News

Isis
University of Oxford
Innovation

Reviewing the latest innovations, collaborations
and technology transfer from Isis Innovation Limited
Edition 35 Spring 2002

Investing in People

Above: *Tim Cook, Managing Director, Isis Innovation*

Welcome to the 35th Edition of Isis News. In this edition you will find exciting new inventions from Oxford University, reports from our most recent Oxford Innovation Society Meeting and Dinner, profiles of new OIS members, and news of Isis Innovation's activities in technology transfer.

Dr Patrick Grant's presentation to the December OIS meeting on rapid formation of press tools by flame spraying gives an exciting account of how new technology is shortening the time from concept to finished vehicle in the motor industry. Novarc Ltd, the University spin-out company based on this technology, is already doing well and its Managing Director, Dr David Field, shared his views on its potential with the meeting audience.

The evening was sponsored by IP2IPO and Beeson Gregory, who recently placed £20 million in what the ***Financial Times*** described as an "innovative investment" in Oxford University's Chemistry Department to facilitate spin-outs from this area. Mr Andrew Beeson, the co-founder of the bank, described this project and Beeson Gregory's reasons for doing it at the meeting. Accounts of the talks given by both Patrick Grant and Andrew Beeson are included in this newsletter.

Inhibox Ltd is a new company using an innovative screen-saver to search for new anti-cancer drug candidates and the first spin-out supported by the Beeson Gregory project. I am pleased to announce that in January 2002, the second spin-out company supported by the Beeson Gregory project, Pharminox Ltd, was established. Pharminox, which deals with a family of new anti-cancer drugs, is described in more detail on page 18. NaturalMotion Ltd, formed in November 2001, is a spin-out from the Department of Zoology and has developed software to enable the realistic portrayal of human and animal movements. Their revolutionary approach – with its applications in computer games and movies – is described further on page 15.

The new technologies available for licensing, which are described in this edition, cover structures ranging from RNA, to superconducting tape to the seabed!

I am delighted to welcome two new members to the Oxford Innovation Society: Vertex Pharmaceuticals, based at Abingdon, and Genzyme, who have recently opened an office in Oxford; both companies are profiled inside.

I am also very pleased to announce that Isis Innovation recently won an Investors in People Award. Isis staff and management are to be congratulated on this achievement. It is gratifying to know that their efforts have been audited and recognised.

I hope you enjoy this newsletter and look forward to hearing from you.

Tim Cook, Managing Director, Isis Innovation

Sprayform Tooling for Rapid Manufacture

Oxford Innovation Society Lecture – December 2001

Dr Patrick Grant, Department of Materials, University of Oxford

Above: *Dr Patrick Grant, Reader, Department of Materials, University of Oxford.*

Introduction

In the development of a new mass production vehicle, the provision of the tooling is frequently the longest lead-time item. The large press tooling sets which press steel or aluminium sheet to form large body panels such as the bonnet or bumper usually take 9 months or more to manufacture. Once available, these tooling sets can produce up to 1 million components. The consequences of these long lead-times are the vehicle design must be finalised far from launch date, and few design iterations are possible. Large tool sets also represent a significant fraction of the overall investment required to introduce a new model. The global tool market is approximately $80bn, with automotive the largest single industrial sector.

Research at Oxford has developed a radical alternative for manufacturing press and other tools

Tooling is currently manufactured by the computer numeric controlled (CNC) machining of large grey iron castings that can easily weigh several tonnes. The CNC practices and technology are well established, optimised and produce robust tools of high tolerances, but with the inherent prolonged lead-times. Research involving the Departments of Materials and Engineering Science at Oxford University has developed a radical alternative to CNC machining for the manufacture of press and other tools. Whereas machining involves the selective removal of material, the new process involves the selective addition of steel onto a sacrificial pattern using a metal spraying technique. This sprayform tool process offers the potential to manufacture tools of sufficient quality and robustness for production applications, at reduced time and cost in comparison with current machining routes. The research is funded jointly by the UK Engineering and Physical Sciences Research Council and the Ford Motor Company, USA.

The spray forming process

The sprayform tool process starts with a pattern or 'master' of the tooling to be produced, and can be:

* an artist's model
* a UV cured model produced directly from a CAD file using stereo-lithography
* a silicone rubber impression of the component to be produced by the tooling
* a machined epoxy bonded ceramic powder board

A silica sol slurry is cast against the boxed-in master, and then frozen at –40°C to produce a solid. On thawing, the resulting ceramic remains solid because of an irreversible freeze-gelation process which has taken place in the sol. The ceramic freeze-cast is then warmed to remove water and is ready for use as the substrate for the sprayform tool process. Because no firing is required to produce the ceramic, freeze-casting is a low cost process that replicates the master with high accuracy. The ceramic also has excellent thermal shock properties, vital to withstand the subsequent steel spraying operation.

The freeze-casting substrate is sprayed using four electric arc spray guns mounted on a 6-axis programmable robot. The robot manipulates the guns and the metal spray in a controlled way, over the surface of the freeze-cast substrate. By careful control of the spraying process, the solidification and thermal contraction stresses that are normally an inherent feature of sprayed metal coatings are eliminated. This stress control enables steel shells up to 2cm thick to be produced with negligible distortion or loss of dimensional accuracy.

A further aspect of the sprayform process is the ability to incorporate contoured cooling channels within the sprayed shell. This is achieved by interrupting the spray process and attaching contoured cooling channels to the back of the

Above: *The sprayforming apparatus for the manufacture of tools and dies, located at the University's Begbroke Business and Science Park.*

sprayed shell, in a pattern designed to provide optimum cooling characteristics when the tool is in operation. Spraying is then restarted and the channels become integrated into the sprayed shell. This type of contoured cooling has been demonstrated to reduce tool cycle times in polymer injection moulding applications.

After spraying, the sprayed shell undergoes trimming, backing and bolstering before entering production service.

Recent research at Oxford

The overall objective of the research programme at Oxford is to scale-up the sprayform process for larger tools, which requires innovations in three areas: off-line path planning software; on-line process control; and microstructural analysis.

Path planning

In order to maintain the required thermal control and hence dimensional accuracy of the finished tool, it is essential that the robot that manipulates the spray guns makes a 'path' over the growing sprayed shell that is optimised to avoid the generation of thermal gradients. This constraint can be analysed and described mathematically in a thermal model of the process, and forms the basis for software developed by the Oxford group. The software is used to generate a plan for a particular shape to be sprayed, optimised to best account for the thermal constraints. The output of the software is a programme in the robot language, sent over the local area network directly to the robot. In this way, the traditional and time-consuming point-and-teach manual programming of the robot is avoided, and an optimum robot path plan developed without expensive trial and error. The software is now used routinely for generating path plans for simple, near two-dimensional shapes such press tools, and a full three-dimensional version is in development. This later version will be able to create optimised path plans for complex shaped tooling, directly from a computer aided design (CAD) file representation of the tool.

Other software has also been developed in parallel to calculate the spatial variation of any porosity in the sprayed steel shell, as a function of any particular path plan selected. Low fractions of porosity are of little consequence to tool performance, but where porosity fractions rise around certain topological features, mechanical and thermal performance of the tool may be compromised. The mechanism by which porosity develops has been shown by high speed, high magnification imaging to be a complex process, involving splashing of the sprayed steel droplets as they impact the surface. The software has been used to show that localised increases in porosity can be reduced by choosing a different robot plan that contrives droplet deposition to occur in a less detrimental fashion.

