Qeios

Peer Review

Review of: "New Approach for TargetingSmall Molecule Candidates for Intrinsically Disordered Proteins"

Pavankumar Vangavolu[1]

1. Northeastern University, United States

General Comments

This manuscript presents an application of the Informational Spectrum Method for Small Molecules (ISM-SM) to identify potential modulators of the intrinsically disordered tau protein, a central pathological factor in Alzheimer's disease. Intrinsically disordered proteins represent one of the most challenging classes of drug targets due to their structural flexibility and lack of stable binding pockets. The author proposes a computational approach based on electron-ion interaction potential (EIIP) descriptors and frequency-domain analysis to identify candidate compounds through spectral compatibility.

The manuscript is well-structured and clearly written. The methodological framework is logically presented, and the computational workflow is adequately described. The results demonstrate that ISM-SM can identify compounds previously reported to influence tau pathology, including approved drugs and natural products. The identification of conserved frequencies across mammalian tau proteins and the correspondence of predicted interaction regions with known functional domains support the biological relevance of the approach.

The integration of Drug Bank and COCONUT database screening provides a comprehensive analysis, and the identification of compounds such as temsirolimus, everolimus, and bryostatin-14 aligns with known biological pathways relevant to tau regulation. Overall, the manuscript addresses an important problem in computational drug discovery and contributes a potentially useful complementary method for identifying candidate molecules targeting intrinsically disordered proteins.

doi.org/10.32388/OX28YU

Major Concerns

1. Lack of structural and mechanistic validation

The ISM-SM method identifies spectral compatibility between small molecules and proteins, but it does not directly model structural binding interactions or molecular dynamics. While the identification of literature-supported compounds provides indirect validation, the manuscript does not establish whether the predicted candidates directly bind tau or influence its function through alternative mechanisms. Additional structural modeling, docking analysis, or molecular dynamics simulations would strengthen the mechanistic interpretation and support the predictive validity of the method.

2. Limited quantitative validation and benchmarking

Although the manuscript demonstrates agreement between predicted candidates and compounds previously associated with tau pathology, there is no quantitative evaluation of predictive performance. Metrics such as enrichment factors, specificity, sensitivity, or comparison with random selection would help assess the robustness and reliability of the method. Furthermore, broader benchmarking against established computational approaches for intrinsically disordered protein targeting would strengthen the methodological validation.

3. Interpretation of indirect pathway associations

Many of the identified Drug Bank compounds influence tau pathology indirectly through modulation of signaling pathways rather than direct tau binding. While this may reflect biologically relevant interactions, it also complicates interpretation of the ISM-SM predictions. The manuscript would benefit from a clearer distinction between direct binding predictions and indirect pathway associations, and a discussion of the implications of this distinction for drug discovery applications.

Minor Concerns

1. Clarification of the biophysical basis of the method

The manuscript would benefit from a more detailed explanation of the physical and molecular basis linking EIIP-derived spectral frequencies to intermolecular recognition and biological activity. This would improve understanding of the mechanistic rationale behind the method.

2. Reproducibility and methodological transparency

Additional details regarding parameter selection, frequency thresholds, and implementation would improve reproducibility and allow independent validation by other researchers.

3. Presentation and clarity

The figures and tables are generally clear and informative. However, some figure captions could provide additional explanatory context to improve accessibility, particularly for readers unfamiliar with ISM-SM methodology.

4. Future validation

The manuscript appropriately acknowledges the need for experimental validation. Expanding this discussion to include specific experimental strategies, such as binding assays or cellular validation models, would strengthen the translational perspective.

Recommendation

The manuscript presents a novel and computationally efficient approach for identifying candidate small molecules targeting intrinsically disordered proteins. The results are biologically relevant and supported by existing literature, and the method shows potential as a complementary tool for drug discovery and repurposing.

The main limitations relate to the lack of experimental validation and limited quantitative benchmarking, which should be addressed in future work. However, these limitations do not undermine the conceptual contribution or the validity of the presented computational analysis.

Recommendation: Accept with minor revisions.

Declarations

Potential competing interests: No potential competing interests to declare.