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

1. Članica UL (*UL member)*:

Medicinska fakulteta

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

Dr. Mirjana Liović, viš. znan. sod. mirjana.liovic@mf.uni-lj.si

3. Raziskovalno področje (*Research field*):

Interdisciplinarno: celična in molekularna biologija proteinov citoskeleta in adhesoma, inducirane pluripotentne matične celice, celični in tkivni modeli za preučevanje dednih bolezni kože, razvoj novih terapevtskih pristopov Interdisciplinary: cell and molecular biology of cytoskeletal and adhesome proteins, induced pluripotent stem cells, 2D and 3D hereditary skin disease models, development of potential therapeutical approaches

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: Bulozna epidermoliza (EB) je skupina dednih bolezni krhkosti kože. Razvrstimo jo v 4 glavne klinične tipe, EB simpleks (EBS), junkcijska EB (JEB), distrofična EB (DEB) in Kindler sindrom (KINDS), ki zajemajo 30 različnih podtipov, katere povzročajo mutacije v 18. genih (1, 2). Pri številnih bolnikih (predvsem pri DEB) se v času življenja pojavi tudi več ploščato-celičnih lezij (spinocelularni karcinom), ki so glavni vzrok njihove predčasne smrti (3). EB prizadane okoli 500.000 ljudi na svetu in je še vedno neozdravljiva bolezen. Kljub napredku medicine in znanosti, zdravijo le simptome bolezni. V zadnjem desetletju so razvili številne eksperimentalne terapevtske pristope. Med te uvrščamo lentivirusne in retrovirusne konstrukte za dostavo zdrave kopije gena ali popravilo mutiranega gena v *in vitro* pogojih, celične terapije z uporabo alogenih mezenhimskih matičnih celic ali fibroblastov, ter transplantacijo kostnega mozga (4, 5, 6). V poskusnih raziskavah so pripravili EB iPSC linije z namenom popravila okvarjenega gena (7, 8). Pred kratkim so pacienta z JEB obliko zdravili celo s kombinacijo *ex vivo* popravila gena v pacientovih keratinocitih, klonalno selekcijo popravljenih celic in nato s transplantacijo epidermalnih plasti pripravljenih iz selekcioniranih celic (9). Tkivo in celice EB pacientov so zelo omejeni, zato presejalnega testiranja spojin, ki bi lahko imele pozitivne učinke na fenotip bolezni, še vedno niso opravili. Delno je to posledica neobstoječega *in vitro* 3D modela EB kože, ki bi omogočil zanesljivi model za potrebe presejalnega testiranja. Pomanjkljivost je tudi nepoznavanje dobro definiranih tarč, ki bi omogočili potencialne pristope za sistemske terapije v prihodnosti. Raziskovalno delo mladega raziskovalca na tem področju bo zajemalo preučevanje skupine citoskeletnih strukturnih proteinov in signalnih poti, ki sodelujejo tudi pri adheziji celic kožnega epitelija na ekstracelularni matriks. Pri tem bodo uporabljene najsodobnejše tehnologije s področja celične biologije in regenerativne medicine, kot so to npr. "gene and base editing", iPSC linije, *in vitro* 3D kožni ekvivalenti, masna spektrometrija, in številni drugi biokemijski in biofizikalni	

raziskovalni pristopi (10, 11). Raziskave bodo v povezavi s sodelujočimi raziskovalnimi skupinami iz Velike Britanije (Kings College London in University of Manchester), ter Hrvaške (Inštitut Rudjer Bošković) in Slovenije (Kemijski inštitut v Ljubljani), in se navezujejo na obstoječi ARRS projekt "EB adhesom".
Glede na to, da gre za delo, ki temelji na celičnih in tkivnih kulturah, je zaželeno, da kandidati imajo izkušnje v delu s celičnimi in tkivnimi kulturami ter iz proteinske biokemije.