The long term aim is to combine the codes that express the thermal constraints and low porosity constraints to produce powerful general purpose software for path optimisation in sprayform tooling manufacture and other deposition processes.

On-line thermal control

Even with optimised robot path plans at the beginning of the spraying process, some real time monitoring and regulation of the spray process is always required in practice once spraying begins. The nature of this control problem is that as previously mentioned, low distortion tools by sprayforming can only be obtained if the phase changes in the steel are carefully controlled as it cools. The phase changes for each droplet in the spray are determined by their thermal history from the point of deposition. Unfortunately, it is not possible to control the thermal history of each sprayed droplet individually. However, by controlling the shell surface temperature, it is possible to fix a point in a droplet thermal history. If the entire sprayed shell surface is at the same fixed temperature throughout spraying then all sprayed droplets have at least three equivalent points in their thermal histories:

Above: *The sprayforming process in action.*

* The temperature of deposition, which is typically 2200°C
* The sprayed shell surface temperature, which is the parameter controlled in real time
* The final temperature, which is always room temperature

It is necessary to use this indirect route to control the dimensional accuracy because a measure of dimensional accuracy or the phases directly are not possible during spraying. In contrast, the surface temperature of the sprayed shell as it is formed can be measured using a thermal imaging camera. Measured temperatures are then controlled in real time by alterations in the spraying rate. As a result, the problem of regulating the dimensional accuracy of the part is reduced to that of maintaining a constant temperature at all points on the surface throughout the spraying process.

Prior to the start of the project, the average tool surface temperature was controlled 'open loop' by a skilled operator, using a single point temperature measurement obtained from an infrared thermometer. A number of innovations have been made by the Oxford group so that an infrared thermal imaging camera is used now to measure temperature at all points on the tool surface, the output of which is used to control the spray rate directly, with no operator intervention. This has removed the need for skilled operators, produced a more robust system, and increased the response time of the system to any thermal fluctuations. These benefits are realised by the manufacture of sprayed tools of increased dimensional tolerance.

This automatic control system is now being extended to generate any desired two-dimensional temperature profile. This is achieved by combining the thermal images with knowledge of the robot position at any instant to change the spray rate, depending upon the position of the guns and the temperature of different parts of the surface. The robot is constantly moving so the spray rate must be varied every 100ms, much faster than a human operator could achieve. If this extended control system is given a flat desired temperature profile, it removes any thermal variations. If it is desirable that the optimal temperature profile for dimensional accuracy is not the same temperature at all positions, then the control system can impose whatever spatial distribution of temperature is deemed more appropriate.

Microstructural analysis

Off-line path plan tools and on-line thermal regulation can only work meaningfully if the appropriate thermal window of operation has been properly identified, and the relationship with tool tolerances and properties understood. A final element of the research therefore involves generating the underpinning understanding of microstructure of the sprayed steel shells. High resolution microstructural studies on shells manufactured under different conditions have for the first time yielded a deeper understanding of the way in which thermal history controls phase transformations, and how the proportion of phases in turn control final dimensional tolerances. With this improved understanding, new alloy compositions are being developed which will enhance tool properties in service.

Summary

In order to understand the complex sprayforming process, to take the first steps to scale-up the technology, and to package it in a commercial format, a large inter-disciplinary research team has been formed involving material scientists and control engineers. A number of innovations have been made in the areas of off-line path planning, on-line thermal control and microstructural characterisation. Four patents have been filed and licensed to the Ford Motor Company. Novarc Ltd, a spin out company from Oxford University, has recently been established and licenses key intellectual property in sprayforming from both Ford and Oxford. Novarc supplies spray formed tools and integrated spray cells to industry. Ford and Novarc continue to fund research in the University, and it is envisaged that further innovations will enable sprayforming of tools to become an important and widely adapted technology in modern toolmaking.

Oxford, Beeson Gregory and IP2IPO – A Landmark Partnership

Oxford Innovation Society Meeting, Sponsor Presentation – December 2001
Mr Andrew Beeson, Beeson Gregory plc

Above: *Andrew Beeson, Executive Chairman of Beeson Gregory Group plc.*

Beeson Gregory and IP2IPO were delighted to co-sponsor the December Oxford Innovation Society Meeting & Dinner. We have been associated with the University for some years, so it was particularly pleasing to be able to introduce Beeson Gregory and IP2IPO to the members of the OIS.

Beeson Gregory is a London based investment bank, founded in 1989. Over the last 12 years we have established the largest dedicated SmallCap team in London and have built a reputation for focusing on high-growth sectors, particularly enabling technologies. The bank now focuses on 9 key sectors: Life Sciences, IT Hardware, Software, Entertainment Software, Support Services, Clean Technologies, Extraction and Resources, Media and Leisure and provides a full range of research, corporate finance, market making and sales and distribution services to its clients. Our private equity expertise was enhanced when, in 2000, just prior to our flotation, we acquired IndexIT, a technology specialist investment house founded by David Norwood. The IndexIT team has become the bank's private equity division and has an active presence in Oxford having raised over £20m of finance for a number of Oxford University spin-out companies at the seed capital stage and subsequent funding rounds.

In December 2000, Beeson Gregory entered into a landmark transaction with the University of Oxford and Isis Innovation. In return for an investment of £20m, it acquired a 15-year interest (equal to the University's own interest) in any intellectual property commercialised from the Chemistry Department. This investment is unique – nobody else has entered into an agreement of this sort before – and it underscores the importance that Beeson Gregory places on world-class intellectual property. From the first, this transaction represented much more than a simple financial investment; it is a genuine partnership of capital, intellectual property, and technology transfer expertise.

During 2001 we reached the conclusion that our initial investment in Oxford University has opened the doors to a wider commercial opportunity: the formation of a University Partnership based business. Accordingly, in August last year, Beeson Gregory transferred its landmark agreement with the University to a new subsidiary company, which we called IP2IPO. Dr Chris Wright became IP2IPO's Chief Executive Officer and shortly afterwards, IP2IPO raised £3m in working capital.

IP2IPO is enjoying an extremely productive relationship with Isis Innovation and already two spin-out companies have been formed, based on technology developed at Oxford University's Chemistry Department. The first, Inhibox, is a drug discovery company that uses computational methods to screen small molecules for potential therapeutic use against cancer. The second, Pharminox, is a drug development company, founded to develop a number of classes of platinum-based compounds that have shown very promising activity against certain forms of cancer. The creation of these two very exciting companies, due in no small measure to the professionalism and hard work of Dr Tim Cook's team at Isis, demonstrates that the partnership between IP2IPO and Oxford University is working extremely effectively and will continue to deliver success stories like Inhibox and Pharminox in the years to come.

Further Information

W www.ip2ipo.com
W www.beeson-gregory.com

Detection of Nascent RNA Transcripts

Isis Project Number 0915

Research at the Sir William Dunn School of Pathology, Oxford University, has resulted in the design of a method for cataloguing the numbers and types of different nascent RNA transcripts expressed in a cell population. This will allow more complete analysis of differential gene expression.

