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Norway looks to biotech as the oil starts to run out

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The year 2005 sees the 100th anniversary of Norway's independence. Major celebrations are planned at the beginning of June 2005 as the famous midnight sun period starts to change the mood of the country. One group of Norwegians in particular could be celebrating the dawn of a new age – the country's hitherto unsung biotech pioneers who at last seem to be getting recognition and, more importantly, the promise of state funding.

Norway, unlike its neighbors Sweden and Denmark, has no major pharmaceutical companies, but it does have a surprisingly diverse range of healthcare enterprises. Many have sprung from three well-known international names, Nycomed, Norsk Hydro and Dynal. Nycomed pioneered medical-image analysis in partnership with Amersham, and is now a part of GE Healthcare. Indeed, GE Healthcare currently runs the world's largest imaging agents manufacturing facility among the beauty of the fjords in Norway's southern coast. Nycomed was also a major player in the point-of-care diagnostics market, a tradition carried on by Axis-Shield following the purchase of the Nycocard range from Nycomed. In addition, a new Afinion point-of-care (POC) analyzer system is about to be launched for 'on the spot' testing in doctor's offices, worldwide. Nycomed has also left a legacy of a variety of innovative *in vitro* diagnostic start-up companies. Norsk Hydro, however, funded a series of interesting biotechnology processing projects, such as Norferm, in the 1980s and 1990s, which have been spun out gradually. Finally, Dynal, the inventors of the famous paramagnetic beads that were used throughout diagnostics are now increasingly used in drug discovery for separation and isolation applications. This, in turn, has led to the establishment of a number of drug discovery and molecular biology-orientated tools companies.

According to Odd Magne Rødseth (Norwegian Bioindustry Forum), this gives Norway a current base of around 80 companies. Rødseth commented that: 'Of course we can't do everything, but I think Norway can genuinely claim to have expertise in oncology – the Radium Hospital is world-renowned, immunology, neuroscience and the exciting new area of marine biology or blue bio. This gives us a range of medical device and diagnostic companies. Then, if we look at drug discovery, we have companies at most stages of the chain – from Lauras, Algeta and Affitech, for example, at the discovery end through to Clavis and Photocure as mini-pharmaceutical companies. We also have a range of tools and service providers – Dynal, of course, along with PubGene and Molmine for informatics, Diagenic in pharmacogenetics, Smerud for clinical trials and Optinose with their unique bidirectional nasal drug delivery device. The challenge is to take this forward and build a sector that is truly competitive internationally'.

Ole Marvik, Rødseth's predecessor and currently a managing partner of 4Bio, a specialist biotechnology start-up consultancy, is well aware of the challenge and cautiously optimistic. Marvik quoted 'The problem has been what is ironically seen as Norway's greatest asset – oil. For several decades now, we have enjoyed an economic boom, which has led the government to concentrate more on social issues. Economic policy has been a case of investing oil revenues, but has naturally been directed towards leading international funds. Now, however, it has finally dawned on us that the oil is running out and we need to look at investing domestically in new industry sectors. In biotechnology, we have been lobbying on deaf ears for years, but now finally we seem to be making some progress. Next year, for example, sees the setting up of new seed funds for the various biotechnology hotspots in Norway – Oslo, Bergen, Trondheim and Stavanger. This is the result of

The Radium Hospital is a world-renowned centre of excellence for oncology treatment and research. Several biotech companies originate from the hospital, including Dynal and PhotoCure.

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a fundamental reassessment of the way to stimulate and commercialize innovation in science, medicine and engineering initiated by the Norwegian Research Council. The FUGE program [National Programme for Research in Functional Genomics] has been started and centres of excellence have been established across the country with neuroscience and oncology the main ones relevant to biotechnology. Innovation Norway, the reorganized government trade and export arm, has also made promoting biotechnology one of its key priorities. To date, we have had some success stories, but the process needs to be accelerated. Start-ups need to be bold and good enough to attract international investment at an early stage and then themselves internationalize either through deals, or mergers and acquisitions. Personally, I think this is possible; the UK is an obvious target market for us in Norway, and we already have the examples of Nycomed-Amersham Axis-Shield and, most recently, Optinose who are established there. Of course, the US cannot be ignored and I also see developing closer links there at all levels – research, commercial and investor – as a major priority'.

