Drug Design—Chemistry and Biology
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At the crossroads of drug discovery and genomic technologies, which have marked a new epoch in science and medicine for the twenty-first century, exists “drug design”—the very essence of interdisciplinary strategies focused on the generation and optimization of lead compounds that may further advance to become clinical candidates and, ultimately, marketed therapeutic agents. From synthetic small-molecules to natural products, peptides and peptidomimetics, proteins, and nucleic acids, there is no question that drug design captivates our imagination and challenges our abilities to advance potent, selective, effective, and safe-acting therapeutic agents to treat various diseases.

After several decades, drug design has successfully emerged due in part to the determination of 3-D structures of specific therapeutic targets: (i) numerous proteases, (ii) an increasing number of signal transduction proteins and other intracellular proteins (i.e., those regulating metabolism, growth, and differentiation), and (iii) a more recent and growing list of receptors and/or their extracellular ligand-binding domains. Such 3-D structures have been achieved and exploited using X-ray crystallography, NMR spectroscopy, and in silico (computer-based) molecular modeling technologies to advance drug discovery.

In this commentary, I will attempt to define contemporary drug design and those technology platforms that significantly impact drug design. In many ways, drug design is an “art” that utilizes key concepts and in silico tools (3-D molecular modeling and related computational methods, including both cheminformatics and bioinformatics), integrates both chemistry and biology, and exploits human creativity and knowledge. Perhaps that is why drug design so strongly pervades our scientific fascination and remains so intriguing for the genesis of new therapeutic agents.

Key Concepts and In Silico Tools
Drug design involves many pathways to achieve a similar endpoint—a “smarter” drug that is more potent and selective for its therapeutic target as well as one that exhibits efficacy in vivo and low toxicity. The conceptual basis for drug design may be historically traced to the pioneering work of Emil Fischer and his “lock and key” hypothesis that was formulated nearly a century ago to address the interactions between a therapeutic target (the “lock”) and its cognate ligand or drug (the “key”). Currently, drug design embraces the 3-D structure of a lead compound and exploits the use of high-powered in silico tools to computationally visualize, analyze, and probe its molecular shape, properties, and interactions with a therapeutic target. Collectively, contemporary drug design strategies integrate (i) chemical synthesis (e.g., combina-

Figure 1. Integrated technology platform to guide drug design (see text for details).
(i) editorial, medicinal, and natural product), (ii) biological screening (e.g., in vitro target, in vivo disease model, and pharmacokinetic-toxicology-metabolism screens), (iii) structural biology, (iv) in silico tools, (v) cheminformatics, and (vi) bioinformatics. As illustrated in Figure 1, such an integrated technology platform may be established to guide drug design strategies and enable the advancement of “smarter” therapeutic agents.

Essentially, all key concepts in drug design ultimately address what is known as “molecular recognition”—the fundamental basis of substrate-enzyme, protein-protein, transcription factor-DNA, hormone-receptor, and a plethora of other biomolecular interactions. Affinity, specificity, and, in many cases, catalytic processes are controlled by an ensemble of non-covalent interactions (e.g., H-bonding, hydrophobic, and ionic), as well as the intimate involvement of water and other “third parties” (e.g., mono- and divalent metal ions, pH, inorganic phosphate ion). Understanding the complexity of molecular recognition has led to key advances in drug design such as the suggestion of specific chemical modifications of a prototype lead compound to create an analog having potentially higher binding affinity and specificity to its therapeutic target. The 3-D structure of a lead compound alone or complexed with its therapeutic target makes possible a rational strategy for designing novel templates, functional group replacement, and/or the introduction of new chemical moieties to access molecular interactions that are otherwise nonexistent for the prototype lead compound.

In silico tools utilize sophisticated computationally driven programs. Molecular modeling technologies vary significantly in how they use structural information related to the lead compound and/or its therapeutic target (1,5,6,19,32,35,44,47,49,52,61,70,78). With respect to the therapeutic target, it is possible that the 3-D structure of a binding site may be exploited by molecular modeling programs to generate in silico a specific molecule (i.e., novel compound) or series of chemically similar (or different)
molecules by a strategy referred to as “de novo” drug design (5,6,36,47). Closely related to such in silico tools in drug design is an emerging methodology referred to as “virtual screening” that involves automated 3-D docking and analysis of large numbers of existing molecules to a 3-D therapeutic target (1,32,36). Finally, major achievements in 3-D structure-based drug design illustrate an iterative process for the design, synthesis, biological screening, and determination of 3-D structures (by X-ray or NMR) of lead compounds for specific therapeutic targets.

