New Technologies in Drug Discovery

The SMR's meeting on New Technologies in Drug Discovery (21 March 1996) was the first to be held at a pharmaceutical industry site and the choice of Glaxo Wellcome's new Medicines Research Centre attracted a very wide audience of 200 attendees.The theme of the meeting was Combinatorial Chemistry and the new screening methods that are being put in place to deal with the huge increase of numbers of compounds for testing.

- The plenary speaker for the first presentation, Dr Eric Gordon, was in the process of moving from Affymax to his new position at Versicor; his replacement, Dr Dinesh Patel, gave an excellent talk on the transition at Affymax from peptide-based to non-peptidic products emanating from combinatorial techniques. He gave examples of biologically-active compounds starting with phosphonate tripeptides as thermolysin inhibitors, through to dihydropyridines as calcium antagonists; other heterocyclic templates successfully made at Affymax included pyridines and pyrimidines, and libraries made from imines as versatile reactive intermediates. Dr Patel made the point that some of the newer therapeutic targets involving extended protein - protein interactions may require modified molcules that span large distances along a receptor binding site, and that the diversity of the combinatorial products is based on a large array of building blocks.
- Dr Tony Czarnik covered the efforts at Warner-Lambert towards the synthesis of smaller numbers of compounds, made on milligram or multi- milligram scales. Dr Sheila Hobbs de Witt, in his laboratory, has developed a set of techniques and pieces of apparatus for this called Diversomer Technology; as a result a new company has been formed to sell this apparatus for making up to 50-100 compounds in parallel. Warner-Lambert have successfully used combinatorial methods for the synthesis of hydantoins, thiazolopyrollidinones, benzodiazepines, benzothiazolones and quinolones. Dr Czarnik pointed out that because most of these syntheses employed solid-phase techniques, this required a major change in organic chemists' attitudes, since tlc could not be used to follow reactions. Alternatives such as 13C NMR were most useful in this regard along with HPLC/MS and magic angle proton NMR. He foresaw that few solution phase reactions would not be applicable to solid phase techniques, except where reactivity of the resin was a problem. When so, alternative resins would need to be developed.
- Brian Main for Zeneca described the Zymate robotic apparatus that works predominantly on solution-phase combinatorial chemistry, typically synthesising 100 - 200 mg of product. Normal liquid-liquid extraction methods are compatible with this apparatus, and the application to the synthesis of some squalene synthetase inhibitors was described. Full structural details of the compounds had to be obscured for patent reasons, and this led nicely into the next session which discussed patenting and publication issues surrounding combinatorial chemistry.
- Professor Steve Ley opened with an account of the problems he had suffered in trying to publish a paper on combinatorial methods to synthesise a series of bicyclic ketones in Tetrahydron Letters. Some of the referees displayed a

fundamental lack of knowledge of combinatorial chemistry, and this paper was rejected. Fortunately, a much more enlightened attitude was evident at Synthetic Letters, a journal of which Professor Ley is editor. If these problems can beset an author whose record and renown as world class, the rest of us need help. We need referees who are aware of the issues in combinatorial chemistry; this may result from the setting up of (yet another) specialist journal.

- The patenting of combinatorial chemistry was dealt with by Roger Milnes (Napp) who pointed out that the technology itself may be difficult to patent, and its use for research purposes would be excluded from coverage under patent acts in most countries. The products from combinatorial techniques should be patentable in the same way as normal composition-of- matter patents, provided satisfactory characterisation had been acquired. However, a potential problem arose where the scope of a patent was so broad that it might inhibit subsequent applications directed towards a subset of the original application. Such selection patents were well-known in the literature, but the treatment of them differed from country to country, and could be particularly problematic in Germany. This should be borne in mind before filing a broad initial application.
- The lunch session was preceded by a tour of Glaxo Wellcome's state- of-the-art robotics facility, which featured the laboratories for combinatorial chemistry and high-throughput screening. Glaxo Wellcome are currently able to screen up to 50,000 compounds per week using their automated procedures; by the end of the year they aim to increase this to 50,000 per day. This drive is part of an attempt to increase in the number of lead compounds entering development and should be important in ensuring greater numbers leaving development as registered drugs; Glaxo Wellcome aim to be producing three new drugs per year by the end of the century.
- The afternoon session concentrated on high-throughput screening (HTS) techniques. John Major (Zeneca) emphasised that improved HTS relies critically on developing the assay technology to enable rapid through- put to be achieved. Typically this has been achieved using purified or partially purified components assayed under cell-free conditions, using biochemical methods. Miniaturisation has enabled more economic use of biological material and radiochemicals (with concomitant economy of waste removal). Current scintillation methods employ proximity assays using beads or flash plates; the requirement of at least one minute for radiation counting has led to an increased interest in fluorescence measures of biochemical activity. Homogenous time-resolved fluorescence (HTRF) is based on the change of signal produced by one fluorophor when in close proximity (eg., by binding) to another. HTRF has advantages in terms of less waste, and greater sensitivity.
- Dr Bill Timberlake reported on the work that is ongoing at Myco Pharmaceuticals (MA, US) on constructing assays suitable for high- throughput screening using recombinant techniques. One elegant method produced two yeast strains, one containing a fungal target, one containing a homologous human DNA. The strains were further engineered to display different colours when activated. Growth of the yeast in a mixed culture gave a lawn, whose colour demonstrated (a) generalised toxicity for both cell types, (b) inactivity or (c) selective anti-fungal activity. This

principle could be extended to develop fluorescent assays as opposed to colourimetric ones.

- Finally, Dr Tony Buss (Glaxo Wellcome) rounded off the day by pointing out that the structural diversity found in natural products retained a special place in drug discovery for this source of compounds as drug candidates; over half the 25 best-selling pharmaceuticals owe part of their discovery to natural products. New developments in natural product screening have made extensive use of HPLC-MS techniques for identification purposes. This had been combined with linked spectroscopic - chromatographic (LC-UV-MS) databases and automated fraction collection for isolation of active metabolites. As a final thought, the possible use of enzymatic modifications of natural product templates in a combinatorial sense suggests that combinatorial biosynthesis may become a further tool for drug discovery.

This was a highly successful meeting, with a packed audience attracted by the twin incentives of a series of quality speakers on diverse topics related to combinatorial chemistry and its sequelae, together with a chance to peek inside the architectural magnificence of Glaxo Wellcome's emporium of medicines research. The SMR's success in staging this symposium at an industrial location has led to the identification of the new SmithKline Beecham site for a meeting on epilepsy in spring 1997. Further details will be available nearer the time.