The research commercialisation office of the University of Oxford, previously called **Isis Innovation**, has been renamed **Oxford University Innovation**

All documents and other materials will be updated accordingly. In the meantime the remaining content of this Isis Innovation document is still valid.

URLs beginning www.isis-innovation.com/... are automatically redirected to our new domain, www.innovation.ox.ac.uk/...

Phone numbers and email addresses for individual members of staff are unchanged

Email : enquiries@innovation.ox.ac.uk

Isis insights

Issue 71 Spring 13

Scanning new horizons

Imaging breakthroughs from Oxford

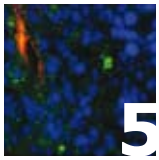
The latest innovations, collaborations and technology transfer

ISIS INNOVATION

Issue 71
Spring 2013

Scanning new horizons

Contents



OxSonics
Ultrasound-enhanced therapies

Non-toxic imaging
Agents for positron emission tomography

Ii is produced by Isis Innovation Ltd, the technology transfer company owned by the University of Oxford.

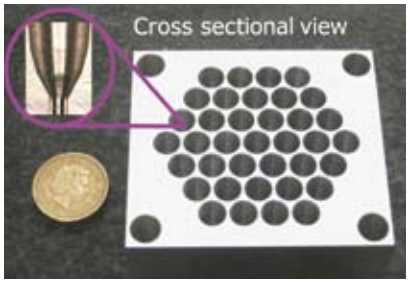
Cover image: Conceptual composition of non-toxic imaging

Newsflash

Isis is a research and technology commercialisation company owned by the University of Oxford.

Automated stroke test to save lives and costs

Building on the ASPECTS stroke programme pioneered by Alastair Buchan, Professor of Stroke Medicine at the University of Oxford, e-ASPECTS is new technology for automating the processing of CT images. "By automating the scoring system, e-ASPECTS will achieve better patient selection for stroke intervention and [increase] the chance of recovering the patient's physical and mental function," Professor Buchan said. e-ASPECTS is from Brainomix, a new start-up from Isis Innovation.



Licencing to innovate

MM Microwave, a Yorkshire-based supplier of waveguides, recently recognised an opportunity to engage with universities in order to accelerate innovation and remain a market leader. Earlier this year MM Microwave signed a licence agreement with Isis Innovation for software from Oxford. The easily-customisable feedhorn antennae design software has allowed the company to realise a twenty five percent reduction in development lead time and doubled the income stream for feedhorn antennae products (pictured). "The straightforward and professional way in which Isis worked made it easy for us to evaluate and incorporate the technology into our business," John McGreevy, the Managing Director of MM Microwave commented. The company also gained from the exposure to members of the University with relevant skills and interests, claiming the link-up could potentially represent an alternative means to more traditional ways of recruiting staff.

Courtesy of Oxford Catalysts Group

Spin-out growth

Oxford Catalysts, spun-out of the University by Isis in 2005 to produce catalysts for the next generation of clean fuels, has raised an additional £30.6m. The company is now valued at approx. £130m. The round was oversubscribed, supported by both existing investors and Roman Abramovich, the Russian billionaire and Chelsea football club owner.

Oxford's strength in Life Science spin-outs was once again highlighted in the latest annual update to the UK Life Science Report from Mobius Life Sciences and Biocity Nottingham. The report noted that "Oxford University remains by far the most prolific creator of life science spin-outs". It also commented that the UK has "An excellent research base; a strong entrepreneurial ecosystem populated by people who genuinely want to make a difference; a sympathetic government and a sophisticated investor base."

International engagements

Isis continues to advise and assist governments, universities and Technology Transfer organisations worldwide. In recent weeks Isis Enterprise welcomed visitors to Oxford from Colombia, Chile and Mexico, and Isis staff delivered training and consultancy to organisations in India, Vietnam and Saudi Arabia. Managing Director Tom Hockaday recently delivered a number of presentations in Australia to university groups and the government's Department of Industry, Innovation, Science, Research and Tertiary Education (DIISRTE). Isis has recently appointed a representative in Australia, Helen Ujvary, to support our business development activities in the region.

Enterprising Consultancy

News from Isis Enterprise and Oxford University Consulting

Software Commercialisation workshop

Isis Enterprise recently held the consultancy's inaugural one-day Software Commercialisation workshop, with further sessions available to interested individuals and organisations throughout the year. The course was run in conjunction with Anderson Law LLP, enabling Isis to provide the technology transfer insights and Anderson Law to provide expertise in software licensing issues.

Technology transfer offices at research institutions across the world have increasing numbers and variety of software commercialisation projects from their academic researchers. It is often unclear what strategies should be taken and how software technologies should be protected, marketed and sold.

Frequently asked questions when it comes to commercialising software include whether to apply for patent protection or rely on copyright, how to deal with phone and tablet apps, and how to approach pricing. Marketing and selling software technologies also raises a number of issues. The licensing process can be somewhat different, with click-wrap licenses being used for demonstration and evaluation purposes. Sales can vary from high value-low volume to low value-high volume transactions, and therefore different strategies need to be considered for each case.

The course tackled many of these common issues, enabling attendees to leave with a clear idea of how to approach their portfolio of software commercialisation projects, part of their initiative for the Leadership for Learning Programme. Isis Enterprise plan to run similar courses in 2013, so please register your interest via enterprise@isis.ox.ac.uk if you would like to find out more.

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Consultancy in the social sciences

Oxford has one of the world's leading social sciences divisions, ranked fourth in The Times' Higher Education World University Rankings 2012-2013, with the largest grouping of social sciences in the UK and an impressive number of departments and research centres. This is a very rich vein of knowledge from which organisations can draw expertise.

Consulting activity is one of the important means by which staff in the Social Sciences Division can make available their knowledge and expertise to benefit government, public sector organisations, community groups and business. Such interactions in turn benefit the University, as staff bring back to their teaching and research the insights, experiences and contacts they have gained as consultants.

With the Research Excellence Framework (REF) peer review process seeking to address not only the academic excellence of Oxford's research but also the impact of that research beyond academia, there has never been a better time for staff in the Division to be involved in consultancy activity.

Oxford University Consulting (OUC) is ideally placed to support researchers in the social sciences to maximise consultancy potential both for individuals and for departments.

The OUC brochure on Consultancy in the Social Sciences gives further information on working with OUC and sets out some case studies of interest.

To access the brochure please go to **http://bit.ly/Xn4fUt**

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The portfolio

The latest **spin-out** and **investment** news

OxSonics – delivering ultrasound-enhanced therapies

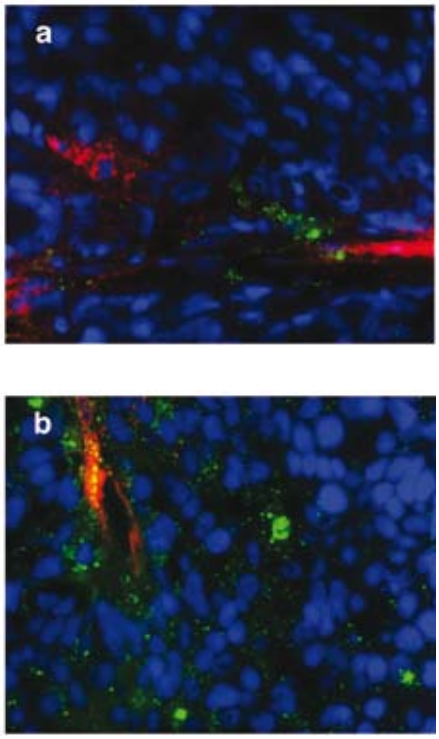
There are significant benefits for both patients and healthcare providers in delivering non-invasive therapies over those that are invasive in nature. Treatments that avoid surgical incision result in reduced trauma to the patient, whilst reduced recovery times directly translate into reduced healthcare costs. Existing non-invasive approaches utilise either ionising radiation, electroporation, laser or high-intensity focused ultrasound (HIFU). Although each approach has both advantages and limitations, HIFU offers great promise due to its ability to deliver "trackless" therapy at depths greater than 15cm in the human body. However, it shares a limitation with each of its counterparts: the inability to adequately map and monitor treatment in real time.

