PROFILE BOOKLET

Life Sciences

December 2019

Oxford University Innovation Limited

Buxton Court, 3 West Way
Oxford OX2 0JB

www.innovation.ox.ac.uk

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Oxford University Innovation
Buxton Court, 3 West Way, Botley, Oxford OX2 0JB
T +44 (0)1865 280830 **E** enquiries@innovation.ox.ac.uk www.innovation.ox.ac.uk
Company No 2199542
Registered Office: University Offices, Wellington Square, Oxford OX1 2JD VAT No 490 7988 85

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Buxton Court, 3 West Way, Botley, Oxford OX2 0JB
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AUTOIMMUNE DISEASES

An inhibitor of the complement system derived from tick saliva

Available to license: A novel peptide from ticks that inhibit the complement system of the innate immune system at the C5 step of the cascade.

Oxford researchers have developed a peptide derived from tick saliva and it targets the C5 step of the complement cascade.

The complement system is part of the immune system which is thought to have a small contribution to overall Immunity. Irregular function of the complement system results in serious diseases that can be debilitating. Despite the overall strong interest from pharmaceutical companies, only two drug inhibitors have been approved.

Ticks are known for feeding on the blood of humans and animals. During blood feeding they secrete a wide range of proteins to maintain haemostasis, prevent inflammation, prevent a host immune response and block angiogenesis. The secreted proteins are pharmacologically useful, since they have certain very stable qualities.

A new approach

Researchers at Oxford have focused on identifying the complement system inhibiting proteins found in tick saliva. The complement system acts as a first line of defence against parasites, such as ticks. What the Oxford team found was a ~50 amino acid peptide which is a highly soluble, chemically and proteolytically stable potent inhibitor of the complement system.

The team has identified a specific step which complements inhibition and allows the peptide to act as the C5 node. There are only two approved drugs for the inhibition of the complement system and one of them (a monoclonal antibody) is widely known as 'the most expensive drug' on the market with an approximate cost of £330,000 per year, per patient. The Oxford inhibitor peptide targets the same C5 node of the complement inhibitor but it is an 50-mer peptide that can be expressed in simple bacterial hosts enabling low cost manufacture.

Licensing opportunity

The Oxford invention is protected by a UK priority application. Isis is seeking for an industrial partner to license, develop, and bring this therapeutic opportunity to the market.

For further information please contact:
Dr Bob Fishleigh
bob.fishleigh@innovation.ox.ac.uk
+44 (0)1865 614429
www.innovation.ox.ac.uk
Project number: 11088

Technology Transfer from the University of Oxford

Oncostatin-M: A novel therapeutic target for inflammatory bowel disease

Oxford researchers have discovered a novel target that could lead to a whole new class of effective inflammatory bowel disease drugs being developed.

Inflammatory bowel disease (IBD) is a term that encompasses a group of diseases, including Crohn's disease and ulcerative colitis, which affect the colon and small intestine. These are debilitating chronic disorders affecting more than 300,000 people in the UK. Patients with IBD suffer periodically with mild to severe symptoms with intermittent remission. There is currently no cure, and so treatments traditionally focus on managing the symptoms by hindering the immune response that drives the disease. Traditionally treatments include anti-inflammatory drugs, but these lack specificity and cause gastrointestinal toxicity.

The current 'gold-standard' therapy

Modern treatments, such as monoclonal antibodies against Tumour Necrosis Factor-α (TNFα), induce and sustain remission by targeting components of inflammatory pathways that are thought to be more specific to IBD. However 40% of patients subjected to this therapeutic regimen do not respond, and up to a further 60% of those that initially respond fail to respond to repeat treatments. These patients are left unable to control their IBD and will eventually require surgery. Anti-TNFα therapy is the current gold-standard treatment for patients with IBD but alongside their low response rate, they also cause immunosuppression. Therefore, there is an obvious need for new therapeutics to treat IBD.

Targeting a solution

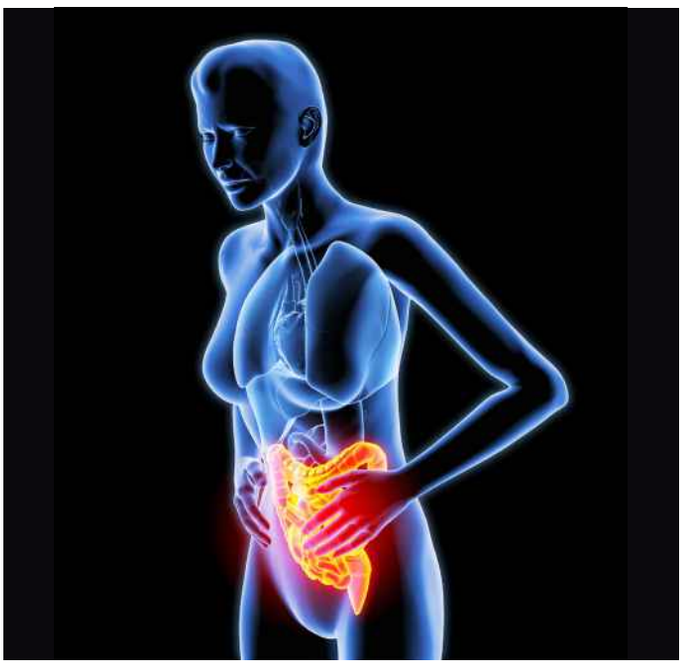
Researchers at Oxford University have identified a potential new target for IBD therapeutics; they found Oncostatin-M (OSM) to be a major component of the cytokine response in the Th17 inflammatory pathway. This pathway is thought to be critical in the pathogenesis of IBD, therefore targeting OSM or its receptor may offer a more effective treatment for a greater proportion of IBD patients.

Additionally, the researchers found that levels of OSM may indicate whether a patient has IBD and whether a patient in remission will have a recurrence of symptoms. Furthermore, the level of OSM correlated with patient response to anti-TNFα therapy and so could be used to determine the most appropriate first-line treatment for IBD and other TNFα-mediated conditions.

Altogether, this research has discovered novel methods to diagnose, prognose and treat IBD which could revolutionise the care of patients suffering from the disease.

Commercialisation

Oxford University Innovation has filed a patent (PCT/GB2016/050185) on this technology. The associated publication can be accessed here: https://www.nature.com/articles/nm.4307



For further information please contact:
Dr Matt Carpenter
matthew.carpenter@innovation.ox.ac.uk
+44 (0)1865 280970
www.innovation.ox.ac.uk
Project number: 11412

Technology Transfer from the University of Oxford

Anti-inflammatory Drugs from Bugs

Available to license: Oxford University researchers have cloned, expressed, and characterised 31 anti-inflammatory peptides derived from ticks.

Targeting chemokines

Inflammation plays a central role in a number of common and debilitating diseases such as rheumatoid arthritis (RA) and inflammatory bowel disease (IBD), in common and fatal infection such as influenza cytokine storm but also in rare, fatal diseases such as myocarditis, idiopathic pulmonary fibrosis (IRF) and inflammatory breast cancer.

Chemokines drive inflammation and immunity by activating the migration of innate and adaptive immune cells to disease tissues. The chemokine network (46 chemokines, 24 G-protein receptors) is complex, with each chemokine typically binding multiple receptors, each receptor binding multiple chemokines, and multiple receptors present on individual immune cells.

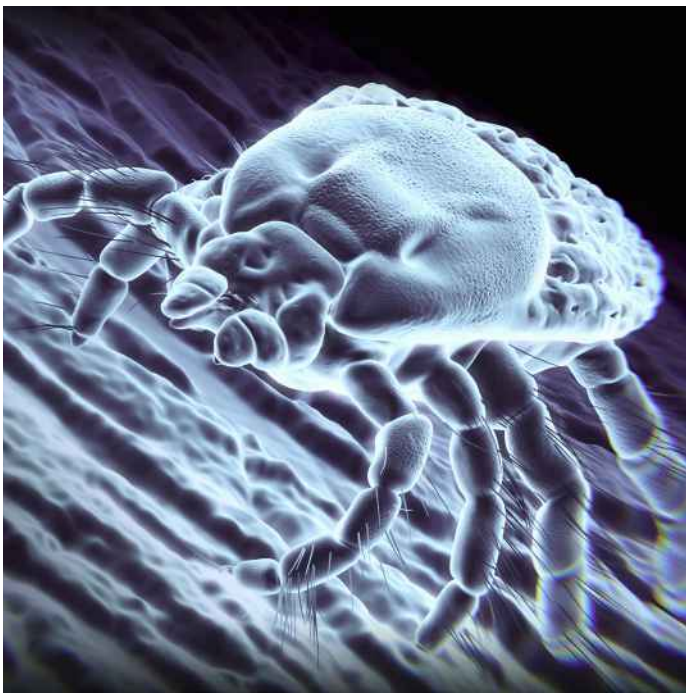
Therapies that target single chemokines or receptors often fail as these targets form a robust network, with multiple chemokines typically overexpressed in disease. For instance, 27/46 chemokines are expressed in RA, 16/46 in IBD, 13/46 in myocarditis, 24/46 in IPF and 9/46 in influenza cytokine storm.

Novel salivary evasins

Ticks have evolved small salivary peptides (Evasins) that suppress chemokine-driven inflammation by acting as “ligand traps” - binding and neutralising multiple chemokines. Using a novel yeast display technology, Oxford University researchers have cloned, expressed, and characterised 31 novel salivary evasins from 8 tick species. These novel evasins bind multiple chemokines with low nM affinities (determined by high-throughput biolayer interferometry), and can neutralise chemotaxis by target chemokines, (demonstrated using high-content video microscopy of chemokine-receptor expressing cell lines).

Each evasin binds and neutralises a distinct subset of chemokines; certain evasins can neutralise complex mixtures of chemokines. The complete pharmacologically characterisation of the novel evasins is underway to identify evasins or their combinations that can functionally neutralise the combinations of chemokines typically found in diseased tissues.

These preliminary pharmacological studies will underpin the application of these novel evasins in inflammatory diseases. Collaborations have been established for pre-clinical and clinical studies in RA and myocarditis, IBD, influenza cytokine storm, IPF and breast cancer.



For further information please contact:
Dr Christine Whyte
christine.whyte@innovation.ox.ac.uk
+44 (0)1865 280921
www.innovation.ox.ac.uk
Project number: 11805

Technology Transfer from the University of Oxford

Complement alternative pathway inhibitor

Available to license: A novel polypeptide isolated from tick saliva that inhibits the alternative complement pathway

Researchers at Oxford have identified and applied for a patent in respect of a novel tick-derived polypeptide inhibitor of a key step in the alternative pathway, which represents an important therapeutic target for a number of complement-mediated diseases.

In recent years the involvement of the complement system in a range of human diseases has been elucidated and the first drugs that inhibit specific parts of the complement cascade have reached the market, with a number of others undergoing clinical development.

Prominent amongst the marketed complement inhibitors is Alexion Pharmaceuticals' Soliris® (eculizumab), a monoclonal antibody that is registered for the treatment of paroxysmal nocturnal hemoglobinuria (PNH) and atypical haemolytic uremic syndrome, and which recorded net product sales of over US$2.6bn in 2015.

This and other complement inhibitors are currently being investigated clinically in the treatment of conditions including age-related macular degeneration, chronic obstructive pulmonary disease, myasthenia gravis, graft-versus-host disease, delayed graft function, and neuromyelitis optica spectrum disorder, and many other potential therapeutic applications have also been identified.

A new approach

Researchers at Oxford have identified a novel polypeptide inhibitor of a key step in the alternative complement pathway that is contained in the saliva of a certain species of tick. The polypeptide is chemically and proteolytically stable and is readily soluble. The polypeptide is the subject of a UK priority patent application that includes composition-of-matter claims.

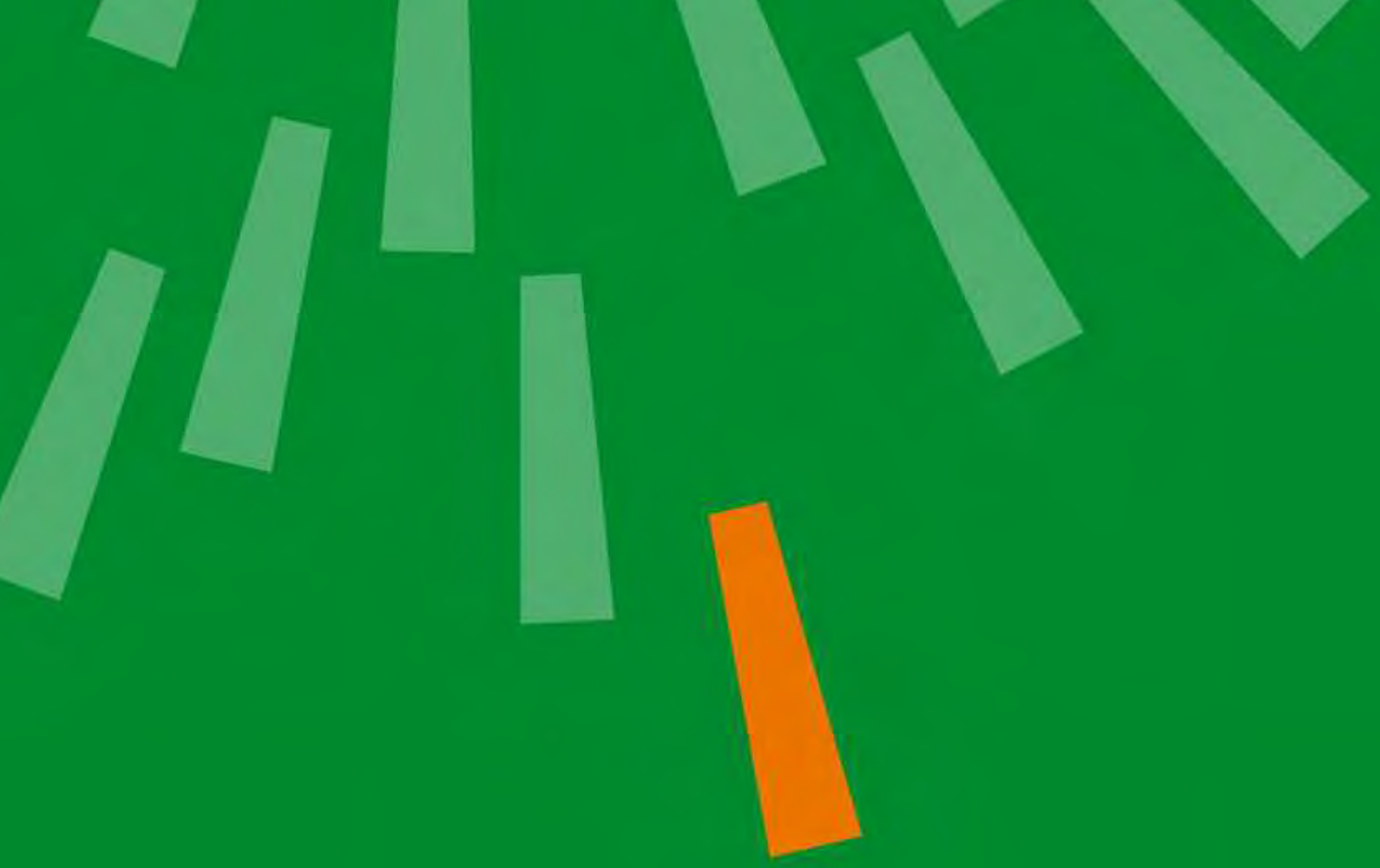
Tick-derived polypeptide inhibitors of the complement system have attracted significant research interest and one, Akari Therapeutics' Coversin, has displayed positive preliminary results in an ongoing clinical trial investigating its use in the treatment of PNH in eculizumab-resistant patients.

Licensing opportunity

Oxford University Innovation is now seeking a commercial partner to develop further and bring to market this new alternative pathway inhibitor for the treatment of conditions such as age-related macular degeneration under an appropriate licence agreement.

For further information please contact:
Dr Bob Fishleigh
bob.fishleigh@innovation.ox.ac.uk
+44 (0)1865 614429
www.innovation.ox.ac.uk
Project number: 13645

Technology Transfer from the University of Oxford



DATA MANAGEMENT TOOLS

Dynamic Consent

Oxford researchers have developed a personalised, web-based interface for the advanced management of fully informed consent. Designed for situations where consent preferences are fluid but of critical importance to the delicate relationship between the researchers and participants. The system is being piloted for biobanks, personalised medicine and conventional clinical trials.

The challenge of retention

Recruitment and retention of participants for research is critical. Poor participant retention rates can be attributed to paper-based systems; particularly obtaining, recording, and auditing consent. Inefficient paper-based systems yield high costs. A plethora of bespoke, opaque and poorly supported electronic systems exist but these do not facilitate adaptive designs and changing research protocols. Since, for example, 45% of clinical trials require costly extensions, the inability to effectively engage participants and obtain consent is highly detrimental. Biobanks and translational genomics must also support new demands and emergent findings.

A patient-centric approach

This participant-centric approach provides an interface that ensures patients can give, review and change their consent preferences whilst allowing two-way interactions between study management and participants. Participants are therefore fully engaged with the process, retention rates are increased and management costs reduced.

Benefits of the Dynamic Consent approach to trial management include:

- Easy collection, storage and retrieval of consent preferences
- On-going communication for improved recruitment, participant engagement and reduced drop-out rates
- Easy identification of participants that can be approached for additional trials
- Enables adaptive study designs through a simple re-consenting procedure
- Legally compliant data collection that is efficient and secure

Benefits to participants include:

- Enhanced interaction and on-going participation due to easy access to information
- Information delivered according to an individual's preferences
- Fully informed and prepared for each stage of the trial
- Enabling, as able to review and revise consent preferences
- Suitable for visually impaired, and those with hearing or learning difficulties
- Secure

Commercialisation

For further information on gaining access to Dynamic Consent, please contact the Oxford University Innovation Technology Transfer Manager.

For further information please contact:
Dr Richard Auburn
richard.auburn@innovation.ox.ac.uk
+44 (0)1865 280956
www.innovation.ox.ac.uk
Project number: 9663

Technology Transfer from the University of Oxford

Sortition clinical trial randomisation

Available to license: Clinicial trial randomisation system

A stand-alone, online randomisation system builder that supports the standard randomisation and minimisation algorithms for both open and blind studies. The tool incorporates full auditing, user management, email notifications, treatment resource management, reporting and monitoring.

Why randomise?

Randomisation is an essential tool for clinical and life science researchers. For example, in a clinical trial, subjects in the control and treatment groups should not differ in any systematic way or the results will be biased. For instance, if a greater proportion of older subjects are assigned to the treatment group, then the outcome of treatment may be influenced by this imbalance. Researchers therefore need to control for factors such as age, sex, pre-existing medical conditions and treatments (such as medication), as well as other factors such as smoking/non-smoking, alcohol consumption, fitness, etc.

A second layer of randomisation is then required to avoid selection bias when allocating patients to a treatment or control group. This can occur if there is any knowledge as to which group a patient is being assigned to, and again may affect the results. It is therefore important that allocation is concealed from the system.

Randomisation strategies

Clearly, randomisation in clinical trial settings is unfortunately not as simple as tossing a coin. A wide range of statistical methods (e.g. simple, block, stratified, and covariate adaptive methods) have been developed to allow proper and effective randomisation, each with their own advantages and disadvantages, and often complex to apply.

A simple, flexible and scalable approach

Sortition puts a complete and easy-to-use study randomisation toolkit in the hands of the clinical researcher, meaning it no longer needs to fall within the remit of a highly skilled statistician. The system comes complete with secure user management, a full audit trail, email notifications and all the reporting and monitoring tools you would expect. Sortition is currently in use in a growing number of trials, with over 1,400 patients randomised to date.

Key advantages

- Clean, uncluttered interface
- Accessible over the internet
- Wide range of powerful randomisation and minimisation methods
- Works for both open and blind studies
- Fully customisable and scalable
- Full audit trail
- Secure user management
- Email notifications
- Built-in treatment resource management, reporting and monitoring tools

For further information please contact:
Dr James Groves
james.groves@innovation.ox.ac.uk
+44 (0)1865 614425
www.innovation.ox.ac.uk
Project number: 10332

Technology Transfer from the University of Oxford

The Rare UK Diseases Study platform

Oxford University researchers have developed an online patient driven research platform to capture reported outcome measures and events within a dynamic consent framework.

Challenges in healthcare

One of the many challenges in healthcare is the lack of information about the disease history and conditions of patients over long periods of time. This is especially the case for chronic and rare diseases. Patients with these diseases may have mobility issues and live geographically far from hospitals and clinical research centres, making it difficult for them to pay frequent visits to these institutions. Furthermore, patients with milder symptoms may be neglected because they are not compelled to seek help at secondary and tertiary care settings. These challenges, if not addressed, can cause a failure in detecting early signals of life-threating diseases and impede clinical research.

RUDY

Oxford researchers have developed an online Rare UK Diseases Study (RUDY) platform which brings together several unique features distinct from many other systems, such as online registration, dynamic consent and participant entry of data.

Patients can securely register online and provide verbal consent over the phone. Once registered and consented, patients can have access to a customisable profile page, scheduled questionnaires and other bespoke content, such as an interactive skeleton for recording the patients' fracture history.

The highlights of the platform:

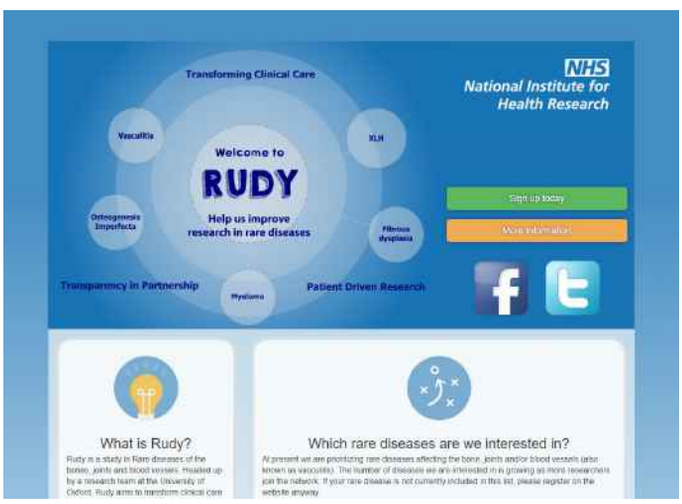
- Enables secure encryption of all patient identifiable information
- Designed with the users in mind
- Built in a framework that allows easy addition of functionality
- Operates through dynamic consent
- Allows patients to access their own data anywhere, anytime
- High patient recruitment and retention rate

RUDY is currently implemented online at https://research.ndorms.ox.ac.uk/rudy/ for patients with rare disease – those affecting the bone, joints and/or blood vessels. Currently, RUDY has 615 participants and a total of 6750 questionnaires completed.

This platform not only relieves the burden on the clinical team and lower the administration costs for patient recruitment but also encourages the collaboration between patients, clinicians and researchers to improve healthcare.

Commercialisation

Oxford University Innovation is interested in speaking with companies or institutions that would like to implement this system to support patient data management.



Homepage of the RUDYstudy.org website.

For further information please contact:
Dr Richard Auburn
richard.auburn@innovation.ox.ac.uk
+44 (0)1865 280956
www.innovation.ox.ac.uk
Project number: 11339

Technology Transfer from the University of Oxford

Clinical trial finance management suite

Available to license: Software for financial management of clinical trials.

An administrative employee of the University of Oxford has developed a unique and comprehensive tool for managing clinical trials finance within the UK regulatory regime.

Clinical trial finance suite

The clinical trial finance suite has successfully been used for 5 years in a clinical trial unit with up to 60 active trials and over £1M annual turnover.

Finance management is a vital part of successful clinical trials. The environment is often complicated due to the mandatory regulatory and reporting regime that defines the methodology for costing of trials and cost attribution and reporting requirements that no off the shelf accounting package could support.

A comprehensive tool

The suite allows detailed costing for:

- Set-up costs, per-patient costs and pass-through costs
- Categorising between procedures and investigations according the Department of Health guidance using a reference table of costs
- Staff timings in categories of doctor, nurse and tech admin
- Attributing costs to research, treatment or service support following ACORD procedures
- Including the Standard of Care comparators as required in NHS R&D assessment
- Mirroring the layout of the UKCRN commercial costing template so that negotiation with commercial entities is facilitated
- Allowing 'providers' and 'funders' to be set at the lowest element of cost to facilitate accurate accounting of payments for service providers and bill funding sources

An accounting tool

The suite collates patient information, creates invoice requests and allows multifaceted reports, including:

- Generating the cost needed for trial grant funding applications and ensuring sufficient funding is in place before the trial starts
- Reporting on actual costs by staff type, investigation type to enable comparison with the forecasted budget for work teams or service units
- Reporting the detail activity by funding stream to enable reclaim
- Calculating cost attribution reports to enable NHS R&D approval at the host trust
- The production of itemised patient activity and progress as backing to invoice to trial sponsor, coping with multiple funders on each project

Effective and efficient

The management software automatically produces data routing, validation and scripting system for costing, invoicing and reporting to save processing time and reduce manual data entry. It automatically prompts and generates reminders to smooth the running of a multi project clinical trial unit. The software is based on the Filemaker platform and can be used on both Apple Mac and PC computers.

Portfolio reporting ability

Reporting is possible slicing data through any attribute and for any time period:

- **Costs:** forecasted vs actual
- **Activities:** recruitment against target, patient visits
- **Staff management:** staff costs recovered vs actual salary
- Income and expenditure reports by trial, PI grouping for any period as desire,
- Invoice status
- Customisable reports
- Trial unit stats and performance indicators

For further information please contact:
Dr Paul Cogswell
paul.cogswell@innovation.ox.ac.uk
+44 (0)1865 280856
www.innovation.ox.ac.uk
Project number: 12664

Technology Transfer from the University of Oxford

Data Acquisition and Management System for Personalised Healthcare

A comprehensive collection of software tools to support the input of electronic personalised information and the subsequent integration, management and usage of clinical and laboratory data.

Personalised medicine aims to identify the most suitable treatment for an individual, for example, by providing a customised treatment based on a patient's genome sequence. This approach has been used to diagnose and treat patients with cancer and rare diseases.

Genome analysis platform

Genome medicine is becoming an accepted approach as the costs of next-generation sequencing have reduced and a network of genomic medicine centres have been established throughout the United Kingdom. Simultaneous analysis of clinical and genomic data can help identify the genetic causes of a disease to support diseases diagnosis, explain why a treatment has not worked and identify a new therapeutic route for a patient. Meta-analysis of these large datasets are expected to revolutionise clinical research by prompting new insights into both rare and common diseases. However, due to the volume and complexity of these datasets - a comprehensive data acquisition and management system is required to streamline data collection, integration and management.

Oxford researchers have created a collection of software tools that allow clinicians and researchers to integrate data originating from various sources and databases, organise the data in a systematic way and then extract useful information to support clinical care and research.

The system confers the following benefits:

- takes advantage of state-of-the-art knowledge in computer and data sciences to deliver an efficient and reliable service
- embodies a flexible approach to software design allowing for run-time configuration of forms and versioning of data schemas
- custom-written for hospitals and clinical laboratories dealing with big data on a regular basis
- efficacy has been validated in practice and at scale

Commercialisation

Oxford University Innovation is interested in hearing from organisations that would like to implement their own data acquisition and management system for hospitals, clinical laboratories and partner organisations.

For further information please contact:
Dr Richard Auburn
richard.auburn@innovation.ox.ac.uk
+44 (0)1865 280956
www.innovation.ox.ac.uk
Project number: 14422

Technology Transfer from the University of Oxford

DEVICES AND DIAGNOSTICS

Sulphide sensors

Oxford researchers have developed an electrochemical sensor has been developed that measures the concentration of hydrogen sulphide (H_2S) or thiols in fluids.

Hydrogen sulphide (H_2S) is a noxious and highly toxic gas. It is formed as a by-product in numerous chemical processes and can be generated through the decomposition of organic matter (e.g. sewage effluent).

Additionally, hydrogen sulphide is present in crude oil, thereby creating a risk to workers in the petroleum industry who may be exposed to unacceptably high levels of this gas. It is therefore important in many industrial processes that monitoring procedures are in place to determine the concentrations of H_2S present in the environment.

Sulphide sensors

Figure 1 shows a schematic view of the Oxford electrochemical sensor. The sensor is exposed to the sulphide/thiol-containing fluid, which may enter the device across a permeable membrane (34). The fluid subsequently passes through two porous blocks (32 & 36), which contain an immobilised reagent that renders the sulphide/thiol-containing fluid conductive.

A potential is applied between electrodes 40 and 44, and the flow of current between electrodes 40 and 42 is measured. The current reading is then de-convoluted to provide the concentration of sulphide/thiol. Critically, immobilisation of the reagent in the electrochemical component (36) of the sensor enables miniaturisation of this technology, which leads to faster response times, lower consumption of reagents and lower unit costs.

Patent status

This technology is protected by several international patents and Isis would like to talk to companies interested in exploiting the above ground use of this sensing technology. Please contact the Oxford University Innovation Project Manager to discuss this further.

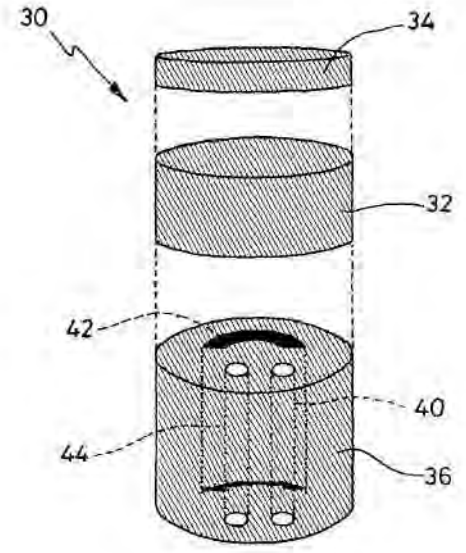


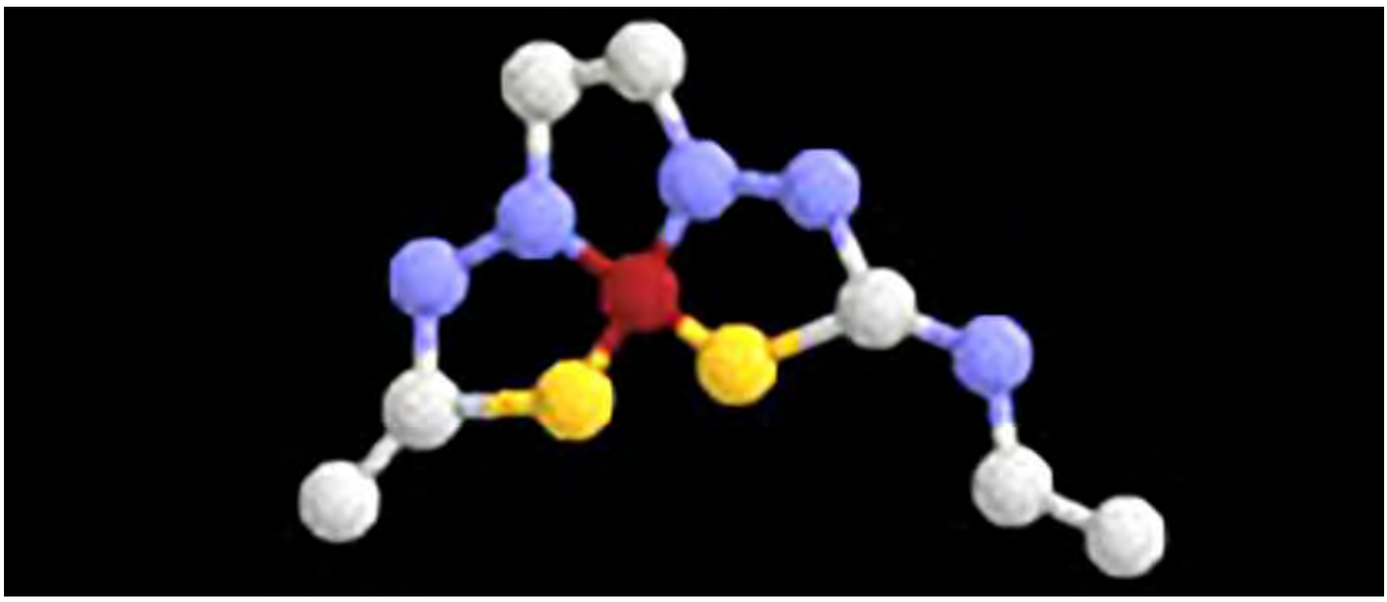
Figure 1

For further information please contact:
Dr Andrew Bowen
andrew.bowen@innovation.ox.ac.uk
+44 (0)1865 614449
www.innovation.ox.ac.uk
Project number: 0706

Technology Transfer from the University of Oxford

Saliva drug testing

Researchers at Oxford University have developed a hand-held device for rapid, quantitive saliva drug testing.



Early detection

The prevalence of driving while affected by drugs is rising. It has been shown that drugs are detected commonly among those involved in motor vehicle accidents, with studies reporting up to 25% of accident-involved drivers testing positive for illicit drugs with cannabis being the most common. It is apparent that drugs in combination with alcohol, and multiple drugs, present an even greater risk and it has been concluded that drug driving is a significant problem, both in terms of a general public health issue and as a specific concern for drug user.

The challenge to further progress in this area is the development of a hand held device, which will enable not only qualitative drug testing, but also quantitative testing.

A better process for collection

The Oxford Invention provides a method for creating a hand-held device for rapid, accurate, quantitative, saliva drug testing.

Unlike currently available hand-held saliva drug testing equipment, the Oxford Invention:

- Is highly sensitive
- Does not require laboratory confirmation of positive tests
- Is not pH dependent
- Provides accurate results in less than 60 seconds
- Is ideally suited for on the spot checks, for example roadside testing

Commercialisation

Oxford University Innovation Ltd. has filed a priority patent application, which covers this technology and is seeking partners to aid in its exploitation.

For further information please contact:
Dr Chandra Ramanujan
chandra.ramanujan@innovation.ox.ac.uk
+44 (0)1865 614434
www.innovation.ox.ac.uk
Project number: 2476

Technology Transfer from the University of Oxford

Real world arsenic detection

Researchers at the University of Oxford have have developed electrochemical techniques to detect low levels of arsenic in the presence of copper.

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 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 low-cost testing devices with high sensitivity that can be directly applied in the field.

For further information please contact:
Dr Chandra Ramanujan
chandra.ramanujan@innovation.ox.ac.uk
+44 (0)1865 614434
www.innovation.ox.ac.uk
Project number: 2718

Technology Transfer from the University of Oxford

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Researchers at the University of Oxford have developed an in-line gas analysis system ŎlˑLJlˑōfŜ 2Ŧ YŜlˑădzNΛyƎ Əlˑă Ŧf2ø lˑyŘ Ŏ2yŎŜyűNlˑűΛ2y˝ăΛYdzfűlˑySƧdzăfè ΛyˇűKŜ ălˑYŜ Ŧlˑ0ŜπYˑlˑă\ Y˝2dzyűŜŘ dzyΛúΦ

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Current technology falls short of the mark

Traditional methods used to analyse breath gas concentration rely on off-line analysis. For example, the Douglas bag method, where expired air is collected over a period of up to 60 seconds and subsequently analysed. Modern approaches have attempted to solve this issue, however, the process of redirecting expired gased to an analyser using a t-piece still results in a disconnect between the flow measurement (in-line) and the gas analysis (off-line). This means that a calibration step is required to ensure that these two parameters are temporally aligned.

A breath of fresh air

Researchers at the University of Oxford have developed an in-line gas analysis technology capable of calculating O_2 and CO_2 concentration and gas flow concurrently. The device uses laser spectroscopy to measure directly the concentration of oxygen, carbon dioxide and water vapour in the breathing tube. The invention allows the calculation of gas exchange occuring at the lungs when both inspiratory gas compositions and flow rates are varying.

Not only does this remove the sampling issue, but the device has been clinically tested and is highly accurate with a volume accuracy of ±0.2% and O_2/CO_2 concentration accuracies of around ±0.5%.

We believe the key advantages of the Oxford technology lˑNŜ lˑă Ŧ2fl2øăY

- Highly accurate flow and gas concentration YˇŜlˑădzNŜYˇŜyűă
- In-line analysis using a face-mask unit
- Clinically tested and verified
- Further functionality to assess lung function is being ŘŜØŜf2LJŜŘ

Patent protection

This technology is covered by a portfolio of granted UK, ¦{ lˑyŘ 9¦ LJlˑűŜyűă lˑyŘ hÈŦ2NŘ ¦ yΛØŜNăΛúè Lyy2ØlˑúΛ2yˇΛă ΛyűŜNŜăűŜŘ ΛyˇűlˑflΛyƎ ú2 lˑyè2yŜ øK2 Yˇlˑè ōŜ lˑōfŜ ú2 lˑΛŘ ΛyˇúKŜ Ŏ2YˇYˇŜNŎΛlˑfŒălˑúΛ2yˇ2Ŧ úKΛă ûŜŎKy2f2Ə\Φ

For further information please contact:
Dr Richard Reschen
richard.reschen@innovation.ox.ac.uk
+44 (0)1865 280872
www.innovation.ox.ac.uk
Project number: 12313, 12309, 3672

Technology Transfer from the University of Oxford

Bacterial identification

Available to license: Rapid, universal bacterial identification system.

Database and scheme for the fast, accurate classification of bacteria, with applications including disease diagnosis.

Universal gene-based identification

High-resolution bacterial characterisation is essential in microbiology, particularly for disease diagnosis, where rapid and precise identification is a high priority.

Gene-based methods have become increasingly important in bacterial classification, complementing and to an extent replacing more traditional phenotypic methods. However, until now, there has been no single system which works for all bacteria.

Scientists at the University of Oxford have developed a universal identification scheme based on ribosomal multilocus sequence typing (rMLST). This represents the first genotypic scheme that can provide both broad and accurate characterisation of bacteria at all phylogenetic levels.

The system works through the identification and analysis of allelic variation within the ribosomal protein subunit (rps) genes, which are universal yet record a wide range of evolutionary diversity, to effect rapid and highly accurate phylogenetic identification.

Benefits of the Oxford system

- Reliable identification
- High resolution
- Results at push of a button
- One system for all bacteria

Supporting data

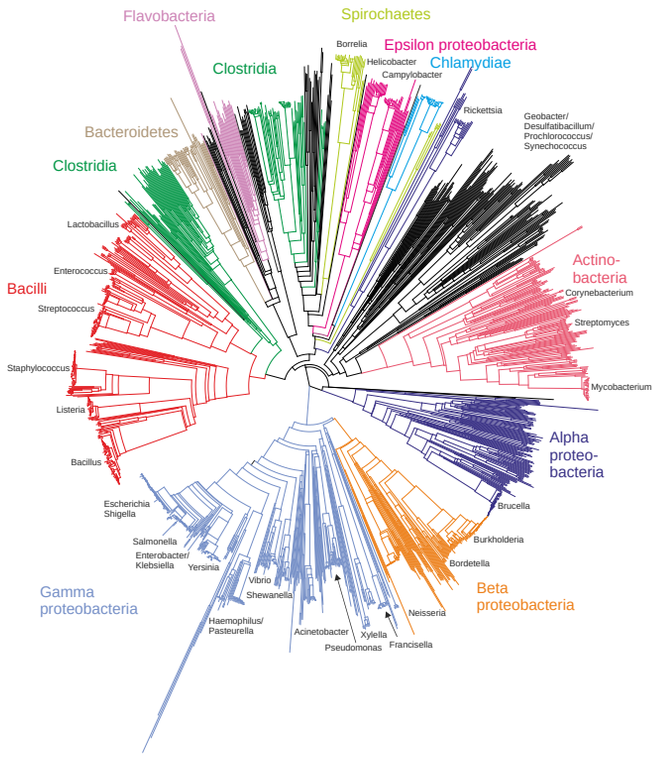
A web-accessible and expandable database comprising genome data from more than 2000 bacterial isolates has been generated. The variation of 53 rps genes is catalogued in this database, providing a means of defining the precise phylogenetic position of any bacterial sequence at the domain, phylum, class, order, family, genus, species and strain levels.

Applications

The data generated for the rMLST scheme could be used in combination with next-generation sequencing to enable the rapid identification of bacterial isolates at the push of a button. Equally the database enables the development of PCR-based, species or strain-specific diagnostic tests.

Applications include:

- Population studies
- Epidemiological investigations
- Diagnostic tests



Above image: Neighbour-joining tree of the entire bacterial domain, reconstructed from concatenated ribosomal protein gene sequences.

For further information please contact:
Dr Matthew Carpenter
matthew.carpenter@innovation.ox.ac.uk
+44 (0)1865 280970
www.innovation.ox.ac.uk
Project number: 7895

Technology Transfer from the University of Oxford

Nanoscale control of graphene electrodes

Available to license: A method to fabricate graphene nano-electrodes

A method that demonstrates precise control over the size and position of the nano-gaps for the fabrication of graphene-based molecular junctions.

Integrated circuits with each functional unit formed by only a single molecule will be the ultimate form of electronic device scaling. To harness the full potential of individual molecules, technological progress towards robust devices is necessary, with a call for alternative electrode materials that are stable at room temperature. Graphene is a promising candidate for the replacement of metal electrodes because of the high-temperature stability and extreme thinness of the material.
Oxford researchers have developed a method that demonstrates precise control over the size and position of the nano-gaps for the fabrication of graphene-based molecular junctions, opening up the possibility to use graphene electrodes for large-scale integrated molecular devices.

Nano-gaps in graphene

Recent advances in the high-throughput fabrication of graphene nano-gaps, by means of electroburning and plasma etching, have paved the way towards scalable room temperature single molecule electronics. Although these methods provide excellent control of either the size or position of the nano-gap, they do not yet provide the full nanoscale control required for large scale integration of graphene nano-electronics with conventional electronic components. Oxford researchers are combining the advantages of the two methods and demonstrate unprecedented control of the formation of single layer graphene nano-gaps.

The Oxford invention

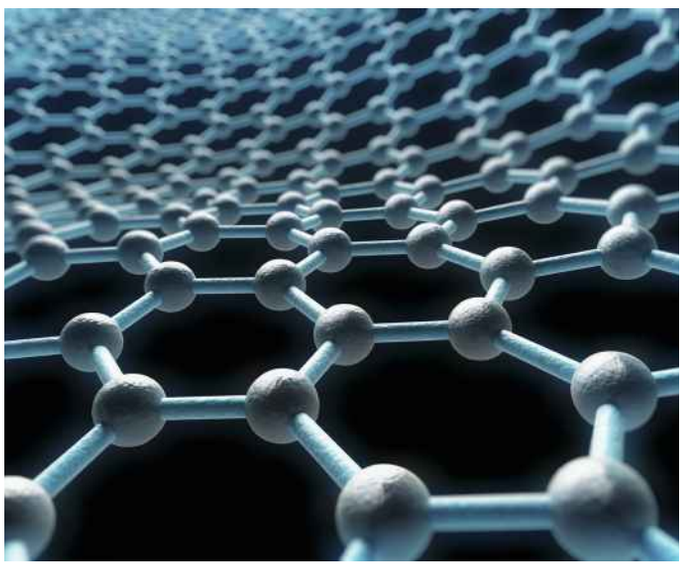
While the method of electroburning has been successfully applied to create nano-gaps in graphene, graphite and carbon nanotubes, the experimental and theoretical understanding of the role of geometry in the formation of nano-gaps has remained limited. Yet, it is precisely the device geometry that provides the handle to control the nano-gap formation. The method developed at Oxford employs a novel device design and feedback-controlled electroburning methodology.

By choosing predefined device geometry, the nano-gaps are reproducibly formed. The geometry of the device determines the position of the nano-gap and the feedback is used to control gap size.

This method allows for controlled fabrication of graphene nano-gaps with yields as high as 85 %, and can be used to create carbon-based nano-electronics. Given the direct relevance of graphene nano-gaps for single molecule electronics and other carbon-based nano-devices, this method will be of strong interest to a broad group of potential licencees in the field of nanoscience and nanotechnology.

Licencing opportunity

A patent application has been filed to cover the method of fabrication and Isis welcomes contact from parties interested in licensing this opportunity. Contact the Licensing & Ventures Manager below.



For further information please contact:
Dr Chandra Ramanujan
chandra.ramanujan@innovation.ox.ac.uk
+44 (0)1865 614434
www.innovation.ox.ac.uk
Project number: 11313

Technology Transfer from the University of Oxford

FieldSense – Next generation tactile feedback systems

Oxford researchers have developed FieldSense, a haptic feedback technology based on the precise placement of magnetic nodes.

Simulating senses

The sense of touch is critical to how we perceive the world around us. It helps us discover and classify new objects, as well as alerting us to change in the environment. Over the last 30 years, haptic technologies have sought to provide more immersive experiences by engaging our sense of touch. This has resulted in developments such as tactile electronic displays, virtual reality gaming and interactive medical devices.

Touching the limits

Current haptic technologies focus on the use of vibrational or electronic stimuli. Vibrations are neither specific nor directional meaning that they struggle to provide precise and detailed feedback. Electronic or "shock" stimuli are more precise, but depending on the magnitude of the stimulus, it could be uncomfortable or even painful for the user.

FieldSense - An attractively simple magnetic solution

Researchers at the University of Oxford have developed FieldSense, a haptic technology, which uses affordable, simple arrays of magnetic nodes to generate precise and rapid tactile feedback.

The stimuli provided by field sense can be tailored to the purpose meaning that it could bring haptic technologies into new applications, as analternative to more widely used electric stimuli.

The main advantages of the technology are as follows:

- Low cost and simple to implement
- Low power usage
- Controllable stimulus
- Pain-free feedback method

Patent Protection

The FieldSense technology is subject to a UK patent application and Oxford University Innovation Ltd. is seeking partners to aid in its commercialisation.

For further information please contact:
Dr Chandra Ramanujan
chandra.ramanujan@innovation.ox.ac.uk
+44 (0)1865 614434
www.innovation.ox.ac.uk
Project number: 12729

Technology Transfer from the University of Oxford

Nuclear quadrupole resonance sensor for safer wireless power

Oxford researchers have developed an innovative safety solution that uses nuclear quadrupole (NQR) resonance to detect biological material within the wireless power transfer (WPT) magnetic field.

