Bioprospecting for leads

The international meeting entitled *Phytochemistry Diversity: a Source of New Industrial Products* was held in April at Sussex University, Brighton, UK, attracted a range of participants with an interest in deriving novel compounds from plants to act as leads for new products with utility in the pharmaceutical, agrochemical and cosmetic industries.

While highlighting the application of the recent technological developments in the areas of high-throughput screening (HTS) and robotics, coupled with the role of ethnobotanical as well as random selection of plants for study, the principal speakers addressed topics such as sustainable supplies, dereplication, intellectual property and royalty rights, and technology transfer from developed countries to developing countries. An apparent fear of some participants was a general decrease in interest in natural products as a source of new and novel structures, especially with the 'spectre' of combinatorial chemistry now dominating many approaches to lead identification and development.

Dr G.M. Cragg (National Cancer Institute, Frederick, USA) began the proceedings with a realistic assessment of the NCI's experience and achievements in screening natural products of plant, microbial and marine origin for anticancer and anti-HIV activity over the past 35 years. In some ways, the NCI's efforts could be described as those of 'the non-profit drug company'. Interest was cyclical – high in the 1960s and 70s, down in the early to mid 80s, up in late 80s and early 90s – but now? The best way (and perhaps only way) to ensure a future with a committed interest in plant natural products will be the identification of new chemical entities and associated products in the next few years. This boost is needed in spite of recent successes with taxol and the camptothecin derivative, topotecan, which were developed in collaboration with Bristol-Myers Squibb and SmithKline Beecham, respectively.

HTS technology

Dr M. O'Neill (GlaxoWellcome Research and Development Ltd., Stevenage, UK) reminded the audience that half of the world's 25 best-selling medicines were derived from natural products. In conjunction with Dr I. Chicarelli-Robinson (Xenova Ltd., Slough, UK) and Dr P. Kulanthaivel (Lilly Research Laboratories, Indianapolis, USA), Dr O'Neill described various complementary strategies in place to apply HTS to natural products, and in particular plant extracts, emphasizing the complementary nature of the chemotypes highlighted relative to those derived from microorganisms and sample banks. These presentations were timely illustrations of the increasing power of the HTS technology necessary to cope with escalating assay numbers from natural sources as well as from combinatorial and sample libraries.

The Shaman strategy

Dr A.I. Gray (University of Strathclyde, Glasgow, UK) recounted his experiences in Colombia following close interaction with local peoples to explore new plant sources and hence novel compounds. A similar approach to drug discovery, though one based on more focused ethnobotanical and ethnomedical field research, was outlined by Dr R. Cooper (Shaman Pharmaceuticals, San Francisco, USA) with a description of the Shaman strategy in seeking new leads with utility against diabetes. In contrast to classical drug discovery procedures via HTS, the process of developing relationships with local healers and testing extracts from plants with a reported effect in man directly in relevant mouse models has resulted in relatively high hit rate of orally active compounds. Hopefully, these compounds would have a reduced chance at failing on toxicological grounds if developed.

The ethnobotanical and traditional healing route to the identification of novel phytochemicals was further developed by Dr M.I. Choudhary (HEJ Research Institute of Chemistry, Karachi, Pakistan) and Dr HRH Princess Chulabhorn (Chulabhorn Research Institute, Bangkok, Thailand) who reviewed some of the current studies, resources and opportunities available in their respective countries to prospect for natural products. Efforts to protect and further the use of the Chinese medicinal plant *Ginkgo biloba*, including the protection of old plants, development of culture practices, as well as the detailed study of constituents, were outlined by Dr Pang Zijie (Institute of Botany, Nanjing, China).

Contrasting institute- and industry-based research

An interesting comparison of the approaches of a research institute and those of an industry-based research effort to identify novel insecticides from plants was made by Dr B. Kambay (International Agricultural Research Centre, Rothamsted, Harpenden, UK). In general, industry targets a narrow range of commercially important species, invariably using high-throughput *in vitro* screens followed by appropriate *in vivo* models. This contrasts with the Rothamsted strategy of tackling a wide range of target pest and model species, initially through low-throughput *in vivo* contact assays. Plant collection is chiefly on an ethnobotanical foundation, although random, chemotaxonomic, and geographical approaches are applied as necessary. A recent success, especially against strains of tobacco white fly, aphids and spider mites, has been the identification of a series of hydroxynaphthaquinone derivatives (BTG 504 and BTG 505) derived from *Calceolaria andina*, which occurs in Chile. Of high significance was the fact that these compounds lacked cross resistance. An extensive synthetic analogue programme coupled with formulation development shows promise in providing novel insecticides with good penetration properties and at a reasonable cost.

