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CONTENTS

Medical Engineering & Surgical

DEPLOYABLE STENTS - Isis Project No 946

Leading research at the University of Oxford, Department of Engineering Science, has resulted in the novel design of stents for use in interventional surgery for stenosis.

Background

A stent is a medical device used to hold open tubular body passageways such as the aorta and oesophagus, it may also be used in the treatment of cardiovascular disease. Stenosis (narrowing or obstruction) of such passageways can result in major medical problems. For example stenosis in blood vessels, supplying the heart muscle or the brain, can reduce the flow of blood to such an extent that the critical areas are no longer able to function. When this happens, a heart attack or a stroke can occur. It is possible to re-open stenosed blood vessels with stents, which are inserted into the lumen of the vessel and are then expanded to keep the vessel open, and maintain adequate blood flow.

Problem

Stents can be made of metal mesh, which allows a good expansion rate and tractability. However, restenosis is a major problem with these types of open structures, as tissue will grow between the mesh to block the lumen again. When this happens, it is not possible to remove the stent, and another one will have to be inserted in order to correct the problem. As this involves stents being implanted inside one another, there is a limit to the number of stents which can be implanted at one location. Covered stents can reduce this problem, however the use of a cover brings the risk of slippage, and hence migration of the stent.

The Oxford Invention

An exciting new research program at the University of Oxford has resulted in the development of several novel design structures for stents. These stents would be made out of a sheet of biocompatible material, thereby preventing restenosis, and the pattern of folds, along with roughening of the outer surface, should greatly reduce slippage and migration compared to other covered stents. The pattern of folds should allow for easy expansion once in position, and if required, the tube can be contracted both radially and longitudinally to allow for easy removal. These new stents should also improve on expansion rate and tractability over existing models.

Commercialisation Opportunity

Due to the enormous incidence of cardiovascular disease in every part of the globe there is a very large market for this technology, which would improve the quality of interventional surgery. Stenosis can also occur in other vital areas of the body such as the trachea, and so this invention would have wide applications in other areas of medicine as well as

cardiovascular. Patent protection has been applied for, and Isis would welcome enquiries from potential partners interested in commercialising this intriguing, innovative technology.

3-DIMENSIONAL ENGINEERED TISSUE - Isis Project No 1088

Researchers at the Department of Engineering Science have developed a nutrient circulation and scaffold system for 3-dimensional bulky tissue culture.

Engineering tissue involves the seeding of appropriate cells in to a scaffold to form a bio-construct or matrix. The Oxford invention comprises of systems of capillaries made of semi permeable membranes where pore size is sufficiently small to keep cells from leaving the system. The capillary network is embedded within the scaffold made from biopolymers or synthetic polymers; cells attach to these scaffolds, are serviced by the capillaries and grow to form tissue.

Figures 1 & 2 are SEM pictures of rat bone marrow fibroblastic cells grown in perfused hollow fibre bioreactors. Cell growth and tissue formation are significantly higher than the control without the membrane capillary perfusion.

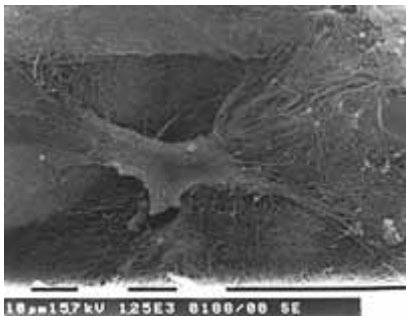


Figure 1
Cells grow on collagen scaffold and produce new collagen fibrils

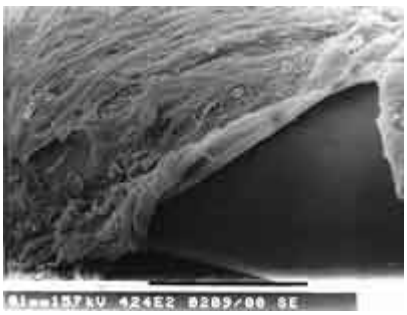


Figure 2
Cells do not grow directly on the hollow fibres and do not block the pores

The Oxford Invention

The invention employs biodegradable porous membrane capillaries to mimic blood capillary network in the natural tissue. No other engineered tissue currently employs a system of capillaries that deliver nutrients and remove metabolic waste deep inside and tissue growth is no longer governed by diffusion of nutrients from outside the scaffold. Biodegradation of the capillary membrane is a useful feature because as time progresses the pores will widen allowing more nutrients in and waste out allowing tissue of greater density to be grown. As the tissue becomes bulkier, epithelial cells can be introduced in to the capillaries to promote blood vessel formation. This invention enables the culture of 3-dimensional tissues opening the possibility of growing more complex structures (such as complete organs).

Commercial Opportunity and Patent Status

Isis Innovation Ltd has filed a patent application on this technology and is interested in hearing from companies wishing to licence this technology.

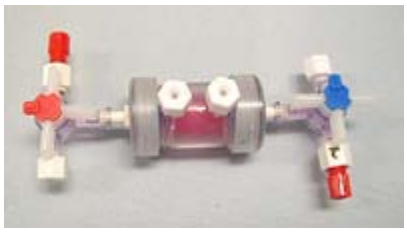


Figure 3

Experimental hollow fibre bioreactor

Keywords

tissue engineering, tissue culture, scafford, membrane capillaries, capillaries, bio-construct , semi-permeable membranes, matrix

ELECTRONIC DEVICE FOR TREATING BACK PAIN - Isis Project No 1141

Novel research at the University of Oxford and the Nuffield department of orthopaedics has resulted in the development of a prototype medical device aimed primarily to relieve musculo-skeletal pain. Presently there is plenty of scope for future licences involving this attractive technology.

Marketing Opportunity

Musculo-skeletal symptoms are widespread and a considerable cause of personal and public hardship. Nearly two-thirds of adults in the UK alone have had experience of back pain; and 2.5 million people have back pain every day of the year. You will know how debilitating back pain can be - whether it is an acute episode or chronic condition. The effects of back pain can be devastating not just for the person living with the problem, but also for their family, friends and carers. The simplest chores and activities from shopping to walking may become impossible. Constant physical pain can impact on an individual's emotional well being. The cost to the NHS, business and the economy is an estimated £5 billion per year. However, good back pain treatment remains patchy and individuals rarely receive speedy attention and treatment needed to prevent an acute episode becoming a chronic problem.

The Oxford Invention

The Oxford invention is a palm-top controlled device to help people with chronic pain (especially in the back and the shoulder) relearn their sense of position and space. This function is severely damaged in people with chronic pain. Pain is relieved when position and

space sense is restored. This device is currently undergoing limited clinical trials at the Nuffield. This device may also be applied to other types of musculo-skeletal pains such as chronic lower back pain, whiplash injuries to the neck and possibly repetitive strain injuries.

The Patent Status

Isis Innovation is seeking commercial partners to exploit and further develop this novel and exciting technology. Isis Innovation has applied for patent protection for this technology.

Keywords

pain, back pain, chronic back pain, injuries, repetitive strain

DEVICE FOR TREATMENT OF BLEPHAROSPASM - Isis Project No 1195

Work in the Eye Hospital at the Radcliffe Infirmary in Oxford has resulted in the design of a simple device for relieving the symptoms of blepharospasm.

Therapeutic Area

Treatment of blepharospasm.

Background

Blepharospasm is a form of dystonia affecting the muscles surrounding the eye and causes uncontrolled blinking and closure of the eyelids. Sufferers may be unable to prevent their eyes from clamping shut leaving them effectively blind. Blepharospasm affects more than 4000 individuals in the UK and it is thought that this number may exceed 400,000 worldwide.

Problem

There is currently no cure for blepharospasm. A number of treatments are available although these are often unsatisfactory and may be invasive or have undesirable side effects. For example, a common treatment involves injecting botulinum toxin into the muscles around the eye which may cause droopy eyelids and double vision and only provides temporary relief. There is clearly a need for a more acceptable treatment.

The Oxford Invention

Scientists at the Eye Hospital at the Radcliffe Infirmary in Oxford have developed a simple device that can be attached to a pair of spectacles and effectively relieves the symptoms of blepharospasm.

Commercialisation Opportunity

Isis Innovation is currently looking for a commercial partner to develop, manufacture and market this device and would welcome inquiries from potential partners interested in commercialising this technology.

QUANTIFYING EXPOSURE TO STRESS - Isis Project No 1254

Novel research at Oxford University has resulted in the development of a quantitative test for measuring stress in mammals, including Humans. Presently there is plenty of scope for future licences involving this attractive technology.

Market

Psychological stress is epidemic in the 21st Century. In humans, it is associated with major causes of death including cardiovascular disease, lung diseases, immune disorders, psychological disorders, workplace absenteeism and ulcers. Stress-related disorders are also extremely financially damaging to the farming industry, and are a dominant feature in veterinary practices. To date, despite various rough indicators of stress, there has been no development of quantifiable and practical measures of stress for use in humans or animals.

Oxford Invention

Researchers at Oxford and Coventry University have developed in vitro a method for quantifying stress from a single drop of blood. It relies on changes in the immune system that can be analysed quickly. Which means, for the first time, it will be possible to produce a quantitative measure of stress.

Applications

1. Monitoring stress in the workplace, optimising the potential of the workforce
2. Selecting individuals for highly stressed jobs
3. Health Screening for insurance purposes
4. Drug Screening
5. Environmental improvements in home & workplace
6. Optimising stress relief e.g. when travelling, in leisure facilities & the use of stress relieving devices
7. Improving farming techniques
8. Veterinary services: monitoring stress levels in domestic pets

Commercial Opportunity & Patent Status

Isis Innovation has applied for patent protection and is seeking commercial partners to exploit and further develop this novel and exciting technology.

Keywords

Stress, tension, blood test, blood testing, welfare human & animal, Neturophils Immune system, insulin pen, blood test medical devices, Luminometers, well-being and lifestyle

BREAST CANCER DETECTION - Isis Project No 1260

Small clumps of calcium salts - microcalcifications - are often the earliest signs of breast cancer, and appear in 25% of mammograms. Oxford inventors have developed a new method to identify more reliably these clusters.

Background

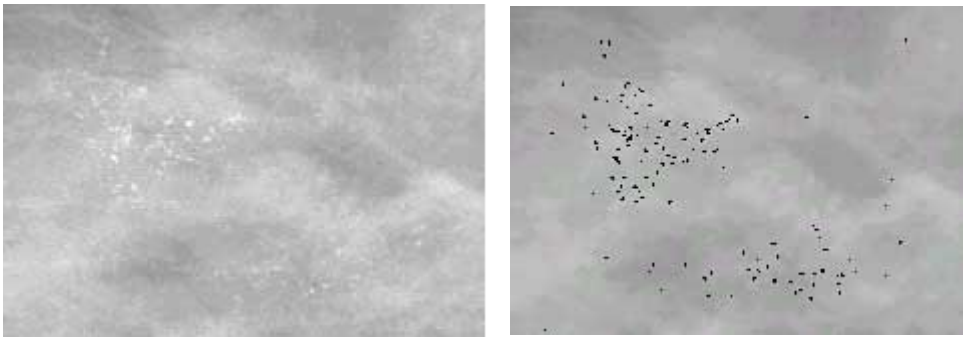
Calcifications appear as bright spots or clusters of spots, and small clustered whorled calcifications are those most likely to indicate malignancy. The existence of microcalcifications in a mammogram is a clear warning of abnormality. Any program to assist a radiologist detect microcalcifications must miss few, if any, clinically important clusters, but equally must not signal too many false positives. With the increasingly vast number of mammograms to be analysed from screening programmes automated computer-aided detection methods are a necessity.

Problem

Although several methods have been proposed for detecting microcalcification clusters they all have limitations including the return of too many false positives.

The Oxford Invention

Mammogram Samples Containing Microcalcification Clusters



Original Standard Mammogram Format Foveal Image Processing

Using a foveal segmentation method based on differential local contrast in the image the new Oxford method has significantly reduced the risk of both false negatives and false positives.

Commercialisation Opportunity

This work is now the subject of a patent application, and Isis is looking to negotiate with any company interested in commercialising this excellent opportunity in cancer detection.

Keywords

microcalcifications, breast cancer detection, breast cancer mammograms, microcalcification clusters, foreal segmentation, false positives, false negatives, cancer detection, malignancy, screenings

IMAGE VELOCITY ESTIMATION IN ECHOCARDIOGRAPHS - Isis Project No 1283

A newly developed enhanced method for extracting cardiac boundary pixels from echocardiographic sequences.

Background

There are many instances in which a subject in an image is moving, and it is necessary to track the subject as it moves from frame to frame; this movement is known as optical flow or image velocity. Such measurement of optical flow may be done to improve the image encoding efficiency, or allow enhancement of the display of the movement of some particular tracked part of the image to assist an observer attempting to interpret the image. Optical flow determination methods fit into one of three groups: differential techniques, frequency based methods and matching techniques.

Problem

Medical images present many difficulties in image processing because of their typically high noise level. Thus, the tracking of cardiac walls in cardiac ultrasound images is difficult because of the inherent high level of noise found in such images and also because of the way in which cardiac motion varies during the cardiac cycle. Several means of identifying and tracking cardiac walls in echocardiograms have been proposed, but it is a difficult task which requires improvement.

The Oxford Invention

The Oxford invention for identifying boundary pixels in echocardiographic sequences or other ultrasound image sequences consists of a phase boundary detection stage followed by an optical flow estimation stage based on block matching methods. New contributions to these basic computer vision processes have resulted in a system that is both fast and robust.

Commercialisation Opportunity

This work is now the subject of a patent application, and Isis now wishes to discuss suitable arrangements with companies interested in developing and using this technology.

Keywords

echocardiographs, image velocity, cardiac, optical flow, ultrasound, boundary pixels, cardiac cycle, ultrasound image, medical image

ENGINEERED TISSUE PROBES - Isis Project No 1378

Researchers in the Department of Engineering Science have developed a technology for the on-line monitoring of cell metabolic activity, cell viability, function and tissue status.

Background

It is important to monitor cell activity and functions inside three-dimensional engineered tissue during the culture process in vitro in order to optimise the design and operation of the tissue culture process. It is also critical to monitor tissue status following transplant/implant (e.g. tissue grafts and implantation of engineered tissue). Possible techniques at present include MRI and ultrasound, both are time consuming, expensive, give low resolution of images and also can only provide limited biochemical data.

In three-dimensional tissue cultures, having a technology that can measure the following would be invaluable:

1. Following an implant or transplant:
   a. Condition of grafted tissue,
   b. Possible signs of cell stress.
2. In tissue cultures:
   a. Correct cell growth,
   b. Correct cell environment.

The Oxford Invention

A micro membrane probe that samples soluble markers of cellular metabolism and tissue turnover both non-destructively and quantitatively within engineered tissue during culture periods in a bioreactor and the subsequent on-line and off-line analyses. The technology also has applications in meat and fish quality inspection (for contaminants such as bacterial toxins, heavy metals and pesticides).

Commercial Opportunity

In order to protect the invention, Isis Innovation Ltd has filed a patent application on this technology. We are interested to hear from companies wishing to licence this technology.

Keywords

micro membrane probes, transplanted tissue, engineered tissue, non-destructive engineered tissue, tissue culture, 3-D tissue cultures, tissue grafts, cellular metabolism, tissue turnover, food contamination

ALIGNMENT OF MULTIMODAL NOISY IMAGES - Isis Project No 1405

Isis Innovation, the technology transfer arm of the University of Oxford, releases a new method for automatically aligning multimodal noisy images.

Marketing Opportunity

The alignment of two or more images is a fundamental image analysis problem with a diverse set of applications. These include Image registration, for example medical image registration, in which the images may be of the same or different types (e.g. MRI, CT, PET in the case of medicine; infrared, visual, synthetic aperture radar in the case of aerial image analysis; etc) or may be of the same or different subjects (patients) at different times. Alternatively, the challenge may include matching two images (for example aerial images) of nominally the same scene; but which differ either because they are taken with different sensors or frequency bands (e.g. Infrared or ultraviolet) or under different imaging conditions. In the case of image motion, the computation of the optic flow or the estimation of three-dimensional structure from motion, require that images be aligned. Finally, in the case of multi-view image analysis such as stereovision, the simultaneously taken images from two or more cameras are combined to form an estimate of the three dimensional locations of points in the scene.

Although primarily aimed at medical imaging (2, 3 and 4 dimensional) applications this technology could be used in any of the imaging fields described.

The Oxford Invention

Image alignment is a difficult problem for several reasons; the signal to noise ratio of many images, particularly medical images, is low; the two (or more) images to be aligned often have different spatial resolutions (e.g. CT and PET); and the objects to be aligned in the two images may require "warping" from one image to the other. The Oxford invention uses a new similarity measure as well as a process for coping with noise content that delivers a technique that supersedes current image alignment methodologies.

SUPPRESSION OF TRANSPLANT REJECTION - Isis Project No 1439 & 2848

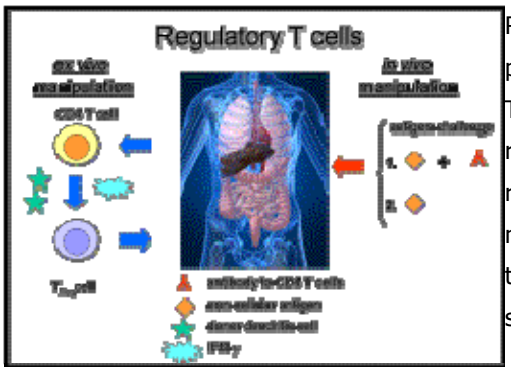
New method for generating regulatory T cell (Tregs) that avoids the need for cell sorting

Marketing Opportunity

Transplantation is the treatment of choice for end stage kidney, heart, liver and pancreas organ failure. Despite considerable advances in the management of transplant rejection in recent years most transplants are still eventually rejected. In addition, current

immunosuppressive approaches leave transplant recipients more susceptible to infections and cancer.

The Oxford Invention



Researchers have devised two new methods for producing important regulatory T cells, known as Tregs. Tregs can control destructive rejection responses so that donor organs are less likely to be rejected by a recipient's immune system. Other methods for ex vivo Treg generation are known but their use is limited by the requirement for cell sorting using flow cytometry.

The patent applications describe novel methods for the generation of Tregs both in vivo and ex vivo.

- For in vivo generation, immunisation with a non-cellular antigen combined with a monoclonal antibody to CD4 T cells is followed by a second challenge with the non-cellular antigen at or near the point of transplantation. This approach can also be used ex vivo.

- For additional ex vivo generation, recipient CD4 T cells are cultured with TGF-b conditioned donor type antigen presenting cells in the presence of IFN-g. This leads to preferential death of effector cells, expansion of naturally occurring Treg and conversion of non-Treg precursors resulting in an enrichment for donor-reactive Treg.

In a clinical context, patients would be pre-exposed to the in vivo therapy before transplantation and their resulting Treg population maintained by re-challenging with the non-cellular antigen until transplantation. This approach does not require that the identity of the organ donor is known before the therapy commences. The ex vivo approaches could enable the administration of regulatory T cells as a cellular therapy to control transplantation rejection at the time of transplantation, or at any point thereafter, to ensure that control of rejection is maintained. The in vivo and ex vivo approaches have the potential to be used in combination. This approach is also potentially applicable for the treatment of autoimmunity.

Patent Status

The patent applications are available for licence and we are actively seeking partners for the licensing and commercial development of this technology.

ANAESTHESIA - CAN THE PATIENT FEEL THE KNIFE? -

Isis Project No 1501

A new method for monitoring changes in the physiological state of a patient during anaesthesia.

Marketing Opportunity

Anaesthetic agents are potentially dangerous drugs, and major patient complications can occur. If the patient is overdosed, death or major body organ damage can occur. Conversely, if the patient is under-dosed, patient awareness can occur. There is a narrow drug concentration "window" for both drug safety and anaesthetic efficacy, and the development of ways in which to monitor drug delivery concentration has been a major driver in anaesthetic agent safety research.

The Oxford Invention

The Oxford invention has met this anaesthesia challenge by using modified statistical techniques to classify the physiological state of a human or animal subject. The classification monitors changes in the physiological state that occur over time either spontaneously or from external stimuli. Typical data are obtained from performing an encephalogram; this classifies the cognitive state of the subject. Subsequent tests on data obtained from anaesthetic trials have demonstrated the efficacy of the method for classifying brain activity, and hence the depth of anaesthesia.

The method may be used with other forms of physiological data: electromyography to indicate muscle activity; analysis of images from magnetic resonance, computed tomography, X-ray and ultrasound; electrocardiography for blood pressure and blood oxygenation.

Other applications include the monitoring of:

- Consciousness
- Sleep
- Neuropathology
- Cerebral intoxication
- Cognitive state
- Muscle tremor

Patent Status

This work is the subject of a patent application, and the Isis Project Manager would like to discuss this licensing opportunity with companies interested in developing the method into a commercial reality.

ANISOTROPIC, SELF-INFLATING TISSUE EXPANDER - Isis Project No 1514

Researchers at the University of Oxford have developed a novel tissue expander, for use in reconstructive surgery, with the ability to expand in only one direction.

MARKETING OPPORTUNITY

Tissue expanders are essential in providing extra soft tissue for a wide range of reconstructive techniques. However they have a number of disadvantages. Inflatable silicone balloons are bulky and unsuitable for small delicate areas. They must be regularly inflated by means of a filling port, which is both time demanding and painful for the patient and there is a risk that the device may leak. Self-inflating hydrogel expanders have heralded a significant advance. However they expand isotropically at an uncontrolled rate and have limited expansion limits. Therefore their use in specific applications such as cleft palate surgery, syndactyly (fused digit) release and facial reconstruction has been limited. There is a clinical need for an anisotropic device, offering unidirectional and controlled expansion, especially in confined anatomical locations.

THE OXFORD INVENTION

A novel, anisotropic, self-inflating, hydrogel tissue expander has been developed using characterised compounds that can be machined or shaped appropriately for the desired application. The device, which can be sterilised, markedly increases the potential indications for which this restorative tool may be employed. By controlling both the anisotropic processing technique and the device composition, it is possible to accurately tailor the ultimate expansion ratio and the expansion rate within a wide range The device may be further enhanced by the incorporation of drugs, growth factors or radio-opacifiers in order to tailor the device to specific clinical indications. The technical feasibility and anisotropic efficacy of the device has been determined by means of a preclinical study.

PATENT STATUS

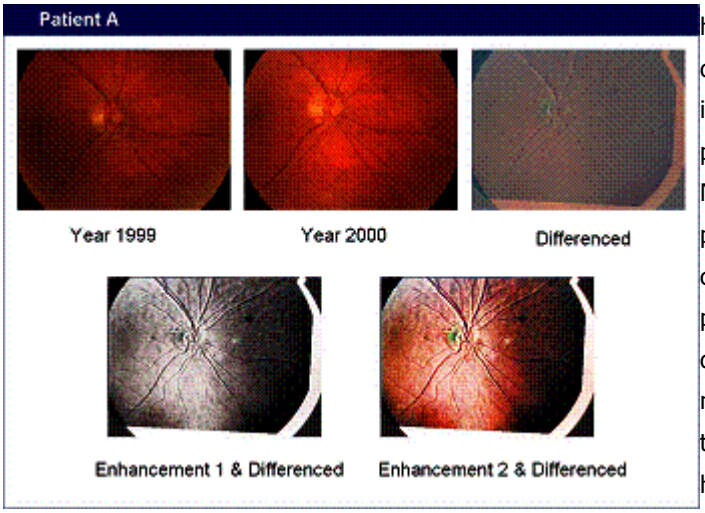
This work is the subject of patent application, and Isis would like to talk to companies interested in developing the commercial opportunity that this represents. Please contact the Isis Project Manager to discuss this further.

