Review of: "Fragment libraries designed to be functionally diverse recover protein binding information more efficiently than standard structurally diverse libraries"

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Potential competing interests: The author(s) declared that no potential competing interests exist.

Current fragment-based drug design relies on the efficient exploration of chemical space though the use of structurally diverse libraries of small fragments. But structurally dissimilar compounds can exploit the same interactions on a target, and thus be functionally similar. Authors show that structurally diverse fragments can be described as functionally redundant, and functionally diverse selections of fragments substantially increase the amount of information recovered for unseen targets compared to other methods of selection. Using these results, authors design small functionally efficient libraries that are able to give significantly more information about new protein targets than similarly sized structurally diverse libraries. The manuscript is clearly written and well organized. However, there are still some concernsthat the auth rs should be addressed..

Major concerns:
(1) Authors defined a series of physicochemical properties for the functional fragments. I think it is important for the fragment selection during the fragment-to-lead optimization. Therefore, I suggest authors give more specific standards for the functional fragments.
(2) The functional fragments in this manuscript rely on the protein-fragment complexes from PDB database. In a previous study, some scientists from D. E. Shaw Research also used these data to analyze the interactions and properties of fragment hits (J. Med. Chem. 2019, 62, 7, 3381–3394). Can authors explain the difference between your work and their work?
(3) Authors state that they design small functionally efficient libraries for fragment-based drug discovery. But I do not find any detailed information about the libraries. I think it is helpful to users if they can obtain the fragment libraries.
(4) Authors compared the structurally diverse fragments and functionally diverse fragments from a series of properties. It is important to verify their differences. In my opinion, some specific binding modes of structurally diverse fragments and functionally diverse fragments with proteins of different drug targets should be analyzed.
(5) Fragment libraries play key roles in the fragment-based drug discovery. But FBDD is a complicated process and sometime is hard to be understands. I suggest authors add some case studies to introduce the potential application of the designed libraries on FBDD.

Minor concerns:

(1) How do authors build their libraries? According to the experience, fragments binding to different classes of targets may exhibit different properties, such as GPCR or kinases. The following article might be helpful to you: ChemMedChem, 2014, 9(2), 256-275 and Trends in Pharmacological Sciences, 2021, 42(7), 551-565.

(2) There are many grammar and spelling mistake in the manuscript. For examples, “Ideally, a fragment screen obtains information about the molecules or functional groups” should be “Ideally, a fragment screening obtains information about the molecules or functional groups”; “Using only binary hit or miss results does not tell us whether these frequently hitting fragments” should be “Using only binary hit or missing results does not tell us whether these frequently hitting fragments”.

(3) The labels in Figure 2 and Figure 6 are too small to be identified.