Pfizer natural products collaboration

Drug discovery from natural products is alive and well at Pfizer (Groton, Connecticut, USA). Pfizer recently announced collaborative research agreements with Drs R. Hill and F. Robb (University of Maryland Biotechnology Institute, Baltimore, MD, USA) and with Dr N. Wainwright (Marine Biology Laboratory, Woods Hole, MA, USA). This will be a collaborative attempt to discover new bioactive chemicals from marine microorganisms. Pfizer's chemists will use the novel chemicals as lead structures to generate new drug candidates. Dr Hill studies actinomycetes from Hawaiian coastal waters, and Dr Robb conducts research on hyperthermophiles – organisms living in the extremely hot water around deep hydrothermal vents. Dr Wainwright studies a highly diverse group of microorganisms from geographically distinct regions of the world. In return for extracts of marine cultures, Pfizer is providing research support to both institutions.

Dr M. Fletcher, Director of the University of Maryland Biotechnology Institute's Center of Marine Biotechnology, believes that the world's oceans offer enormous untapped potential for the discovery of novel bioactive molecules. "The oceans harbor more than 80% of all life on earth," asserted Dr Fletcher, "but less than 1% of marine species have been screened for organisms that contain or excrete novel compounds". Some of the first microbial isolates to be provided were a collection of unique actinomycetes collected by Dr Hill from near shore sediments in Hawaii. According to Dr Hill, "terrestrial actinomycetes are a rich source of compounds with pharmaceutical activity, and there is every reason to believe that the marine organisms will be as good or better". He says only 1% of the actinomycetes present in the water column are believed to have been isolated, and that the actinomycetes so far isolated from marine sediments constitute a small proportion of the total.

Dr Robb is preparing a collection of hyperthermophile cultures that were collected from Yellowstone National Park, the Kamchatka Peninsula of Russia, and Mono Lake in Northern California. Dr Wainwright is providing a diverse group of microorganisms, including some that were isolated from the surface of macroorganisms.

Pfizer will test extracts from the microbes in different high-throughput screening assays designed to identify new antibiotic, antiviral, antiinflammatory and anticancer agents. The results of the tests will be provided to the microbiologists at Maryland and Woods Hole. Dr Wainwright believes that the information provided by Pfizer will provide important clues to understanding the biology of the organisms. The new Pfizer program complements several other ongoing collaborative natural products projects, including collaborations with the New York Botanical Gardens, the Chinese Academy of Traditional Chinese Medicine in Shanghai and the Shanghai Institute of Pharmaceutical Industry, the Sichuan Industrial Institute of Antibiotics, and the Tottori Mycological Institute at the Kinoko Research Center Foundation in Japan.

Robert W. Wallace

People

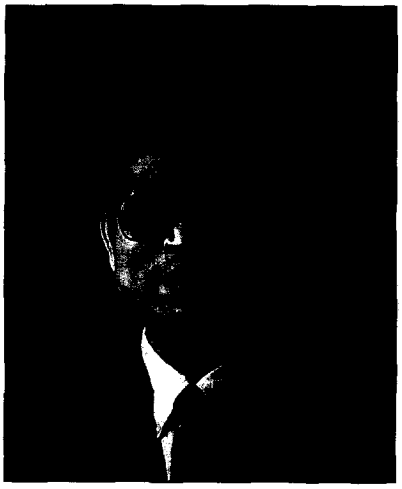
The 'Discoverer's Award' honouring outstanding contributions by scientists in the pharmaceutical industry, presented annually by the Pharmaceutical Research and Manufacturers of America (PhRMA), has been awarded this year to Dr Fu-Kien Lin, Director of Biomedical Sciences at Amgen, Thousand Oaks, CA, USA. He led the team that discovered and developed epoetin alfa, the recombinant human erythropoietin. Dr Lin obtained his BS and MS degrees in Taiwan and completed a PhD in plant pathology at the University of Illinois in 1971. He has worked in nucleic acid biochemistry and genetic engineering at Louisiana State University and at the Medical University of South Carolina, and became one of Amgen's first members of staff in 1981.

A severe consequence of end-stage renal disease is anaemia caused by failure to produce enough erythropoietin. Dr Lin and his group cloned the gene that produces erythropoietin and used this to produce the recombinant form, which is marketed by Amgen as Epogen. The drug was granted FDA approval in 1989 and has been very effective in restoring the red cell count to nearly normal levels in anaemic patients with end-stage renal failure.

Dr Colin Pouton of the School of Pharmacy and Pharmacology, University of Bath, UK, was among the 1995 Pfizer Award winners for his work in designing oligomers and polymers to enhance the oral absorption of hydrophobic drugs. Much of Dr Pouton's research has involved the application of cell culture and DNA technology to pharmaceutical problems, particularly the delivery of peptide and protein drugs, oligonucleotides and gene expression vectors to their appropriate sites of action. He was recently awarded a L106K MRC grant to develop selective agonists and antagonists for CNS melanocortin receptors.

