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POSTER PRESENTATION (PO)

A FRAGMENT-BASED VIRTUAL SCREENING APPROACH TO IDENTIFY E-CADHERIN LIGANDS

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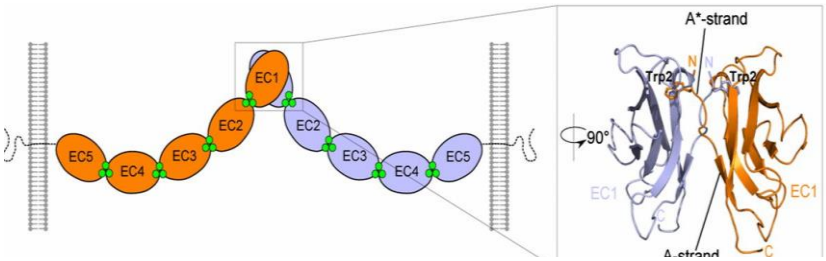
Cadherins are calcium-dependent cell-cell adhesion proteins which are overexpressed in several solid tumors [1]. They contain an extracellular region consisting of five immunoglobulin-like domains that extend from the cell surface. Recent crystal structures have shown that classical cadherins dimerize through a 'strand-swap' trans-adhesive interface involving the N-terminal EC1 domains of two cadherins on adjacent cells [2, 3].



Cadherins as transmembrane cell adhesion receptors forming homophilic interactions between the N-terminal extracellular domains

Despite a growing interest in the field, the rational design of small ligands targeting cadherins is still in a very early stage. Recently, our group set up a docking protocol (Glide v 5.7) to rationally design peptidomimetic ligands mimicking the N- and E-cadherin adhesive homodimer interface. Accordingly, the first mimics based on the tetrapeptide sequence Asp1-Trp2-Val3-Ile4 (DWVI) of the N-terminal adhesion arm were achieved and proved to inhibit the adhesion of epithelial ovarian cancer cells with millimolar potency [4]. Herein, a fragment-based virtual screening approach was applied to identify novel chemical entries targeting the DWVI binding site. Commercially available Maybridge and Life chemicals collections were used. The most promising fragments identified by the docking calculations were purchased and their binding to E-cadherin was evaluated by means of STD (Saturation Transfer Difference) NMR experiments.

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