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Neural network based prediction of site-specific stable mutants in wild type CFTR protein

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Cystic fibrosis is a genetic disorder characterized by defective ion transport across cell membranes, primarily affecting the lungs and other vital organs. The cystic fibrosis transmembrane conductance regulator (CFTR) protein plays a pivotal role in cystic fibrosis pathophysiology, and mutations in the CFTR gene lead to dysfunctional protein function. The CFTR modulators, including ivacaftor, lumacaftor, and tezacaftor, represent promising therapeutic options for improving CFTR function and ameliorating cystic fibrosis symptoms the CFTR (PDB ID: 5UAK) structure stability was assessed by replacing the phenylalanine with other amino acid at 508th position by using the ThermoMPNN tool. The stable mutant structure (F508W) was identified and its structure was generated using the Biopython library. In this study, we employed molecular docking to investigate the interactions between CFTR modulators and CFTR protein structures. For the wild type CFTR and F508W mutant counterpart, docking was performed with ivacaftor, lumacaftor, and tezacaftor using the CB-Dock2 platform. Our results indicate that lumacaftor exhibited the highest predicted binding affinity among the tested CFTR modulators for the F508W mutant CFTR, suggesting its potential as a therapeutic option for individuals with cystic fibrosis carrying this mutation. Additionally, interaction profile analyses revealed stable complexes formed between the CFTR modulators and both wild type and mutant CFTR structures, highlighting their potential effectiveness in targeting CFTR dysfunction. Overall, this study provides valuable insights into the molecular mechanisms underlying the therapeutic efficacy of CFTR modulators in cystic fibrosis. Further experimental validation is warranted to confirm these computational findings and to explore the clinical utility of these drugs in treating cystic fibrosis.

Keywords: Binding affinity, Cystic fibrosis, Molecular docking, Protein structure, Thermostable mutants

Cystic fibrosis is a life-limiting genetic disorder characterized by the accumulation of thick, sticky mucus in the lungs and other vital organs, leading to chronic respiratory infections, digestive problems, and other complications[1]. It is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which encodes the CFTR protein[2]. The CFTR protein is a chloride channel that regulates the flow of ions across cell membranes, maintaining proper hydration of mucosal surfaces in the respiratory, digestive, and reproductive systems[3]. Mutations in the CFTR gene result in dysfunctional CFTR protein, leading to impaired ion transport and the characteristic symptoms of CF[4]. Among the numerous mutations associated with cystic fibrosis, the F508W mutation is the most common, accounting for approximately two-thirds of cystic fibrosis cases worldwide[5]. The F508W mutation disrupts protein folding and trafficking, resulting in reduced CFTR expression at the cell surface and impaired chloride channel function[6]. CFTR modulators, including ivacaftor, lumacaftor, and tezacaftor, represent a promising therapeutic approach for individuals with cystic fibrosis[7]. These drugs target specific defects in the CFTR protein, aiming to restore normal ion transport and alleviate cystic fibrosissymptoms[8]. Ivacaftor is a potentiator that enhances the activity of

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CFTR channels with gating mutations, while lumacaftor and tezacaftor are correctors that improve CFTR protein folding and trafficking[9]. In this study, we employed molecular docking simulations to investigate the interactions between CFTR modulators and CFTR protein structures. Molecular docking is a computational method used to predict the binding mode and affinity of small molecules to protein targets[10]. Specifically, we utilized the Protein Data Bank (PDB) structure with the ID 5UAK, representing the wild type CFTR protein, and its F508W mutant counterpart. Molecular docking simulations were performed using the CB-Dock2 platform to elucidate the binding characteristics of ivacaftor, lumacaftor, and tezacaftor with both wild type and mutant CFTR structures.

