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Research:

1. **Preparation and commercialization of the first DNA-independent mechanism-based inhibitor of the mammalian DNA methyltransferase Dnmt1** (team leader). We are preparing mechanism-based inhibitors of mammalian/human DNA methyltransferases with IC50 values below 50 nM. The most successful inhibitors can be used for control of the functional organization of mammalian genome in research laboratories, biotechnology, and ultimately in clinics for treatment of pathogenic processes that depend on epigenetic regulation.
2. **Modulators of γ-secretase activity as drug candidates for Alzheimer's disease** (team leader). This project has two unique features. First, we are analyzing modulation of γ-secretase activity at different levels of the enzyme saturation with its substrate. Such approach can mimic pathogenic processes in Alzheimer's disease. Second, we are screening exclusively for competitive inhibitors of γ-secretase. Such compounds can have lower competition with the physiological substrates and thus lower toxic side effects.
3. **High-Performance Computation in Studies of Substrate Channeling in Transient Protein-Protein Interactions**. The project is funded by participation in Center of scientific excellence program. Section: Heterogeneous Computing and Advanced Computational Approaches.

Specialty: *enzyme-based, in silico-based,* and *cell-based* approaches for studies of structure and function of biomolecules and the related drug development efforts. All types of enzyme assays, and protein-protein or protein-ligand interaction studies.

Training: biochemistry; medicinal chemistry; medical biochemistry; physical biochemistry techniques such as AUC, fluorescence, ITC, SPR; biophysics MM/MD, MM/QM calculations; molecular genetics; biological membranes; cell biology.

Expertise: molecular mechanisms in epigenetic regulation and chromatin organization; molecular mechanisms in Alzheimer's disease; assay-development and drug-design based on enzyme structure-function principles; substrate channeling.

Teaching: B.Sc. level: "Introduction to *In Silico* Analysis of Structure and Function of Biomolecules", (60 hours/year). M.Sc. level: "*In Silico* Design of Novel Molecules with Biological Activity", (90 hours/year). M.Sc. Level: "Enzymology part in Physical Organic Chemistry classes" (variable contribution). M.Sc. Level: "*Chemometrics: enzymology*", (15 hours/year).

Major accomplishments: 1) DNA methyltransferases: enzymatic mechanism, regulation, and novel drug-design strategies. 2) membrane-embedded protease γ-secretase: enzymatic mechanism, regulation and novel drug-design and early diagnostic strategies for Alzheimer's disease. 3) molecular mechanism of substrate channeling in transient protein-protein interactions.

Education:

1993-1998, **Ph.D. student** at Department of Biochemistry, **Oklahoma State University**, USA. **Thesis title:** "Substrate Channeling between NAD(H) Dehydrogenases: Enzyme Kinetics, Protein-Protein Interaction, and Molecular Modeling Studies". Mentor: Professor H. Olin Spivey.

1992-1993, **Diploma thesis** at **Max-Planck Institut für Biochemie**, Martinsried Bei München, Germany. **Thesis title:** "Purification of *p17* protein; a component of Actin-Myosin complex from *Dictyostelium discoideum*". Mentor: Günther Gerisch, professor and department head.

1988-1992, **undergraduate student** of biochemistry, molecular biology and physics at the **Faculty of Science and Mathematics**. University of Zagreb, Croatia.

Postdoctoral Research:

2002 and 1998-2000; Department of Chemistry, **University of California, Santa Barbara**, USA in collaboration with a biopharmaceutical start-up company Epigenx. **Project**: Enzymology and inhibitors of mammalian and bacterial cytosine DNA methyltransferases. Project leader: Professor Norbert O. Reich.

2001. Department of Biochemistry, **Duke University Medical Center**, USA. **Project**: Enzymology of protein phosphatase CDC25B with Cdk2/CycA protein complex as the substrate (Cdk2= cycline dependent kinase 2; CycA= cyclin A). Project leader: Assistant Professor Johannes Rudolph.