By exploiting the mechanical effects that ultrasound waves have on microbubbles, Professor Constantin Coussios and co-workers at Oxford's Institute of Biomedical Engineering have overcome this limitation. They have invented a next generation ultrasound platform that will enable mapping and monitoring of treatment using a low cost medical device in real-time and in 3D. The research group has then sought to apply this platform technology to address two major healthcare needs: chronic lower back pain and cancer.

In the first approach of its kind to repair degenerated spinal discs, the device will be used to facilitate removal of a degenerated spinal disc "nucleus" before replacing it with a self-polymerising hydrogel. A 1998 study estimated the annual cost of treating lower back pain amounted to £12.3 billion per annum in the UK alone.

(a): in the absence of ultrasonic cavitation, the therapeutic agent (in green) only affects those cancer cells (in blue) that are immediately adjacent to blood vessels (in red).

(b): in the presence of ultrasound-induced cavitation activity, the therapeutic agent (in green) reaches cancer cells (in blue) both proximal and distal to blood vessels (in red), achieving transport over distances in excess of 200 microns. The maximum reported distance between a cancer cell and a blood vessel is on the order of 180 microns



The device, when used in combination with proprietary encapsulation and coating technologies, will also be used to significantly enhance the delivery of cancer drugs. The device will enable a radiologist to map and selectively trigger release of a drug in a chosen tumour volume whilst visually monitoring this release in 3D and in real time. Importantly, the approach has been shown to dramatically enhance delivery of drug from blood vessels into tumour tissue at the site of treatment, overcoming a major limitation of existing cancer therapies, particularly those that are administered intravenously for the treatment of metastatic cancers. According to a 2012 study, the health and economic burden of cancer amounts to £15.8 billion in the UK alone.

OxSonics is a prospective spin-out company for the commercialisation of this groundbreaking technology. Due to the nature and scale of the healthcare needs that will be targeted by the company, the combined global market opportunity for OxSonics is estimated to exceed £1 billion. Isis Innovation has engaged designate CEO Dr. Colin Story to raise funding and incorporate OxSonics.

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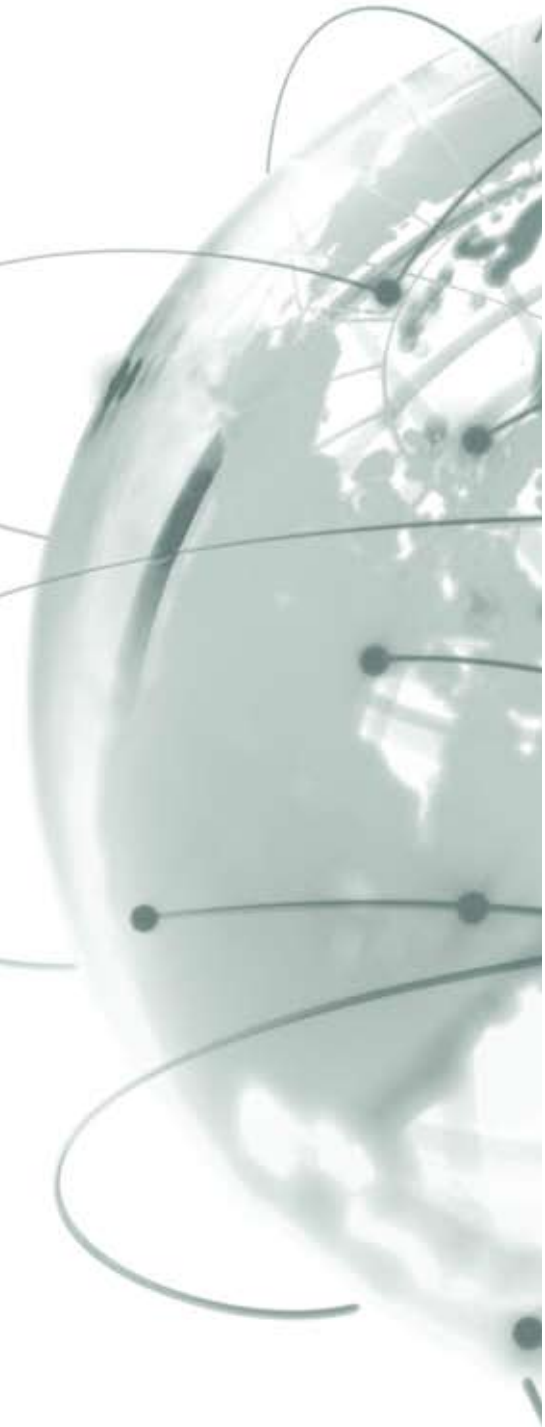

WilmerHale faces East and West for life science and technology clients bidding to enter the world's key markets. Corporate Partner **Joe Pillman** and Associate **Andrew Ross** discuss the law firm's international practice for emerging growth companies.

As a legal practice that has made emerging growth companies the cornerstone of our business for 40 years in the UK, we are keenly aware of the challenges university spin-outs, entrepreneurs and early stage investors face in the current economic climate.

In our Oxford and London offices, we help clients at all stages of the business lifecycle from the spin-out or start-up stage onwards.

The fight for investment has become ever more competitive and exit options are few and far between in the British Isles. Taking Europe as a whole, the value of venture capital financing has barely moved over the past decade, hovering around the €4 to €5 billion mark each year. Happily, these statistics do not seem to dampen the entrepreneurial spirit and ambition among those who have exciting ideas and the drive to realise them. Every day across the life sciences and technology sectors, we speak to and work with inspiring individuals and companies who have an innovative product, disruptive technology or novel drug programme.

What sets WilmerHale apart:

- Adviser to over 25 Oxford University spin-out companies since 1999
- Acted on $1.5 billion worth of venture capital transactions in 2012
- Global practice spanning the US, Asia and Europe with lawyers qualified in the major jurisdictions practicing in London and Oxford

The common challenge these clients face is securing new sources of funding and good exit opportunities. Increasingly, these are to be found overseas and most particularly in the US and China.

An American venture

The US remains the global leader in venture capital. There are more funds with more money there and the possibilities for a successful exit are far more numerous than anywhere else in the world. Similarly, the number of potential partners, customers and suppliers for technology and life science companies far outweigh those in the UK. By way of example, in 2010, our Oxford-based client Biovex was acquired by Amgen for up to $1 billion and, more recently, our client Yandex, Russia's leading internet company, listed on Nasdaq and raised $1.4 billion.