This study aims to investigate the molecular mechanisms underlying the therapeutic efficacy of CFTR modulators, particularly in the context of cystic fibrosis associated mutations. Specifically, we employed molecular docking simulations to explore the binding characteristics of ivacaftor, lumacaftor, and tezacaftor with both wild type and F508W mutant CFTR protein structures. Molecular docking is a computational method used to predict the binding mode and affinity of small molecules to protein targets. In this work, we utilized the Protein Data Bank (PDB) structure with the ID 5UAK, representing the wild type CFTR protein, and its F508W mutant counterpart. Prior to docking simulations, the stability of the F508W mutant structure was assessed using the ThermoMPNN tool, and the mutant structure was generated using the Biopython library. Subsequently, docking simulations were conducted, and the results were analyzed to determine the binding affinities and interaction profiles of the CFTR modulators with wild type and mutant CFTR structures. By elucidating the binding characteristics of these drugs with CFTR protein structures, we aim to contribute to the development of more effective treatments for cystic fibrosis.

Materials and methods

Identification of stable F508W mutant using ThermoMPNN

The stability of various mutations at position 508 of the protein corresponding to PDB ID 5UAK was assessed using the ThermoMPNN tool within a Google Colab environment[11-13]. Initially, the wild-type protein structure was downloaded and parsed using Biopython. The Phe508 residue was mutated to Trp508 using Biopython to generate the F508W mutant structure. Stability predictions for all mutants were performed using ThermoMPNN, which provided ΔΔG values (kcal/mol) for each mutation. Key input parameters, including solvent conditions and energy cutoff values, were explicitly defined to ensure alignment with physiological relevance. The results included a table listing the mutations, their corresponding ΔΔG values, the position of the mutation, the wild-type amino acid (wtAA), and the mutant amino acid (mutAA). Among the various mutations analyzed, the F508W mutation wa selected based on its ΔΔG value of -0.0557 kcal/mol, which was the lowest and indicated the highest predicted stability. This systematic computational approach ensured reliable stability rankings and informed the selection of the F508W mutant for subsequent structural and functional analyses.

Generation of F508W mutant structure

The F508W mutant of the protein structure corresponding to PDB ID 5UAK was generated using the Biopython library within a Google Colab environment[12]. Initially, Biopython was installed in the Colab environment, followed by the retrieval of the wild-type protein structure (PDB ID: 5UAK) from the RCSB Protein Data Bank. The structure was parsed using Biopython's PDBParser class. To introduce the mutation, a custom function was developed to mutate the phenylalanine residue at position 508 to tryptophan. This function iterated over the specified chain and residue, altering the residue name from 'PHE' to 'TRP'. Careful handling of the residue's atomic structure ensured accurate modelling of tryptophan, including adjustments to bond angles and lengths to reflect steric and electronic properties. The modified structure was then saved as 5uak_F508W.pdb. The Python script utilized for these steps involved downloading the PDB file, parsing it, introducing the mutation by changing the residue name and atomic elements, and saving the modified structure. Finally, the resulting mutant structure was visually inspected using PyMOL, a molecular visualization tools to confirm the successful introduction of the F508W mutation. Additionally, the structural integrity of the mutant was verified by assessing bond connectivity and potential steric clashes using computational tools.This method provided a systematic approach to generating the F508W mutant protein structure, enabling further structural and functional analyses.

Docking

Docking were conducted using CB-Dock2 to explore the interactions between the F508W mutant protein structure of PDB ID 5UAK and the ligands ivacaftor, lumacaftor, and tezacaftor. The mutant protein structure, 5UAK_F508W.pdb, was prepared and uploaded to the CB-Dock2 web server, the ligand structures for ivacaftor, lumacaftor, and tezacaftor were retrieved as 3D conformations from the PubChem database, ensuring that they were in their most stable and relevant forms for docking[14, 15]. CB-Dock2 identified binding cavities in the mutant protein and performed docking simulations for each ligand, using default parameters to ensure reproducibility. Docking was then carried out using CB-Dock2's default parameters to maintain consistency and reproducibility across different ligand-protein complexes. These parameters were selected based on prior successful applications of the software for similar docking tasks. The docking results were analyzed to determine binding affinities and orientations of the ligands within the identified cavities, focusing on the binding poses with the lowest docking scores. Visualization of the docking poses using molecular visualization tools allowed for the assessment of key interactions, such as hydrogen bonds and hydrophobic interactions, between the protein and ligands. This comprehensive docking analysis provided valuable insights into the binding characteristics and potential efficacy of ivacaftor, lumacaftor, and tezacaftor with the F508W mutant of 5UAK, contributing to further structural and functional studies.