AUTOMATED RETINAL IMAGE DIFFERENCING - Isis Project No 2158

Isis Innovation, the technology transfer arm of the University of Oxford, announces ARID - a new method for the assessment of diabetic retinopathy.

Marketing Opportunity

Diabetic retinopathy is a serious sight threatening condition. It is still the major cause of visual loss in the UK and the major cause of working age adult blindness. The risk of retinopathy may be reduced by attention to glycaemic control and the treatment of



hypertension. If retinopathy is detected early, then laser treatment is effective in preventing the progression of the disease. The UK National Service Framework working party has recommended the use of camera technology for fundal photography using either film or digitisation with the emphasis being now on digital photography. However the scale of the management task for handling photographs is huge. Taking the conservative estimate that 2% of the UK population has diabetes implies over 1,000,000 ophthalmic screening visits every year leading to at least 2,000,000 photographs in the UK alone annually, for the USA population this equates to approximately 20,000,000 photographs.

The Oxford Invention

ARID is a computer system that highlights change between retinal images over time. ARID analyses similarities in images, matches them up, and identifies the changes between them. This demonstrates what exactly has changed to the user. It does not replace the retinal image screener, but reduces the workload of images that require grading.

ARID can be a care based system where clinicians will be able to detect change in the retina instantly as soon as a new image is taken. This is a real time procedure that will demonstrate to the patient why tight glucose control is important.

Project Status

Isis would like to talk to companies interested in developing the commercial opportunity that this represents. Please contact the Isis Project Manager to discuss this further.

TISSUEFLEX® CELL CULTURE TECHNOLOGY - Isis Project No 2167

Researchers in the Department of Engineering have developed innovative small-scale bioreactors for cell and tissue culture that give greatly improved reliability and reproducibility of results, while requiring minimum operators' intervention.

Background

Culturing cells and tissues is a core activity in medical and biological sciences and is typically carried out in cell culture flasks or microwell plates. Successful cell culture has a number of basic requirements, including sufficient nutrients, gas exchange (oxygen in, carbon dioxide out), and sterile conditions to ensure the culture is not contaminated. As traditional cell

culture vessels are essentially closed (batch or semi-batch) systems, the culture conditions change with time and cells could become starved of nutrients over time. For longer culture studies regular change of growth media is required; this does not eliminate the culture condition fluctuation and also risks contamination. Successful culture of three-dimensional tissue has additional requirements including a supporting scaffold, and nutrient supply to all parts of the bulk tissue.

The Oxford Invention

Engineers at the University have developed simple but highly sophisticated bioreactors, which provide an ideal environment for cell culture. TissueFlex® bioreactors are:

- Perfused: steady state nutrients supply and and waste removal without contamination;
- Gas permeable: good gas exchange again without any risk of contamination;
- Transparent: allowing ready observation of the cells and optically based bioassays;
- Self-sealing: the walls can be injected through to inoculate or sample the culture without having to open the culture vessel;
- Versatile: suitable for multiwell plate format, high throughput applications using commercial equipment;
- Flexible: allowing mechanical stimulus e.g. for musculoskeletal cell culture;
- Sterilisable: by standard methods;
- Scaffold for three-dimensional tissue growth can easily be included.

The TissueFlex® bioreactors have been shown to give substantially greater cell viability than static culture and this is achieved with excellent control of physiologically relevant parameters such as pH and nutrient concentration.

Commercial Opportunity and Patent Status

A patent application has recently been filed to protect this work. Isis would be keen to talk to companies interested in developing the commercial opportunities for this technology.

PHASE CORRECTION AND DIFFRACTIVE OPTICAL ELEMENTS - Isis Project No 2369

Research at the University of Oxford's Department of Engineering Science has resulted in a new method for producing high quality phase correction and diffractive optical elements, for a fraction of the cost of existing manufacturing methods.

Background

A normal "optical window" has flat surfaces and uniform optical properties to ensure that a light wave transmitted through the window does not get distorted, unlike a lens for example, that modifies a light wave by focusing it at a certain point. Phase correction or diffractive

optical elements (DOEs) also change the "shape" of the light waves that pass through them, however using a different method to a normal lens. DOEs have either a surface micro-relief (tiny difference in thickness) and/or non-uniform optical properties (different refractive indexes), which are designed to modify the "shape" of any light passing through it in a controlled manner. A DOE appears to be a thin, flat window, but can reproduce the effects of many large lenses and can produce other unique optical effects.

DOEs can be used with any type of lens system, however currently they are too expensive to be used in mass consumer markets due to the costs of manufacture. Their use is restricted to high value applications, where they are used to correct aberrations in laser beams, or to shape laser beams into extended shapes/multiple beams. These processes are used in imaging instruments, metrology, and laser materials processing, as well as many other specialist applications.

The technology developed at the University of Oxford opens up host of new potential markets, by providing a method of producing inexpensive and high quality DOEs

Market Opportunity

(A DOE shaping a laser)

Current techniques used to manufacture high quality phase correction and DOEs are based on producing a fine surface-relief structure on one side of an optical window. This surface-relief structure is very fine, accurate on the micron scale, and is commonly produced by diamond turning or reactive ion etching. Both of these techniques are time consuming and very expensive, and consequently the use of these optical elements is limited. Plastic elements can be produced cheaply by the replication of etched elements, however these plastic elements are normally of poor quality and therefore their usefulness is also limited.

The Oxford Invention

The Oxford invention makes it possible to produce high quality optical components at a fraction of the cost of existing technologies.

Commercial Opportunity and Patent Status

This invention is now the subject of a patent application. Companies interested in developing this system for commercial applications are invited to contact Isis Innovation to discuss this further.

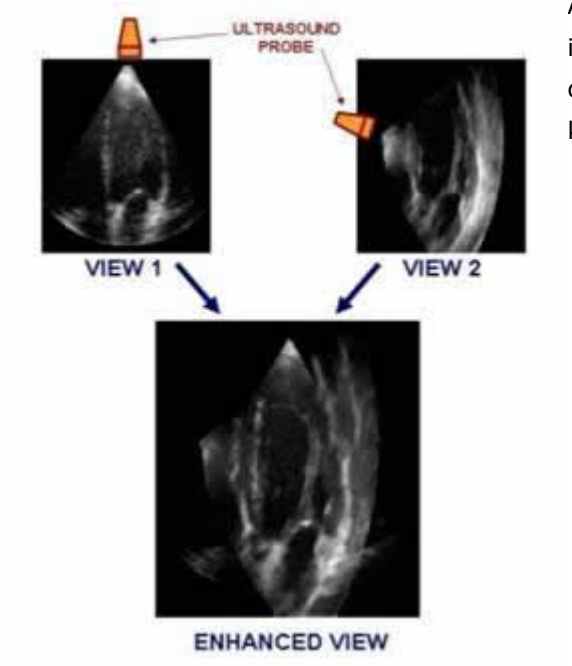
OPTIMAL WHOLE-HEART ULTRASOUND IMAGING - Isis Project No 2586

A new method for combining ultrasound images to produce a single, optimal data set, whilst retaining the quality and content of the original images.

Market Opportunity

Recently developed technology has allowed, for the first time, the acquisition of 3 dimensional ultrasound echo images of the heart in real time. This new imaging modality opens a wide range of possibilities in echocardiography. However, it is not currently possible to scan the whole adult heart in a single acquisition, hence the development of tools to combine acquired images is of great importance. Simple techniques currently used to combine the images, which work by taking the mean or maximum intensity at each pixel (or voxel), can result in the reduction of information content. The difficulty in combining the ultrasound images, while still retaining the original information, limits the visualization and quality of image analysis that can be performed. A solution would be of great benefit to medical ultrasound imaging.

The Oxford Invention



A new method of combining a number of images of a common object has been developed at the University of Oxford. The key features of this technology are:

- Use of a feature measure protocol that identifies key features of interest in each of the original images in order to retain important information in the combined image.
- Use of knowledge of the ultrasound acquisition process to identify the images that better characterize the scanned structures. This invention provides a way to fuse ultrasound images (2D, 3D, 2D+T, 3D+T) taken from different acoustic windows or

views of the object to define a new image

- Relative weights of the images are estimated that result in a combined image in which the information content from the individual images is maximised.

These features combine to give a method that delivers a resultant image that is of better quality for subsequent visualisation and analysis. The resulting combined image may be used in a variety of manners including general tasks such as display, segmentation or tracking. However, the improved quality of the images facilitates their application to more complicated tasks such as object recognition or alignment, for example in image-guided interventions, surgery and therapy.

Patent Status

This work is the subject of a patent application, and Isis would like to talk to companies interested in commercialising this technology. Please contact the Isis Project Manager to discuss this opportunity.

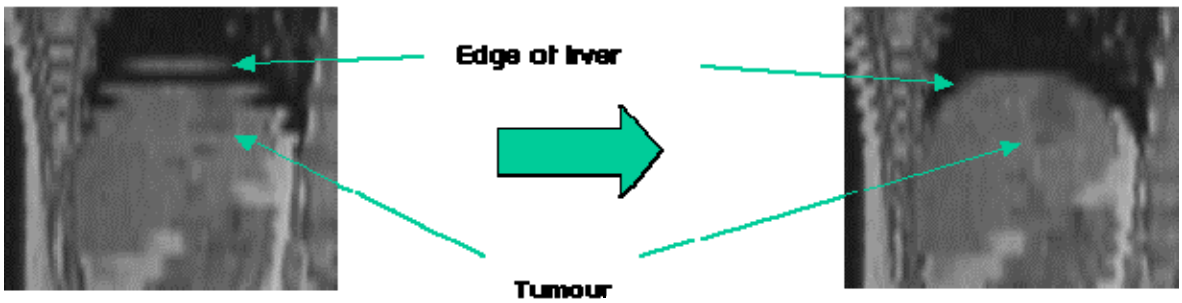
ACQUISITION OF IMAGES OF MOVING ORGANS - Isis Project No 2835

Introduction

Isis Innovation, the technology transfer company of the University of Oxford, releases a new method for the acquisition of medical images of moving organs.

Marketing Opportunity

Worldwide over 1 million people are diagnosed with colorectal cancer annually, with a great proportion developing metastatic liver disease requiring follow up with abdominal Magnetic Resonance Imaging (MRI). Radiographers and Radiologists have raised breathing artefacts as a major issue in accurate diagnosis and estimation of tumour volumes. With current methods, in 19% of cases at least 5% of the liver is missed. Indeed, for lesions between 6 and 30mm in diameter, 3% are missed completely with a further 21% being incorrectly staged, leading to false diagnosis of disease progression or regression.



The Oxford Invention

Working closely with clinical staff, Oxford scientists have used their expertise to find a robust solution. On the left, is an image that is reconstructed from a series of slices. The liver boundary is not smooth and the tumour seems to consist of multiple parts. After application of the Oxford technology, the liver outline is much smoother and the tumour well represented by a spherical shape. The technology significantly improves patient comfort by reducing scan duration and avoiding recalls. The improved quality and accuracy of the dataset provides meaningful estimation of tumour volumes for more precise chemotherapy dose calculation. It is estimated that 25% of the annual 2 million abdominal MRI scans worldwide would benefit from this innovation. The invention reached the Finals of the 2007 Medical Futures Innovation Awards and was also the subject of a recent paper in the European Journal of Radiology.

It is planned to extend the technology to other organs and modalities.

Commercialisation Status

The underlying method is the subject of an International Patent Application and could be implemented on existing and new MRI systems. Isis would like to talk to companies interested in developing the commercial opportunity.

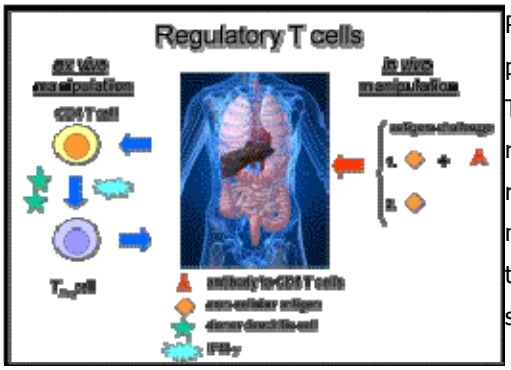
SUPPRESSION OF TRANSPLANT REJECTION - Isis Project No 1439 & 2848

New method for generating regulatory T cell (Tregs) that avoids the need for cell sorting

Marketing Opportunity

Transplantation is the treatment of choice for end stage kidney, heart, liver and pancreas organ failure. Despite considerable advances in the management of transplant rejection in recent years most transplants are still eventually rejected. In addition, current immunosuppressive approaches leave transplant recipients more susceptible to infections and cancer.

The Oxford Invention



Researchers have devised two new methods for producing important regulatory T cells, known as Tregs. Tregs can control destructive rejection responses so that donor organs are less likely to be rejected by a recipient's immune system. Other methods for ex vivo Treg generation are known but their use is limited by the requirement for cell sorting using flow cytometry.

The patent applications describe novel methods for the generation of Tregs both in vivo and ex vivo.

- For in vivo generation, immunisation with a non-cellular antigen combined with a monoclonal antibody to CD4 T cells is followed by a second challenge with the non-cellular antigen at or near the point of transplantation. This approach can also be used ex vivo.

- For additional ex vivo generation, recipient CD4 T cells are cultured with TGF-b conditioned donor type antigen presenting cells in the presence of IFN-g. This leads to preferential death of effector cells, expansion of naturally occurring Treg and conversion of non-Treg precursors resulting in an enrichment for donor-reactive Treg.

In a clinical context, patients would be pre-exposed to the in vivo therapy before transplantation and their resulting Treg population maintained by re-challenging with the non-cellular antigen until transplantation. This approach does not require that the identity of the organ donor is known before the therapy commences. The ex vivo approaches could enable the administration of regulatory T cells as a cellular therapy to control transplantation rejection at the time of transplantation, or at any point thereafter, to ensure that control of rejection is maintained. The in vivo and ex vivo approaches have the potential to be used in combination. This approach is also potentially applicable for the treatment of autoimmunity.

Patent Status

The patent applications are available for licence and we are actively seeking partners for the licensing and commercial development of this technology.

BRAIN ANALYSIS AND MAPPING - Isis Project No 2974

Version 3.3 of the definitive Oxford software library on functional magnetic resonance imaging of the brain is now available.

Marketing Opportunity

Functional MRI (FMRI) has enabled scientists and clinicians to look for the first time into the human brain in vivo. It identifies those parts of the brain that are activated by different physical stimuli such as, for example, sight and sound. Stimulated areas are characterized by increased blood flow, and this shows up on the functional MRI scans: "Brain Mapping". FMRI is a non-invasive and safe technique; studies can be performed again and again in the same individuals.

Typical applications and markets include:

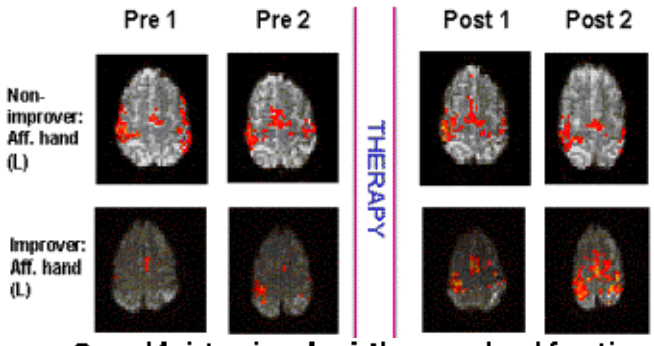
- Understanding the neural basis of many normal human cognitive processes, such as:
    - ability to memorize information;

- recognize faces;
- how we experience pain; and
- neurobiological basis for problems of drug addiction or gambling.

- Clinical applications
  - how those with a disabling neurological disease improve functionally over time;
  - neurobiological basis of rehabilitation strategies associated with function recovery;
  - pre-surgical mapping of the eloquent cortex;
  - new approaches to the early diagnosis of disease; and
  - routine management of patients with neurological disease.

The Oxford Invention

The Oxford FMRIB group is dedicated to the continual improvement and understanding of FMRI, and has recently issued version 3.3 of its well proven software library (FSL). FSL runs on Apple, PCs (Linux and Windows) and Sun, and is very easy to install. FSL courses are run every year to support users.



2 week's intensive physiotherapy - hand function improvement relates to increased brain activation with movement

Commercialization Opportunity

This software library is now available for commercial applications, and companies interested in applying this technology are invited to contact Isis.

PHARMACEUTICAL

CHIRAL PEPTIDE NUCLEIC ACIDS - Isis Project No 66

Peptide Nucleic Acids for Therapeutics and Diagnostics.

Background

Oligonucleotides are potentially useful for the regulation of genetic expression by binding with DNA and RNA. Since natural oligonucleotides are degraded by nucleases, there has been

considerable interest in synthetic oligonucleotide analogues that are stable in physiological conditions.

Problem with Existing Peptide Nucleic Acids

The sugar phosphate backbone of a nucleic acid consists of a repeating unit of six atoms, configuratively and conformationally constrained by the D-ribose or 2'-deoxy-D-ribose ring. Researchers at Oxford have been investigating its replacement by dipeptide unit, so that the new backbone is amenable to preparation by solid phase peptide synthesis. The dipeptide unit compromises a "nucleo amino acid" derived from proline and a "spacer amino acid" which can be any amino acid chosen to provide desired properties.

The Oxford Invention

By using suitable protecting groups, dipeptide analogues of the four standard nucleotides have been prepared. A solid phase technique has been used to convert these nucleotide analogues into peptide analogues of oligonucleotides with both single and mixed base sequences. There is much scope for variation of the "spacer amino acids". Changes can be made to the chiral PNA's hydrophobicity to assist cell penetration or its charge to increase its interaction with DNA. Such molecules are of interest in the diagnosis of genetic disorders, in the identification of gene function from sequence, and as therapeutic anti sense agents against tumours and viruses.

Commercialisation

This work forms the basis of a patent application assigned to Isis Innovation for exploitation by the commercial world. Companies interested in exploiting the technology should contact Isis for further details.

THERAPEUTIC TOLEROGENIC ANTIBODIES - Isis Project No 689

Isis Project Numbers 0009 & 0689

THERAPEUTIC AREAS

Treatments using any immuno or peptide based therapeutic agent that has or may have the potential for tolerance problems when administered in humans.

Marketing Opportunity

Therapeutic antibodies were proposed as a promising treatment for a multitude of diseases, including cancer, in the late 70’s and 80’s. However, when protein based biologicals are administered as therapeutic agents patients generally produce an adverse response to the introduction of the foreign biological to their system. This response can become progressively worse to an extent that the therapeutic agents have to be withdrawn. The most well studied

therapeutic protein biologicals are antibodies. The incidence of patients receiving antibody therapeutics progressing to "therapy rejection" is increasing with time. This problem of therapeutic rejection is not limited to antibodies and all protein therapeutics may give rise to complications. These complications are typically due to immunological responses against the therapeutic agent itself.

The Oxford Invention

Oxford University has developed a platform technology, from Professor Herman Waldmann's laboratories (the William Dunn School of Pathology), that can be used to alleviate these complications and this can open new therapeutic areas previously abandoned as well as rescue existing failing treatments.

CONTROLLED DRUG RELEASE - Isis Project No 957

Chemists in the Inorganic Chemistry laboratory have found that they can intercalate a range of pharmaceutically active molecules between the layers of a layered inorganic host.

Background

While working on the ion-exchange abilities of a family of inorganic materials known as Layered Double Hydroxides (LDH's) they recognised that many commonly prescribed drugs and other over the counter medicines are either anions or can be conveniently and reversibly converted into an anion form. They found that addition of one of these layered double hydroxides to a solution of a chosen pharmaceutical in water at room temperature results in intercalation of the these molecules between the sheets of the host structure. The layered double hydroxides are able swell by up to 20Å to accommodate the size of the new guest molecules.

Problem

Certain drugs require controlled release and/or amelioration of side effects. Layered double hydroxides already have medicinal properties in their own right as antacid and antipepsin agents. Propriety antacids products such as Talcid™ and Altacite™ contain the layered double hydroxide [Mg6Al2(OH)16]CO3.

The Oxford Invention

To date the group have shown that compounds such Diclofenac, Ibuprofen, Naproxen, and Gemfibrozil intercalate rapidly into LDH's. They are then able to quantitatively recover these molecules on demand. At the moment drug release can be achieved by either dissolving the entire drug/LDH composite in dilute acid or adding the drug/LDH to a phosphate buffer at pH 7. Their preliminary kinetics experiments using phosphate buffers show that these drugs can be released back into solution in 1-3 hours at 37 °C.

Apart from the potential of using these materials to deliver drugs in vivo, the host itself could have additional benefits. It will be possible to control the point of release and pharmokinetic profile by selection of the metals ions in the host layers. The antacid performance and pH stability is also controllable by the choice of metal ions in the host layers. Confinement of the drugs between the metals layers restricts molecular interactions and dynamics and should improve long-term stability. In addition improved taste qualities of the formulation are predicted.

Commercialisation Opportunity

This discovery is subject to a patent application. Isis Innovation is interested in discussing suitable arrangements with companies who wish to develop and utilise this technology.

Keywords

controlled release, formulation science, pharmaceutical delivery, layered double hydroxide, LDH, antacid, antipepsin, intercalation, drug release.

NOVEL APPROACH TO CANCER TREATMENT - Isis Project No 1206

Work in the Cancer Research UK Laboratories at the Weatherall Institute of Molecular Medicine, Oxford, has uncovered an exciting new anti-cancer approach that has potential as a stand-alone therapy, and as a means of enhancing sensitivity to conventional anti-cancer treatments

Marketing Opportunity

One effective strategy to treat metastatic cancer is to induce sequence-specific silencing of target gene expression in cancer cells. The use of small interfering RNAs (siRNA) as gene silencing agents in mammalian cells is the most potent method. One important gene target with therapeutic potential in the fight against cancer is the type-1 insulin-like growth factor receptor (IGF1R). IGF1R activation induces tumour cell growth and protection from apoptosis, including that induced by conventional anti-cancer treatments. Its upregulation in tumours relative to normal tissues renders IGF1R a highly attractive anti-cancer treatment target.

The Oxford Invention

The problem associated with IGF1R targeting is the high degree of homology between the IGF1R and the insulin receptor (IR). Because of this close homology, IGF1R kinase inhibitors and blocking antibodies can influence the function or cell surface expression of the insulin receptor, potentially inducing glucose intolerance and diabetes. The Oxford inventors used a scanning oligonucleotide array technology to design siRNAs that interact with IGF1R but not IR mRNA. This strategy has enabled identification of siRNAs that cause profound sequence-specific IGF1R gene silencing without affecting expression of the IR.