Background and Problem

Genetic information flows from a gene, through a primary transcript that is processed into a message, and so into protein. We now have draft sequences of all the human genes, and catalogues of the numbers and types of all mature messenger RNAs and proteins in some cell populations. However, little is known about the nascent transcripts found in any cell type because they are so rapidly processed into mRNAs. While mature mRNAs can be catalogued using microarrays, SAGE and other high-throughput techniques, these techniques do not allow analysis of nascent transcripts. Consequently, little is known about the relative rates of transcription of the different genes in a cell. An enormous gap thus remains in our knowledge of the flow of information from gene to protein, and the changes that occur when cells divide, differentiate, or become diseased (e.g. in cancer).

The Oxford Invention

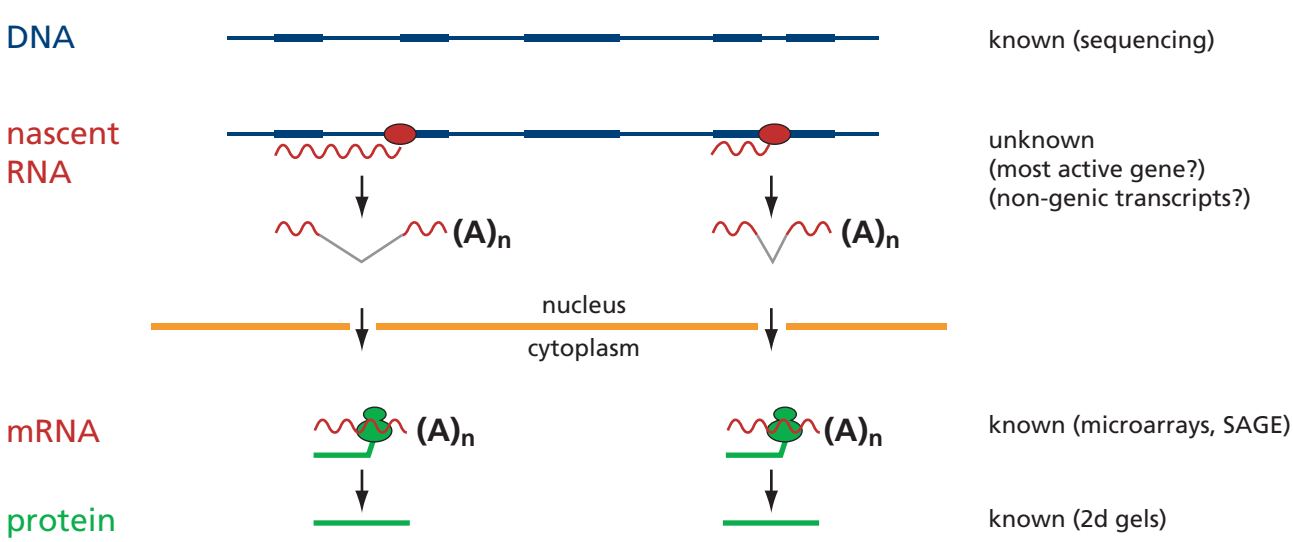
Research at Oxford has generated a method that permits high-throughput analysis of nascent transcripts. It will allow the quantitative analysis of differences in transcription between two related cell populations (e.g. between normal cells and their malignant counterparts), and the analysis of non-genic transcripts that may play important roles in gene regulation.

Commercialisation Opportunity

A Patent application has been filed, and Isis Innovation would welcome any inquiries from potential partners interested in utilising this technology.

Below: *Nascent RNA Genomics. This project combines a sheaf of unrelated technologies in a novel manner and the technique is the subject of a provisional patent application. It gives us catalogues of all parts of the genome that are copied into RNA, allowing comparison between two related cell populations (e.g., tumours and their non-malignant counterparts). It also provides a snapshot of the density of loading of all RNA polymerases on all transcription units in the genome, and so the relative activity of all genic and non-genic transcription units.*

Molecular catalogues



Plant Fertility Technology

Isis Project Numbers 1005 and 1006

Research in Oxford's Department of Plant Sciences has identified genetic mechanisms by which the male fertility of crop plants may be controlled and cross-fertilisation brought about between lines of crop plants which will not normally interbreed.

Background

With the expanding population and the concern over environmental implications of genetically modified crops, there is pressure on plant breeders to produced improved crop lines, particularly in the Solanaceae (potatoes and tomatoes) whilst at the same time preventing environmental contamination by transgenic pollen.

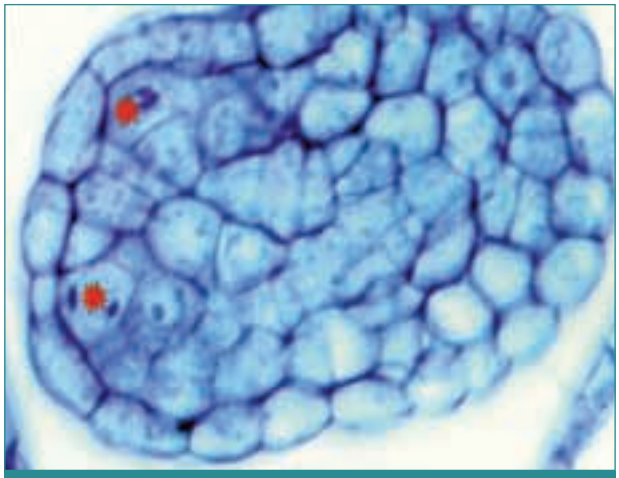
Problem

Production of improved crop plants is hampered by the difficulty of intercrossing existing elite lines. This is because crop plants have double fertilisation, so the number of male and female genomes making up the endosperm must be balanced between crosses (the Endosperm Balance Number) in order for the offspring to be viable. Current practice involving manipulation of the genome through tissue culture steps is an expensive and time consuming procedure.

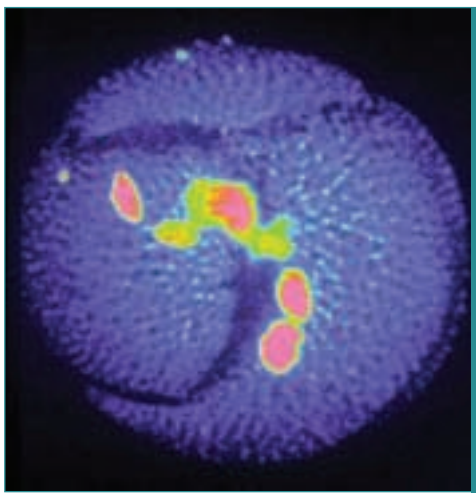
Environmental contamination by transgenic pollen from these plants can be controlled by male sterility systems. However, current sterility systems all have major drawbacks. Some are simply unreliable and thus are of very limited use, and others may affect female fertility. Further strategies, which result in the inducible ablation of the pollen can either leave toxic chemicals in the product plant undesirable to the consumer, or cause cellular damage elsewhere in the plant.

The Oxford Invention

Novel research at the Plant Sciences department of Oxford University has resulted in the discovery of two important genetic mechanisms which could revolutionise transgenic crop production. The first discovery will allow the creation of male plants producing pollen which will 'compensate' for a range of endosperm balance numbers, resulting in a high level of fertile seed production without the need for complicated tissue culture procedures. The second genetic mechanism could enable the specific control of male plant fertility, importantly without affecting female fertility. With this technology, plants can be created which are male sterile, male fertile but inducibly sterile and male sterile but inducibly fertile. There is great scope for improved crop plants with a safer environmental aspect.



