BioRe-18-22

2. Radni sastanak, 14. 2. 2022.

Radni sastanak na BioRe projektu, IRB, Zagreb, 14.02.2022.

Working Meeting of the BioRe project, IRB, Zagreb, 14.02.2022.

IRB

09:30-10:00 Gathering and coffee

10:00-10:20 **Sanja Tomić** INTRODUCTION

10:20-10:40 **Antonija Tomić** Mechanism of the human DPP III catalysed hydrolysis of neuropeptides tynorphin and Leu-enkephalin

10:40-11:00 **Sara Matić** Influence of the DPP III cancer mutations on the KEAP1-NRF2 signaling pathway

11:00-11:20 **Zrinka Karačić** Study of neuropeptides as potential substrates of human DPP III

11:20-11:40 **Antonia Matić** Study of binding of metal ions (Zn^{2+}, Cu^{2+}, Co^{2+}, Mn^{2+}) to human DPP III

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12:30-14:00 ***Lunch***

14:00-14:20 **Mihaela Matovina, Ana Tomašić Paić** Study of the effect of DPP III overexpression on KEAP1-NRF2 pathway in the cell culture

14.20 – 16:00 General **discussion of the project**, coordination of research efforts, *etc*.

(coffee will be available)

16:00 Closing of the meeting

Sudionici na projektu

Mihaela Matovina	IRB	S	30%
Zrinka Karačić	IRB	S	50%
Ana Tomšić Paić	IRB	S	60%
Sara Matić	IRB	S	70%
Antonija Tomić	IRB	S	60%
PhD student Antonia Matić	IRB	D	80%
Filip Šupljika	Faculty of Food Technology and Biotechnology, Zagreb	S	30%
Dejan Agić	Faculty of Agriculture in University of Osijek	S	30%
Hrvoje Brkić	Faculty of medicine in Osijek, University of Osijek	S	30%
~~Postdoctoral~~ researcher (~~Mirsada Ćehić~~)	IRB	P	100%
Karl Gruber	Institute of Molecular Biosciences, University of Graz	S	5%
Marija Abramić	Retired	S	20%
Peter Macheroux	Graz University of Technology, Graz	K	
Ivana Kekez	University of Zagreb	S	10%
~~Saša Kazazić~~	~~IRB~~	~~K~~	
~~Ivo Piantanida~~	~~IRB~~	~~K~~	

1. izvještajno razdoblje (1.10.18 - 30.9.20.)

OCIJENA **A**

Publikacije

Tomić A., Horvat G., Ramek M., Agić D., Brkić H., Tomić S. New zinc ion parameters suitable for classical MD simulations of zinc metallo-peptidases. *Journal of Chemical Information and Modeling* (2019) DOI: 10.1021/acs.jcim.9b00235. (**Q1**)

Ćehić M., Suć Sajko J. Karačić Z., Piotrowski P., Šmidlehner T., Jerić I., Schmuck C., Piantanida I., Tomić S. The guanidiniocarbonylpyrrole - fluorophore conjugates as theragnostic tools for DPP III monitoring and inhibition. *Journal of biomolecular structure & dynamics* (2019) DOI: 10.1080/07391102.2019.1664936. (**Q2**)

Disertacija

Mirsada Ćehić „Eksperimentalno i računalno istraživanje novih konjugata gvanidina s različitim fluoroforima kao liganada humane dipeptidil-peptidaze III"

2. izvještajno razdoblje (1.10.20 - 31.3.21.)

OCIJENA **B**

Publikacije

Matić S, Kekez I, Tomin M, Bogár F, Šupljika F, Kazazić S, Hanić H, Jha S, Brkić H, Bourgeois B, Madl T, Gruber K, Macheroux P, Matković-Čalogović D, Matovina M & Tomić S. Binding of dipeptidyl peptidase III to the oxidative stress cell sensor Kelch-like ECH-associated protein 1 is a two-step process, *J Biomolecular Structure & Dynamics* (2020), DOI: 10.1080/07391102.2020.1804455, PMID: 32811353. (**Q2**)

Blagojević B, Agić D, Serra AT, Matić S, Matovina M, Bijelić S, Popović BM An in vitro and *in silico* evaluation of bioactive potential of cornelian cherry (Cornus mas L.) extracts rich in polyphenols and iridoids, *Food Chemistry* (2021), DOI: 10.1016/j.foodchem.2020.127619. (**Q1**)

3. izvještajno razdoblje (1.4.21 - 30.9.22.)