Commercialisation Opportunity

The IGF1R siRNAs have been tested successfully in vitro. Treatment of tumour cells with siRNAs blocks IGF signalling, inhibits cell survival and enhances sensitivity to cytotoxic drugs and irradiation. Work by the researchers has also shown that tumour cells remain sensitive to IGF1R gene silencing despite the presence of compensatory signaling via other growth factor receptors, or of downstream mutations causing constitutive activation of growth and survival signaling pathways. Following chemical modification to enhance stability and pharmacokinetic characteristics, the in vivo efficacy of these agents is currently being tested in human tumour xenografts.

These agents represent an exciting new anti-cancer treatment with wide applicability for patients with a variety of metastatic tumours.

Patent Status

This work is the subject of a patent application, and Isis would like to talk to companies interested in developing this approach for preclinical and clinical evaluation. Please contact the Isis Project Manager to discuss this further.

T CELL SENSITIVITY - Isis Project No 1223

Research at the Peter Medawar Building for Pathogen Research has identified mutations in peptide-MHC antigens that improve T cell recognition without altering specificity. These mutant antigens are able to target a specific T cell and deliver an enhanced activation signal. This, in turn can lead to up to a 40 fold increase in effector function (eg. Cytokine production). Such mutant antigens will be of use for boosting immune responses to specific T cell antigens. It has also been shown that T cells respond to lower concentrations of the mutant antigen.

Marketing Opportunity

The mutated antigens, either as soluble molecules or when expressed on the cell surface of an antigen presenting cell, have been shown to enhance T cell signalling and T cell effector function. Importantly, the invention appears to enhance T cell function without altering specificity of the T cell response. As a result, the invention can be used to deliver an enhanced activation signal to a specific T cell of interest without affecting other T cells. This invention has great therapeutic potential as it could be used to specifically enhance an immune response in clinical situations such as viral/bacterial infection and improve the weak CTL response seen in tumour patients. As the mutated antigens are recognised at lower concentration, they may also prove to be of use in diagnostic tests.

In addition, similar but more severe mutations in the MHC have been shown to result in the creation of a peptide-MHC 'superantigen' that can be recognised by all T cells irrespective of the T cell receptor they express. This pMHC class I 'superantigen' does not activate MHC class II-restricted T cells.

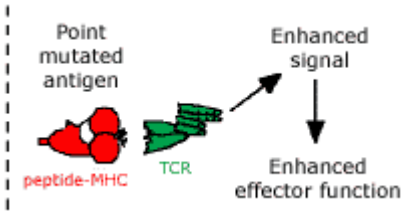
The Oxford Invention

The invention comprises a series of mutations in the conserved parts of the MHC class I molecule and can be applied to any such molecule. Surface plasmon resonance has been used to confirm that these mutations do not affect the interaction between the T cell receptor and the peptide-MHC antigen.

Commercial Opportunity

This technology is subject to a patent application. The potential uses of the invention are numerous, and is likely to be applicable to MHC class II-restricted T cells making it an extremely attractive package.

Increased T cell sensitivity and enhanced effector function by peptide-MHC antigen



This technology could be applied to any antigen without loss of specificity. The benefits of enhanced effector function and increased ssensitivity are seen when peptide-MHC antigen is presented on the cell surface or as a soluble molecule.

IMPROVED VIRAL VECTORS FOR GENE THERAPY AND VACCINATION - Isis Project No 1288

Oxford researchers have used chemical methods to coat virus particles, modifying their properties to retarget them to desired cell types. The invention has applications in gene therapies and in vaccination.

Marketing Opportunity

Viruses are used in vaccines and in gene therapy as vectors to deliver genes or DNA to specific biological targets. A successful vector must have high specificity to the target cell, so that it goes where needed but not anywhere else, and the ability to avoid pre-existing antibodies that would neutralise it. These requirements have caused significant problems in the development of vaccines and gene therapies. There is now a critical need for new vectors and this is the focus of considerable research efforts.

The Oxford Invention

Oxford researchers in the departments of chemistry and clinical pharmacology have approached this goal by modifying the properties of well-known, well-characterized and safe viral vectors. Their method transforms the outside of the virus with sugars, which are used as molecular post-codes to target protein delivery and cellular interactions.

Macrophage cells are found in the blood system and are part of the immune system. They are one of the immune system's three types of **antigen-presenting cells**: cells that display, or present, a foreign substance (antigen) to the rest of the immune system for attention.

Adenovirus is a commonly used vector in therapeutic gene therapy and vaccine development. The researchers have cloaked adenovirus with mannose and showed that the normal broad infectiveness of adenovirus is switched off, and that instead it is re-targeted to macrophage cells. The fragile structure of adenovirus is maintained so that the virus particle is still active after treatment with the sugars.

Because the sugar modification is chemical and not genetic, there are no concerns about the virus reproducing with altered properties. Sugar modification also improves storage and recovery of the virus, which is important for vaccine applications in certain parts of the world.

The technology has clear potential in gene therapy and there are exciting possibilities to apply the technology in the field of vaccination.

Patent Status

This work is the subject of patent application (WO2006/008513), and Isis would like to talk to companies interested in developing the commercial opportunity that this represents. Please contact the Isis Project Manager to discuss this further.

Further reading: Angew. Chem. Int. Ed. 2005, 44, 1057-1061

Keywords

viral vector adenovirus gene therapy vaccination vaccine macrophage vector sugar glycosylation targeting

IMPROVED VACCINATION USING LENTIVIRUS IN PRIME/BOOST PROTOCOLS - Isis Project No 1428

Research at the University of Oxford has resulted in the identification of methods for improved vaccination strategies using DNA encoding an antigen or antigens to prime the immune system, followed by an effective boost using non-replicating lentivirus.

Background and Market Opportunity

Current research initiatives show that delivery of antigen genes to dendritic cells (DC) may allow long-term, high level presentation of the expressed antigen. The development of viral

vectors, such as adenoviral vectors, for gene therapy, has prompted their use in gene delivery to DC. In order to optimise these technologies it is necessary to develop vectors that do not activate DC constitutively (like adenovirus), or block DC activation (like herpes simplex viral vectors).

The Oxford Invention

The inventors chose to study the effects of lenti ral vectors, which are known to be capable of transducing non-dividing human peripheral blood-derived DC and can stimulate specific CTL responses *in vitro*.

The technology allows for use of engineered lentivirus comprising nucleic acid encoding an antigen(s) to stimulate both a cell-mediated immune response and the production of antibodies against the antigen(s). Lentiral vector boosts, following priming with DNA encoding a relevant antigen, are attractive for prime/boost protocols as pre-existing immune responses to the lentiral vector are likely to be absent in most recipients. Multiple injections of lentiral vectors may also be achieved by pseudotyping with different envelopes to avoid neutralising antibodies.

Commercial Opportunity

This exciting Oxford discovery has recently received a favourable International Preliminary Report on Patentability from the EPO, which recognised the DNA/Lenti prime/boost combination as both novel and inventive. Isis Innovation is now actively seeking commercial partners active in the area of DNA vaccines to develop this technology.

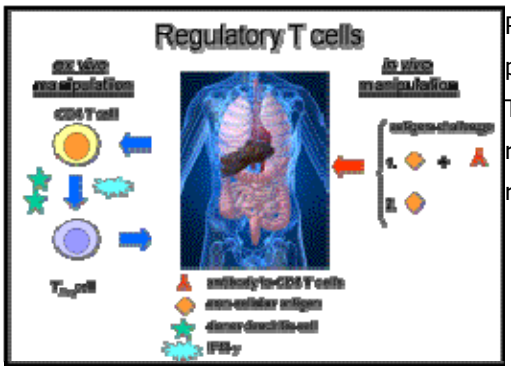
SUPPRESSION OF TRANSPLANT REJECTION - Isis Project No 1439 & 2848

New method for generating regulatory T cell (Tregs) that avoids the need for cell sorting

Marketing Opportunity

Transplantation is the treatment of choice for end stage kidney, heart, liver and pancreas organ failure. Despite considerable advances in the management of transplant rejection in recent years most transplants are still eventually rejected. In addition, current immunosuppressive approaches leave transplant recipients more susceptible to infections and cancer.

The Oxford Invention



Researchers have devised two new methods for producing important regulatory T cells, known as Tregs. Tregs can control destructive rejection responses so that donor organs are less likely to be rejected by a recipient's immune system. Other

methods for ex vivo Treg generation are known but their use is limited by the requirement for cell sorting using flow cytometry.

The patent applications describe novel methods for the generation of Tregs both in vivo and ex vivo.

- For in vivo generation, immunisation with a non-cellular antigen combined with a monoclonal antibody to CD4 T cells is followed by a second challenge with the non-cellular antigen at or near the point of transplantation. This approach can also be used ex vivo.

- For additional ex vivo generation, recipient CD4 T cells are cultured with TGF-b conditioned donor type antigen presenting cells in the presence of IFN-g. This leads to preferential death of effector cells, expansion of naturally occurring Treg and conversion of non-Treg precursors resulting in an enrichment for donor-reactive Treg.

In a clinical context, patients would be pre-exposed to the in vivo therapy before transplantation and their resulting Treg population maintained by re-challenging with the non-cellular antigen until transplantation. This approach does not require that the identity of the organ donor is known before the therapy commences. The ex vivo approaches could enable the administration of regulatory T cells as a cellular therapy to control transplantation rejection at the time of transplantation, or at any point thereafter, to ensure that control of rejection is maintained. The in vivo and ex vivo approaches have the potential to be used in combination. This approach is also potentially applicable for the treatment of autoimmunity.

Patent Status

The patent applications are available for licence and we are actively seeking partners for the licensing and commercial development of this technology.

CDK2/CYCLIN A - Isis Project No 1441

Research within the Department of Biochemistry has lead to the production of an active CDK2/Cyclin A complex phosphorylated on Thr160 in a form suitable for crystallisation to allow studies into the interaction of the complex with potential ligands.

Background

CDK2 is one of the best-studied members of the cyclin-dependent kinase family, which plays a major role in eukaryotic cell cycle regulation. The activity of CDK2 is tightly controlled, requiring two inputs to become fully activated, namely the binding of cyclin A and the phosphorylation of threonine 160. Amongst other roles, fully activated CDK2 is essential for proper S phase progression. Studies have shown that inhibition of CDK2/cyclin A during S phase leads to S phase arrest and apoptosis, which has suggested a pharmacological role for CDK2/cyclin A inhibitors in the treatment of cancer.

Commercial Opportunity (Material Transfer)

Isis can provide phosphorylated CDK2/cyclin A in mg quantities. The potential applications of this compound include:

- Screening of compound libraries for potential ligands
- Crystallisation studies to assess the binding of compounds to the protein

Isis welcomes contact from companies interested in purchasing this protein.

Keywords

Protein, Oncology, Mitosis, Screen, Crystallization, Apoptotic

NOVEL PAEDIATRIC VACCINE ADJUVANT - Isis Project No 1444

A simple, robust, vaccination regime has been developed at Oxford, which uses a viral vector as an adjuvant to activate both cellular and humoral arms of the immune system.

Background

In order to combat diseases more effectively, it is desirable to induce stronger immune responses by vaccination. However, vaccination methods that generate high level antibody responses can differ significantly from those that engender strong cell-mediated or T cell responses. For example, alum is a useful adjuvant for inducing antibodies but generates weak or negligible CD8+ T cell responses. In contrast, heterologous prime-boost immunisation methods have induced strong T cell responses in humans, but only minimal antibody responses. However, immune protection against many diseases can be mediated by either T cells or antibodies at sufficient levels, and optimal protection may be achieved by inducing strong responses of both types. However, no vaccination approach currently exists that allows strong responses of each type to be generated.

The Oxford Invention

Researchers at the University of Oxford, funded by the Wellcome Trust, have developed a vaccination regime whereby a virus is mixed with a material (antigen), which is intended to induce an antibody response. The virus both stimulates a cellular response and also enhances (adjuvants) the antibody response to the co-administered antigen. This result is in itself surprising, but it has also been found that the type of virus used affects the type of antibody response obtained. The approach has been validated with excellent results using MVA virus in combination with B.pertussis vaccine.

Advantages

A strong cellular and antibody response to the same vaccination regime should provide clinicians with much more effective vaccines for a number of diseases. In addition, combinations of vaccines to different diseases could also be envisaged as a result of this method. This would obviously have an impact on the cost of immunisation, and possibly also compliance.

Commercial Opportunity

A strong cellular and antibody response to the same vaccination regime should provide clinicians with much more effective vaccines for a number of diseases. In addition, combinations of vaccines to different diseases could also be envisaged as a result of this method. This would obviously have an impact on the cost of immunisation, and possibly also compliance

SUPPRESSING AUTO-REACTIVITY WITH ANTIBODIES THAT AUGMENT INHIBITORY RECEPTOR FUNCTION -

Isis Project No 1475

Researchers at the University of Oxford have devised a new method to inhibit auto-reactivity using antibody superagonists that specifically target inhibitory cell surface receptors reliant on extrinsic tyrosine kinases

Marketing Opportunity

The therapeutic antibody market currently generates 30% of all biotechnology revenues. Most antibodies used as drugs block cellular functions. However, a new class of potentially therapeutic antibodies that augment signalling by cellular receptors is now emerging. These antibodies directly target a class of cell surface receptors ideally suited to changing cellular behaviour because they form an integral part of the tyrosine phosphorylation network of the cell. The activity of these receptors is governed by their phosphorylation state, which appears to be augmented by antibodies that bind the receptors close to the membrane. Since most of these receptors are inhibitory, it should be possible to quench unwanted cellular responses with these antibodies. In the case of the immune system, it is anticipated that antibodies of this type will be useful for switching off chronic auto-reactive T cells. There is an opportunity for collaborative research to assess the effectiveness of these antibodies in animal models with potential for therapeutic applications in various autoimmune diseases, e.g. diabetes and rheumatoid arthritis.

THE OXFORD INVENTION

The Oxford invention consists of a new, general way to design antibodies that augment signalling by receptors dependent on extrinsic tyrosine kinases. Specifically, antibodies are selected that bind close to the membrane and prevent large tyrosine phosphatases from dephosphorylating the receptor. Because receptor dephosphorylation, but not phosphorylation, is disrupted, overall signalling by the receptor is enhanced. Our initial

therapeutic target is PD-1, which is expressed specifically on activated B- and T-cells, i.e. in the context of on-going inflammatory responses. The discovery that PD-1 is up-regulated in the context of chronic viral infections and responsible for the exhausted phenotype characteristic of virus-specific T cells, has made it one of the most attractive therapeutic targets in the immune system. The Oxford group has developed an antibody that binds to PD-1 in vitro and in vivo in a membrane-proximal manner, and is therefore expected to switch off autoreactive T cells by imposing an exhausted phenotype on these cells.

Patent Status

This work is the subject of a patent application, and Isis would like to talk to companies interested in developing the commercial opportunity that this represents. Please contact the Isis Project Manager to discuss this further.

NEXT GENERATION, HIGH-THROUGHPUT PHAGE DISPLAY - Isis Project No 1506

The technology is the next generation of phage display, allowing the complete molecular diversity in a phage library to be assessed at each selection round and has potential for a multitude of different applications.

Background

Phage display is a very powerful method of probing protein-protein interactions by expressing a vast array of unique polypeptide-based chemical entities on the tip of bacteriophage (viruses that infect bacteria). Phage that bind a specific target can be enriched from non-specific phage by immobilising the target and employing a "bio-panning" procedure. The ability to probe this vast chemical space to select high affinity ligands against novel and existing target classes is well established. The technology is an integral part of biomedical research and drug discovery, but has not been embraced by other sectors.

Opportunity

Although a very powerful technique, phage display does have its limitations. The outcome of repeated rounds of bio-panning from a large peptide phage library (~>109 different phage) is a reduced complexity sub-library (~103-104 different phage) showing affinity for the target. However, the outcome of bio-panning is usually assessed by sequence analysis of a very small sample of the enriched phage population (<20 independent clones) as sequence analysis is both time consuming and cost intensive.

The Oxford Invention

Researchers from The University of Oxford have devised a simple, non-biased, and economical way of sequencing the relevant variable parts of the gene encoding the phage

coat protein from a large number (preferably all) of the phage in the selected sub-library, instead of a tiny and potentially unrepresentative subset. This ensures that target-specific phage are identified after each round of bio-panning allowing phage to be tracked through the process. This method overcomes the problems of clonal dominance, which prevents analysis of interactions on complex matrices (e.g. whole cells, implants etc.), and reduces costs significantly.

Patent Status

Isis Innovation has filed a patent application on this technology and is now seeking a commercial partner interested in pursuing this exciting development in the numerous applications available.

COMPREHENSIVE MENINGOCOCCAL VACCINE - Isis Project No 1538

A new meningitis vaccine, which is broadly protective against many types of this diverse bacterium, has been identified by Researchers from the Peter Medawar Building for Pathogen Research and the Department of Paediatrics, in collaboration with scientists form the National Institute for Biological Standards and Controls.

Background

Neisseria meningitidis, the causative agent in meningococcal disease, is an important cause of life-threatening infections in infants, children and young adults, carrying a significant risk of death. Despite antimicrobial therapy 10% of patients die and another 10-20% are left with brain damage, hearing loss or learning disability. There are a number of different types of *N.meningitidis*, but the most dangerous groups are classified A, B, C W135 and Y.

Opportunity

Routine vaccinations with polysaccharide vaccines have decreased the incidence of bacterial meningitis caused by *Haemophilus influenzae*, but comprehensive vaccines against *Steptococcus pneumoniae* and *N.meningitidis* are proving elusive. Polysaccharide vaccines are not appropriate for routine immunization due to poor immunogenicity in infants and a lack of long term immunity in adults. Repeated doses of some polysaccharide vaccines cause them to become ineffective so polysaccharide vaccines are used primarily in mass vaccinations for the control of epidemics, or for use by travellers visiting high-risk areas. No polysaccharide vaccines are available against group B meningitis as the group B polysaccharide structure is poorly immunogenic and identical to host antigens.

The alternative outer membrane protein vaccines are usually only considered suitable for strain-specific vaccination, as the outer membrane protein antigens are highly diverse between different strains.

The Oxford Invention

Oxford based research has developed a new method to produce outer membrane protein based vaccines using a combination of a limited number of antigenic variants of key outer membrane proteins. This approach provides relatively simple meningitis outer membrane protein based vaccines, effective against a wide range of invasive strains.

Patent Status

Isis Innovation has filed a patent application on this technology and is now seeking a commercial partner to further advance and exploit this important breakthrough in vaccine development.

ANKYRIN REPEAT PROTEINS - Isis Project No 1566

Assays for inhibitors which alter the function of ankyrin repeat proteins, with potential use in the inflammation response

The Background

The Ankyrin repeat is a very common structural motif involved in protein-protein interactions. The ankyrin repeat motif has been found in proteins of very diverse function such as transcriptional initiators and regulators, cell-cycle regulators, developmental regulators, cytoskeletal organizers, ion transporters and signal transducers, and even toxins. Proteins containing the ankyrin repeat motif are central to the inflammatory response.

Currently, over 3500 sequences containing ankyrin structural motifs can be found listed in the SMART domain database (Shultz et al. PNAS (1998) 95 5857-5864). Over 600 human proteins containing ankyrin repeat units are known. Many ankyrin proteins are also present in plants where they are involved in regulation and signaling.

The Oxford Invention

In the inflammation response pathways, the protein IkB-a interacts with the transcription factor NFkB and prevents its nuclear translocation. When IkB-a is degraded and its cellular concentration levels are low, free NFkB is translocated to the nucleus where it associates with various activators and initiates the transcription of many genes involved in the inflammatory response. Researchers at Oxford have now discovered that the enzyme FIH hydroxylates several proteins containing the ankyrin repeat motif and which are involved in the inflammatory response.

The Oxford invention provides assays for inhibitors of the enzymatic hydroxylation of ankyrin repeat proteins. Inhibitors identified through the assays may modify the activity of the ankyrin repeat proteins so that their stability is altered, making the inhibitors useful in treatments of diseases associated with the inflammatory response. The assays are also useful in selectivity screens for FIH inhibitors aimed at other targets.

Commercial Opportunity & Patent Status

A patent application has been filed to protect this work. Isis wishes to talk to companies interested in developing the commercial opportunities for this technology. Please contact the Isis Project Manager to discuss this further.

Key words

inflammation, protein inhibitors, assays

IMPROVED T-CELL IMMUNE RESPONSE - Isis Project No 2101

A simple, robust, vaccination regime has been developed at Oxford, which uses a viral vector as an adjuvant to activate both cellular and humoral arms of the immune system.

Background

In order to defeat many important diseases, such as cancer and malaria, many scientists believe that it is necessary to recruit the cellular arm of the immune system to the fight. This is done through a particular type of immunisation which presents the foreign material to be rejected by the body, the antigen, in a special carrier or vector such as a virus. There is currently much research effort being expended with the aim of increasing the T-cell response in order to make the immunisation more effective.

The Oxford Invention

Researchers in Oxford University have found a simple but effective method for substantially improving the T-cell immune response to an antigen. This method works as an add-on to current standard T-cell vaccination techniques but would not require extra immunisation steps to be performed on the patient. The method includes the use of anti-CD25 antibodies and, in a variety of immunisation protocols, better immune responses are seen with this strategy than have so far been observed by the researchers using any other techniques. Whereas it was initially thought that the anti-CD25 antibodies were depleting regulatory T-cells, new data show that the low doses of antibodies do not deplete this population, but instead increase responses via modulation of IL-2. This is of potential benefit in terms of avoiding the risk of autoimmunity.

Advantages

This novel approach may lead to more effective prophylactic and therapeutic immunisations, allowing currently untreatable diseases to be defeated by a person's own immune system. Due to the particular nature of the method, it should be possible to use it in combination with those T-cell immunisation products already in development by a company.

Commercialisation

A patent has been filed on this method and Isis would like to talk any parties who would be interested in developing the technology further into the clinical setting.

RECOMBINANT OVERLAPPING PEPTIDE VACCINES FOR INFECTIOUS DISEASE AND CANCER - Isis Project No 2452

Research at the University of Oxford has led to a new approach to generating effective vaccines quickly and inexpensively in response to the emergence of new pathogens.

Background and Market Opportunity

A key challenge facing human health is that of rapid generation of new vaccines effective against multiple strains of human pathogens. In particular, the threat of pandemic influenza increases the need to minimise the time between emergence of a new variant pathogen and supply of an efficacious prophylactic vaccine. A need also exists for vaccines able to stimulate cellular immunity, which is believed to be important in mounting a protective immune response against many pathogens and cancers.

The Oxford Invention

The inventor has shown previously that administration of a pool of synthetic, overlapping peptides (OPs) relating to a particular disease-associated protein can generate strong cellular immune responses in vivo. By using such a pool of peptides it is possible to cover multiple epitopes, which overcomes problems associated with HLA restriction. Furthermore, time-consuming epitope mapping is not required, which reduces the time taken to produce an effective vaccine.