These successes are the highlights of our recent work in the UK and we are glad that we have both English and US qualified lawyers (as well as other lawyers from the major

We have helped numerous clients close successful US transactions working alongside colleagues in our Palo Alto, New York and Boston offices

European and Asian jurisdictions) to guide our European clients through the challenges of entering and dealing with the American market. We have helped numerous other clients close successful US transactions working alongside colleagues in our Palo Alto, New York and Boston offices.

Eastern opportunity

Despite a wobble last year, China remains a rapidly expanding market with great potential for ambitious life sciences and technology companies. Our Asian practice allows WilmerHale's UK team and our China-based colleagues to provide a full suite of services to UK companies seeking to tap into that market.

The regulatory and political landscape is as important to deal-making in China as corporate law. WilmerHale's Beijing office is staffed by both native Chinese lawyers and "Westerners", some of whom have been based in Asia for over 30 years.

Access to this expertise allows us to guide emerging companies through what can be a tough and unpredictable environment in a commercially focussed and pragmatic manner. WilmerHale lawyers in the UK and Beijing have worked together to help Oxford University spin-out companies and Oxford-based investors achieve deals in China.

We believe that it is WilmerHale's unremitting focus on quality in the life sciences and technology sectors, 40 years of providing venture capital advice in the UK and our international network in the world's key markets that sets us apart from the crowd.

Get in touch

Whether our clients are sourcing a joint venture partner in China or bringing on board an American investor, they always have a friendly voice at the end of a phone in the UK.

QuickStart

If you are an entrepreneur or start-up, or you are a technical guru considering spinning-out your idea or product, we would be delighted to speak with you about our QuickStart programme. The aim of QuickStart is to help new and young companies get off the ground with the right legal advice and backing without breaking the bank. We believe in this approach to building international companies of the future.

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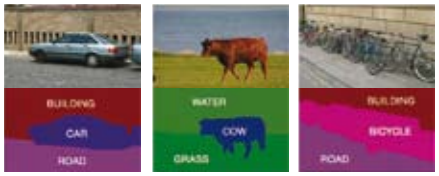
Augmented reality

Kinect for Xbox 360 makes you the controller, allowing you to jump in and play games using your whole body, without holding or wearing anything special. December OIS speaker **Dr Jamie Shotton** tells the behind-the-scenes story of the development of Kinect from his perspective as a researcher in the Computer Vision group at Microsoft Research Cambridge (MSRC).

My PhD had focused on visual object recognition: teaching computers how to recognise categories of object in photographs. From a varied set of labelled training images, a machine learning algorithm would determine patterns of image appearance that correlate with particular object categories such as cars, sheep, trees, etc. The trained model then hopefully generalises to new data, giving a per-pixel categorisation (see images below).



As a fresh-faced post-doc at MSRC, mid 2008, I got a call out of the blue from the Xbox product group who wanted to discuss an 'important, top-secret scenario' with me: real-time, robust human body tracking for playing computer games. This dream of science fiction had always been considered 'five years away' from being commercially viable. So my colleagues and I at MSRC were initially somewhat sceptical of the Xbox vision, especially given their ambitious plan to launch in 2010.

But then they showed us the new high-resolution depth-sensing camera they were developing. Depth information solves several big problems in human tracking. The background can be removed easily; clothing, skin and hair colour are all normalised away; the person's size is known; and the actively illuminated camera can work with the lights turned off. However, the enormous variety of human body shapes and poses (body positions) remains. In particular, the number of poses is exponential in the number of joints in the body.

The Xbox team also showed us their human tracking software prototype. This assumed it knew your pose at time t, then predicted your pose at time t + 1 and refined that prediction using the observed image from the camera. This prototype was incredibly smooth and accurate, but had limitations. First, you initially had to stand in a 'T'-pose so it could lock-on to you. Second, if you moved too unpredictably, it would lose track, and you would have to return to the T-pose. This would typically happen every few seconds. Third, you had to have a particular body shape. These limitations were show-stoppers for the product.

Our brief back at MSRC was to overcome these limitations. Our first

Depth information solves several big problems in human tracking. The background can be removed easily; clothing, skin and hair colour are all normalised away

decision was to look at only a single image at a time, and thus remove the need for the initial T-pose and the risk of losing track. Another thought was to use machine learning to cope with the variations in human size and shape by encoding these variations in the training data. Finally, it was clear that we had to divide up the body into parts to avoid the exponential number of whole-body poses.

I hit on the idea of revisiting my PhD work, but now using body parts such as left hand or right ankle. We designed the pattern of parts you see colour-coded here, and then trained efficient decision tree classifiers to predict the probability that a given pixel belongs to each body part. Accurate predictions of these probabilities from a single depth image, regardless of body shape or pose, give you 3D proposals for the locations of many body joints at extremely low computational cost.

This turned out to be the winning approach, but it still needed a lot of engineering to achieve the required accuracy. First, we needed a vast and varied training set; thankfully, computer graphics allowed us to synthetically generate millions of varied images of people on demand. Second, we then had to learn from such a large training set. We built a distributed training algorithm that partitioned the images into batches, and then trained in parallel on a cluster. This allowed us to train in under a day, acceptable given our need to iterate on a tight time-schedule.

We finally worked with the Xbox team to put everything together. Our body part recognition algorithm gives fast, accurate per-frame predictions of the 3D body joint positions. These are then fed into the Xbox group's tracking algorithm to stitch the skeleton together. This skeletal tracking, together with other new technologies such as voice recognition, gives game designers the platform on which to build the magical experiences you get with games such as Kinect Sports and Dance Central.

Of course, gaming was just the beginning for Kinect, and its technology is fuelling rapid advances in augmented reality, tele-presence, personalised online shopping, and healthcare, to name just a few.

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Upward motion

CEO **Torsten Reil**, speaker at the Isis Software Incubator sponsored OIS event, tells the inspiring story of Oxford Zoology spin-out NaturalMotion's rise and rise in the worlds of film and gaming.

NaturalMotion started out as a spin-off out of Oxford University's Department of Zoology to commercialise research on animal and human locomotion. Colm Massey (who co-founded the company with me) and I had developed simple physical simulations of creatures that would learn how to walk over time, using a process of artificial evolution. Because these creatures were simulated in real-time, they would behave and animate differently each time.

Our vision was to introduce this technology to video games and virtual worlds, thus creating truly interactive characters that would be surprising and much more believable than conventional animation, which was based on playing back canned animation clips.

However, when we founded the company in November 2001 with the help of Isis Innovation, it quickly became clear that the games industry wasn't the right first target market: the PlayStation 2 and Xbox were not yet powerful enough to run our simulations. We therefore focused on the Hollywood visual effects (VFX) industry first, with the goal of creating virtual stuntmen. Our first customer was the Moving Picture Company in London, who used our first product – endorphin – in the movie Troy. Many more films followed, including Lord of the Rings, 300, 10,000 BC and others.

Our breakthrough came with the next generation of game consoles, and with a real-time version of our technology, called euphoria. We were lucky to sign up two big customers early on, Rockstar Games and LucasArts. This led to euphoria being used in some of the biggest games of all time: Grand Theft Auto 4, Star Wars: Force Unleashed, and Red Dead Redemption. It also helped us attract further investment, first from business angels, then from Balderton Capital, the London-based VC.

