A pharmaceutical *Braveheart* – battle lines are drawn

Two of the world's major pharmaceutical companies, Pfizer and GlaxoWellcome, are squaring up for a fight. For those who have seen the film *Braveheart*, Pfizer can be regarded as the Scots, a smaller army but eager to engage the enemy, while numerically superior GlaxoWellcome are confident of victory.

At the beginning of November last year, 200 financial analysts assembled at the new GlaxoWellcome Research Centre at Stevenage for a briefing on the final stages of the integration of the two UK giants that has made the new organization the largest drug company in the world. The summer of 1995 was a very difficult period for the company; every R&D project was under close scrutiny and employees felt insecure. Although the total number of R&D staff has been reduced from 11,500 to 9,700 worldwide, the remaining researchers are assured of a bright future.

In all, 93 projects are to be continued (Table 1), spread across most major therapeutic areas, and although most of the senior management consists of former Glaxo staff, many Wellcome projects are to receive continued funding. In addition, R&D spending is set to remain steady at about £1.2 billion a year for the immediate future. The company plans to invest heavily in robotics and extend its existing automated procedures. According to UK Research Director, Dr Alan Baxter, the present automated system for screening new molecules for biological activity handles 50,000 samples per week and this is set to rise to 50,000 per day during 1996. The company also plans to allocate less money to internal R&D and increase external collaboration with university departments and small biotechnology companies, especially in the USA. Its ultimate goal is an ambitious one, even for such a major company; the company aims to bring three important new drugs to the market each year, starting in 2000.

Table 1. GlaxoWellcome research projects

Therapeutic area	No. projects
Respiratory	22
Antiviral	12
CNS	18
Oncology	11
Cardiovascular	10
Gastrointestinal/metabolic	13
Anti-infective/immunologic	7

Less than two weeks before this announcement, Pfizer's Vice President for R&D, Dr John Niblack, addressed analysts in New York to inform them that Pfizer was going to attempt "something that no other pharmaceutical company has ever really brought off before". This would be the launch of multiple waves of new products. Within the next 2 years, the company will seek approval for five new chemical entities in the USA and elsewhere. These new compounds are: the acetylcholinesterase inhibitor, E-2020, for Alzheimer's disease; the quinolone antibiotic, trovafloxacin; the class III antiarrhythmic, dofetilide; ziprasidone for schizophrenia and sildenafil for erectile dysfunction. Another ten new chemical entities are also at an advanced stage of development and include agents for the treatment of diabetic complications, congestive heart failure, depression, breast cancer, migraine, fungal infections and sepsis.

It is never wise to take historical analogies too far, and although Sir Richard Sykes of GlaxoWellcome makes a convincing Edward Longshanks, Dr John Niblack will not be very keen to play William Wallace, even if his side did win in the end.

David B. Jack

Combinatorial biology

Marine organisms have proven to be an extremely rich repository of bioactive compounds and a source of continuing headaches when it comes down to the practical aspects of drug discovery. Frequently, bioactive compounds are too complex for laboratory synthesis, the marine organism cannot be collected in large quantities, or the organism refuses to grow under laboratory conditions, thereby blocking the acquisition of sufficient material for study.

Now a small company in San Diego, ChromaXome, Inc., has accomplished the transfer of the entire biosynthetic pathway of various secondary metabolites from marine microorganisms into commercial microbes, such as *Escherichia coli*. This will enable the production of large quantities of bioactive chemicals that would otherwise be prohibitively scarce. In addition, the company's scientists have succeeded in mixing and matching synthetic pathways from different microbes to produce totally novel 'natural products'. They call the new technology 'combinatorial biology'.

Just as combinatorial chemistry overturned old paradigms for the synthesis of chemicals for drug discovery, combinatorial biology may revolutionize the pharmacognosy field. In initial studies, ChromaXome focused on the transfer of anti-infective compounds and succeeded in transferring the biosynthetic pathway for the production of various polyketides, a chemical class that has provided a rich source of bioactive compounds in the past. Currently, ChromaXome is involved in a major collaboration to use combinatorial biology to generate novel compounds from the well-characterized

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microbial library belonging to Bristol-Myers Squibb.