However, despite advances in solid-phase methods, use of synthetic peptides can be less than ideal in terms of the large-scale manufacturing required for many infectious disease vaccines. The Oxford researcher has addressed this problem by developing a recombinant method for producing OP vaccines. This approach involves bacterial expression of an amino acid sequence corresponding to OP sequences spanning the length of a protein of interest, interspersed with enzymatic cleavage sites. The recombinant product can then be digested either in vitro, or, if cleavage sites for enzymes present in human cells are chosen, in vivo.

Proof of concept has been achieved with adjuvanted OPs to HIV-Nef protein able to induce specific cellular immune responses in 2 strains of mice. Vaccination with OPs was also able to protect mice from high dose viral challenge of vaccinia virus expressing HIV-Nef. Further in vivo studies with additional antigens are anticipated.

Commercial Opportunity

Isis would like to talk to companies interested in further developing this patented technology, which could be applied as a platform for creation of prophylactic and therapeutic vaccines for a wide range of diseases.

ASSAYS FOR ANTI-CANCER AGENTS - Isis Project No 2664

Oxford researchers have developed a method for identifying inhibitors which can act against the cancer target Mina53. Such inhibitors will be useful in treating colon tumours and oesophageal cancer.

Marketing Opportunity

Colorectal cancer is the third most common form of cancer worldwide and the survival rate after 5 years is only 50% of patients.

Oesophageal carcinoma (or cancer of the gullet) is now the 9th most common cancer in the UK with ca. 7,500 new cases diagnosed every year.

Both these cancer types are linked with a protein known as Mina53 (or to give its full title, MYC induced nuclear antigen, isoform 2). In colon cancer, elevated expression of Mina53 is viewed as a characteristic feature. Proliferation of colon tumour cells in vitro was severely reduced when production of Mina53 in the cells was suppressed. In oesophageal cancer cell lines Mina53 levels were elevated in 83% of cell lines tested, and high expression levels of Mina53 are also linked to shorter survival periods.

These observations indicate that reduction of Mina53 activity would be of benefit in treating these cancers, but little was known about its function and no method has existed for producing and purifying Mina53. These practical issues have made it difficult to study Mina53 in more detail as a target for cancer therapy.

The Oxford Invention

Researchers in the department of Chemistry have now developed a method of producing and purifying Mina53. This has enabled them to show for the first time that Mina53 is an enzyme that acts as an oxygenase, using molecular oxygen to carry out oxidation reactions on a substrate. The Oxford researchers have used these insights to design assay systems for testing new inhibitors of Mina53. Inhibitors identified by the assays may be useful in treatment of cancer.

Patent Status

This work is the subject of patent application, and Isis would like to talk to companies interested in developing the commercial opportunity that this represents. Please contact the Isis Project Manager to discuss this further.

Keywords

anticancer, anti-cancer, Mina53, target inhibitor, cancer colon, oesophageal, carcinoma, colorectal,oxygenase, assay

TRANSFECTION REAGENT ADJUVANT - Isis Project No 2791

Non-liposomal cationic polymers have been shown to be effective as adjuvants able to improve immune responses to HIV antigens

MARKETING OPPORTUNITY

There is a pressing need to develop new vaccines, including an effective HIV vaccine, but to date it has proved difficult to generate protective antibody-based immunity using what are in many cases poorly immunogenic antigens. Adjuvants are frequently added to vaccine compositions to improve the quality or magnitude of immune responses to an antigen, and HIV appears to be a prime example of a disease for which an adjuvant is required. It is further recognised that there is a need to produce better adjuvants for many other infectious disease vaccines for which current adjuvants are ineffectual or suboptimal.

THE OXFORD INVENTION

Researchers at the University of Oxford have discovered that non-liposomal cationic transfection reagents such as poly(ethylenimine) (PEI) may be used in combination with HIV antigens to boost the immune response in rabbits and mice. PEI in particular was able to boost antibody production at least as effectively as Alum, a recognised adjuvant, and at a much lower molar dose. Moreover, the functional (neutralising) antibody response induced by PEI was greater than that induced by Alum. PEI was also shown to up-regulate expression of MHC Class II and co-stimulatory molecules on bone marrow derived dendritic cells, and to generate equivalent systemic and mucosal immunoglobulin responses when compared to Cholera Toxin B-subunit.

The use of a reagent such as PEI may represent an efficacious, safe and cost-effective alternative to other adjuvants in development. The results obtained for PEI when used in combination with HIV antigens also suggest that it may be even more effective when used with more immunogenic antigens from other pathogens.

PATENT STATUS

This work is the subject of patent application covering the use of this class of transfection reagents as adjuvants, and Isis would like to talk to companies interested in developing the commercial opportunity that this represents. Please contact the Isis Project Manager to discuss this further.

DNA NANOTETRAHEDRA FOR DRUG DELIVERY - Isis Project No 2805

Novel drug delivery platform technology based on new DNA nanostructural cages.

MARKETING OPPORTUNITY

A DNA cage system has been developed with potential for application in drug targeting and drug delivery. The DNA cages combine the functions of sensor and delivery vehicle and open the way for a new generation of 'smart' drug-delivery technologies.

THE OXFORD INVENTION

Self-assembling DNA cages have been developed that can be formed into a number of useful shapes including tetrahedra. The ability to be able to incorporate a significantly sized bio-molecule has been demonstrated with Cytochrome C, amongst others. The shape can be tailored to allow the incorporation of differently shaped and / or sized molecules.

Once a drug, marker or other molecule of interest has been incorporated into the cage, it can be targeted to a tissue of interest by the addition of a signal molecule, or the ligand of a receptor found only on the tissue or cell type of interest. Adding a ligand to a tissue specific receptor involves a relatively simple synthetic step, and opens the possibility of getting relatively large molecules and nano-medicines across biological barriers, such as the gastrointestinal tract. Release of the payload may then be accomplished through the presence or action of a selected molecule or chemical environment.

Chemically, these cages are stereo-pure, rigid and adaptable. Crucially, they are simple to assemble, in a single step with a yield of approximately 95%. Importantly for a potential targeted drug delivery technology, they are robust and stable, and are cost efficient in comparison to other DNA technologies.

PATENT STATUS

Isis Innovation has applied for a patent covering this invention. This is a fast moving and exciting area of research and development and with the plethora of potential for this technology to be tailored to a company's specific requirements, licensees are sought who have an interest in co-development. . Please contact Dr David Phillips, Project Manager, at Isis Innovation Ltd. to discuss this further.

ALLERGEN SPECIFIC T-CELL CLONES FOR ANTIBODY TESTING - Isis Project No 2816

Oxford researchers have generated human CD4+ T cell clones specific for house dust mite allergens, for use as research tools.

MARKET OPPORTUNITY

Monoclonal antibodies represent some of the most important and successful therapies of the last few years, and increasing numbers are entering clinical development. However, testing the safety of human antibodies is not without challenges, as their incredibly high level of

specificity increases the probability of misleading results in non-human animal models. The need for accurate animal models for testing human antibodies was highlighted recently via the tragic events surrounding the Tegenero antibody trial at Northwick Park.

THE OXFORD INVENTION

Oxford researchers have developed T-cell clones which could enable safety testing of human antibodies in rodent models. They identified various T-cell receptors which are specific for particular epitopes of Der p 1, and have subsequently produced three CD4 positive T-cell clones expressing different T-cell receptors specific for the same Der p 1 epitope. In contrast to CD8 positive T-cell clones, CD4 T-cells are particularly difficult to generate and there are thought to be only a handful of well-characterised examples worldwide.

These clones produce a well-defined cytokine profile including IL-4, IFN-g and many others. Adoptive transfer of these cells to SCID mice would create a rodent model with human cells producing human cytokines, which offers the potential to test human antibodies designed to block the pertinent cytokines and cell surface molecules. Other uses envisaged for the clones include testing of inhibitor drugs in vitro, transfer into animal models of disease and subsequent manipulation, and possibly T-cell receptor structural or ligand binding work and inhibition.

COMMERCIAL OPPORTUNITY

The cell lines are now available for non-exclusive licensing as research tools, and Isis would like to talk to companies interested in inflammation research. Please contact the Isis Project Manager to discuss this further.

Keywords

allergy, dust-mite, t-cell, research tool, cell-line, assay.

A NEW TREATMENT FOR NEURODEGENERATIVE DISEASE - Isis Project No 2839

Researchers at the University of Oxford have identified a novel mechanism to protect neurons from the cell death underlying Parkinson's disease.

Marketing Opportunity

Parkinson's disease (PD) is a common and fatal disorder, predominantly of the elderly, affecting 1-2% of the population. PD is a slow, progressive illness and patients require long-term hospitalisation and care. PD therefore represents a significant cost to the healthcare system and has enormous implications for the quality of life of sufferers. As Western populations continue to age, this burden is set to increase and there are currently no treatments available which alter disease progression.

The Oxford Invention

The invention comprises a technique for reducing neuronal susceptibility to Parkinson's disease related cell death using RNA interference (RNAi)-mediated knockdown of α-synuclein, a protein which plays a critical role in PD. The Oxford researchers have shown RNAi-mediated knock-down of α-synuclein reduces dopamine accumulation in neurons by reducing the activity of the dopamine transporter which brings dopamine into a cell. This reduces the oxidative stress and neuronal death that underlies Parkinson's disease. The researchers have found that reducing the expression of the normal form of α-synuclein is able to protect neurons from toxic insults which gives this invention broad application in all forms of Parkinson's disease.

At present, treatments for Parkinson's disease are symptomatic and are unable to alter the underlying course of the disease. This invention addresses the heart of the problem by stopping neurons dying. This technique has application to all forms of Parkinson's disease either as a primary prevention intervention or as treatment for pre-existing Parkinson's disease. As such, this represents a method for altering the natural history of the illness and is a significant step towards developing a cure for the disease.

Patent Status

This work is the subject of a patent application. Interested parties are welcome to discuss with Isis Innovation on how to utilise this invention. Please contact the Isis Project Manager to discuss this further.

SUPPRESSION OF TRANSPLANT REJECTION - Isis Project No 1439 & 2848

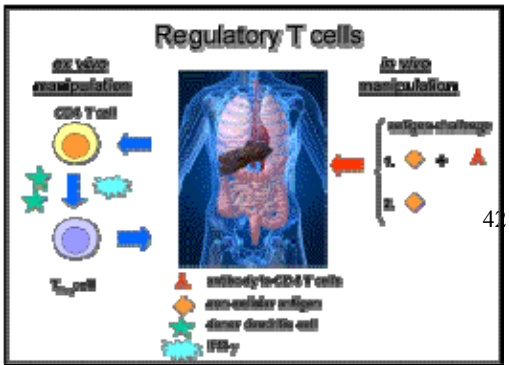
New method for generating regulatory T cell (Tregs) that avoids the need for cell sorting

Marketing Opportunity

Transplantation is the treatment of choice for end stage kidney, heart, liver and pancreas organ failure. Despite considerable advances in the management of transplant rejection in recent years most transplants are still eventually rejected. In addition, current immunosuppressive approaches leave transplant recipients more susceptible to infections and cancer.

The Oxford Invention

Researchers have devised two new methods for producing important regulatory T cells, known as Tregs. Tregs can control destructive rejection responses so that donor organs are less likely to be rejected by a recipient's immune



system. Other methods for ex vivo Treg generation are known but their use is limited by the requirement for cell sorting using flow cytometry.

The patent applications describe novel methods for the generation of Tregs both in vivo and ex vivo.

- For in vivo generation, immunisation with a non-cellular antigen combined with a monoclonal antibody to CD4 T cells is followed by a second challenge with the non-cellular antigen at or near the point of transplantation. This approach can also be used ex vivo.

- For additional ex vivo generation, recipient CD4 T cells are cultured with TGF-b conditioned donor type antigen presenting cells in the presence of IFN-g. This leads to preferential death of effector cells, expansion of naturally occurring Treg and conversion of non-Treg precursors resulting in an enrichment for donor-reactive Treg.

In a clinical context, patients would be pre-exposed to the in vivo therapy before transplantation and their resulting Treg population maintained by re-challenging with the non-cellular antigen until transplantation. This approach does not require that the identity of the organ donor is known before the therapy commences. The ex vivo approaches could enable the administration of regulatory T cells as a cellular therapy to control transplantation rejection at the time of transplantation, or at any point thereafter, to ensure that control of rejection is maintained. The in vivo and ex vivo approaches have the potential to be used in combination. This approach is also potentially applicable for the treatment of autoimmunity.

Patent Status

The patent applications are available for licence and we are actively seeking partners for the licensing and commercial development of this technology.

MOLECULAR SHAPE RECOGNITION - Isis Project No 2932

Introduction

Isis Innovation, the technology transfer company of the University of Oxford, releases a new method for searching a molecular database for compounds that most closely resemble the shape of a molecule of known activity.

Marketing Opportunity

Identifying drug candidates is expensive, slow and ineffective. Increasingly, virtual screening is used to identify molecules likely to have beneficial biological properties. Indeed, it is widely believed that molecular shape is one of the best indicators of biological activity, which has been already demonstrated by recent studies. Hence, the ability to efficiently search a molecular database for compounds that most closely resemble the shape of a

molecule of known activity is highly advantageous (Figure 1). Most methods calculate shape similarity by superposing the molecules to quantify their overlap. This requires an optimal alignment of the molecules, which is computationally expensive and may lead to sub-optimal molecular overlap. Furthermore, the increasing size of molecular databases poses a serious limitation to the use of shape comparison methods.

The Oxford Invention

Ultrafast Shape Recognition (USR) has been developed by scientists at Oxford University. Molecular shape is characterised by a set of 1D distributions of inter-atom distances, which retains 3D shape information. This eliminates any need for alignment or translation, as these distributions are independent of orientation or position. Such innovation also improves efficiency, making USR around 2000x faster than commercially available methods (Figure 2).

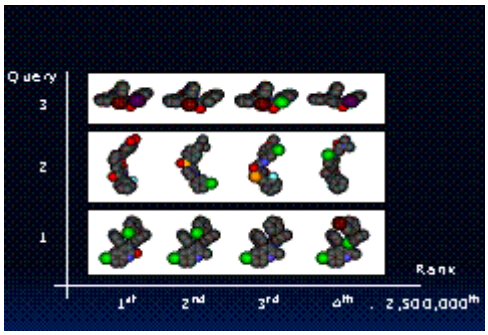


Figure 1

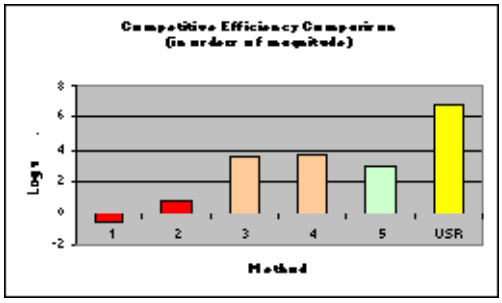


Figure 2

Commercialisation Status

USR software is ready to be implemented as a molecular shape comparison product. The underlying technology is the subject of a US Patent Application. Please contact the Isis Project Manager to discuss developing the commercial opportunity.

LOW WATER BIOREACTOR - Isis Project No 2947

Oxford researchers have developed a more efficient platform technology to produce esters and peptides in a controlled, environmentally sensitive & economic manner.

MARKETING OPPORTUNITY

An increasing number of chemicals are now produced by bioprocesses that typically operate at room temperature. Oxford researchers have developed a new electrokinetic platform technology applicable in industries that utilise enzyme-catalysed condensation reactions. The efficiency of such processes, including the manufacture of esters and peptides, is limited by the need to remove water.

THE OXFORD INVENTION

Condensation reactions such as esterification can only proceed to a certain water content, at which point the reverse reaction starts to take place. Various methods have been employed by others to remove this water. The Oxford invention offers the user the following advantages:

- A more efficient process giving a high product concentration.
- An environmentally friendly, room temperature process with no additives required to remove water.
- A controllable process that proceeds only when the current is switched on.

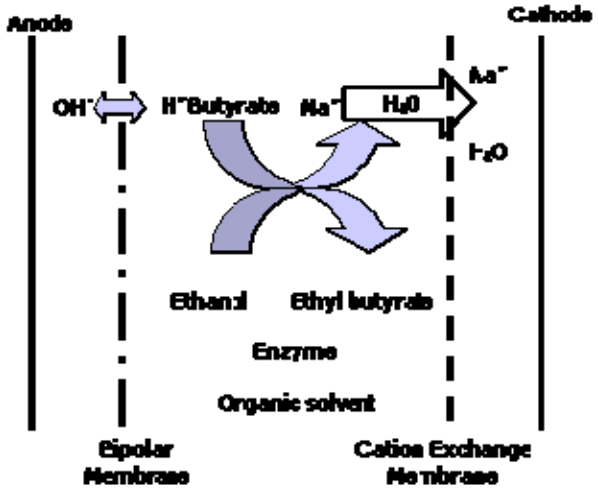


Figure 1

This unique platform technology enables innovative bio-catalysed chemical production, with lower costs, improved product differentiation and greater use of renewable resources than with current technology.

PATENT STATUS

This work is the subject of a patent application, and Isis would like to talk to companies interested in developing the commercial opportunity that this represents. Please contact the Isis Project Manager to discuss this further

ANTI-INFLAMMATORY TREATMENT - Isis Project No 3050

Isis Innovation, the technology transfer arm of the University of Oxford, presents a new drug candidate for treatment of inflammatory disorders.

MARKETING OPPORTUNITY

Inflammation is the response of vascularised tissue to injury and infection. Tissue damage leads to the production of a series of inflammatory mediators that recruit neutrophils and monocyte/macrophages into the site of injury.

Despite the beneficial role of inflammation in host defence, excessive inflammatory responses and prolonged macrophage activation can lead to acute inflammatory disorders such as endotoxic shock, or chronic inflammatory diseases such as inflammatory bowel disease (IBD), rheumatoid arthritis, uveitis and atherosclerosis.

As well as a potential treatment for acute and chronic inflammatory disorders, the Oxford invention could also accelerate the resolution of inflammation - important for treatment of diseases such as age-related macular degeneration and Alzheimer's disease.

THE OXFORD INVENTION

Researchers at Oxford have discovered a series of novel anti-inflammatory peptides that act on activated macrophages via the G protein-coupled receptor (GPCR), ChemR23, substantially reducing production of inflammatory cytokines (TNFa, MCP-1, IL-6 and IL-1b). Peptide agonists of the ChemR23 receptor represent a novel strategy for therapeutic intervention in inflammatory disease that is derived from an endogenous anti-inflammatory mechanism.

These novel peptides exhibit potent anti-inflammatory activity (0.32ng/kg) in well-established pre-clinical models of inflammation. Furthermore, the same peptides dramatically enhance clearance of pathogen and cellular debris, potentially speeding up the resolution of inflammation.

PATENT STATUS

This work is the subject of a patent application, and Isis would like to talk to companies interested in developing the commercial opportunity that this represents. Please contact the Isis Project Manager to discuss this further.

KEYWORDS

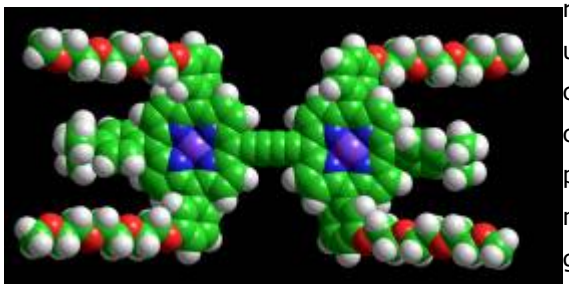
GPCR, G protein-coupled receptor, anti-inflammatory, peptide, ChemR23, chemerin, rheumatoid arthritis, inflammatory bowel disease, endotoxic shock.

USE OF NOVEL PORPHYRIN DIMERS IN PHOTODYNAMIC THERAPY - Isis Project No 3096

Conjugated porphyrin dimmers enable the treatment of non-malignant diseases, non-metastatic benign tumours, and macular degeneration via photodynamic therapy.

MARKETING OPPORTUNITY

Photodynamic therapy (PDT) is a method of treatment for a wide range of diseases and requires a benign photosensitizer, light and molecular oxygen present in the tissue. The treatment involves the activation by light of the photosensitizer to produce a cytotoxic



response that kills nearby cells. PDT can be used to treat a number of conditions characterized by rapid tissue growth including cancer, psoriasis and acne. It is also the preferred therapy for neovascular age-related macular degeneration (AMD), where abnormal growth of new blood vessels at the back of the eye leads to blindness. However, current PDT treatments are limited by the fact that:

- The photosensitizers employed, rapidly diffuse into other healthy tissues, which are subsequently damaged if they are incidentally illuminated.
- The depth of treatment is quite limited.

Therefore, the need exists for the development of new PDT technology to overcome these challenges.

THE OXFORD INVENTION

The Oxford Invention uses a combination of novel conjugated porphyrin dimers and either one-photon (OP) or two-photon (TP) excitation. The compounds of the Invention have good solubility in biological media and afford enhanced delivery to and localization in tissues. In TP-PDT, excitation of the Oxford photosensitizers is confined to the focal volume of the laser therefore the degree of targeting is extremely high. This feature is advantageous because the collateral damage associated with traditional excitation mechanisms is greatly reduced. TP-PDT using these photosensitizers has recently been demonstrated in mice. In OP-PDT, these photosensitizers permit treatment using light of longer wavelengths (>800nm), which reduces the costs associated with the laser. In OP-PDT applications, these photosensitizers also facilitate better depth penetration through tissue, thereby enabling larger tumours to be treated more effectively.

PATENT STATUS

This work is the subject of patent application, and Isis would like to talk to companies interested in developing the commercial opportunity that this represents. Please contact the Isis Project Manager to discuss this further.

Keywords:

Photodynamic therapy, One-photon PDT, Two-photon PDT, Photosensitizers, Porphyrins, Cancer treatment, Oncology, Eye disease

A NOVEL CANCER BIOMARKER AND DRUG TARGET - Isis Project No 3101

Oxford researchers have discovered a novel cancer biomarker with great potential as a target for therapeutic intervention.

MARKETING OPPORTUNITY

The market for cancer therapies is set to experience significant change as newer targeted therapies replace broader spectrum treatments. Targeted therapies are generally better tolerated, less toxic and provide better patient outcomes. In parallel, ageing populations and improved detection methods have led to increases in the number of patients requiring treatment, and there remains an unmet need for more effective therapies.

THE OXFORD INVENTION

Oxford researchers hypothesised that the activity of a particular protein previously thought to be unrelated to cancer may play a direct role in the regulation of tumour cell proliferation and progression. Subsequent investigation of levels of expression of the protein in human tumour samples using immunohistochemical staining confirmed that, compared with normal tissues, the protein is expressed excessively in tissues from patients with lung, breast, head and neck cancers as well as lymphomas.

It has further been shown that:

- Over-expression of the protein promotes cell proliferation by activating cell survival signalling
- Disruption of this signalling or down-regulation of expression of the protein leads to decreased cell migration
- Over-expression of the protein occurs in some human colorectal cancer cell lines
- Over-expression of the protein in cells increases tumour growth

Further studies are underway to evaluate the effects in cancer models of a known ligand, and to screen libraries in order to identify new compounds effective against this target.

