Lipid-based therapeutics: a different approach

The expansion in the number of available targets generated by genome and proteome sciences, combined with the rapid advances in other discovery technologies, mean that the major players will remain focused on small-molecule drug discovery programmes. But is targeting drugs that interfere with protein action too narrow an approach?

Wrong philosophy?

The problem may be one of basic philosophy, according to Dr David Horrobin, CEO of Scotia Pharmaceuticals (Stirling, UK) (Figure 1), who estimates that current drug discovery strategies are aiming at less than half of the potential targets. With the exception of antimicrobial agents, most small-molecule drugs block receptor function or enzyme activity, whereas really successful agonist or activating drugs remain relatively scarce. Effective therapeutic agents in the latter category tend to replace systemically circulating hormones, or be applied topically (such as β-agonists for asthma) or used only for short time periods (such as in prevention of platelet aggregation during heart surgery). Existing methods of drug delivery cannot adequately imitate the local action of locally produced natural compounds nor can they imitate activity that is dependent on rapid appearance and disappearance. In addition, overemphasis on single proteins and assumptions that protein structures *in vitro* (in aqueous solution or as crystals) represent *in vivo* structures (many membrane proteins are at least partially in a hydrophobic environment) ignores the complexity of molecular interactions.

Scotia pursues research aiming to redress underactivity of enzymes or receptors; hence the interest in lipid-based therapeutics. Lipids modulate the environment and activity of membrane proteins, including receptors, ion channels, ATPases and components of cell-signalling systems. Cellular, nuclear and mitochondrial membranes contain about 100 major and 1,000 minor lipids, each with a specific function, and membrane-protein activity can be radically altered by changing membrane composition. Recognizing this has led to re-evaluation of the etiology of schizophrenia – a major disease target for Scotia. The hypothesis that abnormal membrane structure leads to the observed disturbance of several neurotransmitters in this disease generates new concepts for antischizophrenia drug development.

There is reticence among biopharmaceutical companies toward developing lipid-based drugs: lipids are labile, and bioactivity requires all bonds to be in the *cis*-orientation. High temperatures cannot therefore be used in production – enzymes or low-temperature catalysts are required. Nevertheless, Scotia's success to date merits reconsideration of lipids.

From small seeds...

Scotia's staff of 400 are distributed among several sites in the UK, Canada and Sweden (Figure 2). Listed on the London Stock Exchange in 1993, its current turnover is around £20 million but, based on its intellectual property and product pipeline, it is valued on the Stock Exchange at £500 million. Scotia restructured its business in early 1997 around four operating subsidiaries:

- Scotia Pharmaceuticals: to commercialize the company's lipid technology in the pharmaceutical market;
- Scotia QuantaNova: to develop the anticancer photodynamic therapy market;
- Scotia LipidTeknik (the Swedish company LipidTeknik acquired since Scotia's Stock Exchange flotation in 1993): to use its lipid purification and formulation skills to develop new delivery and formulation systems for the pharmaceutical and skincare industries; and
- Efamol Nutrition: to commercialize the OTC nutritional supplements and veterinary range of products.

Figure 1. *Dr David Horrobin, CEO of Scotia Pharmaceuticals.*

Scotia's first-generation products have been based on natural oils. Most widely known, and a major source of income, are the OTC products derived from Efamol Nutrition. Based on evening-primrose oil, and some supplemented by marine oils, these are rich sources of the essential fatty acids γ-linolenic acid, eicosapentaenoic acid and docosahexanoic acid. Efamol Nutrition's year-end results were up by 7% in 1996 at £8.4 million, with a major late trend for growth that has been sustained in 1997. Scotia's fundamental research on lipids as active drugs and as formulation agents is now leading to second-generation products based on single chemical entities and novel drug-delivery systems.

Focus of research

The company now focuses internally on the four therapeutic areas of cancer, diabetes, dermatology and psychiatry, and is licensing out products in other areas.

In-house programmes

Within oncology, drugs under development fall into two groups – those associated with photodynamic therapy (Foscan and the newer SC102 and SQ400) and lipid-based drugs, some of which selectively kill cancer cells and prevent metastasis, reduce toxicity of other chemotherapeutics, or act as anti-cachexia agents.

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Figure 2. *Scotia's newly refurbished Callanish facility on the Isle of Lewis, Scotland, UK.*

Scotia believes that CNS disorders are based on abnormalities in cell signalling and nerve membranes, rather than individual neurotransmitters or receptors. Abnormal activity of phospholipase A_2 in schizophrenia damages cell membranes, and Phase II trials of an enzyme inhibitor are promising. A neurotransmitter-based drug combination targeting multiple sclerosis is now entering Phase III trials, and preclinical evaluation of compounds for other CNS disorders is under way.

Scotia has tackled the long-term complications of diabetes (retinopathy and neuropathy) by cell-membrane modulation. Although disappointed that the UK Committee on Safety of Medicines did not approve Tarabetic (γ-linolenic acid), Scotia believes it can address the issues raised, and is developing a further product, SC103 (ascorbyl γ-linolenic acid).

Dermatology represents a huge, largely underexploited market. The incidence of eczema has risen rapidly in the past 20 years, with around 20% of children under 5 years of age affected. Scotia already sells £7 million annually of a γ-linolenic acid-based product (Epogam, for treating atopic eczema) in the UK alone, and the UK represents less than 5% of the world market. Approval is also being sought for a product to treat seborrhoeic dermatitis, estimated to affect, to varying degrees, 10–20% of the population. Through LipidTeknik, Scotia is also developing less allergenic formulations for improved uptake of topically applied drugs, with the goal of providing a formulation range for all dermatological conditions.

Licensing out

Licensed-out products contribute significantly to Scotia's balance sheet. The company has partners who bear the cost of development and marketing patented chemical entities; Scotia retains the manufacturing rights and revenue is derived from bulk sales and royalties. Among such products is Efamast, approved in 1990 for treatment of noncancer breast pain. In the UK, sales have now reached £9 million, with an 18% annual increase, and Scotia is now seeking to expand sales internationally. The company intends to license out other products for a range of disorders.

Next wave?

With a strengthening product portfolio and a strong basic research program, Scotia's progress is leading many to look again at lipid-based therapies. Lipid drugs that modify membrane structure, patterns of second-messenger production, protein–protein interactions, or activity of gene expression may well contribute to the next wave of therapeutic agents. If so, Scotia is well placed to ride the crest.

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Update on Scotia

In the last week of September Scotia announced it had signed two new licensing agreements covering the further development and commercialization of Foscan®, one of their anticancer photodynamic therapy agents. The agreements, with Boehringer Ingelheim and Kyowa Hakko, will bring in up-front and milestone payments of $54 million, plus around 25% of future sales revenues.

Scotia also signed a collaborative agreement this month with US company Supergen. Supergen is planning to use Scotia's novel platform technology Combinatorial Lipid Chemistry (CLC) to develop an anti-obesity drug and an agent to stimulate bone marrow function. CLC comprises twenty lipids with different biological properties, which can be linked together or to other drugs using novel linking techniques developed by Scotia.