Senior Scientist:

2007 to 2010, a joint appointment at: *i*) the Faculty of Medicine, **The Katholieke Universiteit Leuven**, **Belgium** and; *ii*) Neurodegenerative Diseases Drug Hunting Team, **Eli Lilly Pharmaceutical Company**. **Project**: Molecular pathophysiology of Alzheimer's disease and inhibitors of membrane-embedded protease γ-secretase. Project Leaders: Professor Bart de Strooper (KUL) and Dr. Eric Karran (Eli Lilly, UK and USA).

2003 to 2006; Department of Biochemistry and Biophysics, **Washington State University**, USA. **Project:** DNA damage induced changes in DNA flexibility and DNA-nucleosome interaction. DNA repair in nuclear extracts. Project leader: Regents Professor Michael J. Smerdon. Co-applicant on: National Institute of Environmental Health Sciences, Grant R01 ES004106 (19-23) "DNA repair in Hormone Responsive Gene".

Clinical Chemistry (Medical Biochemistry):

2010 to 2013: a deputy leader of a clinical laboratory at the Psychiatric Hospital Rab and adjunct faculty at the Faculty of Medicine, University or Rijeka and Croatia.

Current position:

2013 to present: Assistant Professor and Head of the Group for Biomolecular structure and function at the "Department of Biotechnology: Drug Design and Development" (www.svedruziclab.com). I am currently managing a multidisciplinary team that is varying in size from 3 to 6 students. Six projects are currently in focus in our laboratory and three projects are international collaborations.

Funded projects:

1. **2005-2009.** Co-applicant with prof. Michael Smerdon, on project: "DNA repair in Hormone Responsive Gene". National Institute of Environmental Health Sciences, NIH, Grant R01 ES004106 (19-23), $1,187,500

2. **2015-2017. Modulators of Catalytic Activity of Membrane Embedded Protease Gamma-secretase: Novel Drug Candidates for Alzheimer's disease.** Project was funded by The Croatian Science Foundation as a part of "Partnership with industry" program. Based on HrZZ data

base, the fundations has funded more than 1600 projects, but only 5 of us had industrial projects. My project was one of only five industrijal projects, and the only one in partnership with international industry http://www.hrzz.hr/default.aspx?id=78&pid=1&rok=2015-02.

3. **2014-2017.** ***Screening and QSAR studies of novel drug candidates for Alzheimer's disease.*** Project is funded by a small biopharmaceutical company: JIVA Pharma, Ann Arbor MI, USA. The project is funding cell-based studies of novel drug candidates for Alzheimer's disease. Four students completed their M.Sc. thesis working on this project.

4. **2014-2018. Development and Commercialization of Mechanism-Based inhibitors of mammalian DNA methyltransferase Dnmt1.** Project is funded by Croatian Ministry of Science through University of Rijeka. The project is funding *In silico* optimization and preparation of novel drug candidates by organic chemistry synthesis. Two M.Sc. students completed their M.Sc. thesis working on this project
https://portal.uniri.hr/Projekti/488?controler=projekti

5. **2018- current** UniRI sveučilišni project Biochemistry on a Supercomputer: Development of New Software, Drug - design and Analysis of Disease Development on a Molecular Level. https://uniri.hr/wp-content/uploads/2019/09/KatalogZnanja_ENG_2019-2021-1.pdf

6. **2016-2018. Center for Scientific Excellence: Heterogeneous Computing and Advanced Computational Approaches.**
http://acrossdatascience.zci.hr/zci/istrazivanje/znanost_o_podatcima/djelatnici
The project is funding computational (bio)chemistry studies on our university supercomputer. GROMACS and NAMD programs are used for MM/MD studies. Cp2K program is used for MM/QM studies. https://www.svedruziclab.com/wiki/Software
Three M.Sc. students did their M.Sc. thesis working on this project. Two students did part of their Ph.D. work working on this project. One M.Sc. student received "university president award for scientific excellence".
http://www.uniri.hr/files/vijesti/2016_04_Odluka_rektora_RN_studentski_rad.pdf

Teaching:

1. **Software:** All-atom, coarse grained and steered molecular dynamics approaches with GROMACS and NAMD. QM methods with GAMESS-US and Spartan. Ligand docking and in silico HTS: Autodock-Vina and Cresset, Torch, Forge, Spark. Statistical analysis of molecular trajectories with Bio3D in Rstudio. Enzyme kinetics: KinTek, Copasi, Maxima. Physical properties of small molecules, DNA; RNA and proteins, including APBS and DelPhi calculations of electric fields and pKa values. All types of molecular visualization software. All types of software for analysis of protein, DNA, or RNA sequence. Homology modeling with Modeller, and MultySeq modeling of protein evolution. Linux and SLURM on desktop computers and supercomputers. Corel, Photoshop, Origin, Excel.