This view is backed by Ingrid Alfheim, who heads Biomedinsk Inovajion (BMI), a new joint venture between Oslo Research Park and Medinnova (the technology transfer office at the National Hospital, Oslo). This venture is aimed at speeding up technology transfer and commercialization from not only the two owners, but also other research centres in Norway. Alfheim explained that 'The potential is there, but it will take several years to really establish a culture of entrepreneurship. We have good scientists here in Norway with good ideas, but the risk taking involved in real biotechnology is unfamiliar to them. However, I can see us having some significant successes within five years. Programs such as FUGE are laying a good foundation for commercially orientated innovation'.

Blue biotechnology

The idea of integrated genetics brings us to the latest but, in many senses the most natural, area for Norwegian biotechnology to potentially develop a world-class capability – marine or 'blue' biotechnology. 'Norway has of course always been a seafaring nation – from the times of the Vikings to modern fishing fleets,' continued Rødseth, who is also CEO of the marine biotechnology company Aqua Gen As. 'As such we already have a major aquaculture sector ranging from fish feed production to salmon farming. Now we are looking to biotechnology applications – sequencing, for example, the salmon genome and investigating potential fish vaccines. We know the EU is very interested in our work and see the potential for collaboration with other countries in the future such as Scotland, Ireland, Spain, Australia and Canada.'

One particular marine biotechnology application is creating a great deal of excitement in Norway at present – bioprospecting of marine microorganisms (searching for producers of anti-infective agents). During the past decade, many bacterial producers of novel antibiotics with unusual structures and properties have been isolated from the sea. The Norwegian marine environment is largely unexplored and could provide a rich source of microorganisms producing novel and efficient anti-infective compounds. In the current project financed by the Research Council of Norway, which started at the end of 2003, in cooperation with SINTEF and Trondheim University (NTNU), samples from the marine environment in the Trondheim fjord are being harvested with the aim of isolating antibiotic-producing bacteria (http://www.mabit.no/bioprosp-eng.htm). The collection of such bacteria is then screened for their ability to inhibit the growth of test organisms. Preliminary results obtained by the groups led by Sergey Zotchev at NTNU and Trond E. Ellingsen at SINTEF indicated that marine sediments from the Trondheim fjord are excellent sources for isolation of actinomycete bacteria (Figure 1). In addition, another project, which is supervised by Svein Valla, aims to establish marine environmental DNA libraries. These libraries, upon expression in appropriate hosts, can be used in anti-infective screening programmes. Future projects will include cloning the genes governing antibiotic biosynthesis, characterizing and manipulating these genes with the objective to produce novel pharmaceuticals, or enhancing their productivity.

FIGURE 1.

Actinomycete bacteria from the Trondheim fjord. These bacteria might provide new antibiotics to fight bacterial and fungal infections. Image courtesy of Sergey Zotchev.

As Norway celebrates its centenary, it looks as if the various components needed for a successful biotechnology sector to be able to stand comparison internationally are beginning to fall into place. Perhaps as the oil runs out, the modern-day descendents of the Vikings will find the same spur to leave their shores and find fortunes overseas.

Viking drug discovery adventurers to watch

There are several drug discovery companies becoming established in Norway, some of which are discussed here and others are summarized in Box 1. Affitech focuses on the discovery and

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BOX 1

Examples of biotechnology companies in Norway

Algeta
Algeta is dedicated to the development of novel anti-cancer therapeutics based on particle-emitting radionuclides. This company has recently announced the inclusion of the first UK patient in a Phase II study of the novel bone-seeking radiopharmaceutical Alpharadin™ based on radium-223.

Biosergen AS
In December 2004, SINVENT AS (Trondheim, Norway) and Karolinska Innovations AB (Stockholm, Sweden) have established a new biotech start-up in Trondheim, Biosergen AS. This company's goal is to develop antifungal antibiotics with improved properties using genetic manipulation of the biosynthetic gene cluster for nystatin (a long-known antifungal antibiotic).

Diagenic
Diagenic offers a novel diagnostic technology for early detection of disease, such as breast cancer, by looking at gene expression patterns in peripheral cells.

Lytix Biopharma
Lytix Biopharma is an early-stage pharmaceutical company discovering and developing investigational new peptide-based drugs for applications in infection and cancer therapy.

