uterus, the endometrial tissue is destroyed. Mirivant scientists believe that this treatment will eventually lead to a reduction in the 600,000 hysterectomies that are performed each year in the USA.

Identifying new photoactive agents

Although all of these applications are currently being pursued with $SnET_2$ as the photoactive agent, Mirivant has an aggressive chemistry program to discover new photoactive agents. According to Crean, the ideal photoactive agent for use in PhotoPoint therapy would require the following properties:

- Easily manufactured, in only two or three steps from inexpensive materials ($SnET_2$ is produced in a five-step synthesis).
- Photostable, so that it is not necessary to work under darkened conditions.
- Chemically well defined.
- Easily formulated.
- Not accumulated in the skin, because the presence of sunlight causes photosensitization.

Crean also points out the utility of having a library of compounds with different maximum activation wavelengths in the 440–650 nm range. Light in this region of the spectrum penetrates human tissues to very different extents. Therefore, use of compounds with different absorption maxima would allow the activation of a photoactive agent in superficial lesions with shorter wavelength light or activation in deeper or denser tissue with light of a longer wavelength.

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Combinatorial technologies – the 'nuts and bolts'

The 3rd IBC Interactive 'Nuts and Bolts' Forum on Combinatorial Technologies was held on 23–24 October 1997 at Coronado, CA, USA. The main conference was followed by a workshop on the 'Advances in Analytical Characterization and Purification of Compounds'. The aims of the meeting were to present practical experiences in the development of chemistry for the generation of libraries and to highlight possible solutions to the problems of purification, analysis and data handling. Some of the presentations during the conference included honest accounts of the difficulties encountered during the development of synthetic protocols for library generation, particularly the development of solid-phase chemistry.

Novel linkers

The linker groups used in solid-phase chemistry usually leave a residual functional group within the final molecule, and there are increasing numbers of reports of linker groups having been developed to leave more pharmacologically acceptable moieties. Dr David Rees (Organon Laboratories, Newhouse, UK) gave an overview of linking strategies, before outlining the development of the REM linker, which produces a tertiary amine[1]. Although the initial linker allows preparation of libraries, it is unstable under certain conditions and as a result modification of the ester group to an amide and sulphone have been investigated (Figure 1)[2].

Dr Jeff Jacobs (Versicor, San Francisco, CA, USA) described the work on the benzyl bromide linker, which highlighted issues concerning the supports used in solid-phase chemistry[3]. During the development of chemistry on the benzyl bromide resin, a common impurity was observed in failed reactions because of cleavage of the linker group

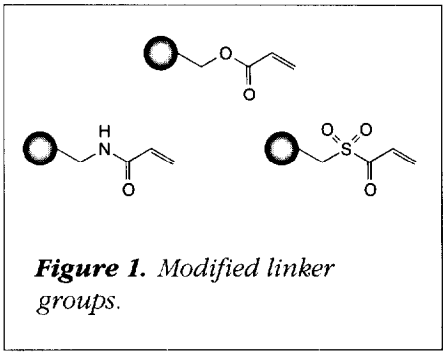

Figure 1. *Modified linker groups.*

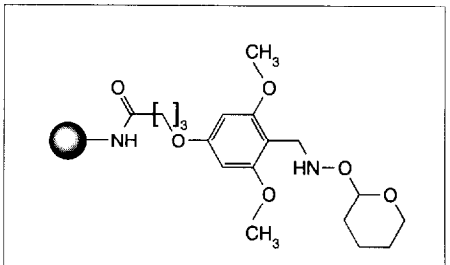

Figure 2. *Hydroxamic acid-producing linker.*

from the support. This problem could be circumvented by the use of ArgoWang™ (Argonaut Technologies, San Carlos, CA, USA), as subtle changes in the support affect the susceptibility of the linker group to cleavage. Jacobs also described a new linker for the preparation of hydroxamic acids using Tentagel S NH resin (Rapp Polymere, Tübingen, Germany) (Figure 2)[4].