2. **Invited lecturer***:* **1**. Alzheimer's disease: molecular mechanisms and design of novel drug candidates and early diagnostic methods. **2**. DNA methylation and epigenetic regulation: molecular mechanisms and design of novel drug candidates. **3**. Computational Biochemistry. **4**. Science Funding and its Influence on Growth of World Economy.

3. **Mentoring** individual students in research and preparation of their M.Sc. thesis (in average about two students per year). Currently I mentor 4 students, in the last 7 years I have mentored 14 students. Co-mentor in Ph.D. thesis Andrea Tomljanović Paravić, Univeristy of Rijeka, thesis title: In silico analiza i antiproliferativno djelovanje novih hibrida pirimidin-2,4-dion-1,2,3-triazola. Co-mentor in Ph.D. thesis to Maciej Gielnik, thesis title: Prion Protein Octarepeat Domain.

Conferences: invited lectures in the last 7 years:

1. Symposium 3rd RIJEKA FORUM ONNEURODEGENERATIVE DISEASES 17-18 October 2019. Alzheimer's disease from the molecular perspective: early diagnostics, and the novel drug-design strategies https://www.eanpages.org/wp-content/uploads/2019/08/3rd-RIJEKA-FORUM-ON-NEURODEGENERATIVE-DISEASES_1st-Announcement.pdf
2. EuroSciCon: Alzheimer's Drug Discovery and Development Wednesday, 25 June 2014 09:00 - 17:00. Cineworld: The O2. Peninsula Square, London, SE10 0DX, United Kingdom. https://www.regonline.co.uk/builder/site/Default.aspx?EventID=1295918
3. 248th ACS National Meeting and Exposition, August 10-14, 2014, San Francisco, CA, USA. ChemEpInformatics: In the Pursuit of Epidrugs Using Chemoinformatics and Computational Approaches. Web-of-Science Accession Number: WOS:000349165103399
4. Institut Ruder Bošković, 23. May 2013 lecture titled: Alzheimer's disease from the molecular perspective: pathogenesis, early diagnostics, and development of new drug candidates. http://www.irb.hr/Razno/Kalendari-dogadanja-na-IRB-u/Tjedni-kalendar/Kolokvij-Zavoda-za-molekularnu-medicinu29.
5. Strah od znanosti i tehnologije u doba globalne ekonomske krize. Internacionalna škola iz psihijatrije i kognitivne neuroznanosti". Organizatori ovog skupa su: Medicinski fakultet Sveučilišta u Rijeci, Hrvatsko društvo za kliničku psihijatriju Hrvatskog liječničkog zbora, Odsjek za neuropsihofarmakologiju i farmakologiju ponašanja Hrvatskog instituta za istraživanje mozga, Klinika za psihijatriju KBC Ljubljana, Hrvatsko psihijatrijsko društvo, Psihijatrijska bolnica Rab. https://youtu.be/5N1a4b_AyH0
6. Utjecaj epigenetike na ljudsko ponašanje, zdravlje i budućnost medicine. 14-06.2014 Društvo za promociju znanosti i kritičkog mišljenja https://youtu.be/7lbLe0IMsEk
7. Side effects of antipsychotics: how to avoid them and how can they be useful, Osijek, Croatia, 2012. http://www.penta-pco.com/2seminarosijek/en/program.html

***Ad hoc* reviewer**: DNA Repair, Elsevier Ltd; Epigenetics, Landes Bioscience; Biochemical Journal; Bioorganic & Medicinal Chemistry. Letters, Elsevier Ltd.; Journal of Neuroscience; Biochimie Elsevier Ltd; Current Medicinal Chemistry; BBA; Molecular Psychiatry .