Above: *Very young anther of* Arabidopsis. *Red stars show two of the four primary archesporial cells, each of which gives rise to a male germline in the anther.*



Left: *Massive pollen grain from the* Arabidopsis tes *mutant. Confocal image showing the presence of at least 4 sperm nuclei (red structures). At least 2 of these sperms are likely to be diploid.*

Commercialisation Opportunity

Patent protection has been applied for, and companies interested in product developments arising from this work are invited to contact Isis Innovation to discuss how they could interact with Oxford to utilise this fascinating, novel technology.

High-level gene expression in antigen presenting cells directed by the Emr1 promoter

Isis Project Number 1159

Research in the Sir William Dunn School of Pathology at the University of Oxford has identified a short DNA sequence within the murine Emr1 gene that directs high-level gene expression in cells of the mononuclear phagocyte lineage. This work has important implications for the development of genetic vaccines and macrophage gene targeting for gene therapy.

Background

Macrophages and dendritic cells play an important role in the body's response to pathogens through their unique roles in innate and acquired immunity.

The murine Emr1 gene encodes the antigen recognised by the F4/80 monoclonal antibody, which stains Langerhans cells and tissue resident macrophages. Langerhans cells are the immature dendritic cells normally present in the skin and mucosal epithelia that present antigens to naïve T cells following mobilisation to draining lymph nodes.

Currently there are very few examples of genetic regulatory sequences that can direct high-level transgene expression specifically in macrophages or Langerhans cells.

The Oxford Invention

Researchers in Oxford have now identified a 110 base pair segment of the murine Emr1 gene that can direct macrophage-specific expression of a linked transgene. Moreover, this sequence can act as a transcriptional enhancer, conferring high level macrophage-specific expression to a minimal promoter from another gene.

This work has important implications for the development of genetic vaccines and macrophage gene targeting for gene therapy

Above: *A section of skin stained with a monoclonal antibody called F4/80 that detects the gene product of the Emr1 gene. The brown F4/80 positive cells are a specialised type of dendritic cell called Langerhans cells which present foreign antigens to other cells of the immune response.*

This technology provides the basis for the development of new expression vectors that direct gene expression in macrophages and Langerhans cells *in vitro* and *in vivo*.

Vectors containing Emr1 sequences may find application in the development of genetic vaccines for pathogens such as HIV, malaria and tuberculosis; the development of new immunomodulatory treatments for diseases such as asthma, psoriasis and arthritis or achieving high levels of therapeutic transgene expression in macrophages.

Commercialisation Opportunity

This exciting Oxford discovery is the subject of a patent application. Companies interested in product development arising from this work are invited to contact Isis Innovation to discuss how they could interact with Oxford to utilise this technology.

Superconductors

Isis Project Number 0836

Background

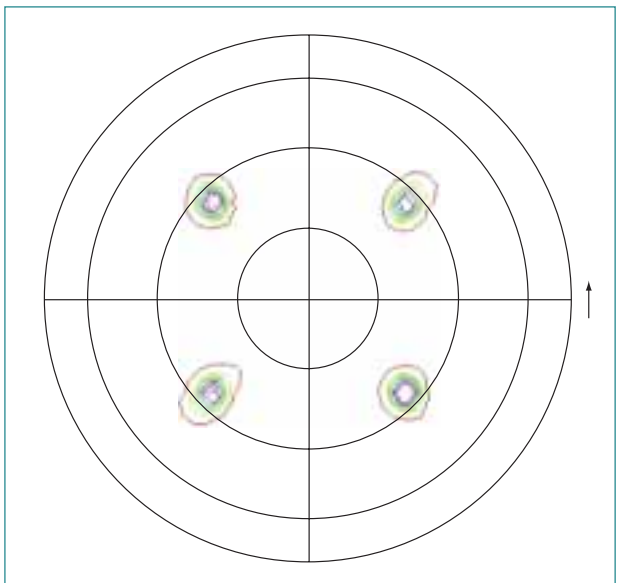
Superconducting cables have important practical applications in the generation of high magnetic fields and efficient current transport, in particular in reducing the size of electrical technology.

Problem

Biaxially textured superconductor materials can support the high current densities required by many superconducting wire and tape applications, but are extremely challenging to prepare in long lengths in both a cost-effective way and by employing rapid fabrication technology. Buffer layers are necessary to prevent reaction between the metallic substrate and the superconductor. It is vital that buffer layers have the same texture as the substrate and can act as a template for the growth of a superconducting layer with the same texture.

The Oxford Invention

Researchers in the department of Materials at the University of Oxford have developed a quicker, more efficient technique with a single process step for producing a biaxially textured metal layer for the manufacture of superconductors.



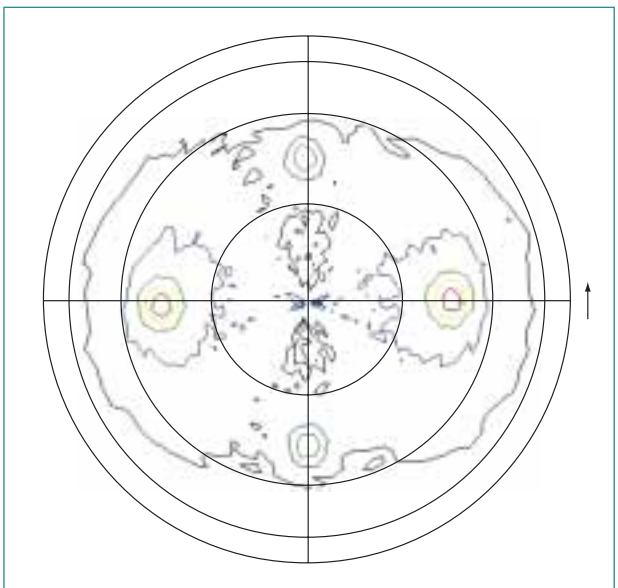
Above: *Single crystal silver buffer layer deposited onto a nickel substrate using our electro-epitaxy process.*

The process can be used to deposit a textured buffer layer in a few seconds, and without the need for further heat treatment. The buffer layer is stable up to 900°C, and lattice mismatch with the superconducting layers can also be minimised. The final composite structure is more mechanically robust than silver substrates.

Commercialisation Opportunity

Isis Innovation Limited has filed an international PCT patent application on this process and is now in a position to offer this technology to the superconductor industry. Interested organisations should contact Isis for further information.

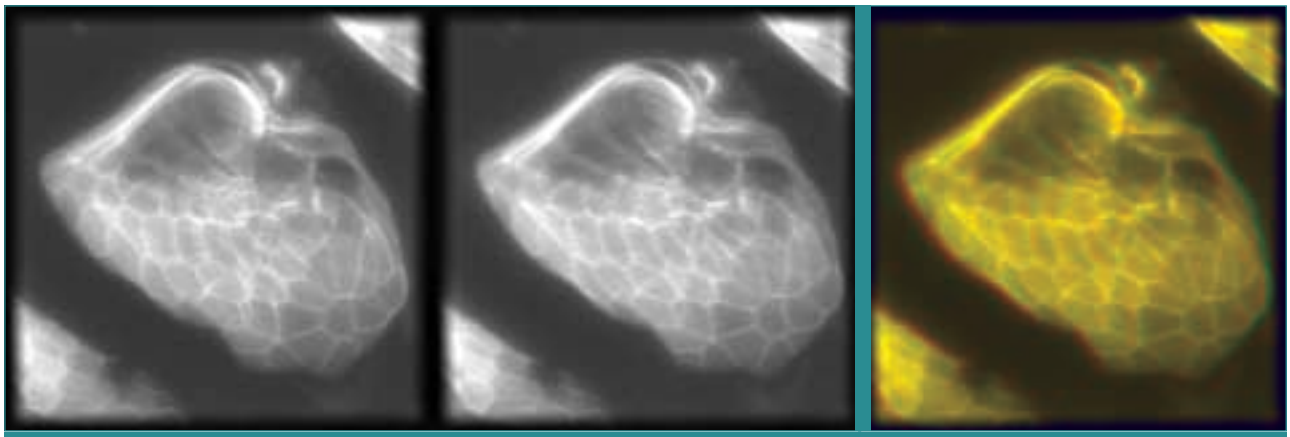
This project was awarded University Challenge Seed Funding (UCSF) for 6 months to demonstrate the novel substrate fabrication method to potential commercial partners. The aim is also to gain vital information about the potential costs of a final product following scale up. The project recently began and first stage milestones are anticipated shortly.