Results and Discussion

The stability of various mutations at position 508 of the CFTR protein (PDB ID: 5UAK) was assessed using the ThermoMPNN tool within a Google Colab environment. Initially, the wild-type protein structure was downloaded and parsed using Biopython. The Phe508 residue was manually mutated to Trp508 to create the F508W mutant structure, which was then uploaded to ThermoMPNN for stability prediction. ThermoMPNN evaluated the stability of this and other potential mutations, providing a ΔΔG (kcal/mol) score for each mutation. The results are summarized in Table 1, listing the mutations, their corresponding ΔΔG values, the position of the mutation, the wild-type amino acid (wtAA) , and the mutant amino acid (mutAA) . Among the various mutations analyzed, the F508W mutation was selected based on its ΔΔG value of -0.0557 kcal/mol, which was the lowest and indicated the highest predicted stability. This identified F508W as the most stable mutant at position 508, warranting further structural and functional analyses. The negative ΔΔG value for the F508W mutation suggests that this mutation stabilizes the CFTR protein, making it potentially more resilient to misfolding compared to other mutations. This enhanced stability could translate into better functional performance of the CFTR protein in individuals carrying the F508W mutation, providing a rationale for further experimental validation[16, 17]. In contrast, most other mutations resulted in positive ΔΔG values, indicating destabilization of the CFTR protein. For instance, mutations such as F508P (ΔΔG = 2.4419 kcal/mol) and F508K (ΔΔG = 2.1432 kcal/mol) show significant destabilizing effects, likely leading to impaired protein function. These results highlight the critical importance of the Phe508 residue in maintaining CFTR protein stability and function[18]. Further structural and functional analyses are necessary to confirm the implications of these computational predictions. Understanding the molecular basis of CFTR stability and the effects of specific mutations can guide the development of targeted therapies aimed at correcting CFTR dysfunction in cystic fibrosis patients[19].

Table 1 — Predicted stability changes (ΔΔG) for mutations at position 508 of the CFTR protein, along with the corresponding wild-type (wtAA) and mutant (mutAA) amino acids

Mutation	ddG (kcal/mol)	Position	wtAA	mutAA
F508A	1.6732	508	F	A
F508C	0.9077	508	F	C
F508D	1.3784	508	F	D
F508E	1.9975	508	F	E
F508F	0	508	F	F
F508G	1.5523	508	F	G
F508H	1.7174	508	F	H
F508I	1.6183	508	F	I
F508K	2.1432	508	F	K
F508L	1.3238	508	F	L
F508M	1.1207	508	F	M
F508N	1.6775	508	F	N
F508P	2.4419	508	F	P
F508Q	1.8288	508	F	Q
F508R	2.0339	508	F	R
F508S	1.3733	508	F	S
F508T	1.8283	508	F	T
F508V	1.6937	508	F	V
F508W	-0.0557	508	F	W
F508Y	0.6589	508	F	Y

Table 2 — Docking scores, cavity volumes, and docking coordinates for Ivacaftor, Lumacaftor, and Tezacaftor with wild type (PDBID:5UAK) and mutant (5UAK_F508W) CFTR structures

Ligand	Vinascore		Cavity volume (Å^3)	Center (x, y, z)	Docking size (x, y, z)
	Wildtype PDBID:5UAK)	Mutant 5UAK_F508W			
Ivacaftor	-8.4	-8.6	3341	168, 166, 153	29, 35, 23
Lumacaftor	-9.8	-10.3	3341	168, 166, 153	24, 35, 24
Tezacaftor	-8.0	-7.7	3341	168, 166, 153	25, 35, 25