In 2009 the iPhone 3GS was launched and we realised it was fast enough to run our technology. We felt there was an opportunity to bring console-quality animation and graphics to the iPhone and combine them with accessible gameplay. Our first

Our breakthrough came with the next generation of game consoles, and with a real-time version of our technology, called euphoria

game, Backbreaker, was a simplified American Football game, powered by our endorphin technology, and reached over six million downloads. Buoyed by this success, we released Backbreaker 2 and Jenga (with the help of Oxford-based Jenga creator Leslie Scott), and in October 2010 we officially announced our subsidiary NaturalMotion Games.

Two more paid games (at $0.99 to $4.99 per download) followed and like our other games became world wide Top-10 chart successes, with an average ROI of 5x. However, it was becoming clear that free-to-play (or f2p, a business model where the download itself is free, and money is charged during gameplay) was an even bigger commercial opportunity. We released our first f2p game in September 2011. My Horse featured photorealistic visuals of a horse in the English countryside, powered by our animation technology. The game was Apple's Game of the Week globally and has since been downloaded 14 million times. Even though the game itself is free to play, the five percent of users who pay in-game (for saddles, rugs and premium food) have made the game our highest-grossing title to date.

The success of My Horse gave us the confidence to go all-out in creating our own high-end f2p games for iPhone and we raised $11m from Silicon-Valley VC Benchmark Capital in early 2012. Mitch Lasky, formerly of EA and Activision, joined our board. In the end, we never used the money, because in July 2012 we released our next f2p game, CSR Racing, which blew all our expectations out of the water. In the first month alone, it made $12 million and it has continued to generate strong revenues ever since.

NaturalMotion now employs just under 200 people, based in Oxford (our HQ), London, Brighton and San Francisco. The company is profitable and we are working on six games for release in 2013 and 2014.

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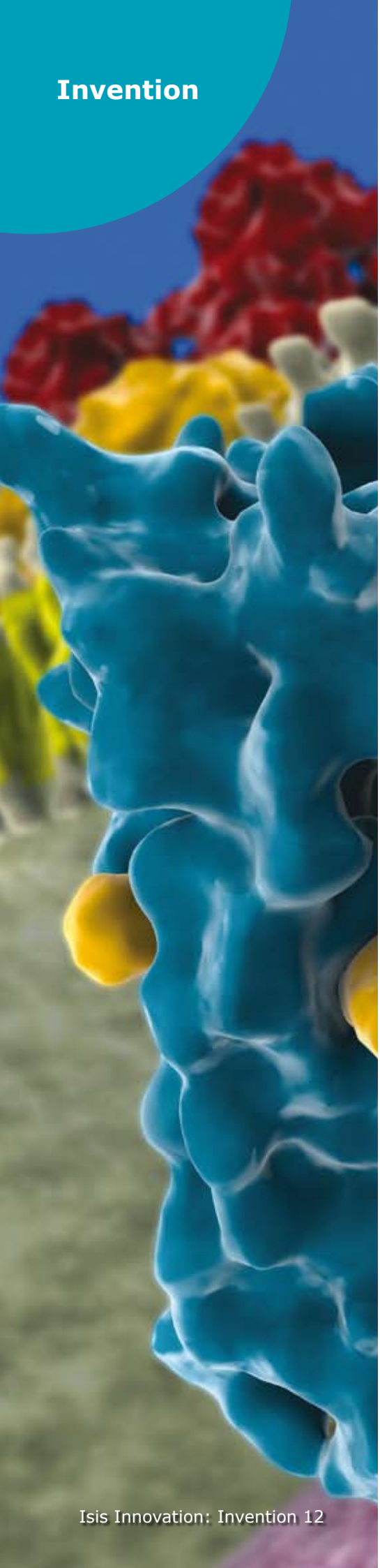

Drug discovery

Dr Nikolaos Chalkias discusses a technique for identifying new drug candidates and aiding research into the effects of protein-drug binding.

Oxford researchers have developed a method for measuring binding of small molecules and lipids to membrane proteins. A modified Mass Spectrometry (MS) methodology used in conjunction with Ion-Motility MS (IM-MS) and specific detergents, the method enables the identification of new drug candidates that target membrane proteins.

Membrane proteins comprise more than 50 percent of current therapeutic targets in the pharmaceutical industry. Understanding the affinity of small molecules for these proteins will greatly aid therapeutic design. However, membrane proteins are difficult to study using current structural biology approaches. The standard technique for confirming the presence and position of ligands in the binding sites is X-ray crystallography. In the latter, conformational flexibility is restricted (within a crystal lattice) and may distort the structural and/or ligand-binding properties of a protein. Moreover, drug binding is often measured using indirect methods such as fluorescence microscopy and calorimetry.

Oxford advantages

The Oxford invention addresses the discussed limitations and measures lipids and small molecule binding to a membrane protein directly. The method uses specific detergents which, for the first time, allow proteins to be examined in their native state in the gas phase. In contrast to crystallography, this method also allows the assessment of the dynamic behaviour of membrane-protein complexes when bound to different compounds. Of equal importance, the method demands significantly less sample than existing methods.

Data and patent status

To date, MS and IM-MS data has been acquired from a membrane transporter binding to three different drugs; these include two stereoisomers of a cyclic peptide inhibitor, and a third potential inhibitor. In addition, the researchers have determined the stoichiometry of both drug and nucleotide binding to this transporter. MS and IM-MS data also revealed a drastic conformational change when the transporter binds the aforementioned drugs. Thus, the method not only allows for identifying new drug candidates but assists in understanding the effect of protein-drug binding.

The technology is at an early stage. Isis has pending patent applications on both the method and the detergents required to practise the method. Isis is looking for companies interested in licensing and further developing this new methodology.

The method uses specific detergents which, for the first time, allow proteins to be examined in their native state in the gas phase

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Movement on malaria

Dr Paul Ashley introduces a new malaria vaccine candidate which induces broadly neutralising antibodies against all parasite strains in pre-clinical tests.

Exceptional potency

Investigators from the Jenner Institute are developing a vaccine based on PfRH5FL, the most promising candidate antigen for a blood-stage malaria vaccine to date. Research has demonstrated that PfRH5FL induces antibodies which possess exceptional potency against genetically diverse parasite strains. This candidate vaccine has the potential to address key challenges in malaria vaccine development namely low efficacy and inter-strain variability. The malaria parasite has a complex life cycle providing multiple targets for immunity. A successful vaccine could act against the liver stage, the blood-stage, or both. PfRH5FL could be the basis for a standalone vaccine or used in combination with other parasite antigens to provide broad, protective immunity.

Unmet need

An effective vaccine is desperately needed but remains elusive despite decades of research and numerous clinical trials. Annually there are 300 – 500 million cases of malaria worldwide and 1 - 2 million people, mostly children, die from the disease. Direct costs associated with treating malaria in Africa alone are $2 billion/annum and the impact on lost GDP in these low income countries is estimated at $12 billion/annum.