PATENT STATUS

This work is the subject of patent application filed in 2007. Isis would like to talk to companies interested in developing the commercial opportunity that this represents, and the patent application can be made available for review under CDA. Please contact the Isis Project Manager to discuss this further.

QUANTISNP SOFTWARE FOR COPY NUMBER VARIANT ID - Isis Project No 3195

Oxford researchers have developed a software application able to analyse SNP genotyping data and identify the presence of copy number variants.

MARKETING OPPORTUNITY

The development and validation of novel approaches to accurately and quickly map copy number changes in the human genome is important for the implementation of novel diagnostic strategies.

Developments in microarray technologies have enabled the high-throughput study of chromosomal aberrations, and there is particular interest in the application of SNP array platforms to detect copy number variants associated with susceptibility to different diseases. This interest stems from the ability of this approach to profile copy number polymorphisms and SNPs simultaneously, which leads to more effective characterisation of the genetic alterations associated with a specific disease. The companies Affymetrix and Illumina have developed platform technologies facilitating such an approach, but there is a need for improved software able to interpret the data generated by these systems.

THE OXFORD INVENTION

Oxford researchers have developed a highly tailored Objective Bayes Hidden-Markov Model to automatically infer regions of copy number variation from the Illumina BeadArray genotyping data; QuantiSNP. The Oxford software significantly improves the accuracy of copy number variant identification and mapping relative to existing analytical tools, as demonstrated by validation of breakpoint boundaries.

While QuantiSNP was developed to analyse SNP data generated by the Illumina BeadArray system, it can also be adapted to other platforms.

A highly accurate statistical algorithm, such as QuantiSNP, for the detection of copy number variant events is vital for the meaningful identification of relevant copy number polymorphisms both in genome-wide and region-specific association studies of complex disease.

COMMERCIAL AVAILABILITY

The QuantiSNP software is available through Isis for non-exclusive licensing. Please contact the Isis Project Manager for further details.

A PROGNOSTIC TEST FOR BREAST CANCER - Isis Project No 3203

Quantification of a single microRNA as a reliable prognostic marker in breast cancer ensures patients receive the most effective and appropriate treatment

MARKETING OPPORTUNITY

Globally, breast cancer is the commonest cancer amongst women and is the fifth most common cause of cancer death. Every year 1.1 million women are newly diagnosed with

breast cancer and will die from the disease. It is the best example of a cancer in which prognostic information is required to guide treatment. Usually the likely outcome of a cancer is determined using indicators such as tumour size and histological features. These indicators are frequently used in combination but a single reliable marker is a more powerful predictor of survival.

THE OXFORD INVENTION

Oxford academics have discovered that the level of a specific microRNA in human breast cancer is enhanced and that its expression correlates closely with mortality. The measurement of this single RNA species provides additional prognostic information, which is independent of other commonly used markers such as tumour size. The marker is easily detectable and can be assayed by any molecular technique for detecting low molecular weight RNA.

A single measurement of a microRNA, as a predictor of breast cancer survival, has considerable benefits over multiple determinations of gene expression, which are currently utilised in attempts to determine prognosis. The benefits lie primarily in the simplicity of the assay, its flexibility, cost benefit and in its strength as a prognostic tool. A simple, low cost assay is amenable to in-house analysis and technicians would not require extensive training in order to undertake the procedure. MicroRNA is relatively stable compared to conventional RNA and DNA molecules. Therefore, the sample material could be tumour specimens, blood, urine or paraffin fixed tumour sections. Since most tumour histology samples are fixed and archived there is a distinct advantage in being able to study this material. An elevated level of the specific microRNA is indicative of an eight-fold decrease in chances of survival and is therefore, a much more powerful predictor than current determinants. The ability to gauge the prognosis of a breast cancer with a simple test will enable clinicians to offer the most appropriate treatment, providing more aggressive therapies to patients with a poor prognosis and minimising side effects and toxicity for those patients with less aggressive disease.

PATENT STATUS

This work is the subject of a patent application, and Isis would like to talk to companies interested in developing the commercial opportunity that this represents. Please contact the Isis Project Manager to discuss this further.

TREATMENT FOR BREAST CANCER - Isis Project No 3209

Isis Innovation, the technology transfer arm of the University of Oxford, presents a new indication for 6-thioguanine in the treatment of breast, ovarian and pancreatic cancers with defects in homologous recombination, e.g., BRCA1 or BRCA2 mutations.

MARKETING OPPORTUNITY

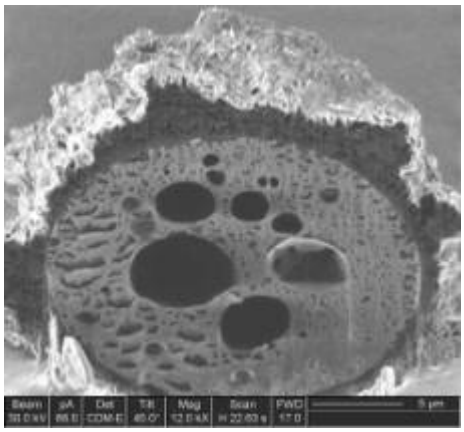
The variability in patient response to cancer therapies has lead to a drive towards a more personalised approach to treating individual patients. One method for deciding which

treatment to use is based on screening for variations in genetic and protein biomarkers in cancerous cells. As more biomarkers are identified and screening becomes more commonplace, there will be an increasing demand for new bespoke treatments for the different patient groups.

PARP inhibitors are a novel group of cancer treatments currently undergoing phase II clinical trials in breast and ovarian cancer. These inhibitors act by specifically targeting cancer cells that are deficient in a DNA repair pathway called homologous recombination. Recent research has shown that a proportion of these cells can mutate and become resistant to PARP inhibitors.

A treatment that overcomes the issue of resistance that could serve as a standalone treatment or adjuvant to PARP inhibitors is the opportunity which the Oxford invention addresses.

THE OXFORD INVENTION



In the search for more effective treatments for homologous recombination deficient cancers, Oxford researchers have discovered that cancer cells that are resistant to PARP inhibitors are highly sensitive to treatment with 6-thioguanine (6-TG). Interestingly, previous phase II clinical trials for breast and pancreatic cancer have shown a response rate which is roughly equivalent to the BRCA1/BRCA2 mutation frequency in the general population.

6-TG is a generically available drug, currently indicated for treatment of leukaemia and as an immunosuppressant prior to transplantation. As well as a novel treatment for a group of resistant cancers, the Oxford invention would be also be a new indication for 6-TG.

PATENT STATUS

This work is the subject of patent application, and Isis would like to talk to companies interested in developing the commercial opportunity that this represents either through licensing or collaboration. Please contact the Isis Project Manager to discuss this further.

KEYWORDS

Cancer, BRCA1, BRCA2, Breast, Pancreatic, Ovarian, Thioguamine, 6-TG-2-Amino-6, Mercaptopurine, Generic, Parp Inhibitor

NOVEL MICROSPERES FOR DRUG DELIVERY TO BONE -

Isis Project No 3303

3-in-1 microspheres provide targeted drug delivery while encouraging new bone growth.

Oxford Researchers have developed a novel micro-particle drug delivery system, which:

1. Binds specifically to bone
2. Aids bone growth
3. Provides a controlled release system for one or a cocktail of drugs.

Marketing Opportunity

Due to an aging population, the number of people with bone diseases is increasing dramatically. The majority of therapeutics for bone related diseases are systemic and this reduces the effectiveness of the therapy and increases its cost. There is a need for a delivery system that targets therapeutics directly to bone, preferably while also providing other functional benefits.

Microscopy image showing the core-shell

structure of HA-coated PLGA microspheres.

The Oxford Invention

A quick and simple method to load drugs within calcium phosphate coated poly (DL-lactic-co-glycolic acid) (PLGA) microspheres has been developed within the Department of Materials in the University. Hydroxyapatite is a form of calcium phosphate that is an essential component of normal bone and teeth. Using hydroxyapatite as a coating material around a core of PLGA, rather than as a composite material with PLGA, gives the 3in1 action to the microsphere. To realise these properties in a single microsphere is a significant advancement on current drug delivery mechanisms and a prerequisite in the design of suitable bone delivery devices.

The microspheres provide a flexible delivery mechanism that can be tailored to suit the needs of different drugs and disease states. The method successfully entraps sensitive components, such as proteins and is thus applicable for a wide range of drugs. There is also minimal drug leakage or polymer degradation during microsphere production due to the design of the manufacturing process. The resultant microspheres lend themselves to local drug delivery either by direct injection into bone, addition into bone cement during a surgical procedure or as a coating on metal implants. It is also possible to deliver combinations of drugs or sequential release of different drugs via the microspheres – for example an antibiotic and an analgesic, a combination of anti-cancer drugs, or a combination of growth factors.

Patent Status

This work is the subject of a patent application, and Isis is actively seeking partners for the licensing and commercial development of this technology. Please contact the Isis project manager to discuss this opportunity.

HIGH DENSITY PROTEIN NANOARRAY - Isis Project No 3310

University of Oxford and NTT researchers have developed a self-assembly approach to low-cost, high-density nanoarrays for use in proteomics and drug discovery.

MARKETING OPPORTUNITY

Although DNA array technology is well developed, the protein equivalent is still at an early stage. Protein arrays have been recognized as a valuable tool to study the function of proteins and to aid drug discovery. Developments made by University of Oxford and NTT scientists show potential to deliver low-cost and high-density protein arrays via a self-assembly method, offering an excellent opportunity to companies engaged in proteomics and drug discovery.

THE INVENTION

This invention offers the following key benefits:

- Increased density of array elements - 109 nanodots are covered by a 10ml sample.
- Lower manufacturing cost - self-assembly and no lithographic processes.
- No loss of protein functionality - proteins are reconstituted into a lipid bilayer and not affected by the substrate.

Self-assembly of the vesicle nanoarray involves three steps, shown in the Atomic Force Microscopy (AFM) images on the left. Firstly, gold nanodots are formed by the self-assembly of gold along silicon steps (Figure 1). Next, vesicles are formed with gold-affinity head groups (Figure 2). Finally, the vesicle and nanodot array are brought together in solution forming the protein nanoarray (Figure 3).

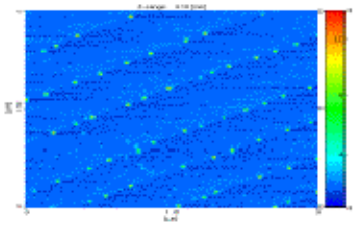


Figure 1

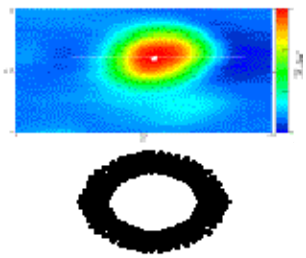


Figure 2

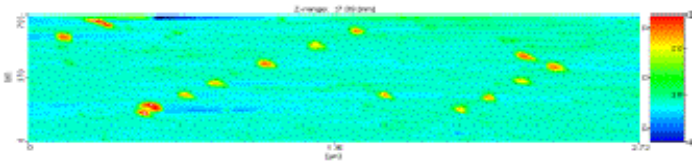


Figure 3

PATENT STATUS

This work is the subject of a US patent application, and Isis would like to talk to companies interested in developing the commercial opportunity that this represents. Please contact the Isis Project Manager to discuss this further.

OBESITY ASSAY - Isis Project No 3342

Obesity assays can aid development of new pharmaceutical candidates for treatment of obesity.

Marketing Opportunity

Globally there are 300 million obese people. In the UK alone over a fifth of adults are obese and of the remaining population, half of men and a third of women are overweight. Obesity is a leading cause of disorders such as type-2 diabetes, some cancers and heart disease. Obesity has a strong genetic component but until recently there was little success in identifying the underlying genetic causes.

Recent evidence shows strong links exist between obesity, type-2 diabetes and variants in the FTO (fat mass and obesity associated) gene1. People with two copies of the "fat" FTO gene have a 70% higher risk of obesity than those with none, and weigh 3kg (6.5lb) more. People carrying one copy of the FTO gene had a 30% higher risk of being obese compared to a person with no copies of the gene.

The Oxford Invention

Oxford researchers have shown for the first time that FTO is an enzyme, and has similar structure and mechanism of action identifying it as a member of a family of enzymes known as oxygenases2. Oxygenases are involved in diverse processes including DNA repair, fatty acid metabolism and post translational modifications. FTO has a potential role in DNA modifications, a way of changing the activity of genes without changing the genes themselves.

The work identifies the FTO enzyme as a new drug target for the control of obesity. The researchers have developed a range of assays, which can be used in identifying and developing pharmaceutical (drug) candidates.

Patent Status

This work is the subject of a recent patent application, and Isis would like to talk to companies interested in developing the commercial opportunity that this represents. Please contact the Isis Project Manager to discuss this further.

HLA TYPING - Isis Project No 3337

A novel, reliable and highly cost-effective method of gaining an understanding of the structure of an individual's HLA profile

MARKETING OPPORTUNITY

1. Available for licensing is a software programme, which allows the mapping and prediction – with a minimum of between 90 and 95% accuracy of an individual's HLA II type, based on any of the widely available DNA chip platforms. For any screening programme, this allows a huge reduction in the number of individuals who actually have to be typed, and consequently a considerable cost saving. This will be of particular interest to drug companies, manufacturers of SNP arrays, users of SNP arrays and those involved in the investigation and treatment of autoimmune disease. It will also be of interest to those involved in understanding and predicting prognosis and disease progression, and to drug developers. It also has considerable application in vaccine trial covariance and clinical study understanding.

THE OXFORD INVENTION

2. An algorithm and statistical software for probabilistic prediction of alleles at classical HLA loci has been developed that allows the determination of the HLA serotype presented by an individual, without the current array of expensive, and often inaccurate, typing methods and technologies. Tissue typing is used in a wide range of biological and medical fields, particularly in relation to screening individuals for transplantation etc. To HLA type an individual currently costs approximately £500, making screening programmes particularly costly. Further, while routine serological methods are reliable for HLA class I typing, they are currently uncertain for HLA class II typing partly owing to the poor quality of the antisera used. Since HLA class II typing is important for BMT, a more accurate method for HLA II typing is needed. If the mutation rate and the recombination frequency at any given locus are known then it is possible to calculate the likely path through the gene. This means that only a minimal set of markers are required for a prediction of the complete region. This avoids the use of tagging methods that require knowledge of what has been investigated previously and expands the possibilities for typing in a highly cost-effective manner.

PATENT STATUS

This work is the subject of patent application, and Isis would like to talk to companies interested in developing the commercial opportunity that this represents. Please contact Dr David Phillips, Project Manager, at Isis Innovation Ltd. to discuss this further.

ANTI-THROMBOTIC TREATMENT - Isis Project No 3435

Isis Innovation, the technology transfer arm of the University of Oxford, presents a potential new anti-thrombotic drug target and therapeutic.

MARKETING OPPORTUNITY

Anti-thrombotic drugs are currently used for a wide range of cardiovascular indications such as myocardial infarction, acute coronary syndromes and stroke. This resulted in global sales for anti-thrombotics of $13.3 billion in 2005 and is predicted to increase to $17.9 billion by 2011.

The anti-thrombotic market comprises anti-platelet drugs, anti-coagulants and thrombolytics, with leading brands such as Plavix and Lovenox accounting for a significant proportion of the market. However, patent protection is due to end in 2011/2012 for the leading brands and the need for more efficacious and safer drugs with fewer side effects are driving growth in the market for new anti-thrombotics.

THE OXFORD INVENTION

Researchers at the University of Oxford have identified a novel target for anti-thrombotic therapeutics, the G6B receptor. Chemically-stimulated platelet aggregation is inhibited when the G6B receptor is activated.

The key advantage of the G6B receptor as a target is that it is expressed specifically on the surface of resting platelets, and this expression increases 2-fold when platelets are activated. Therapeutics targeting the G6B receptor would potentially be more efficacious with fewer side effects compared to existing treatments.

As well as identifying this receptor, the researchers have a specific monoclonal antibody that targets the G6B receptor, which could be developed as a potential therapeutic. The natural ligand for the G6B receptor is yet to be identified but small molecule inhibitors could be developed to inhibit this highly specific target. Further research is ongoing to identify the ligand.

PATENT STATUS

This work is the subject of patent application PCT/GB07/003048, and Isis would like to talk to companies interested in developing the commercial opportunity that this represents either through licensing or collaboration. Please contact the Isis Project Manager to discuss this further.

Keywords: Anti-thrombotic, target, anti-platelet drugs, antiocagulant, therapeutic, thrombolytis

OXFORD GENOME - WIDE ASSOCIATION SOFTWARE SUITE - Isis Project No 3507, 3589, 3591, 3592

A world-leading suite of software for the statistical analysis of genetic information is available to license by commercial organisations

Marketing Opportunity

A number of differences in peoples' genomes, termed single nucleotide polymorphisms or SNPs, have been associated with disease. For example, certain SNPs in the DNA repair gene BRCA1 are very highly associated with breast cancer. The majority of diseases for which there is a genetic component, however, are not associated with one particular genetic mutation, but alterations in a number of genes across the whole genome. Genome-wide association studies (GWAS) are beginning to elucidate these complex interactions, with at least 165 associations now known. This represents a huge range of new drug targets, validated in humans, with the promise of many more as more GWAS are performed.

A world-leading team in Oxford have developed a range of programmes for statistical analysis of genome-wide data using novel algorithms. The programmes allow the user to gain an understanding of the complex interrelationships between many genetic variants and diseases and the conditions with which they are associated. Reliable methods for analysing genome-wide data to understand these complexities have long been desired by geneticists in industry and academia alike. The Oxford Genome Analysis Software Suite has already elicited great interest from both academic groups and industry and we are now able to offer commercial licenses to this leading suite, in whole or in part.

The Oxford Genome-wide Analysis Software Suite (OGWASS)

3507: CHIAMO: This programme incorporates a novel algorithm for calling of overall genotypes from SNP intensity data. Further, it allows calling of genotypes in multiple cohorts at once using a hierarchical model. To our knowledge, this is a unique benefit.

3589: SNPTEST detects disease associations at SNPs in genetic studies and enables genotype uncertainty (a by-product of imputation – see below) to be taken into account.

3591: IMPUTE: A novel algorithm for imputation/prediction of unobserved and missing SNP alleles in a dataset consisting of genotype data on a set of individuals based upon a panel of known haplotype data and a recombination map. The idea of imputing alleles has now become very popular in genetics studies of human disease and is being used to enable researchers to find new disease genes and share data. IMPUTE allows more precise and efficient prediction than other algorithms available.

3592: HAPGEN simulates case control datasets at linked SNP markers, conditional upon a set of known haplotypes based upon known panels of genetic variation.

Patent Status

RECOMBINANT ALPHAVIRUS FOR DNA VACCINATION -

Isis Project No 1049

Research by Professor Vincenzo Cerundolo at the Institute of Molecular Medicine, University of Oxford has identified a method using replication-incompetent alphavirus, and derived constructs, as boosting agents in vaccination regimen.

Therapeutic Areas/Application

Induction of host immune responses, in particular to viruses and tumours

Background

Heterologous prime-boost vaccine regimens (using different priming and boosting agents) are well known to generate greater protective immunity to pathogens than the traditional method of repeated vaccination with identical (homologous) agents. For DNA vaccines, in which the immunising antigen is delivered in the form of DNA, much research has been undertaken to determine appropriate viral vector delivery systems able to ensure expression of the antigen in target immune cells. When choosing an appropriate boosting agent, it is important to ensure that the viral vector is not likely to have been encountered by the patient's immune system previously. Prior exposure to the vector may cause the immune response to react to the vector rather than the antigen, therefore negating the protective effects of exposure to the antigen.

The Oxford Invention

The Oxford inventors have used a replication-incompetent alphavirus – Semliki Forest Virus (SFV) – encoding a specific antigen or antigens as a boosting agent to demonstrate protective immunity in prime-boost models. SFV has previously been shown to exhibit excellent efficacy and biosafety and represents an ideal tool for developing effective DNA vaccines for infectious disease and cancer applications.

The invention also includes a method of boosting an immune response to one or more epitopes via administration of a composition of one or more alphavirus constructs, each comprising one epitope. This has been shown to overcome immunodominance problems in boosting protocols.

Commercialisation Opportunity

This excitingOxford technology is the subject of a patent application covering alphaviruses in general. Companies interested in product developments arising from this work are invited to contact Isis Innovation to discuss how they could utilise this technology .

TETRAMER REAGENTS FOR MONITORING AN IMMUNE RESPONSE - Isis Project No 1049

Research by Professor Vincenzo Cerundolo at the Institute of Molecular Medicine, University of Oxford has identified a powerful method which can greatly accelerate development of new

vaccines by allowing rapid and accurate analysis of human cytotoxic T-lymphocyte (CTL) responses.

Therapeutic areas/application

Development of new vaccines.

Background

In order to develop new vaccines and to test the efficiency of vaccination protocols, it is necessary to accurately, quickly and efficiently test the CTL response that is provoked by the vaccination regimen. Without such testing it is difficult to determine whether the vaccine or vaccination strategy marks an improvement over those that already exist. As an answer to this problem, the Oxford inventors have developed a novel tetramer based technique to directly monitor the CTL population expanded by vaccination.

The Problem

The mouse is often used as an experimental animal to test vaccination strategies. In order to provide a biological environment that is as close as possible to the human environment, transgenic mice with the ability to express human MHC molecules are often used. Mice expressing chimeric MHC in which the alpha1 and alpha2 domains are derived from human and the alpha 3 domain derived from mice have proved particularly useful in this respect. It is possible to monitor CTLs using multimeric MHC molecules displaying peptide/epitope to detect CTLs raised to that epitope. However, the usefulness of MHC multimers is compromised in mouse models since the MHC is usually of human origin whereas the test model is non-human and will therefore have the protein CD8, which does not effectively bind to human MHC.

The Oxford Invention

The Oxford inventors have devised a chimeric multimeric MHC structure that is able to overcome the limitations of using human MHC multimers in non-human test species. These chimeric MHC molecules are more efficient at detecting CTL responses to desired epitopes than non-chimeric structures. The binding of such chimeric MHC structures to CTL is easily detectable by using, for example, fluorescently labelled tetramers. Such chimeric MHC structures can also be used to quickly and efficiently determine epitopes in a particular protein.

Commercialisation Opportunity

This excitingOxford technology is the subject of a patent application. Companies interested in product developments arising from this work are invited to contact Isis Innovation to discuss how they could utilise this technology

IMPROVED VACCINATION STRATEGY - Isis Project No 1049

Research by Professor Vincenzo Cerundolo at the Institute of Molecular Medicine, University of Oxford has identified a method of vaccination using peptides and proteins that produces a powerful immune response that is specific to a broad range of tumour/viral epitopes.