Publications:

The asterisk * marks the corresponding author. I am first author and/or corresponding author on over 90% of the manuscripts. Over 90% of the manuscripts has 4 or less than 4 authors. All manuscripts are invited contributions or published in Q1 journals at the time of publication. https://scholar.google.com/citations?user=fdEi0GkAAAAJ&hl=en

1. Chaudhary H, Iashchyshin IA, Romanova N, Rambaran M, Musteikyte G, Smirnovas V, Holmboe M, Ohlin CA*, **Svedružić ŽM***, Morozova-Roche L*. Polyoxometalates as effective nano-inhibitors of amyloid aggregation of pro-inflammatory S100A9 protein involved in neurodegenerative diseases. * corresponding authors. *ACS Appl. Mater. Interfaces. June 3rd, 2021*. https://pubs.acs.org/doi/abs/10.1021/acsami.1c04163 IF=8.76, Q1

2. Leri M*, Chaudhary H*, Iashchyshin IA*, Pansieri J*, **Svedružić ŽM***, Gmez Alcalde S, Musteikyte G, Smirnovas V, Stefani M, Bucciantini M, Morozova-Roche LA. Natural Compound from Olive Oil Inhibits S100A9 Amyloid Formation and Cytotoxicity: Implications for Preventing Alzheimer's Disease. * equal contribution. *ACS Chem. Neurosci. 2021, 12, 11, 1905–1918. May 12, 2021*. https://doi.org/10.1021/acschemneuro.0c00828 IF=4.5, Q1

3. **Svedružić ŽM**, Vrbnjak K, Martinović M, Miletić V. Structural Analysis of the Simultaneous Activation and Inhibition of γ-Secretase Activity in the Development of Drugs for Alzheimer's Disease. Pharmaceutics. 2021; 13(4):514. Q1. IF=4.4, https://doi.org/10.3390/pharmaceutics13040514

4. F. Rokić, L. Trgovec-Greif, N. Sučić, N. Čemeljić, Đ. Cekinović Grbeša, Svedružić Ž.M., O. Vugrek, I. Jurak: "Diverse SARS-CoV2 variants proceeded the initial COVID-19 outbreak in Croatia". Archives of Virology (Q1, IF,2,3) 2021; https://doi.org/10.1007/s00705-021-05029-7

5. Miletić V*, M.AšenbrenerKatić A, **Svedružić ŽM*.** High-throughput Virtual Screening Web Service Development for SARS-CoV-2 Drug Design. Mipro-proceedings 37, 6335. http://docs.mipro-proceedings.com/dsbe/37_DSBE_6335.pdf

6. Svedružić Ž. M.*, Odorčić I., Chang CH, Svedružić D*. Substrate Channeling *via* Transient Protein-Protein Complex: the case of D-Glyceraldehyde-3-Phosphate Dehydrogenase and L-Lactate Dehydrogenase. Sci Rep. 2020 Jun 26;10(1):10404. https://www.nature.com/articles/s41598-020-67079-2

7. Pansieri J, Ostojić L, Iashchishyn IA, Magzoub M, Wallin C, Wärmländer SKTS, Gräslund A, Nguyen Ngoc M, Smirnovas V, **Svedružić Ž. M.**, Morozova-Roche LA*. Pro-Inflammatory S100A9 Protein Aggregation Promoted by NCAM1 Peptide Constructs. ACS Chem Biol. 2019 Jul 19;14(7):1410-1417. https://pubs.acs.org/doi/abs/10.1021/acschembio.9b00394

8. Miletić V., Nikolić P., Odorčić I, **Svedružić Ž. M.*** *Insilico* design of the first DNA-independent mechanism-based inhibitor of the mammalian DNA methyltransferase Dnmt1**.** PLoS One. **2017** Apr 11;12(4):e0174410. https://pubmed.ncbi.nlm.nih.gov/28399172/

9. Nikolić P., Miletić V., Odorčić I, **Svedružić Ž. M.*** *Insilico* optimization of the first DNA-independent mechanism-based inhibitor of the mammalian DNA methyltransferase Dnmt1**.** Invited contribution to: "Epi-Informatics. Discovery and Development of Small Molecule Epigenetic Drugs and Probes". Elsevier, Academic Press. Pages 113-153. ***2016***. (PDF: www.svedruziclab.com)