The present status of the development of topotecan, the anticancer agent from the Chinese tree *Camptotheca acuminata* was summarized by Dr B.K. Carté (SmithKline Beecham, King of Prussia, PA, USA). A detailed account of the development of taxol, from its first discovery in

1964, to its current position as a major new anticancer agent, was presented by Ms M.D. DeFuria (Bristol-Myers Squibb, Princeton, USA). As taxol occurs in the bark of the Pacific yew (*Taxus brevifolia*; a small slow-growing tree), the collection programme that originally provided the major source of material was strictly controlled. Extensive alternative sourcing initiatives to yield paclitaxol by direct isolation have involved setting up yew plantations (to harvest clippings as a renewable biomass), total synthesis, a fungus and more recently plant cell culture. Currently, stocks of taxol and taxol precursors, and hence the semisynthetic therapeutic candidate taxotere, can be prepared via cell culture of the European or Himalayan yew (*Taxus baccata*).

Common plants

The assumption that to find novel biologically active phytochemicals it is necessary to explore tropical species was destroyed by Dr R.J. Nash (Institute of Grassland and Environmental Research, Aberystwyth, UK) who gave examples of the large numbers of alkaloids to be found in common plants. The compounds described were polyhydroxylated-nor-tropanes (calystegines) and nitrogen analogues of mono- and disaccharides, which are very potent inhibitors of glycosidase enzymes and are obtainable from plants such as potato, aubergine, deadly nightshade, hyacinths, bluebells and various grasses.

Cosmetics industry

Dr J.E. Anderson (Estée Lauder, Melville, USA) outlined how the cosmetics industry utilizes plant natural products and the similarity of many of their targets to those pursued by the pharmaceutical industry. Agents are required to soothe, smooth, moisturize, protect and repair skin, and this involves searching for anti-irritants, anti-allergens, ultra-violet screens and modulators of collagen and elastin. This research is performed using mechanism- and receptor-based assays that are closely related to those used to yield new pharmaceutical agents. The refined components of plants such as centella, licorice, rosemary, horseradish and green tea form the basis of many modern skin care products.

Cell culture technology

Procedures to expand and trigger phytochemical expression with *in vitro* plant cell culture technology as alternative lead generation strategies were described by Dr A.M. Stafford (Phytera Ltd., Sheffield, UK). An aspect of the cell culture approach to new compounds is that it is highly sustainable and it is unnecessary to return to the source for material following the initial collection of seed or other plant part. Gene repression, precursor feeding and metabolic inhibitors were additional pressures that could be applied to cell cultures resulting in extensive, readily available extracts and culture libraries for screening. The potential of biotransformation as a route into new compounds with phytochemicals as the initial substrate was illustrated by Dr J. Sime (Zylepsis Ltd., Ashford, UK) and Dr J.R. Hanson (University of Sussex, Brighton, UK). Microbial transformation could provide derivatives only accessible by extensive chemical manipulation; such compounds are of value in developing leads and have potential in identifying toxicologically important metabolites.

UN Convention

Dr K. Beese (Institute for Prospective Technological Studies, Seville, Spain), Mr M.F. Cantley (OECD, Paris, France) and Ms K. ten Kate (Environmental Strategies [Europe] Ltd., London, UK) reviewed the UN Convention on Biological Diversity and its implications and challenges for economic bioprospecting. They emphasized that collaborative exploitation of the genetic resources of countries and communities with phytochemical biodiversity should ensure conservation, sustainable development, provide adequate benefit sharing and technology transfer, coupled with realistic attitudes to intellectual property rights and confidentiality.

The publication of the proceedings by the Royal Society of Chemistry will provide a timely update and record of current approaches to accessing phytochemical diversity for leads to new medicines, agrochemicals and cosmetics.

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