His current work in gene delivery entails problems similar to those encountered with the delivery of peptides and proteins. However, receptor-mediated delivery is a much more realistic prospect because fewer molecules need to be delivered to a particular site. His group are particularly interested in tissue-specific promoters to obtain selective expression of genes for the treatment of melanoma.

A former President of the Committee for Proprietary Medicinal Products, Prof. Duilio Poggiolini, has just completed the manuscript of a book to be published soon. Provisionally entitled *Drug Policy in Italy from the 1970s to the 1990s*, it may not sound terribly exciting, but it should be



Dr Fu-Kien Lin, Director of Biomedical Sciences at Amgen, California, winner of the 1995 PhRMA 'Discoverer's Award'.

remembered that Prof. Poggiolini disappeared in the summer of 1993 when called for questioning by Italian magistrates in connection with the drug corruption scandal that is still being investigated in Italy. He was subsequently traced to a Swiss clinic and extradited. When police searched a house belonging to his wife in September 1993, they found a safe containing gold, currency, paintings and other valuables together with details of Swiss and Italian bank accounts totalling more than US$15 million.

The charges against 67 defendants, including Prof. Poggiolini, relate to corruption and the illegal financing of political parties, including payments by pharmaceutical companies in return for quicker review of price increases and approval dossiers. The trial will take place in early 1996.

Speaking from prison, Prof. Poggiolini has implicated a number of leading pharmaceutical company executives, health officials and Vatican staff, claiming that he was an innocent victim. Those who have seen the manuscript have said that it contains a vigorous defence of his activities at the Ministry of Health and an attempt to rebut the charges laid against him. Prof. Poggiolini has always claimed that he managed to accumulate his fortune by prudent saving with the ultimate intention of setting up a research foundation on his retirement.

David B. Jack

Progesterone and myelin synthesis

Progesterone plays a critical role in preparing the uterus to accept a fertilized ovum and in the maintenance and development of the fetus. It is an active component of birth control pills, and the progesterone receptor is the target for a 'morning after' contraceptive pill, RU-486. A French research group now reports that progesterone leads a double life. They believe it has a totally different, and so far poorly understood, role in the nervous system of both men and women as a regulator of the synthesis of myelin, the sheath that surrounds and insulates nerve cell axons.

The group, headed by Prof. Etienne-Emile Baulieu, Director of INSERM Unit 33 at the University of Paris and developer of RU-486, observed that progesterone is present in high concentrations in sciatic nerve – in mice, some fivefold to tenfold the levels present in plasma.

Moreover, levels of progesterone in mouse sciatic nerve remain high even after castration and adrenalectomy, which causes disappearance of progesterone in the plasma. Schwann cells appear to be the source of the progesterone in nerve cell axons; cultured Schwann cells synthesize progesterone from radiolabelled precursors. The researchers found that oligodendrocytes also synthesize progesterone. Baulieu and coworkers reported their findings at the Fifth International Congress on Hormones and Cancer, held in September in Quebec City, Canada, and in *Science* (1995) 268, 1500–1503.

Schwann cells and oligodendrocytes both produce myelin; Schwann cells in the peripheral nervous system and oligodendrocytes in the central nervous system. According to Prof. Baulieu, it was natural to guess that progesterone would influence myelin biosynthesis. To test the idea, the researchers first destroyed a section of the sciatic nerve in male rats by freezing. Then they measured progesterone levels in the regenerating nerve and studied the effects of progesterone inhibitors and exogenous progesterone on myelin synthesis. They found that there is an increase in endogenous progesterone in the nerve during regeneration, and that the progesterone inhibitors trilostane and RU-486 reduced the layer of myelin in regenerated axons. When the researchers added progesterone simultaneously with trilostane, the thickness of myelin was much greater than in the control tissues.

At the Quebec congress, Prof. Baulieu's group reported that progesterone induces the *Krox20* gene in nerve cells. This gene codes for a transcription factor essential for nerve cell myelination. They also reported that progesterone triggers a rapid influx of Ca^{2+} into the Schwann cells and the activation of mitogen-activated protein kinase.

According to Greg Lemke, Professor of Neurobiology at the Salk Institute in La Jolla, California, "this work nails down a role for progesterone in development independent of its role as a sex steroid and may be of clinical importance". Lemke considers the inhibitor experiments to be very convincing, especially the significantly increased level of myelination observed when progesterone was added with the inhibitors.

Work is currently underway in Prof. Baulieu's laboratory to identify derivatives of progesterone that can reach the nerve and stimulate myelination without exerting a sex hormone action, according to co-author Dr Yvette Akwa (Scripps Research Institute, La Jolla, CA, USA). Such compounds would have obvious applications in testing the effects of progesterone on myelination in animal models of multiple sclerosis and other demyelinating diseases.

Robert W. Wallace