10. **Svedružić Ž. M.*** Popović K, Šendula-Jengić V. Decrease in catalytic capacity of γ-secretase can facilitate pathogenesis in sporadic and Familial Alzheimer's disease. Mol Cell Neurosci. ***2015*** Jul;67:55-65. (PDF: www.svedruziclab.com)

11. Svedružić Ž. M.*, Popović K, Šendula-Jengić V. Modulators of γ-secretase activity can facilitate the toxic side-effects and pathogenesis of Alzheimer's disease. PLoS One*, January 7th* ***2013****.*

(http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0050759)

12. Svedružić Ž. M.* Popović K, Smoljan I, Šendula-Jengić V. Modulation of γ-secretase activity by multiple enzyme-substrate interactions: Implications in the pathogenesis of Alzheimer's disease. PLoS One*, April* ***2012****.*

http://dx.plos.org/10.1371/journal.pone.0032293*.*

13. Svedružić Ž. M.*, book chapter titled: Mammalian DNA methyltransferase Dnmt1: Structure and Function. Book title: Modification of Mammalian DNA: Mechanism, Management, Missions, and Medical Implications. Elsevier Series titled: *Progress in Molecular Biology and Translational Science.* ***2011****;101:221-54. (www.svedruziclab.com)*

(http://www.bolnicarab.hr/upload/Svedruzic/Ch06_svedruzic_book_complete_2011.pdf)

14. Svedružić Ž. M.* Mammalian Cytosine DNA methyltransferase Dnmt1: Enzymatic Mechanism, Novel Mechanism-Based Inhibitors, and RNA-directed DNA methylation. *Curr. Med. Chem., 15(1): 92-106; (****2008****).*

(http://www.bolnicarab.hr/upload/Svedruzic/referenca%204.pdf).

15. Svedružić Ž. M.* and H. O. Spivey. Interaction between Mammalian Glyceraldehyde-3-phosphate Dehydrogenase and L-Lactate Dehydrogenase from Heart and Muscle. *Proteins, Structure, Function and Bioinformatics, 63:501-511; (****2006****).*

*(*http://www.bolnicarab.hr/upload/Svedruzic/referenca9.pdf*)*

16. Svedružić Ž. M., Wang C., Kosmoski J.V. and Smerdon M.J*. Accommodation and Repair of a UV Photoproduct in DNA at Different Rotational Settings on the Nucleosome Surface. *J. Biol. Chem.*, 280(48): 40051-40057; **2005**.

(http://www.ncbi.nlm.nih.gov/pubmed/16210312)

17. Svedružić Ž. M. and N.O. Reich*. The Mechanism of Allosteric Regulation of Dnmt1's Processivity. *Biochemistry,* 14972-14988; 44(45); **2005**.

(http://www.bolnicarab.hr/upload/Svedruzic/referenca%206.pdf)

18. Svedružić Ž. M. and N.O. Reich*. DNA Cytosine C5 Methyltransferase Dnmt1: Catalysis Dependent Release of Allosteric Inhibition. *Biochemistry*, 9472-9485; 44(**27**); **2005**.
(http://www.bolnicarab.hr/upload/Svedruzic/referenca%206.pdf)

19. Svedružić Ž. M. and N.O. Reich*. The Mechanism of Target Base Attack in DNA Cytosine C5 Methylation. *Biochemistry,* 11460-11473; 43(**36**); (**2004**).
(http://www.bolnicarab.hr/upload/Svedruzic/referenca%206.pdf)

20. Lehoux E. A., **Svedružić Ž.,** and Spivey, H. O*. Determination of Specific Radioactivity of [^{14}C] Lactate by Enzymatic Decarboxylation and CO2 Collection. *Anal. Biochemistry*, 190-195 (***1997***).

Three manuscripts are currently in review for publication.

Note: my name is pronounced as Zhelko Svedruzhich, with "zh" pronounced as letters "asu" in words like: "treasure", "pleasure", "measure".