Opis delovnega mesta mladega raziskovalca/ke (Description of the Young Researcher's position)

1. Članica UL (*UL member)*:

Univerza v Ljubljani, Medicinska fakulteta / University of Ljubljana, Faculty of Medicine

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

Katarina Trebušak Podkrajšek, katarina.trebusakpodkrajsek@mf.uni-lj.si

3. Raziskovalno področje (*Research field*):

1.05.00 Naravoslovje, Biokemija in molekularna biologija 3.03.00 Medicina, Nevrobiologija

4. Opis delovnega mesta mladega raziskovalca/ke (D*escription of the Young Researcher's position)*:
Vključuje morebitne dodatne pogoje, ki jih mora izpolnjevati kandidat/ka za mladega raziskovalca/ko, ki niso navedeni v razpisu za mlade raziskovalce.

slo: Mladi raziskovalec se bo v raziskovalnem delu osredotočil na opredelitev molekularnih mehanizmov, ki vplivajo na razvoj in napredovanje nefropatije pri bolnikih s Fabryjevo boleznijo. Fabryjeva bolezen je izredno redka napredujoča lizosomalna bolezen, povezana z bolezenskimi spremembami v genu *GLA*, ki vodijo v okvaro različnih organov in s tem v razvoj kliničnih značilnosti, kot so nefropatija, kardiomiopatija, srčno-žilna obolenja, in druge. Zgodnje prepoznavanje Fabryjeve bolezni in njenih zapletov ter klinično ukrepanje sta tako ključna za učinkovito zdravljenje in s tem preprečevanje razvoja ireverzibilnih in življenje ogrožajočih stanj. S transkriptomskimi raziskavami je mogoče določiti spremenjene profile mRNA, in s tem povezati genetske dejavnike s funkcionalnimi molekulami v celicah. Spremenjeno izražanje genov so že dokazali pri kronični ledvični bolezni, in to še preden so bile opazne histološke spremembe, ni pa to še bilo raziskano pri Fabryjevi bolezni. Zato načrtujemo longitudinalno vrednotenje profilov mRNA pri bolnikih s Fabryjevo boleznijo, kar omogoča prepoznavanje biološko pomembnih poti, vključenih v razvoj in napredovanje Fabryjeve nefropatije. To hkrati predstavlja nadaljevanje naših dosedanjih raziskav na tem področju, saj smo že prepoznali zvrsti mikroRNA, ki so imele spremenjeno izražanje pri bolnikih s Fabryjevo boleznijo s stabilno ledvično funkcijo in/ali z napredovano nefropatijo. Te zvrsti mikroRNA so povezane s signalnimi potmi, ki so pomembne pri razvoju in napredovanju nefropatije, njihove mRNA tarče pri Fabryjevi nefropatiji pa še niso jasne. Ocena kandidatnih poti na ravni transkriptoma in povezava teh rezultatov z znanimi biološkimi označevalci ledvične funkcije, vnetja in oksidativnega stres je torej potrebna za potrditev in pojasnitev naših predhodnih ugotovitev. Pri raziskavah bo mladi raziskovalec uporabljal različne sodobne molekularno genetske pristope za izolacijo in analizo RNA, ki bodo vključevale sekvenciranje naslednje generacije. Uporabljal bo tudi metode za določanje povezanih proteinov in metabolitov iz bioloških vzorcev ter bioinformacijska in biostatistična orodja. Eksperimentalno pridobljene podatke bo skupaj s kliničnimi podatki vključil v napovedne modele razvoja in pospešenega napredovanja nefropatije. Raziskovalno delo bo potekalo v sodelovanju Inštituta za biokemijo in molekularno genetiko Medicinske fakultete v Ljubljani in Centra za

Fabryjevo bolezen v Slovenj Gradcu. Pričakujemo, da bodo rezultati predlaganega raziskovalnega dela omogočili boljše razumevanje osnovnih molekularnih procesov razvoja Fabryjeve nefropatije in opredelitev novih kandidatnih diagnostičnih in/ali prognostičnih bioloških označevalcev Fabryjeve nefropatije.
V raziskovalno skupino želimo vključiti visoko motiviranega in samostojnega mladega raziskovalca, ki bo v času opravljanja doktorskega dela sodeloval v različnih strokovnih, znanstvenih in izobraževalnih aktivnostih doma in v tujini, zato je zaželeno aktivno znanje angleškega jezika. Zaželeno je tudi, da imajo kandidati izkušnje z delom v raziskovalnem ali diagnostičnem medicinskem biokemijskem ali genetskem laboratoriju.

eng:
The young researcher will focus on studying the molecular mechanisms that influence the development and progression of nephropathy in Fabry disease. Fabry disease is a rare X-linked lysosomal storage disorder associated with causative variants in the *GLA* gene, leading to organ damage and the development of typical clinical characteristics namely cardiomyopathy, cerebrovascular disease, renal failure and others. Early diagnosis is crucial for effective treatment to prevent irreversible and life-threatening complications.
With transcriptomic studies, it is possible to determine mRNA profiles and thus link genetic factors to functional molecules in cells. Alterations in gene expression have been detected in chronic kidney disease, even before histological changes were present. However, this has not yet been studied in Fabry disease. Therefore, the longitudinal evaluation of mRNA profiles proposed here may allow identification of biological pathways involved in the development and progression of Fabry nephropathy. This would be a continuation of our previous work in which we identified miRNAs that were dysregulated in Fabry patients with stable kidney function and/or in patients with progressive nephropathy. These miRNAs were associated with signalling pathways known to play important roles in the development and progression of CKD and diabetic nephropathy, but their mRNA targets in Fabry nephropathy remain to be investigated. Therefore, evaluation of candidate pathways at the transcriptome level and their association with the current biomarkers of nephropathy, inflammation and oxidative stress proposed here is needed to support and confirm these findings. The young researcher will apply various molecular genetic approaches to RNA isolation and analysis, including next generation sequencing. In addition, young researcher will apply methods to analyse proteins and metabolites from various chronological biological samples, as well as bioinformatics and biostatistical tools. Furthermore, experimental date will be integrated with clinical data in a predictive model to identify accelerated progression of nephropathy in Fabry disease. The proposed project is based on collaboration between the Institute of Biochemistry and Molecular Genetics at the Medical Faculty and Centre for Fabry disease at the General Hospital Slovenj Gradec. The results of the proposed research are expected to elucidate the molecular processes that influence the development of renal disease in Fabry disease and identify novel possible biomarkers of the development and /or progression of the nephropathy in Fabry disease.
We welcome highly motivated and independent candidates who are willing to participate in international research, professional and educational activities, so fluency in English is favourable. In addition, we preferably welcome candidates with research or diagnostics experiences in the field of medical biochemistry and /or genetics and the candidates who have passed Ministry of health qualifying examination for the medical professionals.