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J Proteomics Bioinform 2018, Volume 11
DOI: 10.4172/0974-276X-C5-125

JOINT EVENT

12th International Conference and Expo on
Proteomics and Molecular Medicine &

12th International Conference on
Advancements in Bioinformatics and Drug Discovery

November 26-28, 2018 | Dublin, Ireland

Unveiling the binding mechanism of an E3 ubiquitin ligase: covalent versus non-covalent inhibition

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The development of covalent drugs, specifically in cancer therapeutics, has recently sparked interest among the pharmaceutical research community. While representing a significant fraction of the drugs on the market, very few have been deliberately designed to interact covalently with their biological target. One of the enzymes that have been both covalently and non-covalently targeted is the neural precursor cell expressed developmentally down-regulated gene 4-1 (Nedd4-1). This enzyme has been found to have multiple physiological implications, including its involvement in cancer invasion. A critical gap still remains in the molecular understanding of the structural mechanism upon the covalent and non-covalent binding to Nedd4-1. In this study we explore the most optimal binding mechanism in the inhibition of the catalytic site of the Nedd4-1. Our results exhibited a greater stability in the covalent complex compared to the non-covalent complex. This was supported by the secondary structure elements that were more dominant in the covalently inhibited complex. This complex disclosed an optimal free binding energy landscape, induced by the catalytic site energy contributions that showed to be more favorable. The insights demonstrating the above binding mechanism of Nedd4-1 establishes covalent inhibition as the preferred method of inhibition of the enzyme. This investigation aids in the understanding of the structural mechanism of Nedd4-1 inhibition and would assist in the design of more potent covalent inhibitors at the catalytic site of Nedd4-1.

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