The preparation of libraries based on a ketoproline by solid-phase chemistry using the Kenner Safety Catch linker[5] was described by Dr Matthew Plunkett (Arris Pharmaceutical, San Francisco, CA, USA). One of the key steps was the reductive amination of the ketone functional group (Figure 3). Although the reaction on solid phase has been well documented in the literature, optimization of the reaction conditions was necessary for the particular resin-bound substrate. Parameters that were

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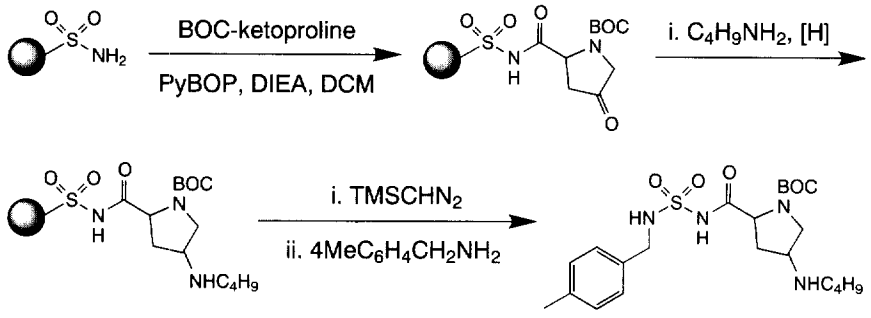

Figure 3. *Solid-phase synthesis of ketoproline libraries. BOC, tertiary butoxycarbonyl; PyBOP, benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate; DIEA, diisopropylethylamine; DCM, dichloromethane; TMSCHN$_2$, (trimethylsilyl)diazomethane.*

simultaneously evaluated were the solvent, the buffering system, the reducing agent systems and the effect of dehydrating agents.

Dr John Mayer of Amgen (Boulder, CO, USA) described the preparation of two heterocyclic systems, namely quinazolinones and benzimidazoles, using a solid-phase approach, which illustrated some of the other difficulties of library preparation. The synthesis of quinazolinones demonstrated the need to develop two alternative protocols for the first step to compensate for the limited commercial availability of monomer units. However, cleavage from the resin under two different conditions and repetition of the synthesis using the Rink linker generated complementary libraries, which capitalized on the development of the initial chemistry.

The preparation of the benzimidazoles highlighted the difficulty of producing a general protocol. Some functional groups were incompatible with the cleavage conditions, and the production of these particular compounds required the use of a different linker unit that cleaved under mild conditions. However, Mayer concluded that one should not be discouraged by the difficulties of solid-phase chemistry because it does increase efficiency and productivity. Success of a combinatorial project requires the development of a general protocol that utilizes sufficient numbers of diversity elements and an approach that is designed with enough flexibility to allow for the diversity of products.

Purification concerns

The need to obtain high-quality samples for both lead discovery and lead optimization has resulted in a more realistic portrayal of the use of purification from both solution- and solid-phase combinatorial chemistry. Several speakers illustrated that automated HPLC systems with cycle times of <15 minutes could be effectively used for serial purification. Alternative methods of purification that had increased throughput included solid–liquid extraction (SLE) and solid-phase extraction (SPE). The SLE was exemplified by Plunkett in the solution-phase synthesis of triazines using hydromatrix in a 96-well filter plate. Dr Michael Poss (Bristol-Myers Squibb, Princeton, NJ, USA) described an automated SPE system capable of purifying 3 × 96 samples per day using an eight-channel robotic system. The purification of samples necessitates the accurate quantification of the material obtained; however, no major breakthrough in this difficult area was disclosed. Specialists in the field agreed that while evaporative light scattering and nitrogen-specific detection have an important role, neither provides a generic answer.

New hardware

Several companies are devoting their resources to the development of new equipment, with and without external collaborators. During the conference, the Myriad™ system developed between the Technology Partnership and ten pharmaceutical companies was disclosed for the first time. The key elements of this system are a novel reaction vessel, a reaction head capable of maintaining an inert atmosphere and a system of positive pressure pipettes for the delivery of liquids, bead suspensions and slurries. Although two smaller variants of the system are available, the Core System (4 × 48 reactors) is available to the consortium members until mid-1999.

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In short...

Animal trials at **Novavax** (Columbia, MD, USA) and **Cistron Biotechnology** (Pine Brook, NJ, USA) have shown that microencapsulation of influenza A into Novasomes with recombinant interleukin 1β as adjuvant boosts the immune response. A more rapid and much stronger immune response was produced than inoculation with the vaccine alone, and no toxic effects were observed. The results provide insight into new ways to alleviate potential shortages of influenza vaccine supply by lowering the vaccine dose required for a patient to confer immunity.