Above: *$NdBa_2Cu_3O_7$ high temperature superconductor layer grown directly on our silver buffer layer showing that the substrate can support epitaxial growth of superconducting layers.*

High Resolution Stereo Microscopy

Isis Project Number 1013



Above: *The photographs are images of a 10µm thick section through a villus in a mouse intestine. The stereo pair may be viewed by focussing on infinity and slowly refocusing back to the image (crossing and slowly uncrossing the eyes works quite well). The red-green anaglyph may be viewed using red-green spectacles.*

A new video camera imaging process provides high resolution stereo microscopy.

Background

The binocular eyepieces in conventional stereo microscopes are arranged to view the object through a single objective lens. The optical axes of the light paths for the two eye-pieces are laterally displaced from each other as they pass through the objective lens. This produces viewing parallax for the two eyes, and this is interpreted by the brain as a stereo or three dimensional image.

Problem

Such stereo microscopes work well at resolutions, down to a few micrometres, but at higher resolutions there are two performance problems. Firstly, because the optical axes of the two light paths are displaced to either side of the objective centre, the effective aperture of the objective is reduced; this reduces the resolution of the microscope.

The problems associated with the reduced aperture effect are eliminated to give an enhanced stereoscopic effect

Perhaps more importantly, as the actual aperture of the objective lens is large, the depth of field at high resolution is very shallow, leading to a 'sectioning' effect. Thus, depth information, interpreted from a lateral shift between the left and right images, is lost, leading to a reduced stereo effect.

The Oxford Invention

The invention overcomes these drawbacks by creating two images with different viewing parallax and a greatly extended depth of focus. A video camera captures two images, which are then processed to produce a stereo pair or even displayed in real time. The problems associated with the reduced aperture effect are eliminated to give an enhanced stereoscopic effect.

Commercialisation Opportunity

This invention may be used in any field of microscopy where specimens are not entirely flat and high resolution stereo imaging is required. Thus, process control in semi-conductor chip fabrication, where 3-D structures can be quite intricate; and imaging thick biological specimens, such as live cell cultures or mammalian tissue, both in transmission and fluorescence are both important potential applications. This invention is now the subject of a patent application, and companies interested in developing the system for commercial applications are invited to contact Isis.

Seabed Texture by Sonar Profiling

Isis Project Number 1083

Background

Information from seabed surveys allows engineers to plan construction. Geotechnical surveys provide useful information such as the presence of exposed basement rock, boulders, gravel, sand, silt and clay as well as man-made structures such as pipes, cables and debris.

It would save considerable time and costs if a geotechnical survey could determine this type of information automatically.

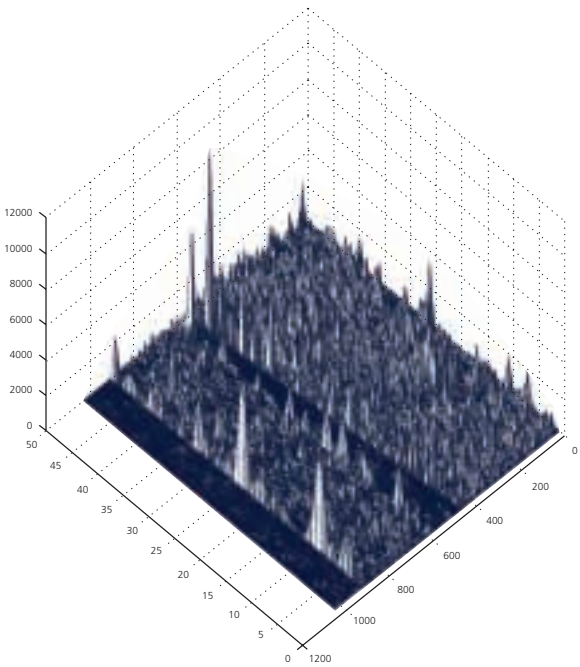
A three stage processing and classifying method has been developed within the Department of Engineering Science at the University of Oxford that will produce real time texture information from sidescan sonar pulses

Problem

Using current technologies, such as hyperspectral sensors, electromagnetic bathymetry and laser line scanning, marine geologists and engineers can map and also three-dimensionally image the seabed. It is still not possible to determine texture reliably without taking samples for analysis. Existing remote technologies such as sonar are not reliable, even with a high degree of computer processing, and are slow.

The Oxford Invention

A three stage processing and classifying method has been developed within the Department of Engineering Science at the University of Oxford that will produce real time texture information from sidescan sonar pulses. It improves the reliability and speed of automatic texture classification. Data predating this technique can also be used to create texture information.



Above: *Wavelet analysis showing four different sea beds, the seabed generated uses signals from 4 different seabeds using a 48 kHz sonar, the boundaries between the different types are clearly visible in the analysis.*

A visual display additionally allows the user to determine the class of texture, or a change between classes.

Commercialisation Opportunity

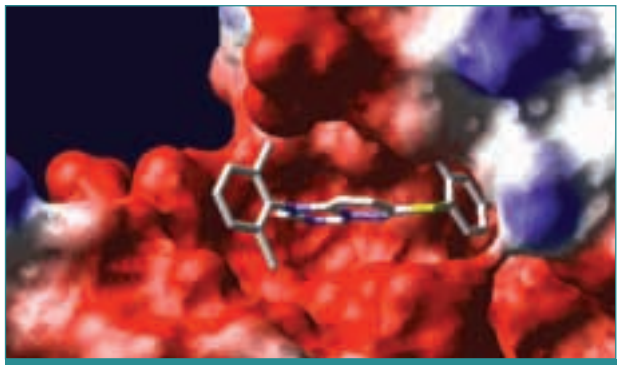
This novel software is the subject of a UK patent application, Isis Innovation is in a position to licence to interested parties.

Vertex Pharmaceuticals Incorporated

New OIS Member

Vertex Pharmaceuticals is a global biotechnology company, seeking to discover, develop and commercialise major pharmaceutical products. The company was founded in 1989 and is trading on NASDAQ. In 1999, Vertex's European research base was opened in Abingdon, Oxford, and now employs 70 scientists. In July 2001, Vertex acquired Aurora Biosciences in San Diego. Vertex currently has 1,000 employees in four locations, with headquarters in Cambridge, Massachusetts.

Vertex's proprietary, systematic, genomics-based platform is designed to accelerate the discovery of new drugs and to expand intellectual property coverage of drug candidate compounds and classes of related compounds. Vertex has engineered its research to enable the pursuit of parallel drug design in gene families. In essence, rather than focusing on a single protein target, as the industry has traditionally done, Vertex investigates entire protein families as it seeks out its lead compounds. Vertex applies a structural based drug design approach and utilises a suite of computational technologies, including X-ray crystallography, NMR and molecular modelling to design desired small molecule leads. The company has created an R&D engine able to compete with Big Pharma's stated productivity goals and has set itself on a path to enable the capability to produce 2-3 NDAs (New Drug Application) per year by 2005 onwards. Vertex anticipates that its gene family strategy will provide a sustained high level of productivity for new drug candidates in the coming years. In the last four years Vertex has discovered twelve NCE's (new chemical entities), nine of which were invented in the last two years. Vertex's clinical pipeline illustrates a strong track record in designing small molecule drugs based on biologically complex targets. The company's pipeline now includes more than ten drug candidates targeting a range of serious unmet medical needs. Vertex's first marketed drug is the HIV protease inhibitor, Agenerase®. The company anticipates an NDA filing for its second HIV protease inhibitor in 2002. Both these drugs are partnered with GlaxoSmithKline.



Above: *A 3-D image of pralnacasan, a first-in-class oral cytokine inhibitor currently in Phase II for the treatment of rheumatoid arthritis.*

Vertex's approach has resulted in multiple alliances with pharmaceutical partners over the last decade and pre-commercial payments from these collaborations total more than $1.5 billion. Going forward, partnerships will continue to be an important feature of Vertex's growth, maximising its commercial opportunities and providing Vertex with the opportunity to retain downstream rights to Vertex-discovered products. The company's solid financial standing has given Vertex the ability to steadily build downstream development and marketing capabilities.

In May 2000, Vertex entered into a collaboration with Novartis worth over $800 million in pre-commercial payments. The goal of this research alliance is to discover small molecule kinase inhibitors and to deliver to Novartis eight development candidates with proof of concept in man. Vertex will continue to enter into new alliances in order to pursue other gene families such as proteases, ion channels and GPCRs.

Vertex believes that its increased output in drug discovery and early development, combined with the depth and quality of its clinical development pipeline, are powerful indicators of the sustained value creation capability of the enterprise. In an industry where great value has historically been created based on the successful market introduction of just one or two major drugs, Vertex believes that it is well positioned for major clinical and commercial success in the years ahead.

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Genzyme

New OIS Member

genzyme GENERAL therapeutics

Above: *Malcolm Johnson, Vice President and General Manager, UK and Ireland.*

Genzyme is one of the top five biotechnology companies in the world and plays an important role in health care in more than 55 countries. Its UK head office is based in the Oxford Business Park.

Characterised by a commitment to the development of products and services specifically designed to meet unmet medical needs, Genzyme is active in areas ranging from therapeutics to biosurgery; from research in human genetics to diagnostic testing and services and from cell culturing to the bulk manufacture of high quality pharmaceuticals.

Since its formation in 1981, Genzyme has undergone considerable growth both in overall size and within its various specialised divisions. It has focussed on research and development, pioneering new markets and new products. It has achieved a leading position in specific markets by combining responsiveness with a dedication to improving quality both in the lives of patients and in health care in general.

Genzyme Corporation is comprised of three divisions:

Genzyme General develops and markets therapeutic products for well-defined patient populations, focusing on treatments for genetic disorders and other chronic debilitating diseases. Products currently on the market cover renal, thyroid and lysosomal storage disorders. The division also markets diagnostic products, genetic testing services and pharmaceutical intermediates.

Above: *Genzyme's UK Head Office in Oxford.*

Genzyme Biosurgery is formed through the combination of Genzyme Surgical Products, Genzyme Tissue Repair and Biomatrix, Inc. The division is a leader in the field of biosurgery, which is being created by the convergence of mechanical and biological approaches to surgery and other treatment methods. Genzyme Biosurgery boasts a portfolio of more than 20 products primarily focused on orthopaedics and cardiothoracic surgery, but includes products for other surgical applications as well.

Genzyme Molecular Oncology is developing a new generation of cancer products, focusing on cancer vaccines and angiogenesis inhibitors. It is shaping these new therapies through the integration of its gene discovery, gene therapy, small molecule drug discovery, protein therapeutic and genetic diagnostic efforts.

Managing Director Malcolm Johnson said, "Genzyme really looks forward to being an active member of the Isis community. We believe that joining such a premier group of forward thinking, dynamic associates is a key to future success."

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Computational Chemistry Aids Cancer Drug Discovery

New Oxford spin-out to use distributed computing for drug discovery

Above: *The completion meeting for Inhibox Ltd. Pictured are: Professor Graham Richards, Chairman, Chemistry Department, University of Oxford; Dr Chris Wright, CEO, IP2IPO; Ms Kate Eavis, Brobeck Hale and Dorr; Dr Edwin Moses, CEO, Inhibox Ltd; Mr John Clements, Director of Finance and Secretary of the Chest, University of Oxford; and Dr Tim Cook, Managing Director, Isis Innovation.*

The University of Oxford's latest spin-out is the drug-discovery company Inhibox Ltd, which uses advanced computational methods to carry out *in silico* screening on a massive scale to discover new leads for drugs quickly and cost-effectively. Initial projects are focused on cancer research, though other indications will be added in due course.

The company has access to a technique called 'massively distributed computing' based on the leveraging of computing power from individual PCs around the world. It uses software developed to screen libraries of molecules for suitable drug candidates, and this has already been the basis of the hugely successful 'cancer screen saver project'. This project was launched in April 2001 and to date involves 1.2 million PCs in more than 200 countries, providing 70,000 years of computer time – more than any supercomputer or the biggest pharmaceutical company could currently provide. The software calculates docking parameters for some 3.5 billion small molecules against binding sites on a macromolecule such as a protein. The opportunity to explore a wide range of potential molecules without the need for prior selection to limit computational requirements could lead to new classes of potential drug candidates.

Inhibox is the first chemistry spin-out to be launched since investment bank Beeson Gregory entered a joint venture with

Above: *Search results for HIV-Reverse Transcriptase showing the final iteration against the inhibitor nevirapine.*

the University of Oxford in November 2000. This deal entitles IP2IPO, a subsidiary of the bank, to half the University's equity in companies spun out of the Chemistry Department in return for a £20m donation towards state-of-the-art laboratories.

The company intends to add value to the intellectual property generated through *in silico* screening by working with a range of partners with appropriate drug discovery assets and skills. The company's Chairman, Dr Edwin Moses, previously Chairman and CEO of Oxford Asymmetry International plc, also a spin-out from the University, said: "Inhibox is superbly positioned to rapidly build on the very valuable intellectual property which has already been generated by the 'cancer screensaver project'. We believe that this is a company with substantial potential."

Inhibox has raised £400,000 in a placing of shares. Its founder, Professor Graham Richards, head of the Chemistry Department at the University of Oxford, has provided his total share entitlement, amounting to 25 per cent of the equity, to the National Foundation of Cancer Research.

Further information about the cancer screen saver project can be found at www.chem.ox.ac.uk/curecancer.html

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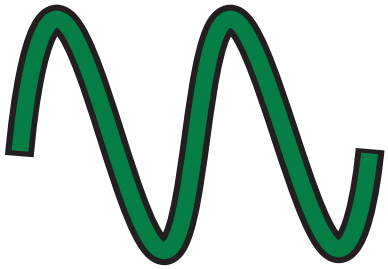
NaturalMotion Ltd

Brains, muscles and computer science – together at last!



