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

1. Raziskovalna organizacija (*Research organisation)*:

Univerza v Ljubljani, Fakulteta za farmacijo (University of Ljubljana, Faculty of Pharmacy)

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

Stanislav Gobec (stanislav.gobec@ffa.uni-lj.si)

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

1.09 Farmacija (Pharmacy)

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:

Propad nevronov pri Alzheimerjevi bolezni (AB) je dokazano povezan s številnimi procesi, pri čemer etiologija bolezni še vedno ni razjasnjena v celoti. Poleg nastanka amiloidnih leh, sestavljenih iz agregiranega amiloida beta (Aβ), so najbolj izrazite spremembe še povečan oksidativni stres, porušena homeostaza kovinskih ionov in predvsem izrazito znižanje koncentracije živčnega prenašalca acetilholina (ACh) v možganih. Znižana koncentracija ACh je posledica propada holinergičnih nevronov v amigdali in hipokampusu. To so predeli možganov, povezani s kognitivnimi funkcijami kot so spomin, orientacija in razumska presoja. Tri od štirih registriranih zdravilnih učinkovin za terapijo AB zavira holin-esteraze (ChE) in s tem poveča holinergični prenos v prizadetih možganih ter omili simptome bolezni. Razvoj novih zdravil za zdravljenje AB se je v zadnjem času zaradi večjega terapevtskega potenciala preusmeril tudi v pripravo spojin z multiplim mehanizmom delovanja, ki bodo hkrati specifično kelirale kovinske ione, zmanjšale agregacijo Aβ in zavirale holinesteraze.

Mladi raziskovalec bo vključen v razvoj novih multifunkcionalnih spojin kot potencialnih novih zdravil za zdravljenje AB. Z uporabo strukturno-podprtega načrtovanja in kemijske sinteze bo v eno molekulo združil kemijske lastnosti, ki bodo omogočale vplivanje na različne patofiziološke procese, značilne za AB (keliranje Cu ionov, zaviranje agregacije Aβ, zaviranje holinesteraz, zaviranje monoamin oksidaze B). Raziskovalna skupina prof. Gobca je nedavno odkrila več selektivnih zaviralcev butirilholin-esteraze (BChE), ki reverzibilno zavirajo BChE s konstanto inhibicije v nizko nanomolarnem območju. Kokristalne strukture BChE z inhibitorji v aktivnem mestu nam razkrivajo način vezave spojin in s tem molekularne osnove zaviranja BChE. Ti strukturni podatki bodo pomembno izhodišče za raziskovalno delo mladega raziskovalca, saj razkrivajo možnosti za uvajanje sprememb, ki bi lahko dodatno izboljšale zaviralne aktivnosti spojin, poleg tega pa bi lahko doprinesle dodatne farmakološke učinke, ki so zaželeni za zdravljenje AB (npr. kelacija kovinskih ionov, zaviranje nastajanja agregatov Aβ, antioksidativno delovanje, zaviranje MAO-B itd.). Poseben poudarek bo na razvoju inovativnih in do sedaj neuporabljenih kombinacij lastnosti (npr. zaviranje holinesteraz in

imunoproteasoma).

Mladi raziskovalec bo v okviru svoje disertacije sintetiziral načrtovane spojine in jih farmakološko ovrednotil z različnimi *in vitro* testi. Zaželeno je, da ima kandidat/kandidatka za mladega raziskovalca predhodno praktično znanje s področja načrtovanja, sinteze in biološke evaluacije zdravilnih učinkovin.

eng:

The etiology of Alzheimer's disease (AD) is not entirely understood, however several conditions are known to participate in the associated neurodegeneration. These include aggregation and accumulation of amyloid-β (Aβ) deposits, oxidative stress, loss of metal ion homeostasis, and a severe decrease in neurotransmitter acetylcholine (ACh) brain levels. The latter is a result of dramatic loss of cholinergic neurons in the neocortex, amygdala, thalamus and hippocampus regions of the brain, which are responsible for cognitive functions such as memory, orientation and judgment. Accordingly, three out of the four currently approved anti-AD drugs exploit cholinesterase (ChE) inhibition, with view to restore cholinergic activity. New drugs are urgently needed to delay further the progression of AD and possibly cure the disease and recently the development of multifunctional compounds that can concomitantly chelate specific metal ions, reduce Aβ aggregation, and inhibit ChE has become of major therapeutic interest.

The young researcher will be involved in development of new multifunctional compounds with the potential to be developed into novel anti-AD drugs. The designed compounds will be able to selectively chelate copper ions, reduce Aβ aggregation, diminish Aβ induced neurotoxicity, and inhibit ChE and monoamine oxidase B. Using structure-based drug design techniques and by merging several structural features into a single chemical entity, we will impinge upon the different processes associated with AD. The group of supervisor Prof. Gobec has recently discovered a series of selective butyrylcholine esterase (BChE) inhibitor displaying reversible inhibition of BChE with low nanomolar inhibition constants. The X-ray crystal structures of BChE in complex with inhibitors were solved, providing insights into their respective binding modes and revealing the molecular basis for their activities. These structural results represent an important starting point for the research work of the young researcher as they suggest modifications that will enable him/her to improve the potency of inhibitors and to explore possibilities for structural modifications that will impart additional pharmacological properties, beneficial for treatment of AD (i.e. metal chelation, inhibition of Aβ aggregation, antioxidative properties, inhibition of MAO-B, etc.). A special attention will be devoted to development of compounds with innovative and hitherto unused combination of properties (for example inhibition of cholinesterases and immunoproteasome).

A young researcher will design, synthesize and pharmacologically evaluate the designed compounds *in vitro*. It is desirable that the candidate for a young researcher has prior practical knowledge in the field of design, synthesis and biological evaluation of active substances.