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The Cancer Control Challenge:
Better Understanding It to Better Face It

MOLECULAR DOCKING OF EX-527 BOUND TO SIRTUIN-2 ENZYME IN CANCER

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Introduction: Sirtuin-2 is a histone deacetylases enzyme (HDAC), involved in inactivation about some genes, and act like a tumor gene supressor, but in many cancers, occurs alterations in this enzyme like mutations and more expression, and the enzyme inhibits another tumor suppressor genes, like a P53 gene known as the genome guardian. This enzyme is an important therapeutic target, when the inhibition of this molecule, other tumor suppressor genes are not inhibited, and like this, more contributions in cancer combat are possible. EX-527 is a potent inhibitor to Sirtuin-1 and it is a great opportunity to study the interaction of this molecule with Sirtuin-2, and propose improvements in chemistry structure in addition to developing new drugs. **Objectives:** Apply molecular docking techniques to study the conformational position of the molecule EX-527 complexed with sirtuin-2 investigate the molecular mechanisms of this bound and propose structural modifications and new molecules to complement the cancer treatment. **Methods:** Protein Data Bank was used to access the Ex-527 structure by PDB code: 4BUZ, and PDB code: 8TGP, all molecules were prepared using UCSF ChimeraX 1.10 and PyMol 3.1. The molecular docking and redocking was used with the Molegro Virtual Docker 5.5, with 1000 runs and 50 possible conformations of the EX-527 in sirtuin-2 cavity, Van der Waals interactions, electrostatic interactions and intramolecular and intermolecular interactions were analyzed. **Results:** The molecular docking results showed a good results by the interaction of the Ex-527 and sirtuin-2, with a -97.54 moldock score, RMSD (Root Mean Square Deviation) 0.46 and Hbond -5.54, which show a good interaction, stability and a strong interaction, showing a important binds with a key amino acids like a aspartate 170 with 2.9 angstroms distance, and isoleucine 169 with 3.09 angstroms distance. **Conclusion**: The cancer treatment of epigenetic alterations is important because modifications in molecules like genes and enzymes are reversible, so the inhibition of sirtuin-2 in some cancers can help the treatment of the patient, reducing the expression of oncogenes. Sirtuin-2 can inhibit tumor suppressor genes in cancer, and inhibiting this enzyme, can reduce cellular activity. The study of the interaction by enzyme and inhibitor can show how this interaction happens, like this the advance in treatment is possible. The study perspective is to test other molecular modeling techniques like molecular dynamics and in the future test in vitro and in vivo models, and from this

interaction studying the enzyme cavity, propose other inhibitors. Tests in vitro were performed showing a reduction in the progression of cancer cells.

Keywords: Molecular docking; sirtuin-2; ex-527.