Global market

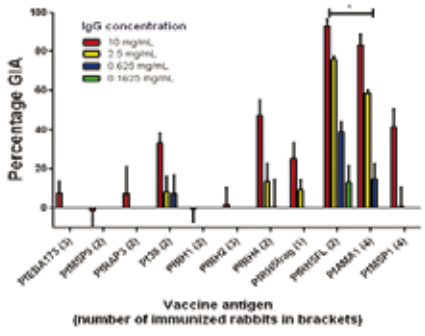
The market opportunity for malaria vaccines is divided into public (developing world) and private, the latter comprising military and travellers from developed world countries as well as emerging private healthcare markets in countries such as India.

Supporting data

- Douglas et al, Nature Communications, 2, 601 (2011) 'The blood-stage malaria antigen PfRH5 is susceptible to vaccine-inducible cross-strain neutralizing antibody'.
- Further pre-clinical efficacy studies are in progress.

Isis has filed an international patent application and would like to speak with companies interested in partnering in the development of this exciting candidate vaccine.

Below: Growth inhibitory activity of rabbit IgG against malaria parasite following immunisation with a panel of blood-stage plasmodium antigens in viral vectors.



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Non-toxic imaging

Dr Martin Procter discusses a simple, direct process for producing ^{18}F-labelled fluoroaromatic compounds, used extensively in positron emission tomography (PET) diagnostics.

Positron emission tomography (PET) is a medical imaging technique that produces a three-dimensional picture of functional processes in the body and is of growing importance for non-invasive diagnosis of patients. PET imaging is achieved by the introduction of a biologically active 'tracer' molecule into the body.

With its ability to provide specific molecular information regarding disease progression, PET imaging has been a major catalyst in driving medicine towards more personalised forms of treatment according to a patient's unique disease state. In addition to the traditional fields of cardiovascular disease and oncology, newer areas such as neurology, infection and inflammation increasingly use molecular imaging techniques for effective diagnosis and staging of the disease. One of the major drivers of the PET field now is the availability of improved radiotracers for imaging applications.

Due to the short half-lives of most positron-emitting radioisotopes, the radiotracers have traditionally been produced using a cyclotron in close proximity to the PET imaging facility. Many experimental and established tracers utilise fluorine-18 and therefore there is an increasing demand for new or simpler ^{18}F-labeling procedures. Fluorine-18 has a half-life of 110 minutes, and therefore its incorporation into radiotracer molecules needs to be rapid and highly efficient. This is in order to produce tracers with high radiochemical yields to produce the best quality images in the body.

Researchers at Oxford University have developed a novel method to produce a range of radiolabelled fluoroaromatics, including 4-fluorophenol, which is an important structural submotif, and fluorotyrosine, fluorometaraminol and ^{18}F-R91150. The Oxford process is significant because it is a conceptually new and efficient ^{18}F-radiolabelling method.

Limitations of existing techniques

A major drawback of many radiofluorination techniques is that fluorine gas is required. Not only is it a highly obnoxious chemical,

This radiochemical transformation stands out as it does not require the synthesis of complex precursors or the use of toxic organometallic reagents

but it can only be produced with a low specific activity, and only one ^{18}F atom is transferred in the reaction, making it highly inefficient and limiting the radiochemical maximum yield to 50 percent.

Highly reactive electrophilic ^{18}F-labeling reagents also suffer as their selectivity can be low and many undesired side reactions take place. This leads to the need for extensive purification procedures to be employed in order to meet the requirements for very high purity prior to administration to patients.

So until now, ^{18}F-fluorination of electron-rich aromatics has only been possible via fluorination methods utilising these imperfect electrophilic reagents.

Solution

The Oxford invention provides a simple, direct process for producing ^{18}F-labelled fluoroaromatics via nucleophilic fluorination, as published in a recent academic paper (Angew. Chem. 2012, 51, 6733). This concept represents a reversal of the polarity over the standard reaction, known as 'umpolung' in chemistry, and has one major advantage of traditional techniques for aromatic labelling of aromatic containing compounds: the required fluorine-18 reagents are much easier to handle and are produced with very high specific activities.

The Oxford labelling reactions are typically completed in less than 30 minutes using a one-pot protocol at room temperature, leading to products with high radiochemical yields. The reaction can also be successfully performed in a commercially available microfluidic device, meaning adoption into established laboratories will be straightforward.

This novel radiochemical transformation stands out as it is applicable to a wide variety of substrates and does not require the synthesis of complex precursors or the use of toxic organometallic reagents.

Utility

Ultimately this method will serve as a valuable new strategy for the rapid, direct nucleophilic ^{18}F fluorination of challenging electron-rich substrates, opening up access to new radiolabelled tracers for patient diagnosis.

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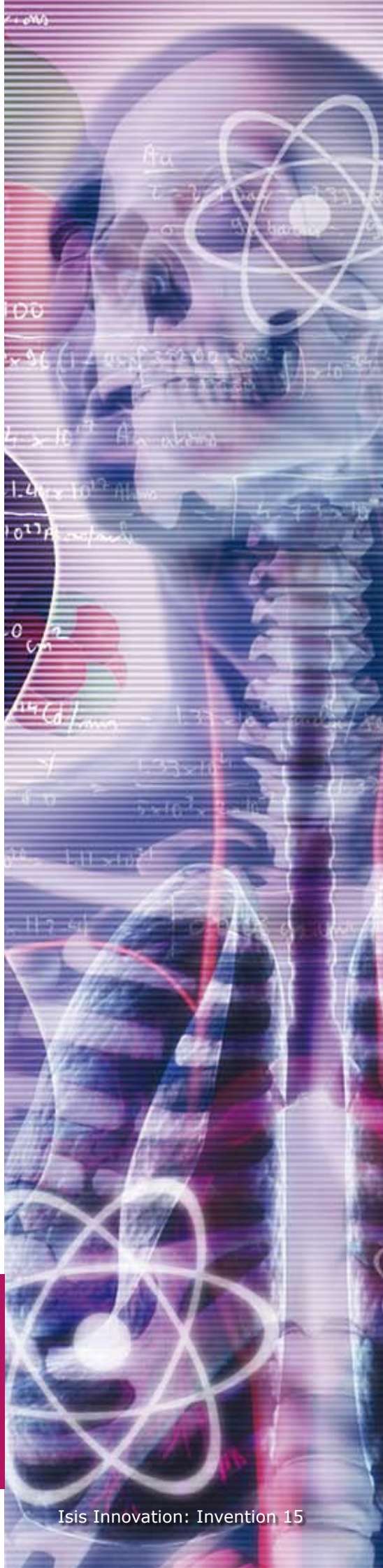


Reducing false alarms

Dr Gayatri Sharma describes a versatile statistical algorithm for enabling fast, accurate decision making.

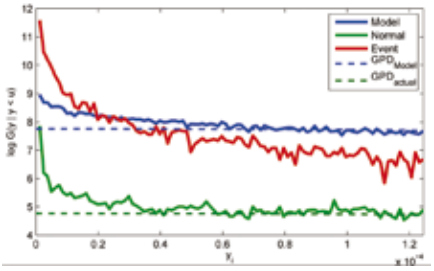
Repeated false alarms not only increase the risk of missing a real emergency (as vigilance levels drop) but also result in inefficient use of limited resources if every false alarm is examined. In medical critical care units, the misallocation of resources could result in fatalities. In the manufacturing sector, a false alarm could halt an entire production affecting the bottom line for the organisation.