NaturalMotion

NaturalMotion Ltd, a newly formed Oxford University spin-out, is using the latest research in biology, neuro-evolutionary computing and control theory to create believable and interactive simulations of characters. NaturalMotion's breakthrough technology is set to have an impact in multiple areas, with 3D computer animation being the initial focus.

"We are pulling together a number of different technologies, most of which didn't exist until a couple of years ago," notes Torsten Reil, co-founder and executive director. "At the core, we use our proprietary neural networks – computer simulations of the nervous system – to control physically simulated bodies, e.g. humans. These brains feed into muscles which in turn move the body."

Artificial Darwinian evolution is used to train the brains to perform a particular task, for example walking.

"Our approach is pretty much bottom-up, that is we don't try to guess everything beforehand, but rather let evolution do the job," explains David Raubenheimer, another co-founder and Senior Research Fellow at Magdalen College and Oxford's Department of Zoology, where the original technology was developed.

Imagine a games character that is not just a hollow computer graphic, but instead made of simulated flesh and blood

The result is realistic and truly interactive simulations of humans, animals or robots. The company is currently focusing on the former, but the technology is equally applicable to all things legged.

As an obvious first market for this technology, NaturalMotion is concentrating on 3D character animation for electronic entertainment such as computer games or movies. For this, it has recruited experienced software engineers, animators, and academics for its core software development team based in Oxford.

"Especially at this crucial stage in development, we have found it extremely valuable to talk to potential customers right from the beginning. What we have learnt from speaking to animators, for example, is how important full control over the animations is for them. On the other hand, they like that our technology allows them to direct our autonomous characters in the same way as a movie director does," says Colm Massey, the third co-founder and former head of the award-winning virtual human project at MathEngine plc.

While creating significant savings in development cost and time, it is ultimately the user who will benefit from NaturalMotion's approach. "Imagine a games character that is not just a hollow computer graphic, but instead made of simulated flesh and blood. It will always react like the real thing. And if pushed, it will fall down stairs like the real thing. None of this will have to be pre-animated."

NaturalMotion's first round of funding has come from private individuals from the games, film industry and business angels, as well as GorillaPark, the venture capital firm. Nick Alexander, former head of Sega Europe, is Chairman of the company. For further information on NaturalMotion and future investment opportunities, please contact Torsten Reil at the address below.

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Oxonica Ltd – Poised for Revenue Generation

From small things grow…

Background

Oxonica Ltd is one of the UK's leading nanotechnology companies. It originally spun out from Oxford University two and a half years ago and is developing, producing and commercialising nano-crystalline particles.

Oxonica's ability to use solid state physics to design the functionality of nanoparticles, and then use colloid chemistry to fabricate the particles and to modify their surface, generates functional benefits that can be applied to a large range of applications including life sciences and healthcare, environmental sciences, catalysis and telecommunications. This ability to provide solutions to many industry problems has resulted in substantial commercial opportunities for the company with significant revenues anticipated in 2002. The company has been angel-funded to date and is currently focused on raising £4 million to fund product commercialisation.

Based at Oxford University's Begbroke Science Park, Oxonica has a team of 11 with wide ranging scientific and commercial experience. Oxonica's CEO, Kevin Matthews, joined the company in 2001 from Rhodia SA, where he was responsible for running a global business and had extensive experience of new product commercialisation and portfolio development through strategic activities. The company employs scientists from the key enabling sciences of physics, materials science, chemistry and biochemistry.

the global market for nanotechnology products will be worth in excess of £80bn

The commercial team is experienced in a number of industries ranging from electronics and telecommunications through to speciality chemicals and pharmaceuticals.

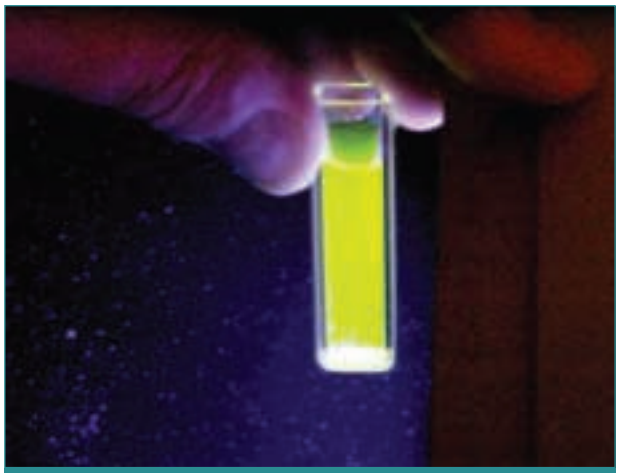
The Nanotechnology Industry

The emerging nanotechnology industry is very diversified and is a sub-sector of the Materials Industry. The UK Parliamentary Office of Science and Technology has estimated that the global market for nanotechnology products will be worth in excess of £80bn. The area of nanotechnology research is attracting significant public funding – the USA invested in a $497m Nanotechnology Initiative in 2001. In 2000 Europe spent $184m and Japan $170m. In addition, multi-nationals involved in funding long term research are estimated, in 1997, to have matched US government spending amounting to $350m.

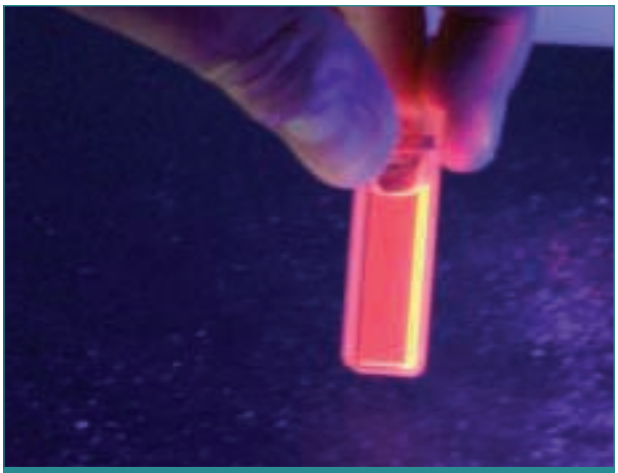
Products

One of the earliest revenue generators is expected to be a highly photostable sunscreen – the company is in advanced licensing negotiations with one of the world's leading suppliers of inorganic UV absorbers for sunscreens. Sunscreens reduce sunburn because their active ingredients are chemicals that absorb or scatter ultraviolet light. Based on work initiated in the Departments of Engineering Science and Biochemistry at the University of Oxford, Oxonica has been working on a modified form of UV absorber for use in sunscreen products with significantly reduced generation of potentially skin damaging free radicals.

Another significant product that Oxonica has developed is a nano-catalyst that improves the combustion process of fuel, and as a result generates significant reductions in emissions as well as improvements in fuel consumption. The initial target market for revenue generation is in Asia, where the health costs of air pollution are billions of dollars per annum. In parallel, formal engine approval tests are being carried out to facilitate roll-out in North America and Europe. Initial commercialisation is focused on the vehicle market, which is a $2bn market opportunity.



Above: *A green-emitting biotag.*



Above: *The optical emission of red-emitting biotags.*

However the Oxonica nano-particles appear to be effective in all types of fuel, and could in future be applied to related industries including marine, airline and power generation.

