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Mining the PDB for tractable cases where X-ray crystallography combined with fragment screens can be used to systematically design protein-protein inhibitors

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The availability of small molecules able to selectively inhibit specific protein-protein interactions (PPI) in the cell would immensely facilitate our efforts to understand and manipulate the protein-protein "interactome". In our manuscript we show how a novel approach that combines X-ray crystallography and fragment screening can be used to systematically design protein-protein inhibitors. Recent technical advances in automated data collection and interpretation of electron density maps have made it possible to combine X-ray crystallography and fragment screening in a medium throughput fashion. This approach is generally used by academia and pharma to develop molecules that target the catalytic site of enzymes. In here we demonstrate that, contrary to the accepted view, the same approach can be used to chemically probe the surfaces used by proteins to interact, and use the outcome of the screens to systematically design protein-protein inhibitors. To prove it we first ran a bioinformatics analysis of the PDB which revealed over 400 protein complexes where the individual protein crystallises in a lattice where large portions of the interacting surfaces are free from lattice contacts and accessible to fragments during soaks. Among the tractable complexes identified, we chose two cases: the Il1β-ILR and p38α-TAB1 complexes and we run a single fragment crystal screen. The output of the screens showed that fragments tend to bind in clusters highlighting the small molecules hotspots on the surface of the target protein and often the hotspots overlap with the binding sites of the interacting proteins. Finally for one of the complexes, p38α-TAB1, we carried out a chemical exploration and improved the initial binding of the fragments bringing it into the micromolar range.
We believe we have developed a new paradigm for a low-cost rapid pipeline utilizing in-crystal fragment screening to develop PPI inhibitors.

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