Allosteric Regulation of Ectopically Expressed Olfactory Receptors in Tumor Cells: Ligand-Receptor Topology and Deep Learning-Assisted Drug Discovery

Bansal, Shivansh (School: Dublin High School)
Gudisay, Saanvi (School: Dublin High School)

This research expands existing Olfactory Receptor (OR) studies, exploring their potential in cancer drug therapy and establishing a novel pipeline applicable to similar G protein-coupled receptors (GPCRs). Numerous ORs have been identified across nine cancer types and over 1000 cancer cell lines; their activation via pathways like ERK1/2 and cyclic nucleotide-gated ion channels can induce apoptosis and inhibit cell proliferation and migration. Our initial focus was OR51E2, utilizing known ligands that modulate cyclic AMP-dependent pathways. Approximately 1.4M candidate molecules were sourced from the ZINC20 database based on molecular weight and refined through Schrödinger Maestro's multi-step virtual screening—including High-Throughput Virtual Screening, standard precision, and extra precision docking—to minimize Gibbs Free Energy upon binding. Compounds with the highest binding affinity underwent descriptor analysis via Mordred, generating ~1,800 molecular descriptors each. Various classification models were then trained and tested on bioassay data from EMBL and DUD-E to predict ligand bioactivity. Predictions were finalized through fine-tuning a Support Vector Machine with a Radial Basis Function kernel and plotting molecular descriptors in 3D chemical space to improve accuracy. SwissADME assessed ADMET profiles for four promising candidates for OR51E2, each exhibiting drug-like characteristics across five metrics, with predicted bioactivity >85%. In-vitro validation utilized a dual-luciferase assay, employing a cAMP-response element driving luciferase expression. The assay revealed significantly viable drug candidates that activated OR51E2. This study identifies ORs as promising cancer therapy targets, alongside introducing a novel drug discovery methodology.

Awards Won: