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

1. Raziskovalna organizacija (*Research organisation)*:

Univerza v Ljubljani, Biotehniška fakulteta

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

Simon Horvat
simon.horvat@bf.uni.lj.si

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

4.06 Biotehnologija (4.06 Biotechnology)

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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Mladega raziskovalca (MR) bi vključili v dva projekta, ki ga letos prijavljamo kot sodelujoča organizacija na razpisu Agencije za raziskovalno dejavnost republike Slovenije (ARRS). Na teh dveh projektih je prijavitelj novo nastali laboratorij »Imunologija in Celična Imunoterapija (ICI), na Nacionalnem Inštitutu za Biologijo (NIB), ki bo razvijal nove celične tehnologije (predvsem CAR-T) za razvoj ciljnih terapij zdravljenja raka in preučevanja imunoloških mehanizmov obrambe telesa proti rakotvornosti. MR bo del svojih analiz opravil tudi na ICI. V projekte je preko že podpisane pogodbe o sodelovanju in prenosu s patenti zaščitenih materialov in metod vključena tudi skupina na Univerzi v Pensilvaniji. Tudi če pri dveh projektih ARRS letos ne bi bili uspešni, se bo sodelovanje začelo in financiralo iz sredstev MR ter obeh programov na naši inštituciji ter programa na NIBu.

CAR (»Chimeric Antigen Receptor«) T celična imunoterapija je prvi FDA-odobren pristop zdravljenja raka s uporabo gensko spremenjenih celic T, ki že rešuje življenja številnih bolnikov v ZDA, medtem ko Evropa, vključno s Slovenijo, na tem področju zaostaja. V nasprotju z izjemnim uspehom pri zdravljenju nekaterih krvnih rakov pa sedanje različice celic CAR T niso tako učinkovite pri zdravljenju trdih tumorjev, ki predstavljajo 90% vseh primerov raka. Klinična uporaba celic CAR T je odprla pot tudi novim terapevtskim aplikacijam celične imunoterapije, vključno s celičnim zdravljenjem avtoimunskih obolenj, kar ima potencial za spremembe paradigme zdravljenja bolezni, kot so multipla skleroza, diabetes tipa 1 in revmatoidni artritis.

Raziskovalni program MRja bo na področju bazične imunologije z najsodobnejšimi platformami za raziskovanje imunskih funkcij, vključno s celostno analizo imunskega sistema z uporabo RNA sekvenciranja in pretočne citometrije. Na podlagi preučevanja celičnih in molekularnih mehanizmov, ki so vključeni v protitumorsko delovanje imunskega sistema, bo MR razvijal nove pristope celične imunoterapije naslednje generacije. Konkretneje, MR bo razvijal CAR T celice, ki so genetsko nadgrajene z določenimi transkripcijskimi faktorji, ki bolj učinkovito modulirajo lastnosti T celic in programe diferenciacije. Cilj je izbojšati ekspanzijo, obstojnost, funkcionalne lastnosti, ter protitumorsko aktivnost. Velik poudarek njegovega dela bo tudi na razvoju predkliničnih mišjih modelov, kjer ima naša skupina vso potrebno infrastrukturo in ekspertizo. MR bi vzpostavil sistem izolacije mišjih celic T, aktivacije, vnosa CAR, TCR in ostalih genov z uporabo retrovirusov in/ali HDR-omogočen CRISPR knock-in preko RNPs z elektroporacijo ter ekspanzijo. Kandidatne konstrukte/celice bo MR testiral za učinkovitost terapije na različnih mišjih modelih. Pri

predlaganemu projektu MR bomo razvili tako imenovani singenski model, pri katerem so miši imunsko kompetentne, kar omogoča analize CAR T celic v okviru funkcionalnega imunskega sistema. Poleg tega lahko singenski modeli razkrijejo toksične učinke na distalne-tumorje, ker zdrave miši običajno izražajo ciljni antigen, ki odraža stanje pri rakavih pacientih.

Prednost pri izbiri kandidata za ta projekt bodo imeli kandidati s končanim študijem 1. ali 2. stopnje na področju biotehnologije ali biokemije. Zaželene so predhodne izkušnje s področja molekularne imunologije ali imunoterapije raka posebej še uporabe novih tehnologij genskega urejanja (npr. CRISPR/Cas9). Zaželeno je tudi, da ima kandidat že izkušnje s projektnim delom ali študijem v tujini in da želi opravljati predklinične študije na mišjih modelih.

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Young researcher would be included in two projects, which we are applying for this year's Slovenian Research Agency (ARRS) grant application as a participating organization along with the lead organisation and a newly established laboratory "Immunology and Cellular Immunotherapy (ICI), at the National Institute of Biology (NIB). The aim of this collaboration is development of new cellular technologies (especially CAR-T) for the development of targeted cancer therapies and immune defense mechanisms. Young researcher will also perform part of its analyzes at ICI. The group at the University of Pennsylvania is also involved in the projects through an already signed cooperation and transfer agreement with patented materials and methods. Even if the two ARRS projects are not successfully granted this year, the cooperation will start and be financed from the funds of the Young researcher and program grant at our institution and at the NIB.

CAR (“Chimeric Antigen Receptor”) T cell immunotherapy is the first FDA-approved approach to cancer treatment using genetically modified T cells that has saved the lives of many patients in the US, while Europe, including Slovenia, is lagging behind. In contrast to the remarkable success in treating some blood cancers, however, current versions of CAR T cells are not as effective in treating solid tumors, which account for 90% of all cancers. The clinical use of CAR T cells has also paved the way for new therapeutic applications of cellular immunotherapy, including cellular treatment of autoimmune diseases, which has the potential to change the treatment paradigm of diseases such as multiple sclerosis, type 1 diabetes, and rheumatoid arthritis.

The research program will be in the field of basic immunology with state-of-the-art platforms to investigate immune functions, including a comprehensive analysis of the immune system using RNA sequencing and flow cytometry. Based on the study of cellular and molecular mechanisms involved in the antitumor function of the immune system, Young researcher will develop new approaches to next-generation cellular immunotherapy. More specifically, Young researcher will develop CAR T cells that are genetically upgraded with specific transcription factors that more effectively modulate the intrinsic properties of T cells and differentiation programs. The goal is to improve expansion, persistence, functional properties, and antitumor activity. Great emphasis of his work will also be on the development of preclinical mouse models, where our group has all the necessary infrastructure and expertise. Young researcher would establish a system of mouse T cell isolation, activation, uptake of CAR, TCR, and other genes using retroviruses and / or HDR-enabled CRISPR knockin via RNPs by electroporation and expansion. Candidate constructs / cells will be tested by Young researcher for efficacy of therapy in various mouse models. In the proposed MR project, we will develop a so-called syngeneic model in which mice are immune competent, which allows the analysis of CAR T cells within a functional immune system. In addition, syngeneic models may reveal toxic effects on distal-tumors because healthy mice typically express a target antigen that reflects the condition in cancer patients.

Priority in the selection of a candidate fort he Young researcher position will be given to candidates with completed 1st or 2nd level studies in the field of biotechnology or biochemistry. Previous experience in molecular immunology or cancer immunotherapy is desirable, especially the use of new genetic control technologies (eg CRISPR / Cas9). It is also desirable that the candidate already has experience with project work or study abroad and that he or she wishes to perform preclinical studies in mouse models.