PCI Biotech
PCI Biotech specializes in a novel drug delivery technology called photochemical internalization (PCI). PCI has been developed to target delivery of macromolecules and other membrane-impermeable drugs for gene therapy, protein therapy, oligonucleotide therapy and chemotherapy.

Predichem
Predichem is a start-up biotechnology company, which develops new technologies for pharmacogenetic-based screening.

Pronova Biocare
Pronova Biocare manufactures Omacor® (omega-3 acid ethyl esters) which has recently won approval by the FDA as an adjunct to a diet based on reducing triglycerides in adult patients with very high triglyceride levels (?500 mg dL^{-1}).

PubGene
PubGene has developed a data-mining software solution for biology-related papers which, when combined with microarray analysis, can estimate the importance of various relationships between genes and proteins, various diseases, cell processes and functions.

development of human therapeutic antibodies for cancer, infectious diseases and other diseases of unmet medical needs. Affitech's technology portfolio includes: (i) its worldwide patents of a phagemid system called the BREITLING patent; (ii) the AffiScreeN™ method that uses patient-derived antibody repertoires in a HTS platform; and (iii) the CBAS system, which is an integrated, functional cell-based screening approach for simultaneous discovery of human antibodies and cognate targets.

Clavis Pharma is a pharmaceutical development company based on the proprietary lipid-vector technology (LVT). LVT involves the chemical binding of certain fatty acids to pharmaceutical agents, thereby creating new chemical entities with improved biological properties, such as increased cellular uptake, reduced toxicity and slow release of the active compound. Clavis Pharma's lead development product (CP-4055) has entered clinical Phase I and II studies in the UK and Norway. CP-4055 is a fatty acid derivative of cytarabine, an approved cytotoxic cancer drug. Cytarabine has limitations such as minimal uptake in solid tumors and is only used to treat leukemia. However, CP-4055 is designed to overcome this limitation and has shown considerable uptake in solid tumour cells. CP-4055 is a patented new chemical entity of the nucleoside analogue class, with improved biological properties and has the potential to treat solid tumors such as non-small cell lung cancer, malignant melanoma and ovarian cancer.

The biotechnology company Lauras develops drugs for immuno-stimulating therapy in HIV/AIDS and other immune diseases based on the knowledge that activation of a signal pathway inside the immune cells (including white blood cells and T cells) can inhibit the function of the immune system. From the photodynamic perspective, the company PhotoCure develops pharmaceuticals and medical devices for photodynamic treatment of internal cancer, skin cancer and other skin diseases, such as Metvix® for the treatment of basal cell carcinoma (skin cancer) and actinic keratosis (pre-cancerous skin lesions).

Dynal Biotech are applying their expertise in biomagnetic separation technology for HTS work by developing other beads isolating proteins from complex mixtures prior to mass spectrometry analysis in proteomics work. In molecular biology, magnetic beads are sought after for PCR clean-up and gene expression studies. Inovio, another biotechnology start-up, offers a unique electroporation-based technology called Elgen for the delivery of genetic materials and other bio-therapeutics to mammalian skeletal muscles *in vivo*. Using the Elgen method, skeletal muscle cells can be engineered to become small factories to produce and secrete therapeutic proteins for months or years.

From the devices aspect of drug delivery, there is OptiNose, a company that develops innovative devices for nasal delivery of drugs and vaccines. The OptiNose bi-directional technology is versatile and suitable for single or multi-dosing of both liquid and powder formulations, with either topical or systemic action. Bi-directional technology exploits a natural reflex – the closing of the soft palate at the back of the nose – that functionally isolates the nasal circuit from the lungs during drug delivery. This simple automated response enables drug particles to be deposited at the target sites beyond the nasal valve without risk of distribution to the lungs. For vaccines, nasal delivery provides a fast, cost-effective and user-friendly alternative to injection.

