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Editorial

In silico Observation of Interaction Pattern Following Docking Simulation has the Potential to Explain the Action of Drugs in Cystic Fibrosis

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Cystic fibrosis is an inherited disease that, unlike several disorders of the same class can be managed to some extent with drugs. The disease is the outcome of a mutation of a gene located in chromosome 7 that codes for a protein transmembrane conductance regulator (CFTR) protein. CFTR works as a cAMP-activated chloride channel and helps the exocrine glands to perform physiological functions. The most common mutation is delta F508. Here the F508 of the CFTR protein gets deleted while translation. The effect of deletion is grave. It leads to misfolding of the protein in the Golgi apparatus. In this case, the protein channel cannot further mature and get upregulated in the cell surface to exert physiological function [1]. G551D is another relatively uncommon mutation. Here in the 551st position, the glycine is replaced by Aspartic acid. In this case, the protein is defective but gets located at the cell membrane and can exert some function. Both are mutations of clinical concern as keeping both mutations unmanaged can have grave consequences.

Ivacaftor (VX-770) is a drug which acts as a potentiator of CFTR function. It works well in cases of G551D compared to F509del [2]. One reason we can understand is that in cases of CF where G551D mutation is present the defective protein is available at the cell membrane but in the case of others it is not present in the cell membrane. Apart from this reason, it is not known that as to how the drugs bind with the two different types of CFTR defective proteins. It is in this context we have performed docking simulation with the CFTR protein (normal and mutated) to gain sight in the matter.

The 3-D structure of CFTR (PDB ID: 6MSM) was downloaded from PDB. Similarly, the 3-D structure of Ivacaftor (Compound CID: 16220172) was downloaded from PubChem. The active site prediction server was used to find the active sites in the structure of CFTR [3]. In the output file, the cavity with maximum volume was selected to look for the residues which are nearby to F508, G551, tm8 (934-946) and ICL4 (1049-1064). The tm8 and ICL4 sites in CFTR were recently shown to bind Ivacaftor (i.e., Ivacaftor binding sites) [4]. It was observed that residues V510, K522 and H950 (present in cavity predicted through active site prediction server) were found near F508, G551 and Ivacaftor binding sites [tm8 (934-946) and ICL4 (1049-1064)], respectively.

Modified CFTR (F508del, G551D) was then prepared by using Pymol software in different sets of experiments [2]. The energy minimization of the modified CFTR was then performed using SPDBV PDB viewer [5].

To understand the interaction of CFTR, the modified or normal CFTR were then subjected to molecular docking studies with Ivacaftor. Autodock version 4.2.6 is used for docking studies. The autodock gives protein-ligand interaction parameters in terms of negative binding energy [6]. The residues V510, K522 and H950 were selected as grid centres respectively, for performing docking in different runs. All the values are represented as mean ± standard deviation. An unpaired t-test was used to find a statistically significant value ($p \leq 0.05$).

Through an in-silico study, it was observed that the Ivacaftor binds with CFTR (modified and normal) with negative binding energy. However, in the case of modified CFTR (i.e., G551D) the obtained binding energy was statistically more significant than the control (normal CFTR) and F508del CFTR (Table 1).

CFTR (Modified or normal)		Modification/mutation	Grid centre Mean ± SD (n = 10)	Binding energy (kcal/mol)
1.	Normal CFTR (Control)		510	-4.945 ± 0.383
			522	-5.577 ± 0.333
			950	-5.675 ± 0.349
2.	Modified CFTR	F508 deletion	510	-4.98 ± 0.264
			522	-5.732 ± 0.275
			950	-5.727 ± 0.581
		G551D	510	-5.471 ± 0.360
			522	-5.59 ± 0.176
			950	-5.696 ± 0.500**

Table 1: Shows the binding energy (kcal/mol) of CFTR (normal and modified) with Ivacaftor by semi-flexible docking using Autodock. The structure of CFTR was modified by deleting the residues F508 and by performing in-silico mutagenesis of G551 to D551) with the help of Pymol software. The docking was performed with ligands at different grid centres as mentioned below.

So, the drug is predicted to interact with the defective protein (G551D) more compared to others (F508del and the normal variant) when docked at V510. This shows that the interaction of the drug is more with the protein variant which is known to be clinically effective. Therefore, we believe that new drug developers can consider drug moieties that interact more efficiently with the other variant and observe whether the drug-bound protein translocates in the cell membrane or not. In case the translocation happens, it will be a positive situation for the F508del mutated CFTR proteins.

Conflict of Interest

None.

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Author Contributions

DK has performed all the experiments and wrote the manuscript. RB supervised in-silico results. DB overall supervises the experiments and manuscript writing.

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