Biological Network Analysis and Protein kinase Inhibition in Breast Cancer Oncosystem

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Abstract:

The research focused on elucidating potential targets for breast cancer therapy through the empirical approach to biological networks involved in disease progression. The study was initiated by collecting targets of FDA-approved small-molecule drugs for breast cancer, specifically focusing on those belonging to the kinase inhibitor class. The Swiss Target database was employed to select the kinase inhibitor targets. These targets are then merged and used to construct a network using the String database, which is visualized in Cytoscape. The network analysis is performed using the Cytohubba plugin to identify the top 10 hubgenes in the network. The analysis revealed several high-ranking hub genes, including well-known regulators of breast cancer like EGFR, ERBB2, AKT1, MAPK1, and biomarkers such as JAK1, JAK3, and PRKCD thereby validating the network's reliability. Furthermore, a drug-target analysis was conducted to identify candidate inhibitors for the identified hubgenes. Selection criteria include kinase-specificity, as well as safety and efficacy profiles. Molecular docking was employed to evaluate the binding affinity of MAPK1 with Tucatinib, a protein kinase inhibitor, revealing a strong interaction having a binding affinity of -9.6 kcal/mol. Molecular dynamics (MD) simulations are then performed to assess the stability and dynamics of the MAPK1-Tucatinib complex. The results provide insights into the initial binding conformation and interactions between the protein and ligand.

The constructed protein-protein interaction networks offer valuable information on the crosstalk and network interactions of Protein Kinase (PK) within breast oncosystems, while hub genes offer significant targets for interventions in personalized medicine in breast cancer treatment.

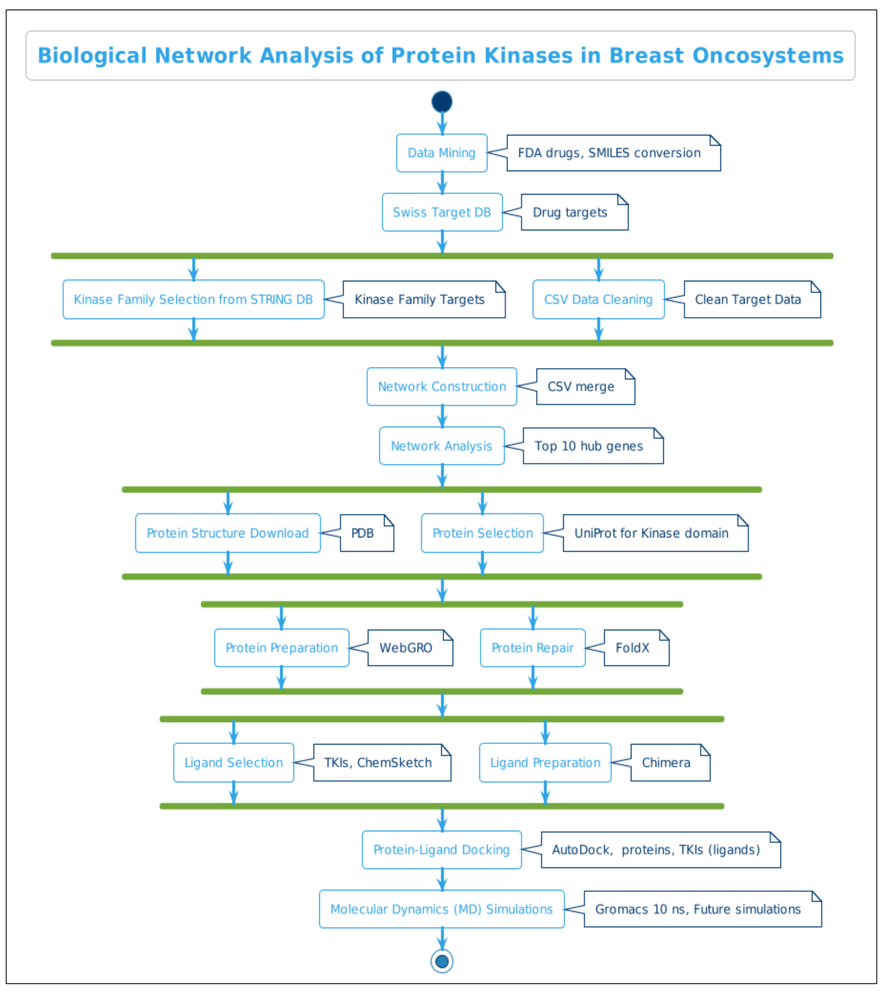
Background

- Breast cancer is a complex disease with diverse molecular subtypes, necessitating a deeper understanding of the underlying mechanisms.
- Protein kinases are key regulators of cellular processes and aberrant kinase signaling is often associated with cancer development.
- Previous studies have demonstrated the effectiveness of targeted kinase inhibitors in breast cancer treatment.

Aim

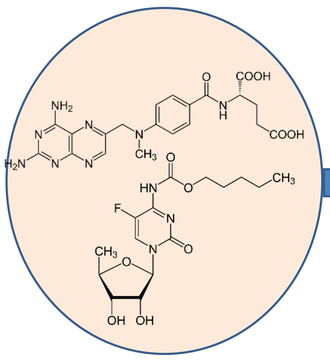
- The primary objective of this study is to explore the role of protein kinases in breast cancer initiation, progression, and therapeutic interventions.
- The research aims to unravel the complex signaling networks and interactions involving protein kinases in breast Oncosystems.
- To identify critical players in breast cancer signaling, the study aims to identify hubgenes within the protein-protein interaction network.
- By analyzing the hubgenes, the study seeks to uncover key signaling pathways and potential therapeutic targets for breast cancer treatment.

Methodology

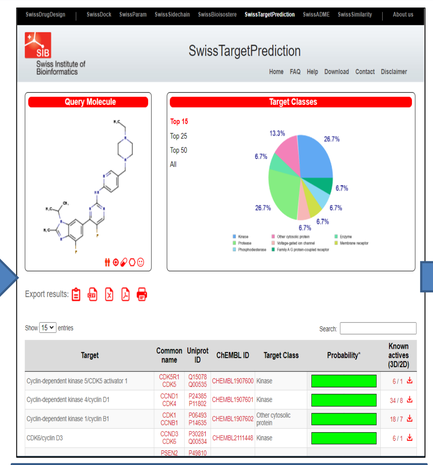


Results

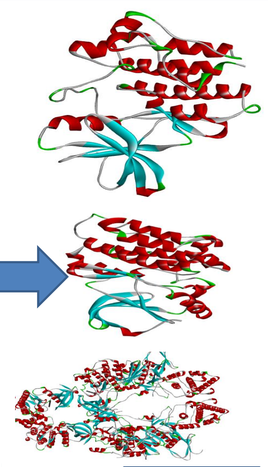
Breast Cancer disease



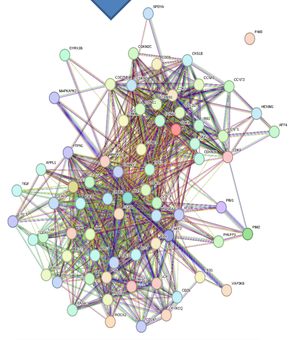
Breast cancer based Kinase inhibitors from multiple sources



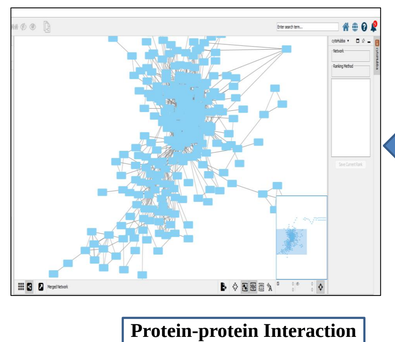
Target mining from the Swiss Target Prediction



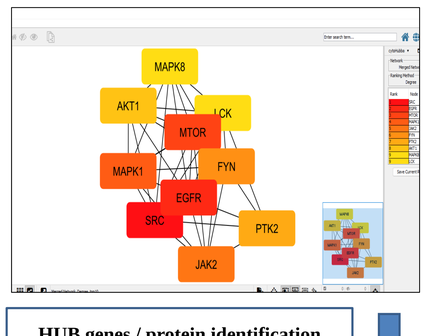
List of Target



Protein-protein Interaction Network from STRING



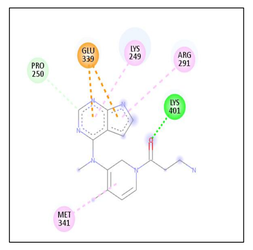
Protein-protein Interaction Network Analysis in Cytoscape



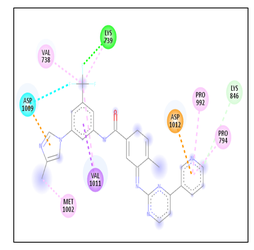
HUB genes / protein identification

Table: Molecular Docking – Binding Affinity Score in (Kcal/mol)

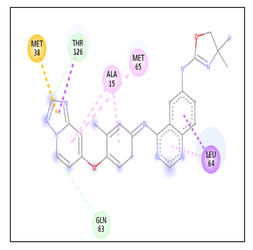
Ligands	Protein Kinases (kcal/mol)							
	SRC	EGFR	MTOR	MAPK1	JAK2	FYN	PTK2	LCK
Afatinib	-1.8	-5.9	-5.6	-8.8	-5.3	-6.5	-6.7	-6.7
Alectinib	-3.4	0.4	-1.1	-8.4	-6.3	-8.3	-7.5	-7.9
Baricitinib	-5.9	-5.1	-5.3	-7.2	-5.6	-6.6	-6.6	-5.5
Bexarotene	-6.2	-6.4	-5.4	-8.9	-7	-7.7	-8.2	-7.2
Bosutinib	-3.6	-5.3	-5.3	-7.5	-5.1	-4.8	-5.8	-5.4
Brigatinib	-3.9	-4.2	-5.5	-8.2	-5.7	-7.4	-6.8	-6.6
Cabozantinib	-2.5	-4.4	-5.3	-8.2	-5.7	-7.5	-6.7	-6.5
Cediranib	-3.9	-5.9	-6	-8.4	-4.6	-7.2	-7.4	-6
Crizotinib	-5.1	-5.6	-6.1	-8.3	-5.8	-8.1	-7.4	-6.6
Dasatinib	-1.2	-5.8	-5.8	-7.8	-5.3	-7.5	-7	-6
Dovitinib	-2.3	-4.7	-6.9	-8.8	-6.3	-8.1	-7.9	-7
Entospletinib	-1.8	-6.1	-7.1	-9.4	-6.5	-8.2	-7.6	-6.9
Erlotinib	-5	-4.8	-4.9	-7.2	-5.4	-5.9	-5.9	-5.3
Fedratinib	-5.5	-4.9	-6.2	-8.8	-6.5	-7.7	-7.8	-6.6
Gefitinib	-5	-5.5	-5	-8.3	-5.3	-6.8	-7	-6.3
Imatinib	-2.9	-6.1	-5.9	-9.6	-6.6	-7.7	-8.4	-7.7
Larotrectinib	-5.7	-5.8	-6.5	-9.6	-6.3	-7.8	-8.2	-6.9
Lenvatinib	-2.7	-3.9	-3.1	-3.4	-2.9	-3.2	-3	-3
Lorlatinib	-2.4	-4.6	-5.6	-9	-6.3	-7.8	-7.4	-6.8
Masitinib	-4.2	-5.3	-5.6	-9.2	-6.5	-7.4	-8.0	-6.9
Midostaurin	-6.1	-5.9	-5.2	-8.8	-5.5	-8.3	-7.5	-6.9
Nilotinib	-4.2	-6.7	-7.1	-7.2	-6.7	-6.8	-6.3	-6.8
Osimertinib	-1.7	-5.3	-5.2	-7.8	-5.3	-7.9	-6.3	-6.2
Pacritinib	-1	-5.6	-6.2	-8.8	-6.2	-7.8	-6.3	-6.2
Pazopanib	-1.6	-5.9	-6.3	-8.7	-6.3	-7.8	-8.1	-6.8
Pelitinib	0.4	-4.7	-5.3	-7.9	-5	-7.9	-6.3	-5.8
Ponatinib	-3.8	-5.2	-6.8	-9.3	-6.6	-8.1	-8.1	-7.6
Poziotinib	-4.8	-5.3	-6.3	-8.8	-5.9	-7.5	-7	-6.5
Regorafenib	-3.7	-6	-6.1	-8	-5.6	-6.3	-7.6	-6
Ruxolitinib	-5.7	-5	-5.6	-7.5	-5.2	-6.5	-6.4	-5.9
Semaxanib	-6.3	-5.6	-6	-7.2	-5.5	-6.3	-6.3	-5.7
Sorafenib	-5.9	-5.6	-6	-8	-5.9	-7	-6.8	-6
Sunitinib	-6.2	-5.3	-5.4	-6.1	-4.7	-5.9	-5.6	-5.2
Tofacitinib	-6.4	-5	-6.1	-7.2	-5	-6.1	-6.1	-5.2
Tucatinib	-1.7	-6.3	-7.6	-9.6	-6.4	-8.1	-7.9	-7.6
Vandetanib	-2.7	-5.5	-5.9	-8.8	-5.5	-6.7	-6.3	-6.1



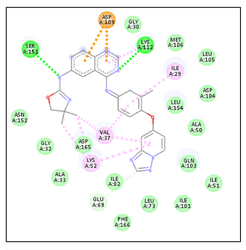
SRC kinase and inhibitor



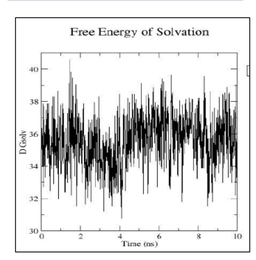
EGFR kinase and inhibitor

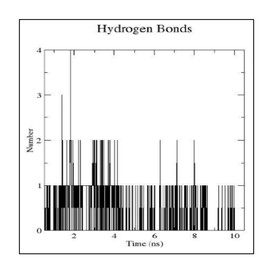


MTOR kinase and inhibitor



MAPK1 kinase and inhibitor





MD simulation of MAPK1 and Tucatinib complex

Conclusion:

1. Investigated protein kinase network in breast oncosystems.
2. Identified key hubgenes associated with breast cancer.
3. Molecular dynamics simulations provided insights into behavior and stability of protein-ligand complexes.
4. Analysis of ligand binding affinities and interactions revealed molecular mechanisms of TKI-target kinase interactions.

References:

Ferlay, J.; Soerjomataram, I.; Dikshit, R.; Eser, S.; Mathers, C.; Rebelo, M.; Parkin, D.M.; Forman, D.; Bray, F. Cancer incidence and mortality worldwide: Sources, methods and major patterns in globocan 2012. *Int. J. Cancer* **2015**, *136*, E359–E386. [Google Scholar] [CrossRef] [PubMed]

Berman, A.T.; Thukral, A.D.; Hwang, W.T.; Solin, L.J.; Vapiwala, N. Incidence and patterns of distant metastases for patients with early-stage breast cancer after breast conservation treatment. *Clin. Breast Cancer* **2013**, *13*, 88–94. [Google Scholar] [CrossRef] [PubMed]

Scully, O.J.; Bay, B.-H.; Yip, G.; Yu, Y. Breast cancer metastasis. *Cancer Genom.-Proteom.* **2012**, *9*, 311–320. [Google Scholar]

Shchemelinin, I.; Sefc, L.; Necas, E. Protein kinases, their function and implication in cancer and other diseases. *Folia Biol. (Praha)* **2006**, *52*, 81–100. [Google Scholar] [PubMed]