Opis delovnega mesta mladega raziskovalca/ke (D*escription of the Young Researcher's position)*

1. Članica UL (*UL member)*:

Fakulteta za farmacijo

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

Prof. dr. Stanislav Gobec; stanislav.gobec@ffa.uni-lj.si

3. Raziskovalno področje (*Research field*):

Farmacija

4. Opis delovnega mesta mladega raziskovalca/ke (D*escription of the Young Researcher's position)*:
Vključuje morebitne dodatne pogoje, ki jih mora izpolnjevati kandidat/ka za mladega raziskovalca/ko, ki niso navedeni v razpisu za mlade raziskovalce.

slo: Mladi raziskovalec bo razvijal nove encimske inhibitorje terapevtsko pomembnih encimov, ki imajo v svojem aktivnem mestu serin (npr. butirilholinesteraza, penicilin vezoči proteini) ali cistein (npr. L,D-transpeptidaze). S tem bo prispeval k razvoju novih spojin vodnic za zdravljenje nevrodegenerativnih bolezni in bakterijskih okužb. Strategija odkrivanja novih inhibitorjev bo temeljila na dostopnih kristalnih strukturah tarčnih encimov in bo vključevala de-novo načrtovanje, virtualno rešetanje, kemijsko sintezo knjižnic potencialnih inhibitorjev in njihovo biokemično, strukturno, mikrobiološko in toksikološko evaluacijo. Objavljene 3D strukture kompleksov z inhibitorji bomo uporabili pri strukturno podprtem virtualnem rešetanju z najsodobnejšo programsko opremo in javnimi knjižnicami dostopnih spojin. Najbolje rangirane spojine bomo kupili in preizkusili v biokemičnem testu inhibicije tarčnih encimov. Spojine, ki bodo imele dobro inhibitorno delovanje bodo služile kot izhodišče za kemijsko sintezo serije analogov, v katere bomo sistematično uvajali majhne strukturne spremembe in nato ugotavljali, kaj to pomeni za njihovo biološko delovanje (povezava med strukturo in delovanjem). Proces bo iterativen, saj bodo rezultati inhibitornega delovanja spojin vplivali na parametre v programih virtualnega rešetanja in na načrtovanje sinteze inhibitorjev z izboljšanimi lastnostmi. Pričakujemo, da bomo razvili več spojin zadetkov in spojin vodnic, ki bodo aktivne v nizkem mikromolarnem koncentracijskem območju, kar bo pomemben korak pri iskanju novih zdravilnih učinkovin. Od kandidata pričakujemo znanje iz farmacevtske kemije in organske kemije. Zaželen je interes za učenje osnov biokemijskega vrednotenja spojin in uporabe računalniških metod pri načrtovanju učinkovin.

eng: The young researcher will develop new enzyme inhibitors of therapeutically important enzymes that have serine (eg butyrylcholinesterase, penicillin binding proteins) or cysteine (eg L,D-transpeptidases) in their active site. In doing so, he or she will contribute to the development of new lead compounds for the treatment of neurodegenerative diseases and bacterial infections.

The strategy for the discovery of new inhibitors will be based on accessible crystal structures of target enzymes and will include de-novo design, virtual screening, chemical synthesis of libraries of potential inhibitors and their biochemical, structural, microbiological and toxicological evaluation. The published 3D structures of complexes with inhibitors will be used in structure-based virtual screening with state-of-the-art software and public libraries of accessible compounds. The top ranked compounds will be purchased and tested in a biochemical enzyme inhibition assay. Compounds that will have good inhibitory activity will serve as a starting point for the chemical synthesis of a series of analogues, in which we will systematically introduce small structural changes and then determine what this means for their biological activity (structure-activity relationship). The process will be iterative, as the results of the inhibitory activity of the compounds will influence the parameters in the virtual screening programs and the planning of the synthesis of inhibitors with improved properties. We expect to develop several hit and lead compounds that will be active in the low micromolar concentration range, which will represent an important step in the search for new therapeutic agents.

We expect the candidate to have knowledge of pharmaceutical chemistry and organic chemistry. An interest in learning the basics of biochemical evaluation of compounds and the use of computational methods in drug design is desirable.