Exposing the DRome ("DNA Repair-ome")

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DNA Damage Response (or DDR) proteins are prime targets in combinatorial therapies and defined cases of synthetic lethality (SL). Our focus is on discovery and development of first-in-class target-specific DDR therapeutics targeting multiple DDR proteins in the DRome ("DNA Repair-ome"), including small molecule inhibitors and targeted protein degraders dependent on fragment- and structure-based drug discovery (FBDD, SBDD). FBDD is widely used in the pharmaceutical industry to generate novel hits for developing new therapeutics. It allows a more efficient scanning of chemical space compared to high-throughput screening, which has important outcomes in early drug discovery.

Our approach, "SaXPy" or "SAR by X-ray Poses Quickly", is founded on a novel technology of using high-throughput X-ray crystallographic screening of fragment libraries as a primary screen for hit generation. Elucidation of fragment-bound crystal structures reveals locations and poses of ligands and details of protein-ligand interactions, target ligandability, and differentiation of orthosteric and discovery of potential allosteric sites, allowing rapid assessment of synthetic tractability and intellectual property. This allows for fast hit-to-lead development by analog scoping, scaffold hopping and fragment growth, potentially leading to several fold reduction in early drug discovery effort.

APE1 is implicated in numerous cancers. With our SaXPy platform, we have discovered novel hits against APE1, from which we have developed novel functional inhibitors with IC50s ~250 nM to ~10 uM in in vitro biochemical assays with robust activity in cell-based assays. POLH (or POL Eta) is implicated in cisplatin resistant ovarian cancers. We have developed a POLH hit with IC50 ~220 uM in an in vitro assay. Our hits for APE1 and POLH represent the first crystal structures of these two DDR proteins bound to small molecule ligands. FEN1 is implicated in several cancers, for which we have identified a novel FEN1 inhibitor with KD ~170 nM.

We will present these results and discuss how we can facilitate new therapeutics development applying our approach to numerous proteins, with a special focus on novel targets that have rich DDR biology and scientific validation but lack clinical inhibitors ("undruggables") as part of our effort on exploring the DRome. We will also present how our APE1 inhibitors can be translated for APE2 and LINE1, which are related DDR endonucleases.

References

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