1. Raziskovalna organizacija (*Research organisation)*:

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

2. Ime in priimek mentorja (*Name and surname of a mentor*):

Stanislav Gobec

3. Področje znanosti iz šifranta ARRS (*Primary research field*):

1.09 - Naravoslovno-matematične vede / Farmacija
1.09 - Natural sciences and mathematics / Pharmacy

4. Kontaktni e-naslov mentorja (*Contact of a mentor)*:

stanislav.gobec@ffa.uni-lj.si

5. Kratek opis programa usposabljanja (*Short description of the program)*:

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 strukturne 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 selektivni zaviralec butirilholin-esteraze (BChE), ki reverzibilno, počasi-vezoče in tesno prilegajoče zavira BChE s konstanto inhibicije v nizko nanomolarnem območju. Kokristalna struktura BChE z inhibitorjem v aktivnem mestu (PDB koda: 4tpk) nam razkriva način vezave spojine in s tem molekularne osnove zaviranja BChE. V skupini so tudi razvili serijo analogov te spojine in jo natančno farmakološko ovrednotili. Ti strukturni in biološki podatki so pomembno izhodišče za raziskovalno delo mladega raziskovalca, saj razkrivajo možnosti za uvajanje dodatnih sprememb, kot so npr. uvedba polarnih funkcionalnih skupin za interakcije s katalitičnimi aminokislinskimi ostanki, kar bi dodatno izboljšalo zaviralne aktivnosti spojin. Poleg tega nakazujejo možnosti za uvedbo novih funkcionalnih skupin z namenom dodatnega farmakološkega učinka, ki je zaželen za zdravljenje AB (npr. kelacija kovinskih ionov, zaviranje nastajanja agregatov Aβ, antioksidativno delovanje, zaviranje MAO-B itd.).

ANG

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 project leader Gobec has recently discovered a selective butyrylcholine esterase (BChE) inhibitor displaying reversible slow-tight-binding inhibition of BChE with low nanomolar inhibition constant. The X-ray crystal structure of BChE in complex with inhibitor was solved (PDB code: 4tpk), providing insights into its binding mode and revealing the molecular basis for its activity. By introducing bioisosterical replacements, a series of analogues was designed, synthesised and pharmacologically evaluated. For some of them, the crystal structures of complexes with BChE were resolved. These structural and biological 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 (e.g. introduction of polar groups to promote interaction with catalytic residues). Furthermore, the structural information will enable the young researcher 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.).