1. Fine JD et al., J Am Acad Dermatol. 70(6):1103-26, 2014; 2. Fine JD et al., JAMA Dermatol. 152(11):1231-1238, 2016; 3. Fine JD et al., J Am Acad Dermatol. 60(2):203-11, 2009; 4. Rashidghamat E and McGrath JA. 6(1):6-20, 2017; 5. Gorell E et al., Gene therapy for skin diseases. Cold Spring Harb Perspect Med. 4(4):a015149, 2014; 6. Abdul-Wahab A et al., Semin Cutan Med Surg. 33(2):83-90, 2014; 7. Tolar J et al., J Invest Dermatol. 131(4):848-56, 2011; 8. Itoh M et al., Proc Natl Acad Sci U S A. 108(21):8797-802, 2011; 9. Hirsch T, et al. Nature. 551(7680):327-332, 2017. 10. Khurana P et al., Stem Cell Res 45:101827, 2020; 11. Gouveia M et al., Int J Mol Sci 21(7):2596, 2020.

eng: EB is a heterogeneous group of inherited skin blistering diseases. The 4 main clinical types, EB simplex (EBS), junctional EB (JEB), dystrophic EB (DEB) and Kindler syndrome (KINDS), include 30 different subtypes that are caused by mutations in 18 genes [1, 2]. Almost all patients with recessive DEB (RDEB) develop squamous cell carcinoma lesions, which are the main cause of their premature death [3]. EB affects around 500.000 people worldwide and is incurable. Despite the progress of medicine and science, patients are treated only symptomatically. In the last decade several experimental approaches for treatment have been devised. These included lentiviral and retroviral constructs to supplement the missing gene or to repair the mutation in vitro, and cell therapy through mesenchymal stromal cells, allogeneic fibroblasts and bone marrow transplantation [4, 5, 6]. EB patient-derived iPSC lines have been also generated for gene repair studies [7, 8]. Recently a JEB patient was even treated by a combination of ex vivo gene repair of patient-derived keratinocytes, clonal selection of repaired cells and epidermal sheet transplantation [9]. EB patient-derived material (cells/tissue) is limited, and high-throughput testing of compounds that may help improve patients' phenotype has not yet been done. This is partly due to the lack of a reliable in vitro EB 3D skin model for high-throughput testing purposes, but also the abscence of well defined targets for potential systemic therapy.
This training program will focus on investigating the role of cytoskeletal structural proteins and signalling pathways involved in cell-to-matrix adhesion. It includes daily use of cutting edge technology from the field of cell biology and regenerative medicine, such as gene editing, iPSC lines, in vitro 3D skin equivalents, mass spectrometry, as well as many other biochemical and biophysical techniques. This research program will be in collaboration with several collaborating groups from Great Britain (Kings College London and University of Manchester), as well as Croatia (Rudjer Bošković Institute) and Slovenija (National Institute of Chemistry, Ljubljana), and is linked to the ongoing ARRS project "EB adhesome".
As this work is heavily based on cell/tissue culture, experience in cell and tissue culture as well as protein biochemistry is desirable.

1. Fine JD et al., J Am Acad Dermatol. 70(6):1103-26, 2014; 2. Fine JD et al., JAMA Dermatol. 152(11):1231-1238, 2016; 3. Fine JD et al., J Am Acad Dermatol. 60(2):203-11, 2009; 4. Rashidghamat E and McGrath JA. 6(1):6-20, 2017; 5. Gorell E et al., Gene therapy for skin diseases. Cold Spring Harb Perspect Med. 4(4):a015149, 2014; 6. Abdul-Wahab A et al., Semin Cutan Med Surg. 33(2):83-90, 2014; 7. Tolar J et al., J Invest Dermatol. 131(4):848-56, 2011; 8. Itoh M et al., Proc Natl Acad Sci U S A. 108(21):8797-802, 2011; 9. Hirsch T, et al. Nature. 551(7680):327-332, 2017. 10. Khurana P et al., Stem Cell Res 45:101827, 2020; 11. Gouveia M et al., Int J Mol Sci 21(7):2596, 2020.