THERAPEUTIC AREAS / APPLICATION

Induction of host immune responses, in particular to viruses and tumours

BACKGROUND

Prime/boost vaccination protocols based on repeated injections of the same antigen are able to generate strong cytotoxic T-lymphocyte (CTL) immune responses. However, during the priming stage of a vaccine regimen the more dominant epitopes of the antigen provoke a greater CTL response than the weaker epitopes – so called immunodominance. This skewing of the immune response is exacerbated **a:** in patients with a pre-existing natural immune response against an epitope encoded by the poly-epitope vaccine construct (e.g., HIV patients and late stage melanoma patients) and **b**: if the same poly-epitope construct is administered during the boosting phase.

The effect of immunodominance is that prime/boost vaccination strategies based on the use of poly-epitope constructs fail to expand a broad CTL response by favouring the proliferation of CTL expanded either during the individual's natural immune response or in the initial priming stage.

THE OXFORD INVENTION

The Oxford inventors have devised a novel vaccination strategy that helps to overcome the potentially negative effect of immunodominance in conventional poly-epitope vaccines, and have shown that this improved regimen leads to the simultaneous expansion of dominant and subdominant CTL of multiple specificities to highly effective levels *in vivo*. This novel vaccination strategy can also be used to boost immune responses to epitopes such as those found on tumour cells and virus infected cells. Furthermore, the inventors have shown that this strategy enables use of peptides and proteins in the boosting stage, either alone or pulsed over the patient's dendritic cells. This overcomes the risk of unwanted side effects associated with viral vectors and also means that it is no longer necessary to identify the exact epitopes against which an immune response is desired, nor to isolate DNA for those epitopes.

COMMERCIALISATION OPPORTUNITY

This excitingOxford technology is the subject of a patent application. Companies interested in product developments arising from this work are invited to contact Isis Innovation to discuss how they could utilise this technology.

DRUG CARRIER FOR THE TREATMENT OF CANCER - Isis Project No 70640

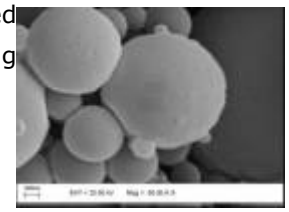
Technology Source: Universidade de São Paulo (USP)

A new drug-carrier system for administration of photosensitive agent for the treatment of skin cancer resulting in reduced side effects.

Marketing Opportunity

Skin cancer is one of the world's most common cancers, with the number of cases increasing annually. According to the World Health Organization, an estimated 132 000 cases of malignant melanoma, the most dangerous form of skin cancer, are diagnosed annually.

The efficiency of therapies used in cancer treatment is directly related to the level of selectivity in targeting the neoplastic tissues, destroying the diseased cells without affecting healthy cells. This is critically dependent upon the development of drug delivery systems with the ability to accumulate drugs selectively in tumour tissues.



The USP Invention

The USP Photobiology and Photomedicine Research Group is dedicated to the continual improvement of new therapies of cancer treatment. Recently, the group combined the benefits of drug delivery systems (DDs) with new pharmaceutical materials (nanoemulsions and nanoparticles) in order to apply photodynamic therapy and other photodynamic process (other non-oncological application). This therapy is based on the systemic or topical administration of a photosensitive-DDs drug followed by illumination with visible light of an appropriate wavelength in the neoplastic tissues. The ensuing photodynamic reaction leads to tumour destruction by necrosis or apoptosis process.

This drug-carrier system has been shown to be more effective than other therapies, such as chemotherapy and radiotherapy, and offers other advantages: photosensitive nanoparticles with anti-cancer drugs presented less side effects in a less invasive treatment regime. This methodology can also be used in other cancers as well as bacterial, viral and fungal diseases, and in the dermatological treatments designed to renew the skin. First phase clinical trials are underway and the results to date are encouraging. There are also studies in Tissue Engineering and in Dentistry area focusing on bacteria diseases.

Patent Status

This technology is owned by USP Innovation Agency, the technology transfer company of USP. USP is the leading research University in South America. This work is the subject of a patent application and USP Innovation Agency would like to talk to companies interested in developing the commercial opportunity that this represents. Please contact the USP Project Manager via Isis to discuss this further.

DETECTION OF LOW AFFINITY TCRS - Isis Project No 71223

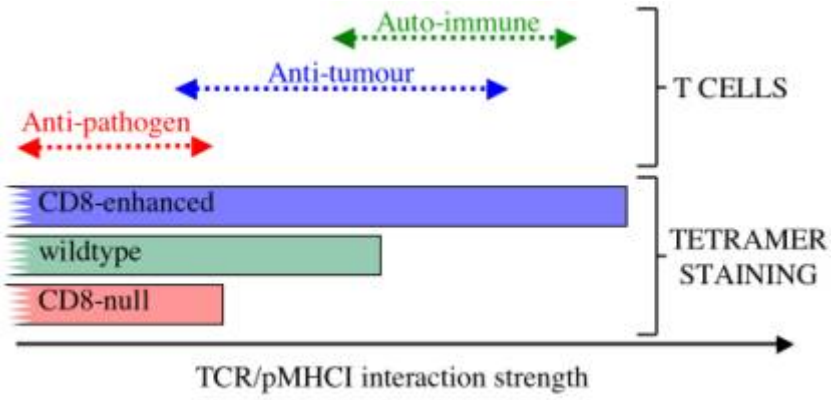
Fluorochrome-conjugated peptide-major histocompatibility complex (pMHC) multimers have transformed the study of antigen-specific T cells by enabling their visualization, enumeration, phenotypic characterization and isolation from ex vivo samples by flow cytometry. The affinity thresholds for identifying T cells with pMHC multimers and that required for antigen-specific activation of T cells differ. As a result, not all T cells that respond to a particular pMHC are amenable to detection with this antigen in multimeric form and pMHC multimers are unable to identify all T cells that respond to a particular antigen. This is a problem when using pMHC multimer to identify T cells with low affinity T cell receptors (TCRs) such as those that predominate in anti-tumour or autoimmune responses. Research at Oxford University has developed CD8-enhanced pMHC multimers. These reagents can identify all T cells that respond to a particular antigen and can be utilized at 100X lower concentration and still produce bright staining of anti-viral T cells.

Marketing Opportunity

There is clearly a market for research and diagnostics for these reagents. They can be applied to any MHC class I molecule to enhance CD8 binding. Surface plasmon resonance has been used to confirm that these mutations do not affect the interaction between the TCRs and the pMHC antigens. Mutant antigens have also been shown to have substantial benefits when used in priming anti-tumour cytotoxic T lymphocytes.

The Oxford Invention

The Oxford invention comprises a series of mutations in the conserved parts of the MHC class I molecule. This unique technology allows the detection of all T cells that respond to a particular antigen and can be used at greatly reduced concentrations yet still give better results in many applications. Numerous requests have been received for these reagents even though their properties have not yet been described in the scientific literature.



The use of CD8-null, wildtype and CD8-enhanced pMHC multimers enables the grading of T cells based on the strength of their interaction with the soluble pMHC ligand.

Commercial Opportunity

This technology is subject to a patent application. The mutated antigens,either as soluble molecules or when expressed on the cell surface of an antigen presenting cell, have been shown to enhance T cell signalling and T cell effector function without altering specificity of the T cell response. There are numerous potential uses of the invention in addition to its application to pMHC multimer technology.

ENVIRONMENTAL

SEASONAL FORECASTING - Isis Project No 1042

Problem

Predicting weather conditions for longer than a day or a week has long been possible. There are aspects of a climate system, which vary on longer time scales, that can bias the probability of their occurrence.

Often the relationship between climate and impact is insufficiently accurate, leading to erroneous predictions. For example, changing levels of greenhouse gases can affect forecasts.

Background

Current climate observations are input into dynamical models of which there are many types, which are then run forward in time to produce a forecast. These types of models are based on a baseline climate that the model will return to once the short-term forecast is produced. This makes them unsuitable for seasonal forecasts.

Perfect ensembles, or weighted averages of analogous past climate systems, can be used for seasonal forecasting. Use of these ensembles has been restricted because it can take millions of years to observe the exact climate. Computer climate modelling speeds up the return time of the atmosphere by making assumptions based on past climates.

The Oxford Invention

A model based approach to seasonal forecasting using perfect and sub-ensembles. The model relies upon distributed computing to provide the necessary processing power and speed. The model is distributed to PCs, each one with different initial values, allowed to run over a period of time in to the future. The simulations that are consistent with recent observed climate change are used as the basis for ensemble forecasts of the future change.

Commercialisation Opportunity

Isis Innovation Limited is in a position to offer licences to this technology. The technology is the subject of a UK patent application.

BREAKTHROUGH ARSENIC REMOVAL TECHNOLOGY -

Isis Project No 2493

Inexpensive method for removing heavy metals from drinking water.

Researchers in the department of Physical Chemistry at the University of Oxford have developed an exciting new method for removing Arsenic and other toxic heavy metals such as Cadmium, Cobalt and Copper from drinking water.

Arsenic and other heavy metals occur naturally in many rock formations worldwide. When underground water flows through rocks or soil that contain heavy metals, the heavy metals dissolve into the water. Drinking water contaminated with heavy metals can cause severe health problems. In particular long-term exposure to arsenic can cause cancer, gangrene and skin lesions.

Market Opportunity

Many countries have problems with arsenic contaminated drinking water. A 1998 British Geological survey showed that 46% of the water wells in Bangladesh had arsenic levels greater than the safe level of 0.01mg/L. Seven out of sixteen districts in West Bengal (India) have been reported to have ground water arsenic concentrations above 0.05mg/L. The US Environmental protection agency estimates that some 13 million of the US population are exposed to arsenic levels at or above the limit of 0.01mg/L. Other areas with major arsenic problems in drinking water include Nepal, Myanmar and parts of Vietnam. Several government-funding bodies are looking to support arsenic removal research and the development of technologies for use in the above-mentioned areas.

Intensive mining operations in many countries have also caused environmental problems. Mining of rocks with heavy metals can cause contamination of these heavy metals into the nearby water systems. The most common contaminants are Cobalt, Copper, Lead, Cadmium, Arsenic and Zinc. Heavy metal pollution from mining is occurring in many areas, including Zaire, Ghana, Korea, Peru and parts of the USA.

Scientists at the University of Oxford have developed a new, simple method, which allows arsenic and other heavy metals to be easily and quickly removed from drinking water.

The Oxford Invention

The Oxford invention is a new material that absorbs heavy metals out of water. Using carbon graphite as the base material, the surface is treated to allow large quantities of modified carbon to be attached. This modified carbon then removes large amounts of toxic heavy metals including Cd(II), Pb(II), Zn(II) and As(III) from water. Key advantages of our technology are:

- Inexpensive starting material

- Simple to manufacture
- Highly efficient removal of heavy metals
- Could be easily scaled up or used in the home

Patent Status

This work is the subject of a patent application, and Isis would like to talk to companies able to develop this technology further. Please contact the Isis Project Manager to discuss this opportunity.

"SMART METERS" OUTSMARTED! - Isis Project No 2871

A new utility metering device helps consumers identify the use, or more appropriately misuse, of appliances in the home and work environment.

Market Opportunity

So-called "Smart Meters" are currently available to measure electricity supply but only provide information on total consumption in half-hourly periods. By altering behaviour when using electricity the consumer can significantly reduce their consumption, save money and reduce their CO2 footprint. The question remains for the consumer "How do I easily identify exactly where I'm wasting electricity?" Until now, there hasn't been any easy and readily available response for the consumer.

The Oxford Invention

A new prototype electricity meter, the Geni-e™ Meter, has been successfully tested within the Engineering Department at the University. The single-point monitoring Geni-e™ interrogates mains supply to the building of interest. Then, by identifying changes to the power drawn from the supply and recording time dependent (both short-term and log-term) characteristics can accurately identify the type, or even the individual appliance being used. The Oxford Geni-e™ meter does not need satellite-monitoring devices (for example on each plug socket); it can identify hard-wired appliances (cookers or immersion heaters) and could easily be linked to a PC. The PC or other user interface could analyse the data supplied by the Oxford Geni-e™ meter to identify appliance use/misuse and direct the consumer towards behavioural or process changes that results in significant reductions in utility use. The Geni-e™ meter uses acquired data including waveform, time of day use and length of appliance operation to determine probabilistically what the appliance is. In this way the Geni-e™ meter incorporates a learning mode and can independently identify appliances when they are used for the first time. As the device could also identify appliances operating outside of their normal modes of electricity consumption, the Geni-e™ could help identify malfunctioning appliances. To summarise the Oxford Geni-e™ meter delivers:-

- Specific information to consumers, helping them make informed decisions about appliance use that can directly save electricity,

- A single-point interrogation of the mains supply into the building providing building-wide information on appliance use or misuse,
- Can clearly identify short and long terms savings by analysing the captured data,
- The theory behind the Geni-e™ electricity meter could also be applied to both gas and water metering.

Geni-e™ - The Genius Meter? Why of course, it is from Oxford.

Patent Status

This work is the subject of a patent application, and Isis would like to talk to companies interested in commercialising this technology. Please contact the Isis Project Manager to discuss this opportunity

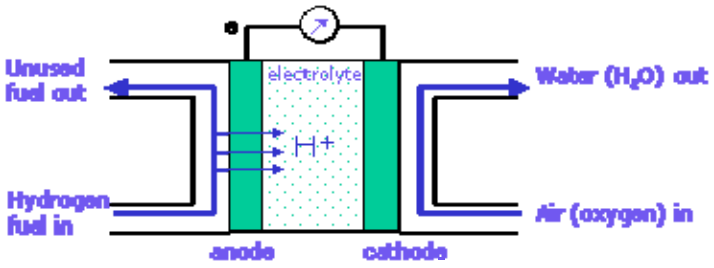
STABLE ENZYME ELECTRODE - Isis Project No 3123

Hydrogen-oxygen fuel cells benefit from a new laccase-coated electrode that gives better lifetime and higher efficiency.

MARKETING OPPORTUNITY

Enzyme-based fuel cells are of interest in applications requiring quick start-up, low power and ease of recycling. No expensive platinum or other precious metals are used. However, enzyme electrodes have limited lifetime. Laccase enzymes are typically used for the oxygen side of the fuel cell; this is an essential part of the fuel cell reaction in which oxygen combines with the hydrogen fuel, to form electricity, with water as a by-product.

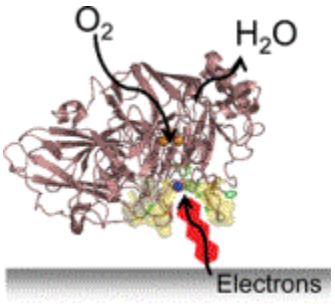
Typical fuel cell design



THE OXFORD INVENTION

Researchers at Oxford have developed a new coated graphite electrode. Laccase electrodes made with the coating have double the active lifetime of the best previous literature reports, together with excellent activity. The coating provides a stable point of attachment for the laccase enzyme, and delivers electrons efficiently from the graphite electrode right into the heart of the enzyme where they are needed. This improvement in stability and activity is a key step towards realising commercially viable enzyme fuel cells.

For further reading, see Chem. Commun., 2007, 1710-1712



PATENT STATUS

This work is the subject of a patent application, and Isis would like to talk to companies interested in developing the commercial opportunity that this represents. Please contact the Isis Project Manager to discuss this further.

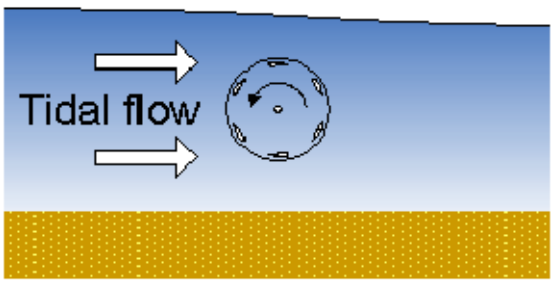
SMALL THAWT, BUT BIG THINKING - Isis Project No 3325

A novel tidal turbine has been designed and tested which allows the scalable exploitation of tidal resources by a device that has low mechanical complexity.

Sea-green energy

Tidal currents provide a highly predictable source of energy that can help to reduce our dependence on fossil fuels. The currents, created by the relative positions of the sun and moon, can be enhanced by geological features to speeds where extraction of energy is an attractive proposition. There are many such sites around the world, and the UK is estimated to have 10% of the global extractable tidal resource. Tidal currents are sub-surface, so tidal turbines have minimum visual impact, unlike wind farms or estuary barrage schemes.

The majority of tidal turbines in development are axial flow devices that rotate perpendicular to the current direction, like a common wind turbine. The size of the device and area of current they can intersect is limited by the depth of water requiring 10s or 100s of these devices in order to achieve large-scale and significant power generation.



Direction of flow relative to device

A novel THAWT

A team of Engineers in Oxford have designed, built and tested lab scale versions of a turbine that is mechanically much simpler than axial flow devices. The Oxford turbine, called THAWT (Transverse Horizontal Axis Water Turbine), has been designed to intersect the largest possible

area of current, and has resulted in a device that can be scaled regardless of the depth of water in which it is situated.

The result is that if THAWT devices were extended across the same area as axial flow devices.

THAWT would require:

- less generators,
- less primary seals
- less foundations

And consequently THAWT would incur:

- lower capital costs
- lower maintenance costs
- lower operational costs

Patent status

This work is the subject of patent application. Isis would like to talk to any companies interested in partnering this timely opportunity. Please contact the Isis Project Manager to discuss this further.

ENVIRONMENTALLY FRIENDLY INDUSTRIAL LUBRICANTS - Isis Project No 70639

Technology Source: Universidade de São Paulo (USP)

New castor oil plant based biodegradable, environmentally friendly cutting fluid for lubricating industrial processes.

Marketing Opportunity

The market for metalworking fluids is valued at nearly Euros 1bn per annum in Europe alone. Lubricants are used in many industrial processes to:

- Improve performance within machines;
- Reduce operating temperatures;
- Ease residue removal; and,
- Improve durability.

However, manufacturing industries employing oil-based lubricants are a major source of pollutant wastes as most current lubricants are made from non-environmentally friendly mineral sources such as petroleum. Across the world, many countries have been establishing regulations to reduce the environmental impact of industrial production and environmentally friendly lubricant alternatives are sought.

The USP Invention

This invention consists of a new formulation of compounds derived from the castor oil plant that characterize an efficient liquid as lubricant for industrial applications, especially in cutting processes.

The main advantages of the technology are:

- The fluid is biodegradable;
- The lubricant has a high water content;
- Low toxicity;
- The lubricant formulation has fewer chemical additives; and,
- Ease of disposal.

Biodegradable cutting fluid for cleaner production. Cutting fluid is based on castor oil plant.

Commercial Opportunity and Patent Status

This technology is owned by USP Innovation Agency, the technology transfer company of USP. USP is the leading research University in South America. This work is the subject of a patent application and USP Innovation Agency would like to talk to companies interested in developing the commercial opportunity that this represents. Please contact the USP Project Manager via Isis to discuss this further.

DIAGNOSTIC

GENETIC VARIANT FOR ASTHMA DIAGNOSIS - Isis

Project No 146

Isis Innovation, the technology transfer arm of the University of Oxford, releases a new method for non-atopic asthma diagnosis and prognosis.

MARKETING OPPORTUNITY

- Anti-TNF drugs used in the treatment of non-atopic asthma are expensive and not always efficacious. This invention provides a method whereby asthma sufferers could be stratified into responders and non-responders to anti-TNF treatment.

- A method allowing individuals and clinicians to test for an individual's predisposition for asthma as well as a prognosis for the likely severity of the condition.

THE OXFORD INVENTION

The present invention is directed to a method for diagnosing an individual as being asthmatic, or having a predisposition to asthma, and a kit therefore, which method comprises demonstrating in the individual the presence or absence of an unusual variant form of a genetic sequence in the MHC region of chromosome 6p, said unusual variant being associated with an increase secretion of TNF.

PATENT STATUS

The invention has a granted US patent 6,387,615.

NOVEL TRANSCRIPTION FACTOR - FOXP1 AND USES THEREOF - Isis Project No 0634 and 1368

Research at the University of Oxford has resulted in the identification of a novel transcription factor, FOXP1. Unlike other subgroups of this family, the FOXP genes contain both the forkhead/winged helix DNA binding domain together with a Cys2-His2 zinc finger. The FOXP1 protein may function as a co-regulator of nuclear receptors, and in particular the oestrogen receptor. The gene encoding FOXP1 has been sequenced, and a monoclonal antibody raised against the protein.

Applications

Potential applications of this technology include early diagnosis and use as a prognostic indicator of lymphomas, leukaemias and carcinomas. Therapeutic applications may be developed through modulating the humoral or cellular functions of the immune system and development of treatments which either modulate or normalise the levels of FOXP1 expression in cancers and autoimmune diseases (including rheumatoid arthritis and multiple sclerosis). Preliminary studies suggest that FOXP1 expression may be associated with poor response to therapy in lymphoma and breast cancer patients making this molecule a potential drug target in these cancers.

Background

Transcription factors have essential roles in regulating gene expression. The forkhead/winged helix (FOX) family of transcription factors play important roles in normal development, including regulating cellular proliferation, differentiation, signal transduction, mitotic program, longevity and cellular transformation. In addition to their normal roles, members of this family also play a part in mammalian oncogenesis.

The Oxford Invention

Tissue localisation studies of FOXP1 have been performed using an antibody raised against this novel protein. FOXP1 is expressed in most normal healthy tissues. When studied in cancerous tissues, however, abnormal levels of nuclear protein expression were identified in a wide range of both solid tumours and haematological malignancies. In addition, changes in FOXP1 expression have been shown to occur early during malignant progression, often before histological changes. Increased expression of FOXP1 mRNA has also been found in the peripheral blood fractions of patients suffering from idiopathic thrombocytopenia purpura and multiple sclerosis.

Commercialisation Opportunity

These technologies will be of interest to companies developing diagnostic and prognostic tests for developmental defects, cancer and autoimmune diseases, and to companies developing therapeutic agents for the treatment of such conditions. These exciting new discoveries are the subject of 2 patent applications (WO 01/40303 A1, and another recent GB priority filing), and some of the data has been published (Cancer Research 61, 8820-8829, 2001). Isis Innovation is actively seeking partners to commercialise this technology.

Keywords

FOXP1, transcription factor, cancer, autoimmune disease, rheumatoid arthritis, prognosis, therapy

UNIVERSAL FLUORESCENT SENSORS - Isis Project No 1037

Research workers in the University of Oxford have devised a development of existing fluorescent probe technology to make sensors capable of detecting a wide range of compounds.

Background

Fluorescence Resonance Energy Transfer (FRET) is a process by which energy that would normally be emitted as a photon from an excited fluorophore can be directly transferred to a second fluorophore to excite one of its electrons. This, on decay, then generates an even longer wavelength photon. The extent of FRET is critically dependent on the distance between the two fluorophores as well as their spectral overlap. Thus FRET is a powerful reporter of the separation of the two fluorophores.

Problem

There is an increasing requirement to detect a wide range of compounds with high sensitivity and specificity. Molecular reporters using FRET had previously been demonstrated for calcium using calmodulin and a calmodulin-binding peptide as linkers between two fluorescent proteins. Calmodulin undergoes a conformational change in the presence of calcium and also

binds to the adjacent peptide sequence to bring two fluorophores closer together, thus increasing the amount of FRET and shifting the emission towards a longer wavelength.