Table 2 presents the results of molecular docking simulations for the three CFTR modulators, ivacaftor, lumacaftor, and tezacaftor, with both wild type (PDBID:5UAK) and mutant (5UAK_F508W) CFTR structures. The docking scores obtained using AutoDock Vina, as well as cavity volumes and docking coordinates, are provided for each ligand. The docking scores indicate the binding affinity of each ligand towards the CFTR protein. Ivacaftor demonstrated a docking score of -8.4 kcal/mol for the wild type of CFTR, while Lumacaftor and Tezacaftor exhibited scores of -9.8 kcal/mol and -8.0 kcal/mol, respectively. For the mutant CFTR (5UAK_F508W) , the docking scores were slightly altered, with ivacaftor showing -8.6 kcal/mol, lumacaftor -10.3 kcal/mol, and tezacaftor -7.7 kcal/mol. These scores suggest that lumacaftor has the highest predicted binding affinity for both wild type and mutant CFTR, followed by ivacaftor and iezacaftor. Moreover, the cavity volumes calculated for each docking pose provide insights into the size of the binding pocket occupied by the ligands. Interestingly, despite variations in the docking scores, the cavity volumes remained consistent for all three ligands with both wild type and mutant CFTR structures. This suggests that the size of the binding pocket does not significantly influence the binding affinity of these ligands.

The docking coordinates provide information about the spatial orientation of the ligands within the binding site. Consistent docking sizes (x, y, z) were observed for each ligand across both wild type and mutant CFTR structures, indicating similar binding poses. This suggests that the structural changes introduced by the F508W mutation do not substantially alter the binding mode of these CFTR modulators. Overall, these results suggest that lumacaftor exhibits the highest predicted binding affinity towards both wild type and mutant CFTR, making it a potentially promising therapeutic candidate for cystic fibrosis. Further experimental validation is warranted to confirm these computational predictions and explore the efficacy of these modulators in clinical settings.

The interaction profiles of ivacaftor, lumacaftor, and tezacaftor with both wild type (PDBID:5UAK) and mutant (5UAK_F508W) CFTR structures are summarized in (Table 3) . The table lists the specific residues within the CFTR protein that form contacts with each ligand during the molecular docking simulations. In the Figure 1, the molecular interactions between lumacaftor and both wild type (PDBID:5UAK) and mutant (5UAK_F508W) CFTR structures are visualized using surface and hidden receptor images. Figure 1A & C depict surface images of wild type and mutant CFTR structures, respectively, with bound Lumacaftor ligands. These images provide a comprehensive view of the spatial arrangement of the ligand within the binding pocket of the CFTR protein. The surface representation highlights the regions of interaction between Lumacaftor and the protein surface, offering insights into the binding mode and potential binding pockets utilized by the ligand. By visualizing the surface interactions, we can observe any notable differences in the binding patterns between wild type and mutant CFTR structures. Notably, the structural rearrangements caused by the F508W mutation may alter the availability or accessibility of certain binding sites, potentially influencing the ligand's binding affinity. In contrast, Figure 1B & D present hidden receptor images, where the protein structure is displayed as a transparent surface, allowing for a focused view of the ligand-binding site. This visualization technique emphasizes the localization of the ligand within the protein's binding pocket, revealing specific interactions between Lumacaftor and critical residues of the CFTR protein. By hiding the receptor surface, these images facilitate a clearer understanding of the spatial orientation and arrangement of the ligand within the binding site, aiding in the identification of key molecular interactions.

Particular attention can be given to hydrogen bonding, hydrophobic contacts, and electrostatic interactions between lumacaftor and the amino acid

Table 3 — Contact residues of Ivacaftor and Lumacaftor with wild type (PDBID:5UAK) and mutant (5UAK_F508W) CFTR structures.

