POSTER SESSION 1: Bioinformatics

P1.1

Molecular Investigation of Wild and Mutant Active Binding Site Expression of GPR15 in Cancer using Computational Approach

Aman Chandra Kaushik[1], Eitan Rubin[2]

[1]*Ben Gurion University of the Negev, Beer Sheva, Israel*
[2]*Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel*

Background: GPCRs play a key role in many signal transduction pathways and are significant as drug targets. GPCRs with unknown ligands and/or target pathway are known as "Orphan GPCRs". GPR15 is an important orphan GPCR that plays a crucial role in many physiological functions. The E144V mutation in GPR15, which is often observed in cancer, makes it an attractive target for therapeutic intervention. Here we present in silico screening for potential compounds that bind the ligand binding site of the wild type and mutant structures of GPR15.
Method: An approximate structure of the mutant GPR15-E144V was created by setting amino acid 144 to Valine. Grid box was generated around 5Å area of the pocket E144 in wild and V144 in mutant. A library of 55,975 compounds obtained from Maybridge Library was used for the screening of compounds for affinity with both wild and mutant structures. Top hits were selected based on scoring function (Chem score + G Score + D Score + PMF Score). We also applied a cutoff (Total score >5) on the docking score function to eliminate false positives. Molecular Dynamics simulation was done for top two potential inhibitors to check their stability and interaction fraction during Molecular Dynamics Simulations. Finally, affinity to the wild-type and mutated version of GPR15 was estimated computationally.
Results:
Similarly, we present an analyzes of the drugs used for the WINTHER trial. We present a comparison of each compound affinity to wild-type and normal GPR15, showing which has the potential to offer specific inhibition of the mutated version of GPR15. Top five potential compounds were obtained from wild type model using screening approach and top five potential compounds were obtained from mutant type model using screening approach; and then compare with each other using Docking score. It means mutation in E144 can affect the binding mode of inhibitors.
Conclusions:
We present top five potential compounds which could be considered in the development of new therapeutic agents for colon cancer.

Keywords:
Cancer Medicine; GPCRs; GPR15; Molecular Modeling; Molecular Dynamics Simulation

Compounds	Wild	H Bond Interactions	Mutant	H Bond Interactions	Differences
Compound1	5.17	ARG143	9.27	LYS143	4.1
Compound2	7.77	ARG143, GLU156	11.16	GLU156, ARG143	3.39
Compound3	7.01	GLU156	10.32	GLU156	3.31
Compound4	7.04	SER167, ARG143	9.70	LYS232	2.66
Compound5	7.04	TRP166, SER167	9.58	ARG143	2.54

Table 1: Docking Scores of top 10 inhibitors (wild and mutant model); and their interactions