Charging ahead without wires

The global sales of electric vehicles are expected to top 1 million for the first time in 2017 (Frost & Sullivan, 2017) and with this increased demand comes a need for a more convenient and efficient method of recharging on-board batteries. Wireless charging is an attractive solution, as it reduces the amount of input required from the vehicle owner and eliminate cumbersome leads and charging stations.

Current wireless charging systems are typically based on inductive charging, where a magnetic field is generated between a coil located on the ground and one in the vehicle. Fields generated in this way generally exceed 85 kHz.

Wireless power transfer safety

There is a widely perceived danger with wireless power transfer (WPT), that humans or animals could step into the generated magnetic field while the device is in use. It is a requirement that such systems do not expose users or animals to harmful levels of electromagnetic radiation and that it adheres to guidelines set out by the International Commission on Non-ionising Radiation Protection (ICNIRP). In order to prevent this, effective “trip switches” are needed, where the power can be cut in the presence of biological material.

Nuclear quadrupole resonance

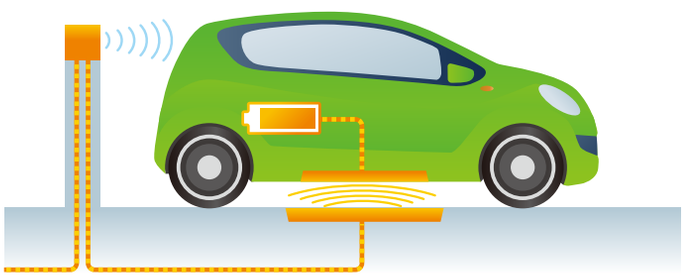
Researchers at the University of Oxford have developed a sensor, based on nuclear quadrupole resonance (NQR), capable of detecting biological material in proximity to the WPT field. The NQR system differentiates between humans or animals and can provide feedback to the WPT device to trigger a shut-down when necessary. The power can then be restored once the biological material is clear of the field.

We believe the main benefits of the Oxford solution are as follows:

- Lower cost and more reliable than current radar solutions
- Differentiation between different biological material
- Fewer false positives than other safety devices
- Easily integrated into existing WPT systems
- Allows WPT manufacturers to adhere to ICNIRP guidelines

Patent protection

A patent has been filed that covers this technology. Oxford University Innovation Ltd. is keen to talk to anyone who could aid in the commercialisation of this device.



For further information please contact:
Adrian Coles
adrian.coles@innovation.ox.ac.uk
+44 (0)1865 614432
www.innovation.ox.ac.uk
Project number: 13249

Technology Transfer from the University of Oxford

Novel biomarkers for non-alcoholic fatty liver disease

Oxford academics have identified new biomarkers for the most common liver disorders in the Western World which could be used to diagnose, prognose or monitor the progression of the disease.

Non-alcoholic fatty liver disease (NAFLD) encompasses a spectrum of progressive liver disease ranging from non-alcoholic fatty liver (NAFL) to non-alcoholic steatohepatitis (NASH). Approximately 1 in 3 people in the US and the UK have some degree of NAFLD and the disease is strongly associated with obesity.

Both hepatic fibrosis and cirrhosis can be seen in NAFLD patients. It is imperative to diagnose fibrosis in the early stages of reversible liver scarring so that irreversible liver damage in cirrhosis can be prevented. Cirrhosis is the cause of over 6,000 deaths every year in the UK, and approximately 27,000 in the USA, making it the ninth leading cause of death.

Currently, the reference standard for assessing liver fibrosis and NAFLD is the liver biopsy, an invasive, painful procedure which can be unreliable, costly and can have a false negative rate as high as 20%. Consequently, there is a need for improved, minimally-invasive methods of determining stages of NAFLD in patients.

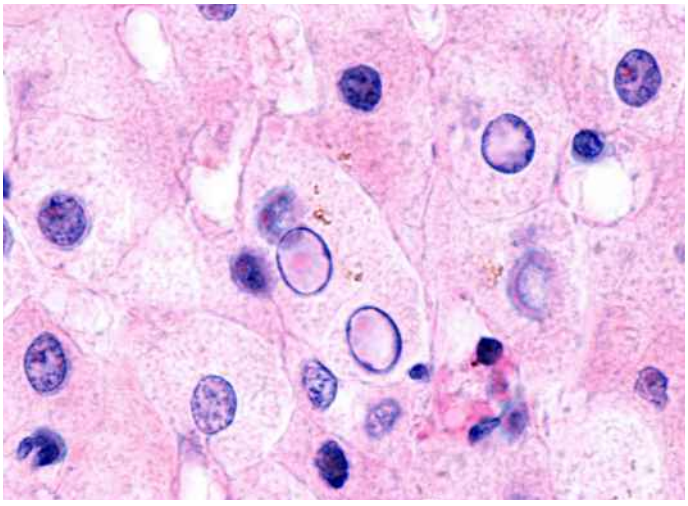
Assessment and diagnosis of patients with NAFLD

Academics at the University of Oxford have now identified protein biomarkers that are either up- or down-regulated in patients who are at different stages of lobular inflammation and fibrosis/cirrhosis as well as differentiating NAFL and NASH. By quantifying the biomarkers in a biological sample, the technology could potentially be used to diagnose, prognose or monitor the progression of NAFLD in an individual.

To utilise these new biomarkers effectively, the academics have developed the first antibody-free serum protein biomarker assay for NAFLD which, unlike currently used immunoassays, has the potential to detect degraded proteins. They are also developing a rapid point of care test (POCT) which can determine biomarker levels from a single drop of finger-pricked capillary blood. These methods are rapid, less invasive and can be performed easily on all patients. They may also stratify patients according to the stage of NAFLD, ensuring treatment can be effective and disease progression can be reduced.

Commercialisation

This technology is at the preclinical stage and will need to be validated in larger clinical cohorts. This technology is subject to a patent application and we are looking for commercial partners who wish to collaborate with us to validate the biomarkers or licence this technology.



For further information please contact:
Dr Richard Reschen
richard.reschen@innovation.ox.ac.uk
+44 (0)1865 280872
www.innovation.ox.ac.uk
Project number: 13726

Technology Transfer from the University of Oxford

Density-of-state based quantum sensitive sensors

Scientists at Oxford University and São Paulo State University have developed a highly sensitive, label-free density-of-states (DOS) based sensing technology operating at the mesoscopic or nanoscale level.

Limitations of current technologies

The ability to detect concentrations that are in the picomolar (10^{-12}) range have proved incredibly challenging. Due to the limitations of the current technologies these challenges include:

- Most techniques aren't sensitive to a range of functional chemical groups
- The signal received from un-labelled biological material can be too weak to be amplified
- Samples require labelling with either an antibody or fluorescent marker to amplify the signal which is costly and prone to error

Electrochemical disruptive technology

Scientists at Oxford University and São Paulo State University have developed a highly sensitive sensor using nanoscale electrochemical disruptive technology. This technology, originally developed for biomedical sensing, detects the change to the potential upon binding of a molecule to an electroactive surface, which is then amplified to allow the detection of picomolar to micromolar concentrations of the item of interest. The device itself is constructed in such a way that allows it to be incorporated into existing Complementary Metal-Oxide Semiconductor (CMOS)-based instruments.

Potential applications

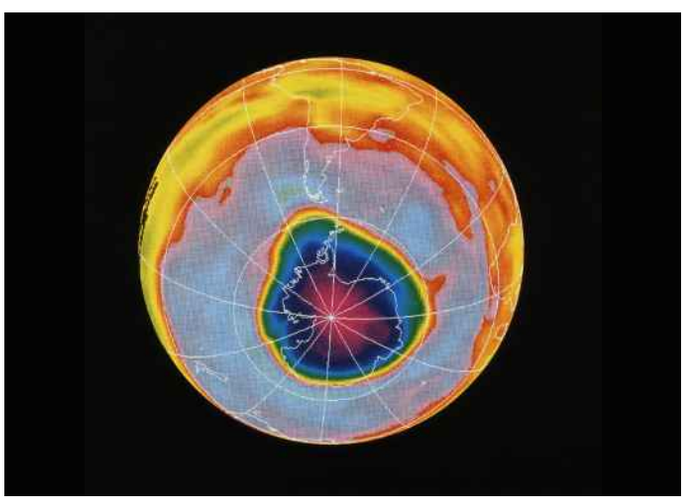
The device can detect molecules that are a few atoms in size, up to those as large as proteins but could also be used to detect electromagnetic radiation. The technology can be adapted to detect specific chemical functional groups. This adaptability enables the device to perform in many different applications such as:

- Point of care medical tests for specific biological markers, using microliter volumes of human fluids
- Chemical detection of banned substances e.g. drugs, alcohol, explosives
- Petrochemical exploration
- Environmental sensing
- Space applications
- Electrochemical solar cells
- Super capacitors
- Photonic devices

The technology has been tested as a device for biomarker detection and has specifically detected the concentration of a marker for inflammation at 55 picomoles.

Commercialisation

Oxford University Innovation is seeking industrial interest from parties wishing to licence and commercialise this technology.



For further information please contact:
Bénédicte Menn
benedicte.menn@innovation.ox.ac.uk
+44 (0)1865 280906
www.innovation.ox.ac.uk
Project number: 13953

Technology Transfer from the University of Oxford

Magnetic microbubble-conjugated thrombin as a novel drug delivery system

Researchers at the University of Oxford have developed a novel drug delivery system to enable targeted delivery of thrombin to induce thrombosis in targeted anatomical locations.

A pseudoaneurysm, sometimes called a false aneurysm, occurs when a blood vessel wall is injured, and the blood is contained by the surrounding tissues. This can occur when blood escapes from the lumen of an artery through a defect in one or more layers of the arterial wall and forms a localised pocket of flow either beneath the outer wall of the artery or in the surrounding tissues.

Symptoms of a pseudoaneursym could result in pain, swelling, bruising, and free extravasation of blood (rupture) into the surrounding tissue. Traditional methods of treatment include open surgical repair, or ultrasound guided compression of the pseudoaneurysm.

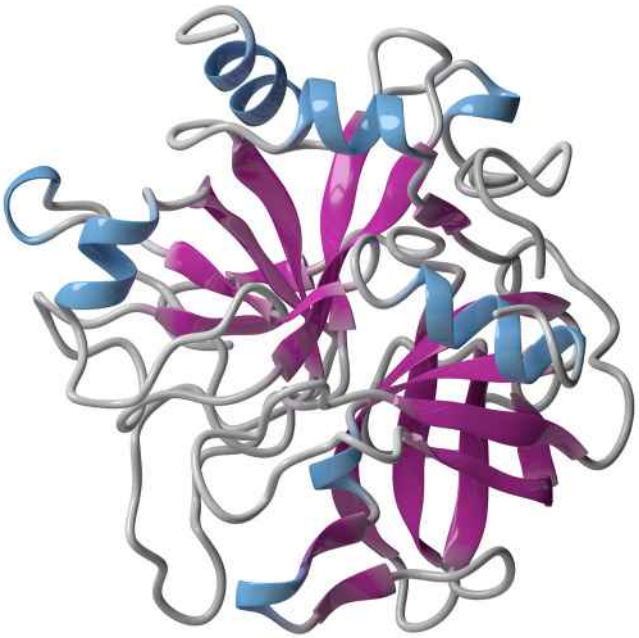
Surgical repair of the pseuodaneursysm requires general anaesthetic and can be complicated by infection of the wound and prolonged hospital stay for aftercare. Ultrasound guided mechanical compression is often avoided as the area affected is often swollen and tender.

For many years, direct injection of thrombin is used to treat pseudoaneurysms by causing thrombosis, which results in the formation of thrombus (clot). Ultrasound guided thrombin injection (UGTI) subsequently became a mainstream therapeutic option.

However, non-targeted delivery of thrombin can result in spill over of thrombin to non-affected area and cause thrombosis where it shouldn't.

Furthermore, when treating a pseudoaneurysm using conventional UGTI, it is difficult for the physician to know whether the treatment has been effective at the time of treatment.

Oxford researchers have developed a drug delivery system to enable targeted delivery of thrombin by applying a focused magnetic field to the area requiring treatment. This method aims to overcome many of the drawbacks of current methods used to treat pseudoaneurysms by delivering thrombin into a pseudoaneurysm much more accurately and thus reducing the risk of a further blood clot due to the thrombin being injected into the wrong place.

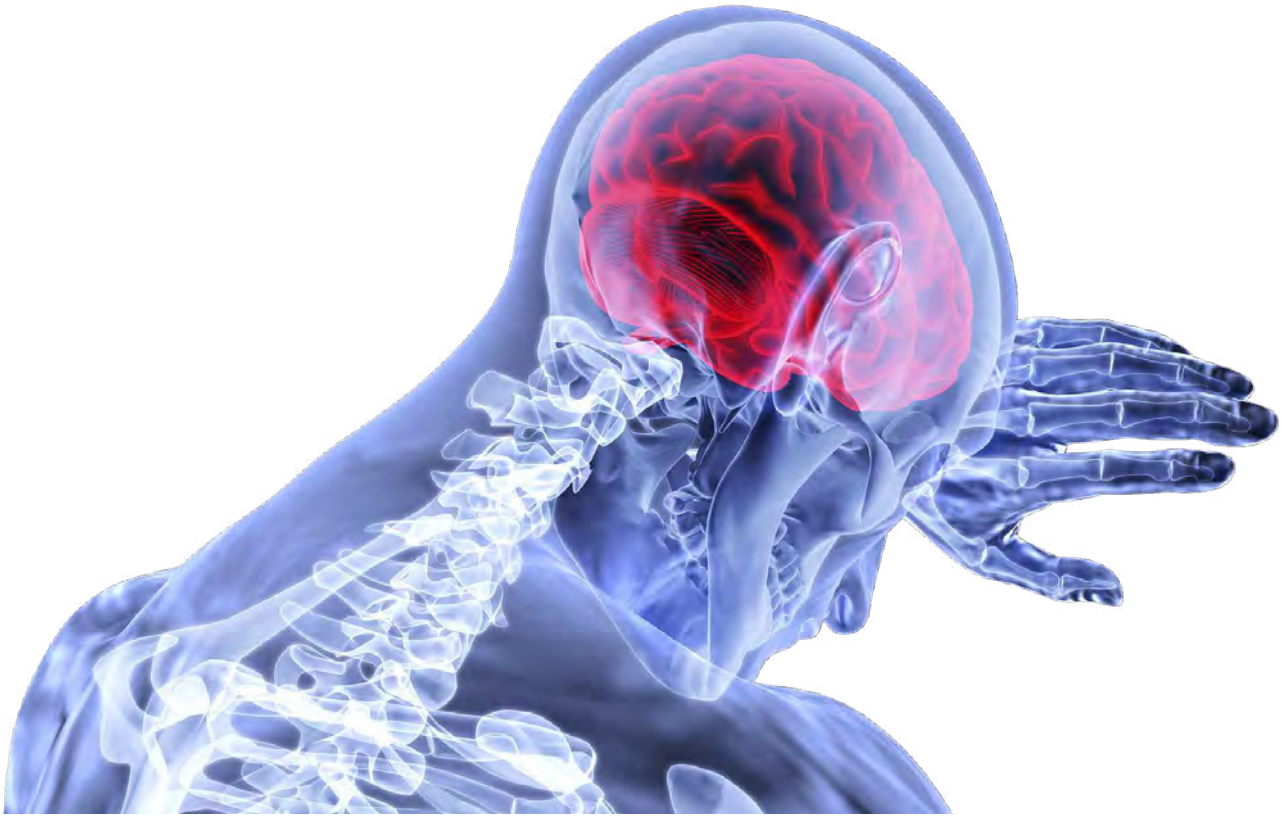


For further information please contact:
Dr Dinali de Silva
dinali.desilva@innovation.ox.ac.uk
+44 (0)1865 614441
www.innovation.ox.ac.uk
Project number: 14262

Technology Transfer from the University of Oxford

Structural functionally graded blast panel for protection against traumatic brain injury

Researchers at the University of Oxford have developed a new design concept to protect individuals from blast explosions, in particular, to protect the wearer's brain from traumatic brain injury.



Blast-induced traumatic brain injuries as a result of explosions have been linked to a range of neurodegenerative and neuropsychiatric disorders.

Scientists at the University of Oxford have developed a new design concept for a structural material panel with varying mechanical properties, that when placed into a helmet or similar device, protects the user from shockwaves created by an explosion and thus from a traumatic brain injury.

Where conventional blast panels aim to reflect or attenuate the shockwave incident from explosions, the technology developed at Oxford works very differently by modifying the shape of the shockwave so as to avoid the concentration of stress to the centre of the skull.

The central region of the brain (around the ventricles) has been found to be particularly susceptible to damage from incident shockwaves.

The blast panel can be easily integrated into a device, which is more practical than conventional devices and by modifying the shape of the shockwave, has the potential to give the wearer better protection both from shockwaves and flying debris.

Blast front modifications have never been done in this manner and the technology has applications in any protective structure aimed at protecting the head against blasts as its primary function is to protect the wearer from incident shockwaves.

For further information please contact:
Dr Dinali de Silva
dinali.desilva@innovation.ox.ac.uk
+44 (0)1865 614441
www.innovation.ox.ac.uk
Project number: 14899

Technology Transfer from the University of Oxford

Deep vein thrombosis diagnostic device

Researchers at the University of Oxford have developed a novel device for reliable point-of-care diagnosis of deep vein thrombosis.

The deep vein thrombosis problem

Deep vein thrombosis (DVT) is a blood clot that forms within the deep veins of the limbs. If left untreated, half of these blood clots will travel to the lungs, forming a pulmonary embolism (PE). This is a leading cause of death, greater than AIDS, breast cancer, prostate cancer and car crashes combined. Each year, DVT affects around 1 person in every 1,000 in the UK and the total cost burden to the UK of management of DVT and PE is estimated at approximately £640 million. Globally, the clot management devices market was valued at $1.26 billion in 2015 and is further expected to reach a value of $1.88 billion by 2024.

Ultrasound is the standard method for diagnosis of DVT. However, an ultrasound procedure has to be performed a trained radiologist and requires a referral to the hospital. Currently, only 15% of hospital referrals have confirmed DVT. Unnecessary referrals for patients with suspected DVT cost the NHS more than £100M per year. There is an added problem with hospital referrals as it often requires the GP to prescribe preventative anticoagulants, posing a further unnecessary health risk. A 2016 survey of over 1000 UK GPs indicated that a more accurate DVT diagnosis is the top need to reduce referrals.

A point-of-care solution

Researchers at the University of Oxford have developed an easy-to-use point-of-care solution that can improve screening of DVT patients in primary care, avoiding the need for unnecessary referrals and treatments.

Oxford University Innovation is seeking partners to license this innovative technology and support its continued development. A patent application has been filed to cover this method.

For further information please contact:
Dr Philippa Christoforou
philippa.christoforou@innovation.ox.ac.uk
+44 (0)1865 280842
www.innovation.ox.ac.uk
Project number: 15595

Technology Transfer from the University of Oxford

A new treatment to predict the growth in abdominal aortic aneurysms

Scientists at the University of Oxford have used the pulsation characteristics of an artery for the prediction of growth of abdominal aortic aneurysms in humans.

What is abdominal aortic aneurysm?

The aorta is the main blood vessel that carries blood from the heart to the rest of the body. An abnormal expansion in the abdominal region of the aorta is called an abdominal aortic aneurysm (AAA). When an AAA continues to expand, there is an increased risk of it bursting and this can lead to internal bleeding and in many cases, death. Ruptured AAAs kill approximately 200,000 people in the world each year, and of these 6000 are in the UK.

To prevent AAA ruptures, AAA screening programs have been implemented in the UK, Sweden, Australia, and Germany – with other countries to follow. In the NHS alone, more than 100,000 ultrasound scans are performed each year for AAA surveillance. However, many of these scans are redundant if we are able to predict the growth of the AAA.

AAA's can be treated by surgery but usually this only occurs when an aneurysm reaches a certain size (>5.5cm). It has been shown that aneurysm size alone may not be an absolute predictor of the risk of rupture. Furthermore, the rate of AAA progression may vary significantly between individuals and the growth rate of an AAA is a good indicator as to whether surgical intervention is required.

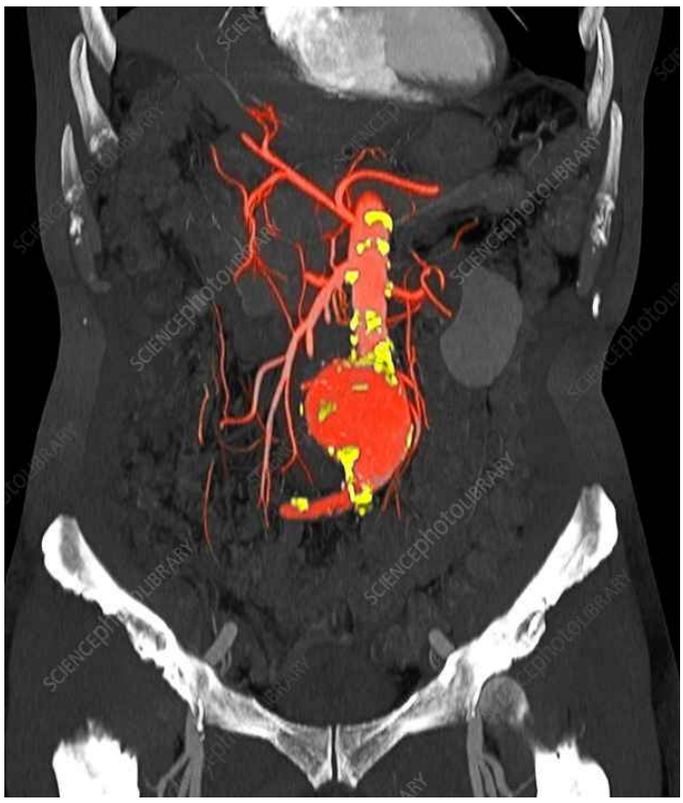
Overcoming challenges

In a recent international survey of vascular surgeons, developing novel methods for the prediction of AAA growth was voted as the top priority for research in AAA. There is, therefore, a requirement for a non-invasive method for the prediction of aneurysm growth and we have found that using the pulsation characteristics of an artery to be such a method.

Scientists at the University of Oxford have devised a method for predicting the rate of growth of abdominal aortic aneurysms in humans using the pulsation characteristics of an artery during ultrasound imaging, such as the brachial artery of the arm.

Commercialisation

Oxford University Innovation has filed a priority patent application on the technology and welcomes discussions with companies interested in licensing it for commercial development .



For further information please contact:
Dr Dinali de Silva
dinali.desilva@innovation.ox.ac.uk
+44 (0)1865 614441
www.innovation.ox.ac.uk
Project number: 15648

Technology Transfer from the University of Oxford

A novel algorithm for biologically inspired lighting solutions

Oxford researchers have developed a method to generate metamers with non-linear light sources to selectively stimulate melanopsin in the human eye, thereby potentially affecting the circadian rhythms and alertness without a change in appearance.

Biologically inspired lighting

Light emitting diodes (LEDs) are widely used for various lighting applications, including display backlighting, automotive lighting and mobile applications. The global LED lighting market is expected to increase at a high growth rate and will reach $80 billion by 2020. In particular, human-centric or biologically relevant lighting, which requires precise control of intensity, colour and level, will dominate the lighting space.

Melanopsin is involved in the regulation of the sleep-wake cycle, circadian rhythms, and many other fundamental physiological aspects. Using multiple LEDs, it is possible to create lights that differ in the amount that they stimulate melanopsin but do not differ in their appearance. These are called metamers and demonstrate how non-visual properties of light can be modulated independently of visual appearance.

The problem with non-linearity of real light sources

Metamers for a light source with multiple LEDs can be accurately characterised to activate a desired photoreceptor given any set of input intensity values for each LED. However, where light sources are non-linear and exhibit spectral shifts as a function of input intensity, it is non-trivial to construct metamers and inaccuracies will necessarily result, leading to problems such as undesired colour distortions.

Novel methods to generate metamers using an algorithm

Researchers at the University of Oxford have developed a novel method to generate metamers with non-linear light sources using an algorithm which incorporates spectral shifts in real light sources. Using a predicted output spectrum, the melanopsin signal and cone signal, for example, can be optimised such that specific spectral properties are achieved. This may include no difference in cone signal between two spectra, and maximal difference in melanopsin.

The method can be used to make biologically inspired spectra to maximally or minimally stimulate melanopsin, thereby modulating the alertness of an individual, or cause differences in circadian or sleep-related outputs, such as melatonin suppression. Other applications include optimising for a specific Colour Rendering Index (CRI), or other colour rendition metrics.

The main advantages of this method are:

- Precise light control with multiple non-linear light sources, such as LEDs
- Generation of calibrated light spectra from a low number of calibration measurements
- Useful for all settings in which the spectrum of a multi-primary light source needs to be controlled, such as biologically inspired solutions or light therapy

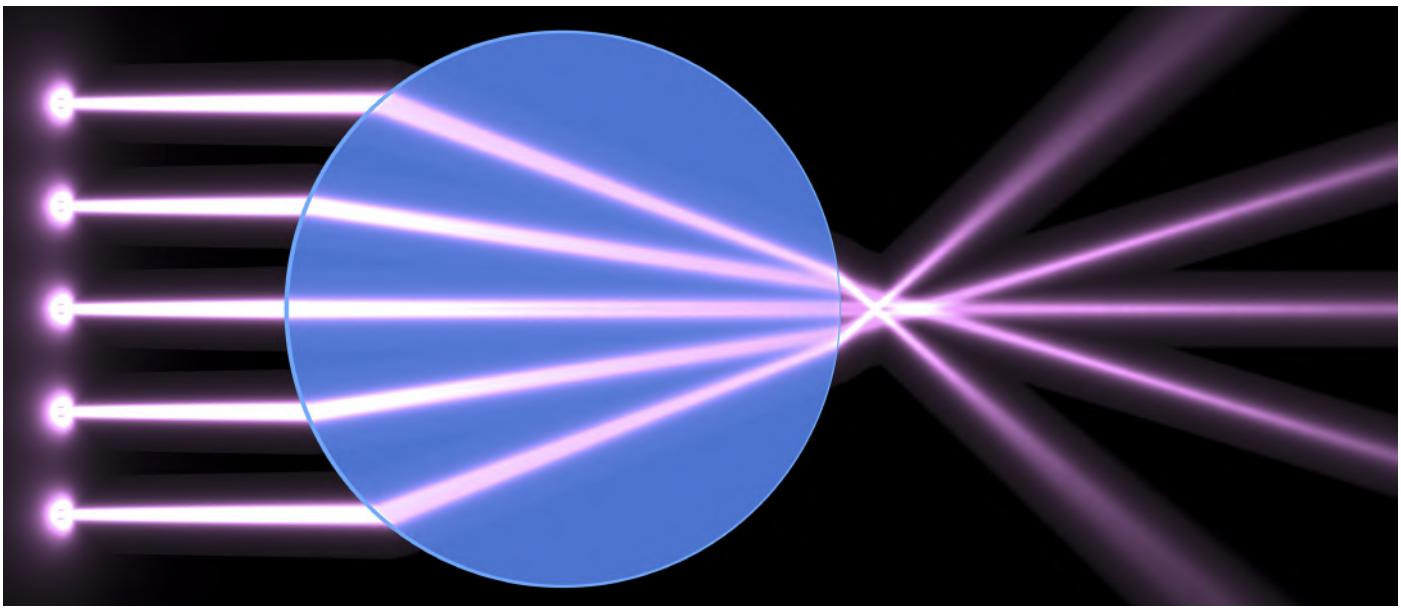
A patent application has been filed on this technology. Oxford University Innovation is interested in talking to potential partners for the commercialisation of this new method.

For further information please contact:
Dr Philippa Christoforou
philippa.christoforou@innovation.ox.ac.uk
+44 (0)1865 280842
www.innovation.ox.ac.uk
Project number: 15823

Technology Transfer from the University of Oxford

Multifunctional device for focusing light through an optical component

Oxford researchers have developed a multifunctional lens which is capable of imaging phase modulation and polarisation modulation simultaneously.



Harnessing birefringence properties in multifunctional GRIN lens based cascades

Graded Index (GRIN) lenses are affordable, flat, rigid lenses commonly used for compact imaging systems. GRIN lenses have the inherent property of radially changing birefringence, a property undesired for most applications.

Researchers at the University of Oxford have drawn previously undesirable birefringence properties of GRIN lenses to build GRIN lens cascades. GRIN lens cascades are light manipulation structures that enable novel extra functionality in commonplace GRIN lens systems, extending their range of applications.

GRIN lenses are sold widely today. Their low mass and size means optical devices using GRIN-lenses can be created in an easier, more stable, compact, low-cost way compared with conventional methods, such as using adaptive spatial light modulators or q-plates.

The GRIN based lens cascade could be applied as a multi-functional optical device which is capable of imaging, phase modulation and polarisation modulation simultaneously.

The main applications include:

- A new vector vortex beam (VVB) generator that could benefit complex light beam engineering as well as modification of the shape of laser beam focus for microscopy and super-resolution applications
- A new orbital angular momentum (OAM) generator that could benefit further microscope techniques including optical tweezing, sensing in astronomy, as well as quantum optics communication
- A new single-shot Mueller matrix measurement probe that could assist minimally invasive surgery techniques to do simultaneous scanning for detecting the boundary of, say a cancerous tumor, as a label-free indicator

Patent protection

A patent has been filed which covers this technology. Oxford University Innovation is interesting in talking to potential partners to aid in the commercialisation of these new methods.

For further information please contact:
Adrian Coles
adrian.coles@innovation.ox.ac.uk
+44 (0)1865 614432
www.innovation.ox.ac.uk
Project number: 16143, 16372

Technology Transfer from the University of Oxford


GENOMICS

Genome-wide association study software

Available to license: A GenoSNP - genotyping without a reference population.

Genetic make-up affects the way in which humans develop diseases, and respond to medical treatment, from drugs to vaccines.

Understanding and preventing disease

Genotyping, a process for identifying genetic make-up and DNA sequencing, plays an essential role in understanding genetic based diseases. The technology is therefore extremely important for the future study of personalised medicine and prevention of disease.

Genotype calling is practiced using a variety of biological assays but current genotyping algorithms typically require the availability of a large number of control samples that have been sampled on the same array and platform. Oxford have now developed GenoSNP, an algorithm which is entirely independent of such control samples, enabling the study of individual samples.

Existing methods

Existing genotype calling methods typically assume that the user has generated data for a large number (100-1000s) of samples, or that a reference panel of data is available. Genotype calling then proceeds by examining data at each genetic location across a number of samples. These approaches are commonly known as “population” methods due to the requirement for a population of samples for genotyping to proceed.

Our approach

Our genotype calling approach, GenoSNP, differs from this standard paradigm by working on one sample at a time. Originally designed for the Illumina Infinium SNP genotyping arrays, GenoSNP takes advantage of microarray technologies where the probe-specific variation is small, relative to the overall signal separation between genotype classes. GenoSNP is able to achieve genotyping accuracies of greater than 99% when tested on the Illumina SNP genotyping platform. It is also immune to many potential biases that are commonly observed in genome-wide association studies and introduced by factors such as DNA batch effects and laboratory or machine-specific calibration effects.

Rare variants

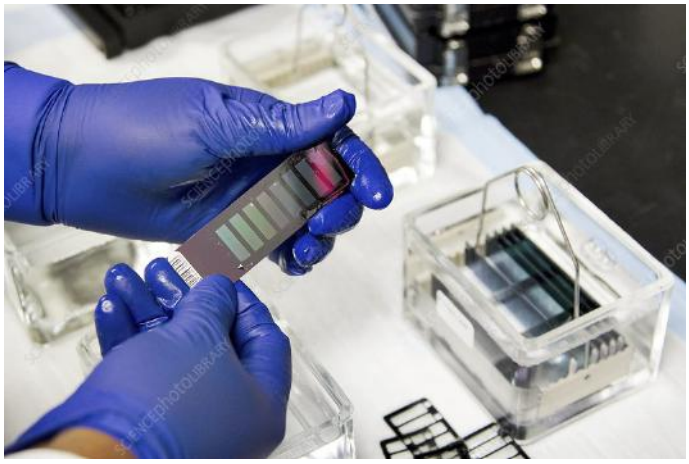
Investigations of rare variants are a further important part of modern genome-wide association studies and accurate genotype calling of these variants is crucial. GenoSNP is highly suited for calling rare variants with high

accuracy by using the information from other probes on the same array as a reference. In contrast, an equivalent population-based genotype calling approach would typically require 10,000s of samples for correct functionality.

Custom arrays

GenoSNP per-sample functionally is also beneficial for users of customisable genotyping arrays where suitable reference panels may not exist, or may have to be produced at considerable additional cost to the user.

This work has been published in Bioinformatics.



For further information please contact:
Dr Richard Auburn
Richard.Auburn@innovation.ox.ac.uk
+44 (0)1865 280956
www.innovation.ox.ac.uk
Project number: 7376

Technology Transfer from the University of Oxford

Stampy algorithm software

Oxford academics have identified a statistical algorithm for sensitive and fast mapping of Illumina sequence reads.

Existing read mapping software

High-volume sequencing of DNA and RNA is now within reach of any research lab and is quickly becoming established as a key research tool. In many workflows, each of the short sequences (reads) resulting from a sequencing run are first mapped (aligned) to a reference sequence, to infer the genomic location that the read derived from; a challenging task because of the high data volumes and often large genomes. Existing read mapping software either excels in speed (e.g. BWA2, Bowtie3, Eland4) or sensitivity (e.g. Novoalign5), but not in both. In addition, performance often deteriorates in the presence of sequence variation, particularly for short insertions and deletions (indels).

Speed and sensitivity of new software

Oxford researchers have developed a read mapper, Stampy, which uses a hybrid mapping algorithm and a detailed statistical model to achieve both speed and sensitivity, particularly when reads include sequence variation. This results in a higher useable sequence yield and improved accuracy compared to existing software. With ever increasing throughput of sequencing machines, time and memory efficient algorithms need no justification. However, sequence error rates are low, so why is sensitivity important? One answer is that reduced sensitivity in the presence of variation leads to unwanted mapping biases, particularly for reads from regions of higher divergence and for reads containing indels. Similarly, improved sensitivity may enable analyses that are otherwise impossible. For example, to analyse samples that are divergent from available reference genomes, or to help identify unknown splice donor and acceptor sites in mRNA-seq experiments.

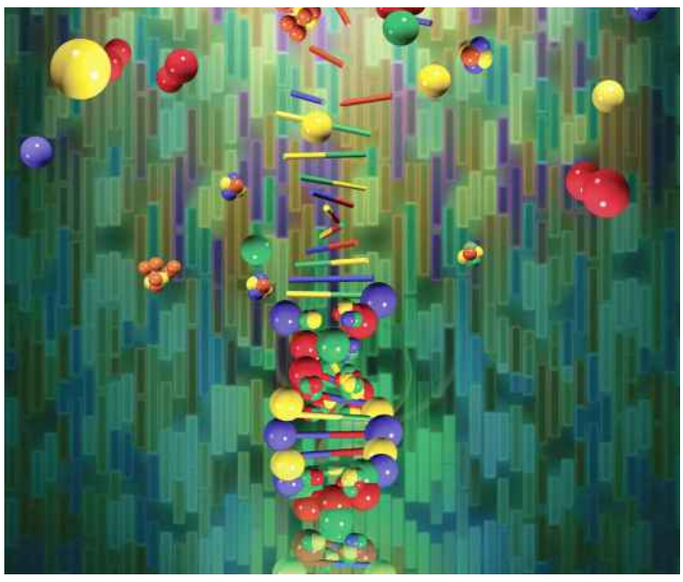
Finally, in any experiment a fraction of reads will exhibit elevated error rates; being able to reliably include data from these reads improves the power of downstream analyses and reduces the total cost of sequencing.

Hashing

To achieve good sensitivity, Stampy also uses a hash table, representing the location of selected 15-mers in the reference genome. The hash table uses a novel data structure, which results in improved search times compared to standard implementations and efficient use of the available memory.

Patent Protection

A patent application covering this method has been filed. Oxford University Innovation would like to talk to companies wishing to licence this technology.



For further information please contact:
Dr Richard Auburn
richard.auburn@innovation.ox.ac.uk
+44 (0)1865 280956
www.innovation.ox.ac.uk
Project number: 7484

Technology Transfer from the University of Oxford

Chiamante: software genotype caller

A statistical method to call genotypes from data collected on individuals using sequencing technology and microarray genotyping technology, representing the first method that uses both sets of data at once to improve performance.

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.

Genetic studies

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 phenotypes. 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, makes 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.

Chiamante model

Chiamante uses a statistical model that combines both the specified 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 that draws on prior information to fit the model to the data. This means the method can be applied to real datasets very quickly.

Chiamante features

- 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

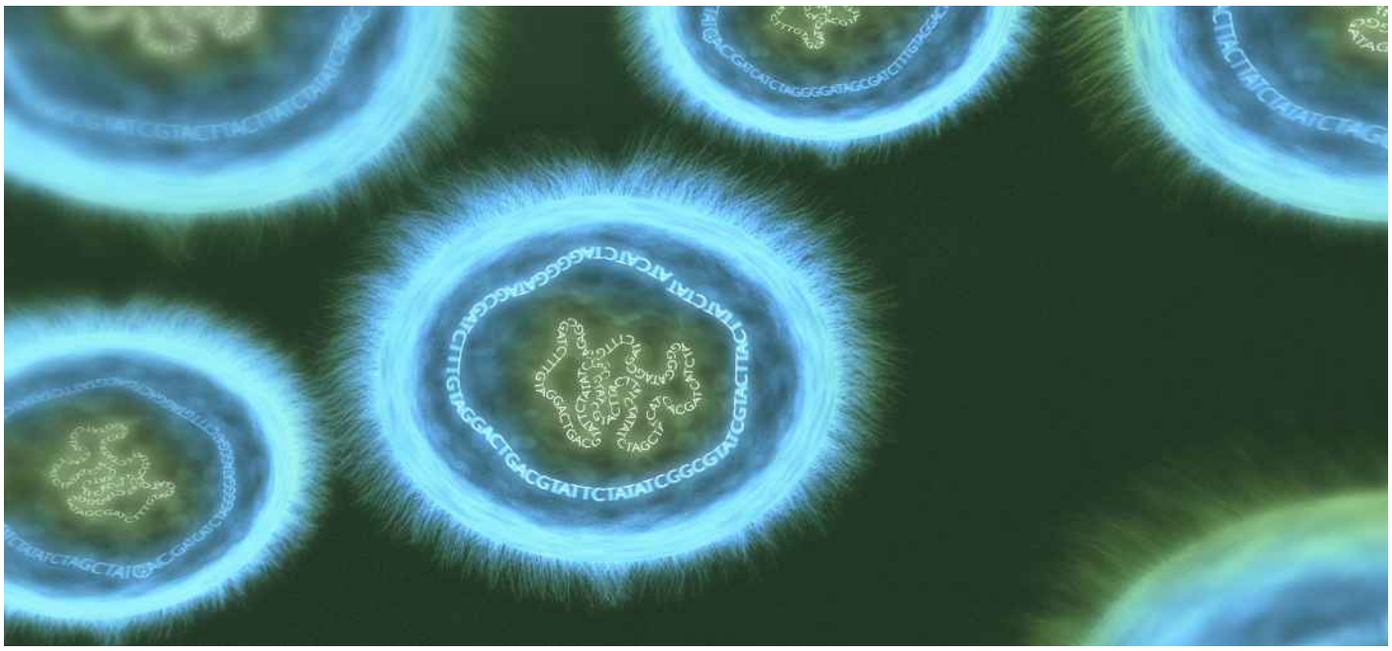
Oxford University Innovation welcomes interest from companies interested in licensing the technology.

For further information please contact:
Dr Richard Auburn
richard.auburn@innovation.ox.ac.uk
+44 (0)1865 280956
www.innovation.ox.ac.uk
Project number: 9513

Technology Transfer from the University of Oxford

PubMLST molecular typing databases

Databases for hosting nomenclatures linked to whole genome sequences for molecular characterisation of bacteria.



Sequencing the bacterial genome

Researchers at the University of Oxford have developed databases for hosting nomenclatures linked to whole genome sequences for molecular characterisation of bacteria.

The PubMLST website **(https://pubmlst.org/)** hosts curated molecular typing data for over a hundred microorganisms, providing sequence and allelic profile definitions for multi-locus sequence typing (MLST) and single-gene methods. In recent years, these have expanded to cover the whole genome with schemes such as core genome MLST (cgMLST) cataloguing the allelic diversity found in hundreds to thousands of genes. These methods provide a common nomenclature for high resolution strain identification and comparison.

The underlying genomics platform, BIGSdb, links molecular typing information to isolate provenance, phenotype, and increasingly genome assemblies, providing a rich resource for outbreak investigation and research in to population structure, gene association, global epidemiology and vaccine coverage.

Scaling up with population genomics

Databases include those for *Neisseria* spp., *Campylobacter* spp., *Staphylococcus aureus* and *Streptococcus pneumoniae*, which between them contain over 61,000 genomes, linked to typing nomenclatures, structured catalogues of gene variants and provenance information.

Data are made available on an open access basis through the PubMLST website and its application programming interface. For private, commercial use Oxford University Innovation offers mirror-site licences to selective databases or on a fully-flexible basis. This facilitates local linking and integration of private data to the large amount of available genome data and authoritative nomenclature schemes.

For further information please contact:
Dr Matt Carpenter
matthew.carpenter@innovation.ox.ac.uk
+44 (0)1865 280970
www.innovation.ox.ac.uk
Project number: 10531, 15179

Technology Transfer from the University of Oxford

IMPUTE 4

Available to license: Fast, memory efficient genotype imputation software

Oxford researchers have developed a software package for statistical analysis of genome-wide data using novel algorithms

Genome-Wide Association (GWA)

GWA studies involve analysing a genome-wide set of genetic variants to probe the relationship between variants and phenotypes. In general, the variants examined are Single Nucleotide Polymorphisms (SNPs) and the traits are major human diseases. GWA has proven to be a powerful tool in identifying the complex genetic linkages that underpin some of the most common, yet complex, human diseases and represents a significant improvement over previous methods.

Imputing variants

At present, GWA studies using commercially available genotyping chips assay a huge number (> 100,000) of markers across the genome, but this represents a small percentage of the overall number of known SNPs. It is therefore unlikely that the true causal variant would be included on the chip. Geneticists have proposed that in order to increase the amount of information gained from a GWA study, and to account for these unidentified variants, the data obtained must be subject to imputation to identify the untyped disease variants.

Evolutionary genetics analysis software

IMPUTE 4 is a software program for imputation/ estimation 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 is very popular in genetics studies of human disease and is being used to enable researchers to find new disease genes and share data.

The software allows more precise and efficient prediction than other algorithms available.

The main benefits of IMPUTE 4 include:

- Best-in-class performance
- Accounts for combinations of different SNP sets (including HapMap)
- Can be used to validate and correct data at genotyped markers
- Fast and flexible modelling strategy – accurate at common and rare SNPs

Oxford Genome-Wide Analysis Software Suite (OGWASS)

IMPUTE 4 is part of the Oxford Genome-Wide Analysis Software Suite (OGWASS) for statistical analysis of genetic information. Oxford University Innovation is seeking licensees who may wish to obtain a commercial licence to IMPUTE 4 or indeed the entire OGWASS family.

For further information please contact:
Dr Richard Auburn
richard.auburn@innovation.ox.ac.uk
+44 (0)1865 280956
www.innovation.ox.ac.uk
Project number: 14128

Technology Transfer from the University of Oxford

Gap-Seq: single molecule sequencing for single-molecule phenotyping

Researchers at the University of Oxford have developed a single-molecule sequencing method capable of connecting the functionality (reactions or interactions) of a single nucleic acid molecule with its sequence.

DNA sequencing is a key method that has had a huge impact on diagnostics, genomics and functional analysis. Although many single-molecule sequencing methods exist, there is currently no proficient way to connect the functional properties of a single DNA molecule with its sequence.

Single-molecule sequencing

Within the last decade, single-molecule sequencing has been utilised in the commercial long-read sequencing market. However, the methods currently used by these companies require specialist equipment and cannot directly link single-molecule phenotype with a DNA sequence. Providing such a link between a single molecule phenotype and its structure would support screening for biomolecules.

There is, therefore, a need for an alternative method that can fulfil this need whilst making use of standard laboratory equipment.

Gap-Seq- a novel sequencing solution

Researchers at the University of Oxford have developed a single-molecule method, called Gap-Seq, that connects the functionality (e.g., chemical reactions and molecular interactions) of large libraries of single nucleic acid molecules (or tagged peptides) with their sequence. This method allows biomolecules of interest (such as aptamers and DNA-binding sites) to be screened rapidly and quantitatively for functionality against specific molecular targets using standard laboratory equipment.

Commercialisation

Oxford University Innovation has applied for a patent for this technology and would like to hear from any interested parties who may wish to commercialise this technology.

For further information please contact:
Dr Richard Auburn
richard.auburn@innovation.ox.ac.uk
+44 (0)1865 280956
www.innovation.ox.ac.uk
Project number: 14526

Technology Transfer from the University of Oxford

Sparse decomposition of arrays (SDA)

Oxford researchers have developed software that decomposes 3D arrays (or tensor) of gene expression measurements to identify gene networks that are associated with genetic variation.

Genetic variability across individuals is responsible, to a certain extent, for the differences in physiological traits of an individual, including their susceptibility to diseases and response to drug treatments.

Due to its clinical relevance, studies focused on discovering components of genome that contribute to genetic variation have been widely conducted.

Gene expression traits

Expression quantitative trait loci (eQTLs) are loci that partly give rise to the variation in gene expression. eQTLs can operate proximally (cis-) or distantly (trans-) on a gene. So far, cis-eQTLs are easier to identify than trans-eQTLs. This is due to potential regulatory effects from the entire genome - as opposed to in the vicinity of a gene - is statistically and computationally difficult.