Ligand	Contact residues	
	Wild type PDBID:5UAK	Mutant 5UAK_F508W
Ivacaftor	TRP846 TYR849 TYR852 ILE853 LEU859 VAL862 LEU863 LEU867 LEU937 THR940 LEU941 ILE991 PHE994 ILE995 LEU998 LEU999 VAL1001 ILE1002 ILE1005 ALA1006 PHE1016 THR1019 ILE1023 PHE1026 ILE1027 ARG1030 LEU1143 ALA1146 VAL1147 SER1150 VAL1153 ASP1154 MET1157	TRP846 TYR849 TYR852 ILE853 LEU859 VAL862 LEU863 LEU867 LEU937 THR940 LEU941 ILE991 PHE994 ILE995 LEU998 LEU999 VAL1001 ILE1002 ILE1005 VAL1022 ILE1023 VAL1024 PHE1026 ILE1027 ARG1030 LEU1143 ALA1146 VAL1147 SER1150 VAL1153 ASP1154 MET1157
Lumacaftor	SER169 LEU172 ASP173 ILE175 ILE177 GLY178 GLN179 VAL181 SER182 SER185 TRP401 THR465 MET469 SER492 GLN493 PHE494 PHE1052 VAL1056 LEU1059 LYS1060 TRP1063	TRP846 TYR849 LEU850 TYR852 ILE853 LEU859 VAL862 LEU863 CYS866 LEU867 LEU937 THR940 LEU941 THR990 ILE991 PHE994 ILE995 LEU997 LEU998 LEU999 VAL1001 ILE1002 ILE1005 ALA1006 THR1019 VAL1022 ILE1023 PHE1026 ILE1027 ARG1030 PHE1107 ILE1139 LEU1143 ALA1146 VAL1147 SER1150 ILE1151 VAL1153 ASP1154 MET1157
Tezacaftor	ILE266 GLU267 ASN268 ILE269 GLN270 SER271 VAL272 ALA274 MET961 LEU964 ASN965 THR966 LEU967 LYS968 ALA969 ILE972 TYR1219 SER1251 LEU1254 SER1255 LEU1258 LEU1260 VAL1288 PRO1290 GLN1291 LYS1292 VAL1293 LEU1368 ASP1370	RP846 TYR849 LEU850 TYR852 ILE853 VAL862 LEU863 LEU937 LEU941 ILE991 PHE994 ILE995 LEU997 LEU998 VAL1001 ILE1002 ILE1005 ALA1006 ALA1009 PHE1016 THR1019 VAL1020 VAL1022 ILE1023 PHE1026 ILE1027 ARG1030 THR1142 LEU1143 ALA1146 VAL1147 SER1150 VAL1153 ASP1154 MET1157

