Prospects for peptidomimetic drug design

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Recent advances in molecular biology, biochemistry, structural chemistry, molecular pharmacology, neurochemistry, molecular endocrinology, immunology and biological screening methods have made it clear that peptides, proteins and their conjugates constitute the major classes of bioactive ligands for drug design and development. From a basic science perspective, this is a highly interesting area of research, both in terms of the ligands and of their macromolecular targets, most of which are proteins.

It has been widely suggested that peptides, peptidomimetics and various classes of nonpeptide organic molecules that might mimic the properties of peptides and proteins will provide the drugs of the future. For this to become a reality, however, some serious scientific issues and knowledge gaps will need to be overcome before systematic, *de novo* methods of peptidomimetic drug design will be practised by the medicinal chemists and others who have developed most of our drugs that are not natural products. With current accelerated strategies for rapid and sensitive biological screening, pharmacologists can continue to discover natural products that will be developed directly into useful drugs. However, the issue addressed here is the prospects for developing peptides and proteins that are not immediately therapeutically effective into useful drugs.

Several peptide and protein chemists have laid out the basic approaches that are likely to be successful in peptidomimetic design (see Refs 1–11). However, as a result of their training, many organic chemists and medicinal chemists working in drug and biotechnology companies have only modest knowledge of peptide and protein chemistry. In particular, understanding is required about the conformational, topographical and dynamic characteristics of peptides and proteins that are responsible for the many desirable biological properties they possess, and that have led nature to utilize them broadly for control and maintenance of homeostasis in complex multicellular living systems, such as humans. Many medicinal chemists ignore these critical areas, and instead primarily continue to develop nonpeptide 'leads' discovered by their colleagues in pharmacology, physiology and other life science disciplines. Of course, these approaches have been successful in drug development in the past and will continue to be so. However, they do not provide much basic scientific insight into true peptidomimetic design. Evidence is accumulating that many (most?) nonpeptide ligands discovered by screening techniques bind and interact differently with receptors/acceptors than the endogenous peptide/protein ligands for these receptors/acceptors. This is important for drug development and raises interesting and important scientific issues that will not be discussed here.

Definition of a peptidomimetic

Rather, I will turn my attention to some of the key issues that need to be addressed in *de novo* peptidomimetic design[5,6,11–19] as an alternative to screening and lead optimization. First, we address the issue of the definition of a peptidomimetic. This itself has been controversial, but as a chemist, my simple definition is that a peptidomimetic is an organic molecule, such as a peptide analogue or nonpeptide ligand, that interacts with a receptor/acceptor in a similar chemical manner as the native peptide/protein ligand to effect the same biochemical (biological) activities. In the parlance of medicinal chemistry, both peptidomimetics and native peptides/proteins should share common chemical pharmacophore elements.

Stability and selectivity issues

What does this imply in terms of design? Certain prejudices regarding peptides must be examined. One such prejudice is that peptides are unstable and subject to rapid proteolytic degradation *in vivo*. Clearly, many peptide hormones, neurotransmitters and other natural products are 'designed' by nature to be rapidly degraded, because they act as biological switches (in this regard, nonpeptide switches such as neurotransmitters also are rapidly metabolized once released). However, many peptides and proteins are stable, and remain in circulation or elsewhere intact for hours, days or even longer. Indeed, it has become possible to design peptides and peptidomimetics that are stable for many hours or even days *in vivo* (for example, see Ref. 20). Our group

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and others have developed systematic approaches to increase the stability of peptide ligands to proteolytic enzymes, while at the same time maintaining the binding properties and bioactivities of the native ligand. Discovering those structural properties that, for example, render peptides and peptidomimetics stable in circulation or for crossing membrane barriers, will continue to be a major goal of *de novo* design, and success can be readily predicted.

On the other hand, nature has 'designed' and utilizes many proteases as a way to process, control and modulate bioactive proteins and peptides. The presence of these specific proteases throughout the body offers, in principle, many opportunities for the design of prodrugs and for site-specific drug delivery, which undoubtedly will be exploited in the future.

Another critical issue that needs to be addressed is that of specificity/selectivity. Specificity is an important issue because many ligands have multiple potential sites of interaction with biological acceptors, and specificity or high selectivity for the desired interaction is necessary for high efficacy and minimal side effects/toxicity in drugs. The toxic side effects of most anticancer drugs, morphine and most immunomodulators are related to lack of selectivity. The low toxicities of peptide drugs such as calcitonin appear to be related to their high potency and selectivity. Under-

ity will be critical for future progress in peptidomimetic design.

Use of scaffolds in rational design

In many cases, the secondary structure, for example α-helix, β-sheet or β-turn, of a peptide or protein serves primarily as a template or scaffold for presentation of specific side-chain groups in three-dimensional space (shape) for molecular recognition (pharmacophore) and biological activity, such as signal transduction. The polypeptide backbone offers many advantages as a scaffold because it possesses thermodynamically and kinetically accessible pathways for transformation from one secondary structure to another, and these three-dimensional structural changes are required for many biological processes. On the other hand, scaffolds that can mimic specific peptide secondary structure have been a major goal of peptidomimetic design, and considerable success has been achieved in developing mimetics that nucleate or bias specific secondary structures[12].

