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Peer Review

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

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The work presents a novel and powerful approach to a developing field, namely that of Intrinsically Disordered Proteins (IDPs). Specifically, the ISM-SM methodology is applied to the paradigmatic example of the tau protein, which is associated with Alzheimer's Disease (AD). The value of the study lies in demonstrating that this method can be effectively used for drug repurposing by screening FDA-approved drugs (DrugBank) and natural compounds (from the Coconut database). This opens up promising avenues for off-label treatments. This aspect is particularly compelling when considering its potential application to ultra-rare and intractable diseases, or anyway diseases whose targets are poorly structurally characterized and thus for which no structure-based approach can be pursued.

I was previously unaware of ISM being applied to drug discovery. In my view, this approach appears particularly well-suited to challenging cases like IDPs, as it characterizes protein-ligand interaction potentials in a non-structure-based manner. This circumvents potential predictive biases introduced by brute-force ensemble docking approaches (e.g., poor structure predictions or hallucinations by AlphaFold, etc.) and avoids false positives (at least due to poor structure predictions). As I understand it, the ISM-SM method is also computationally far more accessible than traditional workflows involving protein structure prediction, molecular dynamics conformer generation, and ensemble docking. I believe this advantage should be more strongly emphasized to highlight the method's potential compared to classical structure-based approaches.

Moreover, the manuscript should explicitly state that this approach, due to its computational efficiency and ability to mitigate docking biases, may also be applicable to structured proteins. This would further underscore its broad utility in drug discovery, especially if coupled with classical structure-based approaches to test eventual shaking hypotheses (e.g., when dealing with low-resolution structures). If

 doi.org/10.32388/0B3WWG

that is the case, I believe that stressing the capability to screen extremely large compound libraries such as the COCONUT database would be helpful.

Regarding clarity: while the manuscript references the methodology, it would be beneficial to provide a more detailed explanation of its practical implementation, perhaps in a supplementary information (SI) file containing the code, workflows, or usage instructions. This would enhance reproducibility and enable broader adoption by the scientific community across various drug discovery subfields.

Using approved drugs is a valid strategy to rapidly identify potential therapeutic candidates. However, relying on the previously known activity of these compounds in the context of AD does not constitute definitive proof that their mechanism of action aligns with that proposed by the ISM-SM method. While this limitation is acknowledged at the end of the manuscript, it should be stated more clearly. Additionally, I suggest referencing specific examples beyond AD, or compounds that function as molecular probes, particularly those for which biophysical validation has been obtained (if any), as this would strengthen the validation of the method.

Finally, there is a mention in the Results section of the potential role of AI in analyzing this type of data, which is repeated at the end of the manuscript. I recommend consolidating this discussion into a single section, preferably toward the conclusion, for clarity and coherence.

Declarations

Potential competing interests: No potential competing interests to declare.