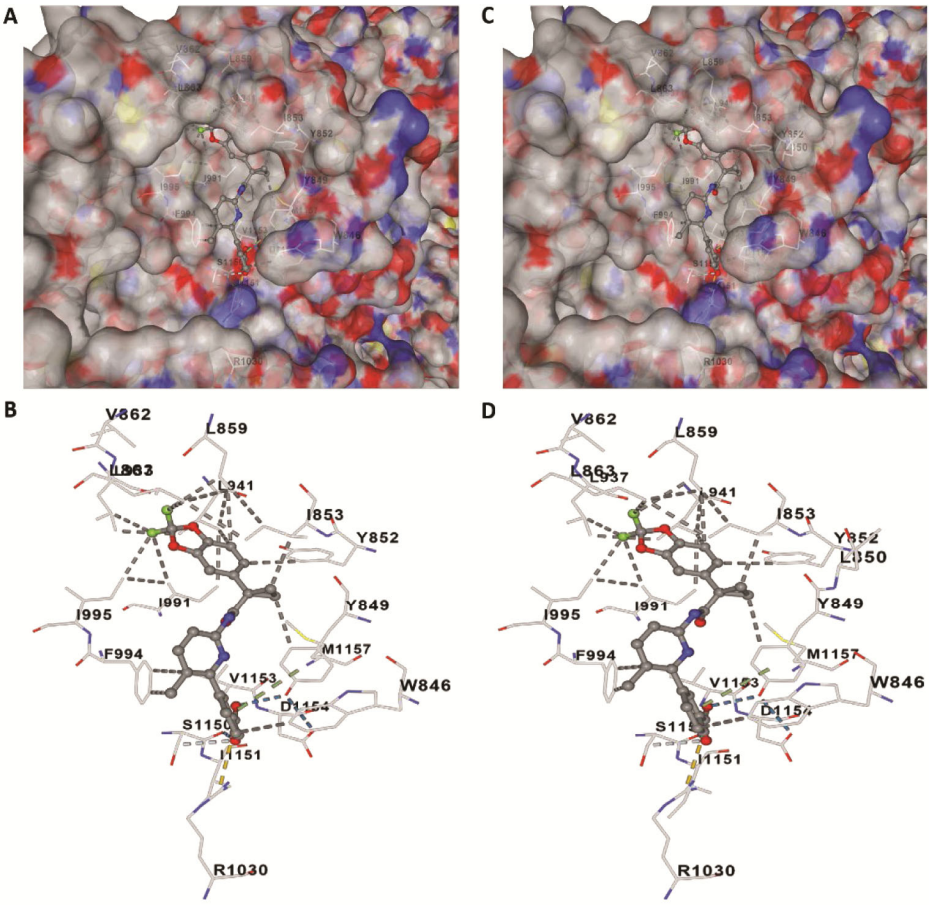

Fig. 1 — A) Surface image of wild type CFTR (PDBID:5UAK) with ligand lumacaftor. B) Hidden receptor image of wild type CFTR (PDBID:5UAK) with ligand Lumacaftor. C) Surface image of mutant CFTR (5UAK_F508W) with ligand lumacaftor. D) Hidden receptor image of mutant CFTR (5UAK_F508W) with ligand lumacaftor

residues within the binding site. These interactions play a crucial role in stabilizing the ligand-protein complex and could potentially be altered by the mutation. Furthermore, the comparison between the wild type and mutant CFTR structures highlights potential alterations in the ligand-binding dynamics due to the mutation. For instance, in the mutant structure (Fig. 1C & D) , the F508W substitution may induce subtle shifts in the ligand's binding pose, which could affect the overall efficacy of Lumacaftor as a therapeutic agent. Understanding these differences is critical for designing more effective strategies to restore CFTR function in patients carrying the F508W mutation. These findings also underscore the importance of accounting for mutations like F508W when developing personalized treatments, as they may influence both the ligand-binding mechanism and the overall drug efficacy.

For Ivacaftor, several key residues were identified in both wild type and mutant CFTR structures. These include TRP846, TYR849, TYR852, ILE853, LEU859, VAL862, LEU863, LEU867, LEU937, THR940, LEU941, and others. Notably, the contact residues largely overlap between the wild type and mutant structures, suggesting that the F508W mutation does not significantly alter the binding interactions of ivacaftor with the CFTR protein. Similarly, lumacaftor displayed interactions with specific residues in both wild type and mutant CFTR structures. These residues include SER169, LEU172, ASP173, ILE175, ILE177, GLY178, GLN179, VAL181, and others. Notably, the contact residues for lumacaftor also exhibit considerable overlap between the wild type and mutant structures, indicating a consistent binding mode irrespective of the F508W mutation. Tezacaftor demonstrated interactions with distinct residues within the CFTR protein, including ILE266, GLU267, ASN268, ILE269, GLN270, SER271, VAL272, ALA274, and others. Interestingly, the contact residues for tezacaftor in the wild type and mutant CFTR structures exhibit a high degree of similarity, suggesting that the F508W mutation has minimal impact on the binding interactions of tezacaftor with the CFTR protein. Overall, the observed interaction profiles suggest that ivacaftor, lumacaftor, and tezacaftor form stable complexes with both wild type and mutant CFTR structures through interactions with specific amino acid residues within the protein. These findings provide valuable insights into the molecular mechanisms underlying the therapeutic efficacy of these CFTR modulators and may aid in the rational design of novel therapeutic agents for cystic fibrosis. Further experimental studies are warranted to validate these computational predictions and elucidate the precise molecular interactions governing the activity of these drugs. Overall, these results provide important insights into the molecular mechanisms underlying the therapeutic efficacy of ivacaftor, lumacaftor, and tezacaftor in cystic fibrosis. Further experimental validation is needed to confirm these computational predictions and explore the potential of these modulators in clinical applications.

Conclusion

In conclusion, our molecular docking simulations reveal that lumacaftor exhibits the highest predicted binding affinity among the tested CFTR modulators, with a score of -10.3 kcal/mol for the mutant CFTR. This finding suggests that lumacaftor holds considerable promise as a therapeutic option for individuals with cystic fibrosis carrying the F508W mutation. The consistent and robust binding affinity of lumacaftor across wild type and mutant CFTR structures underscores its potential effectiveness in targeting the underlying molecular mechanisms of the disease. Further experimental investigations are warranted to validate these computational findings and to explore lumacaftor's clinical utility in treating cystic fibrosis.

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Conflict of interest

All authors declare no conflict of interest.

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