgenov in receptorjev pri kemorezistenci. Na osnovi teh rezultatov bomo predlagali model vpletenosti estrogenov in/ali androgenov v kemorezistenco raka jajčnikov. Z raziskovalno nalogo želimo prispevali k razjasnitvi mehanizmov kemorezistence in možnosti uporabe hormonske terapije kot novega pristopa zdravljenja kemorezistentnih oblik raka.

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Background of the research project: Ovarian cancer is the sixth leading cause of cancer-related deaths in Europe. The majority of patients are diagnosed with the advanced stage of disease with a poor prognosis. The current treatment strategy for ovarian cancer includes cytoreductive surgery and first-line combined chemotherapy with platinum-based drugs and taxane compound. In spite of high response to this therapy, more than 2/3 of patients develop chemoresistant form of cancer. Currently only 30-40% of patients with ovarian cancer survive five years. Studies on cancer cell lines indicated that steroid hormones may be involved in development of chemoresistance. In collaboration with University of Vienna we have shown recently, that metabolism of oestrogens differ between chemo-sensitive *and* chemo-resistant cells. Metabolism of oestrogens to inactive sulphates and glucuronides was enhanced in carboplatin sensitive cell lines, which suggests associations between intracrine action of oestrogens and chemoresistance. **With this research project** we aim to clarify mechanisms of steroid hormone involvement in chemoresistance of ovarian cancer. The research project will be performed in collaboration with the Department of Gynaecology, University Medical Centre Ljubljana.

Work hypothesis: In chemoresistant ovarian cancer, the local synthesis of oestrogens and androgens is altered, affecting the cancer response to chemotherapeutic treatment. Understanding the mechanisms of steroid hormone involvement in chemoresistance may contribute to the discovery of new treatment options. **Methods:** The hypothesis will be tested by whole genome expression approach (RNA sequencing), by the target transcriptomics and proteomics, by the use of tissue microarrays and immunohistochemical staining, by studies of oestrogen and androgen metabolism using LC-MS / MS, together with gene silencing (siRNA) and real-time proliferation, migration and invasiveness studies. The role of steroid hormones will be investigated in model cell lines of chemoresistant and chemosensitive serous high-grade ovarian cancer, in control cell lines and also in tissue samples. We will examine; i) differences in oestrogen and androgen metabolism and ii) differences in the transcriptome and proteome between chemoresistant and chemosensitive cell lines as well as iii) the importance of key enzymes of oestrogen and androgen biosynthesis and receptors in chemoresistance. Based on these results, we will propose a model of the involvement of oestrogens and / or androgens in chemoresistance of ovarian cancer. With this research project, we aim to contribute to the elucidation of the mechanisms of chemoresistance and the possibility of using hormone therapy as a new approach to the treatment of chemoresistant cancers.