Oxford researchers have developed software that decomposes the tensor of gene expression datasets across multiple tissues and individuals in order to identify trans-eQTLs and gene networks that can lead to genetic variation based on a Bayesian method. The software confers the following advantages:

- Based on a novel and efficient algorithm
- Uses a flexible sparse assumption that can help uncover true, sparse underlying effects
- Complements current eQTL analysis pipelines that focus mainly on identifying cis-eQTLs in a single tissue
- Shown to work on real datasets (RNA sequencing data from 854 individuals from the TwinsUK cohort)

The work was published in *Nature Genetics* and the software is available online for academic usage.

Commercialisation

Oxford University Innovation is interested in hearing from organisations that would like to license this software commercially to support their research and development.

For further information please contact:
Dr Richard Auburn
richard.auburn@innovation.ox.ac.uk
+44 (0)1865 280956
www.innovation.ox.ac.uk
Project number: 14872

Technology Transfer from the University of Oxford

RELATE: estimating genome wide genealogies for thousands of whole-genome sequences

Researchers have developed software that enables genome-wide genealogies in the form of trees that adapt to changes in local ancestry caused by recombination.

RELATE is new software from the University of Oxford that enables estimation of genome-wide genealogies. RELATE makes inference of genealogical histories for large sample sizes possible, previously unachievable for all but the smallest datasets. RELATE-estimated genealogies will allow for more comprehensive downstream analyses to be produced.

Genome-wide genealogies for thousands of samples

Genealogies describe how DNA samples are related through most recent common ancestors back in time. In principle, they are the best attainable record of the genetic past of a sample of DNA sequences and therefore, if known, simplify and substantially enhance any inferences we make about our shared genetic past.

RELATE makes inference of genealogical histories for large sample sizes possible, a problem that despite its importance had previously remained infeasible for all but the smallest datasets. RELATE scales to >10,000 sequences and improves on accuracy in scenarios with realistic levels of errors.

Tools for downstream analyses

RELATE comes with tools for downstream analyses of inferred genealogies to tackle a broad range of applications, including for estimating demographic history, mutation rates, and detection of positively selected mutations. Genealogy-based inferences can be more powerful or more accurate than alternative specialist methods.

Main benefits include:

- Scalable to thousands of whole-genome sequences
- Very powerful inference framework applicable to questions related to evolutionary biology, population genetics, and genetic disease.
- All inferences are derived from the same genealogies leading to better consistency across different applications
- Improved accuracy in areas of realistic errors

Commercialisation

Oxford University Innovation is actively seeking partners that may wish to licence this software. For further details, please see the research groups webpage https://myersgroup.github.io/relate/

For further information please contact:
Dr Richard Auburn
richard.auburn@innovation.ox.ac.uk
+44 (0)1865 280956
www.innovation.ox.ac.uk
Project number: 15670

Technology Transfer from the University of Oxford

IMAGING

Targeted MRI contrast agents for detection of brain tumours and inflammation

Oxford University researchers have developed a new generation of targeted MRI contrast agents that enable detection of specific disease-related molecules on blood vessels *in vivo*.

The next generation

Oxford University researchers have developed a new generation of targeted MRI contrast agents that enable detection of specific disease-related molecules on blood vessels in vivo. These multimeric, biodegradable, imaging agents for MRI can be coupled with targeting agents to find, amongst other things, lesions in the blood brain barrier. The imaging agents are comprised of novel sugar coated iron oxide particles and can be used to identify endothelial cell activation in the brain. They are sufficiently sensitive to detect tumours in less than 10 minutes of imaging and has potent MRI contrast.

These imaging agents enabled the researchers to determine the presence of pathology that cannot be visualised using conventional imaging techniques. They also offer advantages over (i) large monomeric particles that can cause microvessel blockage and (ii) small particles that are often rapidly cleared from the target site.

Early detection of brain metastasis

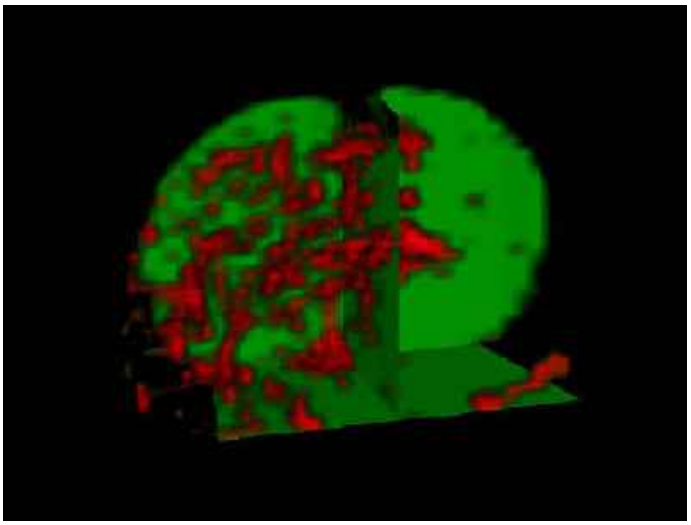
Brain metastasis is one of the greatest hurdles in cancer therapy; 20-40% of all cancer patients will suffer metastatic spread of primary cancer to the brain, and the prognosis is poor. Tumour cells use cellular adhesion molecules, normally associated with leukocyte trafficking, to metastase to non-CNS sites. Although leukocyte recruitment to the brain is atypical, exploratory research has shown the endothelial cells lining the vessels still express cellular adhesion molecules.

The researchers have developed an imaging agent using the new generation of imaging agents in conjugate with a humanised anti-VCAM antibody as a non-hazardous antibody-drug conjugate (ADC) for intravenous delivery. The imaging agents and the ADC are being supported by two MRC DPFS awards, which will take these agents through pre-clinical toxicology and a Phase I trial. The team have demonstrated that this ADC allows very early detection of brain metastasis – secondary cancer in the brain.

Patent Protection

Patent applications for the imaging agents are granted in Europe and USA, and patent applications for the antibody-drug conjugate are in national phase in Europe, Canada and USA.

Oxford University Innovation is looking to licence these agents for further development beyond Phase I.

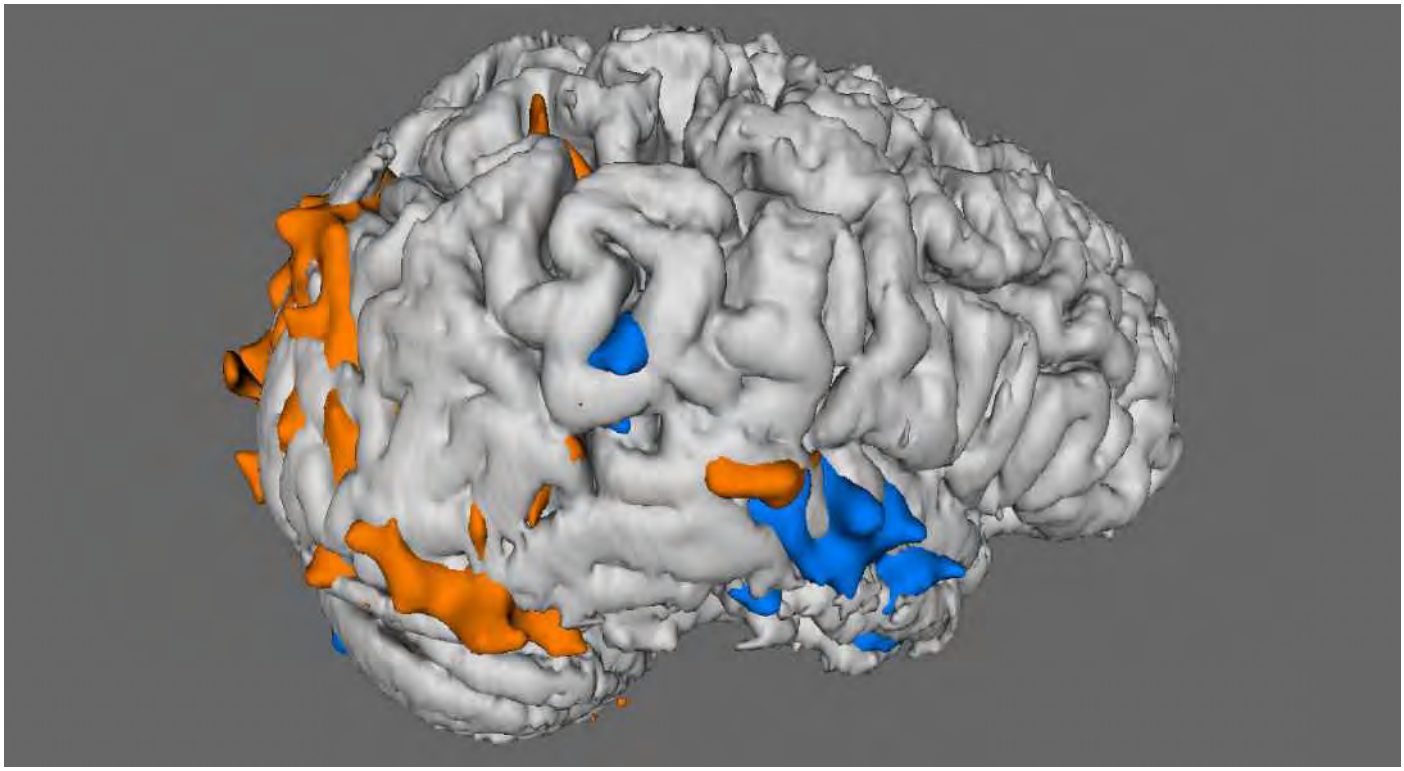


For further information please contact:
Dr Sarah Deakin
sarah.deakin@innovation.ox.ac.uk
+44 (0)1865 614410
www.innovation.ox.ac.uk
Project number: 2924, 6596

Technology Transfer from the University of Oxford

FSL brain-mapping software

Oxford researchers have developed advanced software for analysing images of the brain.



Functional MRI

- FEAT is a software tool for high quality model-based FMRI data analysis, with an easy-to-use graphical user interface (GUI). FEAT automates as many of the analysis decisions as possible, and allows easy (though still robust, efficient and valid) analysis of simple experiments whilst giving enough flexibility to also allow sophisticated analysis of the most complex experiments.

Structural MRI

- BET (Brain Extraction Tool) deletes non brain tissue from an image of the whole head. Can also estimate inner and outer skull surfaces.
- FLIRT (FMRIB's Linear Image Registration Tool) and FNIRT (FMRIB's Non-linear Image Registration Tool) is a fully automated robust and accurate tool for linear and non-linear intra- and inter-modal brain image registration.
- FAST (FMRIB's Automated Segmentation Tool) segments a 3D image of the brain into different tissue types (Grey Matter, White Matter, CSF, etc.), whilst also correcting for spatial intensity variations (also known as bias field or RF inhomogeneities).

Diffusion MRI

- Eddy- a tool for correcting eddy currents and movements in diffusion data. Simultaneously models the effect of diffusion eddy currents and movements on the image.
- Topup- A tool for estimating and correcting susceptibility induced distortions
- Eddyqc- The QC metrics are derived through different stages of FSL's pre-processing tools (TOPUP and EDDY). Using this framework it is possible to distinguish between good and bad quality datasets and, importantly, identify subsets of the data that may need careful visual inspection

GLM/Stats

- FSLeyes (pronounced fossilise) is the new FSL image viewer, released with FSL 5.0.10
- BayCEST- Bayesian analysis for chemical exchange saturation transfer z-spectra. BayCEST exploits a Bayesian non-linear fitting algorithm, providing a (relatively) fast means to quantify CEST data.

The full list of available technologies can be accessed here: **https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/**

For further information please contact:
fsl@innovation.ox.ac.uk
Project number: 9564

Technology Transfer from the University of Oxford

Improved quantification of arterial blood-flow

Available to license: MRI methods enabling the quantification of blood-flow through small vessels without the need for contrast agents.

Angiographic methods which generate images of blood vessels and provide information on vessel morphology and function.

Imaging blood flow

Many angiographic methods only provide qualitative information on blood flow, making objective comparisons between vessels and different patients difficult. In addition, these methods have a number of drawbacks such as the requirement for an invasive procedure, the use of ionizing radiation, and the administration of a contrast agent.

Quantification of blood flow rates from dynamic images have been demonstrated, but typically can only be applied to the larger arteries. Oxford scientists have improved existing quantification by allowing measurements to be made in smaller arteries and arterial segments in a robust manner.

Oxford Invention

The Oxford invention incorporates region-based angiographic methods for the quantification of blood flow rates from dynamic angiography data.

The methods offer several improvements over existing techniques:

- Ability to provide data on all vessels in a group together or to provide vessel-selective information
- Less computation time required, enabling improved patient throughput
- Easier to implement on MRI apparatus for use by clinicians
- Blood flow can be estimated on a finer scale allowing detailed quantification of blood-flow along an entire arterial vascular tree in the brain of a subject.

Applications

Improved quantification of blood flow could assist in the management of:

- Atherosclerosis – imaging of narrowing in small vessels
- Stroke – quantification and assessment of disease state
- Cancer – improved assessment of tumour perfusion to improve treatment planning

Patent protection

A patent protecting the methods developed has been filed and software for conducting this work has been coded. Methods have been demonstrated in model flow phantoms and in healthy human volunteers.

For further information please contact:
Dr Chandra Ramanujan
chandra.ramanujan@innovation.ox.ac.uk
+44 (0)1865 614434
www.isis-innovation.com
Project number: 11771

Technology Transfer from the University of Oxford

Smart Align

Available to license: Quicker and more robust image registration software for (S)TEM images

Researchers at the University of Oxford have developed a software tool for the precise compensation of image offsets and scanning distortions.

Motion sickness

The 'Smart Align' software delivers superior image processing, enhancement and quantification in dark- and bright-field scanning transmission electron microscopy (STEM), conventional TEM registration and scanning tunnelling microscopy (STM). It requires very little human intervention. The software uses a weighted learning filter to guide the rigid-registration stage. Built-in knowledge describes the scanning nature of the serial acquisition and reduces artefact introduction. A mature demo version is available for assessment.

Automated registration

STEM data is recorded serially and acquisition times can be tens of seconds long. At these acquisition times stage/sample drift and low frequency distortions can perturb the image locally. Often the first step in any quantitative interpretation of STEM data is to correct for these drifts and distortions using so-called rigid and non-rigid registrations respectively. The Oxford invention is an improved automated method of performing this registration step, customised for the challenges unique to STEM data. The improvements developed address the challenges of registering images which contain a large proportion of crystalline material and/or local features of interest such as dislocations or edges.

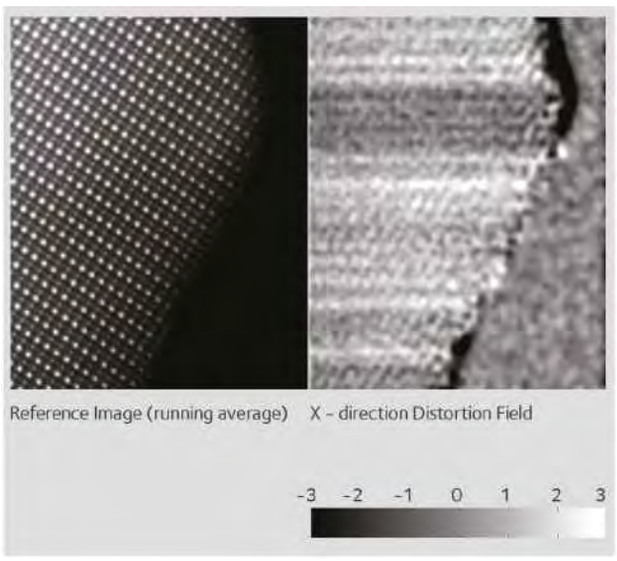
Demonstration available

'Smart Align' uses a new learning mode for rigid registration of images dominated by periodic (crystallographic) features and a 'row-locking' mode for artefact free non-rigid registration of serially acquired data. It includes novel options designed with EM image processing in mind. The software has been rigorously tested and developed to a mature demonstration version.

Superior results

The Oxford invention enables processing and enhancement of microscopy images, delivering superior results and quantification compared with current methods. Through built-in knowledge and a weighted learning filter this is achieved with very little human input. The technology has been specifically developed for the analysis of dark-field scanning transmission electron microscopy images, but can be used with bright-field data, conventional TEM and in other image analysis applications.

Oxford University Innovation welcomes contact from parties interested in licensing this opportunity.



For further information please contact:
Dr Chandra Ramanujan
chandra.ramanujan@innovation.ox.ac.uk
+44 (0)1865 614434
www.innovation.ox.ac.uk
Project number: 11341

Technology Transfer from the University of Oxford

Off-resonance correction method for magnetic resonance perfusion imaging and angiography

Available to license: A novel method to correct for the effects of off-resonance (magnetic field inhomogeneity) with no loss of signal-to-noise ratio and without additional scan time.

Oxford researchers have developed a method for correcting off-resonance effects present in Arterial Spin Labelling (ASL) Magnetic Resonance Imaging (MRI).

Invasive perfusion imaging and angiography – a less than ideal gold standard

Perfusion imaging provides qualitative and quantitative information on blood flow whilst angiographic methods generate images of blood vessels. Both perfusion imaging and angiography are of great importance in the assessment of vascular diseases by providing information on the function and health of tissue and blood vessels in the brain. This knowledge aids clinicians with diagnosis, prognosis and treatment planning in these patients.

Most MRI methods for acquiring perfusion information involve administering a gadolinium based contrast agent, which have been linked to nephrogenic systemic fibrosis in patients with kidney dysfunction. Additionally, X-ray digital subtraction angiography is the gold standard for acquiring vessel-specific angiographic information; however, this requires both the insertion of a catheter to administer a contrast agent and the use of ionizing radiation. Associated risks to the patient include strokes or transient ischemic attacks.

Magnetic resonance imaging – reduced risk for patients

MRI techniques, such as Pseudo-Continuous Arterial Spin Labelling (PCASL) and vessel-encoded PCASL (VEPCASL) are powerful, non-invasive methods available to clinicians to acquire perfusion data and angiograms in the brain without the use of contrast agents. VEPCASL allows acquisition of vascular territory maps and vessel-selective angiograms.

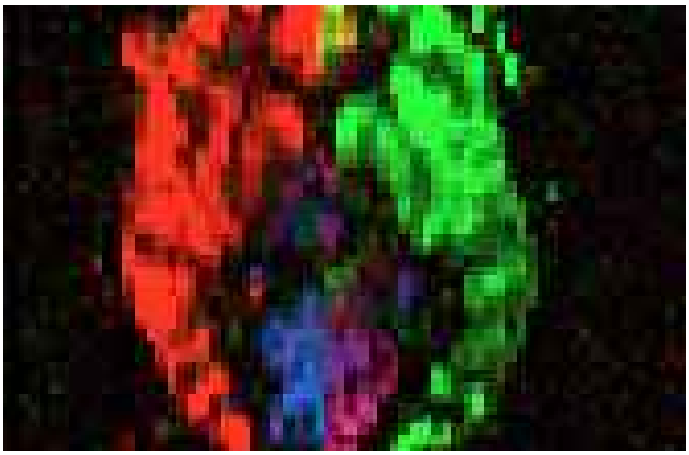
VEPCASL has an advantage over other vessel-selective methods in that it allows vessels to be labelled that are closer together. However, off-resonance (magnetic field inhomogeneity) in the labelling plane can occur in either case, leading to a reduction in labelling efficiency and thus image quality.

Current methods for off-resonance correction are limited, with some requiring additional PCASL scans and/or manual intervention to calculate the corrections needed.

Key features and commercialisation

- Simple to implement
- Based on generating an Optimised Encoding Scheme (OES)
- Applicable to any pattern of off-resonance and any number of vessels
- Works with both conventional PCASL and VEPCASL

A provisional patent application has been filed in the USA. Oxford University Innovation are seeking partners in the MRI software and /or hardware space to commercialise this technology.



For further information please contact:
Dr Chandra Ramanujan
chandra.ramanujan@innovation.ox.ac.uk
+44 (0)1865 614434
www.innovation.ox.ac.uk
Project number: 12191

Technology Transfer from the University of Oxford

Post-processing deblurring for medical imaging

Available to license: Providing a post-processing method for the de-blurring based on the data alone

University of Oxford scientists have created a post-processing method for reducing the effects of blurring introduced in MRI images when acquired using a '3D' readout

Correcting image blurring after acquisition

Blurring is often seen in a particular direction in images from certain 3D readouts. Solutions typically require the 'segmentation' of the readout, which increases the overall image acquisition time substantially.

Oxford scientists have developed methods to provide correction to the data after acquisition - it can thus be applied retrospectively where blurring has already occurred and prospectively where segmentation is not desirable, or only partial segmentation is possible

The method attempts to use the noise on the data to estimate the degree of blurring and derive a kernel that can be used to undo the blurring process. The developed method is specifically for application to MRI data taking into account the special nature of the MRI acquisition process.

Further applications

To date, the method developed has been applied to Arterial Spin Labelling (ASL) perfusion MRI, however in principle the method might be applicable to a wide range of MRI methods that rely upon '3D' readout.

Development status and commercialisation

Code which has been tested on existing human data is available to apply the deblurring techniques to 3D-images. Isis Innovation seeks parties interested in licensing this software.

For further information please contact:
Dr Chandra Ramanujan
chandra.ramanujan@innovation.ox.ac.uk
+44 (0)1865 614434
www.innovation.ox.ac.uk
Project number: 12409

Technology Transfer from the University of Oxford

High throughput image analysis platform for 3D cellular tissues

Available to license: A high throughput image analysis platform for 3D cellular tissues using optical microscopy images and new robust probabilistic segmentation methods.

High throughput analysis of highly complex 3D cellular tissues from optical microscopy images

Automated protein distribution spatial analysis within cellular tissues becomes challenging when looking at highly complex 3D tissues, due to difficulties with segmentation of low resolution optical microscopy images that contain densely packed cellular features.

Using a robust probabilistic tissue segmentation method, the proprietary University of Oxford platform SilentMark, enables high throughput analysis of complex 3D cellular tissues from noisy and difficult to segment optical microscopy images.

Protein fluorescence levels can be quantified in the different sub-cellular compartments, to facilitate the systematic analysis of protein localization under a diverse range of experimental conditions.

Tested in the analysis of 3D tissues of varying complexity

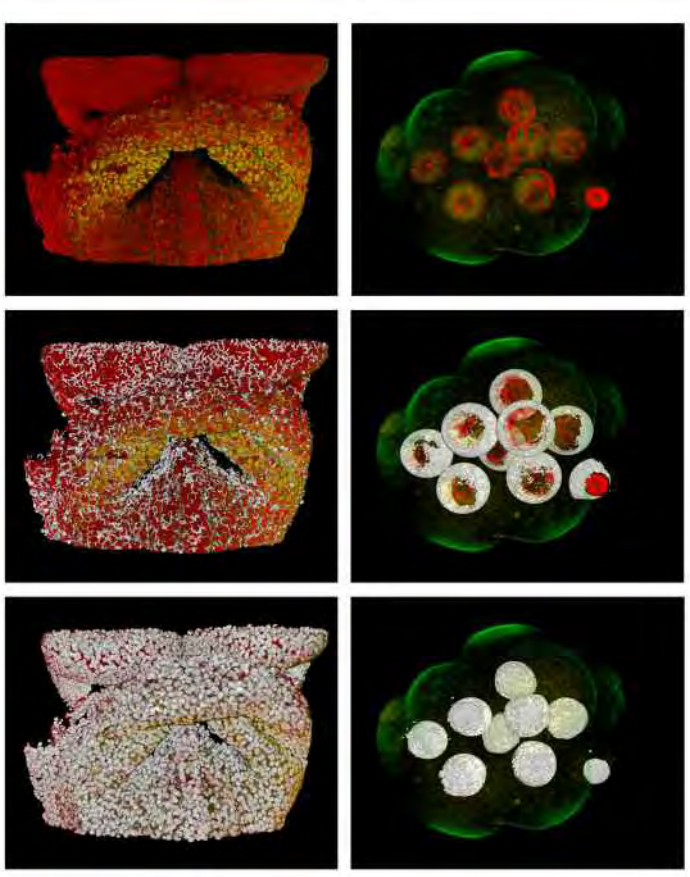
The proprietary University of Oxford platform has a graphical user interface and has been tested in the context of developing tissues where initially low cellular density geometrically simple structures transform into high cellular density geometrically complex structures.

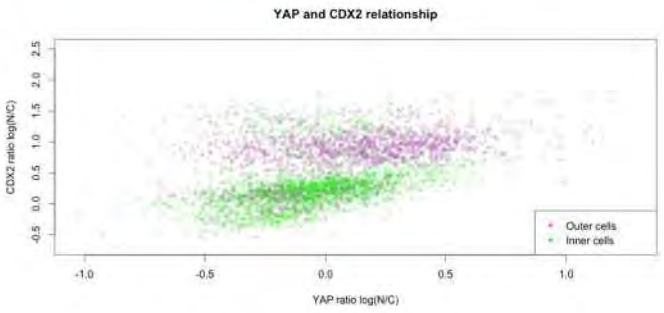
The tissues on which the software has been tested include mouse stem cell embryoid bodies and mouse cardiomyocytes during heart development, tissues comprising from 2 to an estimated 2,000 cells respectively.

Applications in tissue engineering and drug screening

The platform is the first of a kind to provide quantitative three dimensional protein information for developing tissues across multiple organisms. This is particularly relevant where quantitative statistical analysis of protein organisation and gene expression lays the foundation for high throughput cancer research, tissue engineering, and drug screening.

Oxford University Innovation would like to talk to companies or end-users wanting to license or make use of this proprietary University of Oxford software.





For further information please contact:
Dr Richard Auburn
Richard.Auburn@innovation.ox.ac.uk
+44 (0)1865 280956
www.innovation.ox.ac.uk
Project number: 13299

Technology Transfer from the University of Oxford

EM∩IM – Correlating Electron Microscopy (EM) and Ion Mobility (IM) spectra

Oxford researchers have developed EM∩IM, a piece of software capable of accurately calculating Collisional Cross Sections from Electron Microscopy (EM) density maps correlated with Ion mobility data.

Collisional Cross Sections (CCSs)

Ion mobility (IM) experiments measure the travel time of a molecule through a tube of inert gas. Collisions with the gas slow the molecule and increase the travel time. The larger the collisional cross section (CCS) of the molecule, the more collisions will occur.

However, for particularly large or flexible molecules, this “average surface” modelling technique can be inaccurate. To analyse such proteins, scientists often turn to Electron Microscopy, which can provide an electron density map with near-atomistic definition.

Following the map

Although electron density maps can provide information ranging from coarse shape to molecular structure, determination of CCSs from this data has not been possible. Researchers at the University of Oxford have developed EM∩IM, software capable of processing electron density maps to calculate collisional cross sections. This breakthrough enables rationalisation of a completely new range of protein targets.

EM∩IM

The EM∩IM software package works by modelling the electron density map, obtained from EM experiments, as a collection of tightly packed spheres (isosurface).

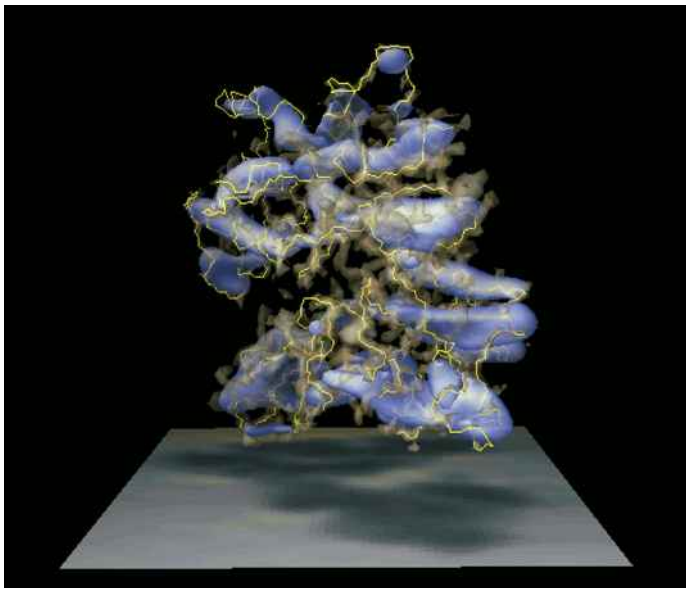
Another piece of Oxford software (IMPACT) is then used to calculate a collisional cross section from the model. This methodology produces a number of possible CCSs, but it is accurately determined by correlation to protein mass.

We believe the main benefits of this approach to be as follows:

- Calculation of CCSs from electron density maps
- Allows analysis of larger, more flexible protein targets
- Correlates IM, EM and CCS data
- Permits validation of IM-MS data where this is possible

Copyright protection

The software is currently free to download for academic users; however Oxford University Innovation Ltd. is also seeking potential commercial users.



For further information please contact:
Dr Richard Auburn
richard.auburn@innovation.ox.ac.uk
+44 (0)1865 280956
www.innovation.ox.ac.uk
Project number: 13366

Technology Transfer from the University of Oxford

Correcting imaging artefacts due to bidirectional scanning

Oxford researchers have developed a post-acquisition image processing technique that enables fast-high resolution acquisition of bidirectional scanning data.

Processing of high-speed acquired dynamic images

Laser scanning microscopy is a powerful technique used by scientists and researchers to improve their ability to view dynamic images. The faster an image can be generated, the wider the variety of biological processes that can be observed.

Particularly in dynamic samples, geometrical distortion is one of the biggest issues of bidirectional image acquisition and it is caused by the variable motion of the flatbed scanning laser.

Currently, there is a need to process images obtained by fast scanning to make accurate measurements with low error bounds.

The technology

Researchers at the University of Oxford have developed a method, based on the combination of two image processing techniques. This enables fast removal of movement artefacts and lessens the distortion caused by laser scanning. This post-acquisition image analysis technique can be applied to different scanning protocols and it enables the use of fast scanning techniques while obtaining distortion-free images.

Image-based artefact removal in microscopy

Laser movement-based distortion has been highlighted as an issue in the imaging of biological samples obtained by laser scanning microscopy. This has been established as a first potential application and the image processing technique has been validated in the analysis of dynamic biological samples.

As a result, it has been shown that the Oxford framework enables reconstruction of distortion-correct images from acquired distorted images, allowing the monitoring of complex, dynamic processes, such as tumour growth, without sacrificing spatial and temporal resolution.

Additional applications include satellite image acquisition

The method developed at the University of Oxford can also estimate displacement caused primarily by the varying speed of the laser during bidirectional data scanning and can be used to compare different acquisition systems quantitatively.

The technique can be applied to any sector requiring fast-acquisition images, including for example:

- Satellite image acquisition
- Naval positioning
- LIDAR systems

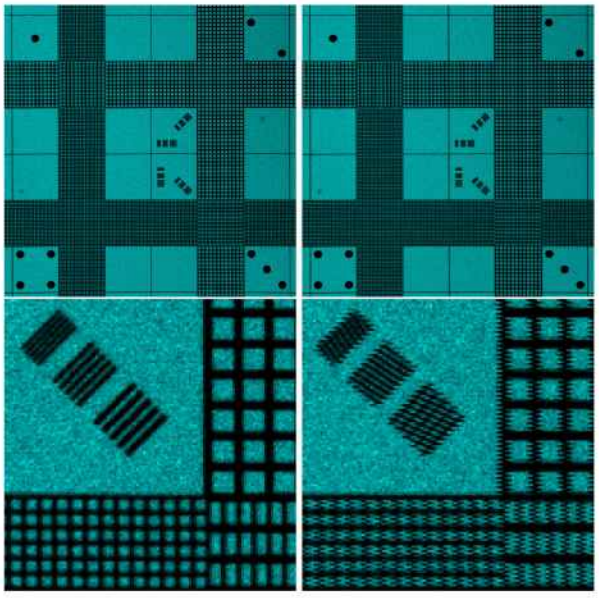


Image: (top left) Image obtained by unidirectional line acquisition, together with zoom (bottom left); (top right) image obtained for the bidirectional line acquisition together with zoom(bottom right). The image obtained by bidirectional line acquisition shows severe jaggedness artefacts for every second line occurring in the correspondence to the speed of microscope laser.

For further information please contact:
Dr Sarah Jones
sarah.jones@innovation.ox.ac.uk
+44 (0)1865 614458
www.innovation.ox.ac.uk
Project number: 14289

Technology Transfer from the University of Oxford

Graphene based sensor system compatible with MRI and CT imaging

Researchers at the University of Oxford have developed a novel graphene-based piezoelectric sensor that is compatible with both MRI and CT imaging.

Body motion monitoring in MRI and CT imaging

Magnetic resonance imaging (MRI) and computerised tomography (CT) scanners are widely used to produce high resolution images of the human and animal anatomy. Due to the high magnetic fields and X-ray radiation used in MRI and CT scanning, respectively, there are significant limitations on the materials that may be placed inside the scanner.

Stable and high-resolution MRI and CT images with minimum artefacts can only be obtained when the effects of body motion are minimised. This is achieved by monitoring both cardiac and respiratory cycles and synchronising the image acquisition with this motion. Respiratory monitoring in small animal imaging is typically achieved with a respiratory balloon, a device that measures the change of air pressure within a capsule placed in contact with the abdomen. Limitations of this method include:

- The need for careful placement and calibration of the device
- Repressurisation and calibration if the animal is transferred between systems, a major drawback when changes in posture must be minimised

An alternative technique for respiratory monitoring uses piezoelectric sensors – devices which use a piezoelectric polymer to convert deflection into an electrical signal. Metallic thin films are deposited on both sides of the polymeric component for signal collection. Both calibration and setup are simple, and the device is insensitive to air pressure, however these sensors have not found widespread use as the metallic films have detrimental consequences for the images produced by both scanning techniques.

Graphene-based piezoelectric sensors

Researchers at Oxford have tackled this limitation and developed a **piezoelectric sensor compatible with MRI and CT imaging.**

Metal has been replaced by thin layers of graphene, providing the following advantages:

- Radiolucency
- Minimal distortion to magnetic fields
- High in-plane conductivity
- High mechanical flexure and strain resilience
- Transparency

In addition, graphene technology has the potential to be used in a wide range of electronic components for MRI and CT imaging systems, thus creating many opportunities **for graphene-based systems in MRI and CT sensing and diagnostics.**

Commercialisation

Oxford University Innovation Ltd. has filed a priority patent application on the technology and welcomes discussions with companies interested in licensing it for commercial development.

For further information please contact:
technology@innovation.ox.ac.uk
+44 (0)1865 280832
www.innovation.ox.ac.uk
Project number: 15727

Technology Transfer from the University of Oxford

A new method for automated 3D blood vessel reconstruction

Oxford researchers have developed a new algorithm for robust and accurate reconstruction of 3D vessel trees from multiple retrospective angiographic projections.

Angiography and its limitations

X-ray angiography is the most commonly used imaging modality for the visualisation of coronary blood vessels. Its advantages include simplicity, high spatial and temporal resolution of lumen structure, and most importantly, its utility to guide coronary interventions in real time. However, despite these clinical advantages, X-ray angiograms pose several challenges, especially in relation to visualising lesions adequately and judging lesion severity.

The 2D projections of the 3D vascular structure in different image planes produce vessel overlap and foreshortening and hence, make it difficult for the cardiologists to interpret the geometry of the object. This leads to high inter- and intra-observer variability in understanding the global anatomical structure and, in turn, affects the accuracy of the estimation of lesion severity and stent size.

The interpretation gets further complicated due to the existence of several motion artifacts, including cardiac, respiratory, and patient or device movement that occur during the acquisition. In addition, potential adverse effects of higher amount of radiographic contrast agent and exposure to X-rays limit the number of image acquisitions.

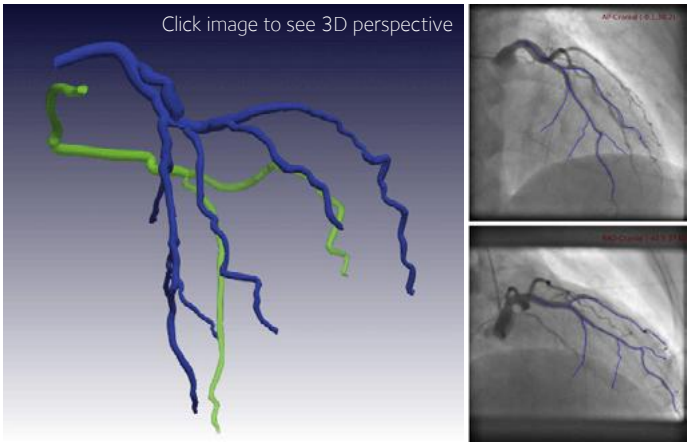
The Oxford solution

Several methods have been developed to extract 3D images from the 2D angiograms, but they have several limitations. While some of them require specific acquisition protocols to be applied when registering the images (breath-hold, no patient movement, etc.), others are only applicable on biplane angiograms and do not involve any motion correction or geometry calibration step.

Oxford researchers have developed a new algorithm using a novel point-cloud approach for robust and accurate reconstruction of 3D blood vessel trees, while removing all motion artifacts. This novel method can be applied to retrospective images and is able to reconstruct specific vascular structures.

Potential applications

This new algorithm has been developed and validated for application on coronary angiograms, but it can be applied to reconstruct other 3D structures, including brain vessels. Additionally, this novel method could enable the amalgamation of angiography and MRI assessment and therefore, would improve the current diagnostics, since at present there is no way to compare severity of the blood obstruction (angiography) and muscle injury (MRI) in the clinic.



Left: Reconstructed 3D coronary arterial tree from 2D angiographic projections. **Right:** 2D angiographic projections of left coronary artery, along with the reprojection of reconstructed 3D centerline of left anterior descending artery (in blue).

For further information please contact:
Dr Chandra.Ramanujan
Chandra.Ramanujan@innovation.ox.ac.uk
+44 (0)1865 614434
www.innovation.ox.ac.uk
Project number: 16185

Technology Transfer from the University of Oxford

METABOLIC DISEASES

UKPDS Cardiovascular Risk Engine - Version 3

Available to license: Type 2 diabetes-specific cardiovascular risk calculator based on 53,000 UKPDS patient-years of data that can be used to educate and inform across the diabetes care landscape.

The UKPDS Risk Engine, developed by researchers at the University of Oxford, is a type 2 diabetes-specific risk calculator that will support a wide range of health care professionals in educating and managing the care of patients with type 2 diabetes

The risk engine

Cardiovascular disease is a significant complication in type 2 diabetes and is responsible for 62% of the 2.2 million disease-related deaths which occur each year. Therefore, it is critical that we are able to understand the relationship between present day risk factors and future cardiovascular disease outcomes, both in terms of patient education and healthcare planning.
To address this issue, a team led by Prof Rury Holman at the Oxford Centre for Diabetes, Endocrinology and Metabolism have developed a type 2 diabetes-specific risk calculator. Based on 53,000 patient-years of data from the UK Prospective Diabetes Study, the software provides risk estimates and 95% confidence intervals for individual patients with type 2 diabetes to develop cardiovascular disease. The risk of developing non-fatal or fatal coronary heart disease or stroke can be measured for any given disease duration based on a variety of factors including:

- Age
- Sex
- Ethnicity
- Smoking status
- Presence or absence of atrial fibrillation and levels of HbA1c
- Systolic blood pressure
- Total cholesterol
- HDL cholesterol

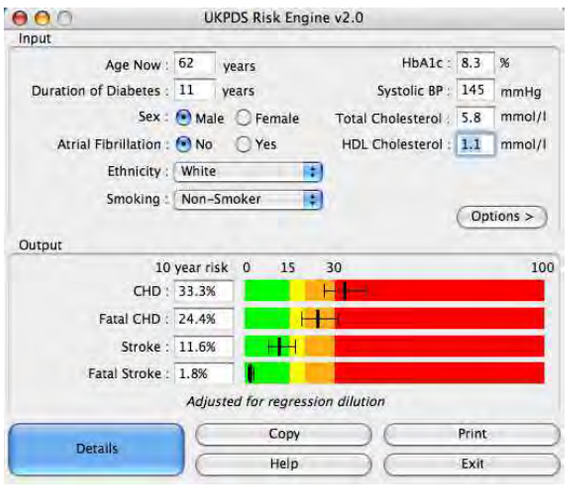
Applications

The UKPDS Risk Engine is of value to healthcare providers in educating and managing the care of patients with type 2 diabetes, as well as to the pharmaceutical industry in educating physicians, payers and prescribers regarding the benefits of positive lifestyle changes and optimal blood glucose control. The UKPDS Risk Engine will furthermore be of value to insurance companies, healthcare service planners and providers.

Software status

The software is currently available for both commercial and academic use in the form of a standalone application for Microsoft Windows, Apple Mac, Palm and Pocket PC platforms. An Excel worksheet version is available on Microsoft and Apple Mac. The software is also available for incorporation in other software packages as an ActiveX module or as a Apple Mac shared library. For further information, and to review academic use licence terms, please visit:

www.dtu.ox.ac.uk/riskengine/



For further information please contact:
Dr James Groves
james.groves@innovation.ox.ac.uk
+44 (0)1865 614425
www.innovation.ox.ac.uk
Project number: 8949

Technology Transfer from the University of Oxford

Glycaemic variability calculator

Available to license: A tool for diabetes researchers

EasyGV is an Excel spreadsheet that calculates glycaemic variability of blood glucose profiles. It puts 10 different methods into one convenient, easy to use tool.

Glycaemic variability

Glycaemic variability is the fluctuation of glucose levels in the human body. In diabetic patients, the level of fluctuation may have an impact on disease complications, and is an area of ongoing clinical research.

The Oxford technology

EasyGV is a macro-enabled Excel workbook and has been tested with Microsoft Excel versions 2007, 2010 and 2011. EasyGV allows you to calculate 10 different measures of glycaemic variability (GV) from continuous glucose monitoring data using a simple interface.

The GV Methods available are:

- M-Value
- Mean Aplitude of Glycaemic Excursions
- Lability Index
- Average Daily Risk Range
- J-Index
- Low Blood Glucose Index & High Blood Glucose Index
- Continuous overall net glycemic action
- Mean of Daily Differences
- Glycaemic Risk Assessment Diabetes Equation
- Mean Average Glucose

Supporting information

An academic paper is available, with more information:

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3160264/

Technology status

Oxford University Innovation welcomes interest from companies interested in licensing the technology.

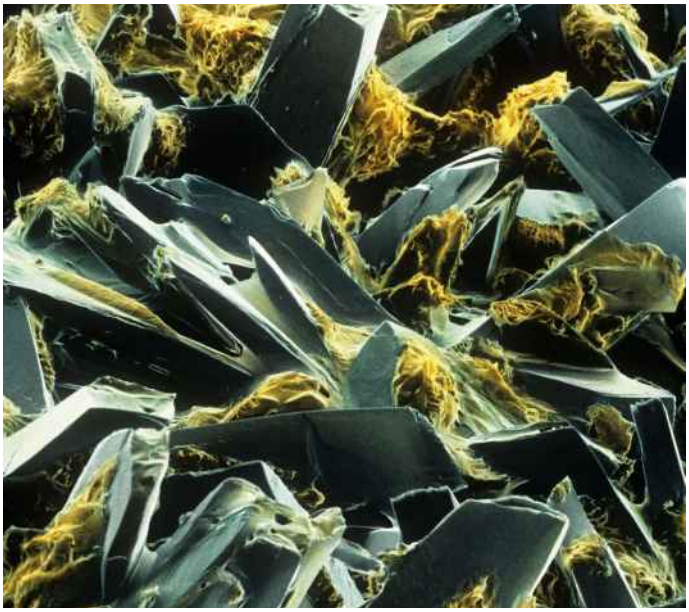


Image: False colour SEM of glucose crystals

For further information please contact:
Dr James Groves
james.groves@innovation.ox.ac.uk
+44 (0)1865 614425
www.innovation.ox.ac.uk
Project number: 9797

Technology Transfer from the University of Oxford

Version 2 of the UKPDS OM - A type 2 diabetes outcomes model

Available to license: Substantially enhanced Type 2 diabetes simulation for use by epidemiologists, health economists and trialists for the evaluation and cost-effective analyses of strategies for diabetes management.

Oxford researchers have made a significant update to their computerised simulation tool designed to estimate life expectancy, quality adjusted life expectancy and the cumulative costs of complications in people with T2D.

Why model type 2 diabetes?

Type 2 diabetes (T2D) is estimated to affect 9% of adults and cost $465 billion each year. With these figures predicted to rise by 50% over the next 20 years, the provision of T2D care represents a major economic challenge for the healthcare industry. Given the extended timeframe and multiple outcomes associated with T2D, stakeholders frequently make use of health economic models to support evidence-based decision making related to funding allocation.

The new and improved UKPDS OM2

The UKPDS OM is a computerised simulation tool designed to estimate Life Expectancy, Quality Adjusted Life Expectancy and the cumulative costs of complications in people with T2D. The newly released Version 2 represents a significant advance, making use of data from all 5,102 UKPDS patients who entered the trial and 4,031 survivors who entered the 10 year post-trial monitoring period. This equates to 89,760 patient-years of data and provides double the number of events compared with Version 1.

Key new features

- Additional risk factors: Albuminuria, Heart rate, WBC, Haemoglobin and eGFR
- Additional clinical events: Diabetic ulcer and CVD death
- New equations predict second events for MI, Stroke and amputation
- Supports up to 3 groups of patients in a single run and provides a summary for each group as well as group differences
- Cost / utility values can now be varied by age and sex
- Addition of therapy costs and pre and post complication costs
- Calculation of Monte Carlo Error allows simulation fine-tuning
- Can queue workbooks to run multiple unattended simulations, while parallel processing can take full advantage of up to 10 computer cores.

Tried and trusted

The UKPDS OM has been adopted by a range of companies, government bodies and Universities.

Key Adopters:

- 4 out of the 5 largest diabetes drug manufacturers
- The UK National Institute of Health and Care Excellence (NICE)
- A wide range of healthcare consultancies

Transparency and Flexibility

The UKPDS OM2 takes a completely transparent approach in which we fully report its development, including the equations that determine all outcomes, and the algorithm used to bring the elements of the model together.

The model uses Microsoft Excel workbooks and can operate on Windows and Mac OS X platforms.

For further information please contact:
Dr James Groves
james.groves@innovation.ox.ac.uk
+44 (0)1865 614425
www.innovation.ox.ac.uk
Project number: 9965

Technology Transfer from the University of Oxford

iHOMA2 - Software for diabetes trials and research

Available to license: An interactive, 23-variable, HOmeostatic Model of Assessment software package for diabetes trials and research.

iHOMA2 allows users to examine and modify the mathematical functions that describe the glucose and hormonal levels of a patient's organs and tissues.

Diabetes

Type 2 diabetes is caused by a combination of progressive β-cell dysfunction, relative insulin deficiency, and variable degrees of insulin resistance that lead to dysregulation of glucose homeostasis. Understanding the biochemistry, phenotypic details, and genetic mechanisms contributing to this can yield important information on pathophysiology. The progressive nature of the disease, as well as measuring the rate of deterioration, has presented an ongoing challenge to clinicians and scientists alike.

Oxford technology

iHOMA2 is an extension of the HOMA and HOMA2 mathematical models which were developed in Oxford from the mid-1980's. iHOMA2 is a software package which enables a user to examine and assess insulin resistance and β-cell functions in the fasting state. The input into the software package can either be fasting insulin and glucose values or percent β-cell function and percent insulin resistance - representing functional insulin secretion capacity and functional activity of insulin, respectively.

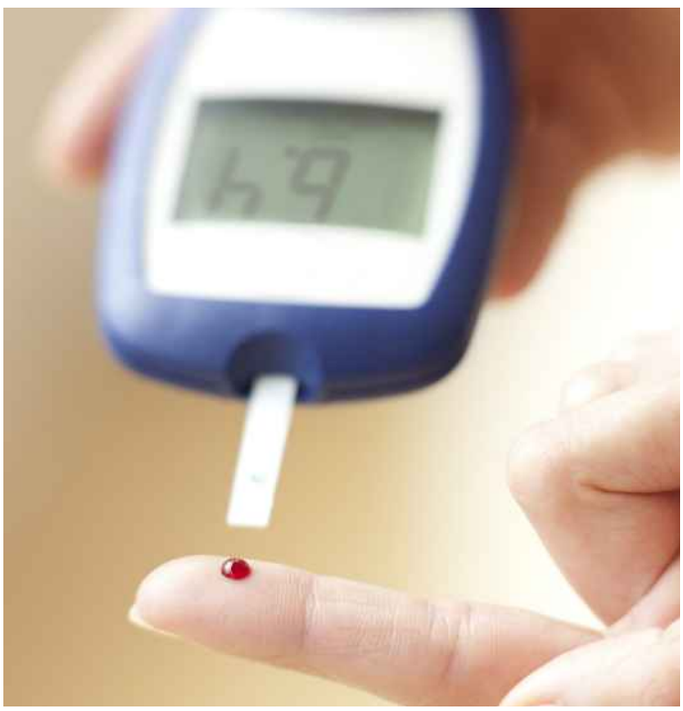
iHOMA2 can be used in:

- default mode - for comparison with all published data using HOMA and HOMA2,
- analytic mode - allows β-cell function and insulin sensitivity to be calculated from fasting insulin and glucose values,
- predictive mode - allows fasting insulin and glucose levels to be calculated from β-cell function and insulin sensitivity.

Advantages

iHOMA2 models 23 interactive variables, representing multiple organs and tissues, which:

- allows descriptions of different states of type 2 diabetes to be modelled,
- allows effect of therapeutic agents to be simulated - whether the agent is used alone or in combination with other diabetes treatments,
- can be used for epidemiological analyses of populations where fasting insulin and glucose values are known.



For further information please contact:
Dr James Groves
james.groves@innovation.ox.ac.uk
+44 (0)1865 614425
www.innovation.ox.ac.uk
Project number: 10766

Technology Transfer from the University of Oxford

Early gestational diabetes diagnostic

Scientists at the University of Oxford have developed a test where circulating biomarkers from the placenta give an early indication of mothers who either are already presenting with gestational diabetes or are highly likely to develop the disease.

Gestational diabetes occurs when a woman becomes resistant to the effects of insulin during pregnancy and isn't able to make enough to overcome the resistance. It usually becomes evident in the second or third trimester.

Gestational diabetes can cause complications for both mother and baby during and after birth. These include the baby growing larger than usual, which may lead to difficulties during the delivery and increases the likelihood of needing induced labour or a caesarean section, and increased risk of premature birth and stillbirth. However, the risk of complications can be reduced if the disease is detected early enough and well managed.

Complications of gestational diabetes

Currently, there is no method of determining whether a pregnant woman is likely to develop gestational diabetes. The only diagnostic test is an oral glucose tolerance test (OGTT), which is done late on in gestation, at around 24-28 weeks, and is dependent upon the patient already has the disease. Moreover, the OGTT is not a particularly effective test, in part because of lack of compliance by patients who are required to fast before having the test.

Scientists at the University of Oxford have developed a test where circulating biomarkers from the placenta give an early indication of mothers who either are already presenting with gestational diabetes or are highly likely to develop the disease. Early diagnosis is key to managing the condition well and reducing complications arising from the disease.

If gestational diabetes is not detected and left untreated, it can increase the risk of serious birth complications for both mother and baby. These include macrosomia (large babies), premature birth, miscarriage and stillbirth. In addition to the increased risk of complications associated with gestation and delivery, there are also serious post-natal complications associated with gestational diabetes, for example, there is an increased risk that both mother and baby will develop type 2 diabetes later in life.

Around 35,000 women are diagnosed with gestational diabetes in the UK alone with the global gestational diabetes market expected to grow at a CAGR of 5.4% up to 2023.

The increase in the obese population and lifestyle factors are driving the growth of the market. Not only can this invention be used to diagnose gestational diabetes early, it can predict whether a subject is likely to develop gestational diabetes and subsequently clinicians can better advise on the prognosis.

For further information please contact:
Dr Dinali de Silva
dinali.desilva@innovation.ox.ac.uk
+44 (0)1865 614441
www.innovation.ox.ac.uk
Project number: 10804

Technology Transfer from the University of Oxford


NEUROSCIENCE

Are you awake?

Available to license: Method for measuring consciousness and depth of anaesthesia.

A personalised approach to preventing awareness during surgery

When an individual undergoes general anaesthesia their level of consciousness is estimated from a variety of indirect measures such as heart rate, blood pressure and respiration. While the risk of an anaesthetic overdose is low, and the chance of waking up during surgery lower still, a direct and accurate measure of patient awareness would be highly beneficial in terms of both patient experience and reducing anaesthetic-related morbidity.

A new brain signature for unconsciousness

Using complementary brain imaging methods researchers have identified a 'slow-wave saturation' signature that may be used to develop a platform for pinpointing sufficient loss of awareness and optimal anaesthetic dose.

- EEG slow-waves increase as a patient is anaesthetised and hit a saturation point following a loss of awareness, despite further dosing
- Point of saturation corresponds with fMRI data showing functional isolation of the brain from external stimuli
- Signature is personalised, correlating with an individual's grey matter volume
- EEG signature could provide a direct indicator of a patient's awareness and regulate the anaesthetic dose accordingly

A foundation for superior anaesthetic monitoring

The slow-wave saturation signature identified in this study provides a platform on which to develop a superior and rationale-driven system for monitoring consciousness during surgical and intensive care anesthesia. We envisage that this discovery will be of interest to companies wishing to either integrate advanced technology into their existing patient monitoring systems or those looking to capitalise on this research through the development of a stand-alone monitor based on slow-wave neuronal oscillations.

Patent protection

A patent application covering the use of slow-wave oscillations to monitor consciousness is currently in PCT phase (PCT/GB2013/051445). Isis Innovation would like to speak to companies interested in developing this method.

"Despite hundreds of thousands of anaesthetics administered daily to patients, remarkably there is no robust, individualised indicator of perceptual awareness available" - Professor Irene Tracey, Director of FMRIB at the University of Oxford

For further information please contact:
Dr Paul Ashley
paul.ashley@innovation.ox.ac.uk
+44 (0)1865 280845
www.innovation.ox.ac.uk
Project number: 8818

Technology Transfer from the University of Oxford

Diagnosing neurological autoimmune disease

Available to license: Autoantibodies against a subunit of the GABAA receptor are involved in neurological and psychiatric disease and represent a new biomarker for the diagnosis of autoimmune disease.

Led by Professor Angela Vincent, Oxford scientists have identified the presence of autoantibodies that target the y2 subunits of the $GABA_A$ receptor.

Protection turned on oneself

Our immune system provides a critical defence against foreign and potentially harmful invaders. However, autoimmunity is a misguided response where renegade immune cells are unable to differentiate self from non-self, resulting in the destruction of the body's own cells.

Autoimmune disorders affect 5-10% of the population and often involve antibodies against proteins of the central nervous system. This can result in a number of neurologic disorders, including encephalopathies, and subgroups of epilepsies and psychiatric disease. However, once the specific antibodies have been identified, prompt diagnosis and therapy can occur.

Revealing a target of GABA autoimmunity

The $GABA_A$ receptor is the principle mediator of inhibitory synaptic transmission in the human brain and is the target for many therapeutic drugs, such as treatments for anxiety, insomnia and epilepsy.

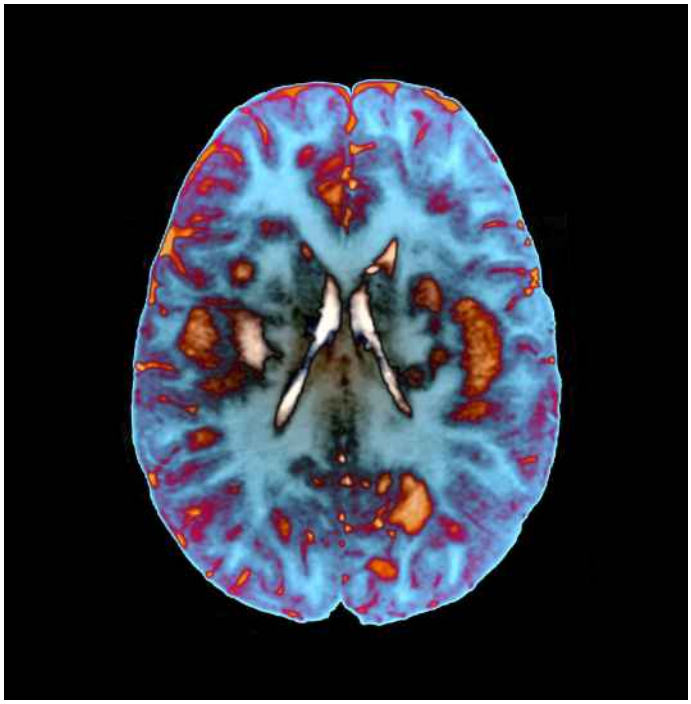
By retrospectively analysing the sera of patients suffering from a range of neurological and psychiatric symptoms, researchers from the University of Oxford have identified the α1 and y2 subunits of the $GABA_A$ receptor as a target of autoimmunity (published in the journal Neurology, Pettingill et al., 2015). Patients who expressed antibodies for α1 and y2 subunits exhibited a range of disorders, including seizures, memory impairments, anxiety and psychosis. Furthermore, when the antibody-containing serum from these patients was washed over neuronal cultures, it resulted in a specific down-regulation of α1 and y2 subunit expression, indicative of a causative effect.

It was also found that immunotherapy was beneficial in this group of α1/y2 autoimmune patients, with one boy suffering from severe catatonia twice exhibiting substantial immunotherapy-mediated improvement that correlated with normalization of his $GABA_A$ antibody levels.

A tool for diagnosis and therapy

Autoimmune channelopathies may have a good prognosis, especially if diagnosed and treated early. This discovery provides the rationale for improving diagnosis and prognosis for this newly identified $GABA_A$ α1 and y2 variant of central nervous system autoimmune disease.

Oxford University Innovation has filed an international patent application PCT/GB2015/051388 (12th May 2015) and would welcome discussions with companies engaged in autoimmunity research and those interested in incorporating this discovery into their antibody screening technology.



For further information please contact:
Dr Angela Calvert
angela.calvert@innovation.ox.ac.uk
+44 (0)1865 280870
www.innovation.ox.ac.uk
Project number: 11128

Technology Transfer from the University of Oxford

Novel blood brain barrier model

Oxford academics have developed a fully defined protocol for generating brain microvascular endothelial cells from induced pluripotent stem cells.

The blood brain barrier (BBB) is primarily composed of brain microvascular endothelial cells (BMECs). These BMECs are connected by adherens and tight junctions resulting into high electrical resistance. They are functionally coupled with neurons, astrocytes, mural cells and extracellular matrix components to form so-called neurovascular units.

The BBB is of critical importance when designing and screening for potential therapeutics and many potential candidate drugs acting in the central nervous system will fail to provide their therapeutic effect if they are unable to cross the BBB in sufficient quantity. It is therefore crucial to study the BBB and transport mechanisms across it when developing new therapeutics. However, it is very difficult to do large scale drug screening to test if new molecules can cross the BBB using *in vivo* models, and hence there is a need for robust and accurate *in vitro* models.

Current barriers to success

Existing *in vitro* models have many drawbacks; they are difficult to reproduce, and often lack sufficient characteristics of a true BBB. The tight junctions between BMECs are often discontinuous in *in vitro* models and many models also show low trans-endothelial electrical resistance (TEER) measurements. Results from models using non-human mammalian cells often fail to translate to humans. Models that use human immortalised and primary cell lines poorly recapitulate normal physiology, have decreased barrier properties after removal from the brain microenvironment, and limited proliferative ability.

A model example

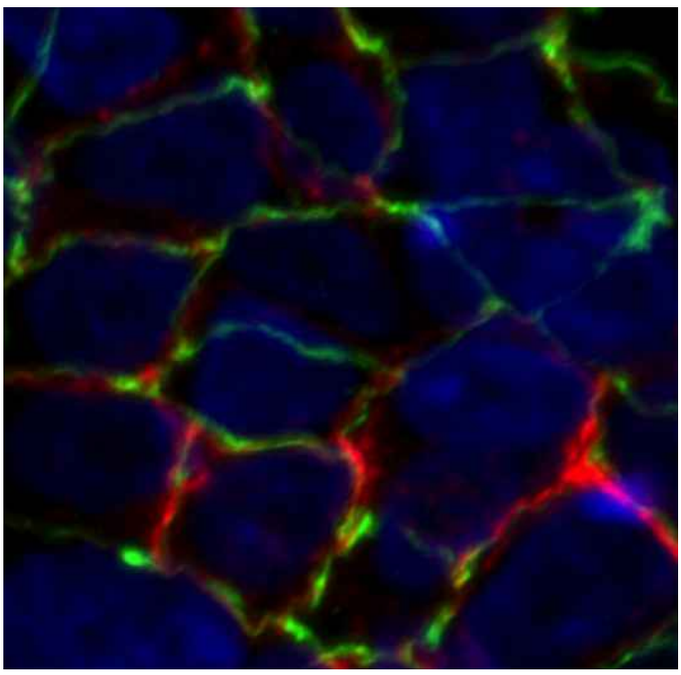
Oxford academics have developed a new protocol for generating BMECs from induced human pluripotent stem cells, for use in BBB models.

It offers many advantages over current methods:

- BMEC properties very similar to those *in vivo*
- Fully defined protocol
- High reproducibility with different IPSC lines
- Effective barrier formation – high TEER
- Cells can be used by themselves or co-cultured for a more representative *in vitro* BBB or neurovascular unit model

Commercialisation

The technology is subject to a patent application and is now available for license from Oxford University Innovation.

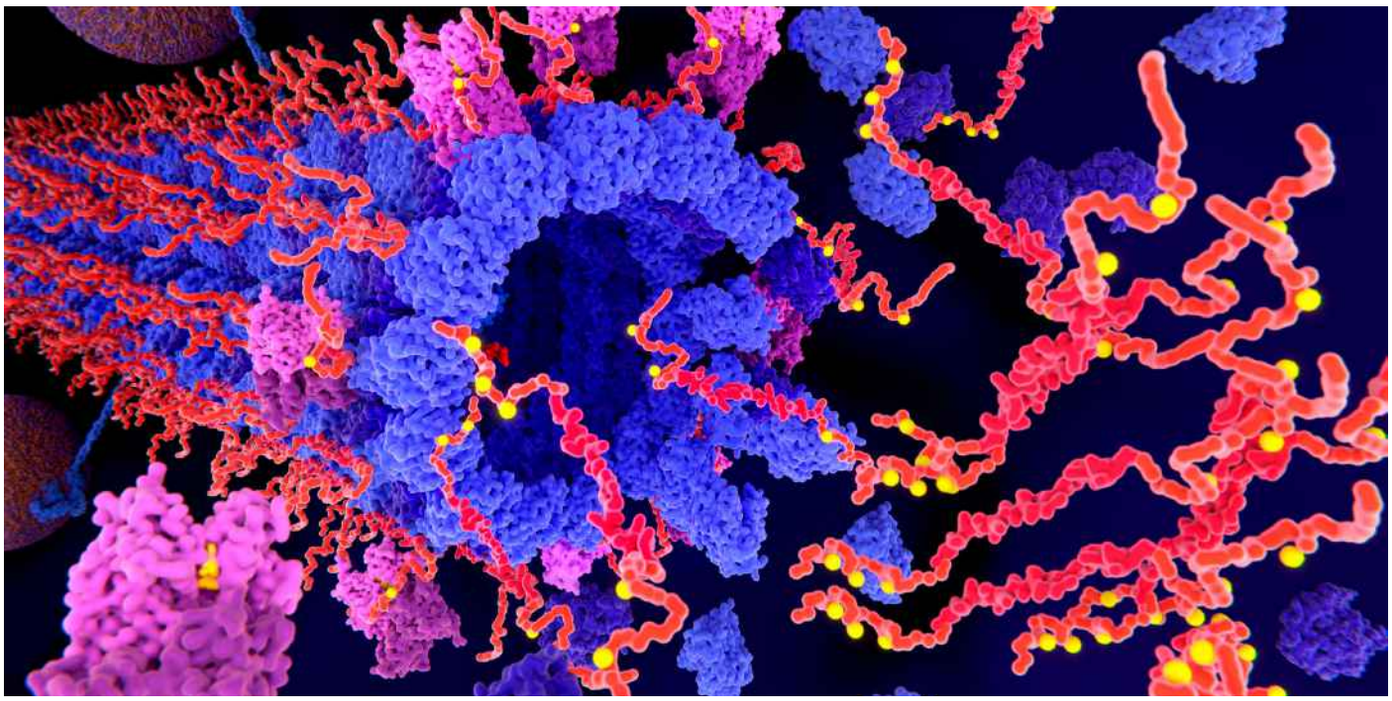


For further information please contact:
Dr Richard Reschen
richard.reschen@innovation.ox.ac.uk
+44 (0)1865 280872
www.innovation.ox.ac.uk
Project number: 12263

Technology Transfer from the University of Oxford

Targeted drug delivery to the brain for treating neurodegenerative diseases

Researchers at the University of Oxford have developed novel drug delivery vehicles capable of directly targeting areas of the brain affected by abnormal tau aggregation, in diseases such as Alzheimer's disease.



Brain targeting of small molecules

Drug targeting to the brain is a major challenge due to the presence of the blood brain barrier which exists between the central nervous system and peripheral circulation. The highly selective and tightly regulated, restricting passage of molecules make it difficult for therapeutics to reach their active site within the brain.

Tau proteins are large sized molecules that stabilize microtubules within cells and are abundant in the central nervous system. Microtubules provide structure to the cell, and so abnormal tau proteins cause toxic effects by aggregating and forming structures known as neurofibrillary tangles that cause microtuble breakdown, cell death and the subsequent cognitive decline seen in Alzheimer's disease, frontotemporal dementia and other tauopathies.

Lipid-mediated transport

Researchers at the University of Oxford have developed a drug delivery vehicle for selectively delivering active agents to affected areas of the brain. It consists of a liposome, a spherical lipid vesicle containing the active agents, conjugated to a targeting agent such as a Lewis antigen.

The targeting agent specifically targets cell-adhesion molecules such as selectins, which are frequently transported across the blood brain barrier and into microglial cells within the brain.

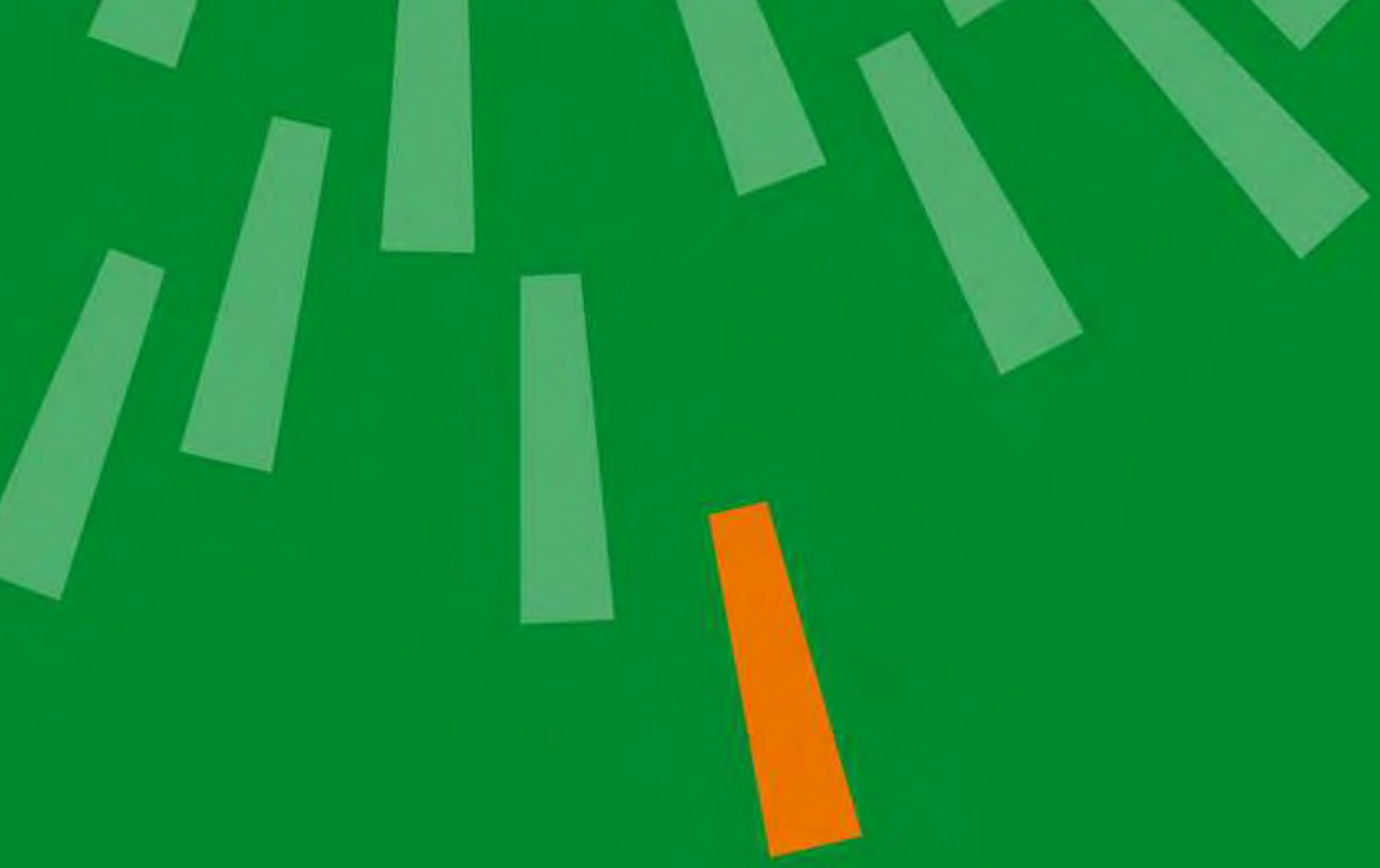
Consequently, the targeting of these molecules enables delivery of drug payload to sites of interest in areas of otherwise inaccessible brain pathology.

Commercialisation

Oxford University Innovation are seeking partners to license this innovative technology and support its continued development. A patent application has been filed to cover this method.

For further information please contact:
Dr Sarah Jones
sarah.jones@innovation.ox.ac.uk
+44 (0)1865 614458
www.innovation.ox.ac.uk
Project number: 15744

Technology Transfer from the University of Oxford



ONCOLOGY

Acute myeloid leukaemia prognostic and diagnostic screening

Oxford researchers, in collaboration with the University of Birmingham, have discovered novel combinations of cell-surface biomarkers (CD molecules) that allow acute myeloid leukaemia to be stratified into 3 different molecular sub-types to allow targeted treatment and better monitoring of treatment response.

Acute Myeloid Leukaemia (AML) is a type of aggressive blood cancer, with several molecular sub-types. Current treatments aim to reduce (to less than 5% of the original amount) levels of leukemic stem cells (LSC), which are thought to be responsible for sustaining the disease and leading to relapse.

However, until now, no technologies were available that could determine the molecular sub-type of AML present in the patient (to predict disease course and inform treatment with targeted therapeutics) and detect and monitor the levels of these remaining LSCs.

Driven by this unmet need, researchers at the University of Oxford have discovered combinations of cell-surface biomarkers which are capable of meeting both objectives.

Advantages of the biomarkers

- Improved sensitivity in AML diagnosis and prognosis
- Patient stratification, saving time and money by avoiding inappropriate treatments and improving patient wellbeing
- Assessment of treatment efficacy

Current challenges in AML therapy

The goal of AML therapy is to reduce the amount of bone marrow leukaemic cells to less than 5%. However, despite this level of reduction, most patients relapse without post-induction chemotherapy or a haematopoietic stem cell transplant. These procedures aim to eliminate minimal residual disease: leukaemic cells that resist therapy. Leukaemic stem cells (LSC) are thought to be responsible for sustaining disease.

The advantage of the Oxford biomarkers is that they follow LSC populations directly and hence provide a novel strategy for following disease progression.

The new biomarkers detect LSC at lower levels than was previously possible.

Recent studies have also demonstrated that AML consists of a group of diseases, and this technology allows stratification of patients by disease sub-type, allowing the most appropriate treatment to be selected, potentially improving treatment efficacy.

AML facts

- Aggressive cancer of the myeloid line of white blood cells
- The most common adult acute leukaemia, affecting over 15,300 people a year in the US and UK combined
- More common in adults aged over 65, with only 5% overall survival in this patient group
- Prevalence is expected to increase as the population ages

Supporting data

Clinical and in vivo proof-of-concept data showing that the biomarker combinations identify LSCs:

Goardon N et al (2011). Cancer Cell. 19(1):138-52
Quek L et al (2016). J Exp Med. Jul 25;213(8):1513-35

Patent position

This technology is subject to a family of international patent applications including use and method claims for biomarkers for AML. Oxford University Innovation would like to hear from companies who wish to license this technology for further development.

For further information please contact:
Dr Richard Reschen
richard.reschen@innovation.ox.ac.uk
+44 (0)1865 280872
www.innovation.ox.ac.uk
Project number: 4130, 11532

Technology Transfer from the University of Oxford

Brain tumour detection and treatment

Oxford University researchers have developed a method to selectively increase permeability of the blood-brain barrier at sites of secondary brain tumours.

Brain Cancer

Brain metastasis (BM) is one of the greatest hurdles in cancer therapy; 20-40% of all cancer patients will suffer metastatic spread of the primary cancer to the brain. Unfortunately, our inability to diagnose BM early enough and to obtain an accurate measure of the number of metastases present is a major limitation in the treatment and management of cancer patients. Clinical diagnosis of BM is limited to larger, late-stage metastases (>5mm) and early detection (<5mm) remains impossible.

Diagnosis and treatment

The presence of the blood-brain barrier is the primary reason why diagnosis and treatment of BM is so problematic, as it has specifically evolved to restrict the diffusion of many molecules into the brain.

Oxford Invention

Using cytokine-enhanced Magnetic Resonance Imaging (MRI), detection of BM of the order of 100µm in diameter in preclinical models has been achieved. Translation of these findings into the clinical setting would equate to diagnosis several months earlier than conventional gadolinium-based MRI. Importantly, this approach would facilitate specific delivery of potential tumour chemotherapies and radiosensitisers to these early stage tumours, to enhance and extend current treatment options.

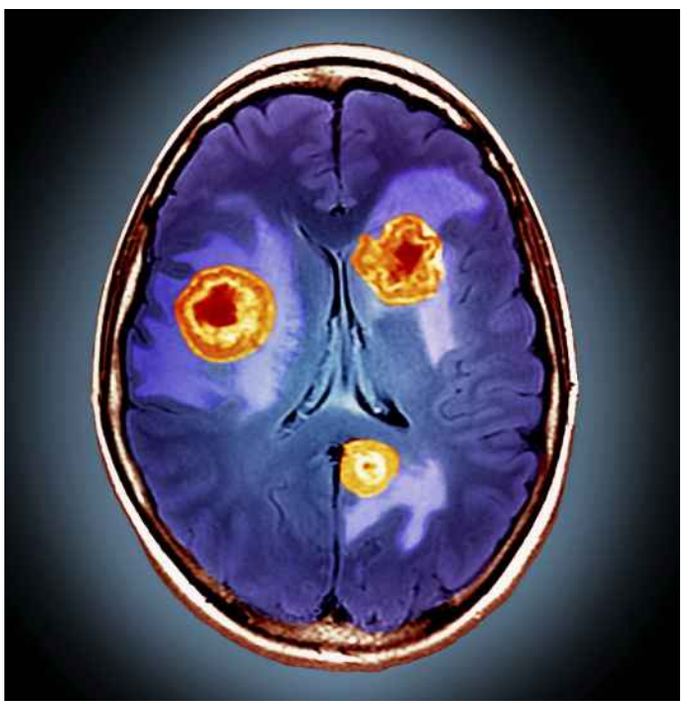
Supporting Data

The work at the University of Oxford has demonstrated:

- Low dose cytokines can be used to temporarily and reversibly increase blood-brain barrier permeability and, thus, improve delivery of imaging agents and anti-cancer drugs.
- Cytokines only induce breakdown of the blood-brain barrier breakdown at tumour sites to enable these sites to be imaged by MRI with contrast agents that are normally excluded from the brain.

Patent Position

The patent application (WO2011/070358 ‘systemic administration of an agent that permeabilises tumour vasculature’) covering the invention was published in June 2011.



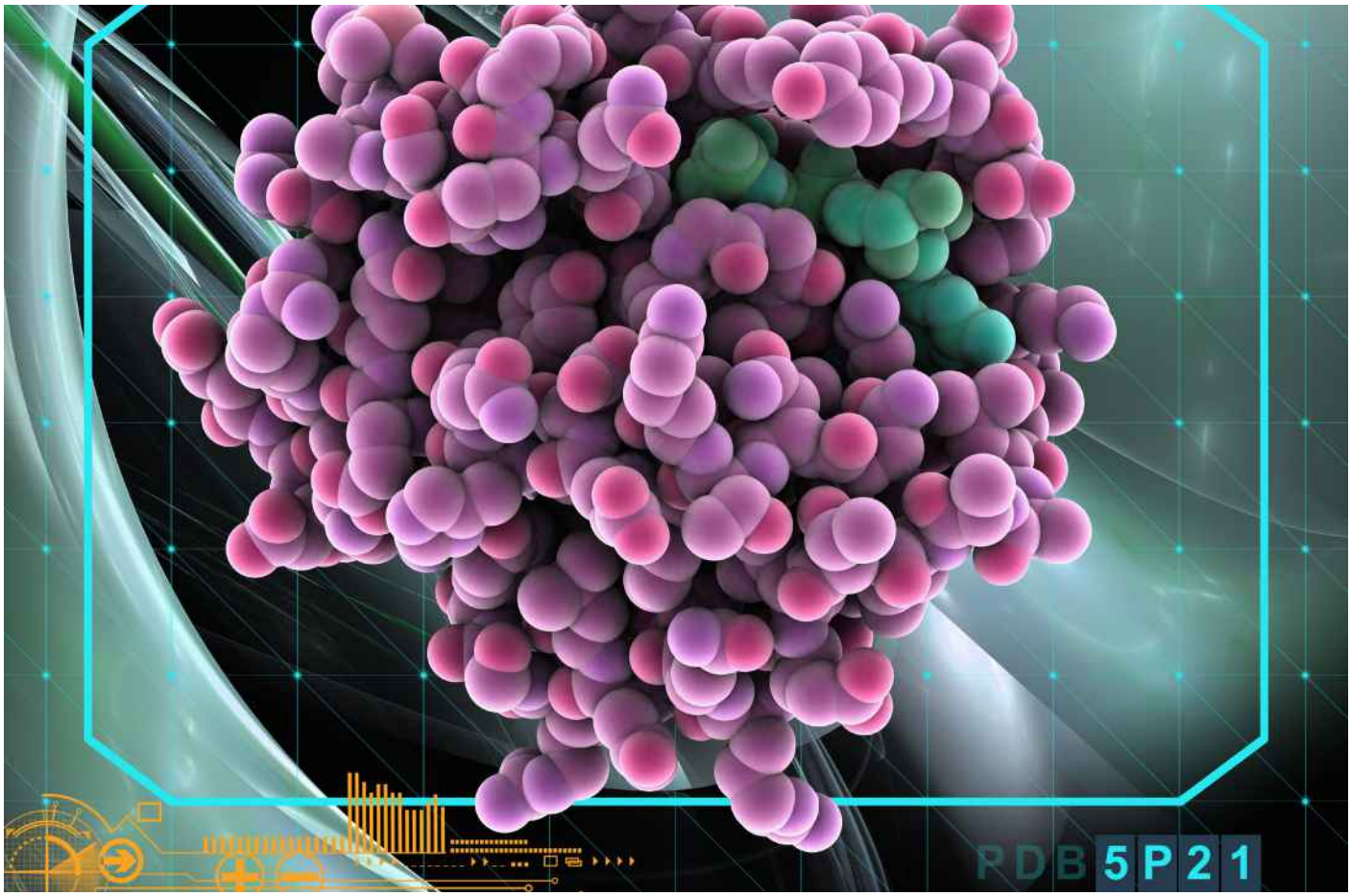
Secondary brain cancer, MRI scan

For further information please contact:
Dr Sarah Deakin
sarah.deakin@innovation.ox.ac.uk
+44 (0)1865 614410
www.innovation.ox.ac.uk
Project number: 6855

Technology Transfer from the University of Oxford

New lead compounds for treating cancers involving Ras mutations

Oxford University researchers have developed small molecule inhibitors of Ras proteins, important therapeutic targets in a large number of cancers.



Cancer is a major global disease burden, costing the NHS approximately £5bn a year. Around 97% of pancreatic cancer and 45% of colorectal cancer are the result of Ras family gene mutations, and a number of other cancers are linked to Ras mutations, making it a key drug target for cancer therapy.

Methods for treating cancer

Attempts to develop drugs that target mutant Ras have so far been unsuccessful, meaning tumours bearing this mutation remain the hardest to treat. Small molecules are able to readily penetrate cells, however, were not initially thought to be able to interfere with protein-protein interactions.

Such small molecules have been discovered by identifying antibody fragments capable of binding to Ras and using their structure to derive smaller compounds that mimic their properties. The antibody fragments are therapeutically ineffective without intracellular delivery, as they are unable to penetrate the cell membrane to reach their targets.

Development of Ras inhibitors

Researchers from the University of Oxford have found numerous small molecule Ras inhibitors, the most potent of which has been shown to effectively block protein-protein interactions between Ras and effector molecules in cell-based assays.

These unique small molecules offer a potential therapy for those suffering from mutated Ras related cancers where there is currently no treatment available.

For further information please contact:
Dr Matthew Carpenter
matthew.carpenter@innovation.ox.ac.uk
+44 (0)1865 280970
www.innovation.ox.ac.uk
Project number: 8636

Technology Transfer from the University of Oxford

Prediction method for skin cancer development risk in renal transplant recipients

Academics at the University of Oxford have developed a method to detect RTRs at risk of developing SCC, by quantifying the proportion of CD8 T-cells that express CD57 on their surface.

Each year in the UK, almost 3,000 adults receive a renal transplant. Within 20 years, 30-40% will develop cutaneous squamous cell carcinoma (SCC), the second most common type of skin cancer. A major contributor to the development of SCC is the life-long immunosuppression given to renal transplant recipients (RTR) to reduce the risk of transplant rejection by the immune system. Some RTR may be taking more immunosuppression than required, particularly patients at high risk of developing SCC.

Predicting at-risk patient groups

Researchers at the University of Oxford have developed a method to determine RTRs who are at increased risk of developing SCC and SCC recurrence, using flow cytometry. The team's recently published results in JASN (http://jasn.asnjournals.org/content/27/5/1505.full) show that by analysing the proportion of certain T-cells that express the CD57 antigen, patients can be grouped into those at higher and lower risk of developing subsequent SCC, before it develops. This represents one of the strongest markers of subsequent SCC development identified and is independent of previously identified clinical risk markers.

Potential proactive patient monitoring

In a clinical setting, this method could be used in routine renal transplant follow-up. A patient's T-cells could be phenotyped to determine the best clinical pathway depending on the result.

For high-risk patients, this may allow for the pre-emptive reduction of drug-based immunosuppression with increased confidence that a patient is less likely to develop transplant rejection. This proactive approach may also reduce the incidence of malignancy in the long term. It could allow low-risk patients to attend fewer follow-up dermatology appointments, saving both time and considerable consultation costs, whilst high-risk RTRs could have more frequent monitoring from a healthcare professional.

The stratification method may also be potentially useful in other organ transplant populations to identify those at increased risk of SCC and to guide immunosuppression intensity.

This technology is subject to a PCT patent application (PCT/GB2015/053176) and is available to license. Oxford University Innovation would like to speak to parties interested in developing this technology.

For further information please contact:
Dr Sdžǎl·y˙ / l·YLJōŜff
sdžǎl·y˙.ǒl·YLJōŜff@innovation.ox.ac.uk
+44 (0)1865 614410
www.innovation.ox.ac.uk
Project number: 11735

Technology Transfer from the University of Oxford

Stratification method for proximal colorectal cancer patients

Available to license: A method for stratifying colorectal cancer patients based on the location and biomarker profile of the tumour.

Oxford researchers have developed a process for classifying CRC tumours allowing for the administration of more targeted therapies, leading to more positive patient outcomes.

Colorectal Cancer

Colorectal cancer (CRC) is widespread in the UK with roughly 40,700 people being diagnosed with CRC in 2010. This is equivalent to more than 110 people every day. Around 1 in 20 people will develop CRC in their lifetime. Treatment of CRC generally involves a combination of surgery and chemotherapy; however, it has been found that some tumours respond poorly to widely used chemotherapeutic agents.

Personalised Medicine

In patients with CRC the location and genetic profile of the tumour drastically affects their prognosis. Accurate characterisation of these tumours through biomarker analysis allows for the administration of more personalised therapies. For this to be possible, new methods are required to differentiate these CRC subtypes.

Molecular Stratification

Oxford researchers have identified a proximal, IL22RA1^{high}, KRAS mutant molecular CRC subtype. The presence of these biomarkers dramatically worsens the prognosis for patients with proximal CRC. In KRAS mutant tumours, IL-22 promotes both chemoresistance and clonogenic outgrowth. Due to this, the group proposes an alternative CRC treatment based on anti-IL-22 monoclonal antibody therapy.

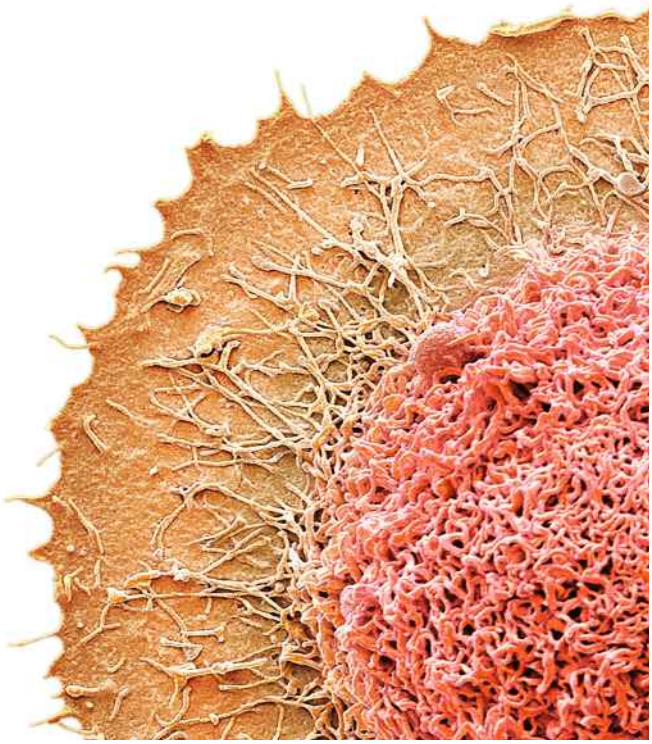
The benefits of this molecular stratification include:

- Identification of CRC subtype with poor prognosis
- Allows adaptation of the treatment administered
- New avenues for treatment of the CRC subtype

This stratification method provides insight into a subtype of CRC potentially allowing for more effective treatment for patients with proximal CRC. This approach may also be applied to other cancer types.

Commercialisation

This technology is subject to a patent application. Oxford University Innovation would like to speak to companies interested in licensing and developing this technology.



For further information please contact:
Dr Matthew Carpenter
matthew.carpenter@innovation.ox.ac.uk
+44 (0)1865 280970
www.innovation.ox.ac.uk
Project number: 12273

Technology Transfer from the University of Oxford

IGF2-TRAP: High affinity receptors to sequester growth factors linked to cancer

Researchers at the University of Oxford have identified key mutations that increase the affinity of Insulin-like Growth Factor 2 Receptor (IGFR2) for its ligand, reducing hypoglycaemia and tumour volume.

Insulin-like growth factors (IGF) are overexpressed in cancer cells and reductions in their expression are associated with tumour reduction. Previous efforts to inhibit IGF signalling by focussing on the IGF1 receptor have so far been unsuccessful.

Researchers at the University of Oxford have investigated the IGF2 receptor (IGF2R) and have identified mutations in domain 11 of IGF2R that increase the affinity of IGF2 to its receptor. These mutated receptors have been shown to treat hypoglycaemia and reduce tumour volume.

Insulin-like Growth Factor 2 (IGF2) encodes a member of the insulin family of polypeptide growth factors, which are involved in development and growth. Overexpression of this growth factor gene has been reported in a wide range of cancers and is associated with an increased risk of developing early childhood tumours.

IGF2 activates MAPK and PI3K pathways by binding to the ubiquitously expressed IGF1 receptor (IGF1R) and isoform A of the Insulin Receptor (IR-A). Unlike IGF1R, which is responsible for active signalling, IGF2R acts as an IGF2 sink to prevent excess IGF2 signalling.

Ligand bioavailability in cancer is often increased due to increased IGF2 expression, proteolytic cleavage of inhibitory proteins and loss of function of the sink receptor IGF2R. IGF2 is thought to be a major driver of resistance to several therapies, including anti-HER2, anti-EGFR and anti-Androgen in breast, colorectal, prostate and lung cancers.

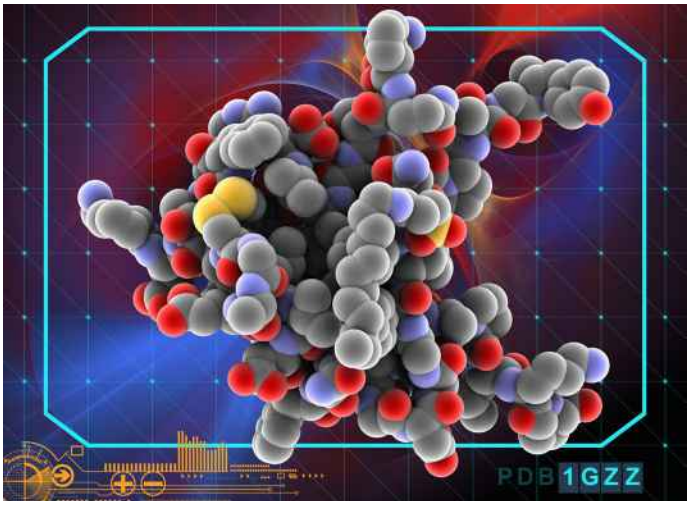
Inhibition of IGF signalling has been an area of major focus by pharma, with many failures due to either receptor redundancy (between IGF1R and IR-A) or the IGF1 feedback loop. This causes the pituitary gland to produce more growth hormone, instructing the liver to produce more IGF1, generating a potential dose limiting toxicity of hyperglycaemia.

Tumours that cause hypoglycaemia overexpress IGF2 and secrete excessive amounts of partially processed precursors of IGF2, named big-IGF2. This causes the rare condition of non-islet cell tumour hypoglycaemia (NICTH).

Researchers at the University of Oxford, along with their collaborators, have identified a number of key mutations in the IGF2R that increase affinity with IGF2. These mutated receptors act as traps for IGF2 (IGF2-TRAP), thus sequestering this overexpressed ligand. The mutated IGF2R have been tested *in vivo* – IGF2-induced hypoglycaemia in mice was abolished in the presence of the IGF2-TRAP, and a reduction in tumour volume was observed in Ewing sarcoma cells xenograft models treated with IGF2-TRAP.

The Oxford researchers have gone on to identify two PI3 kinase inhibitors that act synergistically with the IGF2-TRAP to reduce the dose requirements of these inhibitors and improve the long-term tumour-killing efficacy of IFG2-TRAP.

The IGF2R mutations are protected by a patent now granted in Europe and the USA, and another international patent application.

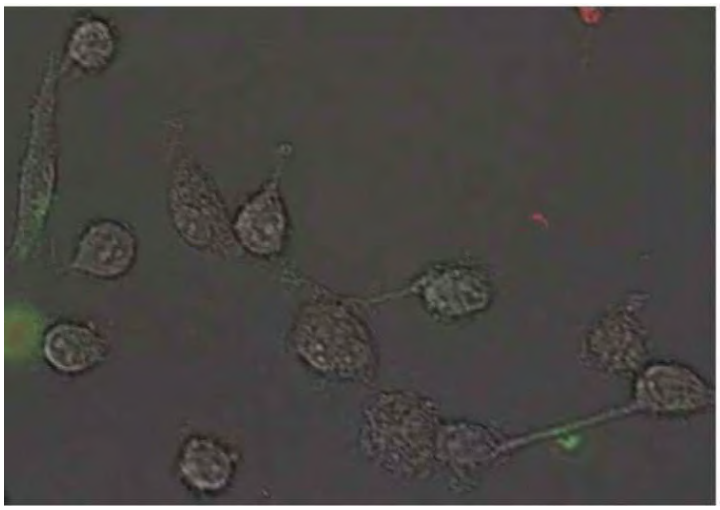


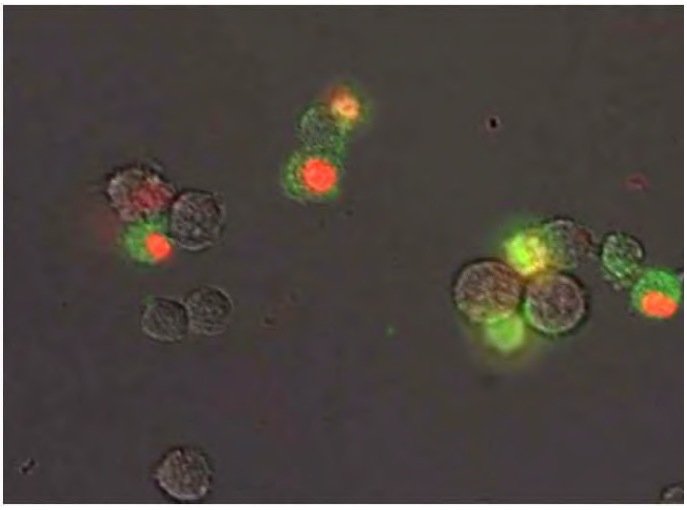
For further information please contact:
Dr Christine Whyte
christine.whyte@innovation.ox.ac.uk
+44 (0)1865 280921
www.innovation.ox.ac.uk
Project number: 15455, 15456

Technology Transfer from the University of Oxford

Preclinical and clinical evaluation of forodesine in patients with leukaemia

Researchers at Oxford University have identified a specific use of the drug forodesine to treat chronic lymphocytic leukaemia in patients with a specific genetic mutation.





Chronic lymphocytic leukaemia (CLL) is a type of cancer that affects the white blood cells and tends to progress slowly over many years. In patients with CLL, the bone marrow makes too many lymphocytes. Symptoms include higher levels than unusual of bruising and bleeding, night sweats, high temperatures and swollen glands. It is one of the most common types of leukaemia in adults and usually occurs around or after middle age with about 90% of chronic lymphocytic leukaemia diagnosed in middle age.

The Incidence rate of CLL is higher in men and women over 50 years of age. It is rarely seen in people under age 40 and is extremely rare in children Over 3000 people are diagnosed with CLL every year in the UK alone and in 2016 there were over 18,000 new cases of CLL in the US.

The CLL market is expected to grow from $7.7bn in 2017 to $9.2bn by 2027 at a compound annual growth rate (CAGR) of 1.8%. Treatment for CLL largely depends on what stage the condition is at when it's diagnosed. The increasing elderly population worldwide is driving market growth and there is a strong need for more effective treatments.

New treatment in CLL

Researchers at Oxford University have identified a specific use of the drug forodesine to treat CLL in patients with a specific genetic mutation.

Scientists have demonstrated greater efficacy of the drug in patients with CLL that have a specific genetic mutation compared to those who do not. It is expected that CLL patients with this mutation will have a higher response rate to the drug which will ultimately improve treatment efficacy and increase life expectancy.

For further information please contact:
Dr Dinali de Silva
dinali.desilva@innovation.ox.ac.uk
+44 (0)1865 614441
www.innovation.ox.ac.uk
Project number: 15790

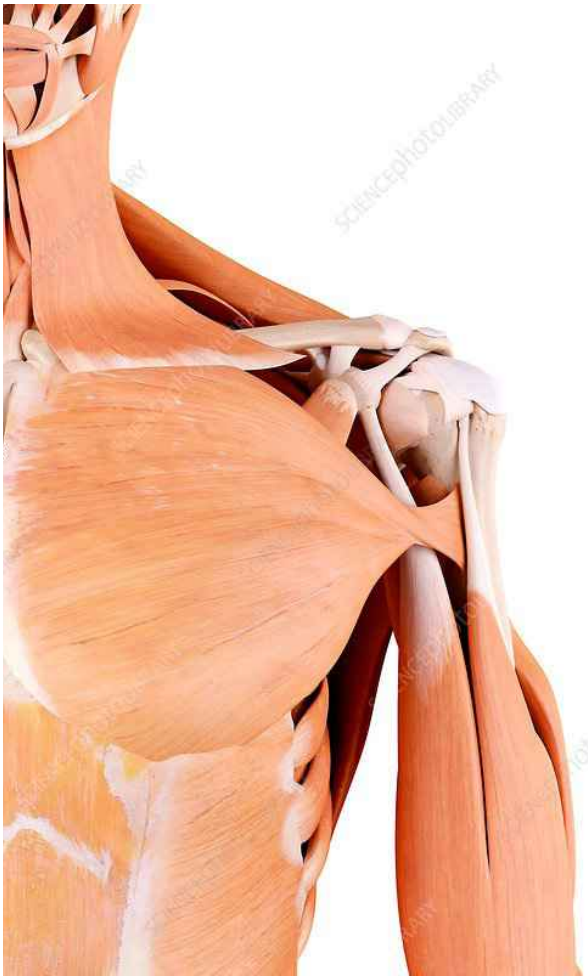
Technology Transfer from the University of Oxford

ORTHOPAEDICS

Degradable implant to enhance surgical repair of musculoskeletal tissue

Oxford researchers have developed a multi-layered degradable patch that enhances the surgical repair of musculoskeletal tissue with improved mechanical and biocompatible properties.

The musculoskeletal system provides form, support, stability and movement to the body. Over 50% of adults who live in the US suffer from musculoskeletal diseases and there are currently no adequate solutions to improve tendon healing after a surgical procedure. A major musculoskeletal system is the rotator cuff, a group of muscles and tendons that surround the shoulder joint. Over 50% of people over the age of 66 suffer from tears of the rotator cuff requiring surgery, on average over 40% of surgical reattachments of the rotator cuff fail. Current structures available are limited due to infection, biocompatibility and loss of integrity in the long-term.



Biocompatible scaffold materials

Oxford researchers have developed an enhanced absorbable and biocompatible implant which enhances the surgical repair of the musculoskeletal tissue. This patch provides a degradable synthetic scaffold.

Existing scaffolds have been able to minimise the risk of infection but are limited in terms of biocompatibility and/or mechanical properties. This invention is unique compared to existing scaffolds because of the innovative combination of non-woven and woven components in a multi-layered degradable patch.

Tissue engineering

The woven component provides the mechanical properties whereas the non-woven electrospun component provides the compatibility by stimulating new tissue formation providing new tendon-like features to the cells. This novel way of layering tackles both mechanical and biological aspects of tissue repair.

This multi-layered implant has the potential to enhance the surgical repair of the rotator cuff and other musculoskeletal repairs but also has potential applications in other fields such as filtration, protective materials and the environment.

For further information please contact:
Dr Angela Calvert
angela.calvert@innovation.ox.ac.uk
+44 (0)1865 280870
www.innovation.ox.ac.uk
Project number: 8573

Technology Transfer from the University of Oxford

OSSKAR – A positioning device for hands-free stress imaging of the knee

Available to license: A CE-marked simple medical device for stress imaging of the lower limb to enable standardised knee arthroplasty radiographs in the absence of a clinician.

The Oxford Stress System for Knee Arthroplasty Radiographs (OSSKAR) is a simple and light-weight medical device for comfortably placing patients in standardised stress positions for x-ray radiography while removing the need for a clinician.

Partial or total knee replacement?

Unicompartmental knee replacement (UKR) has significant clinical benefits over total knee replacement (TKR), such as half the risk of venous thromboembolism, myocardial infarction or deep infection, two thirds the risk of stroke, one quarter the risk of blood transfusion and significantly lower mortality up to eight years following their operation.

However, despite being appropriate in half of patients, UKR is carried out in only 8% of cases, with large variation between centres. The main reasons for this poor adoption rate is the difficulty in identifying which patients demonstrate appropriate pathology for this procedure, such as bone-on-bone arthritis in the medial but not lateral compartment.

The need for an informed decision

While a variety of approaches are available to investigate knee pathology, such as MRI or arthroscopy, X-ray radiography of the joint while placed in a series of standardised stress positions remains the gold standard. However, this requires either complex medical devices or the presence of a clinician. These approaches are either uncomfortable for the patient or place a costly demand on a clinician's time while exposing them to harmful x-rays (approx. 300 times a year).

A patient and practitioner-friendly device

Researchers from the University of Oxford have developed OSSKAR, a simple hands-free device that could greatly facilitate knee stress radiography and consequently ensure all patients receive the most appropriate and cost-effective knee replacement surgery.

Key benefits

- Simple, lightweight and inexpensive to manufacture
- CE-marked
- Allows both legs to undergo stress simultaneously
- Causes minimal patient discomfort
- Removes need for costly and invasive MRI or arthroscopy
- Removes need for manual positioning and therefore clinician radiation exposure
- Potential for horizontal beam lateral x-ray and ligament insufficiency assessment

For further information please contact:
Dr James Groves
james.groves@innovation.ox.ac.uk
+44 (0)1865 614425
www.innovation.ox.ac.uk
Project number: 11194

Technology Transfer from the University of Oxford

Precision joint alignment for total knee replacement

Surgeons at the University of Oxford have developed a surgical tool capable of accurately aligning the knee joint during surgery, resulting in better surgical outcomes.

Total knee arthroplasty

Knee arthroplasty, the process of replacing a damaged knee with an artificial joint, is considered to be a routine procedure, with the new joints lasting up to 20 years. Generally, patients undergoing knee replacements are aged between 60-80 and the most common underlying cause of the damage is osteoarthritis. In the UK, around 80,000 knee replacements are carried out each year and with an ever-ageing population, this number is only set to rise. In fact, in the US, the demand for these procedures is predicted to rise over 600% by 2030.

Results hinge on alignment

A key step in the surgical process is aligning the new joint appropriately to correctly distribute the strain across the joint. Incorrect alignment can lead to a ligament misbalance, a cause of up to 20% of patients being unhappy with their outcome. Recently surgeons have been moving away from classical 2D mechanical alignment to employ a more complex, 3D kinematic alignment method. The kinematic method gives better outcomes as is more patient specific, however it is difficult to implement and often requires the use of patient specific surgical guides.

Simplified alignment

Surgeons based at the world-renowned Nuffield Orthopaedic Centre, University of Oxford, have developed a surgical device capable of simply aligning the new knee in a way that is sympathetic to normal ligament function. By referencing the femoral implant, it can give accurate and reproducible alignment.

We believe the benefits of this device to be as follows:

- Simple to operate
- Accurate and reproducible alignment
- Potential applications in other joint arthroplasties
- Can be adapted to allow for conventional implant positioning

Commercialisation

Oxford University Innovation Ltd. has filed a priority patent application, which covers this technology and is seeking partners to aid in its exploitation.

For further information please contact:
Dr Chandra Ramanujan
chandra.ramanujan@innovation.ox.ac.uk
+44 (0)1865 614434
www.innovation.ox.ac.uk
Project number: 11652

Technology Transfer from the University of Oxford

Medical device facilitating improved patient experience following joint replacement

A combined motion capture and ultrasound device to improve the understanding of post-operative pain in joint replacement and develop solutions to this problem.

Joint replacement

At £5 billion, musculoskeletal conditions account for the fourth largest NHS budget. It is estimated that 30.6 million working days are lost on an annual basis due to absence caused by a musculoskeletal conditions.

It is known that replaced joints do not have normal kinematics, however it remains unclear how far they deviate from normal. There is a clinical need for technologies to enable the design of joint replacements which offer reduced pain post-operation and kinematics closer to those seen in a healthy subject.

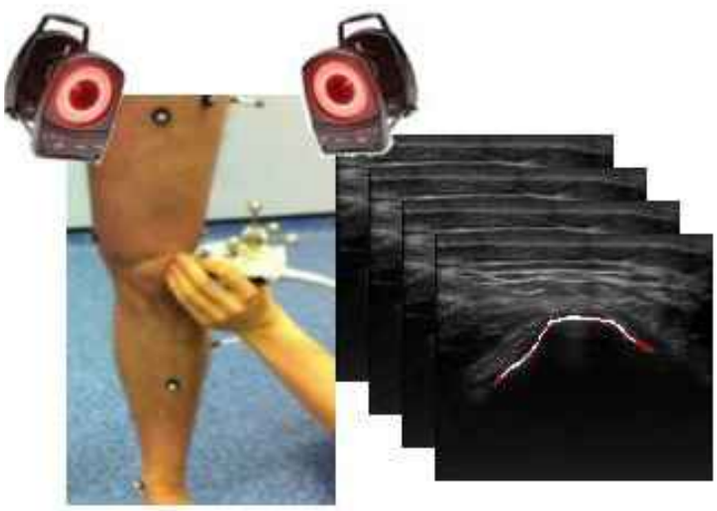
Joint tracker

The current gold standards in musculoskeletal imaging are MRI and CT, with images traditionally acquired in the rested, supine position. This is clearly far from adequate for assessing patients' functional performance and response to loading such as that encountered during walking. The orthopaedics industry is looking to ultrasound to provide radiation-free, non-invasive solutions for the assessment of joint kinematics.

Oxford orthopaedic clinicians and biomedical engineers have worked together to develop a system combining motion capture and ultrasound technologies. Further the system works to analyse the difference in joint kinematics between a healthy volunteer, a patient with a pain free knee replacement and a patient with a painful knee replacement. This is the first phase in plans to develop a portable device suited to the assessment of joints in a clinical setting.

Commercialisation

A patent application protecting a device that combines ultrasound, motion capture and the process of tracking a subject has been filed. Prototype systems and software have been developed and applied in a clinical setting. Oxford University Innovations would like to speak with companies interested in developing a commercial product based on this technology.



For further information please contact:
Dr Chandra Ramanujan
chandra.ramanujan@innovation.ox.ac.uk
+44 (0)1865 614434
www.innovation.ox.ac.uk
Project number: 11979

Technology Transfer from the University of Oxford

Improved tools for corrective surgery of the tibia

Available to license: A novel system to improve the process of tibial osteotomy procedures used to correct leg alignment has been developed by Oxford University researchers and clinicians.

A team of engineers and consultant orthopaedic surgeons at the University of Oxford have developed a novel system to improve outcomes and patient experience in tibial osteotomy.

Tibial Osteotomy

Overloading of the medial (inside) or lateral (outside) of the knee are common causes of early degenerative changes in the knee joint. High tibial osteotomy is an operation designed to realign the tibia (shin bone) to correct loading abnormalities through the knee joint. This provides an attractive 'joint preserving' surgical alternative in younger patients to joint replacement surgery which is usually reserved for later patterns of the disease.

Out with the old...

To date the metal plates used to fix the cut bony surfaces bones in place during a tibial osteotomy have been shown to have a non-anatomical fit to the bone and can result in post-operative problems, where patients experience pain or report general dissatisfaction with the procedure. Additionally, conducting cutting and drilling of the bone during tibial osteotomy has relied on high levels of expertise and little instrumentation, with the potential for human error.

...and in with the new

A team of engineers and consultant orthopaedic surgeons at Oxford have developed a novel system to improve outcomes and patient experience in tibial osteotomy:

- A new generic plate design to improve patient comfort and success rates for tibial osteotomy
- A combined cutting and drilling guide for use during surgery to ensure safe and accurate plate placement
- Improved 'bespoke' wedge designs for use during surgery or as implants to form part of the corrective procedure

Commercialisation

A patent has been filed and a series of plate, wedge and cutting guides are available. Oxford University Innovation is seeking industrial interest from parties wishing to licence and commercialise this technology.

For further information please contact:
Dr Chandra Ramanujan
chandra.ramanujan@innovation.ox.ac.uk
+44 (0)1865 614434
www.innovation.ox.ac.uk
Project number: 12527

Technology Transfer from the University of Oxford

Targeted imaging agent as a companion diagnostic and prognostic for osteoarthritis

Available to license: Targeted contrast agent for computer tomography (CT) as a tool for imaging damaged cartilage in patients with osteoarthritis

Oxford researchers have developed an approach to CT contrast which rapidly creates peptides containing sufficient quantities of iodine to facilitate imaging studies.

Diagnosis and monitoring of osteoarthritis

Osteoarthritis is a common condition characterised by the deterioration of the protective cartilage on the ends of bones, thus provoking pain and stiffness in joints, most commonly in knees, hips and small joints of the hands. The FDA recognises it as a serious disease with an unmet medical need. There is a lack of therapies that treat the underlying pathophysiology of the disease and potentially change its natural course to prevent long-term disability. The absence of a method to reliably assess the ability of a drug to alter the disease progression is among the reasons for such treatment deficiency.

While X-ray imaging remains an insensitive method as the cartilage is invisible under such scanning and MRI imaging shows low resolution with weak biochemical basis for change, contrast computerised tomography (CT) makes cartilage visible during the scanning.

CT contrast is commonly provided by injection of iodine containing chemicals which increases the visibility of blood as it flows through the circulatory system.

While imaging modalities such as positron emission tomography (PET) provide access to disease targeted imaging agents for the imaging of specific cancers or neurological diseases, no targeted agents are currently available for CT contrast.

Targeted computerised tomography

Researchers at Oxford have tackled this limitation and developed a novel and long lasting CT contrast imaging agent for cartilage tissues based on iodine-containing peptides.

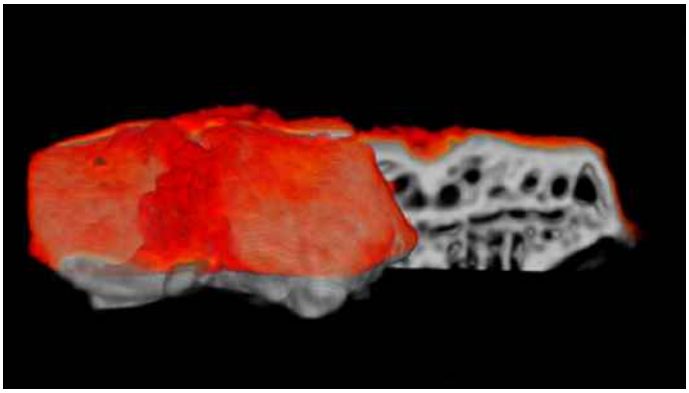
The technology provides:

- A new tool for osteoarthritis prognosis
- Lower cost implications compared to MRI, PET and SPECT
- Higher accessibility since CT scanners are more commonplace than their MRI counterparts

Although proof-of-concept work has been conducted in osteoarthritis, the same technique could be applied to a wide range of indications that can be targeted by peptide-based imaging, meaning that targeted CT contrast using iodinated peptides could be a game changer in the clinical management of a great numbers of patients.

Commercialisation

Oxford University Innovation has filed a patent with scope for international protection of a broad scope of radiopaque peptides and compounds. Commercial partners with an interest in licensing this technology or partnering for further clinical development are currently sought.



For further information please contact:
Dr Sarah Jones
sarah.jones@innovation.ox.ac.uk
+44 (0)1865 280845
www.innovation.ox.ac.uk
Project number: 13952

Technology Transfer from the University of Oxford

Head extractor tool for total orthopaedic hip replacement

Engineers at Oxford University and orthopaedic surgeons at West Middlesex University Hospital have designed and prototyped a novel surgical tool to improve the surgical procedures and outcomes of revision hip arthroplasty.

Limitations with current practices

Total hip arthroplasty is one of the most successful and cost-effective orthopaedic interventions performed today, with 310,000 procedures performed each year in the US. Approximately 2.5 million Americans are living with an artificial hip and this number continues to increase every year. In 10 to 15 percent of cases, patients will develop issues with their hip replacement, such as severe discomfort and pain, which requires revision surgery.

Currently there is no common practice and no dedicated tool for easily separating the implant head component from the stem, which results in varying degrees of success for the procedure. The separation itself can be extremely challenging, requiring a lot of energy from the surgeon, which can result in bone damage, longer operating times and increased financial costs.

A surgical tool designed for the task

Engineers at the University of Oxford and consultant orthopaedic surgeons at West Middlesex University Hospital have developed a novel surgical tool to improve the surgical procedures and outcomes of revision hip arthroplasty. This one-part re-usable tool has been designed to safely and quickly extract the head from a hip prosthetic implant without displacing the stem part.

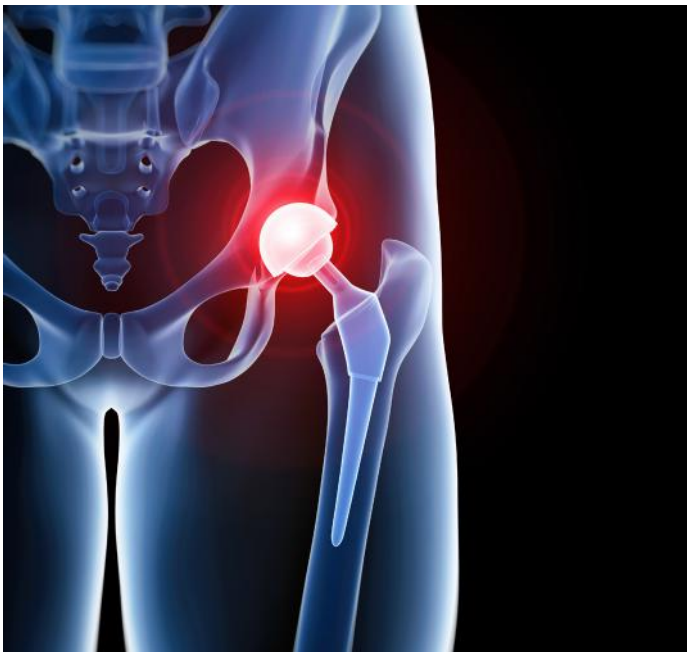
Using mechanical analysis, the tool design has been optimised to allow the surgeon to position the tool accurately before applying a force, to adjust the mechanism to a comfortable working position and to control the force applied.

Advantages provided by a dedicated tool

The Oxford device provides the following advantages:

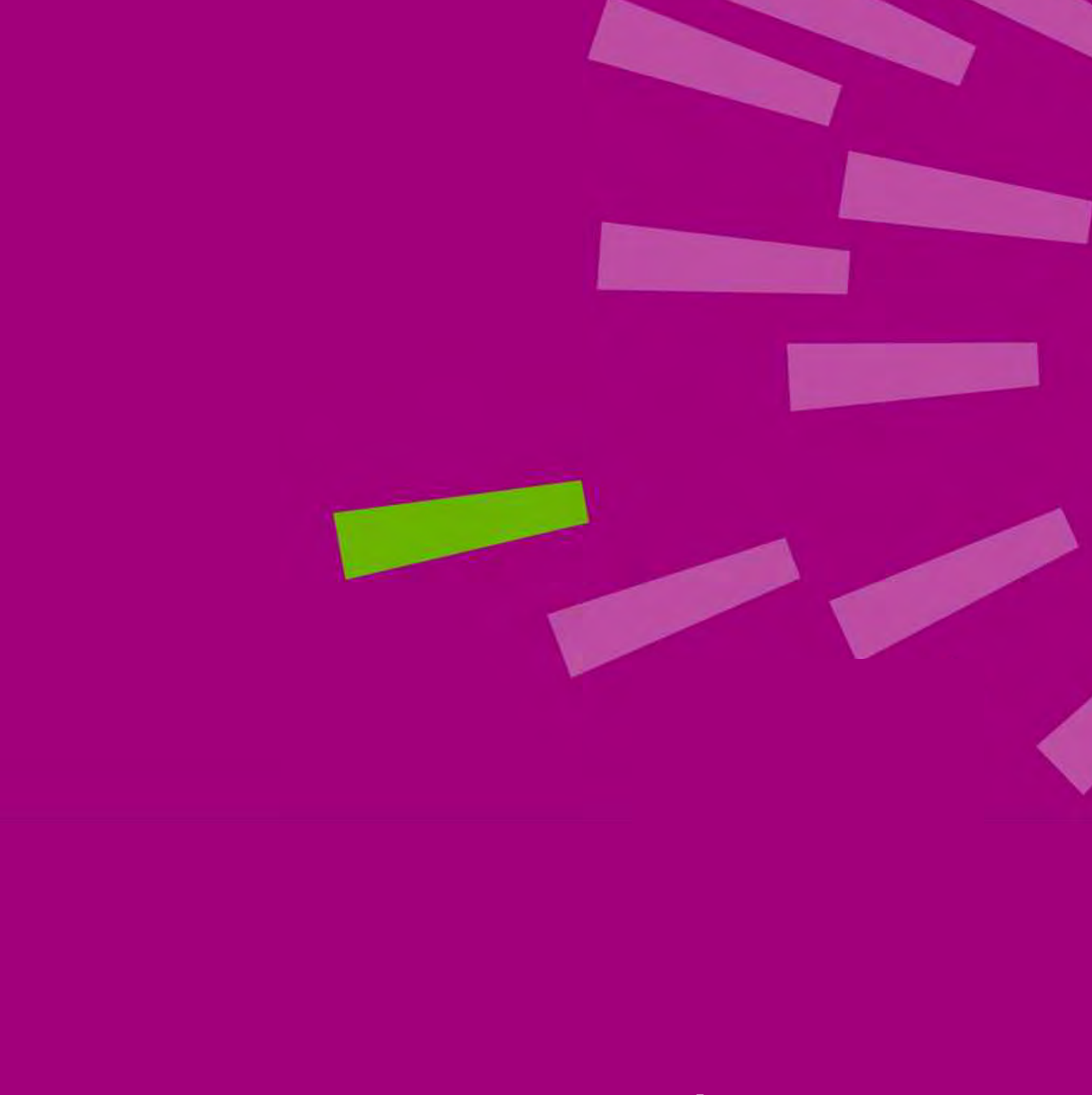
- Compatible with wide range of head-stem combinations
- Adjustable for any size head, including over 40mm heads
- Suitable for primary hip arthroplasties

A patent has been filed and a stainless-steel prototype is available. Oxford University Innovation is seeking industrial interest from parties wishing to licence and commercialise this technology.



For further information please contact:
Bénédicte Menn
benedicte.menn@innovation.ox.ac.uk
+44 (0)1865 280906
www.innovation.ox.ac.uk
Project number: 14859

Technology Transfer from the University of Oxford



PRODUCTION/ MANUFACTURING

Novel iron catalysts for the production of alpha-olefins

Oxford researchers have developed a new and sustainable iron based catalystic system for the production of alpha-olefins from CO_2 and /or CO.

Expansion of light microscope capabilities

Oxford researchers in the Physics department have developed miniature devices for bright-field light microscopes that fit into the slot reserved for DIC objective prisms (also known as the DIC slot). The Oxford devices would very simply and inexpensively convert existing light microscopes with DIC slots into instruments capable of additional applications.

Only one modular device is needed to add these features to a standard microscope. It is also possible to develop individual devices for each technique.

Epi-fluorescence

Epi-fluorescence is a well-established and widely used technique, which has numerous life science and medical applications. It requires relatively expensive kit including a special light source, an epi-illuminator and a set of filters. Using the Oxford epi-fluorescence module, researchers can easily detect fluorescent objects (eg. naturally fluorescent and fluorophore-labelled micro-organisms) using a filter-free setup or just a single emission filter.

Backscattering dark field

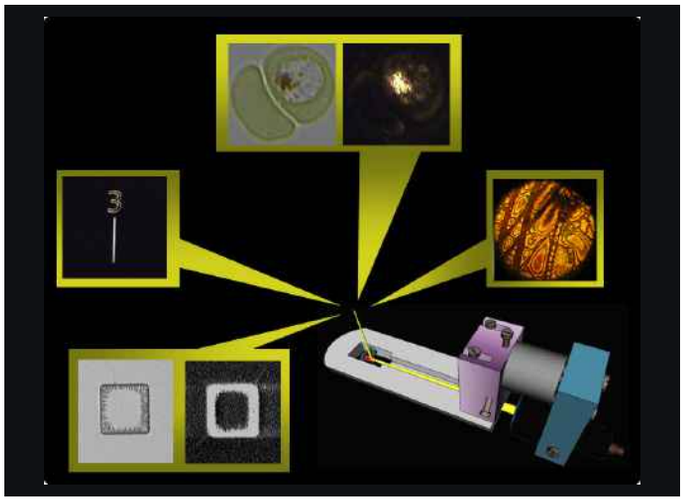
Backscattering dark field microscopy is an emerging field and is useful for detection of nanometre-sized objects below the diffraction limit, which makes it highly sought after in the nanotechnology sector.
To date, research and development in this field has been limited as backscattering microscopes are not commercially available and researchers need to build them themselves. The instruments are bulky and expensive as a result. Using the Oxford dark-field module, researchers are able to clearly view small objects of sub-micrometre size, in particular 50-100 nm gold particles.

Surface reflection

Surface reflection microscopes are widely used in material science and the semiconductor industry to study surface features of various specimens. They require special configuration of illuminating paths and cannot work without expensive special objectives. Used in surface-reflection mode, the Oxford device allows the result of photolithography or other surface modifying methods to be directly visualised.

Interference reflection

Interference reflection microscopy allows the monitoring of the thickness and quality of thin films. Such microscopes usually require additional optical elements like polarizing prisms and special objectives. With the Oxford device researchers can successfully monitor lipid bilayer formation, and estimate how evenly a thin layer of material has been deposited on a surface of interest.



For further information please contact:
Dr Jane Jin
jane.jin@innovation.ox.ac.uk
+44 (0)1865 614458
www.innovation.ox.ac.uk
Project number: 10429

Technology Transfer from the University of Oxford

Tissue bioreactor for drug discovery and tissue engineering applications

A novel device enabling the culture of cellular tissue that is conditioned to the mechanical forces found in the human body, suitable for drug discovery or tissue engineering applications.

Researchers at the University of Oxford have developed a contactless mechanically-enhanced tissue culturing technology which offers control over the mechanical loads exerted on the growing tissue.

The device is capable of exerting a range of precise, temporally and specially controlled forces on tissue cultures that closely mimic real-world conditions. All of the forces exerted are frictionless and contactless. This is in contrast to existing solutions which generally involve contact with the sample or tissue and are only unidirectional.

This new device has multiple applications, these include the development of an in vitro drug discovery platform, a novel drug delivery methodology, and the conditioning of engineered tissues in preparation for human tissue transplantation.

Stretching for perfection: Optimising tissue conditioning for transplantation

The process of evolution has produced human tissues that are optimised for their function. These tissues are also able to adapt during our lifetime to the kind of loading they experience. For example, the forearm bones of elite tennis players are stiffer and denser on their serving side.

Prior to implantation in humans, it is vital that synthetic tissue has been conditioned to receive mechanical loads whilst maintaining a sterile environment. Tissue cultured using the Oxford invention demonstrated excellent viability and mechanical properties equivalent to fresh samples. Relevant tissues include muscle, tendon, cartilage and bone.

Reduction of animal experiments via *in vitro* drug screening

In recent years there has been a concerted effort by scientists and researchers to move away from the use of animals to screen drug candidates. Alternative solutions capable of mimicking *in vivo* conditions are generally under—developed.

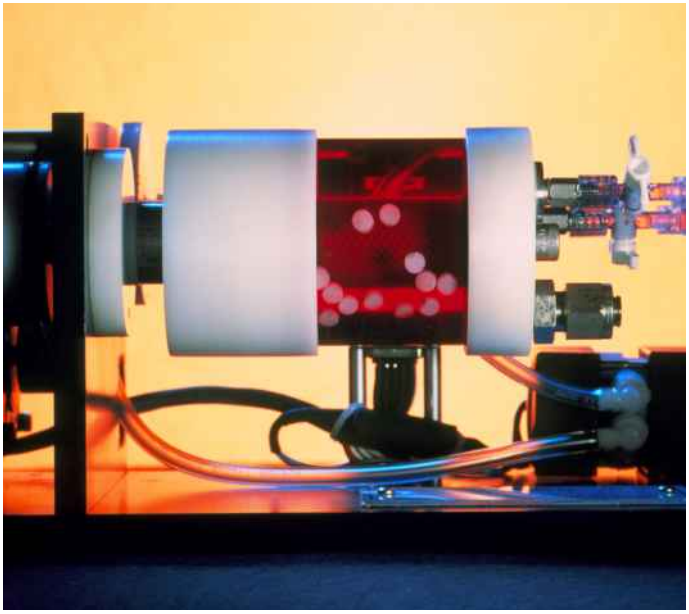
The Oxford device allows for drugs to be screened in an *in vitro* environment, which more closely simulates *in vivo* mechanical conditions and stresses.

Seeking a commercialisation partner

Prototypes have been built and tested and a patent application has been filed in a number of territories worldwide.

Oxford University Innovation is keen to talk to drug development, tissue culture or tissue engineering and bioreactor manufacturing companies interested in licensing this technology.

The technology readiness level is TRL 4.



For further information please contact:
Dr Sarah Jones
sarah.jones@innovation.ox.ac.uk
+44 (0)1865 614458
www.innovation.ox.ac.uk
Project number: 11475

Technology Transfer from the University of Oxford

A new tool for characterising water permeation across films

Researchers at the University of Oxford have developed a new method to study water vapour permeation through films.

The threat of humidity

Water poses an inherent hazard to many technologies and industrial processes. A plethora of different protecting barriers or films has been devised and implemented to fit the needs of specific applications. A key example of this is in the field of optoelectronics where films are necessary to protect organic light emission diodes (OLEDs) used in mobile phone screens. It is of utmost importance to understand how water vapour permeation through these films may occur in order to improve their performance.

Finding the leaks in the current methods

Various methods are currently used to assess water vapour transmission rate (WVTR) through films but none of them present a satisfactory combination of sensitivity, accuracy, reliability and low cost. The electrical Ca test represents a promising methodology. The test relies ona metal Ca plate in contact with the film, which undergoes a change in electrical conductivity when the moisture permeates the film. Unfortunately, the preparation of samples is very cumbersome, requiring the use of a dry box and therefore is expensive to implement.

Increasing accuracy and simplicity

Academics from the University of Oxford have developed a new version of the Ca test that improves its accuracy and overall performance. The method uses a camera to record the build-up of calcium hydroxide on the Ca plate caused by the moisture that permeates across the film. Furthermore, it gives additional information about the mechanisms of permeation (macrodefects or background/nanodefects) allowing better material designs and production controls.

Sample preparation has also been simplified and the need for the use of an inert atmosphere removed.

Advantages of the Oxford technology

Other main advantages of using our technology are:

- High sensitivity
- High throughput
- Control of test environmental conditions
- Facile sample preparation

Commercialisation

This technology is under patent protection and the University is looking for investors willing to help in its development and commercialisation.

For further information please contact:
Dr Chandra Ramanujan
chandra.ramanujan@innovation.ox.ac.uk
+44 (0)1865 614434
www.innovation.ox.ac.uk
Project number: 14776

Technology Transfer from the University of Oxford

Increasing the stability and biocompatibility of chemically synthesised oligonucleotides

Oxford researchers have developed a chemical synthesis strategy for producing DNA incorporating non-natural backbone structures and locked nucleic acid functions which convey desirable properties such as more selective and robust binding to complementary nucleic acids and greater resistance to enzymatic degradation.

Nucleic acids – Encoding life

DNA and RNA are biomolecules that are fundamental to all known forms of life. In recent years, many successful attempts have been made to harness the myriad functions of nucleic acids and apply them in the fields of human medicine, forensics and genetic testing. In general, these applications use DNA and or RNA produced through well-established solid phase synthesis methods. These mostly contain chemical modifications that have been established for very many years. Emerging applications, particularly in therapeutics, require more robust nucleic acid structures, with customisable properties to improve *in vivo* stability and delivery, so new designs and synthetic approaches are required.

New nucleic acid analogues - Improving on nature

To meet the demand for increased efficacy created by breakthroughs such as the recent development of several clinically approved therapeutic oligonucleotides, researchers have sought novel nucleic acid analogues. One such approach utilises azide-alkyne “Click” chemistry to generate a triazole surrogate of the natural phosphodiester backbone. However the presence of such groups in the DNA/RNA backbone renders the resulting biomolecules unable to efficiently bind (by Watson-Crick base pairing) to complementary DNA/RNA sequences. The selectivity and strength of this binding is crucial to its application.

LNA – Locking in new features

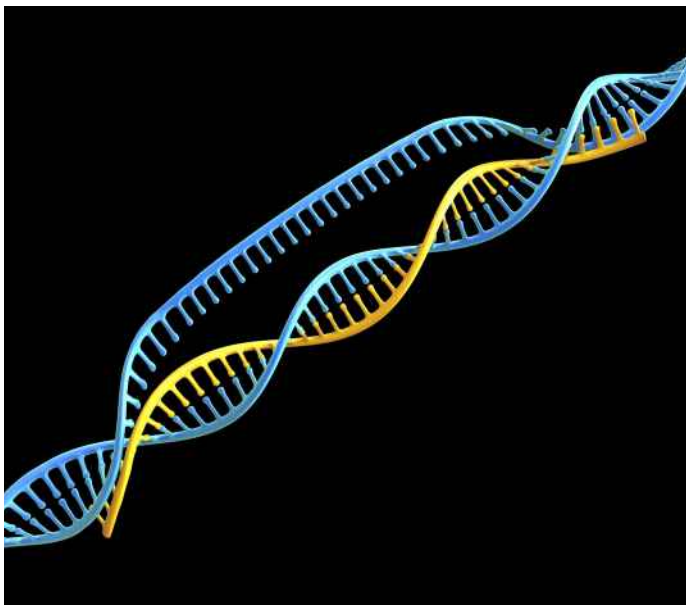
Researchers at the University of Oxford have exploited the triazole linkage in combination with locked nucleic acids (LNAs) to yield oligonucleotides which display higher target binding affinities and greater resistance to enzymatic degradation. In addition, reagents have been developed which allow for easy incorporation of this functionality by standard automated solid phase synthesis methods.

The main benefits of the Oxford Triazole-LNA approach are as follows:

- Significant increase in DNA:RNA duplex stability (target affinity) compared to triazole alone
- Less susceptibility to enzymatic degradation than native DNA/RNA
- Synthesis by rapid, efficient and scalable solid phase techniques
- Ability to modulate or eliminate anionic charge on DNA/RNA analogue

Protection and Applications

This technology is the subject of two patent applications and Oxford University Innovation is keen to talk to anyone who is interested in their commercialisation.



For further information please contact:
Dr Owen Metters
owen.metters@innovation.ox.ac.uk
+44 (0)1865 614416
www.innovation.ox.ac.uk
Project number: 14808, 14955

Technology Transfer from the University of Oxford

Electrocatalytic nanoparticles - Nafion® nanostructures doped with redox active species

Researchers at the University of Oxford have developed a simple synthesis route to Nafion® nanoparticles doped with redox active cationic species such as $Ru(bpy)_3^{2+}$ or methylviologen.

Redox cation doped Nafion® nanoparticles

Researchers at the University of Oxford have developed a simple synthesis route to Nafion® nanoparticles doped with redox active cationic species such as $Ru(bpy)_3^{2+}$ or methylviologen. These nanostructures display the similar facile oxidation/reduction properties as the solution phase cations. The supported catalysts are easily removed from reaction mixtures through filtration or centrifugation, thus reducing wastage. These nanoparticles could be applied to sensors, fuel cells and imaging. We believe the benefits of the redox cation doped Nafion® nanoparticles are as follows:

- Simple manufacture and recovery
- Inert and stable Nafion® support
- Incorporated cations retain their red ox reactivity
- Myriad applications due to the range of cations that can be selected for use

$Ru(bpy)_3^{2+}$ - The current face of electrocatalysis

Electrocatalysts are a subset of catalysts that operate at the surface of an electrode. Ruthenium (II) tris(2,2'-bipyridyl) ($Ru(bpy)_3^{2+}$) is a widely used electrocatalyst due to its accessible oxidation potential of 1.27 V vs SCE. The ability to electrochemically generate excited states of $Ru(bpy)_3^{2+}$ is also attractive as, upon relaxation to a ground state, such species will luminesce. The wavelength of the emitted photon is around 620nm, so will appear as red light.

In a separate application electrochemiluminescence (ECL) exploits the generation of excited species in an electrochemical reaction, which emits light upon relaxation to a lower-level state. ECL has been used in bioanalytical applications (DNA detection and Immunoassays), with $Ru(bpy)_3^{2+}$ featuring as the ECL reagent of choice. $Ru(bpy)_3^{2+}$ possesses excellent stability, a wide range of analyte tolerance and compatibility with many separation techniques. Numerous attempts have been made to immobilise $Ru(bpy)_3^{2+}$ on electrochemically inert substrates to aid with catalyst recovery and stability, however, success has been limited.

Transforming homogeneous redox chemistry into heterogeneous electrocatalysis

The developed methodology enables any homogeneous redox based chemical reaction involving cations as reagents to be transformed into an electrochemically driven catalytic process. It will transform redox solution phase chemistry by making it heterogeneous and catalytic.

Patent protection

A UK priority patent has been filed to protect this technology, and Oxford University Innovation Ltd. is looking to hear from anyone interested in helping in its commercialisation.

For further information please contact:
Dr Chandra Ramanujan
chandra.ramanujan@innovation.ox.ac.uk
+44 (0)1865 614434
www.innovation.ox.ac.uk
Project number: 15101

Technology Transfer from the University of Oxford

Novel method for obtaining conductive films

Oxford researchers have developed a novel method for obtaining conductive CNT films with inexpensive, non-conjugated polymers.

Conductive CNT films

Conductive coatings are widely used for electromagnetic interference shielding applications, anti-static material and other opto electronic devices. The global conductive coatings market was valued at $15,120 million in 2016, and is projected to reach at $24,360 million by 2023, growing at a CAGR of 6.8% from 2017 to 2023 (Allied Market Research).

The most commonly used materials are metal nanoparticles or carbon black where transparency is not a requirement, or conductive oxides and conductive polymers when a transparent coating is required. Materials such as CNTs are projected to make a big breakthrough in the field.

The problem with cost

Generally, conductive CNT films show high conductivity and good mechanical properties, but are expensive to produce. One of the reasons is that using non covalent wrapping with expensive conjugated (semi-conducting) polymers are thought to be essential due to the poor solubility of CNTs in organic and aqueous solvents.
In order to overcome this high cost, an innovative method of obtaining conductive CNT films without using expensive conjugated polymers is highly desired.

CNT functionalisation with non-conjugated polymers

Researchers at the University of Oxford have found a novel method of obtaining semi-transparent conductive films. This has been achieved with inexpensive stable non-conjugated polymers. These films show high transparency and similar conductivities to previous conductive CNT films that use conjugated polymers.

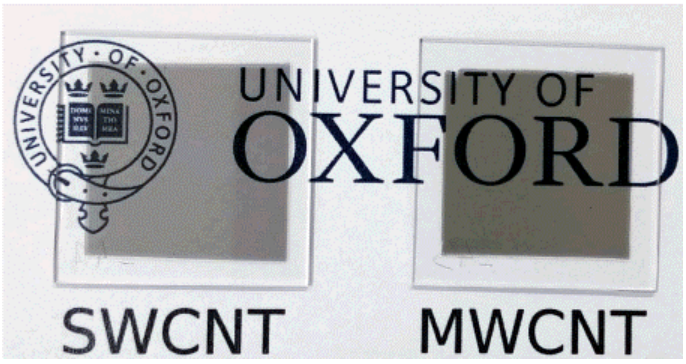
Using this method, conductive films can be directly produced from solution or sprayed onto any surface.

The main advantages of the Oxford method are:

- Similar conductivity but lower cost than previous CNT conductive films using conjugated polymer
- Better environmental stability of non-conjugated polymer than used conjugated polymer
- Can be directly sprayed onto any surface

Patent protection

A patent has been filed which covers this technology. Oxford University Innovation is interested in talking to potential partners to aid in the commercialisation of this new method.



For further information please contact:
Adrian Coles
adrian.coles@innovation.ox.ac.uk
+44 (0)1865 614432
www.innovation.ox.ac.uk
Project number: 15209

Technology Transfer from the University of Oxford

Enhancing crop yields and stress resilience

University of Oxford researchers utilise proteins in a key pathway involved in regulating plant development to improve crop yields and stress tolerance.

Plant cells contain a unique complement of organelles that are entirely absent from all animal cells. The organelles are termed plastids, which function as plant cell chemical factories and storage facilities. Plastids are critical for plant development and numerous important functions and include chloroplasts (photosynthesis), amyloplasts (starch storage), elaioplasts (fatty acid storage) and chromoplasts (fruit ripening). They also play critical roles in the adaptation of plants to their surroundings.

A specific feature of plastids is their ability to switch (also known as transition or interconvert) between plastid types in response to certain cues. These transitions are crucial for plant development and are a key means through which plants can adapt to a changing environment. The transitions rely on proteins that are made within the plant cytosol being imported into plastids via a pathway that includes the TIC/TOC proteins. TIC and TOC are translocon complexes located on the inner and outer membranes of plastids. Modifications to key components of TIC/TOC have been shown to directly affect plastids.

The TIC/TOC pathway can therefore be used as a novel method to regulate a variety of plant functions and thereby control performance traits. Researchers at the University of Oxford have identified two entirely novel proteins that act within the TIC/TOC pathway. One of the proteins has been termed SP2; this is a retrotranslocation channel that enables the extraction of ubiquitinated proteins from the plastid membranes. The second protein is known as PUX10 and is required to recruit a cytosolic chaperone (CDC48) to the plastid surface, where the latter then drives the extraction process. These proteins represent key steps in the TIC/TOC pathway.

The Oxford researchers envisage that by manipulating SP2 and PUX10 they will be able to regulate plant development. They envisage that altering the expression of SP2 and/or PUX10 can promote stress tolerance or delay leaf senescence, to induce a “stay green” phenotype, thereby promoting yield increases and enhanced plant health, or alter fruit ripening.

For further information please contact:
Dr Richard Auburn
richard.auburn@innovation.ox.ac.uk
+44 (0)1865 280956
www.innovation.ox.ac.uk
Project number: 15513, 15608

Technology Transfer from the University of Oxford

Single cell isolation

Researchers at the University of Oxford have developed a novel technique for ensuring monoclonality in a well plate for workflows that rely on single cell isolation.

Single cell isolation is a core part of many biologically important workflows, such as monoclonal antibodies (mAbs) production, stem cell therapy and gene editing. For such applications, it is essential to be able to confirm that a selected colony derives from a single cell to ensure high quality data for research projects and to meet regulatory requirements in a commercial environment.

Several different methods for ensuring monoclonality have been established. For example, fluorescence-activated cell sorting (FACS) can be used to allow fluorescently labelled cells to be sorted and ensure their isolation. Further, simple optical devices can be used to capture images of and examine individual wells holding biological matter. However, these existing methods are time-consuming and prone to difficulties.

Fluorescence activated cell sorting (FACS)

FACS can adversely affect cell viability whilst existing methods of examining wells can lead to uncertainty due to what is known as the “edge-effect”. With conventional methods of examining wells, identifying cells in the region where the well base meets the vertical well wall is particularly difficult as dark/blurred regions in images can occur due to well edge artefacts. Even capturing images of cells situated within and close to the boundary of the droplet can prove problematic due to unwanted optical effects at the interface of the droplet.

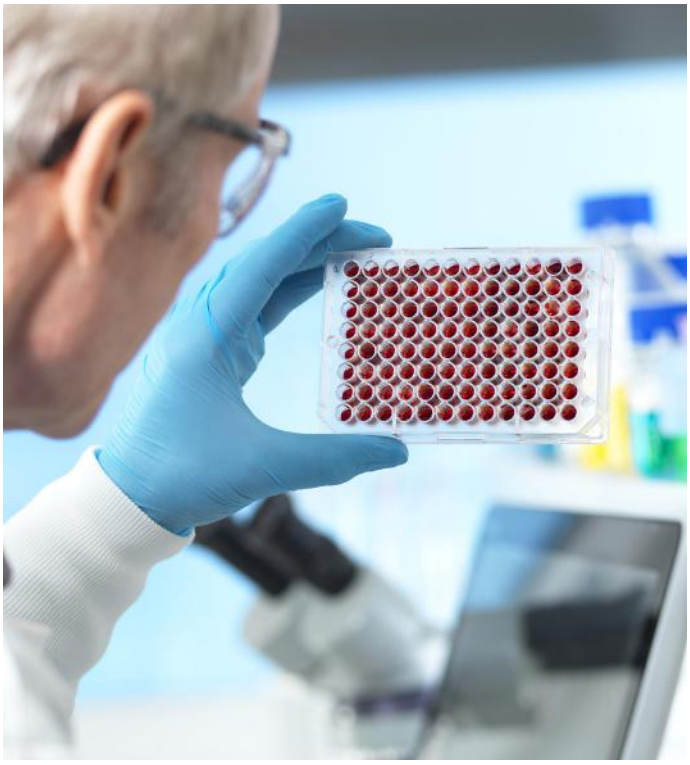
Technologies for single cell isolation

Through appreciating the problems with existing methods, researchers at the University of Oxford have developed a new technique for ensuring monoclonality in droplets for both industrial and research workflows.

The objective behind this new method is to enhance optical clarity by using discrete drops in well plates, thereby eliminating the “edge effect” problems that occur with well plate walls. Further, using this novel arrangement, individual droplets holding cell matter can be “flattened” to provide complete clarity over the entire drop region and provide more certainty over the presence of no, one or a plurality of cells.

Patent protection

The methodology is the subject of a patent application. Oxford University Innovation is actively seeking commercial partners to help commercialise the technology in existing industrial workflows and take an exclusive market position in relation to it.



For further information please contact:
Ben Oakley
ben.oakley@innovation.ox.ac.uk
+44 (0)1865 280869
www.innovation.ox.ac.uk
Project number: 15782

Technology Transfer from the University of Oxford

Tuneable optical coatings

Researchers at the University of Oxford have identified and used a new class of chalcogenide glass materials in optical coatings which have potential applications across a broad range of optical components.

Optical coatings, which are easy-to-manufacture multi-layered stacks of dielectric and metallic thin films, are used in a broad range of different components of devices including data storage mediums, lenses and displays.

Photonic components such as spatial light modulators can also make use of these stacks. Such optical coatings utilise the principle of thin film interference, i.e. phase driven constructive and destructive interference of light waves, to enable a multitude of optical effects.

Often thick optical coatings are required in order to achieve desired optical effects in a device. This means that the process of applying optical coatings can be material intensive. Further, such coatings are passive, meaning they lack tunability due to their static material properties, which limits their usefulness in many potential applications such as solid-state displays and smart glasses.

In recent years, the creation and manipulation of colour reflected off a surface by changing the refractive index of ultra-thin functional layers has been realised through use of phase change materials (PCMs). Optical coatings and devices can be designed with ultra-thin film structures such that white light is reflected as red, green or blue.

Having PCMs in these thin film structures means that the light reflected in the displays can be adapted and tuned on demand.

Whilst PCM's lead the way in tuneable optical coatings, such coatings often require a more complex stack arrangement and can have high optical losses associated with them, which is not ideal in many scenarios where transmission/reflection efficiency is of crucial importance.

With this in mind, researchers at the University of Oxford have identified a new class of chalcogenide glass materials, with highly tuneable properties, reduced stack complexity and applicability across a broad range of devices. This enables components to be manufactured which are thinner and exhibit lower losses than in existing devices. In addition, the optical properties can be continuously tuned, in contrast to many existing devices which are restricted to a limited number of different optical states.

Patent protection

This novel technology is the subject of a patent application. Oxford University Innovation is now seeking commercial partners to adopt the new technology and support its future development.

Image: Chalcogenide glass.

For further information please contact:
Ben Oakley
ben.oakley@innovation.ox.ac.uk
+44 (0)1865 280869
www.innovation.ox.ac.uk
Project number: 16128

Technology Transfer from the University of Oxford

Bespoke reference electrode for electrochemical sensors

Oxford researchers have developed a novel solid-state electrolyte-free reference electrode suitable for miniaturisation.

The use of reference electrodes

High quality reference electrodes, are essential in all electrochemical experiments embracing both amperometric and potentiometric. They are fundamental units in the many chemical sensors which rely on such electrochemical measurements including glucose sensors and fire alarms.

The stability and robustness of a reference electrodes is key for its success as they dictate the sensitivity and longevity of a sensors.

The most popular reference electrode is the silver/silver chloride electrode. This is widely used in pH meters and often the reference electrode of choice in redox potential measurements as well as in a numerous biosensors including those built on screen printed electrodes. For a stable and reproducible potential, a fixed chloride concentration is crucial and this is achieved by having a Ag/AgCl surface in contact with a solution of potassium chloride of a fixed molarity inside or bathing the electrode.

Such requirements are often problematic in applications in which the reference electrode needs to be miniaturised or when the reference electrode is used in flowing solutions. Losses of AgCl from the electrode surface are well known and are the cause of contamination, potential drift, and loss of electrode stability. Alternatives are needed to drive forward and facilitate the highly active area of (electro-) chemical sensing.

Nafion film based reference electrodes

Researchers at Oxford have addressed these limitations through a bespoke design and developed a solid state electrolyte-free reference electrode in which the two components of a redox couple are uniquely immobilised on a Nafion film supported on a metal surface.

Advantages of this novel technology include:

- Simple fabrication
- Deployable on any metal surface
- Readily miniaturised
- Avoids leaching or continuation problems
- Excellent stability and lifetime
- Disposable

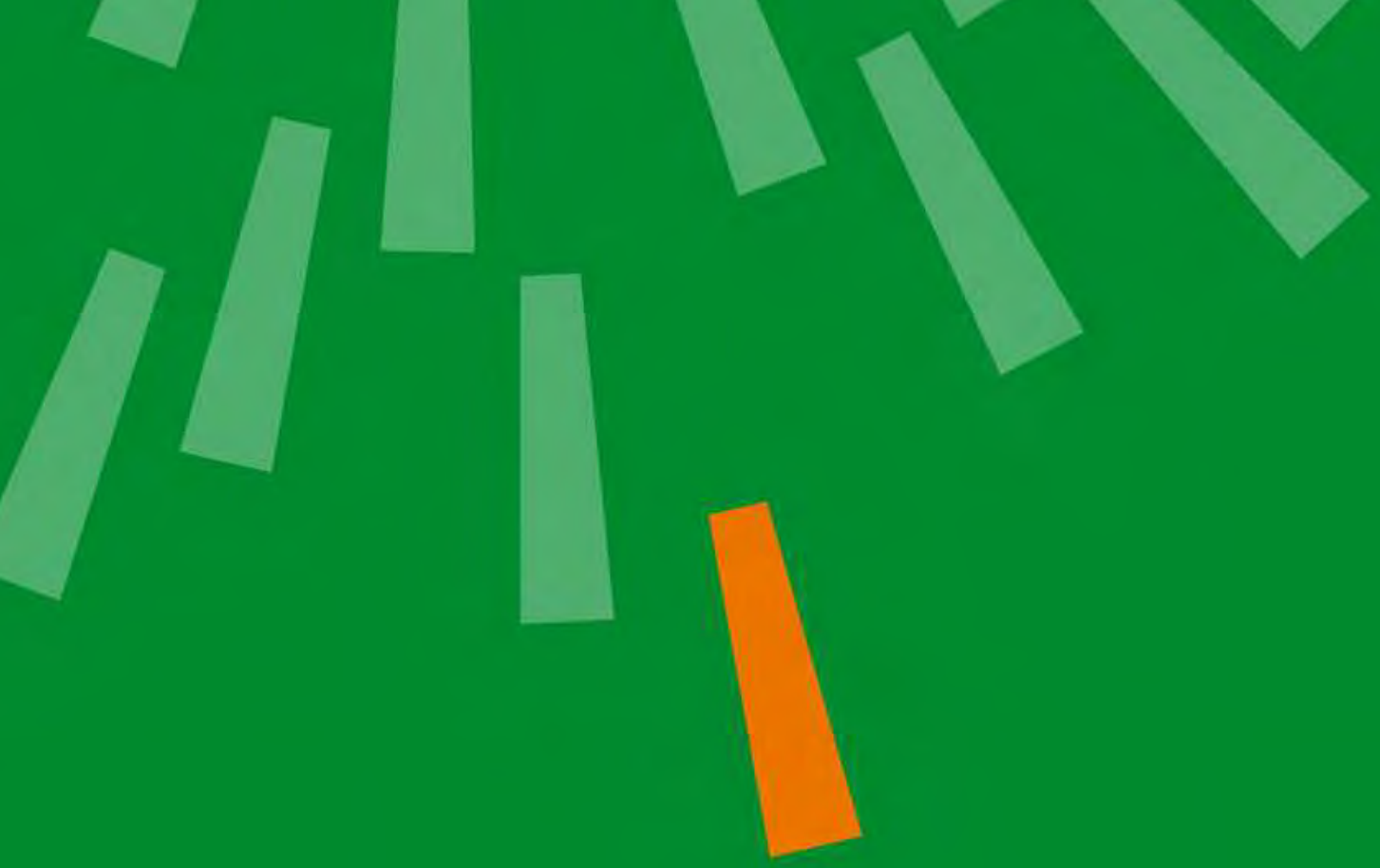
In summary, the doped Nafion film based reference electrode is a robust alternative to the silver/silver chloride reference electrode. Miniaturisation would allow for applications in analytical devices at all scales, as well as in disposable sensors.

Commercialisation

Oxford University Innovation has filed a priority patent application on the technology and welcome discussion with companies interested in licensing it for commercial development.

For further information please contact:
Dr Jamie Ferguson
jamie.ferguson@innovation.ox.ac.uk
+44 (0)1865 280851
www.innovation.ox.ac.uk
Project number: 16771

Technology Transfer from the University of Oxford



RESEARCH TOOLS

Nanoparticle detection

The low-cost, disposable electrodes can be harnessed for in-field detection and quantification of nanoparticles

The antibacterial and antiseptic effect of silver nanoparticles (Ag NPs), in combination with their cost-efficient mass production, has resulted in their use in a wide variety of consumer and medical products. The omnipresence of these nanoparticles and their corresponding release into the environment, in combination with their unknown effect on environmental systems, raises the demand for reliable and affordable techniques for their detection.

Limitations of current detection and characterisation

A number of methods including light scattering, nanoparticle tracking analysis and UV/visible measurements have been successfully used to determine the composition, concentration, size, surface charge density, adsorption and agglomeration of NPs in various systems, including real environmental samples. A limitation of these methods is that liquid samples have to be taken, transported and analysed. This carries the risk of causing changes to the sample, for example by altering the concentration or aggregation state.

Oxford developments

Oxford researchers have developed a novel approach to Ag NP detection, with potential application for long-term field studies and environmental monitoring. Their method uses specially surface-modified glassy carbon electrodes. These “sticky” electrodes are immersed into the medium of interest, the NPs are allowed to stick to the surface over a period of time, and then the amount of NPs immobilised on the electrode surface is analysed either in the field or in the laboratory.

Advantages

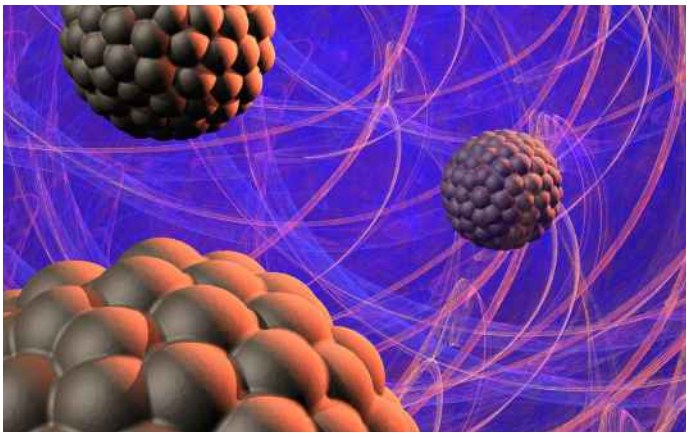
The use of sticky electrodes enables a long sampling time and thus detection of NPs even from media with low concentrations of NPs. The sample can be collected on site without an applied electric potential, i.e. under open circuit conditions. As a result, there is no need to base expensive and sensitive equipment on site. Analysis may be carried out back at the laboratory with a much reduced risk of the sample being changed by transportation. The modified carbon electrodes lend themselves to manufacture via screen printing and therefore have potential to offer a commercial partner a low cost and disposable solution.

Supporting data

The Oxford developments are described in Chemical Communications (2013), entitled “Sticky electrodes for the detection of silver nanoparticles.” Please also refer to related Isis Project No. 7909, “Electrochemical detection of silver nanoparticles.”

Moving forward

The underlying technology is the subject of a UK patent application. Oxford University Innovation is seeking external partners to support the commercialisation of the technology.



For further information please contact:
Dr Chandra Ramanujan
chandra.ramanujan@innovation.ox.ac.uk
+44 (0)1865 614434
www.innovation.ox.ac.uk
Project number: 10098

Technology Transfer from the University of Oxford

IMPACT: Rapid calculation of protein structural parameters

Available to license: An algorithm and software implementation to rapidly calculate the size of proteins with applications in structural biology and proteomics.

The IMPACT (Ion Mobility Projection Approximation Calculation) algorithm developed by Oxford researchers offers a 10^6-fold increase in speed without a significant drop in accuracy.

Protein structure-function correlation

The structure of proteins and multi-component protein assemblies is closely related to their function in biological systems. Knowing the detailed structure of a protein enables analyses of protein function. Methods for the accurate and efficient determination of key structural parameters are vital.

The development of new structure determination methods and improvements to existing methods are critical to advancing the fields of both proteomics and structural biology.

Collision Cross Sections (CCSs)

The Collision Cross Section (CCS) gives an accurate measurement of the size of a protein or protein cluster and can be directly used to predict interactions between multiple proteins and/or between proteins and other biological molecules. A significant bottleneck arises in making structural sense of the CCSs.

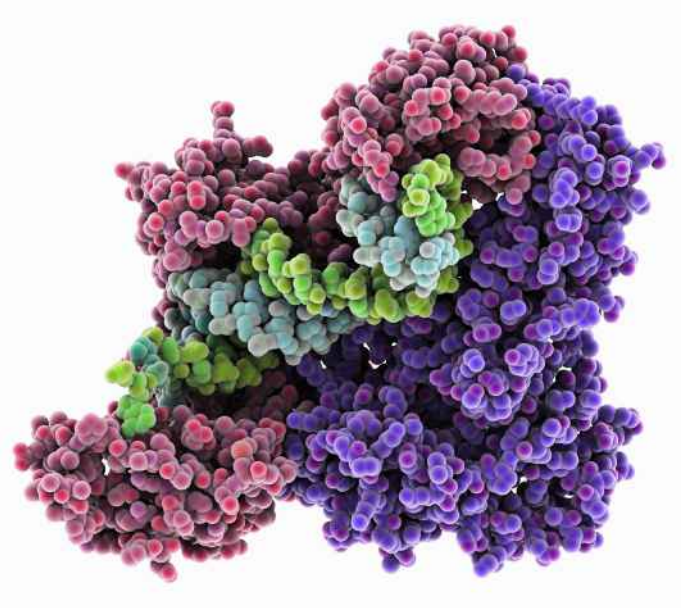
IMPACT (Ion Mobility Projection Approximation Calculation Tool)

Oxford researchers have developed the IMPACT algorithm which achieves a 10^6-fold efficiency increase in the calculation of CCSs when compared to IM-MS data. Whereas existing methods could take approximately 1 day to calculate the CCS for a moderately sized protein, IMPACT arrives at the same result in 0.07s.

The key advantages of this technology include:

- 10^6-fold increase in efficiency
- No significant drop in accuracy
- Interface allows integration with other software
- Readily mimics more rigorous methods
- Already adopted by more than 150 academic laboratories

This algorithm could be used to ensure gas phase experiments can be used in a superfast method for calculating CCSs and ultimately enable modelling solution-phase separation of proteins. Oxford University Innovation is seeking external partners that wish to use this proprietary software.



For further information please contact:
Dr Richard Auburn
richard.auburn@innovation.ox.ac.uk
+44 (0)1865 280956
www.innovation.ox.ac.uk
Project number: 10126

Technology Transfer from the University of Oxford

Protein team assembly for controlling cell signalling and catalysis

Available to license: A simple method to link proteins into programmed chains via spontaneously reacting peptide/protein pairs, generating a new class of tools to manipulate cell behaviour.

Researchers at the University of Oxford have developed a ‘bacterial superglue’, known as SpyTag/SpyCatcher, from *Streptococcus pyogenes*.

SnoopTag

Researchers at the University of Oxford recently developed a ‘bacterial superglue’, known as SpyTag/SpyCatcher, from Streptococcus pyogenes. They have now developed a new peptide/protein pair named SnoopTag/SnoopCatcher, from Streptococcus pneumoniae, which spontaneously locks together through a covalent bond. SnoopTag/SnoopCatcher reaction is high yielding and fast, while the bond can survive extreme pH, high ionic strength and detergents. SnoopTag/SnoopCatcher and SpyTag/SpyCatcher are genetically encodable and are mutually unreactive, so they allow many new opportunities for controlled and irreversible linkage of peptide and protein components. By exploiting these peptide/protein pairs together, a modular and high yielding approach to irreversibly assemble proteins into chains has been developed.

Generating protein chains

Solid-phase synthesis, which involves reactants bound to resin, enabled a revolution in the generation of peptides and oligonucleotides to efficiently explore and control biological function. However, solid-phase linkage for proteins is much more complex because of the large number of potential reactive groups present. Previous methods only generated short protein chains because the methods give a range of undesired side-products, have weak linkages, or use non-genetically-encoded components.

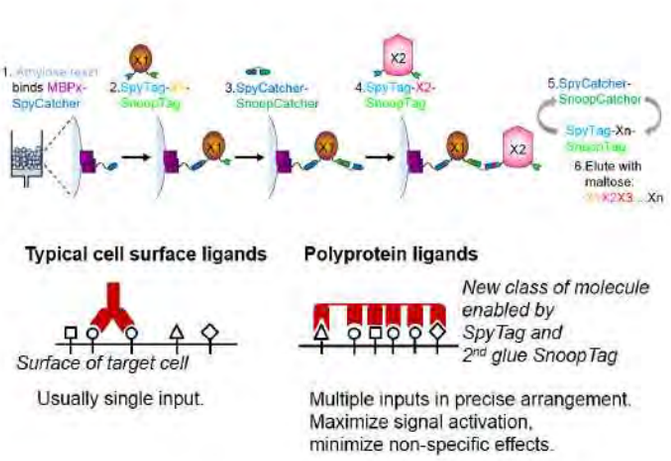
The key properties of SnoopTag/SnoopCatcher-based solid-phase assembly are:

- Simple add-and-wash procedure
- Irreversible linkage
- Completely genetically encoded, with no use of alternative amino acids
- High specificity
- No need to purify intermediates
- Protein unit to be added modified only with two small peptide tags, which can be located at the N-terminus, C-terminus or an internal site on the protein
- No cysteines in the reaction, so applicable to proteins containing free cysteines or disulfide bonds

This approach enables combinatorial assembly of polyprotein teams and should open up a new area for controlling how protein components work together. Uses of this invention include vaccine generation, enzyme substrate channelling, antibody polymerisation, drugs for activating cell signalling and biomaterials.

Current status

This technology is subject to a patent application. Isis is interested in hearing from potential partners who wish to develop the technology and explore the commercial opportunities.



For further information please contact:
Dr Christine Whyte
christine.whyte@innovation.ox.ac.uk
+44 (0)1865 280921
www.innovation.ox.ac.uk
Project number: 12370

Technology Transfer from the University of Oxford

Catalytic double bond migration

Available to license: A low-cost, high-performance photocatalytic method for the isomerisation of terminal olefins to yield internal olefins in high yields and under mild conditions.

Oxford University researchers have developed a novel photocatalytic process for the isomerisation of terminal olefins to high value internal olefins.

Internal olefins – global demand

A strong demand for internal olefins exists across both the petrochemical and fine chemical industries. Internal olefins are widely used in paper sizing, drilling mud, cutting fluids and for lubrication based oil. When derivatised further, internal olefins have applications as agrochemicals, pharmaceutical intermediates, and surfactants. Internal olefins can be considered environmentally benign and offer a higher surface activity in comparison with corresponding terminal olefins.

The deficiencies in internal olefin production

Internal olefins are produced by the isomerisation of readily available terminal olefins. These complex processes require high temperatures, expensive precious metal catalysts, and large solvent volumes. Owing to the high-temperatures, side-reactions such as skeletal rearrangements are common, reducing conversions to the desired product.

Products are often contaminated by the catalyst, which must be removed through a further distillation step. The isomerisation reactions must be conducted in the absence of light and oxygen, and at high pressures for optimum performance, adding further complexity and cost to the process. As many aspects of the current production methods are undesirable, the many lucrative applications of internal olefins have yet to be fully realised.

A green and high performance process

Oxford researchers have developed a low-cost, high-performance process for the isomerisation of terminal olefins to internal olefins through a novel photocatalytic procedure.

The new process offers the following advantages:

- Exceptional conversions (up to 100%)
- Mild conditions
- No requirement for exclusion of oxygen
- No solvent required
- Facile separation of reaction system and catalyst recycle
- No additional purification
- No side-reactions

Implementation of the Oxford process has the potential to address the global demand for internal olefins and other in-demand double bond migration chemicals.

The invention is the subject of a patent application with the potential for international coverage.

Oxford University Innovation would like to speak to companies interested in low-cost internal olefin production with decreased environmental impact.

For further information please contact:
Dr Owen Metters
owen.metters@innovation.ox.ac.uk
+44 (0)1865 614416
www.innovation.ox.ac.uk
Project number: 12535

Technology Transfer from the University of Oxford

MAGMA: Automated assignment of NMR spectra for proteins and complexes

Available to license: MAGMA enables automated assignment of Nuclear Magnetic Resonance (NMR) spectra for proteins, small molecules and intermolecular complexes of proteins and small molecules.

Oxford researchers have developed a method for the robust assignment of methyl Transverse Relaxation Optimised Spectroscopy (TROSY) spectra.

Probing the structure and dynamic behaviour of proteins and complexes

NMR spectroscopy has become an essential tool for solution state studies of proteins and other macromolecules. NMR spectroscopy simultaneously provides information about the structure and dynamics of biomolecules at an atomic resolution, thereby enabling analyses of protein folding, denaturation, folding intermediates and transition states, conformational and dynamic behaviour of a biomolecule, ligand binding and mapping of binding sites.

Pushing the limits

Traditional NMR techniques have provided a wealth of information about small proteins, up to approximately 30 kDa in weight. Translating NMR to the study of larger macromolecules has proved challenging. Methyl TROSY (Transverse Relaxation Optimised Spectroscopy) has recently been developed to provide information on the structure and dynamic behaviour of protein complexes up to 1 MDa in weight: capturing 99% of the human proteome.

Despite the ability to push beyond the traditional weight limit, the assignment of methyl TROSY spectra is presently time-consuming and cost-prohibitive.

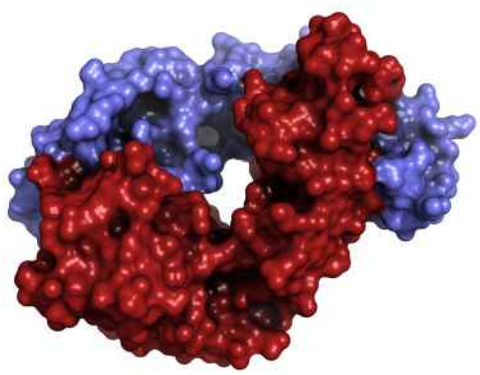
An automated assignment

Currently, assignment of methyl TROSY spectra is typically performed using (multiple rounds of) single point mutagenesis. This requires multiple expensive samples and can provide high cost but potentially unreliable data. Oxford researchers have developed a method that automatically assigns the residues whilst eliminating the need for or enabling targeted (informative) in situ mutagenesis.

Advantages of the Oxford method:

- The graphical user interface supports processing raw data and picking spectral resonances
- Compatible with 'NMR pipe' (from NIH) and 'Topspin' (from Bruker)
- time and cost effective (10^5 faster than MAGMA v1)
- measurements taken on a wild-type sample
- provides all feasible solutions, with a confidence fit to direct downstream analyses
- robust data analysis in the presence of artefacts, incomplete detection of resonances, presence of impurities and other sources of experimental error

Application of this highly disruptive method removes a key barrier to the widespread adoption of methyl TROSY NMR. Thereby enabling usage of this and related NMR techniques for drug, agrichemical and nutraceutical discovery programmes. By using solution NMR, the Oxford researchers were able to experimentally measure inter-methyl distances from the NOESY data. The method has been extensively tested, and the technique is the subject of a patent application. Oxford University Innovation is seeking commercial partners with an interest in incorporating this technique into their discovery programmes.



For further information please contact:
Dr Richard Auburn
richard.auburn@innovation.ox.ac.uk
+44 (0)1865 280956
www.innovation.ox.ac.uk
Project number: 12970, 15255, 15640

Technology Transfer from the University of Oxford

BiobOx: A flexible tool for structural biology

Available to license: Software for the analysis of protein structures from the atomic level up to multimeric quaternary structures.

Researchers at the University of Oxford have developed BiobOx, a structural biology tool, which allows users to analyse and manipulate protein structures, incorporating data from electron density maps and collisional cross sections.

Structural Biology

Macromolecules, such as peptides and nucleic acids, underpin the key functions of all cells. Due to this, determining the exact structure and function of these molecules is of the utmost importance. Studying the ways in which proteins fold (tertiary structure) and combine (quaternary structure) has led to the development of treatments for complex diseases and genetic disorders.

Information overload

In order to determine a macromolecular structure, structural biologists collect information from many sources both experimental and computational. Specialised software can be used to analyse specific components of this information but, at present, no tools exist that can integrate experimental and calculated data to produce new, testable hypotheses. Researchers at the University of Oxford have developed BiobOx, a fully integrated computational tool, which solves numerous problems in structural biology.

Opening the lid on BiobOx

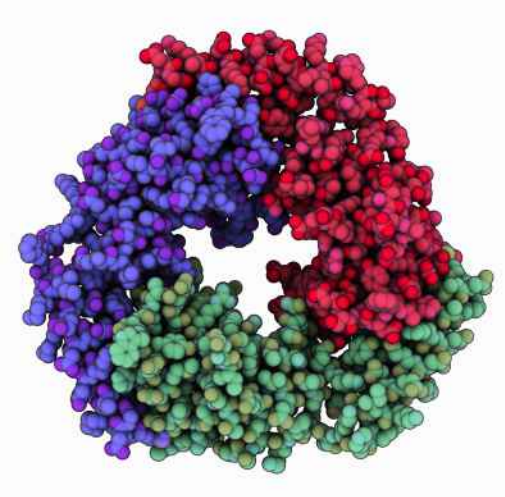
BiobOx allows the user to manipulate and analyse key quantities at all levels of macromolecular structure (primary to tertiary structure). BiobOx can exploit these structures as sub-units to propose highly complex quaternary structures. Structures generated in BiobOx can also be verified using experimentally obtained electron density maps.

We believe that the key advantages of BiobOx are:

- Fully integrated structural biology software solution
- Generates protein assemblies based on custom architecture
- Calculates collisional cross-sections based on the electron density map
- Assesses the amino-acid cross-linking distance as a solvent accessible path

Commercialisation

BiobOx is currently available free for academic users. Oxford University Innovation Ltd is also seeking commercial licensees for BiobOx.



For further information please contact:
Dr Richard Auburn
richard.auburn@innovation.ox.ac.uk
+44 (0)1865 280956
www.innovation.ox.ac.uk
Project number: 13367

Technology Transfer from the University of Oxford

Metal-organic frameworks (MOFs) for application in photochemical sensing

Researchers at the University of Oxford have developed a synthetic protocol, which can access MOFs containing a range of guest species.

Metal-organic frameworks

Metal-organic frameworks (MOFs) are crystalline hybrid materials with pores formed between the organic ligand "struts" and the metal ion or clusters "vertices". These nanoscale voids vary in size and functionality depending on the metal/ligand system employed.

If these holes in the MOF could be filled with functional guest molecules, forming a tuneable host/guest system, this could impart unusual physical and chemical properties on this emerging class of material.

Welcoming the guests

Researchers at the University of Oxford have developed a high-yielding synthetic approach, which facilitates the inclusion of a variety of functional guest molecules into the MOF structure. This one-pot self-assembly methodology simply requires mixing the correct ratios of metal ions, organic ligands and functional molecules to yield a supramolecular hybrid material comprising functionalised 2D nanosheets. For example, incorporation of luminescent zinc-quinolate complexes (ZnQ) in this fashion results in a solvent-sensitive, luminescent, host/guest system.

Sensing volatile organic compounds (VOCs)

Exposure of the Zn-based hybrid material to liquid or gaseous organic compounds results in a dramatic change in its optical properties easily detectable in UV light (see image). Even in the solid state, the emission wavelength changes upon exposure to two different polar solvents. This pattern is observed for fast detection of a vast range of VOCs, both polar and non-polar. We believe that these materials could be applied to photochemical sensors for VOCs.

The main advantages of the Oxford technology are:

- Facile, high-yielding and patent protected synthetic methodology
- Could be used to include a range of functional molecules
- Inclusion of ZnQ provides a route to engineer reversible photochemical VOC sensors
- Material structure, properties and durability have been extensively characterised
- Material can be deployed in solid-state in the form of 2D nanosheets, thin films, polymer-MOF nanocomposites (fibres/membranes), or simply in solution state.

Commercialisation

Oxford University Innovation Ltd. has filed a patent covering this technology and is now seeking an appropriate commercialisation partner.

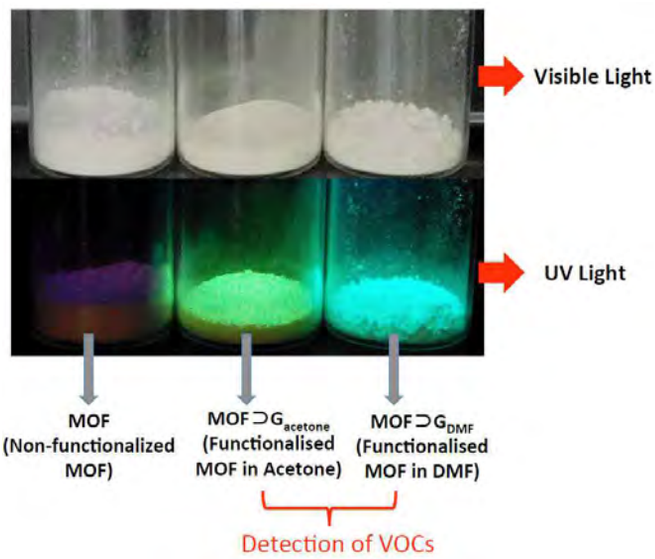


Image: Solid state visible and UV light emissions of functionalised versus non-functionalised MOFs

For further information please contact:
Chim Chu
chim.chu@innovation.ox.ac.uk
+44 (0)1865 280832
www.innovation.ox.ac.uk
Project number: 13774

Technology Transfer from the University of Oxford

SpyTag and SpyCatcher version 2.0

Oxford researchers have improved SpyTag and SpyCatcher, a peptide/protein pair that acts as a 'superglue' for proteins.

Peptide tags

Peptide tags are convenient tools for protein analysis and modification due to their small size, which reduces the chance of affecting protein functionality. The small interaction surface between a peptide and its associating protein partner results in a lack of affinity.

Protein engineers in Oxford have come up with a solution: adapting natural proteins forming covalent bonds to design stronger peptide tags. SpyTag and SpyCatcher are a peptide/protein pair adapted from the adhesins of Streptococcus pyogenes by a group of Oxford researchers.

SpyTag and SpyCatcher Version 2.0

The same group has now designed SpyTag and SpyCatcher Version 2.0, which significantly improves on the performance of the previous technology while retaining all the benefits of their predecessors. They work across a wide range of experimental conditions (e.g. pH values, temperatures and buffers) even in the presence of detergent, show specificity in cellular systems and are also equally heat-resistant.

Version 2.0 exhibits a more than 10-fold increase in the speed of reaction, whilst self-reaction of SpyCatcher is impeded. This increase in reaction rate will be important in improving speed and sensitivity for capture of biological targets that are expressed at low concentrations.

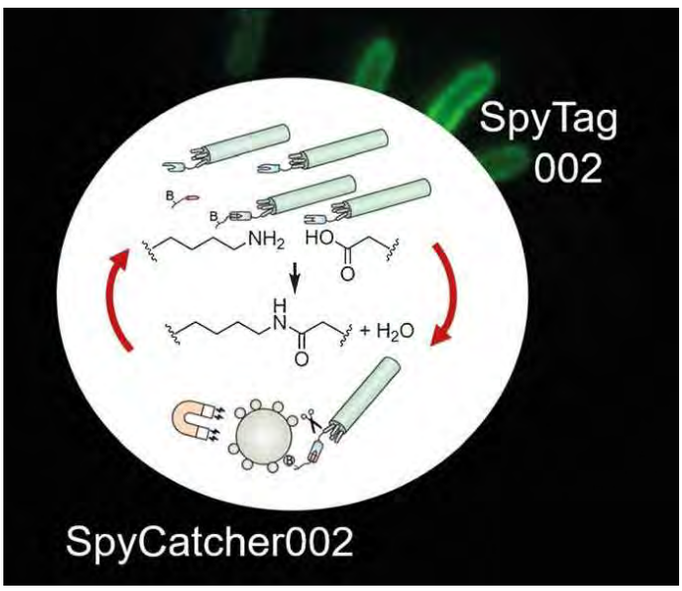
Uses of the technology

SpyTag and SpyCatcher Version 2.0 can be used for a myriad of purposes:

- Targeting fluorescent or other biophysical probes to specific proteins
- Protein immobilisation for proteomics
- Conjugation of antigens to virus-like particles, viruses, bacteria or multimerisation scaffolds for vaccination
- Increasing enzyme resilience by SpyRing cyclisation
- Linking multiple enzymes into pathways to promote metabolic efficiency
- Solid-phase polyprotein synthesis which can activate multiple signalling pathways

Commercialisation

This technology is subject to a patent application. Oxford University Innovation would like to speak to companies who are interested in licensing the technology.



For further information please contact:
Dr Christine Whyte
christine.whyte@innovation.ox.ac.uk
+44 (0)1865 280921
www.innovation.ox.ac.uk
Project number: 14348

Technology Transfer from the University of Oxford

SnoopLigase for catalysis of ligation between two peptide tags

Oxford researchers have developed a tool that greatly enhances the functionality and diversifies the use of the current SpyTag/SpyCatcher peptide technology.

Tag/Catcher systems

SpyTag/SpyCatcher and SnoopTag/SnoopCatcher are powerful bioconjugation tools developed by Oxford researchers by exploiting the natural properties of *Streptococcus pyogenes* and *S. pneumoniae*. The Tags and Catchers act as 'superglue' for proteins – spontaneously forming irreversible isopeptide bonds with each other when combined.

The Tag/Catcher technologies are currently used by researchers worldwide. The functionality of the tools is, however, limited by the size of the Catcher – the partner protein for the corresponding Tag peptide. For example, the Catchers need to be fused at the termini of proteins to prevent protein folding interferences. Moreover, when the Tag/Catcher systems are used for vaccine optimisation, the induction of antibodies or T cells may be directed towards the Catcher rather than the target antigen.

SnoopLigase

The same Oxford research group have solved the problem by developing SnoopLigase. SnoopLigase catalyses the irreversible conjugation between SnoopTag and a novel peptide (known as DogTag). The functionality of SnoopLigase is much better than its predecessor, SpyLigase, with the following improvements:

- Coupling efficiency is much higher (95% vs. 50%)
- Speed of reaction is increased by 6-fold (4 hours vs. 24 hours)
- Works at 25°C and 37°C (while SpyLigase only works at 4°C)
- Works across a broader range of buffers

This invention maximises the potential of the Tag/Catcher system and provides a great deal of flexibility to experimental design and uses. For instance, SnoopLigase can be used for biomaterial construction and conferred exceptional heat resilience when cyclising different enzymes, on top of all the applications of the Tag/Catcher system including:

- Fluorescent or biophysical probe tagging of specific proteins
- Protein immobilisation for proteomics
- Linking multiple enzymes into pathways to promote metabolic efficiency.

Commercialisation

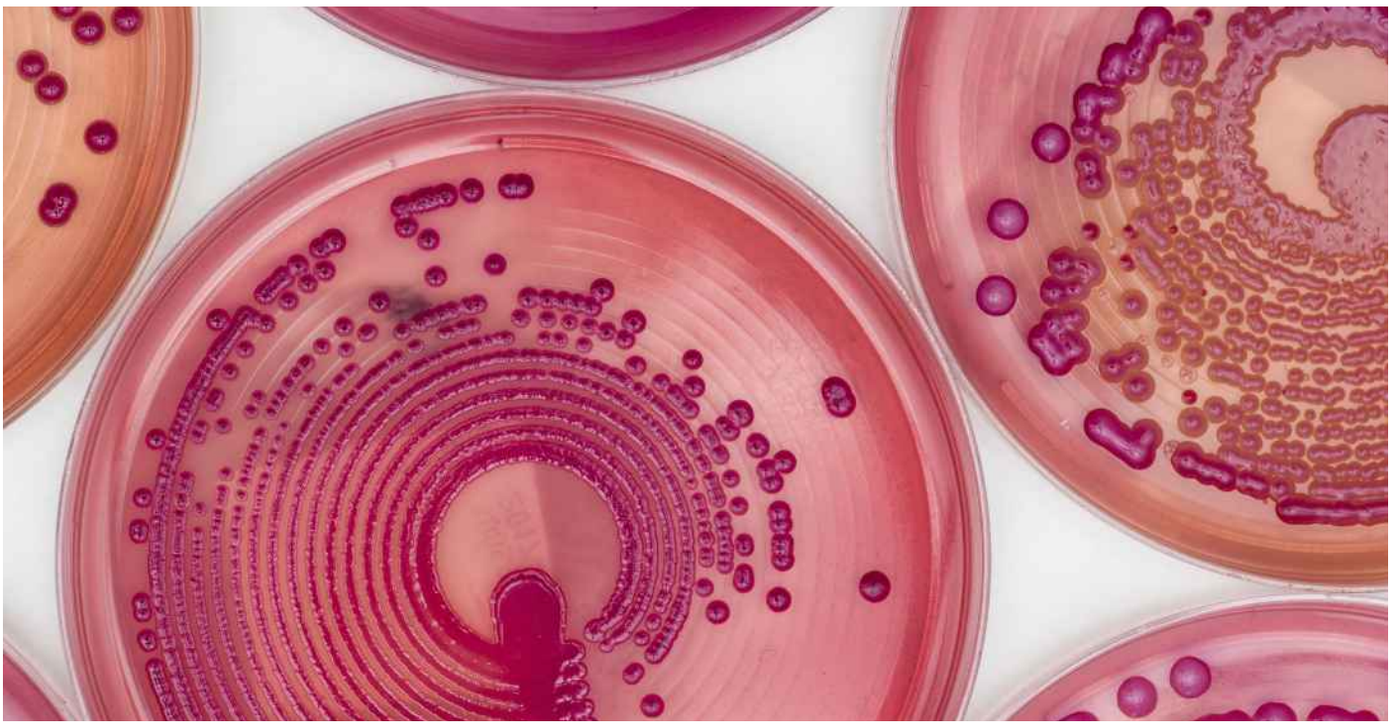
This technology is subject to patent application. Oxford University Innovation would like to speak to companies who are interested in licensing this technology.

For further information please contact:
Dr Christine Whyte
christine.whyte@innovation.ox.ac.uk
+44 (0)1865 280921
www.innovation.ox.ac.uk
Project number: 14383

Technology Transfer from the University of Oxford

Electrochemical oxidase test for identifying and quantifying bacteria

Oxford researchers have transferred the oxidase test to an electrochemical set-up for accurate quantification and detection of bacteria in biological samples.



The global microbial identification market is expected to reach $3 billion by 2022. This includes pathogen detection, human disease diagnosis, pharmaceuticals and food and beverage safety. Rapid and cost-effective methods for measuring bacteria are vital for these industries.

Detecting oxidase-positive bacteria

The oxidase test is a well-known method for detecting bacteria that produce cytochrome C oxidase. The test reagent, N,N,N',N'-tetramethyl-para-phenylene-diamine (TMPD), turns blue in the presence of oxidase-positive bacteria and can therefore be used to detect the presence of certain pathogens.

Researchers at the University of Oxford have developed an electrochemical method of deploying TMPD for the detection of oxidase-positive bacteria, an important improvement to the colorimetric test.

The electrochemical oxidase test can be used for detection and quantification of bacteria in biological samples. It offers an accurate, fast and inexpensive analysis method for pathogenic and non-pathogenic bacteria.

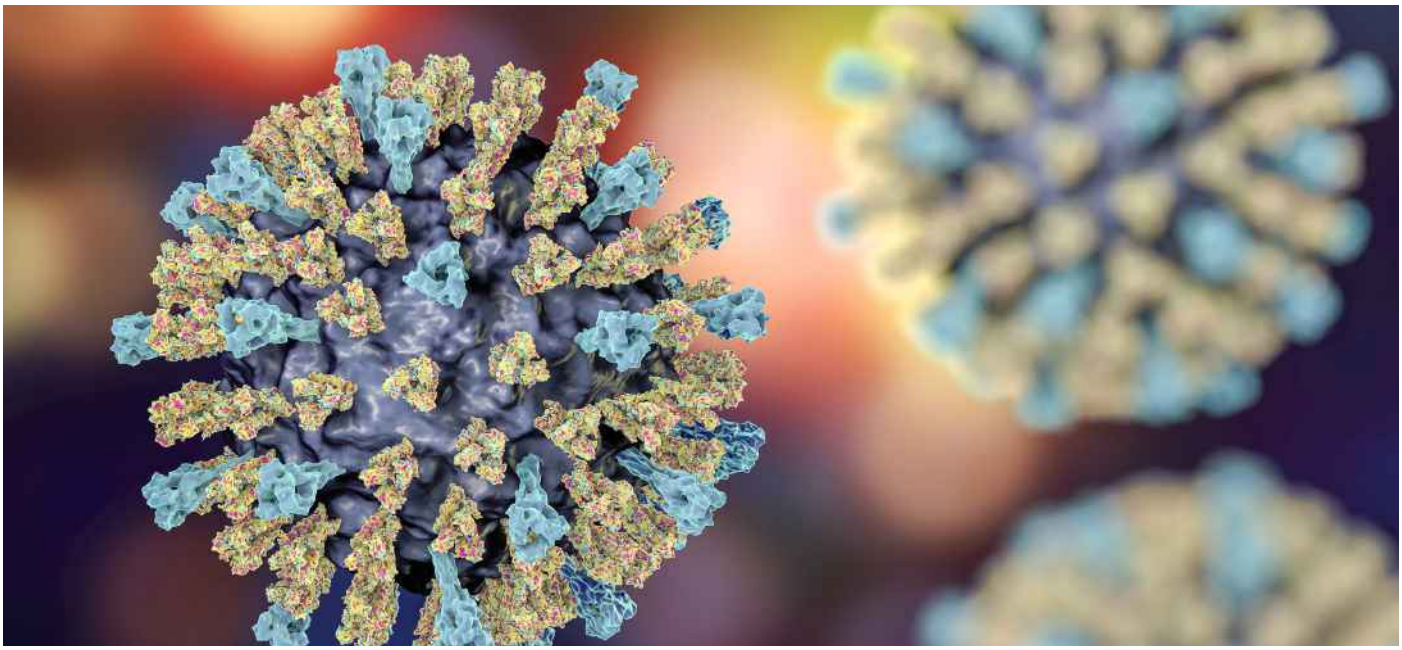
The Oxford Researchers have demonstrated for the first time that cytochrome c oxidase expression can be measured in aerobically grown E. coli, which is currently not possible using any other method. The technique can be applied to a range of pathogenic bacteria and can be used in biosensing technology.