The objective, when monitoring critical scenarios and systems such as patients in intensive care, automated manufacturing and financial modelling, is to classify the data as being either "normal" or "abnormal" in behaviour. For example, the vital signs for patients in intensive care consist of differing parameters including heart rate, blood pressure and the function of vital organs. These variables play a combined role in determining the wellbeing of a patient. It is thus imperative to interpret each of these variables in combination to assess if the patient is in a "normal" or "abnormal" (deteriorating) condition at any given time.

Taking the example of critical care patients further, an increase in any of the mentioned variables can trigger an alarm which may not be reflective of the overall health status of the patient resulting in attention given to a patient when it is not really required. On the other hand, there may be an important need to accurately identify outlying observations in real-time without generating false alarms. Traditional statistical approaches have struggled to set a threshold that provides sufficient safe margin to alarm reliably when a system departs from normality.

Reducing false alarms

A comprehensive solution to this problem has been provided by researchers at Oxford. Their invention allows differentiating between extreme data that is normal from extreme data that is truly abnormal. An example of the application of the model is illustrated below:



The blue line represents the tail of the model of normality. It's demonstrated that the blue and red lines lie in close proximity, making it difficult to separate the model from abnormal data, whereas it is easy to differentiate the truly normal data from the abnormal.

It also overcomes the associated pitfalls of point-wise novelty detection by monitoring relationships between collective variables and thus enables accurate decision making in a critical time frame.

Traditional statistical approaches have struggled to set a threshold that provides sufficient safe margin to alarm reliably when a system departs from normality

Range of applications

The researchers have demonstrated the use of this technology by accurately monitoring patients' vital sign data. Other key applications for the technology fall within financial modelling: variables such as interest rates, currency exchange, growth rate, inflation rates, lending rates and production outputs are just a few variables that could be programmed into the Oxford model, for real time monitoring, to make an astute financial investment in a critical time frame. Moreover, the technology could also be applied to monitoring of automated manufacturing instruments, where there is a need to monitor numerous sensors/ variables and differentiate between normal and abnormal systems.

Technology advantage

- Specific classification of complex systems as "normal" or "abnormal" so as to reduce false alarms
- Continuous, automatic, reliable detection of abnormalities
- Entire series of measurements are tested over specified times
- The tails of actual, high integrity systems are modelled
- Relationships between numerous collective variables are monitored

Commercial opportunity

The technology platform forms part of a portfolio of PCT phase patent applications and Isis welcomes contact from parties interested in licensing this extraordinary technology

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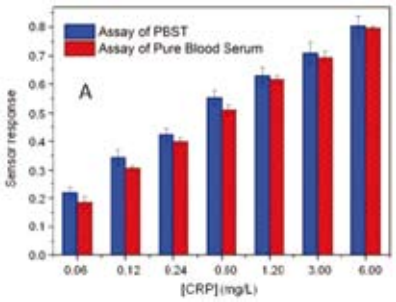
Portable testing: cardiovascular disease

Dr Ruth Barrett describes a fast, low-sample volume, portable test for detecting and quantifying the most widely used cardiac biomarker.



Comparison of assay run with CRP in buffer and in undiluted serum across the linear range.

Oxford scientists have developed a simple, sensitive and quantitative way to test for C-Reactive protein (CRP) in only 5µl of whole blood serum[1]. Low level increases of CRP over basal levels are associated with increased risk of cardiovascular disease (CVD), and the US Centres for Disease Control and the American Heart Association have recommended analysis of CRP levels as the best way to assess cardiovascular disease risk[1].

Clinical need

CVD causes nearly half of all deaths in the western world[1]. It imposes a huge financial burden on society: €192 billion p.a. in the EU alone[1]. Huge effort is going into developing point-of-care tests which can measure key cardiac biomarkers in order to better predict and treat CVD.

The Oxford invention

Using Electrochemical Impedance Spectroscopy, Oxford academics have developed a label-free CRP sensor system comprising simple consumable device strips to be used in a benchtop or handheld instrument. The system can accurately quantify CRP at clinically relevant levels in 5µl undiluted serum samples in five minutes[2]. This technology could replace the current cumbersome CRP immunoassays systems with their complex consumables and large sample requirements – with a miniaturised, portable system that requires only a fingerprick sample. The Oxford sensor system is cheap and readily multiplexed.

Test attributes

- The sensory interfaces are readily prepared and exhibit excellent selectivity over the test's linear range (0.1mg/L to 8mg/L)
- No need for reagents – simple and cheap to manufacture
- Requires 5µl undiluted blood serum
- Readily automated, miniaturised and multiplexed
- Suitable for development with either a benchtop or handheld instrument
- 10 minute assay time

Broad benefits

The Oxford point-of-care-test could enable:

- More regular monitoring of CRP levels in a primary care setting
- Rapid understanding of CVD risk, allowing improved clinical decision-making and improved patient outcome
- No waiting for lab results
- Screening of otherwise healthy at-risk populations
- Clinical trial enrichment to increase likelihood of detecting intervention efficacy

Patent status

This technology is at the preclinical stage and is subject to a patent application. Isis would be interested in talking to parties who are interested in developing and commercialising this technology.

References

1. Allender S., et al. European cardiovascular disease statistics, 2008 edition. British Heart Foundation.

2. Biosens Bioelectron. 2013 Jan 15;39(1):94-8. Epub 2012 Jul

3. http://dx.doi.org/10.1016/j.bios.2012.06.051

Portable testing: diabetes

Dr Ruth Barrett showcases a rapid point of care insulin test in blood serum, for use in Type II diabetes and other indications.

Oxford scientists have developed a simple, sensitive and quantitative method for detecting insulin down to 250pg/L in 5µl of undiluted blood serum samples. The technology makes use of Electrochemical Impedance Spectroscopy, whereby the binding of insulin to an electrode produces a capacitance signal.

Clinical need

The incidence of diabetes is rising rapidly in the western world. It is estimated that 15 percent of US adults will have a form of diabetes by 2015. Today, no point-of-care insulin test exists. The development of an ultrasensitive, cheap, simple and automated diagnostic test to aid treatment choice and patient monitoring would therefore be of considerable value. This technology could also be used to test for doping in competitive athletes, or in diagnosis of other conditions such as Cushing's or insulinomas.

Novel electrode surface chemistry

The Oxford academics have developed novel surface chemistry using photopolymerisable monomers. This coating has excellent anti-fouling properties; background is dramatically reduced. This aspect of the invention is generically applicable to electrochemical assays.

Technology attributes

- The sensory interfaces are readily prepared and exhibit excellent selectivity over the test's linear range: 0.0006-1.2 µg/L; LOD: 0.00025 µg/L
- Uses 5µl (i.e. a fingerprick, as for glucose testing) of undiluted blood serum
- No need for reagents – simple and cheap to manufacture
- Readily automated, miniaturised and multiplexed
- Suitable for development as either a benchtop or handheld instrument
- Assay time: around 10 minutes

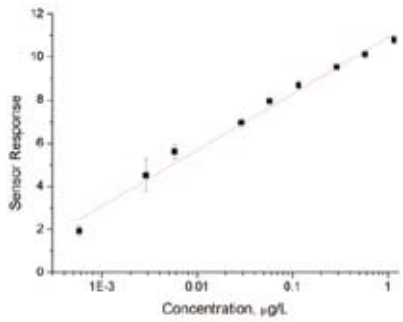
Broad benefits

The Oxford test could enable:

- Better disease staging, allowing improved clinical decision-making around treatment choice
- Screening of populations at risk of developing diabetes
- Distinction between subtypes of Type II diabetes in primary care settings
- Use in other indications or doping testing

Patent status and further development

This technology is the subject of a UK priority patent application. Over the next 12 months c. 100 patient samples will be blind-tested and results compared against current gold-standard assays. Isis would like to talk to companies interested in developing and commercialising this technology.