Integrating Chemistry and Biology

Beyond in silico tools, the integration of chemical synthesis and biological screening provides technologies to advance the generation and optimization of lead compounds. The last decade has witnessed extraordinary accomplishments in both chemistry and biology, highlighted by chemical diversity and chemical genomics (2,4,7,10,21,38,43,64,69,72), cheminformatics and bioinformatics (39,53), structural biology and computational proteomics (13,15,17,22,41,46,51,59,65,73), which interface with pharmacokinetics, toxicology, and metabolism (71), thus accelerating the drug discovery process. Collectively, these chemistry- and biology-driven technologies dramatically impact drug design strategies, and successful drug discovery programs exemplify these points.

Some noteworthy studies in 3-D structure-based drug design include the discovery of novel peptidomimetic and/or nonpeptide inhibitors of a various classes of proteases as represented by HIV protease (28,55,75), renin (56), factor Xa (40), thrombin (11,33), urokinase (50), rhinovirus 3C protease (57), and cathepsin K (42).

Recently, a focus on key signal transduction proteins (catalytic or noncatalytic) has shown the promise of 3-D structure-based drug design to advance effective inhibitors of protein kinases and phosphatases (14,68). Noteworthy studies include inhibitors of Abl (63), CDKs (16,18,23,34), EGFR kinase (20), Lck (79), and Src (62,66,77). The latter case, the nonreceptor tyrosine kinase Src, illustrates a multidomain signal transduction protein that includes two noncatalytic domains (SH3 and SH2) and the catalytic domain (Figure 2). As a prototype protein kinase for a rapidly evolving area of drug discovery, Src has been intensively studied from genomics to the discovery of novel lead inhibitor compounds targeting the SH3, SH2, and kinase domains (Figure 3). Such Src inhibitors illustrate varying strategies within the scope of peptidomimetic, nonpeptide, and small-molecule lead compounds (62).

In addition to signal transduction proteins, other intracellular proteins (e.g., regulatory metabolic, growth, and differentiation proteins) have provided therapeutic targets for 3-D structure-based drug design, including inhibitors of aldose reductase (31), phospholipase-A2 (45), STAT (30), Bcl-2 (29), neuroamidinase (3), and glyceraldehyde-3-phosphate dehydrogenase (9).

Finally, the more challenging—once thought to be intractable—goal of applying 3-D structure-based drug de-

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**Figure 3.** Examples of lead compounds exploiting drug design strategies focused on the discovery of novel Src inhibitors (see text for details). The above Src inhibitors have been screened in vitro and/or in vivo to identify potential therapeutic agents for the treatment of bone diseases and/or
sign to receptors is revealing success, as illustrated by very recent breakthroughs in the 3-D structure determination of the prototype G protein-coupled receptor rhodopsin (54), integrin $\alpha_{\text{b}}\beta_{3}$ receptor (76), gp130 cytokine receptor extracellular domain (12), natriuretic peptide receptor (26), T cell receptor complexed with peptide and MHC class II (27,58) and peptidomimetic inhibitors (8), FGF receptor dimer (74), complement receptor complexed with Cd3 ligand (67), and transferrin receptor ectodomain (30). This work will impact future drug design strategies and take advantage of significant past achievements that have been focused on receptor ligands (naturally occurring or synthetic lead compounds) and predictive 3-D models of receptors (e.g., G protein-coupled receptor models) (25,48). Such work on receptor-ligand interactions also overlaps with current efforts focused on intracellular protein-protein interactions (24,60) and the unraveling of the human proteome.

Exploiting Human Creativity and Knowledge

We live in a time of incredible opportunity in science and medicine that will put to the test our creativity and knowledge. To the extent that drug design exists at the crossroads of drug discovery and genomic technologies, as, hopefully, captured in this commentary, it will be imperative that we understand the power and limitations of our existing in silico tools, chemistry, and biology. As we continue to forge ahead with the inspiration to create “smarter” drugs, we inherit the tremendous legacy of accomplishments in drug design by numerous pioneering scientists.

REFERENCES


Feedback and suggestions for contributions to the “Drug Discovery and Genomic Technologies” section are welcomed by the Scientific Editor, Dr. James Ellingboe (ellingboe@BioTechniques.com).