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Fusicoccin-based Antitumor Agents that Control Protein-protein Interactions

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Fusicoccin, FC and cotylenin A, CN are two of the few reported stabilizer of protein-protein interactions. These two natural products bearing a diterpene glucoside moiety are initially studied in plants. CN was reported as a plant growth regulator while FC was discovered as the toxin that causes the wilting in trees. Both molecules are described to bind to 14-3-3 protein and enhances the interaction of 14-3-3 with its partner protein. The small molecule fit in to the hydrophobic pocket of 14-3-3 adjacent to the phosphorylated sequence motif of the partner protein creating a ternary complex (Figure 1).

In humans, 14-3-3, the primary receptor of FC and CN, is involved in different regulatory process like signaling transduction, cell cycle and apoptosis. It was reported that about 200 partner proteins interact with human 14-3-3. By a non-biased approach our goal is to determine which and how many of the 14-3-3 partner proteins is the target of FC and its synthetic derivatives. As a support tool, the Discovery Studio was used to visualize reported 14-3-3 crystal structure and study the binding of the synthesized FC derivatives to 14-3-3. For the biochemical assays, we had performed pull down experiments in the presence of ISIR-02, an FC derivative that was reported to kill tumor cells under hypoxic conditions. Validation of the identified target protein is currently on-going.

References: