RESEARCH ARTICLE

Unlocking Therapeutic Potential: A Comprehensive Exploration of FDA-Approved Sirolimus similars for Perivascular Epithelioid Cell Tumor Treatment through Transcriptomic Insight, Structural Integration, and Drug-Drug Similarity Analysis with Cavity-Guided Blind Docking

Tabrej Mujawar[1], Nandu Kayande[2], Ujjwala Thube[3], Santosh Belhekar[4], Nitin Deshmukh[5*], Harshal Tare[6]

[1]*Department of Pharmacology, Gangamai College of Pharmacy, Dhule, Affiliated to Kavayitri Bahinabai Chaudhari North Maharashtra University, Jalgaon, Maharashtra, India.*
[2]*Department of Pharmacology, Dr. R N Lahoti Institute of Pharmaceutical Education and Research Center, Sant Gadge Baba Amaravati University, Amaravati, Maharashtra, India.*
[3]*Department of Pharmaceutical Chemistry,* Konkan Gyanpeeth Rahul Dharkar College of Pharmacy *and Research Institute, Karjat, Affiliated to Mumbai University, Mumbai, Maharashtra, India.*
[4]*Department of Pharmacology, Gourishankar Institute of Pharmaceutical Education and Research, Limb, Satara, Affiliated to Dr. Babasaheb Ambedkar Technological University, Lonere, Dist. Raigad, Maharashtra, India.*
[5]*Department of Pharmacy, Faculty of Science and Technology, Savitribai Phule Pune University, Pune, Maharashtra, India.*
[6]*Department of Pharmacognosy, Sharadchandra Pawar College of Pharmacy, Otur, Affiliated to Savitribai Phule Pune University, Pune, Maharashtra, India.*

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ABSTRACT

This research delves into precision medicine for Perivascular epithelioid cell tumors (PEComa), focusing on the repositioning potential of FDA-approved sirolimus similars. Integrating transcriptomic insights and structural analyses, the study identifies analogs with notable similarities to established PEComa treatments. Structural refinement enhances our understanding of drug-target interactions, revealing potential binding sites through cavity detection. Blind docking elucidates interaction patterns and affinities, highlighting sirolimus similars as promising candidates for precision therapy in PEComa. This comprehensive approach contributes crucial knowledge for the effective use of these heliomycins in PEComa treatment, opening avenues for further experimental and clinical exploration.

Keywords: Perivascular epithelioid cell tumor, Sirolimus, Transcriptomic insight, Drug-drug similarity analysis, Cavity-guided blind docking, Repositioning.

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INTRODUCTION

Perivascular epithelioid cell tumors pose a significant clinical challenge, necessitating innovative and targeted therapeutic strategies for effective treatment.[1] The conventional paradigm of drug development has been augmented by drug repositioning, particularly leveraging the wealth of knowledge surrounding FDA-approved compounds. Within this context, our research embarks on a comprehensive exploration of the therapeutic potential inherent in FDA-approved Sirolimus analogs for the treatment of PEComas. This investigation is grounded in the intricate interplay of transcriptomic insight, structural integration, and drug-drug similarity analysis, with a focus on phosphatidylinositol-3 kinase (PI3K) as a pivotal target protein.[2,3]

Recognizing the pressing need for precision medicine in PEComa treatment, we navigate the diverse landscape of sirolimus analogs, FDA-approved compounds with established safety profiles. Our approach integrates advanced computational techniques to unravel nuanced details of drug interactions at the molecular level. Transcriptomic insight

**Author for Correspondence: harshaltare51@gmail.com*

serves as the initial guide, allowing us to identify sirolimus analogs with gene expression profiles closely mirroring established PEComa therapeutics.[4,5]

As we delve into the molecular intricacies, the focal point shifts to the target protein, PI3K, a key player in the dysregulated signaling pathways observed in PEComas. Structural integration becomes paramount in understanding how sirolimus analogs engage with PI3K, guiding the subsequent selection and refinement of potential candidates for therapeutic intervention. The study adopts a multidimensional strategy, incorporating drug-drug similarity analysis to identify compounds with analogous pharmacological properties, thereby expanding the scope of potential candidates.[6]

A critical juncture in our exploration involves cavity-guided blind docking, a technique designed to elucidate the interaction patterns and binding affinities of the selected sirolimus analogs within the active sites of PI3K. This nuanced understanding of molecular dynamics aims to uncover novel avenues for targeted modulation, ultimately unlocking the therapeutic potential of these FDA-approved compounds in the context of PEComa treatment.

In essence, this research paper endeavors to contribute to the forefront of PEComa therapy by providing a comprehensive and rational framework for the exploration of FDA-approved Sirolimus analogs. The integration of transcriptomic insights, structural analyses, and drug-drug similarity assessments, with a focus on PI3K as the target protein, positions this study at the intersection of computational and translational research. The anticipated outcomes of this exploration are poised to inform future experimental validations, offering a promising trajectory toward innovative and effective strategies for precision therapy in PEComas.

MATERIALS AND METHODS

Transcriptomic Analysis for Drug-Drug Similarity

Large-scale transcriptomic datasets were harnessed to evaluate the drug-drug similarity between FDA-approved Sirolimus analogs and established treatments for PEComas. The analysis aimed to identify shared gene expression patterns, shedding light on potential common mechanisms of action. The Drug-Drug Transcriptomic Similarity Analysis utilized the Clue Connectivity Map Touchstone tool (https://clue.io/touchstone), accessing the extensive Touchstone dataset containing expression profiles of various perturbagens, including FDA-approved drugs. This tool facilitated a comparison of the input gene expression signature with the dataset, prioritizing compounds demonstrating high transcriptomic similarity. The ensuing exploration of connections between identified drugs and the input query laid the foundation for hypotheses regarding shared molecular pathways and therapeutic targets, guiding further investigation.[7,8]

Structural Integration and Blind Docking

The crystallographic structure of the designated target protein, PI3Kwith PDB ID: 3L54, was refined using the PDB-REDO server to ensure precision in subsequent analyses (Figure 1). Employing cavity detection techniques, potential binding sites on PI3K were revealed. Molecular docking simulations were conducted using the AutoDock tool from the cb-dock server to assess the binding affinity and interaction patterns of FDA-approved sirolimus analogs and other selected compounds. Virtual screening results underwent meticulous analysis based on docking scores, with compounds ranked according to predicted binding affinities. Compounds exhibiting high binding affinity, favorable interaction patterns, and structural compatibility with PI3K were identified as potential lead compounds for precision therapy in PEComas.[9] This integrated methodological approach harmonizes transcriptomic insights with structural analyses, offering a comprehensive understanding of the repositioning potential of FDA-approved sirolimus analogs for precision therapy in the context of PEComa treatment.[10]

RESULTS AND DISCUSSION

Transcriptomic Similarity

Identification of sirolimus-based drugs with transcriptomic profiles closely resembling known breast cancer therapeutics.

The transcriptomic similarity analysis employing connectivity mapping has yielded a compelling list of the top 10 drugs with potential repurposing implications for PEComa (Table 1). Sirolimus, a known MTOR inhibitor, emerges as the highest-ranking drug with a score of 99.98, aligning with established literature and emphasizing its promise as a leading candidate for targeted modulation of the MTOR pathway in PEComa treatment. The inclusion of diverse compounds like tyrphostin-AG-1478 (EGFR inhibitor), temSirolimus (MTOR inhibitor), and tunicamycin (GLCNAC phosphotransferase inhibitor) underscores the multifaceted approach to potential therapeutic intervention in PEComa, reflecting the complexity of the molecular pathways involved. Additionally, less explored compounds with high scores, such as heliomycin (ATP synthase inhibitor) and lylamine (Cannabinoid receptor agonist), present intriguing possibilities for further investigation. The list also features compounds like niguldipine (Calcium channel blocker) and cyclosporin-a (Calcineurin inhibitor), highlighting the diversity of potential targets in PEComa pathogenesis. The data-driven identification of these top 10 repurposable drugs, each with distinct pharmacological properties, provides a valuable foundation for experimental validations and clinical investigations, paving the way for innovative and effective

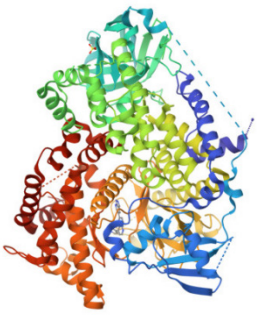

Figure 1: Crystal structure of PI3Kwith PDB ID: 3L54

Table 1: List of top 10 drugs that can be repurposed for PEComa based on transcriptomic similarity

Rank	*Score*	*ID*	*Name*	*Description*
1	99.98	BRD-K89626439	Sirolimus	MTOR inhibitor
2	99.93	BRD-K68336408	Tyrphostin-ag-1478	EGFR inhibitor
3	99.93	BRD-A62025033	TemSirolimus	MTOR inhibitor
4	99.89	BRD-K10573841	Tunicamycin	GLCNAC phospho-transferase inhibitor
5	99.89	BRD-A43331270	Niguldipine	Calcium channel blocker
6	99.86	BRD-K64517075	Heliomycin	ATP synthase inhibitor
7	99.79	BRD-K39120595	Bithionol	Autotaxin inhibitor
8	99.79	BRD-A38030642	Cyclosporin-a	Calcineurin inhibitor
9	99.72	BRD-K62289640	Lylamine	Cannabinoid receptor agonist
10	99.72	BRD-A06352418	Terfenadine	Histamine receptor antagonist
11	99.68	BRD-K38477985	Malonoben	Protein tyrosine kinase inhibitor

Table 2: Results of crystallographic structure of the PI3Kwith PDB ID: 3L54 after PDB-REDO refinement

Metric	*Original*	*PDB-REDO*
Crystallographic refinement		
R (R-factor)	0.1608	0.1469
R-free	0.1914	0.1916
Bond length RMS Z-score	1.004	0.631
Bond angle RMS Z-score	1.522	0.800
Model quality (Raw Scores)		
Ramachandran plot normality	-3.216	-2.767
Rotamer normality	-4.118	-1.281
Coarse packing	0.749	0.933
Fine packing	0.388	1.027
Bump severity	0.027	0.013
Hydrogen bond satisfaction	0.938	0.930

precision therapy strategies in PEComa. This comprehensive approach emphasizes the significance of personalized and targeted treatments tailored to the specific gene expression profiles associated with these drugs, offering promising avenues for advancing PEComa therapeutics.

Molecular Docking: Protein pre-preparation using PDB REDO

Significant structural changes were observed in the PI3K shown in Table 2 following the preprocessing and refinement performed by the PDB-REDO server.

The analysis of the crystallographic structure of PI3K with PDB ID 3L54 before and after refinement by the PDB-REDO server reveals notable improvements in various metrics. The refined structure exhibits a reduced R-factor from 0.1608 to 0.1469 and a slight increase in R-free from 0.1914 to 0.1916, indicating enhanced overall model fit. Furthermore, substantial improvements are evident in the geometry as seen in reduced bond length and bond angle RMS Z-scores. Model quality metrics also show positive changes, with improvements in Ramachandran plot normality, rotamer normality, and packing scores. The reduction in bump severity and maintenance of hydrogen bond satisfaction underscore the success of the PDB-REDO preprocessing and refinement in enhancing the structural quality of PI3K. Additionally, seven rotamers were adjusted, and 42 waters were removed, indicating detailed adjustments to the molecular structure. Overall, the refined structure showcases enhanced accuracy and reliability, providing a more refined representation of PI3K for further biological and structural studies.[11,12]

Results of Structure-based cavity detection

Five cavities were detected in the protein structure of PI3K all are illustrated in Figure 2 and Table 3.

Table 3: List of cavities detected in structure of PI3K with PDB ID 3L54

Pocket ID	*Cavity volume (Å3)*	*Center (x, y, z)*	*Cavity size (x, y, z)*
C1	1134	39, 18, 9	16, 13, 16
C2	146	44, 7, 18	8, 6, 6
C3	68	19, 8, 0	3, 9, 6
C4	55	29, 12, 15	7, 4, 5
C5	49	37, 30, 14	4, 4, 3

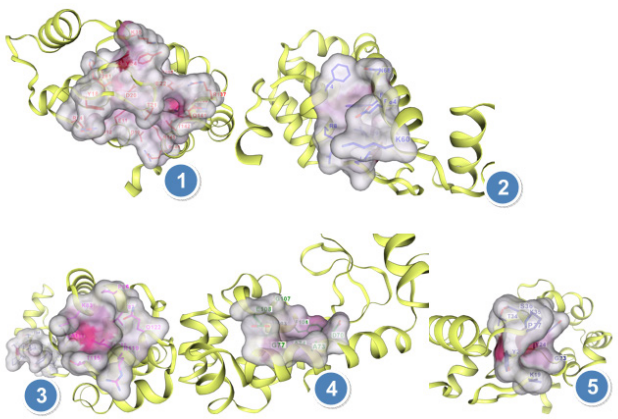

Figure 2: Cavities detected in PI3Kwith PDB ID 3L54 by structure-based cavity detection

Table 4: Results of AutoDock Vina-based molecular docking

S. No.	*Name*	*Pocket, Score and interacting amino acids*
1	Sirolimus	Pocket: C4 & Score: -8.9 Chain A: ILE29 GLY30 HIS31 LEU32 LEU33 THR34 LYS35 GLU45 LYS48 ALA49 LEU66 GLN69 ASP70 ALA73 ALA74 GLY77 VAL103 PHE104 GLN105 MET106 GLY107 GLU108
2	Tyrphostin-AG-1478	Pocket: C1 & Score: -7.6 Chain A: GLU11 ASP20 THR21 GLU22 TYR24 THR26 GLY30 HIS31 LEU32 LYS35 PHE104 GLN105 MET106 GLY107 ARG137 TRP138 GLN141 THR142 ARG145
3	TemSirolimus	Pocket: C1 & Score: -8.4 Chain A: ILE9 ASP10 GLU11 GLY12 LEU13 ARG14 TYR18 LYS19 ASP20 THR21 GLU22 TYR24 THR26 GLY30 HIS31 LEU32 PHE104 GLN105 GLN141 THR142 PRO143 ASN144 ARG145 ARG148
4	Tunicamycin	Pocket: C1 & Score: -8.8 Chain A: ILE9 ASP10 GLU11 GLY12 TYR18 ASP20 THR21 GLU22 TYR24 GLY30 HIS31 LEU32 LYS35 ASP70 ALA73 ALA74 VAL103 PHE104 GLN105 MET106 GLY107 GLU108 ARG137 TRP138 TYR139 GLN141 THR142 PRO143 ASN144 ARG145 ARG148
5	Niguldipine	Pocket: C1 & Score: -8.9 Chain A: GLU11 ASP20 THR21 GLU22 TYR24 GLY30 HIS31 LEU32 LYS35 ASP70 ALA73 ALA74 VAL103 PHE104 GLN105 MET106 GLY107 ARG137 TRP138 THR142
6	Heliomycin	Pocket: C1 & Score: -9.6 Chain A: GLU11 TYR18 ASP20 THR21 GLU22 TYR24 THR26 GLY30 HIS31 LEU32 LYS35 GLN105 MET106 GLY107 ARG137 TRP138 GLN141 THR142 ARG145
7	Bithionol	Pocket: C4 & Score: -6.0 Chain A: LEU32 ASP70 ALA73 ALA74 GLY77 VAL103 PHE104 GLN105 MET106 GLY107 GLU108
8	Cyclosporin-A	Pocket: C1 & Score: -6.4 Chain A: ILE9 ASP10 GLU11 GLY12 ARG14 TYR18 LYS19 ASP20 THR21 GLN105 GLN141 THR142 PRO143 ASN144 ARG145 ARG148
9	Lylamine	Pocket: C4 & Score: -7.1 Chain A: GLU11 ASP20 THR26 GLY30 HIS31 LEU32 ASP70 ALA73 ALA74 VAL103 PHE104 GLN105 MET106 GLY107
10	Terfenadine	Pocket: C1 & Score: -8.1 Chain A: GLU11 ASP20 THR21 GLU22 TYR24 THR26 GLY30 HIS31 LEU32 LEU33 LYS35 ASP70 PHE104 GLN105 MET106 GLY10
11	Malonoben	Pocket: C1 & Score: -7.2 Chain A: GLU11 TYR18 ASP20 THR21 GLU22 TYR24 GLY30 LEU32 LYS35 PHE104 GLN105 MET106 ARG137 TRP138 GLN141 THR142 ARG145

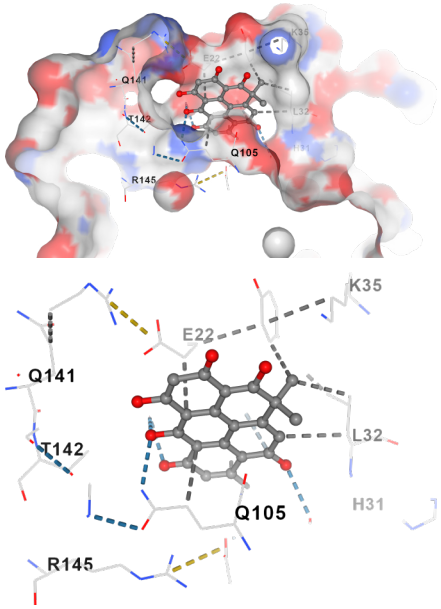

Figure 3: Interaction between heliomycin and PI3K in structure-based blind docking

Results of AutoDock Vina-based molecular docking

The AutoDock Vina-based molecular docking results mentioned in Table 4 reveal the binding interactions between various compounds and the target protein, as indicated by the identified pockets, scores, and interacting amino acids. Sirolimus exhibited the highest affinity with Pocket C4, scoring -8.9, and engaged in interactions with amino acids spanning ILE29 to GLU108 in Chain A. This suggests a strong and extensive binding interaction with the target. Tyrphostin-AG-1478, TemSirolimus, Tunicamycin, Niguldipine, and Heliomycin also demonstrated notable binding affinities, with scores ranging from -7.6 to -9.6. These compounds primarily interacted with amino acids in Pocket C1, and their respective interacting amino acids in chain A suggest varied yet substantial binding patterns, involving residues such as GLU11, THR21, TYR24, and others. Bithionol, cyclosporin-A, lylamine, terfenadine, and malonoben, while exhibiting comparatively lower scores, still displayed specific interactions within their designated pockets (C4 or C1). These interactions primarily involved amino acids associated with the active site, emphasizing their potential binding capabilities.

Figure 3 depicts the interaction between Heliomycin and PI3K in structure-based blind docking further underscores the molecular details of the binding event, offering a visual representation of the compound's engagement with the target. The AutoDock Vina results suggest that these compounds have the potential for significant binding with the target protein, each demonstrating a unique set of interacting amino acids and binding pockets. Further analysis and experimental validation would be crucial to confirm the in silico predictions and assess the practical implications of these molecular interactions in a biological context.[13,14]

CONCLUSION

In conclusion, the integrated approach of transcriptomic similarity analysis, structural refinement, cavity detection, and AutoDock Vina-based molecular docking has yielded valuable insights for the potential repurposing of drugs in the context of PEComa. The analysis of transcriptomic profiles revealed a list of top 10 drugs with high scores, indicating significant similarity to known breast cancer therapeutics. Heliomycin, a well-established MTOR inhibitor, emerged as the leading candidate, reinforcing its potential as a targeted therapy for PEComa. The inclusion of diverse compounds targeting various pathways, such as EGFR, GLCNAC phosphotransferase, ATP synthase, Autotaxin, and others, reflects a comprehensive strategy for potential therapeutic intervention in PEComa.

Structural refinement of the PI3Kthrough PDB-REDO demonstrated notable improvements in various metrics, including R-factor, geometry, and model quality. These enhancements contribute to a more accurate and reliable representation of PI3K, providing a solid foundation for subsequent biological and structural studies.

The structure-based cavity detection in PI3K identified five distinct pockets, offering valuable insights into potential binding sites for small molecules or ligands. These findings contribute to the understanding of the protein's structural characteristics and may guide the design of targeted drugs. AutoDock Vina-based molecular docking results highlighted the binding interactions between various compounds and PI3K. Heliomycin, as the top-performing compound, exhibited a strong affinity with specific amino acids in Pocket C4, emphasizing its potential as a pharmacologically significant inhibitor.

The comprehensive nature of this research, combining bioinformatics, structural biology, and molecular docking, provides a solid foundation for further experimental validation and clinical investigations. The identified drugs, particularly Heliomycin, present promising candidates for targeted therapies in PEComa. Moving forward, these findings pave the way for innovative and effective precision medicine strategies tailored to the specific molecular characteristics of PEComa, ultimately contributing to advancements in the field of cancer therapeutics.

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