Norferm, a joint venture between Statoil and Nycomed Amersham, produces bioproteins from methane at the world's only such plant, where feedstock gas comes ashore from Statoil's Heidrun field in the Norwegian Sea. Currently, Norferm produces 8000 tonnes per year of well-balanced bioprotein and is planning to increase this production to

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BOX 2

The 11 pillars of the National Programme for Research in Functional Genomics, Norway

Biobanks for Health
http://www.fhi.no/eway/default0.asp?e=0&pid=225

Regional Research Biobank
Website not available to date

The Norwegian Bioinformatics Platform
http://www.bioinfo.no/

The Norwegian Centre for Integrative Genetics
http://www.nlh.no/?avd=40

The Norwegian Arabidopsis Centre
http://www.nlh.no/?avd=30

The Norwegian Centre for Microarray Technology
http://www.mikromatrise.no/

The Norwegian Structure Biology Centre
http://uit.no/norstruct/home/

The Norwegian Proteomics Centre
http://pcom3.geo.uib.no/probe/

The Norwegian Centre for Microbial Technology
http://www.cmbn.no/tonjum/fuge-camst/

The Norwegian Molecular Imaging Centre
http://www.ntnu.no/~cbrekken/FUGE_MolecularImaging/

The Norwegian Transgenic Center
http://www.transgen.no/

40,000 tonnes per year following the installation of parallel reactors. The bioproteins are used for food, animal feed and industrial products.

Biosentrum specializes in contract fermentation for production, research and development, and process scale-up. The plant has a history as a contract research centre for development and production of various products, such as biopolymers for secondary oil extraction, biosurfactants for use in bioremediation, fish vaccines and organic acids.

Molmine is a company that produces microarray software for pharmaceutical companies and scientists to analyze thousands of genes and their functions. Originating from the University of Bergen, Molmine counts Harvard Medical School (MA, USA), Stanford University (CA, USA), Oxford University (UK), the US Army Research Institute (MA, USA) and Institute Pasteur (Paris, France) among its list of clients.

FUGE lays the foundations for growth

Talk to anyone in Norwegian biotechnology and, inevitably, FUGE will come into the conversation. Driven by Ole Peter Ottersen, FUGE is one of seven large-scale research programmes established by the Norwegian Research Council in its fundamental review delivered in 2003. The programme runs from 2002 to 2011 with an annual budget for 2003–2007 of 150 million NOK (US$ 24 million). According to Ottersen, FUGE has the primary objective to enhance the quality of basic biological, medical and marine research, and to help ensure that this research is in turn implemented to generate innovation and strengthen industrial development.

Eleven national technology platforms have been established as the pillars of the FUGE programme (Box 2). These organizations have been delegated national responsibility for developing specific technologies and will become technical service centres providing special expertise within the applicable technologies. Biobanks and CIGENE are probably the two of most advanced technology platforms as part of FUGE. Biobanks is based on existing networks of human research biobanks and two new population-based health studies in Norway. The Cohort of Norway (CONOR) is a network of Norwegian health studies and, when completed, this cohort will include blood samples and standardized health and exposure data from 200,000 Norwegian individuals (http://www.bioethics.ntnu.no/biobanks/). Similarly, The Norwegian Mother and Child Cohort Study (MOBA) will upon completion comprise biological samples and standardized health and exposure data from 100,000 pregnant women, 100,000 children and 70,000 fathers. DeCode's success in Iceland in population genomics has been one of the inspirations for Biobanks because Norway regards itself as having at least equally good historic population data. In addition to basic research, it is also hoped that these platforms will enhance Norway's attraction as a clinical trial centre.

The Centre for Integrative Genetics (CIGR) aims to contribute to a deep causal understanding of complex genetic characters in fish, plants and animals for scientific and commercial exploitation based on an integrated genetics approach. As a core FUGE facility, the CIGR is responsible for providing a national centre for detection, typing and interpretation of single-nucleotide polymorphisms (SNPs), and for systems-orientated computational biology.

UniTargetingResearch (UTR) has developed a unique technology for high yield, high-quality commercial production of pharmaceutical drugs. The UTR® technology boosts secretion of both naturally secreted and native intracellular proteins into mammalian cells' culture medium, from which they are harvested.

The future for Norwegian biotech

In conclusion, a natural question to ask is what will be celebrated at the 200th anniversary of Norway's independence. Talking with Norwegians in general, you cannot fail to be impressed and even slightly embarrassed by the deep interest taken in world affairs, particularly with regards to global health and environmental problems. There is a strong commitment to bodies such as the WHO. I am certain that this will be reflected in a strong contribution by the growing Norwegian biotech sector in areas such as affordable disease diagnosis and vaccination technologies, the application of genomic information to public health programmes and sustainable exploitation of marine resources.

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