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*):

Aleš Obreza (ales.obreza@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 tujih jezikov, izkušnje z laboratorijskim delom, potrebne licence za usposabljanje…).

slo:
Alzheimerjeva bolezen (AB) je kronična ireverzibilna nevrodegenerativna bolezen, ki predstavlja najpogostejšo obliko demence s progresivnim upadom kognitivnih funkcij. Trenutno zdravljenje je simptomatsko in predvsem upočasni napredovanje bolezni. V terapevtske namene se med nizkomolekularnimi učinkovinami uporabljajo registrirani zaviralci holin-esteraz (donepezil, galantamin, rivastigmin) ter antagonist *N*-metil-D-aspartatnega receptorja memantin.
Spremenjena paradigma pri načrtovanju novih nevroterapevtikov za zdravljenje kompleksnih bolezni, kamor sodi AB, vključuje učinkovine, ki delujejo hkrati na dve ali več tarč, vključenih v razvoj bolezni ali pojav značilnih znakov. Zanje se uporablja izraz multifunkcionalne učinkovine. Zaviralci holin-esteraz delujejo na dva encima: acetilholin-esterazo (AChE) in butirilholin-esterazo (BChE). Oba katalizirata hidrolizo nevrotransmiterja acetilholina, razlikujeta pa se po substratni specifičnosti in pogostosti v posameznih tkivih. Z mitogenom aktivirane protein kinaze (MAP kinaze) so vključene v razne fiziološke in patofiziološke procese. Zaviralci p38 MAP kinaze so privlačna skupina molekul, ki naj bi zmanjšala sproščanje provnetnih citokinov (TNFα, interlevkinov 1β in 6) in s tem upočasnila napredovanje AB.
Kandidat za mladega raziskovalca se bo vključil v raziskovalno delo skupine P1-0208 z namenom načrtovanja, sinteze in vrednotenja novih molekul z delovanjem na holinesteraze in MAP kinaze. Raziskovalno delo v sklopu usposabljanja bo imelo naslednje cilje: 1) načrtovanje, sintezo in vrednotenje novih selektivnih zaviralcev holinesteraz; 2) razvoj selektivnih zaviralcev posameznih MAP kinaz;3) načrtovanje in sintezo multifunkcionalnih učinkovin s sočasnim zaviranjem holinesteraz in MAP kinaz.
V času usposabljanja bo kandidat za mladega raziskovalca pri reševanju nalog uporabljal moderne metode farmacevtske kemije. Kot primer bo na osnovi strukture biološke tarče in znanih učinkovin z delovanjem na omenjeno tarčo, sodeloval pri z računalnikom podprtim načrtovanju strukture novih zaviralcev. Dobljene spojine zadetke in njihove derivate bo pripravil v laboratoriju in jih samostojno ali v sodelovanju z našimi partnerji tudi biokemijsko ovrednotil.
Za uspešno usposabljanje mladega raziskovalca je nujno kakovostno znanje slovenskega in angleškega jezika, zelo zaželene so praktične izkušnje z sinteznim delom v laboratoriju organske

kemije, poznavanje separacijskih in analiznih metod (NMR, masna spektrometrija, HPLC) in delo s podatkovnimi zbirkami ter uporaba različnih računalniških programov.

Opomba: Uporabljeni izrazi, zapisani v slovnični obliki moškega spola, so uporabljeni kot nevtralni za ženske in moške.

eng:

Alzheimer's disease (AD) is a chronic irreversible neurodegenerative disease that represents the most common form of dementia with progressive decline in cognitive functions. Current treatment is symptomatic and, above all, slows the progression of the disease. Registered choline esterase inhibitors (donepezil, galantamine, rivastigmine) and the N-methyl-D-aspartate receptor antagonist memantine are low-molecular-weight active substances used for therapeutic purposes. The changed paradigm in the design of new neurotherapeutics for the treatment of complex diseases, such as AD, includes active substances that simultaneously act on two or more targets involved in the development of the disease or the appearance of characteristic signs. The term multifunctional active ingredient is used for such compounds. Choline esterase inhibitors act on two enzymes: acetylcholine esterase (AChE) and butyrylcholine esterase (BChE). Both catalyse the hydrolysis of the neurotransmitter acetylcholine and differ in substrate specificity and frequency in individual tissues. Mitogen-activated protein kinases (MAPKs) are involved in various physiological and pathophysiological processes. p38 MAPK inhibitors are an attractive group of molecules that reduce the release of pro-inflammatory cytokines (TNFα, interleukins 1β and 6) and thus slow the progression of AD.

The candidate for young researcher will be involved in the work of the P1-0208 research group with the aim of designing, synthesizing and evaluating new molecules by acting on cholinesterases and MAPKs. Research work within the training will have the following objectives: 1) design, synthesis and evaluation of new selective cholinesterase inhibitors; 2) development of selective inhibitors of individual MAPKs, 3) design and synthesis of multifunctional active substances with simultaneous inhibition of cholinesterases and MAPKs. During the training, the candidate for a young researcher will use modern methods of pharmaceutical chemistry. For example, based on the structure of a biological target and known active ingredients acting on said target, the candidate will participate in computer-aided design of new inhibitors. He will prepare the obtained hits and their derivatives in the laboratory and biochemically evaluate them independently or in cooperation with our partners.

For the successful training of a young researcher, quality knowledge of Slovene and English is essential, practical experience with synthetic work in the laboratory of organic chemistry, knowledge of separation and analytical methods (NMR, mass spectrometry, HPLC), work with databases and the use of various computer programs are also highly desirable.