Detection of insulin in undiluted serum, in triplicate.

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Infection severity surveillance

Brendan Spillane presents an early warning system for new infectious strains occurring in patients.

Hospitals and clinics routinely collect data from patients which Reflect patients' response to infection. The more severe the infection, the more severe the change in particular biomarkers. By monitoring these biomarkers over time, it is possible to spot the effects of new infectious strains on patient populations before normal clinical data (such as a rise in death rate from specific bacteria) identifies the problem. With this in mind, Oxford researchers have developed a set of statistical algorithms to track data that is already available but is not being pulled together and analysed.

Supporting data

Clostridium difficile infection (CDI) is a leading cause of intestinal disease and is endemic in hospitals. In 2005 a particularly virulent strain caused a global epidemic. Analysis of historical hospital data collected over many years has shown that biomarkers such as neutrophil count from routine clinical tests could have, using the Oxford technology described here, revealed the appearance of the new virulent strain and its effects well before the normal clinical data showed a rising death rate and the strain was subsequently identified.

Applications and adaptability

The Oxford technology can be adapted to many types of clinical biomarkers and tests, and to many possible infections. The technology could potentially be applicable to other situations where early detection is desirable.

Patent protection

A patent application covering this method has been filed in the UK. Isis welcomes interest from companies interested in licensing the technology.

The Oxford technology can be adapted to many types of clinical biomarkers and tests, and to many possible infections

Software genotype caller

Brendan Spillane discusses a software tool for genetic and academic researchers.

Chiamante is a genotype caller for Illumina Beadchips that can augment microarray data with genotype likelihoods from sequence data for improved genotype accuracy and call rate. While primarily designed to call genotypes via fusing these two sources of information, Chiamante also functions as a highly accurate array-only caller.

Supporting data

Genome-wide association studies (GWAS) play an important role in the investigation of the genetic component of diseases. These studies involve checking hundreds of thousands of single-nucleotide polymorphisms (SNPs) in individuals. SNP genotypes can be tested using microarray genotyping or by sequencing. Neither technology produces perfect results, especially with rare SNPs and checking these for association with traits, or phenotype. This analysis involves calling of genotypes: determining the genotype for each individual at each site. Studies that collect both types of data are becoming increasingly common.

Combining the data from the two methods of analysis, array and sequencing, make it possible to increase accuracy and call rates for similar computing power and time, especially with rare SNPs. Analysis of rare variants is increasingly important in genetic studies of human disease.

These studies involve checking hundreds of thousands of single-nucleotide polymorphisms

Model and features

Chiamante uses a statistical model that combines both data types. It makes an independence assumption of the two data types so that the model can allow for data quality differences. It uses an Expectation-Maximisation algorithm drawing on prior information to fit the model to the data. This means the method can be applied to real datasets very quickly.

Features include:

- the ability to fuse sequence and microarray data for increased genotype accuracy, particularly at low frequency SNPs
- multiprocessor support for easy parallelism and fast results
- the capacity to handle multiple ancestry within a sample (varying genotype frequency for different ancestries)
- multiple input formats
- output to VCF

Isis welcomes interest from companies interested in licensing the technology.

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Green catalysis

Dr Jamie Ferguson describes two notable catalyst developments in the field of green chemistry from Professor Edman Tsang's laboratory.

New biomass to methanol catalyst (Isis Project 7320)

A new catalytic process to convert ethylene glycol directly into lower alcohols.

Reduction of dependence on fossil fuels

Today over 80 percent of the world's energy and chemical production requires fossil resources, clearly depleting natural reserves and adding to global warming. Fortunately, we are starting to see some reduced dependence on fossil fuels and increasing interest in renewable resources. Lower alcohols such as methanol and ethanol, produced from biomass, may be used as transportation fuels and key platform chemicals.

Other approaches to the production of lower alcohols from biomass

There are several approaches to the production of lower alcohols from biomass. Currently, methanol is synthesized at large scale using an energy-inefficient process which requires an indirect high-energy step to completely break down the biomass to syn-gas (CO/H2) before re-assembly to methanol. Similarly, ethanol is manufactured by fermentation; highly selective but rather slow. For lower alcohols to become widely used green fuels, efficient production routes from biomass are needed.

The Oxford invention

Technologies that convert biomass (starch) into polyols (alcohols containing multiple hydroxyl groups) have been known for some time. Oxford researchers have discovered a catalyst that can convert ethylene glycol, the simplest polyol, directly into the lower alcohols with combined selectivity above 80 percent. [Oxford's non-enzymatic bio-alcohol production depends on concerted C-C or C-O bond breakage and C-H bond formation. A unique metal-support interaction is understood to be responsible for this highly efficient catalysis.] The Oxford catalyst operates at relatively low temperature and pressure, offering the exciting possibility for a new process that will advance the use of lower alcohols as green fuels.

Methanol to hydrogen conversion, with ultra-low CO (Isis Project 8029)

A catalyst that converts methanol to hydrogen – ideal for use with portable fuel cell powered devices.

Hydrogen – an environmentally friendly energy carrier

Hydrogen is considered to be a clean fuel, offering high efficiency when used in conjunction with the PEM fuel cells. Low temperature PEM hydrogen fuel cells are more energy efficient than battery technology; their prevalence is expected to grow in portable consumer products.

Fuel cells for portable consumer products

There are a number of ways to obtain hydrogen on an industrial scale; however storage for mobile use is problematic because of its poor volumetric and weight energy densities. Hydrogen stored in chemical form as liquid organic compounds, then released on demand, is a more promising direction for mobile fuel cells. A liquid fuel can be stored in a disposable or recyclable cartridge, offering safe handling and simpler logistics. Furthermore, PEM fuel cells require ultra-pure hydrogen, indeed being poisoned by very low concentrations of carbon monoxide (CO). However, current solutions require multistage processes and elevated temperatures, precluding their adaptation to small portable devices.

Oxford technology– offers competitive advantages

Oxford scientists have developed a single-step, low temperature catalyst [based on copper nanoparticles in zinc gallium oxide] for the conversion of methanol to ultra-pure hydrogen; well suited for use with small fuel cell powered devices. This is in clear contrast with the conventional multi-stage route involving steam reformation of methanol to syn-gas, followed by a water-gas shift and CO clean-up.

Further information

Both developments have been protected via UK patent applications. Further information on the technologies and results can be obtained from the academic's publications (references below). Companies interested in progressing the commercial opportunities are invited to contact Isis.

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Leadership for Learning

Sue Clark describes the impact that an innovative new teacher-mentoring model, managed by Oxford University Consulting, will have on schooling in Oxford

The Leadership for Learning Programme, a collaboration between the University of Oxford's Department of Education and Oxford Brookes University's School of Education, was officially launched on January 17th.

