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Commentary: New design of nucleotide excision repair (NER) inhibitors for combination cancer therapy

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We recently published a scientific article[1] on the discovery of small molecule inhibitors for the nucleotide excision repair (NER) protein complex, XPA-ERCC1. In this paper, we reported on the computational workflow we adopted to screen for compounds that bind to ERCC1 and block their interactions with XPA. Following this workflow, we identified promising scaffolds with the potential of modulating the NER pathway. In this commentary, we discuss the relevant findings of this study as well as its limitations and future directions.

In our recent study, we identified small molecule compounds with the potential of regulating the NER DNA repair pathway. The compounds were selected to disrupt the XPA-ERCC1 protein-protein interaction. Combining such drugs with DNA damaging agents can improve their effectiveness and allow for the use at a reduced dose in cancer therapy[2]. We employed a computational workflow to screen the entire PubChem[3] and National Cancer Institute (NCI) small molecule[4] repositories to identify potential binders to the XPA-binding site within the ERCC1 protein. This binding site lies within the central domain of ERCC1.

The rationale for our study was to build upon an earlier study by our group[5] which identified two small molecule structures that target the XPA-ERCC1 interaction. These compounds were used as a starting point for our virtual screening (VS) campaign. In this context, we followed two independent screening approaches, namely a similarity-based approach and a pharmacophore-based approach.

For the similarity-based approach, we filtered the PubChem database for compounds that are structurally similar to these two lead molecules. Using a similarity Tanimoto score between chemical fingerprints, we retained only around 22,000 small molecules out of the 68 million compounds in the database. In addition, we performed an *in-silico* filtering step to retain only the molecules with drug-like properties, based on their Adsorption, Distribution, Metabolism, Elimination and Toxicity (ADMET) properties. This approach provided a significant improvement over the original study[5] as it focused on compounds with drug-like properties. This strategy reduced the enormous number of compounds in PubChem and built a focused library of compounds.

As a second screening approach, we used molecular docking simulations to study the binding modes of the originally identified compounds[5] and build a consensus pharmacophore model based on their docked poses. We then employed this model to filter four different subsets of the NCI databases for compounds that satisfy conditions imposed by this pharmacophore. For this approach, we aimed to identify new scaffolds that are able to inhibit the protein-protein interaction, with different chemical structures other than the original lead compounds. As a result, we used a lead-like filter to retain only the structures that can be used as lead compounds for further optimization. These two ligand-based strategies complemented each other. On the one hand, we identified improved drug-like analogues over the original lead compounds and on the other hand, we provided a set of diverse lead scaffolds.

Compounds coming from the two different screening funnels (i.e. similarity-based and pharmacophore-based) were ranked based on their binding energies within ERCC1. Therefore, we adopted a target-based VS protocol. For our docking simulations, we used seven optimized ERCC1 NMR conformations in order to accommodate the flexibility of both the side chains and backbone atoms of the binding site. After the docking simulation for each compound, we ran short molecular dynamics (MD) simulations for the top hits, followed by molecular mechanics/Poisson Boltzmann surface area (MM/PBSA) rescoring[6]. We concluded our study by providing not only a more reliable rank of the top hits compounds, but also to quantitatively represent the binding mode of the molecules to the key residues of the ERCC1 binding site.

Although the two screening approaches provided a comprehensive way to identify new scaffolds with drug-like properties, there are two critical points that we discuss next in this commentary. First concerns the relatively short MD simulations (2 nanoseconds) that were used to relax the top hits from docking simulations. Second is the neglect of the conformational entropy contribution when calculating the binding energies using the MM/PBSA method. For the first aspect, we decided to use this short simulation time scale, because of a deterioration of the ranking power of the MM/PBSA method was reported when applied to longer simulations[7,8]. Moreover, our group has used short timescales in a number of successful drug design studies[5,9]. These considerations, together with the limits derived by the availability of computational resources, drove our choice to use 2 nanoseconds of simulation for the docked complexes. We are aware of the fact that 2 nanoseconds is an insufficient amount of time to simulate any major conformational change of a molecule or a complex. However, we believe this was not relevant to our study. Regarding the entropy contribution, we performed the computationally-expensive calculations only for a subset of structurally-diverse hits. We found entropy values of the same order of magnitude for all the complexes, and hence we neglected that for the remaining hits. It is noteworthy that entropy contributions were shown to introduce large fluctuations to the binding energies in different studies. Also, these contributions can be safely ignored to obtain a relative rank of compounds with similar size and flexibility binding to the same target, as in our case.

In our work, we have adopted a multi-step VS protocol to identify XPA-ERCC1 inhibitors. We initially selected compounds that are either similar in structure or pharmacophore features to the known active inhibitors. In our opinion, this step should reduce the number of false positive results obtained from target-based screening methodologies. We then performed a first target-based screening retaining compounds which showed better binding energies than the lead structures, as calculated with the docking scoring function. Being aware of the limitations

Table 1: Top eighteen hits of the VS experiment, scored according to their MM/PBSA binding energy. All the compounds showed better values of the energy than the lead structures (rank 19 and 20). In total, seventy-two molecules showed lower binding energy values. The ID column indicates the ID associated to the compound in its original database. The MM/PBSA energies do not include the entropy contribution. The VS method column indicates the ligand-based screening technique used to include the compound in the target-based VS step from the indicated database (last column).

Rank	ID	MM/PBSA binding energy (kcal/mol)	VS method	Database
1	6210903	-33.84	Similarity search	PubChem
2	7324126	-33.41	Similarity search	PubChem
3	8486248	-31.49	Similarity search	PubChem
4	7730851	-31.25	Similarity search	PubChem
5	1696060	-30.29	Similarity search	PubChem
6	1161060	-30.11	Similarity search	PubChem
7	1098945	-30.11	Similarity search	PubChem
8	53684246	-29.75	Similarity search	PubChem
9	7260552	-29.48	Similarity search	PubChem
10	6971912	-29.47	Similarity search	PubChem
11	5105640	-29.33	Similarity search	PubChem
12	2645792	-28.56	Similarity search	PubChem
13	8013886	-28.23	Similarity search	PubChem
14	1705254	-28.16	Similarity search	PubChem
15	24539908	-28.06	Similarity search	PubChem
16	5113	-28.24	Pharmacophore	NCI Natural Products
17	106408	-25.41	Pharmacophore	NCI Mechanistic
18	107582	-25.25	Pharmacophore	NCI Diversity
19	Compound 10	-24.86	Lead compound	-
20	NERI01	-23.24	Lead compound	-

of such kind of methods regarding the ranking, we ran MD simulations followed by MM/PBSA rescoring. We believe that our approach was able to identify active inhibitors, having taken into account the physicochemical similarities with the lead compounds and also the binding energy values calculated with two different methods (docking scoring function followed by MM/PBSA rescoring). In conclusion, the outcome of our study was a set of seventy-two small molecules with a binding energy value more favorable than the two lead compounds. The top eighteen hits are reported in Table 1. The details of the remaining fifty-four compounds are available upon request. Our hits showed similar interaction patterns among the residues constituting the XPA binding site of ERCC1. Although it was our strong belief that our hits can be the key to the next generation of NER inhibitors, we recognized that the lack of experimental evidence constitutes a critical limitation of our findings. Hence, we strongly recommend to test these compounds in protein and cell-based assays for their ability to bind to the ERCC1 central domain and to inhibit the interaction with the XPA protein and, consequently, inhibit the NER pathway in cancer cells. Also, further experiments will be required to test the ability of these compounds to act synergistically with DNA damaging cancer therapy such as platinum-based drugs.

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