For further information please contact:
Dr Jamie Ferguson
jamie.ferguson@innovation.ox.ac.uk
+44 (0)1865 280851
www.innovation.ox.ac.uk
Project number: 15033

Technology Transfer from the University of Oxford

Rapid detection of developed viruses and lipid-coated nanoparticles

Researchers at the University of Oxford have developed a new approach for labelling lipid-coated nanoparticles, such as enveloped viruses, for their rapid detection, quantification and isolation.



Traditional approaches for virus detection and quantification, such as cell culture and antigen-based tests, are often limited by long waiting times or limited sensitivity and specificity.

Enhancing rapid detection of viruses

Oxford University researchers have invented a novel approach for labelling lipid-coated nanoparticles, such as enveloped viruses, exosomes or synthetic lipid vesicles. This method uses calcium ions to mediate an interaction between the surface of the lipid particle and DNA. The DNA can be modified with fluorophores for rapid optical detection of the particles, or can include a functionalised group for particle pull-down using affinity purification.

Using enveloped viruses as an example, the researchers used calcium-mediated labelling combined with single-particle tracking to rapidly and sensitively detect and quantify virus particles. Fluorescently labelling viruses using this method has resulted in very bright virus particles, seen using light microscopy. The inventors have successfully combined the labelling technique with a downstream assay for detecting specific virus strains. These methods have been proven effective on several types of enveloped viruses, including both influenza A and B subtypes, respiratory syncytial virus (RSV) and baculovirus.

The inventors have used this approach to detect clinical isolates of influenza, which could be directly detected within just 1 minute, making the assay significantly faster than currently available antigen-based tests. The method is simple, efficient, reversible and rapid, and represents a powerful technique with applications in viral diagnosis, vaccine production and research. The technique does not require bespoke equipment and allows direct detection of virus particles, thereby requiring only a small sample volume and no amplification or purification steps.

The inventors have also shown that is possible to label small synthetic lipid particles in a similar manner. The method is therefore general, and can be used with a wide variety of viruses, particles, and modifying groups. The inventors are currently working on ways to combine the calcium-labelling approach with specific labelling using fluorescently-labelled genome probes.

For further information please contact:
Dr Sarah Jones
sarah.jones@innovation.ox.ac.uk
+44 (0)1865 614458
www.innovation.ox.ac.uk
Project number: 15681

Technology Transfer from the University of Oxford

SOFTWARE

HTSense: Simplifying the analysis and design of high throughput screens

Available to license: A flexible method for visualising complex datasets and designing validation studies.

High throughput screening

The advent of automated high throughput screening (HTS) has revolutionised drug discovery process. Lead compound identification has been streamlined as hundreds or thousands of reactions and interactions can be evaluated simultaneously. Due to its complex nature, HTS generates unprecedented amounts of data. The analysis of which requires specialist tools.

Many experiments mean many tools

Scientists currently use a multitude of different tools for analysing the data produced from HTS experiments. Tools exist for specific experiments, such as siRNA pooling, which explores a single interaction. However, increasing the complexity of the system generally means that the existing tools lack sufficient flexibility to process the additional parameters that are required to make sense of such rich datasets.

HTSense: Embracing complexity

Researchers at the University of Oxford have developed HTSense; a tool capable of analysing the data arising from highly complex HTS experiments. HTSense is able to normalise the results from a range of experiments and conditions. This allows for the biological data to be inspected in a different context that can include plate artefacts, systematic bias, compound/gene information, cell line/cancer profile and many others.

HTSense offers a number of benefits over the current data analysis tools:

- Accommodation of complex design
- Ability to reuse the data and analysis steps
- Allows for different normalisation and QC approaches
- Gives contextual data with respect to the existing knowledge landscape

Ready for license

Oxford University Innovation is seeking commercial and non-commercial licensees for the HTSense software.

For further information please contact:
Dr Richard Auburn
richard.auburn@innovation.ox.ac.uk
+44 (0)1865 280956
www.innovation.ox.ac.uk
Project number: 12350

Technology Transfer from the University of Oxford

Motion sickness solution for electronic device use

Researchers at the University of Oxford have developed a new algorithm which obtains real-time movement data from vehicles and reduces the effects of travel sickness by moving content on the screen accordingly.

Motion sickness

Motion sickness can occur while riding in most types of vehicle, and leads to symptoms ranging from discomfort and dizziness to nausea and vomiting in affected people. These effects make journeys highly uncomfortable for people who try to use their electronic portable devices while traveling.

Although some medications are available to prevent motion sickness (tablets and patches), healthcare services recommend you don't use electronic devices during journeys. Additionally, other types of products are commercialised, such as wristbands for acupressure or mild electric shocks.

However, they are only effective for a limited portion of people, who need to remember to bring them whenever they wish to use portable electronic devices while travelling. Thus, there is a big need to develop other strategies to prevent this condition and allow people to use their devices without feeling sick.

The Oxford solution

Based on this need, researchers at the University of Oxford have developed a new algorithm that can easily be implemented within an electronic device operation system without the user having to take medication etc. The algorithm takes multiple sensor inputs and moves the screen content according to the external movement of the vehicle. Settings can be personalized depending on the user's susceptibility to travel sickness and different settings can be defined, making the system suitable for most types of vehicles.

Advantages of this novel tool are:

- It can be implemented at operation system level
- It does not need to be linked to external apps
- It allows the user to customise the compensation
- It avoids motion sickness without the need for drugs or other therapies

Commercialisation

This technology is subject to a patent application. Oxford University Innovation is actively looking for partners willing to develop and implement this novel technology. If your company could be interested, please do get in touch.

For further information please contact:
Dr Chandra Ramanujan
chandra.ramanujan@innovation.ox.ac.uk
+44 (0)1865 614434
www.innovation.ox.ac.uk
Project number: 14458

Technology Transfer from the University of Oxford

Improved cross-linking models between amino acids with DynamXL software

Oxford researchers have developed software that can precisely model cross-links between amino acids in a protein by accounting for the dynamics of the linker and amino acid side chains.

Structure matters

The growth of systems and structural biology has led to an increasing need to analyse more complex systems faster and accurately. Many diseases are consequences of altered functionality due to altered protein structures. A high-resolution protein structure can greatly improve our understanding of the operating mechanism of that protein and how alterations impact its functions. Furthermore, information about a protein structure can support the discovery and development of drugs that specifically target the protein.

Vital insight

Chemical cross-linking coupled with mass spectrometry (XL-MS) is a revolutionary approach in structural biology that can help identify cross-links between amino acid side chains. It can provide vital insight into both the structure and organisation of proteins in a wide variety of conditions, including in solution. Existing algorithms that simulate cross-links for a given atomistic protein structure are highly error-prone. They fail to take important parameters, for example, the dynamics of amino acid side chains, into consideration.

Dramatic increase in accuracy

Researchers at the University of Oxford have developed software that accounts for alternative orientations of the linker and amino acid side chains and large-scale protein conformational changes. The result is dramatically increased precision of protein structure models.

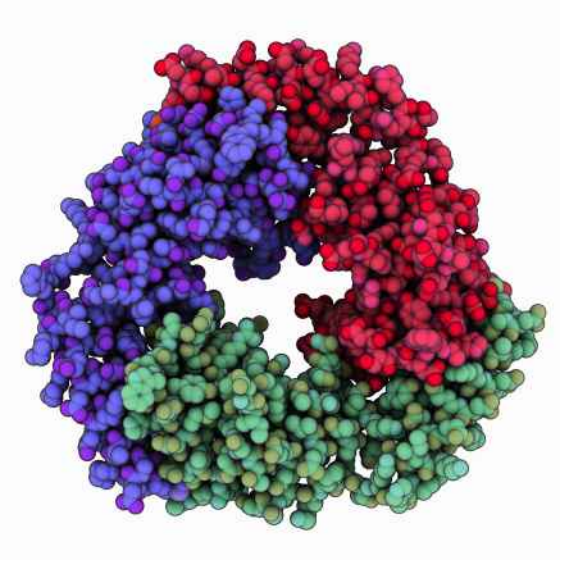
The software also:

- Outperforms existing approaches in interpreting XL-MS data
- Can be performed on an ensemble of alternative atomic arrangements
- Can deal with structural ensembles from various sources (NMR, X-ray crystallography and molecular dynamics etc.)
- Allows significant improvements in protein-protein docking
- Has been validated through exhaustive benchmarking
- Is capable of accommodating motions at both reactive side-chain levels and large-scale rearrangements of the protein backbone

This software represents a considerable increase in the obtainable structural insights attainable using chemical cross-linking.

Commercialisation

Oxford University Innovation would like to hear from companies who may wish to license this software.



For further information please contact:
Dr Richard Auburn
richard.auburn@innovation.ox.ac.uk
+44 (0)1865 280956
www.innovation.ox.ac.uk
Project number: 14605

Technology Transfer from the University of Oxford

Virtual Assay drug screening software V.3.0

Oxford researchers have developed user friendly software for *in silico* drug trials in populations of human cardiac cell models.

Evidence that drug safety and efficacy testing could one day be conducted by a computer rather than on animals has led a team at the University of Oxford to develop Virtual Assay software. The Virtual Assay software has the potential to replace thousands of *in vitro* animal experiments used globally each year for this purpose. A recent evaluation study on 62 reference compounds has predicted the risk that these drugs would cause abnormal heart rhythms in patients with 89% accuracy, while similar studies conducted in animals showed ~75-85% accuracy.

Everyone is different

No two individuals respond to a drug in exactly the same way. Due to sometimes subtle variability at a physiological level, what works for one person may not work for another, even before taking into account any additional complicating factors. This is one of the most significant challenges faced by the pharmaceutical industry; clearly it is neither practical nor desirable to test a new drug on the entire population to ensure it is both safe and effective.

Drug cardiac safety

Ensuring a drug does not have potentially harmful or unexpected side-effects for the heart is a top priority, and a rigorous testing phase is required before a drug can be approved for clinical use. Even then, unforeseen problems can occur due to the large variability in patient populations, exacerbation of other pre-existing diseases or interactions with other drugs. Early detection of potential side effects is crucial, since cardiotoxicity is one of the leading causes of drug failure during development, and it also accounts for about 45% of total post-approval drug withdrawal from the market.

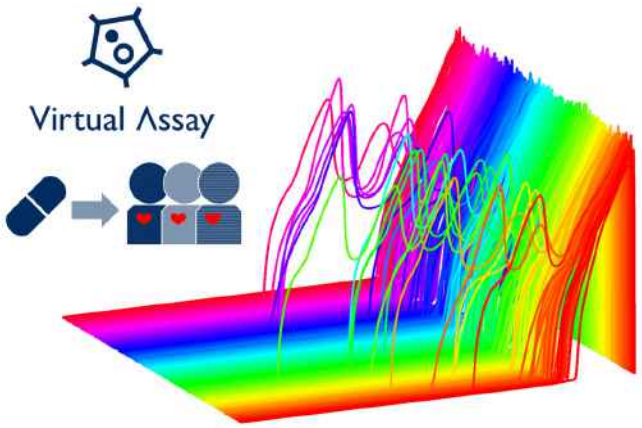
"Virtual" screening with Virtual Assay

To overcome this, *in silico* modelling is becoming increasingly important in pharmacology, for both drug efficacy and safety testing and is attracting significant attention from the commercial sector and regulatory bodies such as the US FDA, UK MHRA, and the European MRA.

Virtual Assay also makes *in silico* drug trials in populations of human models accessible by non-experts in modelling and simulations, providing a user-friendly interface and a very efficient simulation engine (1 drug trials takes about 5 minutes for 100 cells using a modern PC).

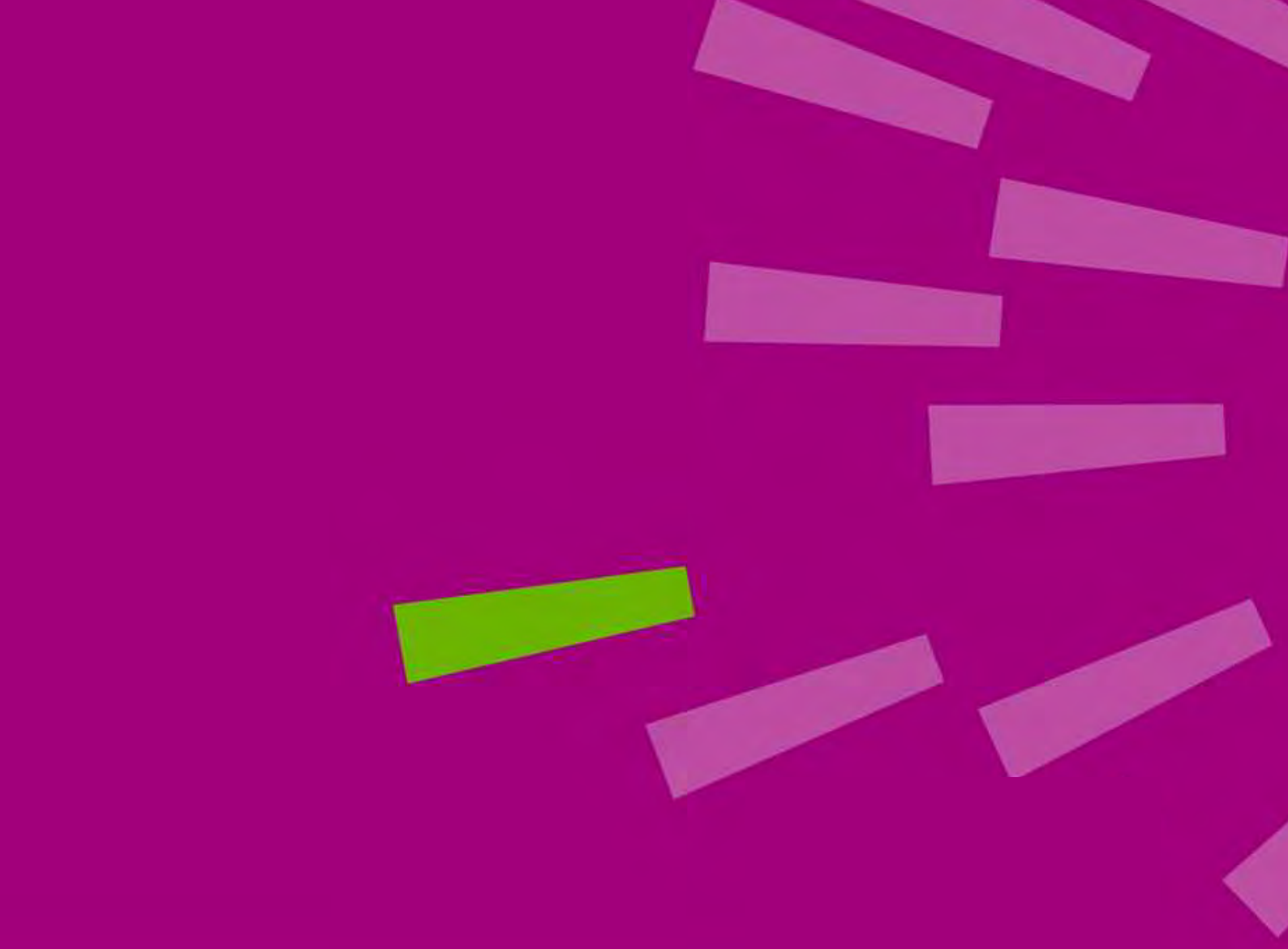
Key advantages:

- Human-based models, tightly coupled with experiments
- Populations of models to account for inter-cellular variability
- Quantitative prediction of the effects of drugs at the population level
- Mechanistic explanations into the causes of drug effects
- Consultancy services also available



For further information please contact:
Sandeep Singh
sandeep.singh@innovation.ox.ac.uk
+44 (0)1865 280907
www.innovation.ox.ac.uk
Project number: 16245

Technology Transfer from the University of Oxford



TARGETED THERAPIES

Stem cell immunotherapy

Available to license: Superior dendritic cells for immunotherapy

Cross-presenting dendritic cells derived from a patient's own skin cells promise to be the ideal starting point for the development of effective immunotherapies

Dendritic cell-based immunotherapy

Dendritic cells are immune cells that play a key role in directing the body to recognise foreign antigens. Utilising dendritic cells to stimulate immune responses to specific antigens is a promising route to immunotherapy. Dendritic cells have been widely used for this purpose, but success of existing therapies has been limited due to the low 'cross-presenting' capacity of these cells that are generated from monocytes, a type of white blood cell.

A novel type of dendritic cell with superior abilities to 'cross-present' foreign antigens to immune cells has been recently found in mice and humans. These superior dendritic cells, identified by markers CD141 and XCR1, have only been found in very small populations insufficient to isolate numbers required for therapeutic development.

Stem cells to dendritic cells

Led by Dr. Paul Fairchild, co-director of the Oxford Stem Cell Institute, Oxford researchers have developed a method to produce these dendritic cells from a patient's skin cells. The researchers took skin cells and turned them into 'induced pluripotent stem cells' (iPSCs) that can renew indefinitely and are capable of forming any cell type. The iPSCs were instructed to become dendritic cells using an approach that would be suitable for clinical use (no animal-based materials were used to aid growth).

Proof of principle that these superior dendritic cells are capable of modulating the immune system was demonstrated by using the cells to stimulate naïve T-cells and elicit a tumour specific immune response.

Key benefits of technology

- Ability to induce specific response from naïve T cells
- Potential to scale-up for therapeutic development
- No animal-based materials used compliant with clinical application

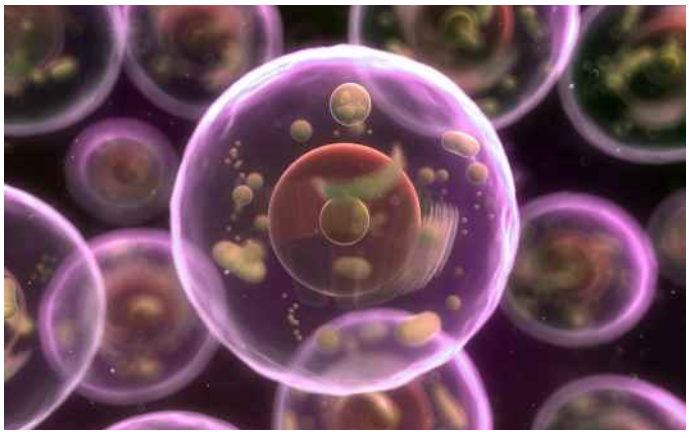
Intellectual property

US and European patent applications have been filed claiming the cross presenting cells and methods for producing them. Oxford University Innovation would like to speak to companies interested in licensing this technology for further development.

References

Silk KM et al., (2011) Gene Therapy DOI:10.1038/gt.2011.177

http://www.bbc.co.uk/news/health-15659972



For further information please contact:
Dr Richard Reschen
richard.reschen@innovation.ox.ac.uk
+44 (0)1865 280872
www.innovation.ox.ac.uk
Project number: 7381

Technology Transfer from the University of Oxford

Dendritic cells from induced pluripotent stem cells with an adult phenotype for immunotherapy

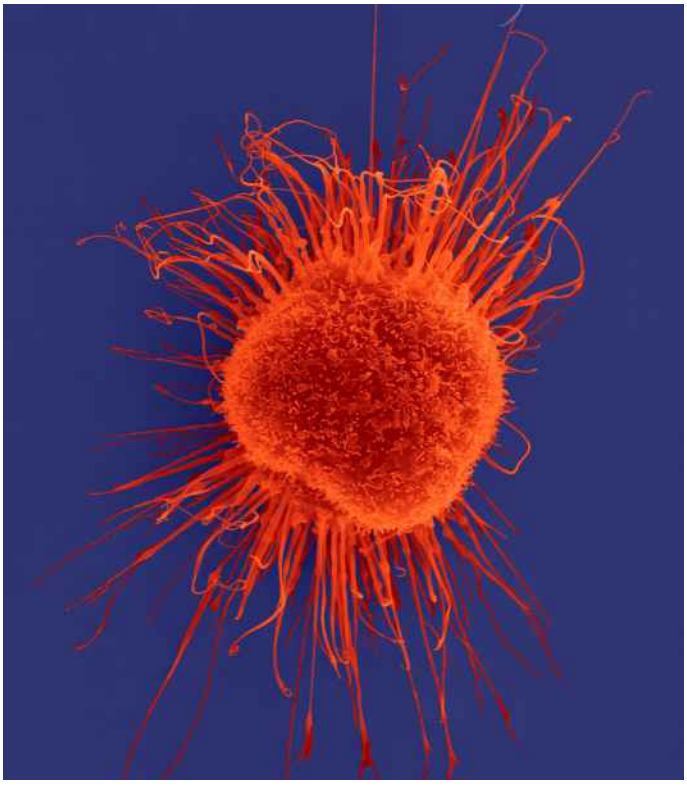
Oxford researchers have developed a method of producing dendritic cells from iPS cells displaying a mature 'adult phenotype', substantially increasing their potential effectiveness in immunotherapy

Dendritic cells

Dendritic cells (DCs) are antigen presenting cells of the mammalian immune system which directly trigger and control responses by T cells. The use of DCs to prime responses to tumour-associated antigens (TAAs) represents a promising approach to cancer immunotherapy, however, clinically relevant responses have often been disappointing. Although these failures are partly due to the properties of the DCs most commonly used, obtaining sufficient quantities of more suitable DCs has proven difficult.

Fetal phenotypes

Existing methods for obtaining scalable quantities of suitable DCs involve their production from induced pluripotent stem cells (iPSCs) or embryonic stem cells (ESCs). However, all cell types differentiated from ESCs and iPSCs display a primitive 'fetal' or 'neonatal' phenotype which may limit their therapeutic utility.



DCs derived from iPSCs and ESCs display a similar fetal phenotype which results in limited immunogenicity and increased tolerogenicity.

All grown up

Oxford researchers have developed a simple method of generating DCs which display a mature 'adult' phenotype through an exploitation of the epigenetic memory that iPS cells possess for the cell type from which they were derived. DCs derived using this approach combine all the functionality of primary DCs with the many advantages of being derived from a pluripotent source. These advantages include the ability to scale-up procedures, tractability for genome editing and availability of otherwise inaccessible subsets of DCs with desirable properties.

DCs displaying an adult phenotype are suitable for applications in a variety of indications, including cancer immunotherapy, vaccination against chronic infectious microorganisms, and the induction of tolerance to defined protein antigens.

Commercialisation

The method, intermediates, and product DCs are the subject of a patent application with scope for international coverage.

Oxford University Innovation is seeking external partners to support the commercialisation of the technology.

For further information please contact:
Dr Richard Reschen
richard.reschen@innovation.ox.ac.uk
+44 (0)1865 280872
www.innovation.ox.ac.uk
Project number: 13048

Technology Transfer from the University of Oxford

A method for precisely tuning gene expression levels in mammalian cells

Researchers at the University of Oxford have developed a method for modulating gene expression in response to effector microRNAs.

Manipulating gene expression

The fascinating cellular diversification characteristic of metazoans relies on a milieu of sophisticated regulatory systems, which act to control gene expression with minute spatial-temporal precision. Errors in these programs can have serious developmental consequences and lead to the onset of numerous human diseases.

Currently, studies aiming to understand the role of gene-products in various biological processes or to engineer cells for therapeutic purposes have relied on gene knock-ins (KI), knock-outs (KO) and RNA interference (RNAi). However, they are not suitable for studying or engineering quantitative changes in expression levels. Therefore, there is a need to develop methods for precisely tuning gene expression in mammalian cells.

Cancer immunotherapy

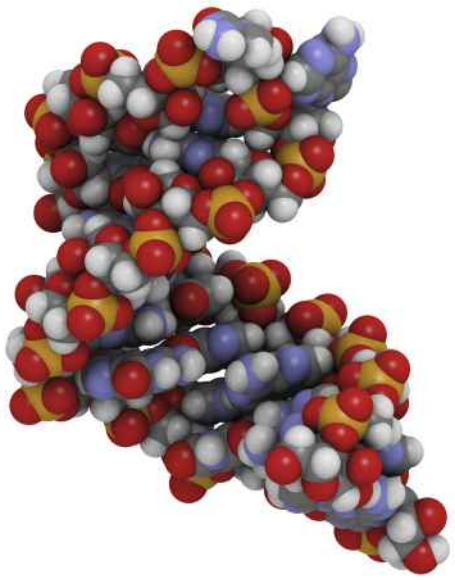
The co-inhibitory receptor *programmed cell death 1* (PD-1) plays a central role in the ability of tumours to cause T-cell exhaustion and escape immune surveillance. Checkpoint blockade therapies that suppress PD-1 signalling can improve the anti-tumour response but also unleash severe autoimmune reactions. PD-1 KO has equally detrimental effects and can, paradoxically, lead to increased exhaustion and impaired survival of T-cells via the compensatory up-regulation of other co-inhibitory receptors. Therefore, precise, stepwise and context-dependent regulation of co-inhibitory receptors expression could help realise the promise of T-cell engineering for next-generation cancer immunotherapies.

A new paradigm to precisely modulate gene expression

Researchers at Oxford have developed a new platform to precisely modulate gene expression that is applicable to a wide range of therapeutic applications. This approach relies on the engineering of synthetic microRNA response elements (MREs), which can harness the repressive potential of endogenous microRNAs to control the levels of user-defined target genes. By introducing defined mismatches in these synthetic MREs the team was able to tune the strength of endogenous miRNA-mediated repression and consequently gene expression output to within 0.02% of any desired level. This strategy could provide an ideal solution for preventing tumor-induced exhaustion of engineered T-cells while mitigating the risk of autoimmune reactions.

Benefits of this method:

- Intergration into existing manufacturing protocols for engineered T-cells;
- Precise tuning of gene expression;
- No exogenous interaction once the system is integrated into native genes or therapeutic transgenes;
- Reduced probability of off-target effects.

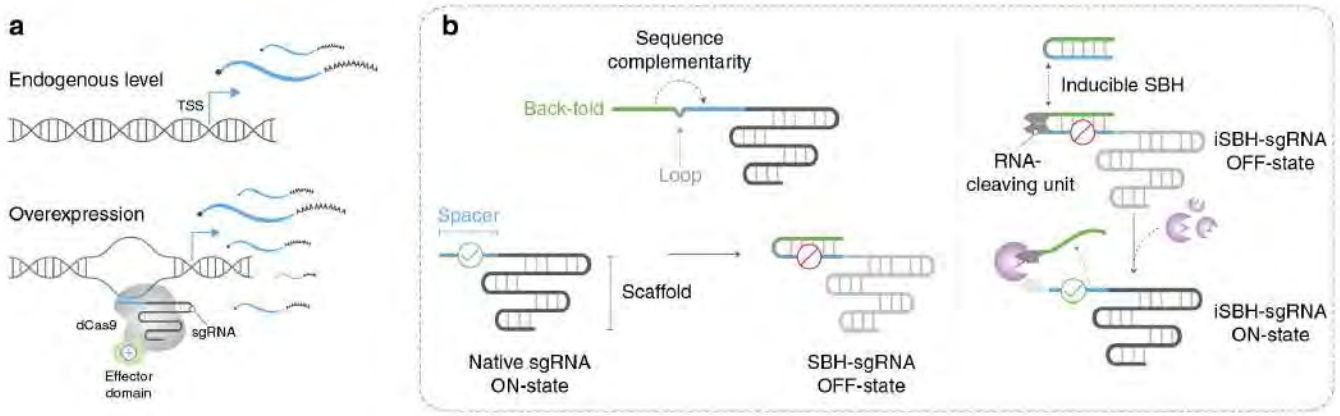


For further information please contact:
Dr Matthew Carpenter
matthew.carpenter@innovation.ox.ac.uk
+44 (0)1865 280970
www.innovation.ox.ac.uk
Project number: 13338

Technology Transfer from the University of Oxford

Inducible CRISPR-TR system for the conditional regulation of gene expression

Oxford researchers have developed an inducible CRISPR-based transcription regulator system that allows for spatiotemporal control of endogenous gene expression and assembly of gene circuits.



Conditional control of CRISPR-TR activity by SBH-sgRNAs. (a) Schematic representation of CRISPR-TR-based transcriptional modulation. (b) Conceptual framework underlying the design of inducible sgRNAs for the control of CRISPR-TR activity. Appending a back-fold extension to the 5' end of the native sgRNA promotes the formation of a spacer blocking hairpin (SBH) expected to switch the sgRNA to a quiescent state (OFF-state) (left). Replacing the basic loop with conditional RNA-cleaving units enables generation of inducible SBH designs (iSBH), which can restore CRISPR-TR activity in the presence of specific inducers (spacer release) (right).

Current CRISPR-TR systems and their limitations

The CRISPR-based transcription regulator (CRISPR-TR) system was designed to control the output expression of any gene of interest. The system relies on a nuclease-deficient Cas9 fused with various effector domains, directed to specific genes by the single guide RNA (sgRNA). Chemically inducible or photo-activated CRISPR/Cas9 solutions are available but they require complex protein engineering and are difficult to scale up to implement synthetic networks across multiple genes.

The Oxford inducible CRISPR-TR system

To address these limitations, Oxford researchers have developed an inducible CRISPR-TR system based on minimal engineering of the sgRNA. In this system, a spacer-blocking hairpin (SBH) structure is appended at the 5' end of the sgRNA to temporally block CRISPR-TR activity. To conditionally enable the activity of Cas9, a range of inducible SBH (iSBH) modules were further developed, including proteins, small molecules as aptazyme and single-stranded DNA oligonucleotides. With the action of these molecules, the full repression of CRISPR-TF activity is annulled and can be controlled.

Compared to current methods, the system confers the following benefits:

- Simple, rapid and highly versatile
- Compatible with all Cas9 based applications
- Possible to encode a complete transcriptional programme in a single RNA molecule
- Facilitates the assembly of more complex gene circuits

As potential applications, the system can be used to:

- Answer fundamental biological questions involving precise spatiotemporal regulation of gene products
- Rewire cellular behaviour in basic research
- Develop smart therapeutics
- Create scalable gene circuits of interest such as orthogonal and parallel transcriptional programmes

As a proof of principle, the system has been used to assemble gene regulatory modules in human cells and the results are published in *Nature Communications*.

Commercialisation

This technology is subject to a patent application. Oxford University Innovation is interested in hearing from companies that would like to license this technology.

Ferry et al, *Nature Communications* **8**, Article number: 14633 (2017)
doi:10.1038/ncomms14633
https://www.nature.com/articles/ncomms14633

For further information please contact:
Dr Matthew Carpenter
matthew.carpenter@innovation.ox.ac.uk
+44 (0)1865 280970
www.innovation.ox.ac.uk
Project number: 13916

Technology Transfer from the University of Oxford

Synthetic Cas9-based programmable transmembrane receptors

Oxford University researchers have created a synthetic Cas9-based programmable transmembrane receptor system that enables a broad range of applications including conditional regulation of endogenous genes, conditional gene editing and implementation of complex transcriptional programs.

Synthetic trans-activating receptors

Synthetic trans-activating receptors take advantage of the diverse signal transduction mechanisms in eukaryotic cells to achieve customisable sensing and response engineering. However, current synthetic trans-activating receptors are limited to the control of exogenous transgenes carrying specific enhancer elements. As a consequence, they are not suitable for user-defined control of endogenous gene expression.

Cas9-based programmable transmembrane receptors

Oxford researchers have engineered a family of Cas9-based programmable transmembrane receptors that allows for conditional transcriptional regulation, conditional gene editing and rewiring of endogenous cellular pathways. This is achieved by combining an intracellular domain that consists of a proprietary engineered – dead or active – Cas9 molecule with a wide range of extracellular domains, such as synthetic GPCR, receptor tyrosine kinase, synNotch and others. Various inducers including small molecules, drugs, epitopes, viruses, lipids, sugars, cell-cell interactions etc. can be used to trigger the system depending on the nature of the chosen extracellular domain. This system can be used widely to reconfigure cellular pathways *in vitro* and *in vivo* for basic research and therapeutic applications.

Highlights of the receptor system:

- Programmable and versatile
- Enables user-defined control over when and where to regulate (activate/repress) the gene of interest
- Allows for dose-dependent control of gene expression
- Minimal OFF-state baseline activation and robust ON-state ligand-induced signal transduction
- Can easily implement parallel and orthogonal transcriptional programs by single guide RNA multiplexing

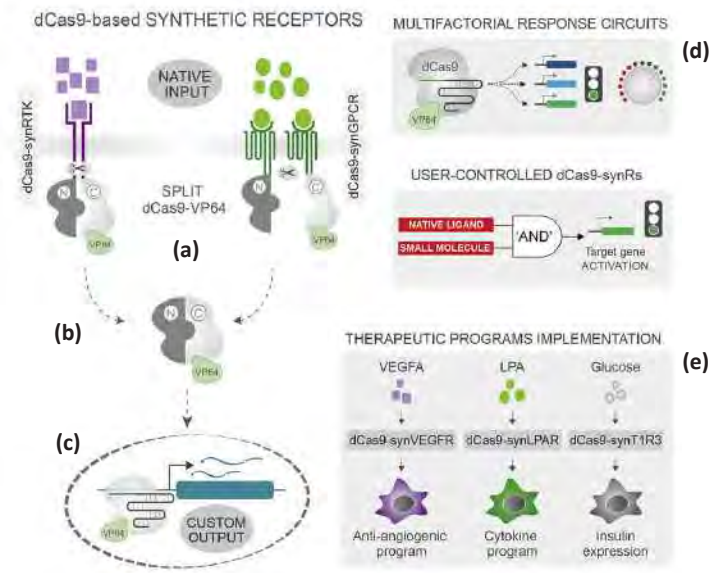
The system has been successfully tested for transcriptional activation of both a reporter construct and endogenous genes using programmable GPCR and RTK extracellular domains. Plans for the system to be tested in mouse models are in place.

Commercialisation

This technology is subject to a patent application. Oxford University Innovation is interested in hearing from companies that would like to license this technology.

Baeumler, Ahmed & Fulga Engineering Synthetic Signalling Pathways with Programmable dCas9-based Chimeric Receptors, 2017, *Cell Reports* **20**, 2639 – 2653

http://dx.doi.org/10.1016/j.celrep.2017.08.044



dCas9-based SYNTHETIC RECEPTORS (dCas9-synR) rely on a highly programmable, optimized split-dCas9 signal transduction module **(a)**, which can be standardised across multiple classes of sensing domains. Ligand binding results in reconstitution of a functional dCas9-based transcription factor **(b)**, enabling highly specific and robust activation of custom gene expression programs **(c)**. Owing to their modular architecture, dCas9-synRs provide a powerful scaffold for the incorporation of user-controlled systems (safety switch mechanisms) **(d)**. The unprecedented versatility of dCas9-synRs in redirecting cellular information flow makes them ideally suited for engineering designer cells capable of sensing specific disease markers and in turn driving custom therapeutic programs **(e)**.

For further information please contact:
Technology@innovation.ox.ac.uk
+44 (0)1865 280830
www.innovation.ox.ac.uk
Project number: 13925

Technology Transfer from the University of Oxford

Logical control of CRISPR gene editing system

Researchers at the University of Oxford have developed a control system that allows spatio-temporal activation of CRISPR, based on an engineered RNA guide strand.

CRISPR/Cas9 approaches and limitations

CRISPR is described as “the technology of the century” and brings the hope of treatments for currently incurable diseases, by excising or silencing genes that drive tumour proliferation, repair of faulty genes, or by killing diseased cells.

However, unwanted DNA cuts, resulting from non-specific delivery to off-target cells, remain a serious problem in the successful clinical translation of CRISPR-based therapeutics. Exact spatio-temporal control of CRISPR/Cas9 activity would lead to the development of new therapies and new tools for biotechnology with great translational potential.

Improvement on current methods with the Oxford technology

Oxford academics have developed an innovative control system allowing gene editing to be activated only in response to precisely defined combinations of biomolecular signals in targeted cell populations.

This technology is based on engineered Cas9 guide strands that incorporate sensor motifs that allow the nuclease Cas9 to cut DNA only when conditions characteristic of target cells are met. By improving the CRISPR/Cas9 constructs with the use of these modified guide-RNAs (gRNA) containing the blocking module, a nucleic-acid dependent activation of the Cas9 enzyme is allowed.

Furthermore, this unique design provides Cas9 sensing abilities with minimal leakage of activity, which is desirable for precise enzyme activity.

Several RNA guide strands have already been developed in the laboratory. Efficiency and selectivity of the system has been succesfuly tested *in vitro* and in cellular models.

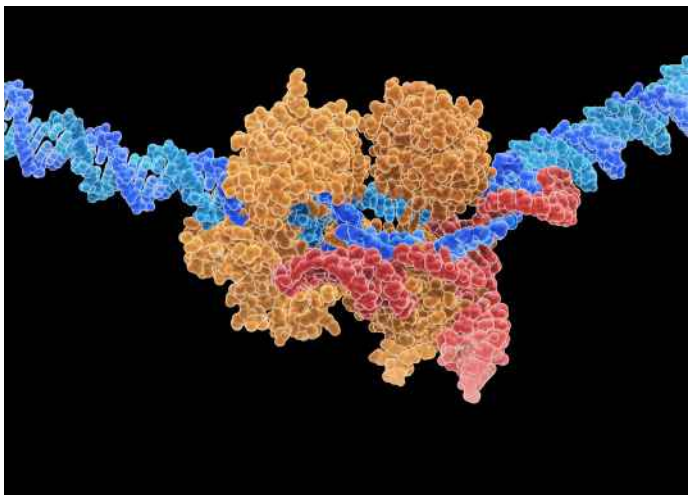
Main applications of conditional regulation

This new approach improves the current CRISPR/Cas9 gene editing applications and it can be applied to any gene regulation technique but with improved implementation and results:

- Use in biomedical applications for cell-type specific activation of the CRISPR/Cas9 system
- Tool for synthethic biology: genetic circuits or nucleic-acid nanotechnology
- Production of other conditionally activated CRISPR/Cas9 systems based on the use of other activation molecules, such as proteins or small molecules

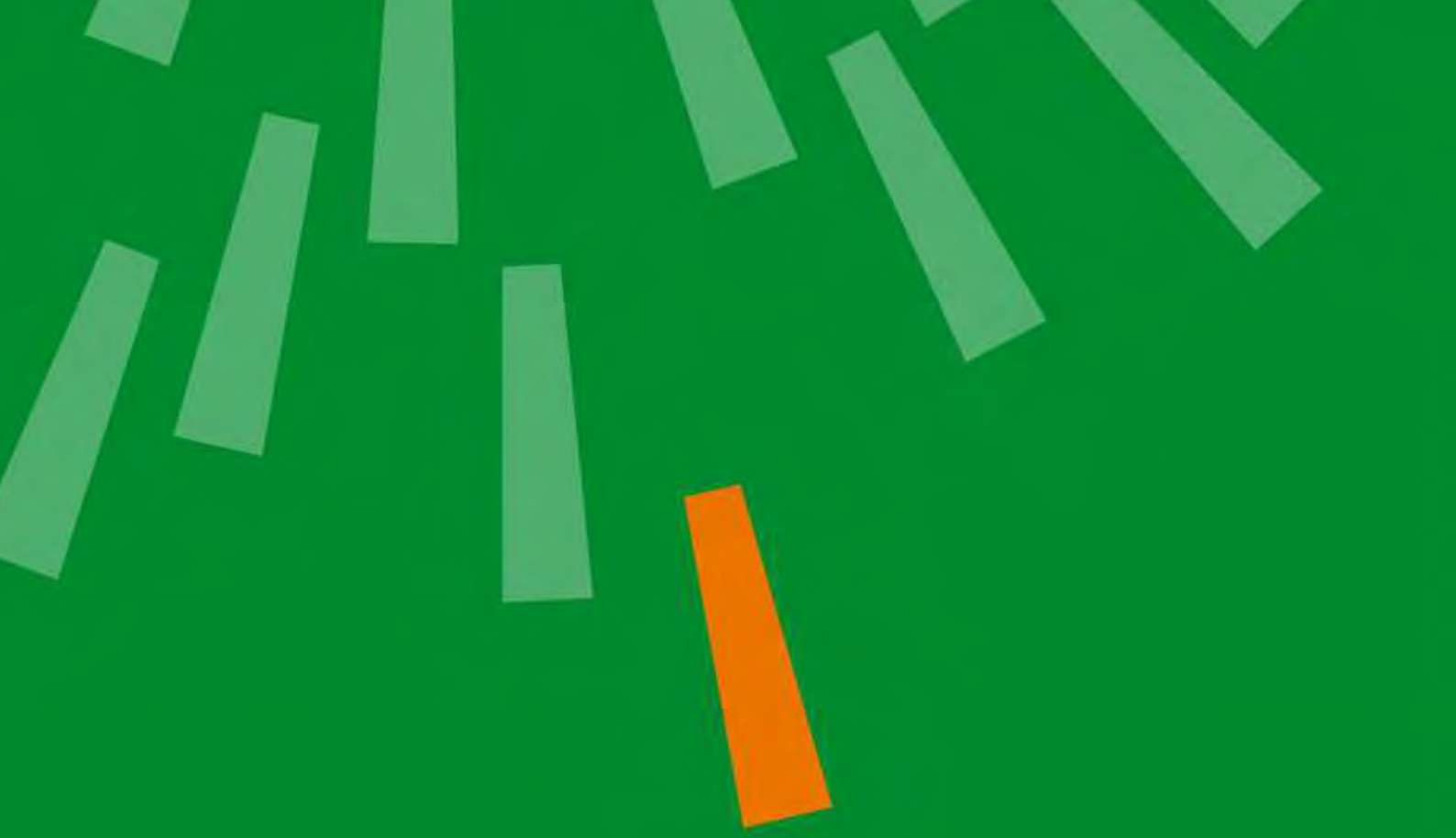
Commercialisation

This technology is subject to a patent application. Oxford University Innovation is interested in hearing from companies that would like to license this technology.



For further information please contact:
Bénédicte Menn
benedicte.menn@innovation.ox.ac.uk
+44 (0)1865 280906
www.innovation.ox.ac.uk
Project number: 14361

Technology Transfer from the University of Oxford



VACCINES

S-FLU: Broad spectrum flu protection with a superior safety and delivery profile

Oxford researchers have developed a novel live attenuated influenza virus vaccine that could be used safely in the face of a new pandemic strain of influenza, and for seasonal strains.

Proactive pandemic prevention

An influenza pandemic remains a persistent threat to world health. While bespoke vaccines can be developed following the emergence of a novel strain, it would be a significant benefit to have a universal vaccine that could provide immunity across all influenza strains to proactively limit both pathology and viral transmission. While live vaccines represent the most effective approach to achieve this goal, they carry the inherent risk of transferring their genetic information to a circulating seasonal virus, which could render this strain highly virulent and inadvertently cause a pandemic.

A live vaccine without the risks

S-FLU is a novel live attenuated influenza virus vaccine that has been engineered with the unique ability to provide broad T cell-based protection across type-A viruses, the constantly changing form of influenza responsible for both seasonal flu and the vast majority of epidemics.

Key facts

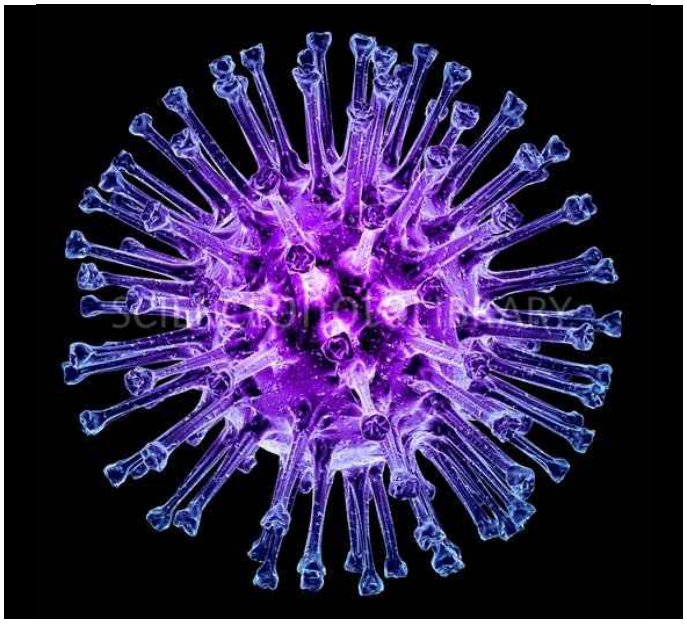
- Suppression of haemagglutinin signal sequence expression enables infection without replication
- Generates a T-cell mediated immune response shown to protect mice and ferrets from a broad range of type-A influenza strains
- Efficacy comparable to FluMist®, the best-in-class licensed live attenuated influenza vaccine
- Risks associated with genetic transmission eliminated
- Optimal lung delivery is safe and feasible via small droplet aerosol
- Lower cost manufacture in mammalian cell lines

This novel approach to influenza vaccination represents a breakthrough in exploiting the enduring and broad spectrum benefits of live vaccination, yet without the serious risks of a full blown infection or viral gene transfer.

Innovative vaccine opportunity and patent protection

It is envisaged that S-FLU will be of interest to companies wishing to strengthen their vaccination portfolio, or those looking to use S-FLU to enter the growing billion-dollar influenza therapeutics market.

Oxford University Innovation has filed a patent application, published as PCT/GB2012/052341, covering S-FLU, and would like to speak to companies interested in licensing this exciting technology.