The Product Pipeline

Oxonica has chosen to follow a business model which focuses on the company's strength in the generation of intellectual property.

Oxonica has successfully developed a simple patented route to potential biolabels with the possibility of preparing commercial quantities of nano-crystals in aqueous solutions. The labels can be coupled to biomolecules via a linker molecule and used in diagnostics. The main applications for this technology will be drug discovery, molecular assays and biotissue imaging. The current market for biolabels is $4 billion and is estimated to grow to $7 billion by 2005.

In addition Oxonica, as part of a joint project with Johnson Matthey plc, has also succeeded in winning a grant under the Solar Section of the DTI's Programme on New and Renewable Energy. The grant supports a project that aims to develop New Transparent Conducting Oxides. Successful development of low cost processes to create such materials will lead to cheaper solar cells, making clean, affordable solar energy a reality. The project met the DTI's criterion; innovation that promises reduced cost and improved performance of new and renewable energy and that aims to improve the competitiveness of UK industry.

Dr Kevin Matthews explains: "A common misconception is that commercial applications for nanotechnology will exist only at some point in the distant future. Many applications exist today. Oxonica is proud of its constant stream of creative and innovative research, but it is important that the results of this research are turned into a commercial reality. Oxonica intends to ensure a continued stream of significant new product opportunities that will drive the growth of the company."

In Brief

Oxonica is a leading UK company in the rapidly developing nanotechnology industry. It has globally competitive break-through technology that was built over a number of years within the University of Oxford and has been further added to by Oxonica since being spun-out of the University in August 1999. The company has real near-term revenue generating opportunities in significant markets and has an experienced team of professionals to ensure delivery. The Company has an enabling platform technology that continues to generate a pipeline of high potential business prospects. Oxonica is currently engaged in securing £4 million in Venture Capital funds to drive the business forward.

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Pharminox Ltd

First spin-out company of 2002

Above: *The completion meeting for Pharminox Ltd. Attendees pictured are Mr John Clements, Director of Finance and Secretary of the Chest, University of Oxford; Dr David Phillips, Project Manager, Isis Innovation; Professor Gordon Lowe FRS, Emeritus Professor of Biological Chemistry, University of Oxford; Mr Tom Hockaday, Director, Isis Innovation; Dr Chris Wright, CEO, IP2IPO (Investors in Pharminox); Mr Jonathan Loake, Brobeck Hale and Dorr (Pharminox company lawyers).*

Wednesday, 16th January marked the formation of the first Isis spin-out company of 2002 – Pharminox Ltd. Pharminox has been established to develop and exploit a new family of platinum based anticancer compounds for the treatment of ovarian, testicular and colorectal cancer. A second family of compounds will also be developed for other indications including rheumatoid arthritis.

The intellectual property behind the new class of platinum complexes has been developed by Professor Gordon Lowe FRS, Emeritus Professor of Biological Chemistry at the University of Oxford. The compounds were developed by Professor Lowe during a study of DNA chemistry. The new compounds act through a completely novel pathway in the treatment of cancer. Tumour cells treated with these complexes are starved of the materials required for DNA synthesis through inhibition of the synthesis of DNA building blocks. It is also thought that the new compounds have a novel mechanism of delivery to solid tumours that will enhance their efficacy. It is hoped that the mechanism of action will remove the side effects traditionally associated with chemotherapy in general and platinum therapies in particular.

"this is one of the most exciting opportunities I have yet seen"

Initially the company will obtain full data on the activities of the family of over seventy novel compounds. The company will then focus development of the most promising compounds, aiming to develop the products and formulations in the clinic. Dr Neil Brown, Pharminox's CEO, has an established track record in this area. Formerly CEO of Debioclinic, Neil was responsible for bringing Oxaliplatin, one of the current leading platinum based cancer therapies, through to the market place.

Pharminox Ltd has been set up with funds raised by IP2IPO Ltd, a subsidiary of the investment bank Beeson Gregory, and funds provided by the Oxford University Challenge Seed Fund. Steven Lee, Vice President – Life Sciences at IP2IPO, said: "We are delighted to have been involved with the formation of Pharminox. Through my experience in the pharmaceutical industry I gained a good understanding of both the economics and technical aspects of anti-cancer drug development, and find this is one of the most exciting opportunities I have yet seen."

Pharminox Ltd and NaturalMotion Ltd (see page 15) have both been supported by BioForm. BioForm resides with Isis and is a DTi Biotechnology Mentoring & Incubation Challenge (BMI) award winner. BioForm helps create and support biotechnology start-up companies.

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Investors in People

Isis meets the Investors in People Standard

Above: *Tom Hockaday, Director, with Isis Innovation's Award*

INVESTOR IN PEOPLE

In November 2001 Isis Innovation Ltd was recognised for its commitment to staff development when it was awarded the Investors in People UK Standard. Isis now employs 23 staff, having grown steadily from a base of three staff in mid-1997. This growth has led to many changes, some which are essentially process and system based (e.g. filing more patent applications and marketing more technologies), and some to the culture and management of Isis.

We have seen Isis grow from a 'friends and family' culture where everyone knew what everyone else was involved in, towards more specialised roles and diffuse activities. We have by no means lost the friendly and supportive atmosphere, and are fortunate in the commitment and work ethic of all the staff, but need to be aware it is harder to maintain these as we grow. It is commonly understood and easily said that people are the key to any business and that communication is essential to successful growth. It is less straightforward to assess how an organisation is actually looking after its people and whether information is effectively being transmitted and received in all directions; Investors in People provided us with a framework to assess these points.

Investors in People is the national standard which sets a level of good practice for training and development of people to achieve business goals. Assessment is based on the principles of commitment, planning, action and evaluation, and examines twelve core indicators. The Standard was developed in 1990 by the National Training Task Force in partnership with leading business, personnel, professional and employee organisations.

We started to consider the programme in May 2001, provided information on our existing activities and approach in the following months, met with our assessor in October and received notification that we met the Standard in November. Isis is neither a conventional nor straightforward business and we were impressed by the flexibility and insights of the assessors in understanding our activities. The actual assessment involved a single day of short interviews with approximately half our staff, with immediate initial feedback from the assessor that day. The interviews are confidential and comments in the subsequent written report are unattributed; this hopefully encourages staff, should they need it, to comment on their employer's shortcomings.

The Investors in People Standard is aimed at all organisations to help them improve performance. Organisations who meet the Standard need to show that their investment in people is effective because: they are committed to developing their people; they have clear goals and make sure that everyone understands them; their investment in people directly helps them to meet those goals; they understand the impact that their investment has on their performance.

We entered the process wanting to learn and improve Isis, expecting shortcomings to be identified so we could resolve them. Meeting the Standard shows we are on the right track, but also highlights that remaining on track requires hard work as we continue to grow. Overall we found the process highly informative in helping direct future staff development at Isis. It is a practical tool that can help harness training and development to meet organisation goals. Running an organisation so that it meets the Standard is a good way of managing people and doing business.

Further Information

W www.investorsinpeople.co.uk

Meetings

Isis
University of Oxford
Innovation Society

Forthcoming meetings of the
Oxford Innovation Society
will be held on the following dates:

Thursday 21st March 2002

Thursday 26th September 2002

Thursday 12th December 2002

All meetings will be held at 5:30 p.m. followed by a Reception and Dinner for members and invited guests at a University college.

For information about the OIS contact Jennifer Johnson, Marketing Administrator:
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