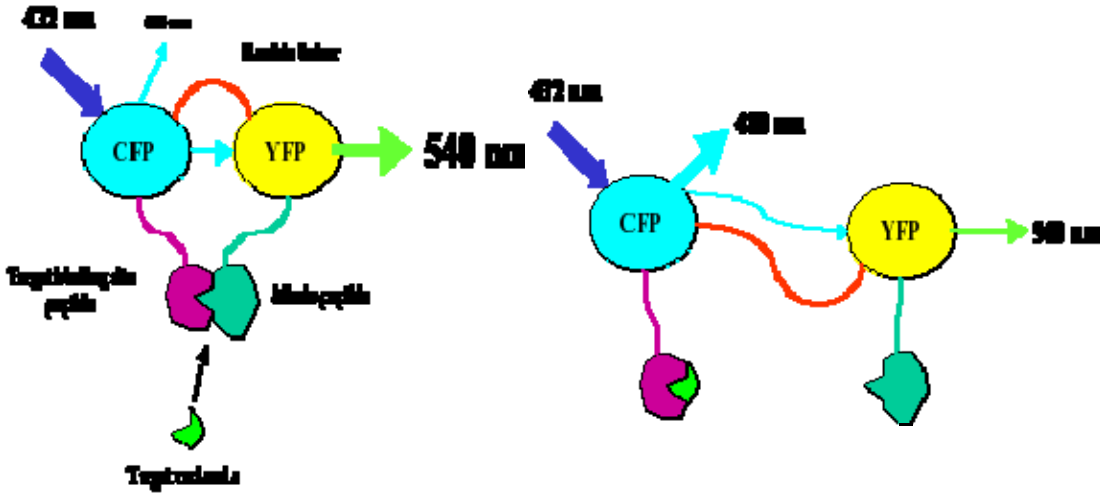
The Oxford Invention

The new probes consist of two peptides, that normally bind together, attached at opposite ends of two fluorophors separated by a flexible peptide linker. In this configuration, the fluorophores are held in close proximity, allowing FRET to take place. In the presence of a target molecule which preferentially binds to one of the peptide sites, the link is broken allowing the fluorophores to spring apart with a concomitant reduction in FRET.

The range of probes that can be generated is therefore only limited by the range of interacting binding sites that can be characterised. A large number of antibody combinations or substrate binding sites are already known and further sites are being discovered daily.

These probes could be used in the detection of metabolites, drugs, contaminants, environmental pollutants and many others where high specificity and low detection limits are necessary. Usage in industry and in research is envisaged.

Figure: Design and principle of operation of the new probes



In the absence of the target compound, the mimic peptide binds to the target-site peptide. The flexible linker allows the two fluorophors to approach each other and a high level of FRET results.

The target molecule competes with the mimic for the target binding site causing separation of the two fluorophors and a decrease in FRET.

Commercialisation Opportunity

This discovery is subject to two patent applications. Isis is interested in discussing suitable arrangements with companies wishing to develop and exploit this technology.

Keywords

Biosensor, flourescent resonance, fluorescent probe, fluorescent sensor, FRET, canary sensor, chameleon probe, canary probe, sensitive biosensor, fluorophor probe, mobile biosensor, field test biosensor

MONOCLONAL ANTIBODIES DIRECTED AGAINST SUBUNITS OF HUMAN RNA POLYMERASE FOR USE IN IMMUNOFLUORESCENCE AND IMMUNOPRECIPITATION - Isis Project No 1138

Research at The Sir William Dunn School of Pathology, Oxford University, has resulted in the isolation of eight monoclonal antibodies directed against subunits of RNA polymerases I, II and III.

Background

During the final stages of the Human Genome Project, interest has increased in how information is transferred from genes to proteins, in which the RNA polymerases play a vital role. The nuclei of human cells contain three different types of RNA polymerase, characterised by their elution profile, drug sensitivity and location within the cell: polymerase I, II and III, each consisting of 12 to 17 subunits.

The Problem

Although the composition of RNA polymerases is the subject of constant study, the detection and localisation of many of the subunits has been restricted by the limited number of antibodies suitable for use in immunofluorescence and immunoprecipitation. Clearly it would be an advantage to know the function and location of all the subunits of such important cellular enzymes.

The Oxford Invention

Research at Oxford has generated eight monoclonal antibodies (mAbs) specific for different subunits of RNA polymerases which are suitable for use in immunofluorescence, immunoblotting and immunoprecipitation. Three mAbs are specific for subunits found in RNA polymerases, I, II, and III. Five further antibodies are specific for subunits of RNA polymerase III, and different ones are suitable for different applications. All have performed well in trials and, as RNA polymerases are highly conserved, these antibodies may cross react with the homologous subunits found in other eukaryotic cells.

Commercialisation Opportunity

Isis Innovation would welcome any inquiries from potential partners interested in utilising this technology.

Keywords

Antibodies, RNA Polymerase

LYMPHOMA AND TUMOUR ANTIGENS - Isis Project No 1185

Research at the University of Oxford has resulted in the identification of various antigenic proteins using antibodies present in the blood of patients with aggressive diffuse large B cell lymphoma (DLBCL).

Applications

The molecules identified are believed to be proteins whose expression in the cancer cell leads to a tumour associated immune response. They may represent important markers for prognostic or diagnostic purposes and for the potential treatment of lymphomas of various types including diffuse large B cell lymphoma.

Background

Diffuse large B-cell lymphoma accounts for 30-40% of all adult non-Hodgkin's lymphomas. The genetic abnormalities underlying DLBCL remain poorly understood and, in contrast to other lymphoma types, no single characteristic genetic alteration has been found. Approximately 50% of patients relapse after treatment and their tumours frequently become resistant to therapy, therefore alternative therapies are urgently needed for this group of patients.

The Oxford Invention

The Oxford inventors have used the serological analysis of recombinant cDNA expression libraries technology (SEREX) to identify DLBCL-associated proteins expressed from a testis cDNA library. Some of the antigens identified represent novel molecules hitherto unidentified whilst others represent partially characterised antigens for which no function has yet been ascribed. A number of the antigens identified encode known proteins that are already linked to human cancer.

Commercialisation Opportunity

The potential exists for prognostic / diagnostic tests to be developed and therapeutic potential may be found through vaccination, gene therapy, the use of the protein (or peptide analogues) or derivatised antibodies. This exciting Oxford discovery is the subject of a patent application. Isis Innovation is actively seeking partners to commercialise this technology.

Keywords

Lymphoma, tumour antigens, 'large B cell lymphomas', cancer, therapy, diagnosis

SINGLE MOLECULE ARRAYS - Isis Project No 1348/1349

A Researcher at the Wellcome Trust Centre for Human Genetics has developed a novel platform for genomics, which combines microarrays with single molecule technology. The approach can add significant value to the existing microarray technologies, in particular for mRNA profiling. It may even allow for expansion of microarray technologies into new markets.

Marketing Opportunity

This technology is seen as a significant improvement and can be viewed as an evolution of microarray technology. While it adds significant value to existing mRNA profiling it does not require the customer to shift from the market accepted microarray formula to an unfamiliar alternative that may require re-training and perhaps significant capital expenditure. Applications of the technology extend from DNA analysis (mRNA profiling, SNP typing, Resequencing) to proteomics, epigenomics and small molecule drug interactions.

The Oxford invention

Involves the linking of single molecule technology and microarray technology, first patent application. The combined features of which should bring massive parallelization to the former and ultra sensitivity to the latter. Analysing individual molecules not only increases sensitivity, it also adds confidence to an analytical decision. It can also allow for information to be revealed, which is ordinarily masked by the averaging effect of the ensemble analysis.

The microarray is used to sort a complex mixture of DNA or RNA molecules to distinct spatial locations on a surface and the single molecule methods enable each individual molecule to be detected as a point of fluorescence and separately resolved. Furthermore, array captured DNA molecules can be linearised on a surface to enable long-range genome analysis. A second patent application extends the invention in two distinct ways:

1. Firstly, spatially addressable arrays are taken into novel applications by using multiple array elements to analyse a single DNA polymer. This can be applied to haplotyping and is particularly amenable to electronic transduction in a diagnostic device

2. Secondly, it develops the concept of arrays of molecules, which start as being spatially random but are then characterized and made spatially addressable.

The patent status

Isis Innovation has patented this unique technology. Companies interested in discussing the commercialisation of this exciting and potentially lucrative invention are invited to contact Isis Innovation for further information. WO 02/74988.

Keywords

METHOD FOR MASSIVELY PARALLEL DNA SEQUENCING

- Isis Project No 1451

Researchers at University of Oxford have developed a method that will enable high throughput, low-cost DNA sequencing.

MARKETING OPPORTUNITY

DNA sequencing has traditionally utilised the Sanger gel migration method which is both time-consuming and expensive. There is currently a major drive to develop alternative lower-cost and faster methods to meet the demand for large-scale automated genomic scale sequencing. The Oxford invention addresses many of the issues encountered when striving to achieve this.

THE OXFORD INVENTION

The Oxford invention offers a method for DNA "sequencing by synthesis" using a ligation method that can be employed on a large scale, with lower costs and faster speeds on a conventional array platform or on a novel single molecule microarray format.

Features of the technology are:

- can be employed for large scale sequencing with multiple parallel reactions
- will be cheaper than existing and emerging alternatives (no highly modified nucleotides are required)
- can be readily automated
- the high accuracy of ligation reactions
- can be adapted to utilise multiple labels
- has the potential to achieve long read lengths
- does not suffer from de-phasing as read length increases (with single molecule analysis)
- can potentially provide more informative sequence reads than existing technology
- can be applied on standard microarrays/genchips (i.e. 3' to 5' oligonucleotide orientation)

Although the ligation method has been described utilising a microarray platform (subject of another Isis project number 1348), it is adaptable and not restricted to this platform.

PATENT STATUS

This is the subject of Patent application WO 2005/040425

RECOMBINANT OVERLAPPING PEPTIDE VACCINES FOR INFECTIOUS DISEASE AND CANCER - Isis Project No 2452

Research at the University of Oxford has led to a new approach to generating effective vaccines quickly and inexpensively in response to the emergence of new pathogens.

Background and Market Opportunity

A key challenge facing human health is that of rapid generation of new vaccines effective against multiple strains of human pathogens. In particular, the threat of pandemic influenza increases the need to minimise the time between emergence of a new variant pathogen and supply of an efficacious prophylactic vaccine. A need also exists for vaccines able to stimulate cellular immunity, which is believed to be important in mounting a protective immune response against many pathogens and cancers.

The Oxford Invention

The inventor has shown previously that administration of a pool of synthetic, overlapping peptides (OPs) relating to a particular disease-associated protein can generate strong cellular immune responses in vivo. By using such a pool of peptides it is possible to cover multiple epitopes, which overcomes problems associated with HLA restriction. Furthermore, time-consuming epitope mapping is not required, which reduces the time taken to produce an effective vaccine.

However, despite advances in solid-phase methods, use of synthetic peptides can be less than ideal in terms of the large-scale manufacturing required for many infectious disease vaccines. The Oxford researcher has addressed this problem by developing a recombinant method for producing OP vaccines. This approach involves bacterial expression of an amino acid sequence corresponding to OP sequences spanning the length of a protein of interest, interspersed with enzymatic cleavage sites. The recombinant product can then be digested either in vitro, or, if cleavage sites for enzymes present in human cells are chosen, in vivo.

Proof of concept has been achieved with adjuvanted OPs to HIV-Nef protein able to induce specific cellular immune responses in 2 strains of mice. Vaccination with OPs was also able to protect mice from high dose viral challenge of vaccinia virus expressing HIV-Nef. Further in vivo studies with additional antigens are anticipated.

Commercial Opportunity

Isis would like to talk to companies interested in further developing this patented technology, which could be applied as a platform for creation of prophylactic and therapeutic vaccines for a wide range of diseases.

TARGETED IMAGE CONTRAST AGENT - Isis Project No 2468

Background

Oxford researchers have developed the first of a class of novel sugar-targeted imaging contrast agents for use with MRI brain scanning.

Contrast agents are widely used with MRI (magnetic resonance imaging) – these compounds increase the contrast between the area of interest and the background and in many cases have been found to improve sensitivity and/or specificity. Such agents operate either by:

- Specifically enhancing the signal that is produced
- Localizing in a specific cell type or tissue.

Typically, image contrast agents are either based on gadolinium complexes or super-paramagnetic iron oxide (known as USPIO), the latter of which is used for imaging lymph nodes. MRI is currently the preferred method of imaging the brain to confirm diagnosis and track disease progress for multiple sclerosis - there are 400,000 patients in the US alone. However, although existing contrast agents are clinically useful, it is known that conditions such as multiple sclerosis produce lesions that cannot be seen with conventional technologies – this shows there exists a clear need for the development of improved image contrast agents.

The Oxford Invention

Researchers at the University's Experimental Neuro-imaging Group, departments of Pharmacology and Chemistry have collaborated to develop a new imaging agent for MRI brain scanning, which targets lesions in the blood brain barrier.

The imaging agent comprises an ultra-small super-paramagnetic iron oxide particle (USPIO) that is attached to a sugar tag. The sugar tag acts like a postal code for the USPIO:

Delivering it to the site of inflammatory lesions in the blood brain barrier

Selectively binding it to the protein produced there.

The researchers have exciting experimental evidence showing that the imaging agent provides extremely sensitive imaging, that is far superior to that obtained with existing imaging agents. The invention, by providing a more advanced method of detecting damage to the blood brain barrier, could potentially provide much advancement for the diagnosis and monitoring of multiple sclerosis and other inflammatory diseases of the central nervous system.

Commercialisation Opportunity

A patent application has recently been filed to protect this work. Isis would be keen to talk to companies interested in developing the commercial opportunities for this technology.

SWARM INTELLIGENCE FOR RAPID BIOMOLECULAR STRUCTURAL DETERMINATION FROM NMR DATA - Isis Project No 2536

Researchers at the University of Oxford have developed a new high-speed method for determination of macromolecule structures from raw NMR spectroscopy data.

BACKGROUND

Structural determination of proteins is particularly challenging for those that are unsuitable for X-ray crystallography analysis (at least 15%), many of which are highly relevant drug targets. Current best practice uses an iterative process to solve the structure of such proteins from NMR spectroscopy data. This process is subjective, error-prone, can take several weeks if not months, and may ultimately be unsuccessful. Despite current limitations, the NMR spectroscopy market is estimated at $500M-1B.

THE OXFORD INVENTION

Oxford researchers have developed a straightforward technique to alleviate the problems associated with current iterative methods by utilizing the principle of swarm intelligence (SI) to achieve a single-step determination of biomolecular structures from NMR data. (SI) is the property of a system whereby the collective behaviours of unsophisticated agents interacting locally with their environment cause coherent functional global patterns to emerge. In the case of the Oxford invention, a swarm of individual "molecular generators" working in parallel is able to rapidly form a consensus protein structure.

By using the Oxford software, biomolecular structures can be accurately determined from proteins in solution in only a few hours, once raw data has been acquired. The software should also enable more accurate protein structure determination on low and mid range spectrometers. It has been validated with two proteins for which the structures have been previously determined using either X-ray crystallography or NMR, with excellent results. Structural determination of further proteins and protein-ligand complexes is underway.

COMMERCIALISATION OPPORTUNITY

A patent has been filed to protect the technology and Isis would like to talk to potential commercial partners.

A NOVEL CANCER BIOMARKER AND DRUG TARGET - Isis Project No 3101

Oxford researchers have discovered a novel cancer biomarker with great potential as a target for therapeutic intervention.

MARKETING OPPORTUNITY

The market for cancer therapies is set to experience significant change as newer targeted therapies replace broader spectrum treatments. Targeted therapies are generally better tolerated, less toxic and provide better patient outcomes. In parallel, ageing populations and improved detection methods have led to increases in the number of patients requiring treatment, and there remains an unmet need for more effective therapies.

THE OXFORD INVENTION

Oxford researchers hypothesised that the activity of a particular protein previously thought to be unrelated to cancer may play a direct role in the regulation of tumour cell proliferation and progression. Subsequent investigation of levels of expression of the protein in human tumour samples using immunohistochemical staining confirmed that, compared with normal tissues, the protein is expressed excessively in tissues from patients with lung, breast, head and neck cancers as well as lymphomas.

It has further been shown that:

- Over-expression of the protein promotes cell proliferation by activating cell survival signalling
- Disruption of this signalling or down-regulation of expression of the protein leads to decreased cell migration
- Over-expression of the protein occurs in some human colorectal cancer cell lines
- Over-expression of the protein in cells increases tumour growth

Further studies are underway to evaluate the effects in cancer models of a known ligand, and to screen libraries in order to identify new compounds effective against this target.

PATENT STATUS

This work is the subject of patent application filed in 2007. Isis would like to talk to companies interested in developing the commercial opportunity that this represents, and the patent application can be made available for review under CDA. Please contact the Isis Project Manager to discuss this further.

HLA TYPING - Isis Project No 3337

A novel, reliable and highly cost-effective method of gaining an understanding of the structure of an individual's HLA profile

MARKETING OPPORTUNITY

1. Available for licensing is a software programme, which allows the mapping and prediction – with a minimum of between 90 and 95% accuracy of an individual's HLA II type, based on any of the widely available DNA chip platforms. For any screening programme, this allows a huge reduction in the number of individuals who actually have to be typed, and consequently a considerable cost saving. This will be of particular interest to drug companies, manufacturers of SNP arrays, users of SNP arrays and those involved in the investigation and treatment of autoimmune disease. It will also be of interest to those involved in understanding and predicting prognosis and disease progression, and to drug developers. It also has considerable application in vaccine trial covariance and clinical study understanding.

THE OXFORD INVENTION

2. An algorithm and statistical software for probabilistic prediction of alleles at classical HLA loci has been developed that allows the determination of the HLA serotype presented by an individual, without the current array of expensive, and often inaccurate, typing methods and technologies. Tissue typing is used in a wide range of biological and medical fields, particularly in relation to screening individuals for transplantation etc. To HLA type an individual currently costs approximately £500, making screening programmes particularly costly. Further, while routine serological methods are reliable for HLA class I typing, they are currently uncertain for HLA class II typing partly owing to the poor quality of the antisera used. Since HLA class II typing is important for BMT, a more accurate method for HLA II typing is needed. If the mutation rate and the recombination frequency at any given locus are known then it is possible to calculate the likely path through the gene. This means that only a minimal set of markers are required for a prediction of the complete region. This avoids the use of tagging methods that require knowledge of what has been investigated previously and expands the possibilities for typing in a highly cost-effective manner.

PATENT STATUS

This work is the subject of patent application, and Isis would like to talk to companies interested in developing the commercial opportunity that this represents. Please contact Dr David Phillips, Project Manager, at Isis Innovation Ltd. to discuss this further.

INSTRUMENTATION

MAGNETICALLY SENSITIVE TRANSISTOR - Isis Project No 25 & 813

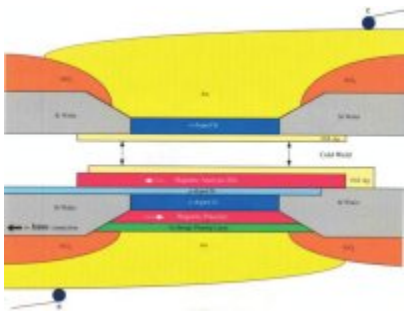
Modern semiconductor electronics has advanced according to Moore's Law, however new technology will be needed for future performance improvements. Spintronic devices use the spin or magnetic properties of electrons, not their electric charge, to process data. This new generation of advanced electronics promises dramatically improved levels of performance with low power usage.

MARKETING OPPORTUNITY

A modern microprocessor contains more than 125 million individual transistors, so improvements in transistor design have a significant technical and commercial impact. University of Oxford researchers have now developed a new design of "spin-transistor" with exceptional *power gain*.

One potential application is replacing the giant magnetoresistive stacks that are currently used to read data from hard-disc drives, increasing speed and reliability. Looking further into the future spin transistors will be integral to the next generation of non-volatile magnetic memory, known as MRAM. Spin transistors can also be used as highly sensitive magnetic sensors - for example in the automotive industry as high precision position sensors to enhance engine performance.

The Oxford Invention



Structure of a spin transistor

The Oxford "Spin Transistor" technology has several important technical advantages:

- Based upon silicon technology, it can be integrated into existing manufacturing processes
- The only spin transistor with a gain approaching unity (up to 1,000 times better than previous designs)
- It is an "active" electronic device with magnetically tunable characteristics, which can be combined with its unique levels of power gain to produce novel electronic devices

Magnetic RAM (MRAM)
MRAM uses "magnetic" charge to store information, promising higher density memory chips that retain information even when power is switched off.
Based upon arrays of spin transistors, MRAM will combine processing and storage hence removing the distinction between working memory (RAM) and longer-term storage (hard-disc drives etc).

Patent Status

This work is the subject of a series of patent applications and granted patents, including two granted US patents. Isis would like to talk to companies interested in developing this exciting new technology. Please contact the Isis Project Manager named below to discuss this further.

Keywords

GMR, spin transistor, hard disc reader heads, magnetic field sensor, charge polarisation, magnetic field, magnetic memory

UNIVERSAL FLUORESCENT SENSORS - Isis Project No 693 and 1037

A novel procedure, for the generation of fluorescent sensors capable of detecting a wide range of compounds.

Marketing Opportunity

There is an increasing requirement to detect a wide range of compounds with high sensitivity and specificity. Molecular reporters using Fluorescence Resonance Energy Transfer (FRET) has previously been demonstrated for calcium using Calmodulin and a Calmodulin-binding peptide as linkers between two fluorescent proteins. This approach has two main drawbacks: (1) It has a very small dynamic range (2) It cannot detect small conformational changes.

The challenge to further development of this area is identification of a new method to generate more versatile fluorescent sensors, which are able to operate at higher sensitivity and lower detection levels than existing ones.

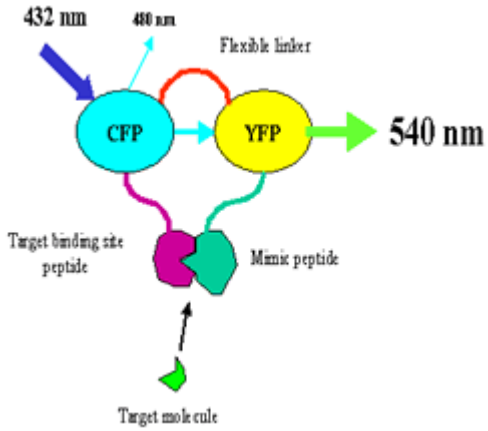
The Oxford Invention

The Oxford Invention provides for the first time a novel method of generating **highly sensitive, highly specific, fluorescent sensors**. The Oxford Invention is **inexpensive** and **simple**. The range of probes that can be generated by the invention, is limited, only by the number of interacting binding sites that can be characterised - this number is growing daily.

