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*):

doc. dr. Stane Pajk – stane.pajk@ffa.uni-lj.si

3. Raziskovalno področje (*Research field*):

1.09.00	Naravoslovje	Farmacija *(Pharmacy)*

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:
Razvoj novih prob in učinkovin v prvi stopnji poteka z iskanjem strukturnih sprememb spojine vodnice, ki izboljšajo aktivnost merjeno z različnimi biokemijskimi testi. Ko je najdena spojina z zadovoljivo aktivnostjo na tarči, preidemo na kompleksnejše teste, npr. na celični kulturi, na tkivih ali *in vivo* teste na modelnih organizmih. Ob prehodu na kompleksnejše teste, številne spojine, ki so bile zelo aktivne na biokemijskih testih, ne izkazujejo več učinka. Za izgubo učinka je pogosto odgovorna slaba topnost spojin, slaba celična permeabilnost (kadar se tarča nahaja v celici), nestabilnost v plazmi, metabolna pretvorba učinkovine, omejen prehod preko hematoencefalne bariere pri učinkovinah delujočih na centralni živčni sistem itd. Pomembno je da ugotovimo, zakaj je spojina izgubila aktivnost, saj lahko nato predlagamo spremembe v strukturi spojine, da npr. izboljšamo topnost, povečamo kemijsko in/ali metabolno stabilnost … Prav tako je pomembno, da spojine okarakteriziramo iz stališča topnosti, stabilnosti, celične permeabilnosti …, preden so lotimo dragih bioloških testov. Pri omenjeni karakterizaciji spojin uporabljamo predvsem tekočinsko kromatografijo sklopljeno z UV-Vis, CAD ali masnim detektorjem. Zlasti masno spektrometrijo se v farmacevtski kemiji uporablja širše, predvsem pri iskanju in razvoju novih učinkovin. Primera uporabe sta npr. iskanje novih zadetkov oz. novih spojin vodnic (npr. z affinity selection-mass spectrometry) in potrjevanje kovalentne interakcije spojin s tarčnim proteinom z metodo peptidnega mapiranja.
Mladi raziskovalec bo v prvi fazi vključen v razvoj raznih testov za zgoraj opisano karakterizacijo aktivnih spojin, ki jih pripravljamo v raziskovalni skupini prof. Gobca. Gre predvsem za zaviralce bakterijskih encimov (MurF, Ddl, InhA, PBP …) in zaviralce človeških encimov MAO-A, MAO-B, imunoproteasom, BChE … Vzporedno pa bo mladi raziskovalec udeležen v razvoj metod za iskanje novih zadetkov in metod za potrjevanje kovalentnih interakcij med spojinami in proteini. Glavno orodje pri delu mladega raziskovalca bo tekočinska kromatografija sklopljena z UV-Vis in/ali z masnim detektorjem. Zaželeno je, da ima kandidat/kandidatka za mladega raziskovalca predhodno praktično znanje s področja farmacevtske/organske kemije in analitike malih molekul s tekočinsko kromatografijo.

eng:

The development of new probes and active compounds is carried out in the first phase by searching for structural changes in the lead compound that improve the activity measured by various biochemical tests. When a compound with satisfactory activity on the target is found, we move on to more complex assays, such as cell cultures, tissues, or in vivo assays on model organisms. When we move to more complex assays, many compounds that were very active in biochemical assays no longer show activity. Poor solubility of compounds, poor cell permeability (when the target is in the cell), instability in plasma, metabolic conversion of the drug, limited passage through the hematoencephalic barrier for drugs acting on the central nervous system, etc. are often responsible for loss of effect. It is important to find out why the compound has lost its effect, as we can then propose modifications to the structure of the compound to, for example, improve solubility, increase chemical and/or metabolic stability ... It is also important to characterize compounds from the point of view of solubility, stability, cell permeability, etc., before performing expensive biological tests. In the above characterization of compounds, we mainly use liquid chromatography coupled to UV-Vis, CAD or mass detectors. Mass spectrometry in particular is used in pharmaceutical chemistry, especially in the search and development of new active ingredients. Examples of applications include the search for new hits (e.g., using affinity selection mass spectrometry) and confirmation of the covalent interaction of compounds with the target protein using the peptide mapping method.

In the first phase, the young researcher will be involved in the development of various assays for the characterization of compounds described above, which will be prepared in the group of prof. Gobec. These are mainly inhibitors of bacterial enzymes (MurF, Ddl, InhA, PBP...) and inhibitors of human enzymes MAO-A, MAO-B, immunoproteasome, BChE ... In parallel, the young researcher will participate in the development of methods for identification of new hits and methods to study covalent interactions between compounds and proteins. The main tool for the young researcher's work will be liquid chromatography coupled to UV-Vis and/or a mass detector. It is desirable that the candidate for a young researcher position has practical knowledge in the field of pharmaceutical/organic chemistry and small molecule analysis with liquid chromatography.