Ciljevi	Kontrolne točke	Rezultati	Suradnici
O1 (Zn- parametri) i O3 (inh. vezno mjesto metala)		**Znan. publ. D1.9** – Zn-par. **D3.13** – inh. vezno mjesto metala ☺ **Q1**	AT, HB, AM, ST
O2 (DPP III – uloga u oksidativnom stresu)	**M2.16.1** Rezultati ko-imunoprecipitacije i Western blot analize - utjecaj mutacija na interakcije Keap1-hDPP III u stanici	**D2.16** – izvješće vezano uz **M2.16.1** **D2.17** – izvješće simulacije **D2.18** – izvj. inhibitori/supstrati DPPIII utjecaj na DPP III – Kelch vezanje **D2.19** – Javna prezentacija Keap1-hDPP III - ligandi **D2.20** – izvj. *in vivo* istraživanja OS	MM, ATP SM, ST SM,FŠ SM MM, ATP
	M2.21 *In vivo* potvrda uloge hDPP III u preživljenju stanica u uvjetima oks. stresa		MM, ATP
		D2.22 znanst. publikacija ☺ **Q1** **D2.23** znanst. skup	SM, ATP, SS, MP, GP, MM, MM, ST MCC/CTB?
O2 (uloga metalnih iona na aktivnost DPP III)		**D3.4** Pripremljeno po 1 mg holoenzima s met: Zn, Mn, Cu i Co	ZK, AM, ATP
		D3.5 omjeri metala i proteina	ZK, AM, ATP
	M3.6 broj veznih mjesta metala		ZK, AM, ST
		D3.8 kinetički podaci za vezanje metala i utjecaj metala na enzimsku aktivnost	ZK, AM, ATP
		D3.10 konferencijska prez. 1 ☺ **D3.11** izvješće ITC ☺ **D3.12** konferencijska prez. 2 ☺	HSKIKI-21 (AM) ZK, FŠ, AM MCC-21 (ST)
		D3.13 Publ. inhibit. vm. utjecaj metala na aktivnost DPP III povezati se na rad D1.9	

3. izvještajno razdoblje (1.4.21 - 30.9.22.)

Ciljevi	Kontrolne točke	Rezultati	Suradnici
O4 neuropeptidi – DPP III		**D4.3** izvješće – rezultati kinetičkih mjerenja	ZK, ATP, MA
		D4.7 izvješće – MD simulacije	AT, ST
	M4.8 afinitet hDPP III prema neuropeptidima		ZK, FŠ, MA, ST
		D4.9 konferencijska prez. 1 ☺	HSKIKI-21 ZK
		D4.10 Znanstvena publikacija	ZK, FŠ, ST, AT …
O5 fluorescentni inh. DPP III		~~**D4.3** izvješće – rezultati kalorimetrijskih mjerenja~~	AM, FŠ
		D4.7 izvješće – MD simulacije	ST
	M5.10 Uspoređeni računalni i eksperimentalni rezultati		ZK, FŠ, AM
		D4.10 Znanst. publ. Ban; Z; Karačić, Z.; Tomić, S.; Amini, H.; Marder, T.B.; Piantanida, I. Triarylborane Dyes as a Novel Non-covalent and Non-inhibitive Fluorimetric Markers for DPP III Enzyme. Molecules 26, x (2021). https://doi.org/10.3390/molecules26164816	ZK, ST
O6 DPP IIII minisimpozij			

DODATNO NAPRAVLJENO U SKLOPU HRZZ PROJEKTA

- Istraživanja na kumarinskim derivatima –novim inhibitorima ljudske DPP III

(Agić D, Karnaš M, Šubarić D, Lončarić M, Tomić S, Karačić Z, Bešlo D, Rastija V, Molnar M, Popović BM, Lisjak M. Coumarin Derivatives Act as Novel Inhibitors of Human Dipeptidyl Peptidase III: Combined In Vitro and In Silico Study, Pharmaceuticals 2021, 14(6), 540; https://doi.org/10.3390/ph14060540)

- Mehanizam reakcije hidrolize tinorfina katalizirane ljudskom DPP III + resetiranja enzima u početno stanje nakon izbacivanja produkata -> potpuni enzimatski ciklus ua tinorfin i Leu-enkefalin

(Tomić A. and Tomić S. Demystifying DPP III Catalyzed Peptide Hydrolysis— Computational Study of the Complete Catalytic Cycle of Human DPP III Catalyzed Tynorphin Hydrolysis // International Journal of Molecular Sciences, 23 (2022), 3; 1858, 24. https://doi:10.3390/ijms23031858)

3. izvještajno razdoblje (1.4.21 - 30.9.22.)

1. Publikacija - neuropeptidi

2. Publikacija - metali - eksperiment (AM doktorat)

(priprema enzima s metalima u različitim koncentracijama,
Stopped Flow mjerenja - utjecaj metala na aktivnost DPP III)

3. ?DPP III MINISIMPOZIJ

4. AŽURIRANJE MREŽNE STRANICE

5. ?Inhibitori DPP III - Kelch interakcija

Što nas još od posla očekuje, a u vezi je s projektom

Dejan Agić, Antonia Matić, Sanja Tomić	Utjecaj flavonoida i flavonolignana (suradnja s grupom iz Varšave – Prof. V. Kren) na aktivnost DPP III
Tea Pavkov Keller, Fran Miočić Stošić, Ivana Kekez, Sanja Tomić	kristalizacije kompleksa Kelch -hDPP III (WT i R623W mutant) - Snimanje mono kristala na sinhrotronu - - kristalizacije kompleksa KEAP1 -hDPP III (KEAP1 - provjera – Fran u Grazu) - SAXS (nije nužno dobiti monokristal) *Bilo bi dobro prije prijave projekta napraviti DLS mjerenja na KEAP1 proteinu da se vidi da li agregira*
Sara Matić, Mihaela Matovina, Sanja Tomić	Kompleksi DPP III proteina s mutantima u Kelch domeni

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Tomić A., Brkić H., Matić A., Tomić S., Unravelling the inhibitory zinc ion binding site and the metal exchange mechanism in human DPP III, *Physical Chemistry Chemical Physics*, 2021, **23**, 13267 – 13275, DOI: 10.1039/D1CP01302E