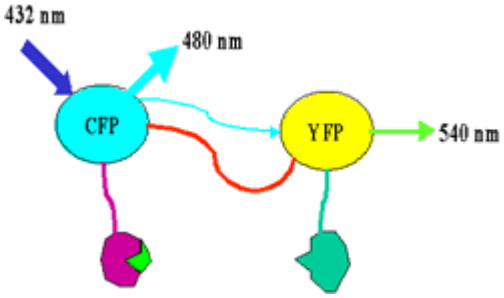
These probes can potentially be used to detect:

- Metabolites, drugs and toxins in blood
- Contaminants in water/foodstuff
- Environmental pollutants

Design and principle of operation of the new probes



A. In the absence of the target compound, the mimic peptide binds to the target-site peptide. The flexible linker allows the two fluorophores to approach each other and a high level of FRET results.



B. The target molecule competes with the mimic for the target-binding site causing separation of the two fluorophores and a decrease in FRET.

Patent Status

This work is the subject of two patent applications, and Isis would like to talk to companies interested in developing the commercial opportunity that this represents. Please contact the Isis Project Manager to discuss this further.

OBJECT MATCHING IN VIDEOS - Isis Project No 1484

Isis Innovation, the technology transfer arm of the University of Oxford, now has for licensing a new approach to object matching in videos.

Marketing Opportunity

Retrieval of objects from video footage is a challenging problem because an object's visual appearance may be very different owing to the viewpoint and lighting, and it may be partially occluded, but some successful methods do now exist. Typically, in such methods, an image of an object is represented by a set of overlapping regions, each represented by a vector computed from the region's appearance. Other methods have been proposed whereby object matching and retrieval has been achieved based on colour and/or texture histograms. However, known methods for object retrieval possess several shortcomings; none are sufficiently robust against occlusion, clutter, viewpoint changes and image intensity changes. Additionally they tend not to be efficient enough if a search for an object is required to be carried out in respect of large numbers of individual images. Potential applications include security, archived library footage and screening of products for offensive material.

The Oxford Invention

The Oxford Invention describes an approach to object and scene retrieval that searches for and localizes all the occurrences of a user outlined object in a video. The method is analogous to text retrieval where matches on descriptors are pre-computed. Retrieval is immediate returning a ranked list of key frames or shots in the manner of a text search engine. We now have immediate run-time object retrieval throughout a movie database, despite significant viewpoint changes in many frames.

Patent Status

This work is the subject of patent application, and Isis would like to talk to companies interested in developing the commercial opportunity that this represents. Please contact the Isis Project Manager to discuss this further.

IMPROVED HEATING CONTROL IN BUILDINGS - Isis Project No 1489

A joint initiative between Oxford University and BRE

A new model-based algorithm for building heating control automation has been developed which delivers energy efficiency while maintaining internal comfort.

Market Opportunity

Reducing energy consumption is one of the most obvious ways of saving money and reducing the impact on the environment. However there are many existing, medium sized heating installations that are only part way through their life but are relatively poorly controlled. As a result, many buildings managers struggle to satisfy the challenges of cutting heating costs and at the same time maintaining a comfortable environment for the occupants. This problem is made far more difficult in buildings with multiple zones that have complex heat inputs and outputs.

The Oxford and Buildings Research Establishment (BRE) Invention

A new model-based predictive boiler controller has been successfully commissioned and tested by BRE and Oxford University. The controller uses an advanced mathematical model to predict the average temperature inside the building and find the optimal supply water temperature. It uses a novel dual-loop control strategy that is currently the subject of a patent application. It requires no permanent measurement of the air (room) temperatures inside the building and reduces the energy consumed by the boiler without any associated loss in thermal comfort. The improved heating control is easily retrofitted to existing heating systems and can be commissioned over a short period of time.

- Saves Energy (initial results show between 10% to 30%)

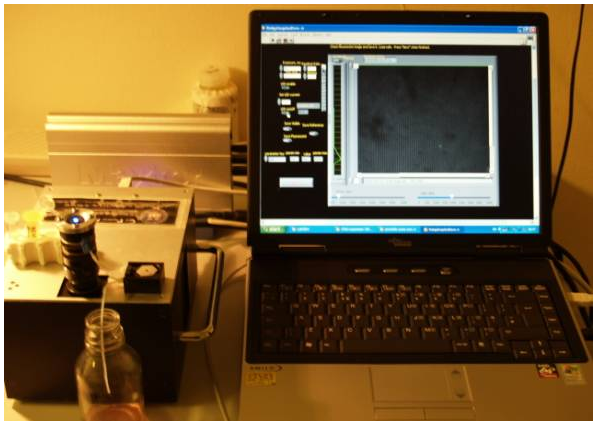
- Simple 'boiler room' solution that delivers greatest savings on poorly controlled systems
- Relatively simple to install and easily commissioned
- Provides for a comfortable building environment
- Approach could be adapted to control chillers/air-conditioning systems

Patent Status

This work is the subject of a patent application, and isis and BRE would like to talk to companies interested in commercialising this technology.

CELL POPULATION ARRAY IMAGER (CPAI) - Isis Project No 1547

Researchers at the University of Oxford have invented a cost-effective, portable and powerful Cell Population Array Imager.



The Oxford Invention

The CPAI is a specialised simple microscope which measures weak light signals over minutes to hours. The signals come from individual live cells introduced into it as a suspension, such as blood cells. Fluorescent or luminescent reporter molecules are pre-incorporated into the cells by well-established methods. The heart of the CPAI is an imaging optical fibre-bundle forming a close-packed array of ultramicrowells imaged by a sensitive digital camera. Each well accommodates just one cell. Images of thousands of cells are acquired every few seconds. The fibre-bundle is in a closed flow-chamber so that cells can react with substances micro-pumped through it in solution. Some of the cells may brighten transiently, with characteristic patterns. For instance T lymphocytes react to anti-receptor antibodies that stimulate calcium oscillations. For a few tens of minutes some of the cells wink like lighthouses, displaying a range of time-variant patterns. Proprietary neural-network-based pattern-recognition algorithms running on an ordinary laptop computer then automate the classification of the winks into characteristic cell subpopulations. For the first time we can classify cells into subsets primarily according to their biochemical function, not by molecular marker. This CPAI is an inexpensive and portable research instrument, in comparison with conventional flow cytometers or fluorescence microscope. It is likely to improve "'omic"

strategies by screening large tethered arrays of protein or RNA ligands, and also has the potential to be developed as a field-portable cytometer with primary healthcare and third-world applications.

Solutions provided by this invention

The CPAI solves all the limitations that afflict two related technologies:

1. Conventional video-imaging by fluorescence microscope to record signals from cell populations is constrained by:

- limited number of cells analysed, so subset-typical patterns aren't identifiable
- cells being displaced by reagent passage during image acquisition, so data are lost
- cumbersome and expensive equipment
- requirement for relatively large cell numbers

2. Flow cytometers, when used for time-varying functional studies, assume each cell behaves identically to all the others in the sample. They measure only the average of the whole poputaion; so individual differences are hidden.

Patent Status

This work is the subject of a patent application. Interested parties are welcome to discuss with Isis Innovation on how to utilise this invention. Please contact the Isis Project Manager to discuss this further.

SENSITIVE GAS DETECTORS - Isis Project No 2350 and 2401

Marketing Opportunity

The monitoring of reducible and oxidizable gases has become increasingly important as the effects of such gases upon health and the environment have been brought into the public eye. Reducible and oxidizable gases may be toxic and environmental pollutants. The gases may be formed from burning fuel in motor vehicles, electric power plants, and other industrial, commercial, and residential sources that burn fuel. They may be present in enclosed spaces such as ice rinks from ice surface renewal machines and in kitchens or apartments from using a gas stove. Exposure to some reducible and oxidizable gases may exacerbate a pre-existing pathogenic condition in people who spend a large amount of time in such places and/or cause respiratory health problems. Consequently, continuous monitoring is required.

Known methods of gas detection include, for example, chemiluminescence, fluorometric and spectrophotometric analysis. A favoured alternative uses amperometric sensors have been found to enable low cost of components, small size, and lower power consumption than other types of sensor, and are ideal for use in portable analysis systems. Electrochemical techniques for the quantification of gases have been described but sensitive systems almost invariably employ noble metals which dramatically increase costs.

The Oxford Invention

A new methodology has been developed based on low cost carbon based electrodes for the detection of trace quantities of toxic gases such as nitrogen dioxide (NO2) and chlorine (Cl2). The technology has been successfully applied to the detection of low levels of chlorine and nitrogen dioxide gas but is likely to have broader application in the detection of sulphur dioxide, hydrogen, hydrazine, arsine, nitrogen monoxide, hydrocarbons including methane, oxygen, ozone, carbon monoxide, carbon dioxide, hydrogen sulphide, and carbon disulphide.

Patent Status

This work is the subject of patent application, and Isis would like to talk to companies interested in developing the commercial opportunity that this represents. Expertise in manufacturing low cost electronic devices is particularly sought. Please contact the Isis Project Manager to discuss this further.

HIGH THROUGHPUT SURFACE TENSION MEASUREMENT

- Isis Project No 2538

Researchers at the University of Oxford have invented a novel measurement for high throughput screening to prevent false negatives in drug discovery.

Marketing Opportunity

High throughput screening in pharmaceutical drug discovery (prevention of false negatives)

Process control in manufacturing surface active products (inks, detergent products, agrochemicals)

Quality control in production lines

Screening tool for microfluidics compatibility (lab-on-a-chip samples)

Multiplexing multiwell assays using combined ELISA and enzyme-linked immunosurfactant assay (ELISURFA)

The Oxford Invention

The invention offers a rapid method for the measurement of surface tension at a fluid-gas (or fluid-fluid) interface in multi-well plates, based upon computer-generated repetitive high contrast patterns imaged through the samples using a CCD camera controlled by dedicated image analysis software. Rapid well-by-well feedback control of the optimal spatial frequency of the analytical pattern ensures the widest possible measurement range (by keeping the signal in the image within the most accurate linear range despite wide variation due to different lensing effects).

Applications

A dedicated stand-alone instrument offers very high throughput with minimum constraint on sample size and composition, except for the requirement that the sample be at least translucent at a wavelength between 400-900nm. A reflection mode variant removes even this constraint.

A wide range of applications are envisaged; a subset are suggested in the marketing section above.

Advantages

Measurements are very rapid (96 wells read in parallel with a reading time of less than one second), use small samples (typically 50-200 microlitres), require no contact (so sterility is maintained and toxic aerosols are never created), and may be made at any temperature and in non-air atmosphere if required. Furthermore, measurements may be made repeatedly such that reactions may be followed dynamically in real time, rather than being constrained to an end-point value.

The method is especially suitable for robotic plate handling systems and may be incorporated efficiently into the work flow of a high throughput screening assay. This makes the method particularly relevant for screening HTS assays for unexpected surface tension changes (predominantly due to the library compounds that vary from well to well, but also able to detect bubbles and foreign bodies in wells) that might otherwise give rise to false negatives or false positives in the screen.

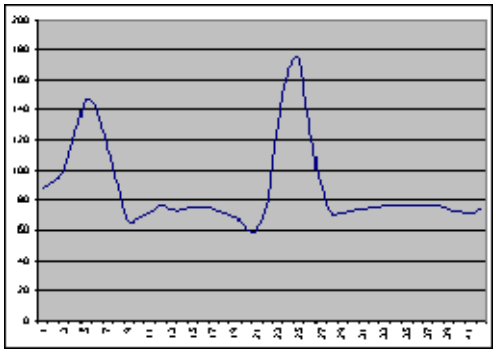
Application of a feedback between the image analysis software and the pattern generator is used to maximize the range of surface tension effects that can be measured. This is achieved by feedback regulation of the spatial frequency of the pattern until a waveform with a wavelength in the linear range is detected in the image.

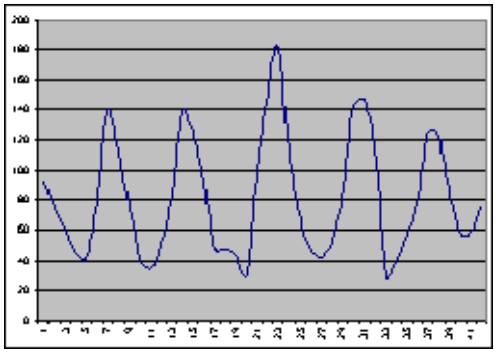
Patents Status

This work is the subject of a patent application. Interested parties are welcome to discuss with Isis Innovation on how to utilise this invention. Please contact the Isis Project Manager to discuss this further.

Figures

A digital demonstration of the dynamic measurement; a line scan or simple photodiode system could provide an analog voltage varying so that processing could remain in an analog frequency domain.





REAL WORLD ARSENIC DETECTION - Isis Project No 2618 and 2718

Marketing Opportunity

Arsenic is a naturally occurring element widely distributed in the earth's crust and a common contaminant of drinking water. Exposure to arsenic can cause a variety of adverse health effects, including dermal changes, respiratory, cardiovascular, gastrointestinal, genotoxic, mutagenic and carcinogenic effects. Arsenic contamination of drinking water has been reported globally with dangerously high levels present in for example Argentina, Bangladesh, Cambodia, Chile, China, Ghana, Hungary, Inner Mongolia, Japan, Mexico, Nepal, New Zealand, Philippines, Taiwan, the United States and Vietnam. The World Health Organization's recommended maximum arsenic contamination level for drinking water is 10 ppb. A particular practical issue when addressing arsenic contamination in the real world (as opposed to the academic laboratory) is the large variation in arsenic contamination levels in wells only a few metres apart.

More than 56 million Americans could be drinking tap water containing average levels of arsenic that pose unacceptable cancer risks (source: US NRDC)

Laboratory based analytical procedures have previously been developed to allow detection of low levels of arsenic contamination. The development of reliable electrochemical methods suitable for the development of low cost hand-held test instruments has been hampered by the presence of other contaminants (lead, copper, zinc, iron, antimony, bismuth, selenium, silver and mercury) in real world water samples. The presence of copper as Cu(II) is the most common source of interference and has to date prevented the development of instruments for use in field testing.

The Oxford Invention

Using novel modified glassy carbon electrodes electrochemical techniques have been developed which allow determination of low levels of arsenic contamination even in samples containing high levels of Cu(II) as a co-contaminant. This invention will enable the development of new testing low-cost devices with high sensitivity that can be directly applied in the field.

Patent Status

This work is the subject of patent application, and Isis would like to talk to companies interested in developing the commercial opportunity that this represents. Expertise in manufacturing low cost electronic devices is particularly sought. Please contact the Isis Project Manager to discuss this further.

WET FLOOR DETECTOR - Isis Project No 2775

Marketing Opportunity

According to statistic published by the National Safety Council (a non-profit, non-governmental, international public service organization dedicated to protecting life and promoting health), slips and falls are a leading cause of unintentional injury in the United States. This is supported by the fact that more than 1 million Americans, most of who are over the age of 60, have sought emergency room treatment for such accidental falls; a growing number of these accidents are occurring in retail stores, hotels, restaurants, supermarkets and office buildings.

Over the last decade, slip and fall accident rates have more than doubled and this is becoming a major concern to US retailers, for example it has been estimated that one of the major retailers, is sued on average once every two hours, totalling thousands of lawsuits each year - many of these being for slips and falls1; one such lawsuit cost approximately $545,000.2

The escalation in the number of such accidents shows that existing methods of wet floor, accident prevention - portable warning signs that are only erected after someone alerts management - are obviously not adequate.

The need therefore exists for a more proactive slip and fall prevention strategy.

The Oxford Invention

The Oxford Invention represents a new, versatile, sensor for wet floor detection that is based on light scattering.

The Invention has several advantages over existing methods:

• It is inexpensive
• It is simple
• It can detect wet floors rapidly and accurately. • It is a remote device i.e. it doesn't need to be in contact with a wet surface.
• It can give audible and visible warnings

1 Occupational Health & Safety, 130-131, September 2002

2 Risk & Insurance, March 2004
(http://www.findarticles.com/p/articles/mi_m0BJK/is_3_15/ai_114004918)

Patent Status

This work is the subject of patent application, and Isis would like to talk to companies interested in developing the commercial opportunity that this represents. Please contact the Isis Project Manager to discuss this further.

ENGINEERING AND PHYSICS

OPTICAL ID - Isis Project No 532

An alternative to ubiquitous RFID technology based on optical systems with clear advantages for applications where power usage, range or security are issues

MARKETING OPPORTUNITY

According to a recent survey there will be a trillion wireless devices serving a billion people by 2020 (Vision of the Wireless World Research Forum). The market for active and passive RFID devices is anticipated to reach $10bn by 2010.

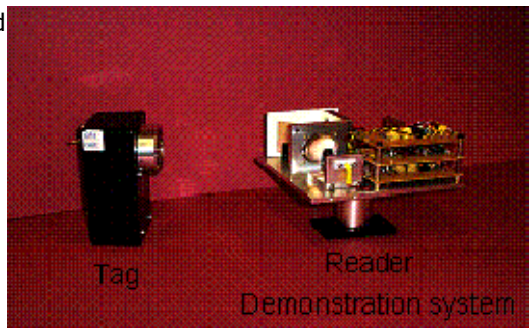
While the market applications are growing, RFID technology is not without flaws. For example,

- the range of passive RFID devices is limited,
- RFID technology struggles in metallic environments,
- RFID is intrinsically insecure, and,
- encryption of RFID transmission costs device power.

THE OXFORD INVENTION

This invention relates to an optical communications transceiver that is simple and robust and provides a platform for optical ID technology. For selected applications optical ID based solutions are superior to RFID counterparts. For example, optical ID devices can be made which communicate over large distances (>100m) and as a line-of-sight technology optical ID is not susceptible to eavesdropping.

The advantages of the specific Oxford retro-reflector designs are:



- direction of illumination is not important,
- simple devices can be powered by the illumination, and,
- complex devices (say with an embedded sensor) can work on very low power.

The new technology is idea for a broad range of applications including:

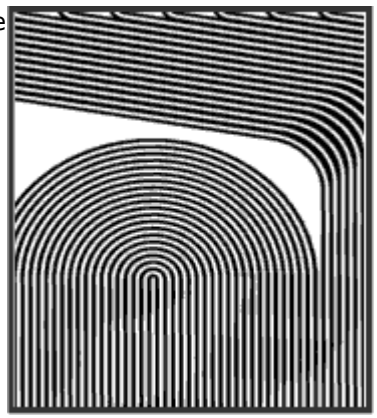
- logistics tracking in metal rich environments such as container loads in ports,
- using optical ID rather than RFID for secure passports, and even,
- monitoring the environment by deploying disposable sensors over a broad area and using a model aircraft coupled with a reader to interrogate the sensors on the ground.

PATENT STATUS

This invention is the subject of a granted patent.

FABRICATION OF HIGH RESOLUTION PRINTED CIRCUIT BOARDS - Isis Project No 591

By precise control of the etching process Oxford inventors have made the reliable production of High Resolution Printed Circuit Boards (PCBs) with conductors down to 10 μm wide more of a cost effective reality.



Introduction

With ever increasing demands for greater miniaturisation and the use of flexible circuitry the need for improved fabrication methods for high resolution printed circuit boards is becoming more important. PCBs currently include conductors as narrow as

150 µm, but there is now a requirement for conductors to be as narrow as 25 µm and even down to 10 µm. With current manufacturing techniques it is not possible to attain the required precision especially where the spacing between the conductors varies. The etching rate is highest where the conductors are furthest apart. This leads to over-etching and subsequent under-cutting of the very fine conductors in these areas. The resultant PCB has copper conductors of variable width, and its performance is, therefore, not optimum.

The Technology

By controlling the etch conditions and the area to be etched the Oxford inventors have reduced the amount of over-etching to an acceptable level and under-cutting has been virtually eliminated. The spaces between the conductors are now all of uniform width, but with more redundant copper remaining on the PCB; the etching has been confined to narrow tracks. In the magnified view of an actual PCB the white areas represent the exposed copper tracks, while the black show the intervening non-conducting substrate.

Benefits

This technology will benefit many of the applications that now demand PCBs with fine conductors or alternatively require flexible circuitry to facilitate yet further miniaturisation. Typically these include applications such as mobile phones, personal flip-top organisers and inkjet printers.

Commercialisation Opportunity

This invention is now the subject of a patent application and companies interested in developing this technology commercially are invited to contact Isis Innovation.

MONITORING & CONTROLLING A LINEAR MOTOR - Isis Project No 917

A University of Oxford researcher has developed new and improved software for controlling and operating a linear motor or compressor.

Background

Monitoring the state of mechanical, electrical or electronic systems is normally achieved by including sensors that are designed to measure specific operating parameters. Direct measurement by sensors can on occasion be detrimental especially where the sensor changes the system being monitored, for example, by requiring power itself.

The linear electric motor is a linear transducer which combined with non-contacting bearings and seals offers a number advantages, such as oil free operation, over conventional rotary motors. Of particular importance in operating a linear motor is the measurement and control of the stroke and the offset, where the offset is the mean position of the moving part of the transducer. Such mean position is not easily measured when the transducer is in sinusoidal

motion, unlike in a rotary machine where such parameters are fixed by geometrical restraints.

Problem

If the stroke and the offset are not controlled, damage can occur if the axial movement exceeds the design range resulting in inadvertent contact between different parts of the system. Close control is necessary to optimise machine efficiency. Currently these parameters are controlled by attaching a displacement transducer to the moving part of the linear transducer; this together with the associated electronics adds significantly both to cost and weight. The additional complexity also reduces reliability.

The Oxford Invention

A linear motor model having a high level of correlation with a working system has been developed. By matching the actual voltage and current inputs with those in the model, values of parameters corresponding closely to real values can be found, and these can then be used to monitor and control the motor's operation. The process has the major advantages of being simple to operate, no additional hardware is necessary, therefore no additional weight, and the degree of complexity is much reduced.

Commercialisation Opportunity

This patent application is available for licensing, and companies interested in developing and using this technology are invited to contact Isis Innovation for further discussion.

OPTICAL LOCAL AREA NETWORK COMMUNICATIONS - Isis Project No 923

A team of Oxford University researchers, in collaboration with other UK universities, has developed a device for high speed optical communication for mobile users.

The Technology

"Hard-wired" solutions for connecting personal computers to local servers are not always convenient for mobile users. Alternatives, known as "wireless" solutions, include radio and optical links. Radio links may not be particularly suitable in applications where security is paramount, for example, in financial institutions, and in military and aerospace applications. Also, in hospitals and other environments where there is a danger that the radio waves will disrupt the operation of sensitive equipment radio links are not suitable. The researchers have developed a transmitter and receiver system based on CMOS technology, and resonant cavity LEDs. The system communicates on a line of sight principle to maximise the communication speed, and currently operates at 155Mbps. It provides a secure and safe way for users to communicate with a local server.

The Oxford Invention

- Secure communication
- Suitable for use around sensitive equipment
- Fast communication speeds
- Line of sight communication
- Proven technology
- CMOS technology
- Self tracking
- Medical applications
- Aerospace applications
- Military applications
- Finance applications

Commercial Opportunity & Patent Status

This work is patent protected, and Isis wishes to talk to companies interested in developing the commercial opportunities for this technology. Please contact the Isis Project Manager to discuss this further.