The new technology is possible, according to Dr Michael Dickman, President of ChromaXome, because of the development of very large vectors for transferring foreign DNA into bacteria. ChromaXome uses standard cosmids to transfer up to 30 to 40 kb of DNA and newly developed bacterial artificial chromosomes to transfer up to 300 to 400 kb of DNA. Assuming that, on average, an enzyme can be encoded in 1 kb of DNA, the genetic information for 30 to 400 enzymes can be transferred at one time into the commercial vector.

In many combinatorial experiments, the DNA from up to 100 different organisms is combined and then randomly transferred into the commercial microbe. To ensure that 90% of the total DNA is represented in the library requires the production of 100–200 million distinct clones. Approximately 1% of the clones produce compounds through pathways transferred from the marine organisms. Screening such a large number of clones is a major challenge, which ChromoXome has met with novel screening assays that use fluorescence-activated cell sorting.

ChromaXome is seeking to establish agreements with several other companies who have expressed an interest in the technology. According to Dickman, "ChromaXome intends to remain small, seek collaborative relationships with major pharmaceutical companies and focus on what we do best – the use of our novel technologies to discover new drug leads. We do not intend to get involved in drug development".

Robert W. Wallace

New Alzheimer's model from Japan

Efforts to discover the underlying mechanism in Alzheimer's disease have been hampered by the lack of a suitable animal model. Attempts have been made to mimic Alzheimer's disease by producing brain lesions surgically or chemically, feeding animals on a choline-deficient diet and using aged animals. However, only humans and chimpanzees are known to suffer from the condition naturally, and the models have achieved very limited success. Now a group led by Professor Toshitaka Nabeshima of the Department of Neuropsychopharmacology at the Nagoya University School of Medicine, Japan, have produced a new model, which appears to be more effective and to mimic the real condition more accurately. They have induced memory impairment and neural dysfunction in rats by infusing β-amyloid protein, the core of the plaques that are so characteristic of the disease, into the cerebral ventricles. The protein is administered by mini-osmotic pump continuously for a period of 2 weeks at doses of 3, 30 and 300 pmol per day.

The performance of the treated animals in standard behavioural tests was impaired, and there was an associated reduction in choline acetyltransferase activity in the frontal cortex and hippocampus. Oral administration of agents known to be potent *in vitro* stimulators of nerve growth factor (NGF) synthesis, such as propentofylline, idebenone and trimethylquinone, produced significant improvements in the behavioural deficits, increased levels of NGF protein and mRNA, and stimulated choline acetyltransferase activity.

The results support the hypothesis that β-amyloid protein deposition in the brain is linked to impaired learning and cholinergic neuronal deterioration. The model should therefore be suitable for rapid screening of the many novel agents in development as potential treatments for this disease.

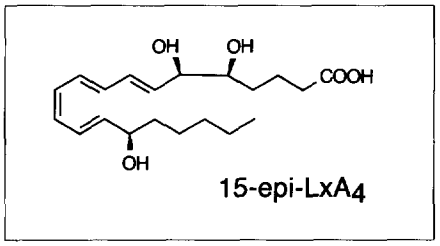
David B. Jack

Better use aspirin

Researchers in the USA have discovered a new mechanism that could help explain some of the pharmacological properties of aspirin (acetylsalicylic acid) that have so far been poorly understood. This may ultimately lead to improved treatment for inflammation and arthritis based on aspirin but without its side-effects, notably gastrointestinal inflammation.

Dr Joan Clària and Professor Charles Serhan at the Department of Medicine, Brigham and Women's Hospital and Harvard Medical School (Boston, MA, USA) have found that aspirin triggers the release of a new group of eicosanoids by a previously unknown biosynthetic pathway [Clària, J. and Serhan, C.N. (1995) *Proc. Natl Acad. Sci. USA* 92, 9475–9479].

Other researchers have demonstrated that the biosynthesis of eicosanoids is influenced by transcellular and cell–cell interactions. Such interactions can amplify and control the release of new mediators in the inflammatory response.



15-epi-LxA$_4$

"We are interested in elucidating the natural 'stop signals' of the inflammatory response – namely chemical mediators that naturally downregulate leukocyte functions" says Serhan. The team were looking at the effects of aspirin on the interaction between white blood cells and blood vessel endothelial cells. They found that they could isolate four members of a new group of compounds belonging to a lipoxin sub-class from their culture. Further biosynthetic studies with human leukocyte and endothelial cells in culture revealed that the production of these lipoxin subtypes resulted from the

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