Nervous Hawaiian plants

A new, fast and effective screening technique that can screen tissue without the need to extract the chemical components first has been developed by US scientists. The method could accelerate the search for novel neuroactive compounds with pharmaceutical potential from plant species, according to the researchers.

Nature has acted as a rich source of medicines; many drugs, from aspirin to Taxol (paclitaxel), have their derivations in plants, moulds and bacteria. The rainforests and the seas have been the focus of much research. According to Professor Garry Rechnitz, a chemist at the University of Hawaii in Honolulu, Hawaiian plants in particular represent an especially rich and untapped source of potential novel pharmaceutical agents because many of the native species grow nowhere else. "Conventional analytical techniques are of limited utility", he says, "because the demonstration of the desired medicinal activity must precede the identification and isolation of the responsible agent." Rechnitz and his team in the University's Biosensor Laboratory have turned the traditional approach on its head and developed a sensor system that can screen a plant tissue sample for particular activity first and, if a positive result is obtained, allows the researchers to then isolate the compound or compounds responsible [*Anal. Chim. Acta* (1997) 337, 297]. Thus, numerous plants could be screened without the usual expense and time incurred in analysis.

To demonstrate the power of the technique, the researchers have incorporated neuronal tissue from a crayfish into a sensor probe. When the neuronal tissue is stimulated it produces a measurable signal in the probe. Tissue from the plant of interest is simply crushed into solution or, if the suspected components are insoluble in water, lipid vesicles are added to act as carriers for the hydrophobic components. Dipping the probe into the solution then either gives a signal or not depending on the presence or absence of a neuroactive component.

The team first tested the approach on various local anaesthetics, such as lidocaine, which all rewarded the scientists with a fast and reversible response in the neuronal tissue. They then turned to Hawaiian plant species, such as the awa plant (*Piper methysticum*) and the Tahitian hutu tree (*Barringtonia asiatica*), which were already known to contain neuroactive compounds; the early Polynesians used the plants in medicinal and in religious ceremonies. For instance, extracts from the awa plant were used to cause temporary paralysis to allow the medicine man to treat ailments, and preparations from the hutu tree were used to stun tidal pool fish temporarily, so that they could be gathered without toxic effects on the people eating them.

The team has identified several neuroactive compounds in this way from awa root, such as kawain and dihydromethysticin. Rechnitz points out that there is a rich folklore describing the use of plants in Hawaiian medicine and religion, and this history should allow the team to make a more educated guess as to which plants to screen first for neuroactive properties.

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Book reviews

Molecular Diversity and Combinatorial Chemistry: Libraries and Drug Discovery edited by I.M. Chaiken and K.D. Janda, American Chemical Society, 1996. $109.95 (ix + 328 pages) ISBN 0 8412 3450 7

Interest in the creation of vast numbers of chemical entities has exploded over the past five years. Whatever you call this area of science – and here the book title covers all bases – there hasn't been this much hype in chemistry since molecular modelling was claimed by some in the 1970s to be on the verge of calculating its way to magic bullets. While molecular modelling now has an established role in drug discovery, it is too soon to say precisely what impact molecular diversity technology will have, but currently its future looks bright. It is notable that this book contains chiefly methodology and descriptions of the potential and promise of the technology; presumably, if these are to be fulfilled, a similar book in five years time will be full of examples of the part molecular diversity has played in the discovery of new drug candidates.

Molecular Diversity and Combinatorial Chemistry: Libraries and Drug Discovery is published in the ACS Symposium Series, which aims at providing a snapshot in time of research in the field. This the book certainly achieves, although as it is based on presentations made at two conferences in early 1996 (CHI, 28 January–2 February 1996, Coronado, California) there is little that will be new to most practitioners of the art. However, the format does have the virtue of collecting a range of literature pertinent to the area, including some material that one might not pick up in a narrow literature search.

For example, it was interesting to see contributions covering molecular diversity derived from 'natural' sources given space in the book, as natural products are sometimes thought to be 'in competition' with purely synthetic molecules. In a chapter on gene transfer, Thompson puts forward a powerful case that only 1% of microbes and plants have so far been used as natural sources of molecular diversity because only that small proportion can be cultured or cultivated. The chapter suggests that using molecular biology techniques to extract genes from these organisms, to clone them into appropriate expression systems, should allow us to access a large part of the remaining 99%, delivering a richness of chemical structures as yet untapped. A complementary

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approach is described in the chapter by Khmelnitsky and coworkers, which covers the generation of solution-phase libraries of organic molecules using enzymatic reactions and microbial transformations of existing leads.

