Commentary

Peptide Revolution: Genomics, Proteomics and Therapeutics

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AN ITERATIVE REVOLUTION

Peptide science has emerged as one of the most interdisciplinary fields for basic research, and it has integrated many technologies to advance drug discovery. Indeed, the identification and optimization of peptide analogs and first- and next-generation peptidomimetic and non-peptide ligands for various therapeutic targets have provided abundant opportunities to synthetic, computational, and biophysical chemists, biochemists, cell biologists, immunologists, pharmacologists, and biomaterials and drug delivery scientists (1–33). It's almost unimaginable now to realize that, only a few decades ago, the synthesis of a relatively simple peptide was not the generally straightforward automated task that exists today. On the other hand, contemporary peptide chemistry continues to push the limits of creating synthetic peptides of complex structure or large size. In particular, iterative achievements in peptide chemistry have progressed to the use of global or local cyclizations, novel amino acids or peptidomimetic building blocks, and the synthetic mimicry of post-translational modifications (e.g., glycosylation, phosphorylation, and prenylation). Furthermore, current technology can incorporate more sophisticated conformation-inducing modifications that give rise to intermolecular complexes having protein-like structural and/or functional properties (24–40). Such achievements take into account significant improvements in synthesis (e.g., reagents and protecting groups) and purification technologies. Lastly, the development of novel homologs of peptides constructed using β -amino acids or N-substituted Gly scaffolds has expanded the toolbox of synthetic building blocks as well as our fundamental understanding of peptide 3-D structure, metabolism, and molecular recognition (31–33).

Efforts to minimize the molecular complexity of large peptides (>30 amino acids) to create novel synthetic peptidomimetics or non-peptides that mimic or block the biological properties of such peptides have met with some success, but the challenges and opportunities remain significant. "Smart" chemistry, which integrates both combinatorial libraries and 3-D structural insights from peptide ligands and/or their therapeutic targets (e.g., receptors, proteases, and signal transduction proteins), has resulted

in the discovery of promising lead compounds having varying degrees of peptide, peptidomimetic, or non-peptide chemical nature (1–4,6–18,32–44). However, there are a few examples that illustrate the successful transition of large peptides having non-contiguous amino acid sequences comprising the pharmacophore (i.e., key molecular recognition elements for therapeutic target binding and/or functional properties) to de novo designed peptidomimetics or non-peptides.

Peptide drug discovery seems relatively far advanced compared to current strategies focused on both existing and forthcoming therapeutic targets—the latter including those recently identified from the human genome (45,46) as well as the genomes of other human pathogenic organisms (e.g., bacterial, fungal, and viral). In many cases, we may not yet know what the endogenous "ligand" (peptide, protein, or other molecule) is for a genetically implicated therapeutic target. Nevertheless, an iterative genomics/proteomics/therapeutics revolution is ongoing and accelerating the process of target-ligand basic research and drug discovery (Figure 1). Such efforts will exploit peptide science in terms of molecular diversity and drug design to advance novel peptide, peptidomimetic, and non-peptide ligands. That is, peptide, peptidomimetic, and/or non-peptide ligands can be developed to fulfill the critical molecular recognition and functional properties involved with the activation, inhibition, association, or dissociation of therapeutic targets (i.e., singular or "multicomponent assemblies" as recognized for several receptors and signal transduction proteins).

Without question, the iterative revolution of peptide science will also be powerfully influenced by 3-D structure-guided drug discovery. These include a rapidly emerging worldwide "database" of X-ray and NMR structures providing high-resolution molecular maps of the therapeutic target (or surrogate target), including complexes thereof with peptides, peptidomimetics, and non-peptides (3,15–18,34,37,41,44,47,48). The Protein Data Bank is already growing at a rapid pace with new 3-D structures, high-throughput X-ray crystallization and NMR methods (49–53), and more powerful in silico drug design technologies (54–66). Further convergence of such structure-based drug design strategies with both emerging

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Figure 1. The iterative genomics/proteomics/therapeutics revolution and the potential role of peptide, peptidomimetic, and non-peptide ligands.

therapeutic targets and biological screening with synthetic libraries of chemically diverse ligands has been established (2,9,12,33,40). Without question, peptide, peptidomimetic, and non-peptide ligands will play a critical role in this evolving paradigm of drug discovery.

AN INTEGRATING REVOLUTION

Milestones in peptide, peptidomimetic, and non-peptide ligand chemistry, biology, structure, and drug design have been achieved for several superclasses of therapeutic targets—namely, receptors, proteases, and signal transduction and gene regulatory proteins. Some examples of

receptors for which key 3-D structural information and/or a novel ligand have been advanced include recent studies on G protein-coupled receptors (14,18,33,36,42,75,76), integrin, growth factor receptors (34,77–79), and cytokine and other immune-related receptors (80–83). Furthermore, some examples of proteases for which key 3-D structural information and/or a novel ligand have been advanced include recent studies on aspartyl proteases (15,18,37,48,84,85), cysteinyl proteases (86,87), serinyl proteases (88,89), and metalloproteases (90,91). Finally, some examples of signal transduction and gene regulatory proteins for which key 3-D structural information and/or a novel ligand have been advanced include recent studies on protein transferase (38,92), protein kinases (93,94), protein phosphatases (95,96), and several non-catalytic protein-protein interactions (34,41,44,97–100).

AN INSPIRED REVOLUTION

The peptide revolution of the third millennium will be extraordinary in terms of both basic research and drug discovery. It will meet the challenge with inspiration from a legacy of achievement in chemistry, biology, structural studies, and drug design that have been pioneered by prominent scientists, including many Nobel Laureates, each of whom have contributed immensely both conceptually and experimentally to the interdisciplinary knowledge of today. The world of peptide science exists within various scientific societies, including the American Peptide Society, which provide international forums to disseminate new advances in basic research and drug discovery. In this regard, the Eighteenth American Peptide Symposium (to be held in Boston on July 19–23, 2003) will provide an inspiring forum to usher in this new era in peptide science as suggested by its theme “Peptide Revolution: Genomics, Proteomics, and Therapeutics.”

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