Peptide mimetic drugs: A comment on progress and prospects

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The need for "translating" information from protein and peptide structures into the sort of small organic molecules typical of traditional pharmaceuticals has long been a high-priority goal for pharmaceutical research.

The progress made, due largely to the application of new technical approaches, was in evidence at a May 2–3 Cambridge Healthtech Institute (Newton Upper Falls, MA) conference on peptide mimetic drugs held in Washington, DC. Prominent among the new approaches is the use of computational-chemistry techniques to model peptide and protein structures as a foundation for directly designing analogs or selecting analogs from existing chemical collections, both public and private. These computational approaches have been greatly aided by improvements in structure determination, both by X-ray crystallography and by nuclear magnetic resonance. Perhaps equally useful has been the development of combinatorial-chemistry building blocks that are well suited to making initial analogs that are minimally altered from the parental peptide structure.

The number of successful efforts at this level of accomplishment has grown from around 5 to around 20 in the past 2–3 years[1,2]. In about half of these cases, further elaboration of the structure to eliminate most peptidyl character has been accomplished, yielding low-nanomolar potency compounds, often with significant selectivity for the target protein. However, two limitations in the reported work are apparent: First, the techniques work best when applied to short, linear peptides. This is a significant limitation, because the search for short, linear-peptide mimics of folded epitopes has proven substantially more difficult than predicted. Second, almost all of the successes have been in creating antagonists. The few agonist candidates being studied have not come from the strategy of directly comparing structures, but have relied, instead, on clever chemistry or screening approaches.

Each of the successes has required an infrastructure of substantial interdisciplinary sophistication. Consequently, the checklist of translation targets worth attempting five years ago has still not been exhausted. Since new targets are appearing at an exponential rate do to progress in genome mapping, the gap between what is needed and what is feasible has widened, in spite of the progress. Thus, competing approaches, ranging from direct screening to gene therapy, continue to merit significant attention.

The flood of new gene discoveries requires some kind of prioritization process, defining likely use of the encoded proteins as drug targets. Every gene product is probably important for some aspect of normal biological function. Identifying those suitable for therapeutic intervention in a particular disease state, however, is a quite different matter. Even direct involvement in the disease does not automatically qualify a target; for example, sickle-cell hemoglobin has been studied for almost 50 years without yielding a useful small-molecule drug.

The success stories of the past few years have included a substantial number of independent efforts focused on the same target (for example, HIV protease, thrombin, and RGD-containing integrin ligands). These efforts have been aided, in part, because the technologies for translating peptides into other backbones are inherently useful for translating one lead into another—and cannot be covered by standard composition of matter patents[3]. From a societal perspective, such duplication of effort is a poor use of expensive resources. The likely result of this trend will be increased reliance on trade secrets to lengthen the period of exclusivity on lead structures. Academia will thereby tend to be excluded, and progress retarded. Furthermore, small companies, which have been in the vanguard of exploring new therapeutic approaches, will also be hurt because they depend on publicizing their early-stage results to obtain financing.

How to deal with this issue remains an open question. One approach is to depend on the patenting of gene sequences as the regulating force. Patents on sequences per se have become controversial, however, in the absence of evidence documenting utility. Obtaining a particular lead structure may provide the evidence needed for obtaining field-of-use patents on proprietary targets, which would then cover an indefinite range of structures. If such patents become widely respected within the industry, the talents of the highly trained and well-equipped teams involved in peptidomimetic work will be directed to different targets, allowing the sharing of insights into the overall process to continue, based on concrete examples.

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