As one would expect, the majority of the book covers the methodologies of solid- and solution-phase combinatorial chemistry: synthetic methodology, analysis, automation systems and design/planning software. I particularly enjoyed the chapter by Russell and coworkers covering the use of FTIR spectroscopy in the analysis of resin-bound compounds. Part of this work involves the use of deuterium labelling; the C–D stretch frequency, which is well separated from other vibrations, can give an accurate picture of the progress of solid-phase reactions.

Most of the chapters are well written and nicely structured, the synthetic chapters in particular; perhaps they benefit from the greater freedom of style allowed in a book compared with many journals. Given that each chapter has different authors, there is surprisingly little overlap between them, save the odd introductory paragraph or two – a compliment to the editors.

Although not a complete 'Who's Who' of molecular diversity, many of the major players in the field have contributed chapters to this book. To those with a little knowledge of the field this nicely presented book offers an appealing way to gather more information. However, for understandable reasons, books of symposia, and this one is no exception, do not offer much in the way of advice about the strengths or weaknesses of different approaches. For this, the only substitute for personal experience is to talk to others – perhaps this book could be your airport lounge companion *en route* to the next conference.

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Outsourcing in the Pharmaceutical Industry by Patrick Taaffe, Financial Times Pharmaceuticals and Healthcare Publishing, 1996. £325.00 (100 pages) ISBN 1 85334 613 6

Timely and informative, this report represents one of the first dedicated publications on the topic of outsourcing, although presumably it will not be long before others reach the booksellers' catalogues. The report stretches across the myriad operations involved in pharmaceuticals, including well-delineated sections dealing with R&D, sales and marketing, and manufacturing and distribution. The layout of the report is well set out in the 'Contents' section, but this reader would have found an index of great help.

Despite the rapidly increasing interest in outsourcing, the author makes it clear that it is not new to the pharmaceutical industry. In the area of distribution in particular, outsourcing has operated in one form or another for many years, because of the fragmented individual systems operating in different countries. The incursion of this strategy into other areas of pharmaceutical operations is clearly due to the pressures from pricing, regulatory authorities and from increasingly difficult therapeutic areas for which a medical need remains. Taaffe mentions that these pressures have forced an inward examination within large pharmaceutical companies on what is their core expertise. This, he says, has often been identified as 'Discovery and Distribution', or 'D & D'. However, this analysis is clearly at odds with the historic prevalence of outsourced distribution networks, and with the tremendous increase in innovation as a target for outsourcing to the biotechnology and academic sectors in this decade.

Perhaps Taaffe attempts too much, given the differing reasons for the outsourcing that has taken place in the different areas of the pharmaceutical industry, and the result is a potpourri of generalities with no clear messages that apply to all areas. For instance, there is clearly a great difference in the strategic input that can be expected from a technological expert in genomics, compared with one who provides a complete research programme, or even an in-licensed product at the end of Phase I. These providers are lumped into the category of biotechnology, but the pharmaceutical business analyst, for whom this report is ideally suited, will remain confused by the lack of separation. Although published in late 1996, the rapid change in this area means that some remarks have been overtaken by events; readers will note that this report was written before the merger of Elan and Athena Neurosciences, and the name change of Corning to Covance.

These criticisms aside, the report is to be commended for its coverage. Few commentators can provide such a broad overview of the operations of the industry. In its conclusion, the report offers comparisons with the motor industry, and the extensive outsourcing that that industry has had to undergo as a result of the pressures it has suffered in the past decade. The role of the car component supplier is to be compared with that of the outsourcing provider, namely an expert who may supply multiple clients. The 'just-in-time' philosophy has brought about a minimization of fixed costs in much the same way that outsourced clinical trials offer a conversion to variable costs in the pharmaceutical industry. It is the roller coaster cycle of demand for resources that is one of the major drivers for the outsourcing of clinical trials or manufacturing. The utilization of 85–90% of capital manufacturing resource in the motor industry compares favourably with the figure of 60% in pharmaceuticals, and suggests that there is fat still to be trimmed from pharmaceutical manufacturing operations.

This report is written for business analysts, but some of the messages are of relevance to a wider audience. It is therefore unfortunate that, at a price of £325, it seems unlikely that it will find its way onto bookshelves of those with less than a dedicated and specific interest.

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