The two-year programme will involve up to 40 staff and governors receiving up to 12 training days a year with leading national and international researchers and practitioners. There will be three one-day workshops and two meetings twice a term to address shared concerns, as well as coaching and mentoring link-ups with senior management teams from some of the most experienced educational leaders in the county. Parents will also be invited to take part in a series of six public seminars planned for each year to explore relevant issues affecting their child's primary education.

Programme Director Ian Menter, Professor of Teacher Education and Director of Professional Programmes at Oxford University, said: "Oxford University's Department of Education and Oxford Brookes University's School of Education are recognised UK leaders in teacher education. We hope that through this partnership and working with the Oxfordshire school consortium Education Excellence in Oxford we will be able to support primary education in the city of Oxford."

The Professor continued, "Every day, primary teachers are faced with a myriad of challenges: for example, working more closely with parents so that they can offer more effective support to their child's education or supporting bilingual learners for whom English is an additional language. How to tackle these issues is not always easy or straightforward. We hope that through the Leadership for Learning programme, teachers and governors will be able to tap into a pool of expertise and support each other and that this will help them to develop new leadership strategies. By working in this way, and building upon many recent positive developments, the quality of teaching in our primary schools should continue to improve."

The programme was commissioned following a competitive tendering process by Oxford City Council as part of their initiative, "The Oxford Challenge World Class Teaching". The objective is to develop the leadership skills of staff and governors from 11 participating schools in the city of Oxford to

improve literacy and numeracy levels in the city's primary schools.

The eleven schools involved are: Bayards Hill, Church Cowley St James, Cutteslowe, East Oxford, Larkrise, Pegasus, Orchard Meadow and Windale (three schools forming the new Blackbird Leys Academy), St Francis, St John Fisher, and Wood Farm.

On completion of the programme, each participant will be eligible to receive accreditation towards a Master's degree (20 module credits towards the 180 credits required for a Master's degree).

Oxford University Consulting has been responsible for putting in place the contractual framework with the various parties to support the project.

Consultancy in the Social Sciences

Over the past three years, OUC has seen a steady increase in the number and diversity of consultancy projects that call upon the advice and expertise of colleagues based in the Social Sciences Division. Since 2010, OUC has managed 138 consultancy projects across the Division, successfully contracting work for over 240 academic consultants.

The University's Department of Education has made a major contribution to the study of education for over 100 years and today it has a world class reputation for teaching and research in this field. The Department maximises its impact by applying its research expertise to provide consultancy services to governments, NGOs and commercial organisations. The consultancy ranges across the spectrum of educational age groups, from nursery associations such as the NDNA, to school improvement programmes, to higher education with the British Education Research Association. OUC works closely with the Department. Over the last year, for example, it has arranged 22 departmental consultancy projects.

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Accelerating Mexican innovation

Dr Mireya McKee explains how Mexican organisations are drawing heavily from the Isis technology transfer model.

With a population of over 110 million and a Gross Domestic Product of over £730 Billion in 2012, Mexico's economy is the 13th largest in the world, and second highest in Latin America after Brazil. Although Mexico continues to be a fast growing economy, its Gross Domestic Expenditure on R&D (GERD) is one of the lowest among the countries in the Organisation for Economic Co-operation and Development[1].

Moving towards a knowledge-based economy

Like other emerging economies, Mexico is realising the importance of Science and Technology (S&T) in relation to improved competitiveness and sustained economic growth, and is currently taking important steps to becoming a knowledge-based economy with S&T at the centre of its economic activity. The 2007-2012 National Development Plan (NDP) included clear strategies to promote and increase funding programmes related to scientific and technological development and innovation. Additionally, the newly-elected Government is committed to making Science and Technology a priority. It is planning to increase Mexico's GERD to one percent over the next six years.

Developing technology transfer capabilities

In line with the objectives of the NDP, the Mexican Council of Science and Technology (CONACYT) and the Ministry of the Economy have designed a series of funds and programmes to facilitate a connection between Science and Technology providers, intellectual capital suppliers and business demand. In this context, a programme was designed to encourage the creation of Technology Transfer Offices (TTOs) nationwide and to promote a high level of standardisation of procedures related to knowledge transfer and liaison with the private sector. CONACYT and the Ministry of Economy are planning to continue

Mexican movement

Many Mexican organisations are developing their Technology Transfer capabilities with Isis' support:

- Biological Research Centre of the Northwest (CIBNOR)
- UNAM's Chemistry Liaison Unit (UVQ)
- Mexico City's Science and Technology Institute (ICYT)
- The Centre for Research and Technological Development in Electrochemistry (CIDETEQ)
- The Advanced Technology Centre (CIATEQ)
- The Autonomous University of Sinaloa
- The Autonomous University of the State of Morelos
- The Autonomous University of Queretaro
- The University of Guadalajara
- Monterrey Tech (ITESM)
- The Hidalgo State Science and Technology Council (COCYTEH)

to support TTOs in the medium to long term to promote their growth and maturation once they complete training and certification requirements.

Learning from the Isis Innovation model

Through this programme, Isis Enterprise has had the opportunity to contribute to the development of technology transfer capabilities of TTOs from various Mexican Universities, Research Institutions, and Government agencies (see inset). IE has conducted IP policy workshops, technology portfolio evaluations, business plan development, and high-level training focused specifically on the structures, procedures, and policies required for a TTO to operate efficiently and to strengthen their technology transfer capabilities. Isis is also in discussion with several Mexican institutions to help set-up and manage Innovation Seed Funds.

Isis' contributions to these institutions have received wide acceptance, both from training and implementation standpoints. In many ways, the Isis technology transfer models are more suitable to the innovation ecosystem present in Mexico than prevailing US models. Rather than trying to replicate the American models, which require a well-developed ecosystem of experienced entrepreneurs and readily available early-stage investment funds, Isis promotes best tech transfer strategies and practices from emerging economies around the world. Isis has worked with an extensive range of clients in over 50 countries, identifying different models that work in different economies and cultures, and is able to provide tailored support according to individual institutional needs.

Remaining Challenges and Looking to the Future

Mexico is overcoming several challenges related to intellectual property. Statistics on patents show a strong predominance of foreign patents (of the 14,576 Mexican patent applications in 2010 93.5 percent were filed by foreigners, mostly on behalf of US or transnational firms)[2], making clear the current technological dependency of Mexico. To overcome this, TTOs will need to continue training their staff with the requisite skills and experience; obtain financial resources for TTO development, funds for national and international patenting, and proof-of-concept; develop mechanisms to market and promote available technologies; and be able to access value-added risk capital for the creation and funding of new companies. Although the challenges can be significant, Mexico is heading in the right direction, implementing strategies that are helping them rise as a knowledge-based economy. Isis expects to continue working with Mexican institutions to accelerate their rate of innovation, establishing long term partnerships and developing a stronger presence in Mexico and Latin America.

[1] OECD Statistics [2] IMPI and WIPO

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Oxford Innovation Society

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

- Thursday 21 March 2013
- Wednesday 18 September 2013
- Thursday 5 December 2013

Meetings are held in Oxford for OIS members and invited guests, and are followed by a formal reception and dinner in an Oxford college hall.

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