Bioinformaticki Pristup Izucavanju Mehanizma Aktivacije Angiotenzin II Tip 1 Receptora (GPCR) u Svrsi Dizajniranja Novih Lekova

G protein-kuplovani receptori (GPCRs) pripadaju velikoj familiji membranskih proteina, izgradjenih od 7 transmembranskih heliksa i dodatnim osmim heliksom na intracelularnoj strani, usidrenim i paralelnim sa membranom. GPCRs prolaze kroz konformacione promene kao odgovor na siroku paletu ekstracelularnih signala, oslovljenih kao ligandi ili primarni glasnici, kao sto su fotoni, joni, monoamini, nukleozidi, lipidi, peptidi i proteini, inicirajuci intracelularnu signalnu kaskadu.

Homeostaza celije zavisi od odgovarajuce (auto)kontrole ovih signalnih puteva; ukoliko je narusena, posledica moze biti patoloska. U ovim slucajevima farmaceutski lekovi nejcesce su korisceni za uspostavljanje ispravne funkcije GPCRs. GPCR ligandi su podeljeni na agoniste, antagoniste, inverzne agoniste i pristrasne agoniste, a kojoj od ovih klasa ce farmaceutski lek sa najpovoljnijim farmakoloskim dejstvom pripadati, zavisi o kom receptoru je rec.

U ovom projektu se predlaze mehanizam aktivacije klasicnog i pristrasnog puta signalinga za AT1R, odgovornog za hipertenziju. Takodje predlazemo nacin dizajniranja lekova za kompletnu klasu GPCRs koji ce smanjiti negativne efekte istih.

Curriculum Vitae

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Education

Jan 2013 – Dec 2016	Ph.D. student in Biomolecular Structure and Mechanism, Department of Biology, Swiss Federal Institute of Technology, ETH Zurich Supervisor: Dr. Xavier Deupi and Prof. Gebhard Schertler Thesis Objective: Molecular Basis of Biased Signaling in The Angiotensin II Type 1 Receptor
Oct 2010 - Oct 2011	M.Sc. in Biochemistry, Department of Chemistry, Biochemistry and Environmental Protection, Faculty of Sciences, University of Novi Sad Supervisor: Prof. Mirjana Popsavin Thesis Objective: Synthesis and Antiproliferative Activity of Novel Tiazofurin Analogue with 2'-Dodecanamido Isosteric Group
Oct 2006 - Sep 2010	B.Sc. in Biochemistry, Department of Chemistry, Biochemistry and Environmental Protection, Faculty of Sciences, University of Novi Sad

Research Experience

Jul 2010 - Aug 2010	Summer Program in Biochemistry at the Institute of Biotechnology and Biochemical Engineering, Graz University of Technology

Academic Conferences

Jun 2014, Jun 2016	Department of Biology, ETH Zurich Symposium, Davos, Switzerland

Jul 2013, Jul 2014, Jun 2015, Sep 2016	Graduate School Retreat, ETH Zurich and University of Zurich, Switzerland
Oct 2013	GLISTEN: GPCR-Ligand Interactions, Structures and Transmembrane Signalling, COST European Research Network

Awards

- Kostic Foundation Award for Bachelor/Master Thesis in the field of Chemistry Sciences, Second Prize (2012)

Other

- Software skills: PyMOL, VMD, NAMD, Modeller, AutoDock Vina, Chimera
- Proficient in English
- Outside interests: art, photography

Papers (in preparation)

- Duarte DA, Parreiras-e-Silva LT, Alves FL, **Matkovic M**, Prando EC, Lima V, Miranda A, Deupi X, Bouvier M, Costa-Neto CM, Angiotensin II binds to the AT1 receptor in a stepwise manner: a proposed mechanism for binding of peptides to GPCRs, (in preparation)
- **Matkovic M**, Schertler GFX, Deupi X, Molecular basis of biased signaling in the angiotensin II type 1 receptor, (in preparation)

Publications

- Singhal A, Guo Y, **Matkovic M**, Schertler GFX, Deupi X, Yan ECY, Standfuss J, Structural role of the T94I rhodopsin mutation in congenital stationary night blindness, EMBO Rep. 2016 Jul 25.
- Sun D, Flock T, Deupi X, Maeda S, **Matkovic M**, Mendieta S, Mayer D, Dawson RJ, Schertler GFX, Babu MM, Veprintsev DB, Probing Gαi1 protein activation at single-amino acid resolution, Nat Struct Mol Biol. 2015 Sep;22(9):686-94.
- Heydenreich FM, Vuckovic Z, **Matkovic M**, Veprintsev DB, Stabilization of G protein-coupled receptors by point mutations, Front Pharmacol. 2015 Apr 20;6:82.
- Manni S, Mineev KS, Usmanova D, Lyukmanova EN, Shulepko MA, Kirpichnikov MP, Winter J, **Matkovic M**, Deupi X, Arseniev AS, Ballmer-Hofer K, Structural and functional characterization of alternative transmembrane domain conformations in VEGF receptor 2 activation, Structure. 2014 Aug 5;22(8):1077-89.