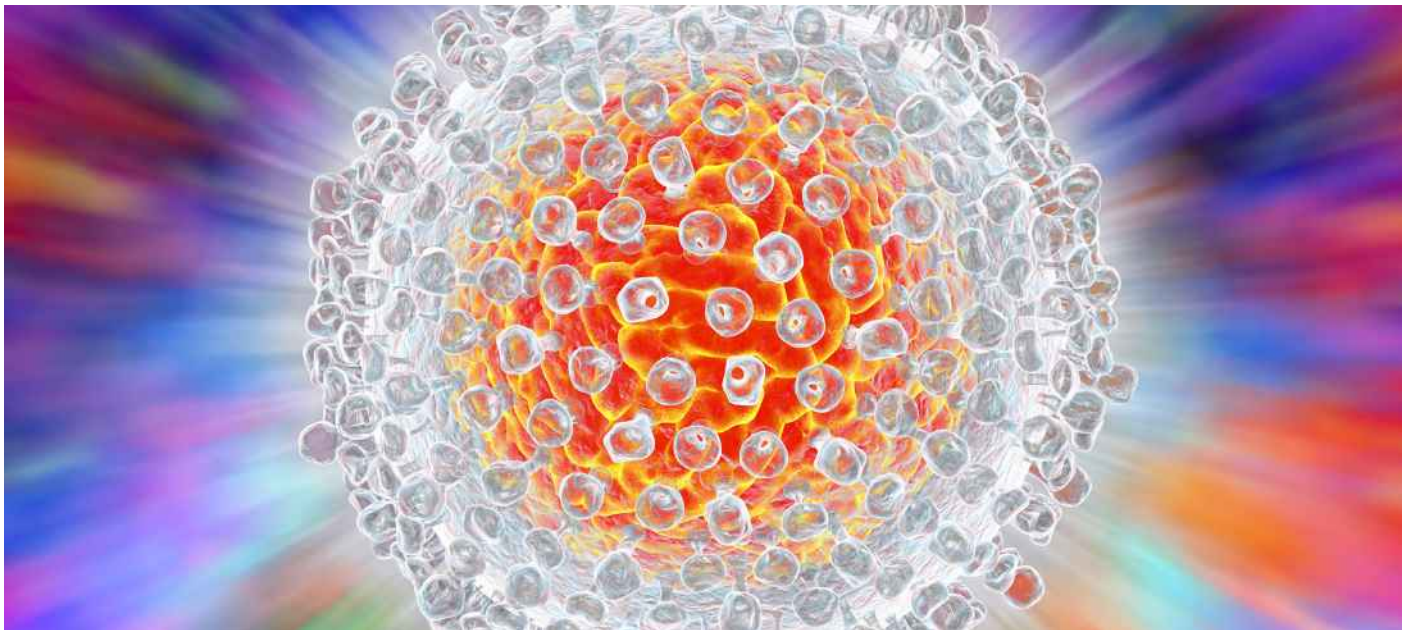


For further information please contact:
Dr Matt Carpenter
matt.carpenter@innovation.ox.ac.uk
+44 (0)1865 280970
www.innovation.ox.ac.uk
Project number: 7968

Technology Transfer from the University of Oxford

Hepatitis C Vaccine

Oxford researchers have developed a vaccine using the most conserved sequences of a Hepatitis C virus, including non-structural proteins.



Hepatitis C virus (HCV) infection is a major global health concern - 170 million people are infected worldwide, with 3 – 4 million new infections annually. Many chronically infected patients develop complications of liver disease that include hepatocellular cancer, liver cirrhosis and liver failure.

Despite advances in HCV treatment, a prophylactic vaccine remains the most cost-effective and realistic means to significantly reduce the worldwide mortality and morbidity associated with persistent HCV infection.

A major challenge for HCV vaccine development is the significant viral diversity. However, parts of the viral genome are conserved, making these excellent targets in the context of a T cell vaccine. Hope for a vaccine for HCV lies in the fact that after primary infection spontaneous viral eradication occurs in a significant minority of patients, T cell immunity critically affects the clinical outcome.

The Jenner researchers have developed a HCV vaccine using non-replicating viral-vectored vaccines to induce T-cell responses against a single immunogen incorporating the most conserved proteins of HCV, including non-structural proteins. The use of specially selected conserved viral segments from the non-structural proteins can provide protection against multiple HCV genotypes.

The HCV immunogen was designed using a software based approach to identify the most conserved and functionally critical protein sequences in all HCV genotypes. The researchers have developed a single immunogen that has been expressed in a simian adenoviral vector.

Immunogenicity trials of the HCV vaccine in mice have shown the induction of abundant T cells against the individual components of the antigen.

For further information please contact:
technology@innovation.ox.ac.uk
+44 (0)1865 280830
www.innovation.ox.ac.uk
Project number: 10355

Technology Transfer from the University of Oxford

HIV Vaccine

Available to license: A series of chimeric immunogenic polypeptides capable of inducing robust, effective and cross-strain immunity to the Human Immunodeficiency Virus (HIV).

Human Immunodeficiency Virus (HIV)

In 2015 it was estimated that 37.7 million people were living with HIV with the number of new infections estimated at 2.1 million. The disease resulted in 1.1 million deaths from AIDS-related illnesses. The development of new treatments for the disease is hampered by the genetic diversity of the virus.

HIVconsv Protein

Delivered by simian adenovirus ChAdV63 and poxvirus MVA, the 1st-generation conserved vaccines were tested in 8 trials in UK, EU and Africa and showed high immunogenicity, replication control in vitro of 4 major HIV clades A, B, C and D and, in a pilot study in combination with early ART (antiretroviral therapy) and latency-reverting agent Romidepsin, produced a signal of viremic control during monitored ART pause in 36% of vaccine recipients. The vaccines with Vorinostat were also used in the first randomized blind 'kick and kill' trial RIVER.

New developments

Learning from the trials, the researchers from Oxford and Los Alamos National Laboratory had an opportunity to upgrade the immunogens. The main improvements of the 2nd-generation tHIVconsvX include a bioinformatics-assisted redefinition of conserved regions, inclusion of protective & conserved epitopes and maximizing vaccine match to global HIV variants by bivalent mosaic design, while induction of responses against inter-regional junctions was minimized by a region scramble.

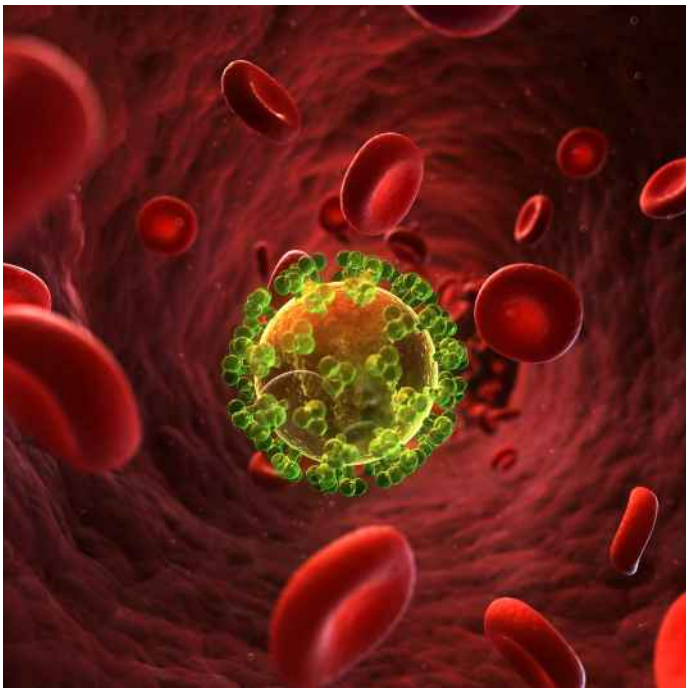
Administering the tHIVconsvX proteins as pairs using different vaccine modalities ensures a maximum match to global circulating HIV and the induction of effective, robust immunity.

The main benefits of this vaccine:

- Computer-optimised mosaic sequences designed to yield maximum HIV epitope match
- Effective and robust cytolytic T cells against the most vulnerable parts of the virus
- Could be used as part of a therapeutic or prophylactic vaccine

Patent protection

Oxford University Innovation has filed a priority patent covering this project (WO2015048785A3 – Mosaic conserved region HIV immunogenic polypeptides) and is seeking partners to help commercialise the technology.



For further information please contact:
Dr Matt Carpenter
matthew.carpenter@innovation.ox.ac.uk
+44 (0)1865 280970
www.innovation.ox.ac.uk
Project number: 10599

Technology Transfer from the University of Oxford

New class of molecular adjuvant

Oxford researchers have identified a family of enzymes that can increase immunogenicity towards a wide range of fused antigens.

The adjuvant advantage

An adjuvant is a substance that is able to enhance or prolong the body's antigen-specific immune response to an administered vaccine. Simple inorganic aluminium salts, such as aluminium hydroxide or aluminium phosphate, have been commonly used as adjuvants since the 1930s. Recently, attention has turned to organic or biological adjuvants to tackle more challenging and complex disease targets.

4-Oxalocrotonate tautomerase (4-OT)

4-OT is an enzyme, which forms part of a key metabolic pathway in bacteria. The monomer unit contains just 62 amino-acid residues, making it one of the smallest known enzyme subunits; however, 4-OT forms a hexamer in solution. Researchers at the University of Oxford have been exploring the use of 4-OT proteins as vaccine adjuvants.

Beating the superbugs

The group at Oxford have successfully fused a member of the 4-OT family (SAR1376) to a range of pathogen antigens from *Staphylococcus aureus* and *Plasmodium falciparum*. Following delivery of these fused complexes by DNA or viral vectors, increased immunogenicity has been observed *in vivo*. The 4-OT tag mutimerises in solution and it is the aggregation that is thought to cause the observed increase in immunogenicity. This methodology represents a rare discovery of a non-human multimerisation domain that enhances immunogenicity when fused to a range of antigens.

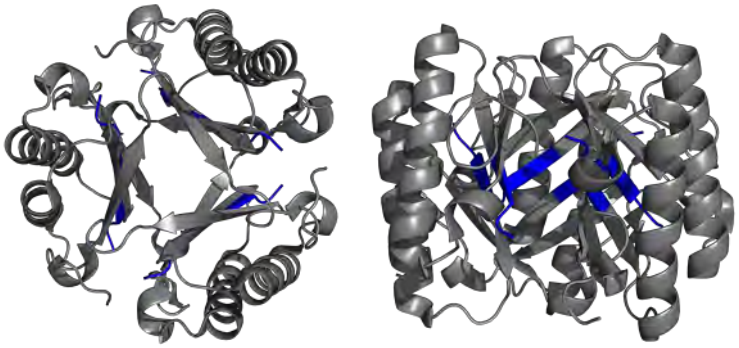
Perhaps most importantly, 4-OTs are widespread in pathogenic bacteria (both Gram positive and Gram negative). Their conserved structure may allow this to be a generalised approach for enhancing antibody responses to vaccine antigens, offering an attractive alternative to virus like particles (VLPs).

We believe that the key advantages of this technology include:

- Adjuvant shows *in vivo* efficacy when fused to antigens from *S. aureus* or *P. falciparum*
- New platform technology for vaccine development
- Hundreds of potential adjuvants identified in diverse bacterial species
- Rare class of multimerisation tags that can enhance immunogenicity
- Fills need for more antigen scaffolding strategies

Commercialisation

Oxford University Innovation Ltd. has filed a patent, which covers this work and is currently seeking a commercial partner to develop the technology.



Above image: Crystal structure of the SAR1376 multimerizing protein, obtained from the Protein Data Bank

For further information please contact:
Dr Matthew Carpenter
matthew.carpenter@innovation.ox.ac.uk
+44 (0)1865 280970
www.innovation.ox.ac.uk
Project number: 10924

Technology Transfer from the University of Oxford

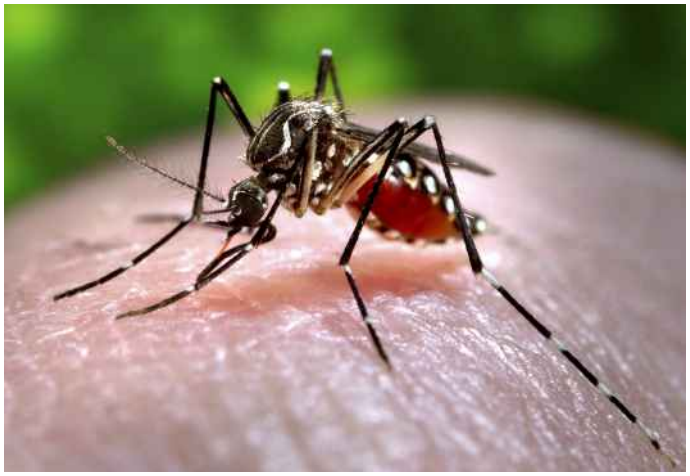
Multivalent Dengue Vaccine

Available to license: A universal Dengue vaccine to induce cellular immune responses against all dengue virus serotypes.

Dengue fever is the most rapidly spreading mosquito-borne viral disease in the world. The World Health Organisation estimates that almost half of the world's population lives in at-risk areas, with ~390 million new infections every year. The disease is caused by four dengue virus (DENV) serotypes, infection with one serotype only confers protection against re-infection with the same serotype. Multiple serotypes commonly circulate together in a particular geographical region and secondary infection with a different serotype carries the risk of developing haemorrhagic fever and shock due to antibody-dependent enhancement (ADE) where non-neutralising antibodies facilitate virus entry into host cells, leading to increased infectivity. Following infection with a secondary DENV serotype, the immune response can be skewed by the memory of the previous infection, with the titre of antibodies specific to the earlier virus being higher than for the currently infecting serotype; a phenomenon known as "antigenic sin".

A safe and effective DENV vaccine must induce strong, long-lived and equal protection against all four serotypes in order to avoid the risk of ADE or antigenic sin. Most DENV vaccines in development have been designed to induce protective antibodies against external proteins of each of the four virus serotypes and are formulated with components from each of the four serotypes.

An alternative approach has been pioneered at the University of Oxford's Jenner Institute. Researchers have developed a vaccine to induce protective T-cell immunity against all four serotypes of DENV with minimal risk of inducing ADE or antigenic sin.



Oxford Invention

The Jenner researchers have developed a DENV vaccine using non-replicating viral-vectored vaccines to induce T-cell responses against a single immunogen incorporating the most conserved non-structural DENV proteins. This vaccine has been designed to generate full protection against all DENV serotypes.

The vaccine was designed using a bioinformatics approach, to identify the most conserved and functionally critical protein sequences in all four serotypes of DENV, representative of the true global virus population. The researchers have developed a single immunogen comprising the most conserved segments of the internal NS3-NS5 genes across all four serotypes. This single, pan-serotype, universal dengue antigen has been expressed in a simian adenoviral vector and in the vector modified vaccinia Ankara, for use in a heterologous prime-boost vaccination regimen.

Cellular Immune Response against all DENV serotpes

Immunogenicity trials of the DENV vaccine in mice have shown the induction of abundant T cells against all four serotypes represented in the novel dengue antigen, and studies in macaques show vaccine safety and immunogenicity.

The Jenner DENV vaccine is being currently evaluated in a DENV challenge model, which uses several strains of the virus which have been adapted to infect mice. In this model, induction of DENV-specific cytotoxic T-cells should prevent DENV infection in the mice.

For further information please contact:
technology@innovation.ox.ac.uk
www.innovation.ox.ac.uk
Project number: 11715

Technology Transfer from the University of Oxford

Staphylococcus aureus (*S. aureus*) vaccine

Researchers at the University of Oxford have identified two key proteins that could offer an alternative vaccine against *S. aureus.*

Staphylococcus aureus - A resistant threat

The evolution of multi-drug resistant strains of *S. aureus* brings with it new challenges in treating the infections caused by these pathogens. It is likely that strains of *S. aureus*, which display resistance to our most potent antibiotics, will become more prevalent in the coming years. As *S. aureus* infections contracted during clinical procedures start to bypass our last line of defence, the clinicians will need to turn to alternative measures to halt the spread of these potentially deadly diseases.

Prevention is the best cure

A viable option in the fight against drug resistant pathogens is prophylaxis. Although vaccines against *S. aureus* infections have entered clinical trials, they have resulted in high profile failures as late as stage III. Researchers at the University of Oxford have identified two antigens as new candidates for *S. aureus* vaccine development. The two Eap proteins in question are highly conserved homologues that are present in nearly all *S. aureus* studied.

REap the benefits

All members of the Eap protein family interact with the innate immune response of the host to ensure the safety of the growing bacteria. Work at Oxford has shown immune neutralisation of the Eap protein family through vaccination could protect the host from *S. aureus* pathogenesis upon infection, and even prevent the organism establishing colonisation, a key step in *S. aureus* transmission. By generating vaccine antigens from Eap proteins, then delivering them using a non-replicating viral vector the immune system can be trained to attack these parts of the *S. aureus* pathogen.

We believe the benefits of this approach include:

- Vaccination offers a route to bypass drug resistance in pathogens
- Eap proteins are promising new vaccine candidates
- Early results indicate effectiveness in animal models
- Could be used in combination with other antigens
- Uniquely, suppresses establishment of colonisation

Commercialisation

The technology discussed is covered by an International patent application PCT/GB2017/053301 (2 November 2017). Oxford University Innovation Ltd. is seeking a partner who could help take this promising vaccine lead to a clinical setting.

For further information please contact:
Dr Matthew Carpenter
matthew.carpenter@innovation.ox.ac.uk
+44 (0)1865 280970
www.innovation.ox.ac.uk
Project number: 13619

Technology Transfer from the University of Oxford

Zika viral vector vaccine

Oxford researchers have developed a Zika vaccine that can induce immune responses against the African and Asian lineages of the Zika virus.

Zika virus

Zika virus (ZIKV) is a mosquito-borne virus that belongs to the family Flaviviridae. Initially detected in Africa, it has spread through Polynesia and is now spreading rapidly throughout the Americas and Asia. Since the outbreak of ZIKV disease in Brazil in 2015, ZIKV infection has been linked to neurologic conditions in developing foetuses, such as microcephaly and Guillain-Barre syndrome. Importantly, only 2 out of 5 people exhibit signs and symptoms of ZIKV infection, and person to person transmission makes ZIKV a very challenging flavivirus to tackle.

The virus has now spread to more than 45 countries, 25 of which reported severe ZIKV-associated disease. An estimated 100 million people in the Americas are predicted to be at risk of acquiring ZIKV. According to a recent WHO report, ZIKV remains an enduring public health challenge requiring intense action. There is an urgent need to protect women, either before or during pregnancy, from infection by the virus. Currently, there is no vaccine for ZIKV or effective treatment for the disease.

Designing an effective vaccine is highly challenging. When introduced with a viral vector, the antigen should be produced and secreted at an amount that is sufficient to stimulate robust antibody and cytotoxic responses. Ideally, the antigen should also induce an immune response against many (or all) strains of the virus.

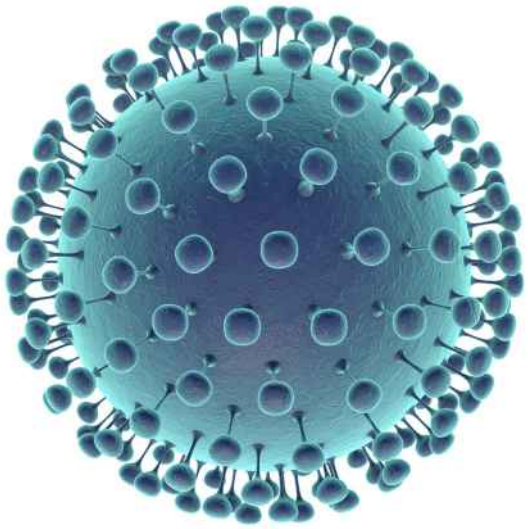
Zika viral vector vaccine

Oxford researchers have developed a Zika vaccine based on a viral vector which contains a sequence encoding a ZIKV structural antigen. Using a bioinformatic approach, the antigen consensus sequence that has been carefully designed using the published ZIKV genetic sequences. It is highly similar - at least 99% - to the strains causing the epidemics in the Americas but also matches closely with the African genotype. The ZIKV antigen has been designed to allow high titers of antibody production after a single and non-adjuvanted vaccination dose. Therefore, the vaccine should suitable to be used in many countries affected by various strains of ZIKV.

The vaccine induced a substantial immune response against ZIKV after a single dose with high levels of ZIKV antibodies up to 9 months after a single ChAdOx1 Zika vaccination, in mice.

Available for licensing

A patent has been filed for this technology. Oxford University Innovation is seeking a development partner to license this technology and support its future developments.



For further information please contact:
Dr Christine Whyte
christine.whyte@innovation.ox.ac.uk
+44 (0)1865 280921
www.innovation.ox.ac.uk
Project number: 13769

Technology Transfer from the University of Oxford

COA - CLINICAL OUTCOME ASSESSMENT

The Amyotrophic Lateral Sclerosis Assessment Questionnaire (ALSAQ)

Clinical Outcomes

Enhance your value proposition with the Patient Reported Outcome (PRO) measure for ALS: the ALSAQ-40 and ALSAQ-5

Background

Differentiate your product through the use of the ALSAQ (Amyotrophic Lateral Sclerosis Assessment Questionnaire) to generate a value proposition that shows efficacy over and above that of clinical and safety measures. Created by world-renowned experts in health status measurement in Oxford's Department of Public Health, the ALSAQ is a disease-specific PRO validated for measuring subjective health status in ALS (also known as Lou Gehrig's Disease or Motor Neurone Disease).

Enhance your competitive advantage

The use of PROs to measure intervention success is becoming increasingly common in studies concerning incurable conditions such as ALS where the desired outcome is to improve patient health status and ameliorate symptoms. The ALSAQ is highly sensitive to disease-related changes where generic scores are not, offering you the maximum chance of detecting health status change with your intervention. ALSAQ data can achieve the approval of additional label claims that directly target patients' needs, and supports your European Summary of Product Characteristics, so that practitioners understand the impact that your therapy has on patients' wellbeing.

Development

All key ALS health status issues were captured by in-depth interviewing of ALS patients. Questionnaire items constructed from the interviews cover five discrete scales:

- physical mobility
- activities of daily living
- eating and drinking
- communication
- emotional reactions

The ALSAQ is highly responsive to intervention efficacy, regardless of the mechanism of action. Available in a 40 item (ALSAQ-40) or a short form five item (ALSAQ-5) version, the ALSAQ may be employed in surveys or clinical trials for ALS/MND patient groups. Rigorous testing has shown this PRO measure to:

- be exceedingly reliable, robust and sensitive to change
- be easy to complete, resulting in an excellent response rate
- be straightforward to interpret (answers are on the five point Likert scale)
- have high face, internal and construct validity.

ALSAQ Users

The research, subsequent development and validation of the ALSAQ was supported by the UK's Motor Neurone Disease Association

Biogen

mnda motor neurone disease association

Mitsubishi Tanabe Pharma

Apply to use

The ALSAQ is managed, as part of a wide portfolio of Patient Reported Outcome measures, by Clinical Outcomes; an activity within the University of Oxford's technology transfer company, Oxford University Innovation Ltd. For further information on how to apply please get in touch via:

healthoutcomes@innovation.ox.ac.uk

+44 (0) 1865 614480

Find out more!

The Diabetes Health Profile

diabetesprofile Patient research

Clinical Outcomes

How are you measuring outcomes in your diabetes studies?

Background

The Diabetes Health Profile (DHP) is designed to measure the impact of diabetes in a variety of settings from clinical practice to clinical trials. The DHP is simple to complete, acceptable to patients, easy to score, with established validation that delivers interpretable findings.

With its track record and proven performance the DHP is a valuable tool for providing metrics in trial settings.

Advantages

With proven psychometric and operational performance the Diabetes Health Profile (DHP) has a number of distinct advantages over other diabetes-specific measures of the psychological and behavioural impact of living with diabetes:

- A clearly defined conceptual framework of the measurement model which conforms to the FDA PRO guidance for Industry (2009)
- Content reported by patients as highly relevant to living with diabetes
- The measurement of dysfunctional eating behaviour – which, despite its importance in the management of diabetes, is absent in other scales
- Norm referenced database and MID's
- The use of straight forward language and simple phrasing
- A simple scoring algorithm

Development

The Diabetes Health Profile (DHP-18) was developed for people with Type 1 and Type 2 diabetes to measure the psychological impact of living with diabetes. It is based on a clearly defined conceptual model and framework, and comprises 18 items which capture the three key domains:-

These are:

1. **Psychological distress** - 6-items (dysphoric mood, feelings of hopelessness, irritability)
2. **Barriers to activity** - 7-items (perceived limitation to activity, operant anxiety)
3. **Disinhibited eating** - 5-items (lack of eating control, response to food cues

The DHP-18 has been used in community surveys, clinical trials, research studies and educational interventions internationally involving over 15,000 patients. User acceptability of the DHP-18 is high with item completion rates >90%.

The DHP-18 has demonstrated good measurement properties (including reliability coefficient >0.70) and the ability to discriminate between different treatment groups and patient groups experiencing severe hypoglycaemic episodes.

Apply to use

The DHP is managed, as part of a wide portfolio of Patient Reported Outcome measures, by Clinical Outcomes; an activity within the University of Oxford's technology transfer company, Oxford University Innovation Ltd. For further information on how to apply please get in touch via:

healthoutcomes@innovation.ox.ac.uk

+44 (0) 1865 614417

New

Now available as short form (3 + 5 item) utility weighted versions for calculation of QALYs!

Find out more!

The Endometriosis Health Profile (EHP)

Clinical Outcomes

The Endometriosis Health Profile is a Health Related Quality of Life (HRQoL) patient self-report PRO, used to measure the wide range of effects that endometriosis can have on women's lives.

Background

The EHP is the only condition-specific PRO designed from the patient's perspective to assess health related quality of life in endometriosis. The EHP is available in various formats to suit users study requirements, the long-form core instrument, the EHP-30, the short-form core EHP-5 and a selection of 6 modules that can be used alongside the core instrument.

Published evidence concludes that the EHP is a reliable and valid instrument for assessing areas of concern to women with endometriosis that are not addressed by other condition-specific and generic questionnaires.

The EHP is particularly appropriate for use in clinical trials to assess the effectiveness of medical or surgical therapies for endometriosis on the HRQoL of affected women. For this reason the EHP has been used by four of the top twenty global pharmaceutical companies, supporting numerous clinical trials.

Modules

The EHP consists of a core instrument, available as either a long-form 30 item instrument (the EHP-30), or the short-form (EHP-5) PRO.

The core instruments have five scale scores covering:
Pain (11)
Control and powerlessness (6)
Social support (4)
Emotional well-being (6)
Self-image (3)
Numbers in brackets represent the number of items in each scale of the (long-form) core EHP-30.

In addition, there is the option of deploying alongside the core instrument six supplementary modules, a total of 23 items (EHP-30 + 23).

These modular scales cover areas of health status that may not affect every endometriosis sufferer and are therefore provided as an option.

Development

The EHP system including the core and modular scales was developed in a 3 step approach:

Stage 1 – Item generation.
From qualitative in-depth interviews with 24 women who had laparoscopic diagnosis of endometriosis. This generated a large number (86) of candidate questionnaire items. This 86-item questionnaire was developed and piloted (Group 1) to test basic acceptability and comprehension.

Stage 2 – Item reduction and scale generation.
A second survey was administered using the 87-item questionnaire to 1000 women from the National Endometriosis Society, U.K. (Group 2). The items were reduced using factor analysis of the survey results to produce a shorter (53-item) questionnaire and enable the most salient dimensions of endometriosis which affect HRQoL to be identified.

Stage 3 – Establishing test-retest reliability and validity.
To establish test-retest reliability and validity, a third survey was administered to 83 women recruited from an out-patient gynaecology clinic at the John Radcliffe Hospital, Oxford, (Group 3) using the 53-item questionnaire generated at stage 2. Construct validity was assessed in a postal survey (n = 40) to women undergoing conservative surgery for endometriosis at the John Radcliffe Hospital (Group 4) who completed the EHP-30 and SF-36.

Apply to use

The EHP is managed, as part of a wide portfolio of Patient Reported Outcome measures, by Clinical Outcomes; an activity within the University of Oxford's technology transfer company, Oxford University Innovation Ltd. For further information on how to apply please get in touch via:

healthoutcomes@innovation.ox.ac.uk

+44 (0) 1865 614480

Find out more!

HASMID-10
Health and Self-Management in Diabetes

The University Of Sheffield.

HASMID- 10

Clinical Outcomes

The HASMID- 10 is a measure that determines the impact of self-management in diabetes

Background

HASMID-10 is a short questionnaire that contains ten items each with four response levels to measure the impact of self-management in diabetes for both Type 1 Diabetes and Type 2 Diabetes.

The measure was developed using a mixed-methods approach that involved semi-structured interviews with people with diabetes. The measure has high face validity. Ongoing research is being undertaken to assess the validity of this questionnaire for measuring the impact of self-management interventions in economic evaluation (**HRQoL**).

The measure

The HASMID-10 identifies Eight management attributes. The three attributes from the DHP and energy for the attributes designed to capture **HRQoL**, and the four attributes identified from the patient interviews cover self-management, resulting in the following eight attributes for inclusion in the questionnaire.

1.Mood
2.Hypoglycaemic attacks
3.Social Limitations
4.Energy
5.Control
6.Hassle
7.Stress
8.Support

Four of these self-management attributes (Control, Hassle, Stress + Support) were selected with four health attributes; mood, fear about hypos (hypoglycaemic episodes), energy and social limitations

Advantages

The HASMID-10 questionnaire is a short, easy-to-complete PROM. It has been developed following a series of rigorous iterations, with high involvement of patients and service-users to ensure good face validity.

- Appears to perform better than EQ-5D-5L
- Ability to differentiate between treatment groups
- Can be scored using total summative scores
- Utility and monetary values are available
- Can be used in a range of applications including cost-utility and cost-benefit analysis

Apply to use

The HASMID-10 is managed, as part of a wide portfolio of Patient Reported Outcome measures, by Clinical Outcomes; an activity within the University of Oxford's technology transfer company, Oxford University Innovation Ltd. For further information on how to apply for a licence please get in touch via:

healthoutcomes@innovation.ox.ac.uk

+44 (0) 1865 614480

New

Preference-based utility tool used to extract health economic data from the existing HASMID-10, now available!

Find out more!

The Liverpool University Neurologic Side Effects Rating Scale (LUNSERS)

Clinical Outcomes

LUNSERS was developed by researchers within the University of Liverpool to indicate the extent of side-effects experienced by patients medicated with neuroleptic drugs.

Background

- Present findings indicate that LUNSERS may be a useful tool, as a brief and cost-effective measure of side-effects in research studies
- The scale is completed by the patient and can be easily administered by members of various health care disciplines without specialist training
- LUNSERS assesses a wide range of neuroleptics side-effects
- Patients find the scale to be easy complete within 5-20 minutes
- 'Red-herring' items helped to test the robustness of the results

Development

The measurement scale consists of 51 items, which were mainly based on adaptions to the physician-rated items in the UKU side effects rating scale. Forty-one items, covering psychological, neurological, autonomic, hormonal and other miscellaneous side-effects, were constructed by rewording the appropriate UKU items, so that they could be self-rated.

In addition, 10 'red herring' items were included, referring to symptoms that are not known neuroleptic side-effects (e.g. chilblains, hair loss), to help validate the results.

In order to assess the validity of the questionnaire the study team has administered it not only to patients being treated with neuroleptics (n=50) but also to normal control subjects (n=50) from which none were receiving psychiatric treatment or medications of any kind.

The LUNSERS was found to be a valid and reliable assessment of patients' experiences of neuroleptic side-effects.

Scoring

The scale consists of 41 known side effects of neuroleptics. Each 'side-effect' listed is scored on a five point rating scale of 0 - 4, i.e. 0 = 'Not at all' and 4 = Very much. It can be used to provide a general overview of the person's experience to side effects over the last month.

It is useful also in pinpointing specific troublesome side effects for further assessment and / or changes in the medication strategy. Details of the scoring system for the LUNSERS can be downloaded in Dossier Extracts section.

Apply to use

The LUNSERS is managed, as part of a wide portfolio of Patient Reported Outcome measures, by Clinical Outcomes; an activity within the University of Oxford's technology transfer company, Oxford University Innovation Ltd. For further information on how to apply please get in touch via:

healthoutcomes@innovation.ox.ac.uk

+44 (0) 1865 614480

Find out more!

Musculoskeletal Health Questionnaire (MSK-HQ)

Clinical Outcomes

The Musculoskeletal Health Questionnaire (MSK-HQ) is a Patient Reported Outcome which has been developed to assess outcomes in patients with a variety of musculoskeletal conditions

Background

The Musculoskeletal Health Questionnaire (MSK-HQ) is a Patient Reported Outcome which has been developed to assess outcomes in patients with a variety of musculoskeletal conditions. The MSK-HQ has been found to be acceptable to patients, have good internal consistency, convergent validity and excellent test-retest reliability. It can be used to measure the impact of an MSK condition on a patients' health, regardless of the location of the pain and the care the patient is currently receiving.

Development

The MSK-HQ was co-produced with patients and clinicians to identify aspects of MSK health important to both. A consensus workshop provided initial domains, and individual items were formulated. Stakeholder acceptability was assessed during a second workshop and a candidate MSK-HQ was then taken forward to quantitative testing in physiotherapy and orthopaedic cohorts (n=570).

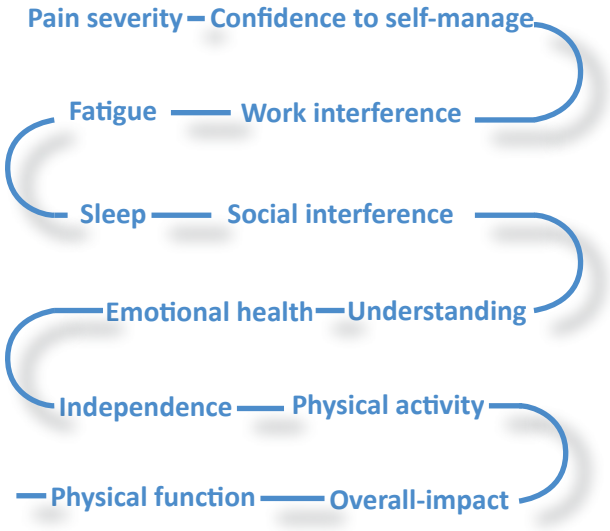
The Versus Arthritis MSK-HQ contains 14 items and measures the health status in patients with MSK conditions over the past two weeks. MSK-HQ was developed as a collaboration between Keele and Oxford Universities.
The development of MSK-HQ was supported by Versus Arthritis and the NHS.

Scoring

The MSK-HQ is scored on a range of 0-56, with a better score indicating better MSK-HQ health status. In order to calculate the respondents total score, add the numbers next to the box that the respondent has ticked on the questionnaire form. The total of all of these scores, will give the overall result of the MSK-HQ.

The Instrument

The Arthritis Research UK MSK-HQ contains 14 items and measures the health status in patients with MSK conditions over the past two weeks. There are a number of different dimensions to the instrument:



Apply to use

The MSK-HQ is managed, as part of a wide portfolio of Patient Reported Outcome measures, by Clinical Outcomes; an activity within the University of Oxford's technology transfer company, Oxford University Innovation Ltd. For further information on how to apply please get in touch via:

healthoutcomes@innovation.ox.ac.uk

+44 (0) 1865 614480

Find out more!

The Oxford Depression Questionnaire (ODQ)

Clinical Outcomes

epression Questionnaire (ODQ) is a patient-centred, self-report measure of emotional symptoms present in patients treated with antidepressants.

Background

Some patients with major depression report a restricted range of emotions that may appear to arise as a side-effect of treatment with antidepressants. It is uncertain whether this phenomenon, sometimes called emotional blunting, represents residual symptoms of depression or side-effects of antidepressant treatment. The Oxford Depression Questionnaire (ODQ) is a patient-centred, self-report measure of emotional symptoms present in patients treated with antidepressants.

The Oxford Depression Questionnaire (ODQ) was formerly called the Oxford Questionnaire on the Emotional Side-Effects of Antidepressants (OQESA).

The measure

The ODQ is a 26-item patient self-complete measure, spread over 3 sections and covering 4 dimensions (derived from qualitative research) of

1. Not caring (NC)
2. Emotional detachment (ED)
3. Positive reduction (PR)
4. General reduction (GR)

The 3 sections of the ODQ are:

1. 12 items, three items from each of the 4 dimensions (NC, ED, PR and GR). Recall period is the last week.

2. 8 items, 2 from each of the four dimensions, comparing respondents experiences during the previous week with in comparison to their experiences before they developed their illness / problem.

3. 6 items, is for completion by those respondents currently prescribed antidepressants. This section addresses the extent to which participants attribute their emotional difficulties to their antidepressant, and the extent to which they would therefore be considered by participants to be "emotional side-effects". It also addresses the possible impact of emotional side-effects on antidepressant adherence.

Advantages

The key characteristics and benefits of the ODQ (based on results acquired during development) are:

Acceptability

Completion of the questionnaire by patients was extremely high with 96% completing the instrument on 3 separate occasions (weeks 0, 1 and 4)

Validity

The ODQ has high construct validity with four dimensions (reduction in positive emotions; general reduction in emotions; not caring; and emotional detachment) being represented in the ODQ. In addition, items in the ODQ demonstrate close relationships to contents of other scores measuring emotional blunting.

Sensitivity to change

When compared to a "gold standard" question (relating to the participant's experience of emotional side-effects) the ODQ appears to be sensitive to change.

Reliability

The ODQ has high reliability, both in terms of internal reliability (items within each construct were highly correlated) and test-retest reliability.

Apply to use

The ODQ is managed, as part of a wide portfolio of Patient Reported Outcome measures, by Clinical Outcomes; an activity within the University of Oxford's technology transfer company, Oxford University Innovation Ltd. For further information on how to apply for a licence to use the ODQ please get in touch with the Clinical Outcomes team via:

healthoutcomes@innovation.ox.ac.uk

+44 (0) 1865 614417

Find out more!

Measuring the success of surgery – The Oxford orthopaedic outcome Scores

Clinical Outcomes

How are you measuring outcomes of THA and TKA?

Oxford is not only synonymous with excellence in world-class research and teaching, but also well regarded for its portfolio of Patient Reported Outcome (PRO) measures. At the leading edge of this collection of high quality, condition-specific, PRO measures is our portfolio of orthopaedic/MSK PRO measures including the highly regarded and globally recognised Oxford Hip and Knee Scores.

The Oxford Hip and Knee Scores are short (12-item) patient-reported outcome (PRO) measures specifically designed, developed and validated to assess function and pain when undergoing total hip or knee replacement (THA or TKR) surgery. The Oxford Hip and Knee Scores (OHS and OKS) are short (resulting in low respondent burden), reproducible, valid and sensitive to clinically important change. The Oxfords are supported by a wealth of published evidence in the routine use of the measures in health outcomes assessments.

The Oxford Hip and Knee Scores are:

- now widely recognised as the gold standard questionnaires to measure patient health outcomes following hip/knee surgical intervention
- the outcomes measures of choice for hip and knee arthroplasty in U.S. CMS and U.K. NHS National Patient Reported Outcomes Measures (PROMS) program
- originally published in the late 1990's as a result of a collaboration between researchers at University of Oxford, now consolidated with over 300 international institutions relying on the Oxford orthopaedic scores.

Clinical Outcomes has:

Licensed the Oxford Hip and Knee Scores to over 300 institutions internationally, who now rely on it for their healthoutcomes assessments,

Commissioned comprehensive user manuals covering all aspects of using the Oxford Scores,

Assembled over 50 culturally adapted translations of the measures for international use, including English for USA,

Advised and assessed the migration of the validated paper-based measures to electronic format, so the all-important measurement properties of the Oxford scores are not invalidated.

OXFORD Knee Score (OKS)

OXFORD Hip Score (OHS)

For further information please contact:

healthoutcomes@innovation.ox.ac.uk

or visit

innovation.ox.ac.uk/health-outcomes/

The Oxford Participation and Activities Questionnaire (Ox-PAQ)

Clinical Outcomes

The Oxford Participation and Activities Questionnaire is a short, 23-item, patient-reported outcome measure developed to assess participation and activity in patients experiencing a range of health conditions.

Background

There is growing interest in the management of long-term conditions and keeping people active and participating in daily life (1-4). Testing the effectiveness of interventions which aim to impact upon activities and participation, however, can be challenging without the availability of a well-developed, valid and reliable instrument.

The Oxford Participation and Activities Questionnaire is a patient-reported outcome measure that is grounded on the World Health Organization International Classification of Functioning, Disability, and Health (ICF) and is fully compliant with current best practice guidelines, such as those published by the FDA.

The Ox-PAQ was developed by researchers within the Health Services Research Unit, part of the Nuffield Department of Population Health at the University of Oxford.

The Ox-PAQ also comes as an 'acute' version, with emphasis on the recall period being more recent; 1 week rather than 4 weeks.
The development of the OxPAQ was funded by the European Brain Council.

Validation

The primary use of the Ox-PAQ is intended to be in clinical trials and related forms of evaluation of interventions targeted at maintaining activity and participation.

Further work by the OxPAQ development team at the University of Oxford, has resulted in the populations that the OxPAQ is validated for being extended to include:

- Chronic Obstructive Pulmonary Disease (COPD)
- Aneurysmal Subarachnoid Haemorrhage (SAH)
- Valvular heart disease.

Development

Ox-PAQ items, which had previously been informed using the nine chapters of the ICF, 41 patient interviews, expert reviews and 13 cognitive interviews , were administered by postal survey to 386 people with three neurological conditions; Parkinson's disease, amyotrophic lateral sclerosis, and multiple sclerosis. Participants also completed the MOS 36-Item Short Form Survey (SF-36) and EQ-5D-5L. Consenting participants were also sent the OxPAQ items to complete again after a period of two weeks.

162 men and 172 women completed the survey achieving a response rate of 86.5%. The mean age of the sample was 60.06 years (SD 12.10).

Ox-PAQ domains

Routine Activities (14 items), assesses individuals' capacity to engage in regular activities that form the basis of daily life.

Emotional Well-Being (5 items), gives an indication of current mental health status.

Social Engagement (4 items), reflects how well, or otherwise, individuals are able to maintain relationships, both personal and from a wider community perspective.

Apply to use

The Ox-PAQ is managed, as part of a wide portfolio of Patient Reported Outcome measures, by Clinical Outcomes; an activity within the University of Oxford's technology transfer company, Oxford University Innovation Ltd. For further information on how to apply please get in touch via:

healthoutcomes@innovation.ox.ac.uk

+44 (0) 1865 614480

Find out more!

The Parkinson's Disease Questionnaire (PDQ)

Clinical Outcomes

Enhance your value proposition with the gold-standard Patient Reported Outcome (PRO) measure for Parkinson's Disease: the PDQ

Background

Substantial evidence is available to suggest that the PDQ is reliable, valid, responsive, acceptable and feasible as the tool for the assessment of quality of life in Parkinson's disease patients. For these reasons it has been widely adopted and generally considered the industry 'gold standard'.

The PDQ is primarily used in clinical trials of therapeutics intended to benefit individuals with Parkinson's disease.

The PDQ is the most comprehensive Parkinson's disease assessment questionnaire because it is:

- simple to complete so benefits from an excellent response rate
- proven by validation and feasibility studies (reported in the manual) covering topics such as cross-cultural evaluation
- supported by a comprehensive 114 page user manual
- available in over 80 language versions
- available in the core PDQ-39 (39 items) or the short form PDQ-8 (8 items), it can be supported by expert advice available from the developers for the use, delivery and data assessment of the PDQ.

PDQ Users

The PDQ has been used to support more than 150 clinical trials, involving more than 20,000 patients, including many of the world's largest pharmaceutical companies:

NOVARTIS

Abbott

gsk GlaxoSmithKline

Boehringer Ingelheim

Development

All key Parkinson's Disease health status issues were captured by in-depth interviewing of patients.
Questionnaire items constructed from the interviews cover eight discrete scales:

- mobility
- activities of daily living
- emotional well-being
- stigma
- social support
- cognitions
- communication
- bodily discomfort

The PDQ is highly responsive to intervention efficacy, regardless of the mechanism of action – it has been used to assess patient outcomes in trials employing drug, surgical (e.g. Deep Brain Stimulation) and alternative therapies.

Modules

Also available to licence is the PDQ-Carer, a 29-item measure of health related quality of life for use with carers of people with Parkinson's disease. New validation work is planned for the following modules:

- PDQ-Sleep
- PDQ-Exercise
- PDQ-Medication

Apply to use

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Find out more!

ReQoL™
Recovering Quality of Life

The University Of Sheffield.

Recovering Quality of Life (ReQoL) Questionnaire

Clinical Outcomes

The Recovering Quality of Life (ReQoL) is a Patient Reported Outcome which has been developed to assess the quality of life for people with different mental health conditions.

Background

ReQoL is a brief outcome measure focusing on the process of recovery for users of mental health services. Developed by a team at The University of Sheffield to capture the concerns of service users on their quality of life. This work was commissioned and funded by the Department of Health Policy Research Programme in England for use in the NHS.

Development

In the development of ReQoL, qualitative and quantitative techniques were implemented to produce a psychometrically robust measure using inputs from service users with a broad range of mental health diagnoses and severity. A significant contribution was received, at all stages, from governance groups including a stakeholder group, an advisory group, a scientific group, clinicians, and an expert user group.

Advantages

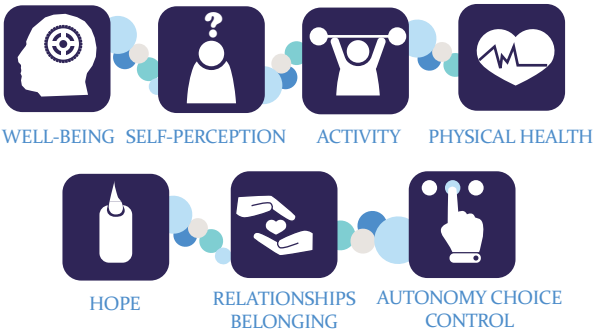
Comprehensive psychometric testing has shown that the ReQoL is:

- Valid for a population with mental health conditions
- Easy to complete
- Straightforward to score and interpret
- Considerable inputs of service users in the design and item selection
- Face and content validity with service users and clinicians

The Instrument

ReQoL has two versions: a brief 10-item measure (ReQoL-10), and a 20-item measure (ReQoL-20). The ReQoL measures are generic and can be used across all mental health populations including common mental health problems, severe and complex, and psychotic disorders. They are suitable for mental health populations aged 16 and over in primary, secondary, and tertiary care.

There are seven themes captured by ReQoL, and these themes overlap and are not mutually exclusive:



Apply to use

The ReQoL is managed, as part of a wide portfolio of Patient Reported Outcome measures, by Clinical Outcomes; an activity within the University of Oxford's technology transfer company, Oxford University Innovation Ltd. For further information on how to apply for a licence to use the ReQoL, please get in touch via:
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Further work is planned to generate preference weights for the ReQoL. These can be used to calculate quality adjusted life years (QALYs) for use in economic evaluation of health care interventions

Find out more!