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Recent Advances in Fragment-Based Drug Design: Applications in Medicinal Chemistry

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Commentary

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ABOUT THE STUDY

Fragment-Based Drug Design (FBDD) has emerged as a powerful and innovative approach in medicinal chemistry for the discovery of small molecule therapeutics. Unlike traditional high-throughput screening methods that rely on large libraries of compounds, FBDD focuses on screening small, low molecular weight fragments that serve as starting points for drug development. These fragments typically bind to biologically relevant targets with low affinity but high ligand efficiency, providing valuable starting points for optimization into potent and selective drug candidates. FBDD offers several advantages over conventional drug discovery approaches, including the ability to explore chemical space more efficiently, the potential to target protein-protein interactions and challenging drug targets, and the opportunity to minimize compound library size and reduce screening costs. Moreover, advances in structural biology, fragment screening techniques, and computational modeling have further accelerated the application of FBDD in medicinal chemistry, enabling the discovery of novel therapeutics for a wide range of diseases. This review explores recent advances in fragment-based drug design and its applications in medicinal chemistry, highlighting key technological developments, successful case studies, and future directions in the field.

Fragment-Based Drug Design (FBDD) represents a paradigm shift in medicinal chemistry, offering a rational and efficient approach to drug discovery. Unlike traditional high-throughput screening methods, which rely on screening large libraries of compounds, FBDD focuses on the screening of small, low molecular weight fragments that bind to biologically relevant targets with low affinity but high ligand efficiency. These fragments serve as starting points for the design and optimization of potent and selective drug candidates through iterative cycles of fragment elaboration and optimization. Fragment libraries are

typically composed of diverse chemical scaffolds, allowing for the exploration of chemical space and the identification of novel binding motifs.

Moreover, FBDD offers the flexibility to target challenging drug targets, such as protein-protein interactions, allosteric sites, and protein surfaces, which may be inaccessible to larger, more complex molecules. By using structural biology techniques, such as X-ray crystallography, Nuclear Magnetic Resonance (NMR) spectroscopy, and cryo-electron microscopy, researchers can elucidate the three-dimensional structures of target proteins and characterize fragment binding modes, providing valuable insights for rational drug design. Additionally, advances in fragment screening methodologies, including Surface Plasmon Resonance (SPR), thermal shift assays, and fragment-based NMR screening, have enabled the rapid and efficient screening of fragment libraries against a wide range of drug targets. Computational modeling approaches, such as molecular docking, molecular dynamics simulations, and structure-based drug design, play an important role in fragment hit identification, lead optimization, and facilitating the rational design of potent and selective drug candidates. Successful applications of FBDD have been reported across various therapeutic areas, including oncology, infectious diseases, central nervous system disorders, and metabolic diseases. For example, the development of vemurafenib, a potent inhibitor of serine/threonine-protein kinase B-Raf (*BRAF*) for the treatment of melanoma, exemplifies the success of FBDD in drug discovery. By using FBDD principles, researchers identified a fragment hit that selectively bound to the ATP-binding pocket of *BRAF* kinase, leading to the rational design and optimization of vemurafenib as a highly selective and clinically efficacious drug for the treatment of *BRAF*-mutant melanoma. Similarly, the discovery of venetoclax, a selective inhibitor of BCL-2 for the treatment of chronic lymphocytic leukemia, highlights the utility of FBDD in targeting protein-protein interactions involved in cancer pathogenesis. By screening a fragment library against the BH3-binding groove of BCL-2, researchers identified a lead fragment that served as a starting point for the design and optimization of venetoclax, ultimately leading to its approval as a first-in-class therapy for patients with relapsed or refractory chronic lymphocytic leukemia. Recent advances in fragment-based drug design have transformed the landscape of medicinal chemistry, offering a rational and efficient approach to drug discovery. By focusing on small, low molecular weight fragments with high ligand efficiency, FBDD enables the exploration of chemical space more efficiently, the targeting of challenging drug targets, and the minimization of compound library size and screening costs. Structural biology techniques, fragment screening methodologies, and computational modeling approaches, researchers can identify and optimize fragment hits into potent and selective drug candidates with improved pharmacological properties. Successful applications of FBDD have been demonstrated across various therapeutic areas, including oncology, infectious diseases, and central nervous system disorders, leading to the discovery of clinically efficacious therapies with novel mechanisms of action. Moving forward, interdisciplinary collaborations between chemists, biologists, and clinicians will be essential for translating promising fragment hits into clinical candidates and ultimately to the bedside, where they can make a tangible impact on patient care and outcomes. With continued innovation and investment in fragment-based drug design, we can expect to see further advancements in drug discovery and the development of novel therapeutics for unmet medical needs.