**Project:** Artificial Intelligence-Guided Design, Synthesis, and Pharmacological Evaluation of Innovative PROTACs

as Degraders of HDAC4, an Epigenetic Target for Spinal Muscular Atrophy

**Akronim:** SM*AI*PROTACs

**Project logo:**



**Graphical abstract:**

Diagram

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**Figure.**  HDAC4 (Target protein, POI) degradation could be mediated by E3 ligase upon its initial ubiquitination. Ubiquitination is a posttranslational modification catalyzed by a ubiquitin-activating enzyme (E1), a ubiquitin-conjugating enzyme (E2), and a ubiquitin ligase (E3). To downregulate HDAC4, ubiquitin is going to be activated in an ATP-dependent fashion and attached to E1 *via* a thiol-ester bond, then transferred from E1 to E2 *via* transesterification, and finally attached to a lysine residue of the HDAC4, catalyzed by the E3 ligase, upon which the target could be recognized by the 26S proteasome complex and degraded

**Abstract:**

*Background of the research problem:* Spinal muscular atrophy (SMA), a neurodegenerative recessive disease, caused by mutations in the motor neuron 1 (SMN1) gene and deficient expression of the SMN protein, is one of the leading genetic causes of death in early infancy and childhood, with an increasing frequency in Serbia. Due to a rather expensive genetic therapy with ZOLGENSMA® (2.1 million US dollars per treatment), novel, cost-efficient approaches in therapy are required.

*Novelty of the research proposal:*This Project aims to develop innovative PROteolysis TArgeting Chimeras (PROTACs) as degraders of histone deacetylase isoform 4 (HDAC4), an epigenetic target whose expression is associated with motor neuron loss and severe muscle atrophy, due to muscle protein breakdown through the ubiquitin-proteasome system. Only few PROTACs as HDAC4 degraders are literature-reported, of which none of them have been tested against SMA.

*Methods which will be used:* Innovative PROTACs will be designed using artificial intelligence-guided protocols including QSAR, PCM, 3-D QSAR, COMBINE, 3-D Pharmacophores, and reinforced learning for lead optimization of HDAC4 inhibitors (HDAC4Is) and *de novo* design of PROTACs. The following synthesis performed by coupling lead-optimized HDAC4Is and VHL, CRBN or other available E3 ligase recruiting ligands *via* various linkers will produce HDAC4 degraders. These degraders will be biologically evaluated in both *in vitro* experiments in HDAC4 expressing cell lines and *in vivo* experiments in the SMA animal model.

*Expected results of the project:* Newly developed PROTACs are expected to provide proof of concept, *i.e*., to demonstrate the potential to degrade HDAC4 and to modulate the status of SMA in the animal model.

*Impact of the Project:* Through innovative HDAC4-based PROTACs, a new perspective for treating SMA in infants will be presented.

**Team members (Faculty of Pharmacy):** Dr Vladimir Savic, Dr Milena Simic, Dr Predrag Jovanovic, Dr Gordana Tasic

**Budget:** 299.962,40 EUR

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