Reactive fragments in covalent drug discovery

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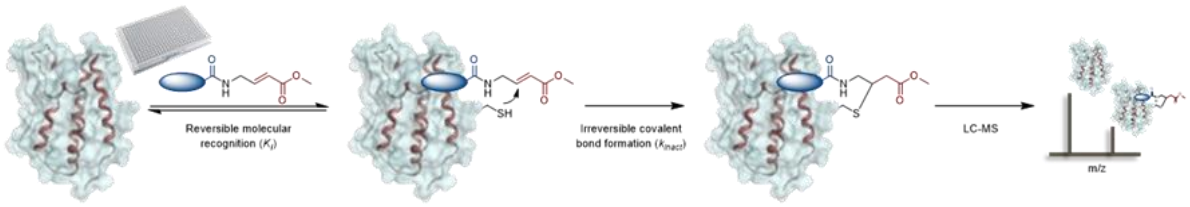
Advances in genomic analyses enable the identification of new proteins that are associated with disease.[1,2] To validate these targets, tool molecules are required to demonstrate that a ligand can have a disease-modifying effect.[3,4] Currently, as tools are reported for only a fraction of the proteome, platforms for ligand discovery are essential to leverage insights from genomic analyses. Fragment screening offers an efficient approach to explore chemical space.[5] The use of reactive fragment libraries has emerged within chemical biology as a powerful approach for the identification of fragment–protein interactions. Electrophilic and photoreactive fragments covalently modify the protein, facilitating the use of intact protein liquid chromatography-mass spectrometry (LC-MS) for rapid and robust screening of libraries (≈10^3 compounds) to identify binders.[6]



These electrophilic and photoreactive fragments (reactive fragments) offer rapid assessment of tractability and tool generation on timescales suitable for application to the large numbers of targets emerging from functional genomics analyses.[7,8] In this way, these platforms complement other binding assay approaches, such as ASMS and DELs, which are not typically compatible with fragments. Following hit identification, reactive fragments enable determination of the site of binding, providing actionable information before optimisation of secondary assays and crystallography. High-throughput chemistry can be leveraged to rapidly iterate and expand upon reactive fragment hits to explore SAR and develop series that can be progressed through the drug discovery pipeline to develop covalent modalities.

Further, screening of reactive fragment collections in cells can broadly profile the potential tractability of the proteome. Chemoproteomic analysis can deconvolute reactive fragment-protein interactions with site-specific information. In this way, it can be envisioned that ligands for previously unexplored protein targets can be identified.

1. V. Tam et al., Nat. Rev. Genet. 2019, 20, 467– 484.
2. F. M. Behan et al., Nature 2019, 568, 511– 516.
3. G. Drewes, S. Knapp, Trends Biotechnol. 2018, 36, 1275– 1286.
4. R. M. Garbaccio, E. R. Parmee, Cell Chem. Biol. 2016, 23, 10– 17.
5. M. Congreve, R. Carr, C. Murray, H. Jhoti, Drug Discovery Today 2003, 8, 876– 877.
6. E. Resnick et al., J. Am. Chem. Soc. 2019, 141, 8951– 8968.
7. Vinogradova et al, Cell, 2020, 182, 1009
8. Gygi et al, Nat Biotech, 2021, 39, 630-641