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

1. Raziskovalna organizacija (*Research organisation)*:

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

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

Prof. dr. Damjana Rozman, damjana.rozman@mf.uni-lj.si

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

1.05 Biokemija in molekularna biologija /Biochemistry and molecular biology

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 angleškega jezika, izkušnje z laboratorijskim delom, potrebne licence za usposabljanje…).

slo: **Delovni naslov:** Molekularni mehanizmi s holesterolom povezanih nealkoholnih bolezni jeter. Nealkoholna zamaščenost jeter (NAFLD) je najbolj razširjena oblika kronične bolezni jeter na svetu. Dosega 25% globalnega odraslega prebivalstva in kar 1/3 ljudi v razvitem svetu. Bolezen se kaže s spektrom jetrnih patologij, ki segajo od preproste steatoze do poškodb jetrnih celic s fibrozo in se lahko končajo s cirozo ali rakom jeter (HCC). Naraščajoča incidenca NAFLD je povzročila dramatično povečanje raka jeter, ki velja za bolezen s slabim izidom in omejenimi terapevtskimi možnostmi. Brez zdravljenja je HCC usoden, s 5-letnim preživetjem le v petih odstotkih. Izsledki naše raziskovalne skupine kažejo, da motnja aktivnosti gena *Cyp51* iz sinteze *holeste*rola povzroči progresivno poškodbo jeter ki privede do hepatocelularnega karcinoma. Namen predlagane doktorske naloge je odkriti s holesterolom povezane presnovne poti, mreže interakcij in regulatorna vozlišča, udeležene pri napredovanju nealkoholne (maščobne) bolezni jeter pri ženskah in moških pacientih z različnimi stopnjami NAFLD. Pri tem se bomo oprli na lastne eksperimentalne podatke kot tudi podatke iz javno dostopnih podatkovnih zbirk. Cilj je določiti podskupine pacientov, pri katerih bolezen napreduje od preproste zamaščenosti do višjih stopenj, npr. nealkoholnega steatohepatitisa (NASH) ali hepatocelularnega carcinoma, a so za progresijo bolezni pri podskupinah odgovorni drugačni genetski ali biokemijski dejavniki. Tovrstna stratifikacija pacientov predstavlja nov, modern pristop, ki izkorišča zmogljivost po-genomskih tehnologij za korake proti posamezniku prilagojeni, perosnalizirani medicini. Metodologija bo obsegala delo z vzorci jeter in krvi bolnikov s klinično določenimi stopnjami NAFLD in kontrol, ki so podpisali informirano soglasje za preiskavo, določevanje metabolitov z metodo LC-MS, globalno profiliranje izražanja genov (z mikromrežami ali sekvenciranjem RNA), bioinformatsko analizo za obdelavo podatkov in rudarjenje v

podatkovnih zbirkah, druge klasične molekularno-biološke tehnike ter delo z nesmrtnimi celičnimi linijami.
Kandidati morajo imeti izkušnje z laboratorijskim delom s širšega področja biokemije in molekularne biologije. Prednost bodo imeli kandidati, ki že izkazujejo tudi izkušnje pri računskem delu s podatki ali imajo željo, da se dela s podatki naslednje generacije sekvenciranja priučijo.

eng: **Working title:** Molecular mechanisms of cholesterol-related non-alcoholic liver diseases.
Non-alcoholic fatty liver disease (NAFLD) is the most widespread form of chronic liver disease in the world. It achieves 25% of the global adult population and 1/3 people in the developed world. The disease is manifested by the spectra of hepatic pathologies that range from simple steatosis to liver cell damage with fibrosis and may end with cirrhosis or liver cancer (HCC). The increasing incidence of NAFLD has resulted in a dramatic increase in liver cancer, which is considered a disease with poor and limited therapeutic options. Without treatment, HCC is fatal, with 5-year survival only in five percent. The findings of our research group show that the diminished activity of gene *CYP51* in the synthesis of cholesterol causes a progressive liver injury which leads to hepatocellular carcinoma.
The purpose of the proposed doctoral work is to detect cholesterol-related metabolic pathways, interaction networks and regulatory nodes involved in the progression of non-alcoholic (fatty) liver diseases in women and male patients with varying degrees of NAFLD. We will rely on by our own experimental data as well as data from publicly available databases. The objective is to identify subgroups of patients whose disease is progressing from simple steatosis to higher levels, e.g. non-alcoholic steatohepatitis (NASH) or hepatocellular carcinoma, but different genetic or biochemistry factors are responsible for the progression of the disease in different subgroups. This kind of stratification of patients presents a new, modern approach that exploits the capacity of post-genomic technologies for steps towards an individually adapted, perosnalized medicine.
The methodology will cover work with samples of the liver and blood of patients with clinically-defined NAFLD stages and the controls, which all have signed informed consent for the investigation, determination of metabolites by the LC-MS method, global profiling of gene expression (with microscopes or RNA sequencing), bioinformatics analysis for data processing and mining in databases, other classical molecular-biological techniques and working with immortal cell lines.
Candidates must have experience of laboratory work within a broader field of biochemistry and molecular biology. Priority will be given to candidates who are already showing the experience of data computation or have the desire to learn to work with the next generation of sequencing data.