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|  | **Objectives** | **Relevant Paper** | **Methodology in the paper** | **Paper About** |
| **Objectives** 1 | Develop an AI-driven virtual screening platform for identifying PPI inhibitors targeting CFTR-related interactions | **Trepte et al. (2024) –** *AI-guided pipeline for prioritizing and targeting protein–protein interactions* | PPI Mapping  Structure Prediction  Scoring System  Virtual  Screening | -Describes an integrated AI pipeline combining **machine learning**, **AlphaFold-Multimer**, and **VirtualFlow** for identifying and ranking PPI targets.  -Offers a scalable and modular framework adaptable to CFTR PPI discovery. |
| **Objectives** 2 | Validate shortlisted inhibitors through molecular docking, molecular dynamics simulations, and binding free energy calculations | **Tang et al., (2024) -** *In silico discovery of potential PPI*  *inhibitors for anti-lung cancer*  *activity by targeting the*  *CCND1-CDK4 complex via the*  *P21 inhibition mechanism* | Protein Preparation  Molecular Docking  Molecular Dynamics (MD) Simulation  Binding Free Energy Calculations | -Outlines a full validation workflow using **AutoDock**, **MD simulations**, and **MM/GBSA binding energy** calculations.  -Shows practical examples of ranking and validating PPI-targeting compounds. |
| **Objectives** 3 | Apply machine learning models for predicting and ranking small molecules based on binding affinity, interaction profiles, and therapeutic potential | **Trepte et al. (2024) –** *AI-guided pipeline for prioritizing and targeting protein–protein interactions* | Machine Learning Algorithm – SVM  Feature Engineering for Small Molecule Ranking  Ranking Strategy  Validation and Scoring | -A **support vector machine-based model (SVM)** was developed to classify high-confidence PPIs using data from multiple binary interaction assays.  -Compounds screened using **VirtualFlow**, with binding interfaces to target PPI  -Compounds were ranked based on combined features from ML classification scores and docking performance.  -Experimental results confirmed the **biological activity** of top-ranked compounds. |
| **Objectives** 4 | Evaluate ADMET and pharmacokinetic profiles of lead compounds using AI-based predictive tools | **Basu et al. (2024) –** *Cystic Fibrosis: AI in Prognosis and Drug Discovery* | AI-Driven Repurposing  ADMET Prediction  Integration - Drug-likeness and Bioavailability | -Highlights the application of **AI-based tools like pkCSM, SwissADME**, and ML models for **ADMET prediction** and drug-likeness evaluation.  -Applies specifically to CF-related candidate screening pipelines. |

**REFERENCES TO OBJECTIVES**

**REFERENCES TO CFTR PROTEIN TARGETS**

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| **Protein targets** | **Role** | **Impact of Targeting** | **Reference** |
| CFTR-CAL | CAL promotes lysosomal degradation of CFTR by interacting with its C-terminal PDZ-binding motif, competing with stabilizing proteins like NHERF1. | Disruption of this interaction increases CFTR trafficking to the membrane and enhances function. | Cheng, J., Moyer, B. D., Milewski, M., et al. (2002). **"A Golgi-associated PDZ domain protein modulates cystic fibrosis transmembrane regulator plasma membrane expression."** *Journal of Biological Chemistry, 277(5), 3520–3529.* |
| CFTR-Hsp70/ Hsp 90 | Hsp70 and Hsp90 chaperones assist in CFTR folding; however, in misfolded states (e.g., ΔF508-CFTR), they recruit CHIP (E3 ubiquitin ligase), leading to proteasomal degradation. | Inhibiting this degradation pathway may help stabilize misfolded CFTR and rescue its function. | Meacham, G. C., Lu, Z., King, S., Sorscher, E. J., Tousson, A., & Cyr, D. M. (1999). **"The Hsc70 co-chaperone CHIP targets immature CFTR for proteasomal degradation."** *Nature Cell Biology, 1(7), 386–390.* |