complex. Dr Chaiken's group examined the structural elements responsible for 4-helix bundle cytokine receptor recognition sites. Using libraries of coil–coil step loop mini proteins, they can mimic the coil–coil interactions of IL-5 and are now exploring the use of these libraries to search for small molecules that may bind to the helical portion or use the constrained loop to bind to other proteins. They expect to be able to predict a structure around a hit by point mutation and then predict a scaffold for further use in small molecule discovery efforts. If ways of antagonizing classes of proteins, such as 4-helix bundles, can be found, these classes of compounds might be used for recognition of other proteins in the family.

Applications for drug discovery

Dr M.C. Pirrung (Duke University, Durham, NC, USA) opened this session and emphasized the pragmatic strategies available to medicinal chemists for lead optimization and discovery. The presentations highlighted a new line of thinking for diversity generation stressing smaller, well defined libraries of individual compounds with Dr P.L. Myers (CombiChem), Dr A. Polinsky (Alanex Corporation, San Diego, CA, USA) and Dr G.T. Wang (Abbott Laboratories, IL, USA) describing libraries of discrete compounds for lead optimization and lead generation.

Perhaps the most intriguing discussion brought the participants full circle to the opening presentations – the debate on the size of libraries required for lead generation was reopened. Dr Myers initiated the dialogue by describing a universal informer library containing less than 10,000 reasonably flexible and feature-rich molecules. Needless to say, a lively discussion ensued in which it was debated which types of descriptors and which numbers are needed to completely explore pharmacophore space.

Automation for solid-phase synthesis

In the *Solid Phase Synthesis* conference, Dr G. Grethe (MDL Information Systems, San Leandro, CA, USA) described a solid-phase organic reaction database (SPORE) that will allow searches based on using information unique to solid-phase synthesis, such as polymer-used, linker, tagging-method and substrate-linkage chemistry. This enables the chemist to make a rapid assessment of synthetic strategy in the context of a rapidly expanding set of known solid-phase reactions, instead of having to translate from solution-phase reaction conditions.

On the analytical front, Dr K. Russell (Zeneca Pharmaceuticals, Wilmington, DE, USA) described a quantitative FT–IR method for analyzing resin-bound molecules. This relies on the C–D stretch of deuterium incorporated into the molecule of interest, as exemplified by determining the number of d_9-BOC-lysines incorporated into a target peptide but, of course, is limited to cases where deuterium incorporation is feasible. Dr C.M. Tarby (CombiChem) highlighted product isolation as one of the advantages of solid- over solution-phase chemistry. However, she then described two templates (hexahydroindolyl-5,6-dicarboxylic and iminodiacetic anhydrides) offering reactivity and functionality that permit solution chemistry without this disadvantage.

Heterocycles

Dr A.M.M. Mjalli (Ontogen Corporation) reviewed the high-yielding Ugi four-component reaction, which has given an array of nitrogen heterocyclic libraries of considerable biological relevance. For example, resin-bound isonitriles can be condensed with α-ketoaldehydes in the presence of an amine and a carboxylic acid to give an intermediate diamide that can be cyclized to imidazoles. A tetrahydroisoquinoline library can be constructed from resin-bound imines having two positions of diversity in condensation with homophthalic anhydride (Dr J. Kiely, Torrey Pines Institute for Molecular Studies, San Diego, CA, USA). The resulting unmasked carboxylic acid was further derivatized by coupling with amines to generate a library of 52 subsets, with each subset having 836 compounds. Perhaps the most adventurous chemistry was the synthesis of 18–26 macrocyclic ring targets formed by intramolecular Heck coupling of resin-bound acrylamides and aryl iodides (Dr J.R. Hauske, Versicor, Marlborough, MA, USA).

In summary, whilst a significant amount of new chemistry was reported, there were rather too many 'second showings' and, with the added inconvenience and repetition of yet another combinatorial meeting the previous week, conference fatigue was clearly evident.

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Swedish scientist honoured for Turbohaler

The University of Lund has awarded an honorary doctorate to Professor Kjell Wetterlin for his role in developing the Turbohaler inhalation system. The multidose dry powder inhaler is designed to deliver anti-asthma drugs, and it is operated by the patient's own effort during inhalation. Previous inhalers were difficult to use, and often only about 10% of the dose was actually delivered. Professor Wetterlin's own daughter is asthmatic and her experience prompted his work; she also took part in the early trials.

The Bricanyl® Turbohaler, delivering terbutaline, was launched in 1987 by Astra Parmaceuticals in Sweden. It was enthusiastically received, and the system is now licensed by health authorities in 40 countries around the world. The main advantages of the inhaler over previous devices are that it is much easier to use in very young and old patients alike, it is robust and the multidose capacity means that it can take up to 200 doses of a particular drug before needing reloading and it offers a high lung deposition and consequently lower doses can be used.

David B. Jack