Considerably less success has been obtained with the design of nonpeptide templates that place side-chain and/or backbone groups in three-dimensional space to specifically mimic topographical properties of peptides or proteins that result in potent biological activity. Prospects for success in this area, however, are good, but a more in-depth understanding of peptide shape and the ability to predict three-dimensional peptide and protein structures and their related physical–chemical properties (including dynamic properties), and then to develop nonpeptide templates that can reliably translate these three-dimensional structural properties *along with* necessary physical–chemical and dynamic properties, are required. Such rational design can best be done when the three-dimensional structure of the target macromolecules is known[19], but increasingly effective computational and other methods should aid the process considerably even when the target three-dimensional structure is not known.

Bioavailability

As in all areas of drug design, bioavailability is a major issue for peptidomimetics. Knowledge of peptide metabolism and distribution and its application to peptidomimetic drug design has been limited relative to that established for many other kinds of drugs. Nature has developed methods for distributing peptides throughout the body and considerable progress has been made in understanding the biochemical mechanisms for some of these processes. Much more knowledge will be needed, including systematic investigations of the structural basis and requirements for such processes, before they can be used in the *de novo* design of peptidomimetic drugs, especially when it is necessary for the ligands to traverse membrane barriers and to remain in circulation for extended periods. However, the development of new modes of drug delivery and prodrug design, coupled with new, more sensitive tools being developed to examine in molecular detail the physical–chemical basis for peptide and peptidomimetic distribution and metabolism will allow dramatic improvement in *de novo* peptidomimetic drug design of therapeutically effective agents.

Summary

Peptidomimetic drug design offers many exciting opportunities and challenges for the basic research scientist interested in understanding the chemical and physical principles critical for drug action, and for medicinal chemists, biochemists, molecular biologists and others to apply these principles to the next generation of drugs. Considerable success already has been achieved, and it is likely that continued research in peptide and protein structural chemistry, coupled with the development of novel scaffolds and templates that can predictably mimic the stereoelectronic, stereostructural and dynamic properties of peptides and proteins, will provide the tools for successful *de novo* peptidomimetic design.

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InfoTech Pharma: the information revolution in the pharmaceutical industry

Key IT personnel from the major companies gave presentations at IBC's inaugural industry-wide European IT conference and exhibition *InfoTech Pharma '97* at the Olympia conference centre in London. The conference was streamed into various focal areas discussing IT strategies for the different functions within the industry, including R&D, sales and marketing, regulatory affairs and manufacturing. This provided the opportunity for delegates to update themselves on those IT developments most relevant to their professional roles.

IT in pharma R&D strategy – case studies

Merck

Dr Charles Popper (Merck & Co, Inc., USA) gave a keynote address to open the first session of the conference, in which he described Merck's holistic, process-oriented approach to the development of systems for pharmaceutical R&D. A detailed and workable strategy emerged, in which the company's overall business IT infrastructure is integrated with that of R&D. Dr Marcia Zweerink (Merck & Co, Inc., USA) showed how the company has developed and implemented a web-based strategy for the internal management of information inside the corporate firewall. Comparing the profound impact of the WWW on information-sharing externally with that conducted within the company, Dr Zweerink emphasized that intranets must be well-managed (in contrast to Tim Berners-Lee's concept of the 'self-managed' WWW). Among the potential pitfalls of an unmanaged intranet are security with proprietary information, copyright violation, a highly variable quality of information and increasingly difficult navigation.

Merck included NetScape in its infrastructure in '95, with the result that '40,000 people are running the same client'. There was clearly a lot of interest in the development of the company's intranet.

Novartis

The merger between Ciba-Geigy and Sandoz to form Novartis was made logistically easier by their sites on the banks of the Rhine being adjacent, but the challenge of how to integrate their large existing IT infrastructures rationally, and according to business requirements, is perhaps not so easy. Dr Rene Ziegler (Novartis Pharma, Inc., Basel, Switzerland) described some of the problems and how they are being overcome. Dr Ziegler presented two business models that should facilitate an effective IT infrastructure for R&D in any large pharmaceutical company, but at a cost (for example, SFr 67 million to install Windows NT).

Zeneca

Dr Neil Sutchbury (Zeneca Pharmaceuticals, Alderley Edge, UK) gave an outline of Zeneca's recent IT project, 'Vista', which received board-level backing after a change of CEO in 1995, with the aim of standards-based, global information sharing within the company.

'ISDN: I Still Don't Need It' – Dr Chris Jones of CERN

Zeneca have not yet combined their several intranets, but intend to do so, providing a common interface via a single, customizable web-browser. The goal is a single international chemical/biological database, and to combine new data with historical data from legacy systems more easily. 'Old' IBM systems at plants all over the world are now managed using 'object broker request' technology from Digital, streamlining the processes of manufacture and distribution. In a 'framework-based environment', database queries are wrapped specifically for each system before processing, and this stock query system is now in place in eight countries, communicating via a TCP/IP WAN. In a few years, the company has merged eight separate database management systems into one [Oracle/ISIS(MDL)] with flexible access. Two-thirds of desktops are now linked through Windows NT servers.

As a result of the Vista project, Zeneca now have half as many application and development support staff than they had in 1992, with concurrent breakthroughs in document handling in regulatory