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

1. Raziskovalna organizacija (*Research organisation)*:

Univerza v Ljubljani, Medicinska fakulteta, Inštitut za patološko fiziologijo, Laboratorij za nevroendokrinologijo-molekulsko celično fiziologijo

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

Matjaž Stenovec, e-mail:matjaz.stenovec@mf.uni-lj.si

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

3.03. Medicinske vede. Nevrobiologija

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…).

slo: Cilj predloga usposabljanja mladega raziskovalca je pridobitev novega znanja o mehanizmih astrocitne signalizacije v fizioloških in patoloških stanjih: »Mehanizmi funkcionalne plastičnosti reaktivne astroglije«

Astrociti so heterogene celice nevroglije v centralnem živčnem sistemu (CŽS), ki so poznane že dobro stoletje. V možganski skorji človeka po številu prekašajo nevrone. Dolgo je tudi znano, da se ob patoloških pojavih v CŽS spremenijo v »reaktivno astroglijo«. Morfološke značilnosti le-te so relativno dobro opredeljene, medtem ko so spremljajoče spremembe v delovanju reaktivne astroglije zelo slabo poznane. Predvsem je nepojasneno ali te celice pospešijo ali upočasnijo patološki proces. Na eni strani lahko različni dejavniki spodbudijo aktivacijo astrocitov (npr. ishemija, nevrotrauma, infekcija), na drugi strani pa se predvidevajo mehanizmi, ki inhibirajo to transformacijo. Cilj predlaganega usposabljanja je predvsem v študiju endogenih mehanizmov, ki zavirajo reaktivacijo astroglije.

Med staranjem nevroni iz jedra *locus coeruleus*, enega od možganskega centrov, ki se odzivajo na stres, postopoma propadejo. S tem se v možganovini zmanjša količina noradrenalina, ki ga izločajo noradrenergični nevroni na druge celice. Prevladuje mnenje, da je upad noradrenalina povezan s povečano stopnjo živčno-vnetnih procesov, ki med drugim pospešijo kognitivni upad in razvoj demenc, kakor tudi druge nevrodegenerativne procese. Način na katerega noradrenalin inhibira provnetno transformacijo astrocitov, še ni raziskan. V raziskavi bomo zato testirali hipotezo, po kateri noradrenalin preko delovanja še neprepoznanih sekundarnih prenašalcev inhibira predstavljanje antigenov na molekulah poglavitnega histokompatibilnostnega kompleksa razreda II (kompleks MHC II) na astrocitih. Pred kratkim smo odkrili, da pri tem procesu sodelujejo lizosomi, ki so po velikosti bistveno večji celični predelki kot sekrecijski mešički astrocitov. Z elektrofiziološkimi (membranska kapacitivnost) in optofiziološkimi (superločljivostna fluorescentna mirkroskopija) ter molekulskimi metodami bomo raziskali, kako se uravnava transport mešičkov s kompleksi MHC II na površino astrocitov. V procesu, ki je povezan z

endogeno inhibicijo reaktivne astroglioze preko draženja z noradrenalinom, bomo testirali vlogo amizina, pred kratkim odkritega proteina, ki se veže na predele plazmaleme obogatene z lipidom fosfatidilinozitol 4,5-bifosfatom (PIP2).

Rezultati te raziskave nam bodo omogočili ne le vpogled v naravo molekulskih mehanizmov, ki uravnavajo vnetno transformacijo astrocitov, temveč bodo ključno prispevali tudi k novim možnostim za farmakološko obvladovanje provnetnih procesov, ki so povezani s postopnim propadom noradrenergičnega sistema pri človeku med staranjem in nevrodegeneracijo.

Pri kandidatu za mladega raziskovalca je zaželeno poznavanje temeljnih tehnik aseptičnega laboratorijskega dela, izkušnje dela s programskimi orodji Microsoft Office (Word, Excel, PowerPoint,...), Sigma Plot in Adobe Photoshop ter znanje angleškega jezika. Pretekli doktorandi iz našega laboratorija so bili po zaključku svojega dela praviloma zelo uspešni in so začeli neodvisno raziskovalno delo v tujih laboratorijih, za kar je potrebna tudi močna motivacija. Posebej dobrodošli so tako kandidati z visoko stopnjo motiviranosti postati bodoči neodvisni znanstvenik, s ciljem voditi lastni raziskovalni laboratorij; bodisi na univerzah in inštitutih, bodisi v industriji.

eng: The aim of research proposal for Young Researcher is acquisition of new knowledge about mechanisms of astroglial signalization in physiological and pathological states: »Mechanisms of functional plasticity in reactive astroglia«

Astrocytes are heterogeneous neuroglial cells that have been known for more than a century. In human neocortex they outnumber neurons. It has long been known that when pathological events occur in the central nervous system, they turn into »reactive astroglia«. Morphological features of this complex cellular alteration are relatively well defined, however, the accompanying changes in astrocyte function are poorly known. Above all, it is unclear whether these cells accelerate or slow down the pathological process. On one side, different factors favor activation of astrocytes (e.g. ischemia, neurotrauma, infection); whereas on the other side, mechanisms are proposed that counteract this transformation. The main goal of the research proposal is thus study of endogenous mechanisms that suppress reactivation of astroglia.

During aging, neurons from the nucleus *locus coeruleus*, one of the brain's stress-response centers, gradually fail. This reduces the amount of noradrenaline in the brain, which is secreted by noradrenergic neurons to other cells. The prevailing opinion is that the decline in noradrenaline is associated with an increased rate of neuro-inflammatory processes, which, among other, accelerate cognitive decline and the development of dementia, as well as other neurodegenerative processes. The exact way in which noradrenaline inhibits the inflammatory transformation of astrocytes has not been studied yet. We will therefore test the hypothesis that noradrenaline inhibits the presentation of antigens on major histocompatibility class II molecules on astrocytes via the action of as yet unidentified secondary messenger(s). Recently, we have discovered that lysosomes, which are much larger subcellular organelles than the secretory vesicles of astrocytes, participate in this process. Electrophysiological (membrane capacitance) optophysiological (super-resolution fluorescence microscopy), and molecular methods will be used to investigate how is the transport of MHC II-positive vesicles to the astrocytes surface regulated. In the process of endogenous inhibition of reactive astrogliosis via noradrenaline stimulation, we will examine the role of amysin, a recently discovered protein that binds to the plasmalemmal domains enriched with lipid phosphatidylinositol 4,5-bisphosphate (PIP2).

The results of this research will not only provide insights into the nature of molecular mechanisms involved in regulation of inflammatory astrocyte transformation, but will also contribute to new possibilities for pharmacological control of inflammatory processes associated with the gradual decline of the human noradrenergic system during aging and neurodegeneration.

Basic skills of aseptic work in cell culture laboratory and experiences with software tools, such as MS Office (Word, Excel, PowerPoint,...), Sigma Plot and Adobe Photoshop, and knowledge of English language are desired in candidates for Young Researcher. Former PhD students conducting scientific work in our laboratory have been very successful and have started independent research work in foreign laboratories, which also requires a strong motivation. We thus especially welcome highly motivated candidates, who strive to become independent scientists in the future and have set a goal to run their own research laboratory; either in universities and institutes, or in industry.