16th World Congress on Tissue Engineering, Regenerative Medicine and Stem Cell Research

6th World Congress on Oncology and Cancer Research

MAY 12, 2022| Webinar

Anti-proliferative effect of potential LSD1/CoREST inhibitors based on molecular dynamics model for treatment of SH-SY5Y neuroblastoma cancer cell line

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Lysine-specific demethylase is a demethylase enzyme that can remove methyl groups from histones H3K4me1/2 and H3K9me1/2. It is expressed in many cancers, where it impedes differentiation and contributes to cancer cell proliferation, cell metastasis and is associated with inferior prognosis. LSD1 is associated with its corepressor protein CoREST, and utilizes tetrahydrofolate as a cofactor to accept CH2 from the demethylation process. The fact that the cofactor is best bound to the active site inspired us to explore its interactions to LSD1/CoREST enzyme complex utilizing molecular dynamics simulation, which aids designing novel and potent inhibitors. We have implemented a previously derived model from the MD simulation study and the key contacts to the active site in a subsequent structure based drug design and *in silico* screening. *In silico* mining on National Cancer Institute (NCI) database identified 55 promising and structurally diverse inhibitors toward LSD1/CoREST complex. The anti-proliferative activities of the identified compounds were tested against neuroblastoma SH-SY5Y cancer cell line which known to highly express LSD1/CoREST complex. Applying the abovementioned molecular modelling procedure yielded Four compounds of LSD1/CoREST inhibiters with IC50 <2μM. The four lead compounds were tested against SH-SY5Y neuroblastoma cell line that known to express high level of LSD1 and illustrated a potent activity with an IC50 ranging from 0.195 to 1.52μM. To estimate the toxicity of the selective leads, they were tested against normal fibroblast cells and scored a relatively high IC50 ranging from 0.303 to ≥100μM. These compounds are excellent candidates treating cancers that overexpress the LSD1 enzyme.

Keywords: Lysine-specific demethylase 1 (LSD1), Neuroblastoma, Cancer, Molecular Dynamics Simulation, *In silico* Screening, LSD1 inhibitors.

Speaker Biography

Hiba Zalloum is a Researcher in Hamdi Mango Center for Scientific Research at the University of Jordan. She holds a Master's degree in Chemistry from The University of Jordan. Her practical research dealt with the synthesis, chelation and sorption properties of chelating polymers. Recently, her research interest is turning to molecular modelling and drug discovery field. She has 15 publications, 13 ISI-published articles, 2 book chapters and is now running 6 funded research projects.

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Received date: May 2, 2022; **Accepted date:** May 4, 2022; **Published date:** May 24, 2022